International Symposium on

Trends in Radiopharmaceuticals

28 October–1 November 2019

Vienna, Austria

Programme & Abstracts

Organized by

Colophon

This book has been assembled from the abstract sources submitted by the contributing authors via the Indico conference management platform. Layout, editing, and typesetting of the book, was done by Ms. Julia S. Vera Araujo from the Radioisotope Products and Radiation Technology section, IAEA, Vienna, Austria.

This book is PDF hyperlinked: activating coloured text will, in general, move you throughout the book, or link to external resources on the web.

INTRODUCTION

Progress in nuclear medicine has been always tightly linked to the development of new radiopharmaceuticals and efficient production of relevant radioisotopes. The use of radiopharmaceuticals is an important tool for better understanding of human diseases and developing effective treatments. The availability of new radioisotopes and radiopharmaceuticals may generate unprecedented solutions to clinical problems by providing better diagnosis and more efficient therapies.

Impressive progress has been made recently in the radioisotope production technologies owing to the introduction of high-energy and high-current cyclotrons and the growing interest in the use of linear accelerators for radioisotope production. This has allowed broader access to several new radionuclides, including gallium-68, copper-64 and zirconium-89. Development of high-power electron linacs resulted in availability of theranostic beta emitters such as scandium-47 and copper-67. Alternative, accelerator-based production methods of technetium-99m, which remains the most widely used diagnostic radionuclide, are also being developed using both electron and proton accelerators.

Special attention has been recently given to α-emitting radionuclides for in-vivo therapy. A few years ago, the first α-emitting radiopharmaceutical, Xofigo, (pharmaceutical-grade radium-223 dichloride solution) has been approved by the US FDA for cancer treatment. Many other α-emitting radiopharmaceuticals based on astatine-211, bismuth-212, bismuth-213, actinium-225, radium-223, lead-212, thorium-227 and terbium-149, are currently being developed. However, numerous research groups worldwide are working on efficient production of these much sought after α-emitters as demand for these α-emitting radionuclides significantly exceed their supply

The field of radiopharmaceuticals has witnessed continuous evolution thanks to the immense contributions of scientists from diverse disciplines such as radiochemistry, inorganic chemistry, organic chemistry, organometallic chemistry, biochemistry, molecular biology, physiology and pharmacology. Several milestones can be cited in the trajectory of this growth, which include continuing development of technetium-99m radiopharmaceuticals, automated synthesis of fluorine-18 labelled compounds, radiopharmaceuticals labelled with generator eluted gallium-68, labelled peptides and monoclonal antibodies for accurate diagnosis and treatment of tumours. The concept of theranostic radioisotopes, that combines the diagnosis and therapy properties of one radioisotope or a pair of similar radioisotopes, may provide an attractive paradigm for future development of medical applications of radionuclides. Biomolecules developed for specific molecular target and labelled with theranostic radionuclides provide clinically significant information for diagnosis, suitability of radionuclide therapy, dosimetry and post therapy planning, making personalised medicine a reality.

Purpose and Objectives

The International Symposium on Trends in Radiopharmaceuticals, ISTR-2019, will provide scientists and professionals working in the fields of radioisotope production and radiopharmaceuticals an international forum for discussing the most recent developments in the field. Various topics will be covered during the Symposium including development, production, and uses of diagnostic, therapeutic, and theranostic radioisotopes and radiopharmaceuticals, as well as regulatory and licensing issues related to their production. Education, certification and training methodologies will also be addressed.

The ISTR-2019 will provide a great opportunity for chemists, biologists, pharmacists, physicists, medical researchers, and other experts in the international community to meet and discuss their most recent work. This meeting will help maintain existing and establish new collaborations to address common problems and expand the worldwide use of radiopharmaceuticals.

Structure, Themes and Topics

The symposium programme will consist of an opening session, plenary sessions, technical sessions, poster sessions, exhibitions, side events and a closing session. The opening session will include welcoming addresses by representatives of the IAEA, cooperating organizations and other relevant organizations. The plenary sessions will continue with a combination of invited keynote presentations and submitted papers addressing the main themes and topics of the symposium. Each topical session will include presentations and/or panel discussions delivered by participants which will have been selected based on the abstracts submitted. The symposium will also include poster sessions, and enough time will be provided for discussion and interaction with colleagues. The final plenary session on the last day of the symposium will be dedicated to conclusions and recommendations on the way forward.

The scope of the symposium is meant to cover, but is not limited to, the following topical areas:

- Production of PET- and SPECT-based diagnostic, therapeutic and theranostic medical radioisotopes
- Production of radionuclide generators
- Production of PET- and SPECT-based diagnostic, therapeutic and theranostic radiopharmaceuticals
- Research and Development related to the production of medical radioisotopes and radiopharmaceuticals
- Quality control and quality assurance of medical radioisotopes and radiopharmaceuticals
- Pre-clinical evaluation of radiopharmaceuticals
- Good Manufacturing Practices for production of medical radioisotopes and radiopharmaceuticals
- Design of radiopharmacy (industrial, hospital and centralized) facilities
- Health regulatory aspects related to the production of radiopharmaceuticals
- Radiopharmacy Chapter in Pharmacopoeias
- Education, including e-learning, certification and training methodologies for professionals involved in radiopharmacy.

SCIENTIFIC COMMITTEE

Name	Country/International Organization
Adriano Duatti	Italy
Alfred Morgenstern	Germany
Ana Rey Ríos	Uruguay
Antero Abrunhosa	Portugal
Boris Zhuikov	Russian Federation
Brigitte Guérin	Canada
Cathy Cutler	United States of America
Charles Smith	United States of America
Clemens Decristoforo	Austria
Guillermina Ferro-Flores	Mexico
Ibrahim Aljammaz	Saudi Arabia
Jason Lewis	United States of America
Jeong Hoon Park	Republic of Korea
Jim Ballinger	United Kingdom
Li Hongyu	People's Republic of China
Meera Venkatesh	India
Miguel Ávila Rodríguez	Mexico
M.R. A. Pillai	India
Mohammad Haji Saeed	United States of America
Mouldi Saidi	Tunisia
Oscar Pozzi	Argentina
Philip Elsinga	The Netherlands
Raisa Krasikova	Russian Federation
Renata Mikolajczak	Poland
Rene Leyva Montana	Cuba
Sabine Kopp	World Health Organization
Salah Eddine Bouyoucef	Algeria
Serge Lyashchenko	United States of America
Sietske Rubow	South Africa
Suzanne Lapi	United States of America
Syed M. Qaim	Germany
Tamer Sakr	Egypt
Uday Bhonsle	United Arab Emirates
Valery Radchenko	Canada
Vijay Kumar	Australia
Internal Members:	
Amirreza Jalilian	IAEA
Aruna Korde	IAEA
Valeriia Starovoitova	IAEA

Names are listed alphabetically

IAEA Symposium Secretariat:

Radioisotope Products and Radiation Technology Section
International Atomic Energy Agency
Vienna International Centre, PO Box 100
1400 Vienna, Austria
ISTR2019@iaea.org

Scientific Secretary:

Mr João Alberto Osso Júnior
tel: +43 1 2600 21748
ISTR2019@iaea.org ; J.A.Osso-junior@iaea.org

Local Administration Support:

Team Assistants	Yasser Al Ghraoui
	Corinna L. Herden
	Olha Bilous
Administrative Assistant	Kristina Pleskach
Consultants	Julia S. Vera Araujo
	Vojna Ngjeqari
Communications Officer	Aleksandra Peeva
Voluntary Contribution Co-ordination	Veronika Komaromi
	Larysa Tanchuk
Symposium Clerks	Ayham Aldhairi
	Gil Levanon
	Leo Chavanne
	Minja Jovanovic
	Sarah Balah

Conference Services:

Division of Conference and Document Services (MTCD)
International Atomic Energy Agency
Vienna International Centre, PO Box 100
1400 Vienna, Austria

Conference Coordination:

Ms. Julie Zellinger
tel: +43 1 2600 21321
J.Zellinger@iaea.org

Exhibition Coordination:

Mr. Sanjai Padmanabhan
tel: +43 1 2600 24838
S.Padmanabhan@iaea.org

Exhibits

Exhibits will be located in M–Building, on floors M0E and M01, and on the corridors between B and M Building and between M and A Buildings. Participants are encouraged to view the exhibits during the hosted coffee breaks. The following organizations and companies will have information stands during the symposium:

- Berthold Technologies GmbH
- Best ABT Molecular Imaging Best Cyclotron Systems
- Bioemission Technology Solutions P.C. Bioemtech
- Bruker BioSpin GmbH
- Baltic Scientific Instruments
- Cardinal Health Nuclear & Precision Health Solutions
- China Isotopes & Radiation Corporation, CNNC-
- COMECER S.p.A.
- DSD Pharma GmbH
- Eckert & Ziegler Radiopharma GmbH
- Elysia Raytest
- ENVINET GmbH
- GEMS PET Systems AB
- Department of Nuclear Sciences and Applications, IAEA
- Permanent Mission of India Vienna
- Institute of Isotopes CO. LTD.
- ITG Isotope Technologies Garching Gmbh
- LabLogic Systems Limited
- Mediso
- MILabs B.V.
- Eczacibaşi-Monrol Nuclear Products CO.
- Nanolife
- piCHEM Forschungs- und Entwicklungs GmbH
- National Centre for Nuclear Research Radioisotope Centre POLATOM
- Publishing Section, IAEA
- Ridgeview Instruments AB
- Rotem GmbH
- Scintomics GmbH
- SHIMADZU HandelsgesmbH
- Tema Sinergie S.p.A.
- Trasis SA
- TrisKem International
- Von Gahlen Nederland B.V.
- World Council of Isotopes
- World Nuclear University
- Zag Zyklotron AG

Names are listed alphabetically

The fact that the IAEA has provided facilities for exhibiting equipment and products at the symposium does not imply that it endorses the equipment and products.

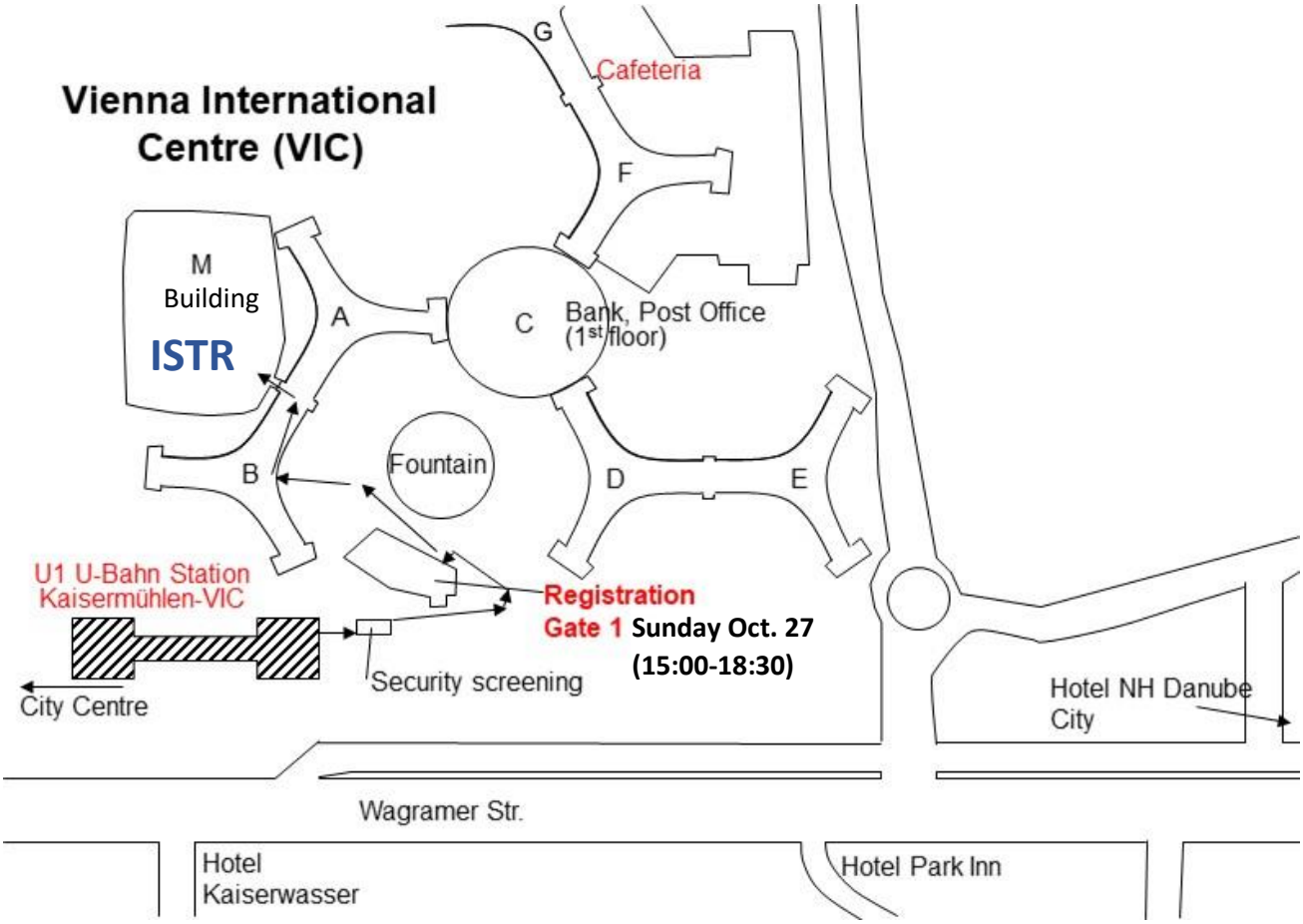
Working Language & Resolutions

Working Language: English. No simultaneous interpretation will be provided.

Resolutions: No resolutions may be submitted for consideration on any subject; no votes will be taken.

Symposium Location

International Atomic Energy Agency (IAEA)
Wagramer Str. 5, 1220 Vienna, Austria



Wireless Internet

Public access WiFi is available throughout the IAEA buildings. Select access point wlan-guest and the connection will be automatic: there is no password.

Hosted Coffee Breaks

There will be complimentary mid-morning and afternoon refreshments which have been funded using the voluntary contributions from those exhibitors acknowledged in the last few pages. Participants are encouraged during these breaks to not only enjoy the refreshments but to profit from the posters and exhibition stands displayed on M–Building floors M0E, M01, M02, and A building.

Refreshments, snacks and lunch can be purchased either from the VIC Cafeteria and Restaurant on the ground floor of the F–building, or from the coffee corners located on the M–Building ground floor.

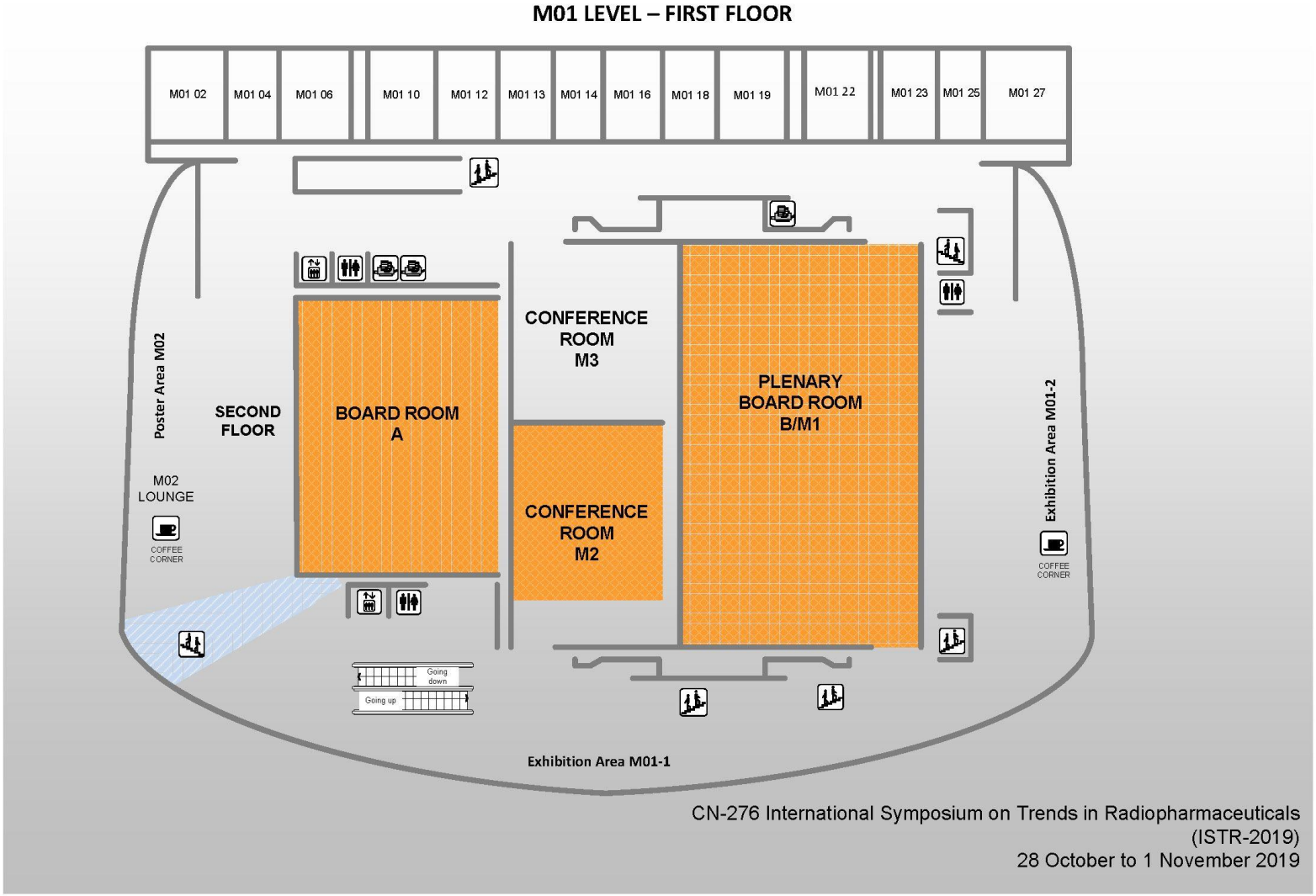
Posters

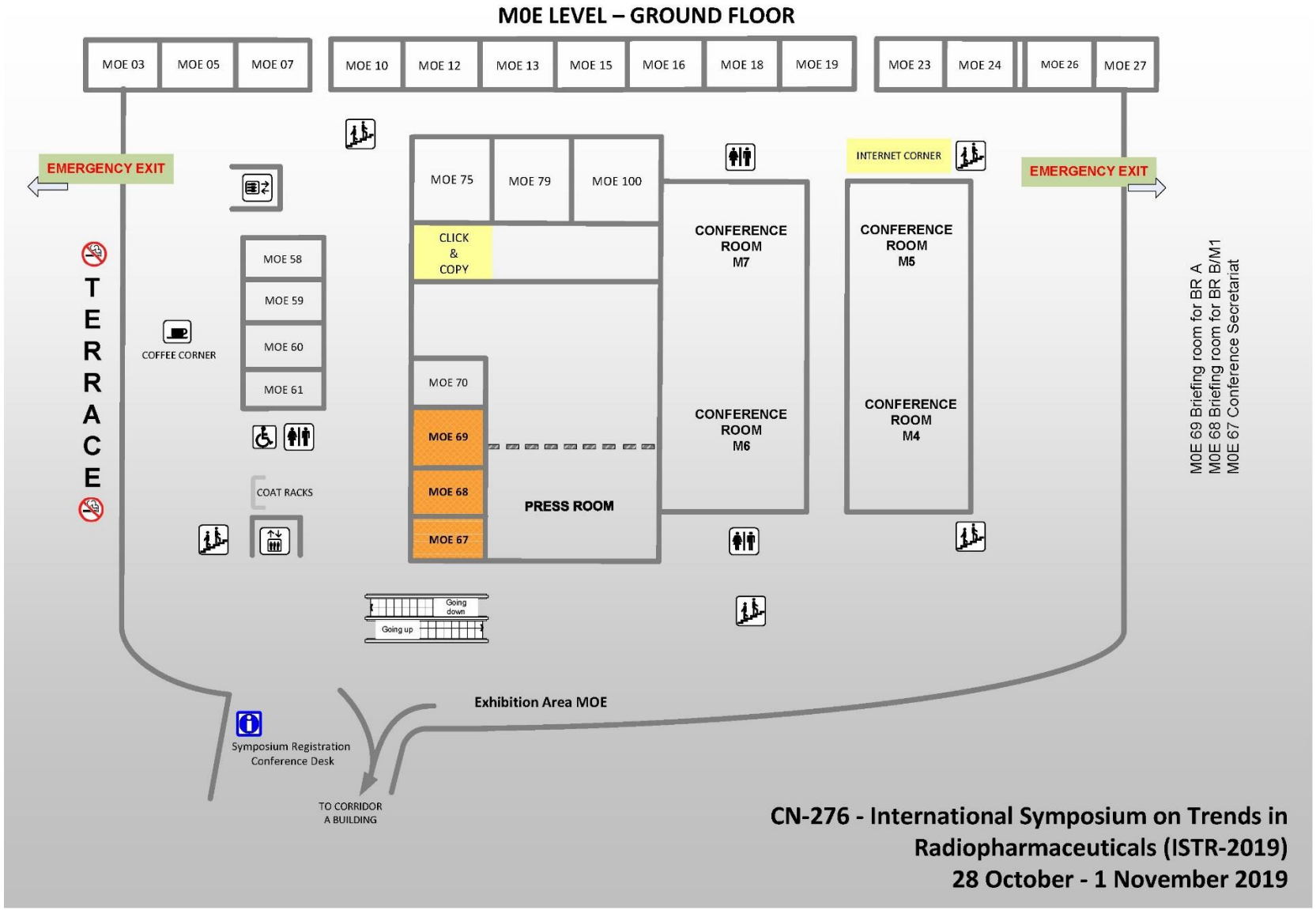
Posters will be displayed on their respective time and day on M–Building in MO2. Authors are asked to be available at their posters for discussions with interested participants according to their assigned poster session (Tuesday or Thursday, 14:00–15:30). Participants are also encouraged to view the posters during the hosted coffee breaks.

Book of Abstracts and Symposium Proceedings

This book contains all contributions and abstracts to be presented at the symposium. Abstracts have been edited for IAEA style uniformity. The views expressed remain the responsibility of the named authors. No responsibility is held by the organizers for any material reproduced, or linked, in this book.

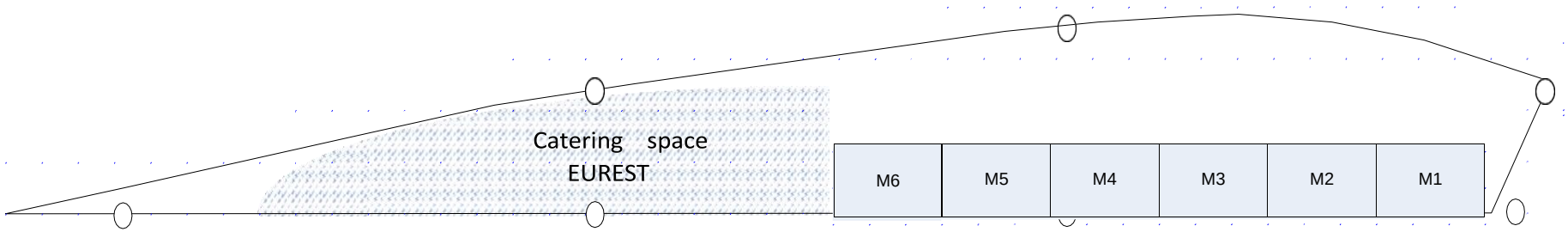
The Proceedings of the symposium will be published by IAEA and made available for free download by participants and interest persons at IAEA's website. The Proceedings will contain the contents of the Programme & Abstracts, together with a review of each session and highlights of the symposium. The guest editor of the Proceedings is Mr Natesan Ramamoorthy.


M01 LEVEL – FIRST FLOOR
M01 02
M01 04
M01 06
M01 10
M01 12
M01 13
M01 14
M01 16
M01 18
M01 19
M01 22
M01 23
M01 25
M01 27
Poster Area M02
SECOND FLOOR
BOARD ROOM A
CONFERENCE ROOM M3
CONFERENCE ROOM M2
PLENARY BOARD ROOM B/M1
Exhibition Area M01-2
M02 LOUNGE
COFFEE CORNER
COFFEE CORNER
Going down
Going up
Exhibition Area M01-1
CN-276 International Symposium on Trends in Radiopharmaceuticals
(ISTR-2019)
28 October to 1 November 2019


M0E LEVEL – GROUND FLOOR
MOE 03
MOE 05
MOE 07
MOE 10
MOE 12
MOE 13
MOE 15
MOE 16
MOE 18
MOE 19
MOE 23
MOE 24
MOE 26
MOE 27
EMERGENCY EXIT
EMERGENCY EXIT
TERRACE
MOE 75
MOE 79
MOE 100
CLICK & COPY
CONFERENCE ROOM M7
INTERNET CORNER
CONFERENCE ROOM M5
MOE 58
MOE 59
MOE 60
MOE 61
COFFEE CORNER
MOE 70
MOE 69
MOE 68
MOE 67
PRESS ROOM
CONFERENCE ROOM M6
CONFERENCE ROOM M4
COAT RACKS
Going down
Going up
M0E 69 Briefing room for BR A
M0E 68 Briefing room for BR B/M1
M0E 67 Conference Secretariat
Exhibition Area MOE
Symposium Registration Conference Desk
TO CORRIDOR A BUILDING
CN-276 - International Symposium on Trends in Radiopharmaceuticals (ISTR-2019)
28 October - 1 November 2019

CN-276 International Symposium on Trends in Radiopharmaceuticals (ISTR-2019)

M BLDG – M0E EXHIBITION AREA

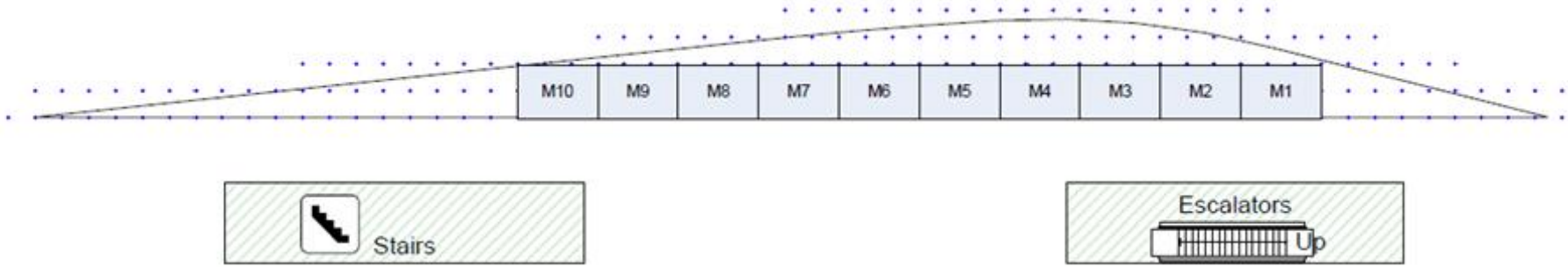


LIST OF EXHIBITORS

M1 – Baltic Scientific Instruments
M2 – LabLogic Systems Limited
M3 – VonGahlen Nederland B.V.
M4 – National Centre for
Nuclear Research Radioisotope
Centre POLATOM
M5 – Trasis SA
M6 –Eczacibaşi-Monrol Nuclear Products Co.

N-276 International Symposium on Trends in Radiopharmaceuticals (ISTR-2019)

M BLDG – M01 EXHIBITION AREA 1

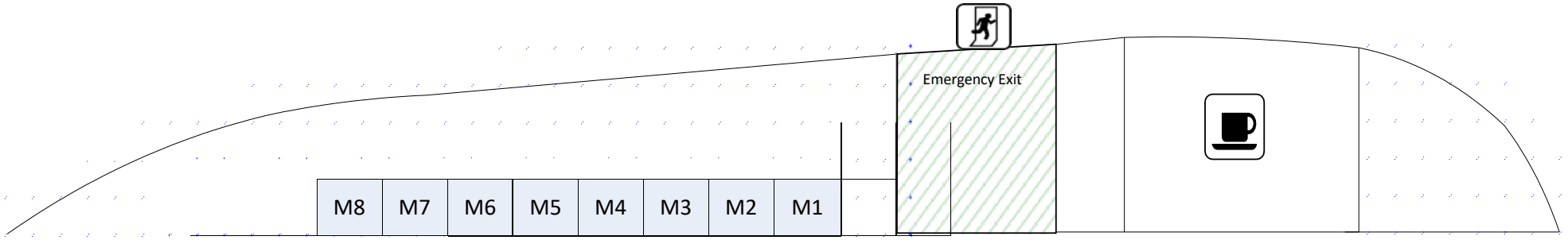


LIST OF EXHIBITORS

M1 – Bruker BioSpin GmbH
M2 – Bioemission Technology Solutions P.C. Bioemtech
M3 – Shimadzu HandelsgesmbH
M4 – Rotem GmbH
M5 – ITG Isotope Technologies Garching Gmbh
M6 – Comecer S.P.A
M7– Institute of Isotopes CO. LTD
M8 – Triskem International
M9 – Zag Zyklotron AG
M10 – GEMS PET Systems AB

CN-276 International Symposium on Trends in Radiopharmaceuticals (ISTR-2019)

M BLDG – M01 EXHIBITION AREA 2

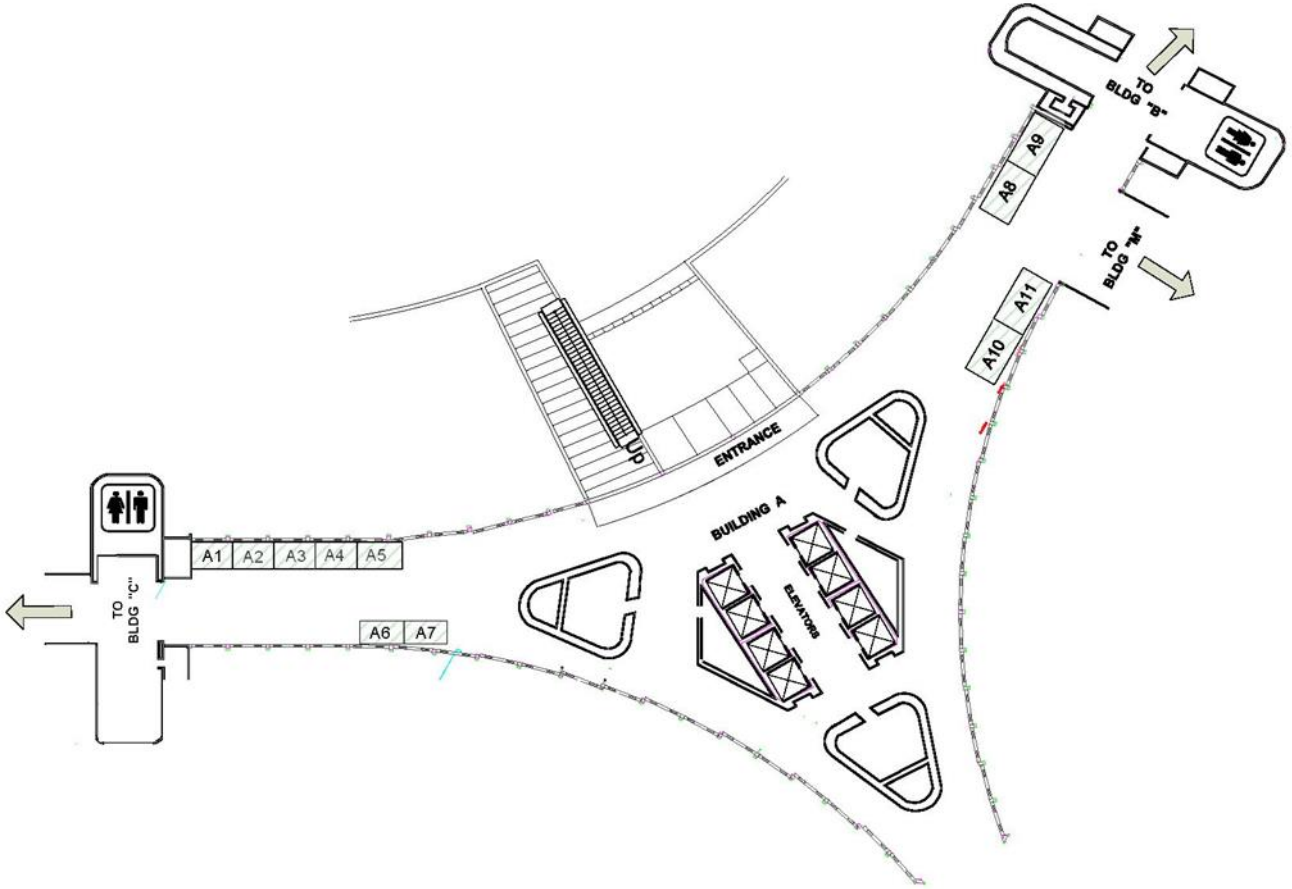


LIST OF EXHIBITORS

M1 – Best ABT Molecular Imaging Best Cyclotron Systems
M2 – Cardinal Health Nuclear & Precision Health Solutions
M3 – Eckert & Ziegler Radiopharma GmbH
M4 – Ridgeview Instruments AB
M5 – MILabs B.V.
M6 – Berthold Technologies GmbH
M7 – Scintomics GmbH
M8 – Nanolife

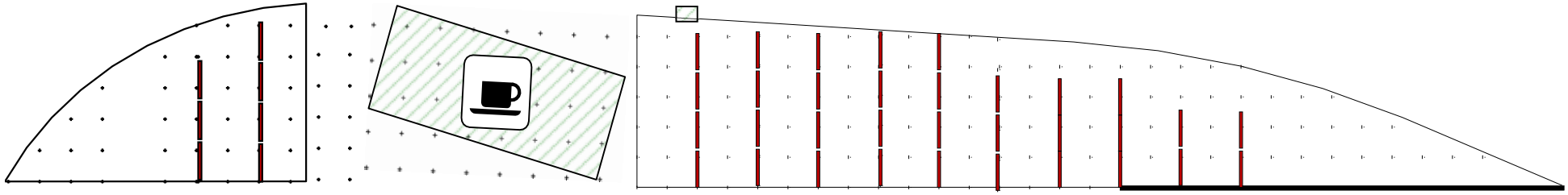
CN-276 International Symposium on Trends in Radiopharmaceuticals (ISTR-2019) A-building

A1 – China Isotopes & Radiation Corporation CNNC
A2 – Tema Sinergie S.p.A.
A3 – World Council of Isotopes
A4 – Mediso
A5 – World Nuclear University
A6 – Elysia Raytest
A7 – Pichem Forschungs und Entwicklungs GmbH
A8 – Department of Nuclear Sciences and Applications, IAEA
A9 – Envinet GmbH
A10 – DSD Pharma GmbH
A11 – Indian Permanent Mission of Vienna



CN-276 International Symposium on Trends in Radiopharmaceuticals (ISTR-2019)

M BLDG – M02 EXHIBITION AREA



Posterboard area

40 Poster boards

TIMETABLE

ISTR 2019 - DRAFT PROGRAMME AT A GLANCE							
	Monday 28-10-2019	Tuesday 29-10-2019	Wednesday 30-10-2019		Thursday 31-10-2019		Friday 1-11-2019
09:00 – 10:30	Registration (8:00 -9:30) Opening Session (9:30-10:30)	S4. Production of Radiopharmaceuticals: Theranostic	S7-A. Production of Radiopharmaceuticals: PET	S7-B. Parallel Session: Clinical Advances in Nuclear Medicine	S11-A. Production of Alpha Emitters and Radiopharmaceuticals	S11-B. Parallel Session: Technical Cooperation Success Stories	S15. Education in Radiopharmacy
10:30 11:00	Morning Coffee Break						
11:00 12:30	S1. Production of medical radioisotopes: Research Reactor	S5. Production of Radiopharmaceuticals: SPECT	S8. QA/QC/Pre-clinical		S12. Emerging Radioisotopes for Radiopharmacy		WNU Olympiad Finals
12:30 14:00	Lunch	Working Lunch: MILabs (12:45-13:45)	Lunch (12:30-14:00)				
14:00 15:30	S2. Production of Medical Radioisotopes: Accelerators	Poster Session I	S9. Health Regulations: Production of Radiopharmaceuticals		Poster Session II		Closing Session/Awards Ceremony
15:30 16:00	Coffee Break						
16:00 17:30	S3. Production of Medical Radioisotopes: Generators (Focus on Mo-99)	S6. Production of Radiopharmaceuticals: Therapy	S10. New Trends in Radiopharmaceuticals: Chemistry		S13. Radiopharmacy Installations		
18:00 20:00	Welcome Reception	Side Event: India	Side Event: Women in Radiopharmaceutical Sciences: Challenges and Opportunities		S14. Databases and Apps (17:30-18:30)		

Boardroom B/M1 | M2 | MO2

Monday 28 October 2019

REG 08:00-9:30 Symposium Registration

Venue Entrance M–Building

OS 09:30-10:30 Opening Session

Venue Board Room B/M1

T.Sec J. Osso Junior

Time	ID	Presenter	Country/Org	Title
09:30	OS-01	C. Feruta	IAEA	Opening Remarks by Acting Director General
09:40	OS-02	N. Mokhtar	IAEA	Welcome by Deputy Director General, Head of Department of Nuclear Sciences and Applications
09:50	OS-03	M. Abdel-Wahab	IAEA	Welcome by Director, Division of Human Health
09:55	OS-04	M. Denecke	IAEA	Welcome by Director, Division of Physical and Chemical Sciences
10:00	OS-05	S. Lapi	United States of America	From isotopes to images: radioactive materials as tools in medicine

S1 11:00-12:30 Production of medical radioisotopes: Research Reactor

Venue Board Room B/M1

Chair: S. Lapi

T.Sec: A. Jalilian

Time	ID	Presenter	Country/Org	Title
11:00	S1-01	M. Venkatesh	India	Production of reactor-based radioisotopes: an international scenario
11:25	S1-02	R. Mikolajczak	Poland	Production and supply of medical radioisotopes: a Polish experience
11:45	S1-03	J.L. Crudo	Argentina	Laboratory scale production of medium specific activity ^{177}Lu (carrier added) through the [^{176}Lu (n,γ) ^{177}Lu] nuclear reaction under standardized conditions
12:00	S1-04	B. Ocampo-García	Mexico	Synthesis and neutron activation of Lu_2O_3 nanoparticles functionalized with target specific peptides
12:15	S1-05	T. Tielens	The Netherlands	Towards a robust supply chain for medical radioisotopes

S2 14:00-15:30 Production of medical radioisotopes: Accelerators

Venue Board Room B/M1
Chair: M. Venkatesh
T.Sec: A. Korde

Time	ID	Presenter	Country/Org	Title
14:00	S2-01	S.M. Qaim	Germany	Accelerator based production of non-standard positron emitters and therapeutic radionuclides
14:25	S2-02	S. Lapi	United States of America	Production of radiometals using a medical 24MeV cyclotron
14:45	S2-03	A. Abrunhosa	Portugal	Production of radiometals using liquid targets: status and perspectives
15:00	S2-04	J. H. Park	Republic of Korea	Radioisotope production and development with 30MeV cyclotron
15:15	S2-05	V. Radchenko	Canada	Production and application of ^{225}Ac/^{213}Bi: TRIUMF experience and perspectives

S3 16:00-17:30 Production of medical radioisotopes: Generators

Venue Board Room B/M1
Chair: R. Mikolajczak
T.Sec: V. Starovoitova

Time	ID	Presenter	Country/Org	Title
16:00	S3-01	J. Osso Junior	IAEA	The role of the IAEA on the supply of ^{99}Mo
16:15	S3-02	B. Grimshaw	IAEA	Nuclear safeguards in radiopharmaceutical facilities
16:30	S3-03	C. Cutler	United States of America	Supply of ^{99}Mo: focus on US
16:55	S3-04	B. Zhuikov	Russian Federation	Radionuclide production at high energy accelerators: the new possibilities for radioisotope generators
17:15	S3-05	R. Walczak	Poland	Cyclotron production of ^{47}Ca for ^{47}Ca/^{47}Sc generator

18:00-20:00 Welcome Reception

Venue MOE

Tuesday 29 October 2019

S4 09:00-10:30 Production of radiopharmaceuticals: Theranostic

Venue Board Room B/M1
Chair: A. Duatti
T.Sec: J. Osso Junior

Time	ID	Presenter	Country/Org	Title
09:00	S4-01	J. Lewis	United States of America	Development and application of monoclonal antibody-based radiopharmaceuticals
09:25	S4-02	C. Decristoforo	Austria	Theranostic radiopharmacy
09:45	S4-03	V. Gadelshin	Germany	Innovative medical radioisotopes for theranostic application, and how they are produced
10:00	S4-04	B. Alirezapour	Islamic Republic of Iran	Preparation and preclinical evaluation of ^{64}Cu-NOTA-anti MUC1 as a radioimmunoconjugate for diagnosis of MUC1+ breast cancer by PET
10:15	S4-05	L. Melendez-Alafort	Italy	Development of a new prostate cancer theranostic radiopharmaceutical

S5 11:00-12:30 Production of radiopharmaceuticals: SPECT

Venue Board Room B/M1
Chair: J. Lewis
T.Sec: A. Korde

Time	ID	Presenter	Country/Org	Title
11:00	S5-01	A. Duatti	Italy	Revisiting ^{99m}Tc radiopharmaceuticals with recent advances in chemistry & imaging tools
11:25	S5-02	G. Ferro-Flores	Mexico	Production of radiolabelled peptides for SPECT-based theranostics
11:45	S5-03	S. Bouyoucef	Algeria	Radiopharmacy and growth of nuclear medicine in developing countries
12:00	S5-04	C. Bolzati	Italy	Selective αvβ3 integrin detection using [^{99m}Tc(N)PNP43]-tagged RGDechi peptides: synthesis and pharmacological studies
12:15	S5-05	E. Araujo Perini	Brazil	The past, present and future trends in radiopharmaceuticals production in Brazil

12:45:13:45 Working Lunch: MILabs

Venue Board Room M2

PS1 14:00-15:30 Poster Session 1

Venue MO2

ID	Name	Country	Title
Track	*Production of PET- and SPECT-based diagnostic, therapeutic, and theranostic radiopharmaceuticals*		
PS1-01	M. Agolti	Argentina	Tc-99m octreotide in Neuroendocrine tumours: a different radiotracer from traditional ^{111}In: our experience
PS1-02	B. Alirezapour	Islamic Republic of Iran	Preparation and biological assessment of ^{64}Cu-NOTA-anti ROR1 as a radioimmunoconjugate for diagnosis of ROR1+ breast cancer by PET
PS1-03	T. Assaad	Syrian Arab Republic	In house preparation and biodistribution of ^{64}Cu-ATSM, ^{64}Cu-PTSM and ^{64}Cu-DOTATATE for theranostic application
PS1-04	M. Avila Rodriguez	Mexico	Trends and perspectives in prostate-specific membrane antigen based radiopharmaceuticals in Mexico: the experience of the National University
PS1-05	J. Bhatt Mitra	India	Membrane interacting peptides as positron emission tomography (PET) based infection imaging probes
PS1-06	C. Bolzati	Italy	[^{99m}Tc(N)(DASD)(PNPn)]+ (DASD=1,4-dioxa-8-azaspiro[4,5]decandithiocarbamate, PNPn=bisphosphinoamine) for myocardial imaging
PS1-07	S. Bouyoucef	Algeria	Clinical indications and labelling procedures influencing in vitro stability and early myocardial uptake of ^{99m}Tc-tetrofosmin
PS1-08	M. Cardoso Moreno	Uruguay	Development, characterisation and in vivo evaluation of two ^{68}Ga-labelled NPY analogues as potential tracers for breast cancer imaging
PS1-09	E. Cazzola	Italy	[^{89}Zr]ZrOx/Cl preparation based on commercial cassette base, synthesis module.
PS1-10	E. Cazzola	Italy	[^{18}F]-FPSMA1007 synthesis HPLC free on fastlab platform qc evolution
PS1-11	A. Chakrabotry	India	Preparation of single patient dose of Lu-177-DOTA-Rituximab – using low specific activity Lu-177-Chloride
PS1-12	A. Charef	Algeria	Synthesis of m-Iodobenzylguanidine (m-IBG) by solid phase method and its evaluation
PS1-13	P. Charoenphun	Thailand	In-house radiocolloid development for sentinel lymph node detection
PS1-14	E. Chilug	Romania	Comparative preclinical evaluation of ^{68}Ga-labelled Neuromedin N and B for targeting glioblastoma malignant tissues
PS1-15	V. Chouthkanthiwa	India	Development of ready-to-use ^{177}Lu-PSMA-617 formulation for treatment of inoperable metastatic prostate cancer
PS1-16	J. Costes	Switzerland	Impact of hospital production vs commercial kits purchase of ^{68}Ga-DOTA peptides
PS1-17	I. Daruwati	Indonesia	Optimization of labeling α,γ-mangosteen isolated from mangosteen cortex fructus (garcinia mangostana l) with radionuclide technetium-99m for cancer detection

PS1-18	N. Delgado Lopez	Colombia	Radiopharmaceutical production of ^{68}Ga-PSMA at the National Cancer Institute, Bogotá, Colombia
PS1-19	B. Egorova	Russian Federation	Complexes of copper and bismuth cations with acyclic and macrocyclic polyamines bearing picolinic pendant arms
PS1-20	G. Ferro-Flores	Mexico	Synthesis and preclinical evaluation of ^{64}Cu-NOTA-HYNIC-iPSMA
PS1-21	W. Gawęda	Poland	Bioconjugates of barium ferrite as a Ra-223 carriers in alpha-radioimmunotherapy
PS1-22	R. George	India	Comparison of ^{68}Ga-NOTA-Bisphophonate with ^{99m}Tc-MDP in 34 patients with skeletal metastases in various type of cancers
PS1-23	S. George	India	Methods of integration of radio Cu-64 label in luminescent copper nanoclusters for pre and intra operative imaging and therapy of pancreatic cancer
PS1-24	N. Gomzina	Russian Federation	Potential radiotracers based on the 4'-O-methylhonokiol structure for PET visualization of neuroinflammation
PS1-25	B. Guérin	Canada	Direct production of ^{68}Ga using ^{68}Zn-pressed target
PS1-26	M. Guleria	India	Preparation of ^{177}Lu-DOTA-Trastuzumab: an insight into the in-house optimized radiochemistry procedures employed for patient dose preparation
PS1-27	P. Halik	Poland	In vitro NK1R affinity evaluation of novel radioconjugates based on peptide antagonist SPANTIDE I and Ga-68/Lu-177 theranostic-like isotopes for glioma cancer
PS1-28	W. Hamouda	Egypt	Synthesis, characterization and radiolabeling of iminodiacetic acid derivative with technetium-99m
PS1-29	S. Kar	India	Radiosynthesis of 1-{4-[4-(2-[18F] Fluoroethoxy)-phenyl] Piperazine-1-yl} ethenone and its evaluation in animal models bearing C57BL6 melanoma xenograft
PS1-30	K. Kolevska	North Macedonia	Correlation between the yield of produced [^{18}F]FDG and the activity retained during synthesis
PS1-31	R. Krasikova	Russian Federation	Nucleophilic synthesis of 6-[^{18}F]fluoro-L-DOPA via copper mediated radiofluorination
PS1-32	A. M. K	India	Evaluation of oxygen-18 water enriched for the production of fluorine-18 in a medical cyclotron
PS1-33	D. Kumar	India	Radiolabeled TATE functionalized gold nanoparticles for potential use in imaging and therapy of neuroendocrine tumours
PS1-34	V. Kumar	Australia	Recent advances in Ga-68 radiopharmaceuticals and Ga-68 bisphosphonates for the theranostic management of neuroendocrine tumours.
PS1-35	J. Le Roux	South Africa	An automated synthesis method for Ga-68 labelled ubiquicidin 29-41
PS1-36	W. Lestari	Indonesia	Formulation and radiolabelling of ethambutol with technetium-99m for detection of extrapulmonary tuberculosis
PS1-37	R. Leyva Montaña	Cuba	Radioconjugates based on the monoclonal antibody Nimotuzumab® for use in radioimmunotherapy.

PS1-38	M. Luna-Gutiérrez	Mexico	Preclinical evaluation of the theranostic ^{68}Ga/^{177}Lu-[DOTA-CXCR4-L] pair
PS1-39	A. Majoul	Tunisia	Study of the physicochemical stability of HMPAO-Technetium (^{99m}Tc)
PS1-40	N. Malek	Tunisia	Synthesis and biodistribution of 1-((2-methoxyphenyl) piperazine)ferrocenecarboxamide labeled with technetium-99m as a potential brain receptor imaging ag
PS1-41	J. Manrique-Arias	Mexico	A practical method for the preparation of ^{18}F[TFB] labeled with sodium fluoride, using a ITG IQS fluidic labelling module
PS1-42	J. Manrique-Arias	Mexico	Radiation dosimetry in healthy subjects of ^{68}Ga-DOTA-BBN, a potential theranostic tracer in oncology
PS1-43	A.A. Marie	Ethiopia	Tc-99m labeled human immunoglobulin G polyclonal antibody – different approach for better results
PS1-44	K. Masłowska	Poland	Radiolabeled peptidomimetic inhibitor of the VEGF/NRP-1 complex for the imaging of malignant tumours - preliminary research
PS1-45	M. Maurin	Poland	The critical parameters of Ga-68 labelling of POLATOM's PSMA-11 kit
PS1-46	G. Mercanoglu	Turkey	Development of synthesis method for the automated production of ^{177}Lu-EDTMP with ml-eazy and pharmtracer modules
PS1-47	Z. Mohd Ashhar	Malaysia	Preparation, characterization and in-vitro studies of [^{68}Ga]NODAGA-Pamidronic acid for PET bone imaging
PS1-48	R. Nanabala	India	Nucleophilic synthesis of [^{18}F]FDOPA by using an automated module : a summary of the results of 18 batches
PS1-49	R. Nanabala	India	Synthesis of [^{18}F]PSMA-1007 for imaging prostate cancer by using an automated module and clinical studies
PS1-50	S. Nandy	India	Fully automated radiosynthesis of ^{18}F-16-α-Fluoroestradiol ([^{18}F]FES) with solid phase extraction cartridge purification by sep pak® plus alox n
PS1-51	S. Nandy	India	Development and evaluation of ^{18}F-radiolabeled acetaminophen (paracetamol) for tumour imaging based on COX-2 overexpression
PS1-52	N. Naseer Ahmed	Pakistan	Comparative evaluation of Tc-99m octreotide, synthesized by different labeling methods: for diagnostic accuracy assessment in neuro-endocrine tumours
PS1-53	N. Naseer Ahmed	Pakistan	Utility of gamma camera as an effective non-invasive imaging modality for docetaxel loaded liposomal chitosan nanoparticles: synthesis and the in-vivo trafficking in animal model
PS1-54	Y. Ng	Malaysia	Radiolabelling and preliminary biodistribution study of Samarium-153-Zoledronic Acid as a novel bone pain palliative agent
PS1-55	S. Okarvi	Saudi Arabia	Development and evaluation of a ^{68}Ga-labeled angiotensin peptide coupled to rhodamine for diagnostic imaging of heart
PS1-56	S. Okarvi	Saudi Arabia	Total solid-phase synthesis of DOTA-Functionalized tumour targeting peptides for PET imaging and therapy

PS1-57	V. Orlovskaya	Russian Federation	Use of tetrabutylammonium tosylate in conjunction with chiral NiII complex precursor for automated synthesis of [^{18}F]FET
PS1-58	M. Pereira	Uruguay	Optimization of the automatic synthesis of 16α-[^{18}F]fluoroestradiol in the SYNTHRA RNplus Research Module
PS1-59	M. Pino Peraza	Cuba	Labelling of anti-cd20 monoclonal antibody cimabior with ^{90}Y
PS1-60	S. Rubow	South Africa	Influence of the source of Lu-177 on radiopharmacy waste management – an estimate
PS1-61	M. Saidi	Tunisia	Synthesis and biodistribution study by rats of two new ^{99m}Tc-Tricarbonyl complexes as potential brain imaging agents
PS1-62	M. Sterjova Arev	North Macedonia	Freeze-dried kit formulation of ^{177}Lu- and ^{90}Y-labeled immunoconjugates of Trastuzumab – formulation and characterization
PS1-63	H. Shamseldin	Egypt	A novel therapeutic phthalimide derivative for cancer: Synthesis, radioiodination and biological evaluation
PS1-64	S. Shiratori	Thailand	The first proof-of-concept theranostic radiopharmaceutical in Thailand
PS1-65	J. Shukla	India	Exploring Ga-68 Trastuzumab Fab for noninvasive PET imaging to detect HER2 expressing lesions.
PS1-66	T. Siriprapa	Thailand	Improvement of synthesizing material and method for an in-house production of [^{18}F]-florbetapir PET tracer for imaging beta amyloid deposition in the brain
PS1-67	N. Tag	Oman	Evaluating quality control ^{18}F-FDG: experience in Sultan Qaboos University Hospital, Oman
PS1-68	M. Tejeria	Uruguay	Design, synthesis and evaluation of a family of ^{99m}Tc estradiol derivatives for breast cancer imaging
PS1-69	K. Urbanová	Czech Republic	Labeling of PSMA-11 with ^{68}Ga in $NaHCO_3$
PS1-70	K. Vats	India	Influence of ^{99m}Tc-chelation at N-terminal and/or C-terminal on receptor binding affinity of NGR peptides
PS1-71	A. Vukadinovic	Serbia	Development of automatic system for production of small batches of radioiodine capsules
PS1-72	F. Vultos	Portugal	^{111}In-labelled bifunctional agents for dual targeting of breast cancer cells
PS1-73	T. Wibawa	Indonesia	Cancer drugs and ^{99m}Tc-glutation radiopharmaceutical interaction to achieve optimal result of cancer diagnostics in nuclear medicine
PS1-74	E. Widyasari	Indonesia	In vivo study of radiolabeled flavonoid ^{99m}Tc-quercetin as cancer radiotracer on normal balb/c mice
PS1-75	B. Guerin	Canada	The synthesis and cytotoxicity of ^{64}Cu/NOTA-terpyridine platinum conjugate, as a novel theranostic agent

Surnames are listed alphabetically (exceptions for modifications made after the Programme was created).

S6 16:00-17:30 Production of radiopharmaceuticals: Therapy

Venue Board Room B/M1
Chair: C. Cutler
T.Sec: A. Jalilian

Time	ID	Presenter	Country/Org	Title
16:00	S6-01	M.R.A. Pillai	India	Production and quality control of beta emitters bone pain palliation agents using β-emitters
16:25	S6-02	J. Rijn Zeevaart	South Africa	Comparison of promising new short-range therapeutic radiopharmaceuticals using ^{225}Ac, ^{213}Bi and ^{161}Tb
16:45	S6-03	V. Chirayil	India	Freeze-dried kit for quick and efficient preparation of ^{188}Re-DEDC/lipiodol in hospital radiopharmacy
17:00	S6-04	C. H. Yeong	Malaysia	Production of theranostic ^{153}Sm labelled polystyrene microspheres for hepatic radioembolization
17:15	S6-05	A. Chakrabotry	India	Radiolabelling and pre-clinical evaluation of ^{90}Y-DOTATATE formulated using ^{90}Y-acetate from high level liquid waste

18:00-20:00 Side Event: India

Venue Board Room M2

Wednesday 30 October 2019

S7-A 09:00-10:30 Production of radiopharmaceuticals: PET

Venue Board Room B/M1
Chair: J. Smith
T.Sec: J. Osso Junior

Time	ID	Presenter	Country/Org	Title
09:00	S7-A1	P. Elsinga	The Netherlands	Recent advances in the development of ^{18}F and ^{11}C radiopharmaceuticals
09:25	S7-A2	C. Decristoforo	Austria	Recent advances in the development of ^{68}Ga radiopharmaceuticals
09:45	S7-A3	I. Aljammaz	Saudi Arabia	Synthesis and in vitro and in vivo evaluation of ^{124}I labelled PSMA peptides: potential theranostic radiopharmaceuticals for prostate cancer
10:00	S7-A4	V. Kumar	Australia	A radiocopper somatostatin anolog (Cu-Sartate) for NET theranostics
10:15	S7-A5	W. Chintawan	Thailand	Comparative study of [^{18}F]PSMA-1007 and [^{68}Ga]PSMA-11 for prostate cancer PET imaging in Thailand

S7-B 09:00-10:30 Clinical advances in nuclear medicine

Venue Board Room M2
Chair: E. Bombardieri
T.Sec: A. Jalilian

Time	ID	Presenter	Country/Org	Title
09:00	S7-B1	D. Paez	IAEA	IAEA activities related to nuclear medicine
09:30	S7-B2	H. Macapinlac	United States of America	Recent advances in nuclear medicine: diagnostic and therapy
10:00	S7-B3	D. Le	United States of America	Production and use of cyclotron-produced radiopharmaceuticals at MD Anderson Cancer Center

S8 11:00-12:30 QA/QC/Pre-clinical

Venue Board Room B/M1
Chair: C. Decristoforo
T.Sec: A. Korde

Time	ID	Presenter	Country/Org	Title
11:00	S8-01	S. Rubow	South Africa	Quality control of hospital-based radiopharmaceuticals
11:20	S8-02	J. Smith	United States of America	Development and preclinical evaluation of ^{64}Cu radiolabelled compounds
11:40	S8-03	B. Guérin	Canada	Preclinical evaluation of ^{68}Ga-PET tracers using ^{68}Ga produced by cyclotron, a Canadian experience
12:00	S8-04	E. Bombardieri	EANM	Ethics in animal experiments in nuclear medicine and the application of the directive 2010/63 EU
12:15	S8-05	R. Teodoro	Germany	PET for the imaging of cerebral α7 acetylcholine receptors: from tracer development to clinical application

S9 14:00-15:30 Health regulations: Production of radiopharmaceuticals

Venue Board Room B/M1
Chair P. Elsinga
T.Sec: J. Osso Junior

Time	ID	Presenter	Country/Org	Title
14:00	S9-01	S. Kopp	WHO	A move towards harmonization of GMP regulations in radiopharmacy
14:20	S9-02	C. Decristoforo	Austria	The status of radiopharmaceutical regulations in Europe
14:40	S9-03	S. Lyashchenko	United States of America	The status of radiopharmaceutical regulations in the US
15:00	S9-04	Y. Chakrova	Kazakhstan	GMP certification of a radiopharmaceutical production facility in Kazakhstan
15:15	S9-05	S. Nazarenko	Estonia	Compounding radiopharmaceuticals: any regulatory difference with extemporaneous preparation?

S10 16:00-17:30 New trends in radiopharmaceuticals: chemistry

Venue Board Room B/M1
Chair: M.R.A. Pillai
T.Sec: A. Jalilian

Time	ID	Presenter	Country/Org	Title
16:00	S10-01	B. Guérin	Canada	Development and evaluation of chelators for specific radiometals
16:20	S10-02	S. Lyashchenko	United States of America	Novel radiopharmaceuticals for clinical translation
16:40	S10-03	J. Smith	United States of America	Translation of new chelators for old pairs: Tc/Re NODAGA
17:00	S10-04	K. Katti	United States of America	Radioactive ^{198}Au nanoparticles in nanomedicine
17:15	S10-05	P. Brust	Germany	New strategies for imaging of brain cancer with radiopharmaceuticals

18:00-20:00 Side Event: Women in Radiopharmaceutical Sciences: Challenges and Opportunities

Venue Board Room M2

Thursday 31 October 2019

S11-A 09:00-10:30 Production of alpha emitters and radiopharmaceuticals

Venue: Board Room B/M1
Chair: M. Betti
T.Sec: V. Starovoitova

Time	ID	Presenter	Country/Org	Title
09:00	S11-A1	A. Morgenstern	Germany	Production and quality control of radiopharmaceuticals labelled with ^{225}Ac and ^{213}Bi
09:30	S11-A2	C. Cutler	United States of America	U.S. DOE Tri lab production effort to provide accelerator produced ^{225}Ac
10:00	S11-A3	M. Lesinki	Canada	Recent results of the joint CNL and TRIUMF project on the production of ^{225}Ac
10:15	S11-A4	O. Pozzi	Argentina	Argentinian project for developing production of ^{225}Ac and ^{213}Bi in cyclotrons for targeted therapy

S11-B 09:00-10:30 Technical cooperation success stories

Venue: Board Room M2
Chair: U. Bhonsle
T.Sec: A. Elrefaei

Time	ID	Presenter	Country/Org	Title
09:00	S11-B0	D. Yang	IAEA-TC	Opening Remarks by Deputy Director General, Head of Department of Technical Cooperation
09:10	S11-B1	S. Abdulrazak	IAEA-TC	Technical cooperation programme: enhancing capacities in radiopharmacy in Africa
09:30	S11-B2	R. Montaña	Cuba	Sustainable production of ^{99m}Tc generators and radiopharmaceuticals an IAEA/Cuban experience
10:00	S11-B3	Y. Chakrova	Kazakhstan	Gel generator production project in Kazakhstan: IAEA support
10:15	S11-B4	A. Duran	Argentina	Strengthening capacities for the development of radiotracers labelled with ^{18}F, different from fluordesoxyglucose in the FCDN

S12 11:00-12:30 Emerging radioisotopes for radiopharmacy

Venue: Board Room B/M1
Chair: A. Duatti
T.Sec: A. Jalilian

Time	ID	Presenter	Country/Org	Title
11:00	S12-01	V. Radchenko	Canada	Development of production strategies for new emerging research radionuclides using cyclotrons
11:25	S12-02	M. Avila Rodríguez	Mexico	Emerging clinical applications of [^{64}Cu]$CuCl_2$ radiopharmaceutical
11:45	S12-03	P. Martini	Italy	Towards large-scale ^{67}Cu cyclotron production
12:00	S12-04	I. Cieszykowska	Poland	Production of ^{47}Sc from ^{47}Ca: comparison of four separation methods

12:15	S12-05	G. Pupillo	Italy	Accelerator-based production of ^{47}Sc: results of the PASTA project

PS2 14:00-15:30 Poster Session 2

Venue MO2

ID	Name	Country	Title
Track	*Design of industrial, hospital and centralized radiopharmacy facilities*		
PS2-01	N. Ayachi	Tunisia	Creation of the first public PET unit at Sahloul hospital in Sousse, Tunisia
PS2-02	S. Bertrand	Belgium	A new compact high-power e-beam accelerator for radiotherapeutic production: a first evaluation
PS2-03	S. Bertrand	Belgium	Optimized non-conventional radioisotopes production with industrial mid-energy cyclotron
PS2-04	A. Bulos	Philippines	Research and development initiatives on radiopharmaceutical production in the Philippines
PS2-05	F. Ekoume	Cameroon	A comparative study of passive air sampling in different radiopharmacies
PS2-06	H. Elkhatib	Egypt	Studying and assessment of clean area for Tc-99m production in radioisotope production facility
PS2-07	Y. Lagebo	Ethiopia	Survey on arduous challenges and possible tracks of heightening the radiopharmacy and nuclear medicine services in Africa
PS2-08	M. Maneiro	Argentina	Parametrical study for iodine plate out theoretical model in fission radioisotope production plant ventilation pipes
PS2-09	J. Norenberg	United States of America	An overview of commercial nuclear pharmacy in the US safely delivering 35,000 patient-ready radiopharmaceuticals doses each day
PS2-10	D. Schick-Martin	Canada	Saskatchewan centre for cyclotron sciences: a new multi-user research and production facility
PS2-11	M. Waheed	Bangladesh	Development of radiopharmaceutical production in Bangladesh
Track	*Education, including e-learning, certification and training methodologies for professionals involved in radiopharmacy*		
PS2-12	B. Darju	Liberia	Education/Awareness-2
PS2-13	E. Huanca Sardinas	Bolivia	Relevance of the study of radiopharmacy at San Francisco Xavier university
PS2-14	N. Mat Ail	Malaysia	Development of nuclear pharmacy training module in Malaysia
PS2-15	A. Rey Ríos	Uruguay	Diploma of radiopharmacy specialist in Uruguay: a flexible tool to achieve a certificated postgraduate education in radiopharmacy
PS2-16	O. Riabukhin	Russian Federation	Accelerators of Ural Federal University as a base for student education and stuff training
PS2-17	M. Siddig	Sudan	Status of radiopharmacy practices in Sudan
PS2-18	D. Wata	Kenya	Assessment of training needs for radiopharmacists in Africa

Track	*Health regulatory aspects related to the production of radiopharmaceuticals*		
PS2-19	M. Baracaldo Cortes	Colombia	Regulatory aspects related to good practices of preparation of radiopharmaceuticals in Colombia
PS2-20	J. Giglio	Uruguay	Optimization of ^{18}F-radiopharmaceutical production with a new platform, in accordance with GMP
PS2-21	S. Marques de Carvalho	Brazil	Current status of radiopharmaceuticals production in Brazil: Licensing and radioprotection aspects
PS2-22	L. Pozzo	Brazil	[^{68}Ga]PSMA PET/CT: which HTA tools can be used in local or regional reimbursement decision?
PS2-23	R. Ssekajjugo	Uganda	Regulation of radiopharmaceuticals in Uganda: current situation
Track	*Nanosized radiopharmaceuticals*		
PS2-24	F. Bin Madin	Malaysia	Synthesis of radioactive gold nanoparticles and bimetallic gold nanoparticles for cancer therapeutic application
PS2-25	A. Heitor Ferreira	Brazil	Radiation crosslinked protein-based nanoparticles as delivery system for radiopharmaceuticals
PS2-26	A. Majkowska-Pilip	Poland	Multimodal radiobioconjugate Octreotide-PEG-^{198}AuNPs-PEG-DOX for targeted cancer therapy
PS2-27	M. Żuk	Poland	Gold-198 coated Superparamagnetic iron oxide nanoparticles (SPION) for cancer radiotherapy and magnetic hyperthermia
Track	*Pre-clinical evaluation of radiopharmaceuticals*		
PS2-28	E. Azorin-Vega	Mexico	Dosimetric model based on the distribution of PSMA targeted radiopharmaceuticals to bone metastasis
PS2-29	A. Chakraborty	India	In-vitro and in vivo pre-clinical evaluation for Lu-177, Y-90 and Ga-68-DOTATATE in SSTRII positive AR42J cell line and negative HCT116 and MCF7 cell line
PS2-30	T. Dallagi	Tunisia	Evaluation of Rhenium and ^{99m}Technetium of tamoxifen derivatives as potential breast cancer radiopharmaceuticals
PS2-31	A. Escudero-Castellanos	Mexico	Biological evaluation of ^{177}Lu-DOTA-PSMA(inhibitor)-RGD in LNCaP and PC_3 prostate cancer cells
PS2-32	L. Fernández	Uruguay	[^{99m}Tc]Tc labelled levonorgestrel derivative as potential ER+/PR+ imaging agent
PS2-33	H. Honarvar	Sweden	In vitro kinetics property evaluation of ^{11}C-acetate in real time
PS2-34	N. Jiménez-Mancilla	Mexico	Application of the Cerenkov radiation produced by ^{177}Lu-radiopharmaceuticals in preclinical studies
PS2-35	M. Maurin	Poland	Evaluation of biological properties of radiolabelled nanogel-bombesin conjugates
PS2-36	D. Niculae	Romania	Comparative radiobiological evaluation of intracellular effects induced by $^{64}CuCl_2$ in different tumour cells
PS2-37	L. Ondrák	Czech Republic	In-vitro study of therapeutic radionuclides' impact on selected tissue and tumour cell lines
PS2-38	G. Rabiller	Argentina	Factors and drug interactions that cause altered biodistribution of radiopharmaceuticals
PS2-39	C. Santos-Cuevas	Mexico	^{99m}Tc-CXCR4-L: Biokinetics and radiation dosimetry in humans

PS2-40	M. Silindir Gunay	Turkey	In vitro cell binding detection of novel radiopharmaceuticals: a radionuclidic evaluation
PS2-41	S. Treiger Borborema	Brazil	The advantage of using radiotracers for pre-clinical assays with conventional drugs: the case of meglumine antimoniate
Track	*Quality control and quality assurance of medical radioisotopes and radiopharmaceuticals*		
PS2-42	A. Ahmad Zikrileh	Malaysia	An experimental study on radiochemical purity (RCP) of ^{99m}Tc-Tetrofosmin compounded outside manufacturer's guideline using TEC-Control™ chromatography system
PS2-43	A. Aiboud	Morocco	Development of a new method for the microbiological analysis of Iodine-131
PS2-44	C. Arjun	India	User-friendly sterility testing method for injectable radiopharmaceuticals – feasibility study and validation
PS2-45	C. Arjun	India	Feasibility of a green analytical method for radiochemical purity determination of sodium [^{99m}Tc] pertechnetate
PS2-46	C. Arjun	India	Bacterial endotoxin testing of injectable radiopharmaceuticals: BRIT experience
PS2-47	M. Bricha	Morocco	"^{99}Mo/^{99m}Tc radionuclide generators" optimization: new quality control standards of alumina columns and kinetic study of Molybdenum adsorption on α alumina
PS2-48	A. Duran	Argentina	Effect of autoclaving, activity concentration and ethanol on the stability of [^{18}F] -FDG
PS2-49	O. Fedorova	Russian Federation	Enantiomeric purity of radiolabelled amino acids is influenced by the type of chiral column
PS2-50	A. Larenkov	Russian Federation	Quality control of ^{68}Ga radiopharmaceuticals: pitfalls and solutions
PS2-51	L. Piola	Argentina	^{89}Sr and ^{90}Sr/^{90}Y activity by cherenkov counting in medical ^{99}Mo quality control
PS2-52	K. Skovorodko	Lithuania	Implementation of a quality assurance program and quality control results of radiopharmaceuticals
Track	*Production of radionuclide generators*		
PS2-53	A. Alberti Ramírez	Cuba	Production of radionuclide generators: Cuban experience
PS2-54	E. Aliaga	Peru	Design and development of an automated mini-plant for ^{99m}Tc production
PS2-55	S. Chattopadhyay	India	Recovery of highly pure ^{99m}Tc from low specific activity (n,g)^{99}Mo using activated charcoal column
PS2-56	K. Fialová	Czech Republic	Development of Ge-68/Ga-68 radionuclide generator for nuclear medicine
PS2-57	M. El-Gizawy	Egypt	Selective separation of no carrier added Sc-47 from reactor irradiated Ca using zirconium vanadate gel for nuclear medical applications
PS2-58	M. V. Gonzalez	Argentina	Evaluation of alternatives for the removal of heat within the Mo-99 production cell by fission from the estimation of the radionuclidic composition and power of filters with uranium precipitate

PS2-59	D. Kottuparamban	India	Fluorine-18 Production Yield in an 11 MeV Medical Cyclotron: Comparison of Theoretical and Practical Yields
PS2-60	K. Kushwaha	India	Production, Separation and Purification of In-111 from Irradiated Natural Cd: Produced In-111 Quality Evaluated after Radiolabeling with Pentetreotide
PS2-61	P. Martini	Italy	Worldwide ten-year trend analysis of the scientific literature on therapeutic radiometals (2008-2018)
PS2-62	O. Odintsov	Ukraine	Preparation of zirconium molybdate gel as material for ^{99}Mo/^{99m}Tc chromatographic column generator
PS2-63	A. Tsechanski	Israel	Photonuclear production of ^{67}Cu radionuclide using “one-stage” setup
Track	*Production of PET- and SPECT-based diagnostic, therapeutic and theranostic medical radioisotopes*		
PS2-64	A. Abrunhosa	Portugal	Fully automated liquid target production of [^{68}Ga]$GaCl_3$ in line with GMP requirements
PS2-65	N. Bentaleb	Morocco	Study of the optimization of the use of the reducing agent in the formulation and production of sodium iodide-131 oral solution
PS2-66	S. Brinkevich	Belarus	Long-lived radionuclidic impurities in the production of ^{18}F labeled radiopharmaceuticals
PS2-67	S. Campos	Argentina	Analysis and model of radioactive noble gases and iodine emissions from a fission Mo-99 production process
PS2-68	L. Canton	Italy	Nuclear reaction calculations applied to cyclotron production of emerging radiopharmaceuticals
PS2-69	J. Červenák	Czech Republic	Measurement of excitation functions of proton-induced nuclear reactions on gold
PS2-70	I. Cieszykowska	Poland	Separation of ^{99m}Tc from low specific activity ^{99}Mo
PS2-71	S. Cisternino	Italy	Yttrium cyclotron solid target preparation for zirconium-89 production
PS2-72	A. Kellerbauer	EU	Production of actinium-225 at JRC Karlsruhe
PS2-73	A. Boschi	Italy	Technetium-99m production by medical cyclotron
PS2-74	L. Melendez-Alafort	Italy	Assessment of dose increase after administration of radiopharmaceuticals prepared with cyclotron-produced ^{99m}Tc
PS2-75	J. Merino	Argentina	Development of a copper oxide reactor to convert hydrogen to water in the dissolution of radioisotopes production targets
PS2-76	L. Mou	Italy	The LARAMED project at INFN-LNL: Laboratory of Radionuclides for Medicine
PS2-77	F.L. Navarro Marques	Brazil	Production of ^{89}Zr and radiolabeling of phosphatidylserine liposome
PS2-78	M. Pasquali	Italy	Towards multimodal PET/MRI imaging with cyclotron-produced 52/51 min
PS2-79	O. Pozzi	Argentina	Effect of the radiolysis produced by the high levels of radiation dose (Gy) delivered by alpha particles on the production and supply of Ac-225, and the labeling of radiopharmaceutical for therapy

PS2-80	H. Skliarova	Italy	High energy vibrational powder plating for cyclotron solid target preparation for radiopharmaceuticals production
PS2-81	V. Uvarov	Ukraine	The yield of ^{47}Sc at photonuclear production
PS2-82	W. Wojdowska	Poland	Cyclotron production of scandium-44
PS2-83	B. Zhang	China	Biodistribution of nanoradiopharmaceuticals in internal organs

Surnames are listed alphabetically (exceptions for modifications made after the Programme was created).

S13 16:00-17:30 Radiopharmacy installations

Venue Board Room B/M1
Chair: B. Guerin
T.Sec: A. Jalilian

Time	ID	Presenter	Country/Org	Title
16:00	S13-01	A. Duatti	Italy	How to set up a medium size ^{99m}Tc generator facility: IAEA experience
16:25	S13-02	V. Kumar	Australia	Design and successful operation of a SPECT hospital radiopharmacy
16:45	S13-03	M.R.A Pillai	India	Cyclotron and PET radiopharmacy installation: experience in setting up in a commercial centre
17:00	S13-04	U. Bhonsle	United Arab Emirates	How to set up a PET radiopharmaceutical facility: IAEA experiences
17:15	S13-05	K. Washiyama	Japan	An effort to diagnostic and therapeutic nuclear medicine at Fukushima Medical University using two medical cyclotrons

S14 17:30-18:30 IAEA Databases and Apps

Venue: Board Room B/M1
Chair: M. Haji-Saeed
T.Sec: J. Osso Junior

Time	ID	Presenter	Country/Org	Title
17:30	S14-01	A. Koning	IAEA	The medical isotope browser
18:00	S14-02	N. Pessoa	IAEA	The IAEA's research reactor database (RRDB)
18:15	S14-03	A. Jalilian	IAEA	Introduction to the new IAEA database “Cyclotrons used for Radionuclide Production”

Friday 1 November 2019

S15 09:00-10:30 Education in radiopharmacy

Venue Board Room B/M1
Chair: S. Rubow
T.Sec: A. Korde

Time	ID	Presenter	Country/Org	Title
09:00	S15-01	P. Elsinga	The Netherlands	Development and performance of a radiopharmacy platform certification, EANM experience
09:20	S15-02	A. Rey Ríos	Uruguay	Education and qualification of radiopharmacists in Latin America
09:40	S15-03	N. Bentaleb	Morocco	Master's degree in radiopharmaceutical sciences: step forward to enhance regional capacities in nuclear medicine in Africa
10:00	S15-04	E. Janevik-Ivanovska	North Macedonia	Developing, testing and installing e-learning system for radiopharmacy as a tool to harmonize education in developing country
10:15	S15-05	P. Wieland	WNA	The World Nuclear University's 7 approaches to enhance professional performance

S16 11:00-12:30 WNU OLYMPIAD: FINALS

Venue Board Room B/M1
Chair: A. Rey Ríos

Time	ID	Presenter	Country/Org	Title
11:00				Introduction Remarks
11:15	S16-01	T. Almeida	WNA	Public opinion about nuclear science and technology in Brazil
11:30	S16-02	Z. Deziel	WNA	Public opinion on radiopharmaceuticals and the nuclear industry in USA
11:45	S16-03	S. Tian	WNA	Public opinion on nuclear science and technology in China
12:00	S16-04	V. Fernandes	WNA	Acceptance and knowledge of the Brazilian population on nuclear science and technology
12:15				Closing Remarks and Awards Ceremony

CS 14:00-15:00 Closing Session

Venue Board Room B/M1
Chair: J. Osso

Time	ID	Presenter	Country/Org	Title
14:00	CS-01	N. Ramamoorthy	India	Highlights of ISTR2019
14:30	CS-02			Awards Ceremony
14:45	CS-03	M. Denecke	IAEA	Closing Remarks
15:00	CS-04	J. Osso	IAEA	Closing of the Symposium

ABSTRACTS

S1. Production of medical radioisotopes: Research Reactor

S1-01

Production of reactor based radioisotopes: An international Scenario

Author: Meera Venkatesh

Former Director of Nuclear Applications Physics and Chemistry, IAEA, Vienna, Austria

Corresponding author: Venkatesh.meera@gmail.com

Radioisotopes have been used for applications since almost eight decades in varied fields, healthcare being the most vital and widely known. Nuclear research reactors, through production of radioisotopes, have played a key role in enabling and sustenance of such applications, including in nuclear medicine.

A quick overview of the reactor produced isotopes used in radiopharmaceuticals over the past several decades shows the trend from the initial predominant use for therapeutic purposes (Iodine-131 and Phosphorus-32) with limited non-ideal diagnostic uses, to a dramatic shift and steep growth in diagnostic nuclear medicine with the advent of technetium-99m (the most widely used medical radioisotope), to be followed by a surge in therapeutic applications using particulate (especially β- emitting radionuclides among which Lutetium-177, Samarium-153, Rhenium-188/186 and Yttrium-90 are noteworthy) in the past 2 decades.

While the advances in closely associated fields such as cancer molecular biology influence radioisotopes used in nuclear medicine, the feasibility of production is dictated by the capacity of the nuclear reactor facilities and the regulations to be followed. The reactors worldwide have continuously adapted to the needs, improvised to meet the requirements and gear up for future demands, albeit often with severe constraints, owing to the ageing and the stringent regulations. The last decade witnessed acute short supply of important medical isotopes, especially Tc-99m, owing to the unavoidable long shut downs of the aged long serving reactors. Although radioisotope production in accelerators has seen a huge growth, it is beyond doubts that research reactors are essential for production of a huge range of important radioisotopes in large quantities and at affordable cost, recognizing which, efforts to build a few new research reactors have been initiated to cater to the global needs.

An overview of the above aspects and a general status of the production of radioisotopes in the world will be provided, keeping the focus on the use in radiopharmaceuticals, aligning with the theme of the Symposium.

S1-02

Production and supply of medical radioisotopes: A polish experience

Author: Renata Mikolajczak

Radioisotope Centre POLATOM, National Centre for Nuclear Research, 05-400 Otwock, Poland

Corresponding author: Renata.Mikolajczak@polatom.pl

Nuclear reactors are the main source of neutrons of various energies (thermal, epithermal and fast) which can be utilized for irradiation of various target materials to produce radionuclides for therapy. The characteristics of neutron flux, a parameter specific for each individual reactor, and the composition of the target material will determine the final specific activity of the desired radionuclide. Maria Research Reactor at the National Centre for Nuclear Research in Poland is one of the worldwide leading suppliers of iodine-131 and plays an important role as a source of other radionuclides for therapeutic use. The availability of beta emitters, ^{90}Y and reactor produced ^{177}Lu, allowed to initiate the peptide receptor radionuclide therapy of neuroendocrine tumours in Poland already in 2004. Special attention is given to radiometals which can be obtained in carrier-free form from (n,p) and (n,γ)→β^-reactions giving a parent radionuclide decaying in short time to required daughter radioisotope, an example of the latter being n.c.a. scandium-47. The processing of such targets requires separation chemistry and further pharmaceutical formulation. The ultimate goal is to obtain the radiometal with high specific activity, radionuclide and chemical purity, in the solution suitable for radiolabeling of various molecules for medicinal use.

S1-03

Laboratory scale production of medium specific activity lutetium-177 (carrier added) through the [^{176}Lu (n,γ) ^{177}Lu] nuclear reaction under standardized conditions

Author: José Luis Crudo

Co-author(s): Sofía Aguilar; Diego Martin; Marisa Trotta; Noemí Nevares; Ana Lopez Bularte; Alfredo Zapata; Dino Isolani; Jorge Quintana

National Atomic Energy Commission CNEA, Argentina

Corresponding author: joseluiscrudo@cnea.gov.ar

The goals were:

1) To calculate ^{176}Lu target enrichment percentage, ^{177}Lu specific activity (S.A.) and its uncertainties and chemical impurities;
2) To calculate ^{177}Lu S.A. normalized error between four batches;
3) To compare methods of target volume recovery from quartz ampoule.

The product was obtained by irradiation in the RA-3 research reactor neutron trap of the Centro Atómico Ezeiza using an 86.5% ^{176}Lu enriched target provided by IAEA. ^{176}Lu target enrichment determination was carried out by Inductively Coupled Plasma–Mass Spectrometry (ICP-MS). Calculation of Lu mass in the ampoule was done by gravimetry. Geometry factor was used to correct the measured ^{177}Lu activity of the quartz ampoule. ^{177}Lu S.A. and its uncertainty were calculated for every single batch (n = 4). Metal impurities determination was performed by total reflection X-ray fluorescence spectroscopy (TXRF). ^{177}Lu S.A. normalized error were obtained according standard ISO 13528:2015. Manual pipetting and reverse centrifugation of 20 µL volume recovery from quartz ampoule were compared.

Results showed that ^{176}Lu/ (^{175}Lu + ^{176}Lu) ratio was 86.8 ± 0.9 %. ^{177}Lu S.A. and its uncertainties at EOB for batches 1, 2, 3 and 4 were 26.7 ± 2.0, 18.5 ± 2.4, 16.6 ± 2.4 and 16.2 ± 2.3 mCi/µg of Lu respectively. Fe, Mn, Sr, Cr, Ni, Cu and Zn concentration referred to ^{177}Lu activity in batch 2 were 0.03, 0.0005, 0.0002 µg of metal / GBq of ^{177}Lu and less than 0.0001 µg / GBq for the last ones respectively. Average and standard deviations for Lu mass, irradiation time and ^{177}Lu S.A. at EOB (n =4) were 2.4 ± 0.1 µg, 151.7 ± 0.4 h and 19.5 ± 4.9 mCi/ µg of Lu respectively. Percentage (%) error of irradiation time, Lu mass and ^{177}Lu S.A. were 0.2, 2.6 and 25.2 % respectively. ^{177}Lu S.A. normalized error calculation showed that result of batch 1 was inconsistent. Comparison between manual pipetting and reverse centrifugation showed that 0.6 ± 0.8 mg and 1.7 ± 2.0 mg of target solution was not recovered from the quartz ampolle (n = 10). This was equivalent to 97.0 and 91.3% of total target volume recovery respectively. Metal impurities level complied with quality control specifications referred in table II-6 of IAEA-TECDOC 1856. Then, if the radionuclides were delivered in a short time since EOB, the product can be used for preparing moderate S.A. therapeutic radiopharmaceuticals. A recent internal report by S. Siri et al, showed that S.A. determined by gamma spectrometry was 12.7-16.1 Ci/mg. In conclusion, ^{177}Lu (c.a.) can be efficiently produced under standardized conditions in the RA-3 with a medium S.A. and low level of chemical impurities using a commercially available enriched target. This fact is highly significant because there are no industrial producers of high S.A. ^{177}Lu in Latin America and ^{177}Lu (c.a.) S.A. decrease 50 % with the time consumed for delivery from the Europe and North America.

S1-04

Synthesis and neutron activation of Lu_2O_3 nanoparticles functionalized with target specific peptides

Author: Alejandra Ancira-Cortés[1]

Co-author(s): Blanca Ocampo-García[2]; Enrique Morales-Avila[3]; Myrna Luna-Gutiérrez[2]; Nallely Jiménez-Mancilla[2]

[1]Instituto Nacional de Investigaciones Nucleares, Universidad Autónoma del Estado de México, Mexico
[2]Instituto Nacional de Investigaciones Nucleares, Mexico
[3]Universidad Autónoma del Estado de México, Mexico

Corresponding author: aancira2@gmail.com

The preparation of ^{177}Lu-peptides for targeted radionuclide therapy requires the use of lutetium-177 from medium to high specific activity (from 400 to 3000 GBq/mg), which cannot be obtained in low flux research nuclear reactors. However, the synthesis of ^{176}Lu in the form of injectable nanoparticles functionalized with target-specific peptides, would allow to irradiate in the TRIGA (Training, Research, Isotopes, General Atomics) Mark III reactor, a mass of lutetium enough to obtain radiopharmaceuticals with activities suitable for direct medical use.

The objective was to synthesize and characterize Lu_2O_3 nanoparticles functionalized with the RGD peptide, as well as to study the effect on their structural properties after neutron irradiation in the Triga Mark III reactor.

Lu_2O_3 tablets were prepared and immersed in an injectable solution containing the DOTA-RGD peptide. The sample was irradiated in a Nd:YAG laser equipment (Q-Smart-100, quantel laser)(50 mJ) with a repetition rate of 10 Hz (irradiance of 16 Watts/cm2), producing instantaneously a turbid solution containing the lanthanide oxide nanoparticles with the peptide (Lu_2O_3-NPs-peptide) attached on their surface. The solution was purified and concentrated by ultracentrifugation and filtered through a 0.22 µm membrane (Millipore). The nanosystem was analysed by TEM, DLS, UV- Vis and IR techniques. The Lu_2O_3-NPs-peptide solution (1 mg/mL), contained in a sealed vial of pharmaceutical grade plastic, was irradiated in the Triga Mark III reactor (3x1013 n.cm-2.s-1) for 20h. After decay, the sample was reanalysed by TEM, DLS, UV-Vis and IR techniques.

The TEM, DLS, UV-Vis and IR analyses of the Lu_2O_3-NPs-peptide sample, showed that the method of synthesis by laser irradiation (thermo-reduction) is suitable for the preparation of nanosystems based on lutetium oxide functionalized with target-specific peptides (size from 2 to 100 nm), which were not significantly affected when subjected to neutron irradiation in the Triga Mark III reactor. The irradiation of the Lu_2O_3-NPs-peptide (sterile solution) for 20h, yielded 9.2 GBq useful for direct clinical use. The Lu_2O_3-NPs-RGD system could potentially be applied in targeted radiotherapy of intrahepatic carcinomas. In order to produce significant amounts of Lu_2O_3-NPs, other methods of synthesis can be applied, such as thermo-reduction by calcination.

In conclusion, laser irradiation is suitable for the synthesis of lutetium oxide nanoparticles functionalized with target-specific peptides, which are not significantly affected after neutron irradiation. The Lu_2O_3-NPs-RGD nanosystem is potentially useful for targeted radiotherapy purposes.

Acknowledgment: this study was supported by the Mexican National Council of Science and Technology (“Laboratorios Nacionales” and CONACyT-SEP-CB-2018, A1-S-36841).

S1-05

Towards a robust supply chain for medical radioisotopes

Author: Titus Tielens

Co-author(s): Hermen Van der Lugt; Alex Rood; Anneloes Geldermans

PALLAS, the Netherlands

Corresponding author: titus.tielens@pallasreactor.com

Demand for nuclear medicines for diagnostic, therapeutic and theranostic use is growing fast, driven by the development of highly effective novel drugs against cancer and life-threatening diseases. Whereas molybdenum-99 is the most commonly used isotope for diagnostic SPECT scans, it is expected that lutetium-177 will be the main workhorse in the coming decades for therapeutic applications. However, security of supply is at risk, especially for therapeutic isotopes, as radioisotopes are irradiated by only a handful of aging reactors, some of which will stop production in the coming decade. The objective of this paper is to assess if any shortage of production may emerge and to identify options for creating a robust supply chain.

PALLAS has built a bottom-up model to estimate potential global demand for medical isotopes, based on an analysis of medicines under development, their indications and potential adoption among patient populations. PALLAS has also made a forecast model of available reactor capacity for both diagnostics and therapeutics. Finally, PALLAS has developed scenarios to assess any gap in production capacity.

The resulting demand and supply scenarios indicate that while the number of diagnostic scans will grow moderately, the number of therapies could grow steeply to several hundred thousand by 2030.

PALLAS research shows that the available capacity for a key isotope such as lutetium-177 will not be able to meet demand as of 2025. As no effective alternative production methods exist for most therapeutic isotopes, it is clear that new reactor capacity will be required.

The PALLAS foundation was initiated with a loan from the Dutch government with the objective of constructing a new nuclear reactor, to replace the current High Flux Reactor in Petten, the Netherlands, for the production of medical isotopes and research, but under the explicit condition that the reactor be privately financed. Driven by the need for private investment, the PALLAS team has developed a market-oriented approach and value proposition that will help transform the nuclear isotope sector.

S2. Production of medical radioisotopes: Accelerators

S2-01

Accelerator-based production of non-standard positron emitters and therapeutic radionuclides

Author: Syed M. Qaim

Institut für Neurowissenschaften und Medizin, Nuklearchemie, Forschungszentrum Jülich, Germany

Corresponding author: s.m.qaim@fz-juelich.de

The radionuclide production technology with regard to patient care studies is well developed, both at reactors and accelerators. For some newer emerging medical applications, however, there are increasing demands for two types of novel radionuclides: (a) longer lived positron emitters to study slow metabolic processes and to quantity radiation dose, (b) low-energy, highly ionising radiation emitting radionuclides for efficient internal radiotherapy of deep-lying tumours (targeted therapy). The development of a novel radionuclide demands interdisciplinary studies involving nuclear data measurements, target construction for high-current irradiations, devising chemical separation schemes to obtain high purity products and finally elaborating quality assurance tests for human use. The chain of work involved in the development of an accelerator-based radionuclide will be illustrated through a few examples.

Over the last three decades about 25 non-standard positron emitters have been developed, the most important ones being ^{64}Cu ($T_{½}$ = 12.7 h); ^{86}Y ($T_{½}$ = 14.7 h); ^{89}Zr ($T_{½}$ = 3.3 d) and ^{124}I ($T_{½}$ = 4.2 d). Many of the non-standard PET radionuclides are produced at a cyclotron via the low-energy (p,n) reaction on a highly-enriched target isotope. In general, small-sized solid targets are used, provided an extracted beam is available. At a few medical cyclotrons, however, attempts to use solution targets have also been fairly successful. On the other hand, a few positron emitters, like ^{52}Fe ($T_{½}$ = 8.3 h), ^{73}Se ($T_{½}$ = 7.1 h), ^{152}Tb ($T_{½}$ = 17.5 h), etc. can be produced only using accelerators delivering protons of energies up to 120 MeV. Exceptionally the spallation process is also utilized. All those possibilities will be elucidated.

With regard to novel therapeutic radionuclides, the present emphasis is on low-energy β^- emitters, e.g. ^{47}Sc ($T_{½}$ = 3.35 d) and ^{67}Cu ($T_{½}$ = 2.58 d), low-energy conversion and Auger electron emitters, e.g. ^{117m}Sn ($T_{½}$ = 13.6 d) and ^{193m}Pt ($T_{½}$ = 4.33 d), and α-emitters, e.g. ^{225}Ac ($T_{½}$ = 10.0 d). The on-going work on those radionuclides at intermediate energy accelerators will be briefly described, including the role of the α-particle beam in the production of the high-spin isomers like ^{117m}Sn and ^{193m}Pt. The most recent attempts to produce a few therapeutic radionuclides like ^{47}Sc and ^{67}Cu via the (n,xp) process induced by d/Be breakup neutrons at a cyclotron or via the (γ,p) reaction at a powerful electron linear accelerator (LINAC) will be outlined. Finally, the significance of the non-standard positron emitters and novel therapeutic radionuclides in theranostic applications will be briefly considered.

S2-02

Production of radiometals using a 24 MeV cyclotron

Author: Suzanne E. Lapi

University of Alabama at Birmingham, United States

Corresponding author: lapi@uab.edu

With the expansion of approved ^{18}F based agents for medical imaging using positron emission tomography (PET), low energy (11-24 MeV) cyclotrons are now used at many commercial and academic centers to produce isotopes for medical imaging. The energy of these machines is ideal for isotope production via (p,n), (p,α) and in some cases (p,2n) reactions. Using the UAB TR24 cyclotron, our group has focused on the development of reaction routes, target materials and the separation chemistry of isotopes to expand the toolbox of nuclear imaging agents. These have included transition metals such as ^{52}Mn, ^{55}Co, ^{89}Zr, $^{43,47}Sc$ and ^{45}Ti. Additional research has developed chemistry to incorporate these isotopes into new imaging radiopharmaceuticals for preclinical or clinical research.

S2-03

Production of radiometals using liquid targets: Status and perspectives

Author: Antero Abrunhosa

ICNAS/University of Coimbra

Corresponding author: antero@pet.uc.pt

The ever-increasing demand of radiometal isotopes for PET imaging is not being met by the currently available sources that rely mainly on radioisotope generators (when available, e.g. for Ga-68) and cyclotrons equipped with solid targets.

Our group has been actively involved in developing processes for the production of commonly used PET radiometals using liquid (solution) targets. This approach presents considerable advantages over the conventional solid targets as it much simpler, faster, amenable to automation and easier to comply with GMP production requirements. Moreover, these processes can be adapted, with minimal adaptation, to virtually all existing cyclotron facilities, most of them devoted F-18 production during the night and idle during the rest of the day.

This technology enables easy on-demand access to isotopes such as Ga-68, Zr-89, Cu-64 and Cu-61 among others that are essential to supply the ever-increasing requests of research and clinical theranostic applications. Ga-68 production is especially critical as current GMP generator production is far from being able to meet the fast-expanding market needs of this important isotope.

In this presentation we will discuss important issues regarding the production of radiometals using liquid targets including purity of target materials, irradiation conditions, purification processes, automation, GMP and regulatory considerations.

We believe that the widespread use of this technology could provide a stable supply of radiometals to fulfil current and future market needs for research and clinical applications with minimal adaptation of currently existing infrastructures.

S2-04

Radioisotope production and development with a 30 MeV cyclotron

Author: Jeong Hoon Park

Korea Atomic Energy Research Institute, Jeongeup, Republic of Korea (South)

Corresponding author: parkjh@kaeri.re.kr

RFT-30 is a 30 MeV cyclotron research facility at Korea Atomic Energy Research Institute in Jeongeup city located to the south east of Seoul. Radionuclide based pharmaceuticals are playing major role in several medical procedures. Medical community has experienced a rapid growth for radionuclide applications in the field of therapy, diagnosis and/ or therapeutic purposes due to the technological development in cyclotron-based radionuclide production. We have been successful in irradiating targets for producing bulk quantities of Zr-89 and Ge-68. Complete process optimization has been finished for Zr-89 targetry, production, separation and purification. We have started regular supply of high purity Zr-89 (oxalate/ chloride) to hospitals such as Seoul national hospital, Samsung Seoul hospital etc. based research groups in Korea. Process optimization for Ge-68 production has been achieved and we are working on purification of Ge-68. And furthermore, the electroplating associated with nickel target was optimized for Cu-64 and Co-57. Simultaneous efforts are made towards electrodeposition of Zn-70 for the production of Cu-67 respectively. One of the major activities at the Cyclotron Application and Research Facility (CARF) is research and development in the field of production of cyclotron-based radionuclides and its applications. We at CARF are routinely involved in performing preliminary studies and process development required for the bulk production of high purity radionuclides for medical applications. As a part of this activity the major R& D efforts are dedicated towards targetry, production, separation/ purification, applications and achieving the efficient technologies for cyclotron based emerging radiometals (viz. Zr-89, Ge-68, Cu-64/67, Sc-44/47, Co-55/57, etc.) production, ensuring its sustainable supply for research and medical purposes. An overview of the efforts made by the researchers at CARF towards developing and optimizing production of radiometals using RFT-30 cyclotron is the sole purposes of this presentation. Methods from target production, irradiation conditions, target processing, separation and purification of radionuclides of interest, recovery of enriched target material would be discussed in brief.

S2-05

Production and application of Ac-225/Bi-213: TRIUMF experience and perspectives

Author: Valery Radchenko[1]

Co-author(s): Paul Schaffer[1]; Caterina Ramogida[2]; Cornelia Hoehr[1]; Patrick Causey[3]; Randy Perron[3]; Andrew Robertson[1]; Peter Kunz[1]

[1]TRIUMF, Canada
[2]SFU/TRIUMF, Canada
[3]Canadian Nuclear Laboratories, Canada

Corresponding author: vradchenko@triumf.ca

Targeted Alpha Therapy (TAT) showed recently very promising clinical results and it is a superior therapeutic tool compared to chemotherapy and beta radionuclide therapy. Due to the high Linear Energy Transfer (LET) and higher energy than beta particles, alpha particles are ideally suitable for localized therapy with selective delivery systems (e.g. peptides, antibodies etc.). Ac-225 (t1/2 9.92 days) and daughter Bi-213 (t1/2 45.6 minutes) are two very potent candidates for TAT, but their wide clinical application is limited due to the limited supply. TRIUMF (Canada's Particle Accelerator Centre) has unique capabilities to produce Ac-225/Bi-213 via several production routes and significantly increase world supply of these emerging isotopes for TAT.

Several production routes are currently utilized to make available Ac-225 at TRIUMF. The first one is based on production of beam of mass number 225 with TRIUMF ISAC (Isotope Separator and Accelerator) facility, which enables to produce isotopically pure beam of actinium-225 and its parent radium-225. Produced research quantities (KBq- MBq's) enabled us to establish handling procedures for radiochemical purification and radiolabelling of actinium and bismuth isotopes and conducting unique research in chelation for preference of both elements.

Further, we have active collaboration with the Canadian Nuclear Laboratories (CNL), Ontario, Canada where the limited source of Th-229 is available and we are working together on testing the quality of this material and establishing sufficient radiochemical purity for radiolabelling. We are also working on a comparison study of Ac-225 sources derived from ISAC and CNL and establishing quality control tests and highest specific activity.

In addition to the above mentioned sources, TRIUMF has the world largest (520 MeV, 100 μA) cyclotron, which has capabilities at the target station at the end of the beam line 1A to produce a clinically (GBq) amount of Ac-225 and other promising alpha emitters suitable for TAT, via spallation reaction of thorium target. The main challenge in this production route is the radiochemical separation to purify actinium from the bulk mass of thorium target and several hundreds of co-produced fission products. Life sciences are currently working on developing several radiochemical separation methods for extraction of actinium isotopes from irradiated thorium as well as coextraction of other useful medical isotopes.

With the upcoming ARIEL facility, TRIUMF will enable two additional routes for production of actinium-225. First, by using ARIEL proton beam line in the same fashion how we utilize beamline 1A, to irradiate bulk mass of thorium for production of actinium isotopes. Appropriate infrastructure including irradiation station, transfer system and processing hot cells are currently under design. Additional promising production capability, which is still under consideration, for TAT isotopes will be electron beamline of ARIEL which will enable photonuclear reaction on radium (Ra-226(γ, n)Ra- 225→Ac-225) and will enable to produce clinical quantity of Ac-225 and other promising medical isotopes.

S3. Production of medical radioisotopes: Generators

S3-01

Role of IAEA on the supply of ^{99}Mo

Author: Joao Osso Junior

IAEA, Vienna, Austria

Corresponding Author: J.A.Osso-Junior@iaea.org

Technetium-99m (^{99m}Tc), the daughter product of molybdenum-99 (^{99}Mo), is the most utilized medical radioisotope, amounting to about 30 million studies per year and more than 80% of all procedures in diagnostic nuclear medicine. The IAEA supports its Member States in various areas related to the production of ^{99}Mo and ^{99m}Tc, without using high enriched uranium (HEU), through activities such as coordinated research projects (CRP), thematic technical meetings, technical cooperation projects and publications. Some recent activities are: CRPs on (i) Direct cyclotron production of ^{99m}Tc (ii) Guidelines on how to reduce radioactive gaseous releases during radioisotope production (iii) New Ways of Producing ^{99m}Tc/^{99m}Tc Generators. Additionally, the HEU minimization project and the Peaceful Uses Initiative project on supporting the global ^{99}Mo production without using HEU are being implemented. A Symposium on the supply of ^{99}Mo, organized by the National Academies of Sciences of United States of America and Russian Federation, was supported in 2017. All activities will be discussed along with future planning.

S3-02

Nuclear safeguards in radiopharmaceutical facilities

Author: Bret Grimshaw

IAEA, Vienna, Austria

Corresponding author: b.grimshaw@iaea.org

One of the many functions of the International Atomic Energy Agency (IAEA) is to undertake verification of nuclear materials (uranium, plutonium and thorium) in peaceful use, including within radiopharmaceutical facilities, to verify states' undertakings under their respective safeguards agreements with the IAEA. This function includes the specific verification of nuclear materials associated with the production of radiopharmaceuticals used in shielding, and for both pre-irradiated and post-irradiated nuclear material as seen in Mo-99 production. The verification of nuclear material employs a variety of IAEA verification techniques including, gamma ray spectroscopy and neutron coincidence counting. This presentation will cover definitions of nuclear material and nuclear material verification using analytical techniques deployed.

S3-03

Supply of Mo-99: Focus on US supply

Author: Cathy S. Cutler

Collider Accelerator Department, Brookhaven National Laboratory, Upton, NY USA

Corresponding author: ccutler@bnl.gov

There has been no large-scale production of Mo-99 in the United States since Cintichem shut down in 1989. The US the largest user of Mo-99 for the supply of Mo-99/Tc-99m generators has relied on outside production of Mo-99 traditionally produced by neutron irradiation of highly enriched uranium targets (HEU). The world supply was largely provided by four irradiation sources NRU, HFIR, BR2 and NTP reactors. The NRU reactor was able to supply roughly 80% of the world's supply and was able to cover the production if the other reactors unexpectedly went down. This all came to a head when these aging facilities started having unexpected shutdowns that resulted in worldwide shortages in supply. Further around the same time the US government became concerned about the shipment of HEU targets around the world and the possibility that they could fall into the wrong hands and be used for nefarious purposes and thus wanted to see production switched to the use of low enriched uranium (LEU)targets and LEU fuel. In 2010 the NNSA began funding cooperative agreements with partners that were able to come up with 50% of the funding to create a redundant reliable supply of Mo-99. The initial goal was for the partners to produce 50% of the needed Mo-99 supply in five years. In 2018 with only one US supplier approved by the FDA and producing at levels that were relatively minor the NNSA issued a new funding opportunity announcement to produce Mo-99 without the use of HEU. Earlier this year the DOE announced that four US companies were under negotiation for potential new cooperative agreement awards. The NNSA has also made available technical expertise from the Department of Energy national laboratories on a non-proprietary basis. The current state of Mo-99 supply will be presented with a focus on US supply.

S3-04

Radionuclide production at high energy accelerators: New possibilities for radioisotope generators

Author: Boris L. Zhuikov

Institute for nuclear Research of Russian Academy of Sciences, Moscow, Russia

Corresponding author: bz@inr.ru

Radionuclide production on high energy protons is considered as a prospective approach for creating medical generators providing diagnostic or therapy, in particular: ^{82}Sr/^{82}Rb, ^{68}Ge/^{68}Ga, ^{72}Se/^{72}As, ^{44}Ti/^{44}Sc (PET diagnostics), ^{225}Ac/^{213}Bi, ^{223}Ra/^{211}Pb, ^{230}Pa/^{230}U/^{226}Th (radioimmunotherapy). Besides the old accelerators in BNL (200 MeV), LANL (100 MeV), TRIUMF (120 MeV), iThemba (66 MeV) and INR RAS (160 MeV), two 70 MeV cyclotrons and processing facilities in Nantes, France (ARRONAX) and in Indianapolis, USA (ZEVACOR) have been installed recently and are successfully operated now. Several more facilities are proposed to be installed soon in different countries.

Several new generators are under development basing on the above radionuclides. In particular, INR RAS has created a new design of ^{82}Sr/^{82}Rb-generator of activity up to 160 mCi providing PET diagnostics for cardiology and neuro-oncology of about 600 patients with each generator (30 L of eluent before breakthrough). Clinical trials successfully passed in Russia for the both medical applications.

At the old high energy (more than 100 MeV) proton irradiation facilities in INR RAS, LANL, BNL and TRIUMF one can produce in future via irradiating metallic ^{232}Th a big amount of a prospective alpha-emitter ^{225}Ac (tens of Ci per year) with a small admixture of ^{227}Ac (0.2%). INR RAS has successfully solved targetry problems using specially constructed diffusion high temperature welding facility. New ^{225}Ac/^{213}Bi-generators for high activity basing on cycling scheme and/or inorganic sorbents are under development. The new generator has been already tested for labeling, providing pure ^{213}Bi with breakthrough of ^{225}Ac less than 10^{-6} %.

A new commercial accelerator facility with proton energy more than 100 MeV is necessary to develop in future to provide routinely a high level production ^{225}Ac and ^{213}Bi-generators along with other important radionuclides.

S3-05

Cyclotron production of ^{47}Ca for ^{47}Ca/^{47}Sc generator

Author: Rafał Walczak[1]

Co-author(s): Mateusz Sitarz[2/4]; Ryszard Misiak[3]; Marek Pruszyński[1]; Agnieszka Majkowska-Pilip[1]; Jerzy Jastrzębski[2]; Ferid Haddad[4] Aleksander Bilewicz[1]

[1]Institute of Nuclear Chemistry and Technology, Warsaw, Poland
[2]University of Warsaw, Warsaw, Poland
[3]Institute of Nuclear Physics Polish Academy of Sciences, Cracow, Poland
[4]GIP ARRONAX, Saint-Herblain, France and Subatech, Nantes, France

Corresponding author: r.walczak.ichtj@gmail.com

Scandium-47 is a low energy β- emitter which together with β+ emitters ^{43}Sc and ^{44}Sc, creates very attractive theranostic pairs for nuclear medicine. As far, obtaining ^{43}Sc and ^{44}Sc are well developed, whereas ^{47}Sc production is still difficult. In our work, we propose a new cyclotron method for producing ^{47}Ca in ^{48}Ca(p,x)^{47}Ca nuclear reaction and design and construction of ^{47}Ca/^{47}Sc generator. ^{48}Ca target in $CaCO_3$ form (enriched with 69.2% ^{48}Ca) and mixed with graphite was irradiated at the ARRONAX cyclotron in Saint-Herblain, France in the energy range 60 → 13 MeV. Results show that recalculated TTY production for ^{47}Ca on commercially available 97.1% enrichment ^{48}Ca is 140(11) MBq/μAh. This result is consistent with our previous measurements at the AIC-144 cyclotron in Cracow, Poland and with the predictions based on TENDL-2017. Therefore, after 24 hours of irradiation, with a current of 30 μA, it is possible to generate 94 GBq of ^{47}Ca. During this process also ^{46}Sc, ^{47}Sc, ^{48}Sc are generated, and as impurities, they must be separated from ^{47}Ca.

For separation of scandium radioisotopes, we applied a precipitation method using microfilters with PTFE membrane (0.22 μm). After the irradiation, $CaCO_3$ target was dissolved in 1 M HCl and then alkalized with 25% ammonia. In this environment scandium forms insoluble compounds and can be separated from calcium by using microfilters. After separation of impurities the Ca solution was left 5.6 days for the maximum growth of ^{47}Sc. Our results indicate that with 100% effective dissolution, about 60 MBq/μAh of pure ^{47}Sc without other contaminating scandium activity could be separated on the filter for the highly enriched $^{48}CaCO_3$ target. Therefore, by irradiation of ^{48}Ca target for 24 hours with 30 μA protons is possible to produce 39 GBq of ^{47}Sc, which is enough for about 10 therapeutic doses. After next 5.6 days another 17 GBq of ^{47}Sc is generated, which is about 4 doses.

Scandium-47, separated by our developed method, has sufficient quality for labelling biologically active molecule, which has been confirmed by labelling bioconjugates of Trastuzumab, anti HER2 nanobody and Substance-P with DTPA and DOTA chelators. For DTPA-Trastuzumab, DTPA- nanobody and DOTA-Substance-P efficiency of labelling was 99% (T=95℃) and for DOTA-nanobody 60% (T=50oC).

Acknowledgement: this study was financed by the Ministry of Science and Higher Education of Poland from funding for science in the years 2016–2019 (co-financed international program) and by IAEA Research Contract No: 20488 and NCN grant “Nanobodies labelled with alpha emitters as potential radiopharmaceuticals in targeted radioimmunotherapy” no: 2013/09/D/ST4/03791. This work has been, in part, supported by a grant from the French National Agency for Research called “Investissements d’Avenir”, Equipex ArronaxPlus noANR-11-EQPX-0004 and Labex IRON noANR-11-LABX-18-01.

S4. Production of radiopharmaceuticals: Theranostic

S4-01

Development and application of monoclonal antibody-based radiopharmaceuticals

Author: Jason lewis

Memorial Sloan Kettering Cancer Centre, New York, United States of America

Corresponding author: mailto:lewisj2@mskcc.org

The use of Positron Emission Tomography (PET) for cancer imaging is a well-established and widely used molecular imaging modality both in clinical and research settings. PET offers the ability to quantitatively measure biological and receptor-based processes using a wide spectrum of specifically designed radiopharmaceuticals. The use of PET is expanding and the inclusion of longer-lived radiometal positron-emitters is broadening the application and appeal of this imaging modality.

The remarkable specificity and selectivity of antibodies for cancer biomarkers have made immunoglobulins some of the most flexible and adaptable tools in modern medicine. For therapeutic purposes, a wide range of non-labeled antibodies has now entered the clinic. Antibody-based PET and SPECT imaging agents are not far behind. For example, an array of ^{89}Zr-labeled radioimmunoconjugates has shown significant promise in both preclinical and clinical studies.

Zirconium-89 has a number of distinct advantages which make it ideal for immunoPET: (i) the radioactive half-life of 78.41 h matches closely the extend times required for optimum biodistribution of intact mAbs, (ii) the positron yield of 22.7% is comparable to that of Cu-64, Y-86 and I-124 which improves counting statistics in PET imaging, (iii) zirconium and its ions are generally inert to biological systems and have no known biological role or function, (iv) cyclotron production of Zr-89 via the (p,n) transmutation reaction using a 100% naturally abundant Y-89 solid target is highly efficient and cost effective, and (v) high purity and high specific-activity Zr-89 is now available in various chemical forms which are suitable for radiolabeling mAbs.

This presentation will review the current state-of-the-art in non-standard PET nuclide application with an emphasis on the use of radiometals with antibody constructs. In addition, since the effective use of a radiometal nuclide often relies on their attachment to the targeting probe via a bifunctional chelator, this talk will focus on novel strategies for using “click” chemistry methodology for attachment of the radiometals to active antibodies.

S4-02

Theranostic radiopharmacy

Author: Clemens Decristoforo

Medizinische Universität Innsbruck, Austria

Corresponding author: Clemens.Decristoforo@tirol-kliniken.at

The concept of theranostics has found increasing interest in the Nuclear Medicine community. Even though applied for decades in the context of radioiodine therapy recent interest is driven mainly by combining the use of ^{68}Ga-radiopharmaceuticals in PET with Lu-177 for therapeutic applications. The two major radiopharmaceuticals are Somatostatin analogs and PSMA ligands. In this talk the requirements for the small scale preparation of these radiopharmaceuticals in a combined theranostic settings are discussed. Preparations cane be performed manually, but today are usually made using automated modules allowing to use similar and well documented processes for preparation of both the diagnostic as well as the therapeutic radiopharmaceuticals. Technological differences are discussed and strategies to comply with Good Manufacturing Practices. Recent trends towards kit based preparation for ^{68}Ga-radiopharmaceuticals and centralized production of therapeutic analogs provide new opportunities for wider application of the theranostic concept in Nuclear Medicine.

S4-03

Innovative medical radioisotopes for theranostic application, and how they are produced

Author: Vadim Gadelshin[1]

Co-author(s): Roberto Formento-Cavaier[2]; Férid Haddad[3]; Ulli Köster[4]; Frank Rösch[5]; Thierry Stora[6]; Dominik Studer[1]; Klaus Wendt[1]

[1]AG LARISSA, Institute of Physics, Johannes Gutenberg University Mainz, Germany
[2]Advanced Accelerator Application, Novartis Group, Ivrea, Italy
[3]GIP ARRONAX, Nantes, France
[4]Institut Laue-Langevin, Grenoble, France
[5]Institute of Nuclear Chemistry, Johannes Gutenberg University Mainz. Germany
[6]Engineering Department, CERN, Geneva, Switzerland

Corresponding author: gadelsh-invm@mail.ru

Nowadays, there are several developments focused on the expanding of the availability of innovative medical radioisotopes. One of them is the use of mass separators, which can extract a desired isotope from a mixture of others of the same element, a task nearly impossible just by means of chemical methods. An electromagnetic mass separator, dedicated for medical isotope production, has been launched in the frame of CERN-MEDICIS facility. This R&D project is intended: to study and to establish production routes for radionuclides, having a potential for the theranostic approach, like terbium isotopes (Tb-149, Tb-152, Tb-155, Tb-161); to test a purification method for carrier-added Lu-177; and to demonstrate the availability for other innovative isotopes, like Er-169, a nearly pure short-range beta-emitter with similar chemistry to Lu-177.

To identify the optimal requirements for extraction of isotopes of interest, different types of ion sources were studied. It was done by a direct comparison of the performance of surface ion source with laser ion source in a separation of a quantified sample of elements of interest. The ratio between a number of atoms collected after separation and known number of atoms in the sample initially gives an ionization efficiency value, which can serve as a direct measure of the performance. The experiments were performed at the MEDICIS facility in-situ (surface ion source), and at the Mainz University mass separator setup RISIKO (laser ion source).

During the in-situ measurements with the surface ion source, the production of Tb-155 and Er-169 with a high specific activity was demonstrated. On the other side, the collected quantity was only enough for pre-clinical tests. Thereby, the obtained ionization efficiency was around 5 % for Tb-155 and 0.3 % for Er-169. The experiments with laser ion source gave exceptionally high ionization efficiency results above 50%, what should increase the production performance of terbium and erbium at least by one or two orders of magnitude respectively.

The highly efficient laser ionization process of considered elements has a clear potential to be applied to radioactive ion beam facilities. It will allow the production of radionuclides in a quantity being sufficient for a regular supply of nuclear medicine institutions. In 2019, the MEDICIS Laser Ion Source Setup MELISSA is going to be launched. The combination of the laser resonance ionization and electromagnetic separation will become a starting point for production of many other nuclides, not accessible before because of a strong isotopic contamination. Several experiments are foreseen, to test additionally the performance for scandium and actinium isotopes.

S4-04

Preparation and preclinical evaluation of ^{64}Cu-NOTA-anti MUC1 as a radioimmunoconjugate for diagnosis of MUC1+ breast cancer by PET

Author: Behrouz Alirezapour[1]

Co-author(s): Saeed Rajabifar[1]; Miad Hashemizadeh[2]; Ehsan Maadi[2]; Javad Mohamadnejad[3]

[1]Nuclear Science and Technology Research Institute, Tehran, Islamic Republic of Iran
[2]Pars Isotope Company, Iran
[3]University of Tehran, Tehran, Islamic Republic of Iran

Corresponding author: balirezapour@aeoi.org.ir

Radioimmunoscintigraphy (RIS) has attracted considerable clinical applications in tumour detection. Underglycosylated MUC1 antigen is one of the early hallmarks of tumour genesis and is overexpressed in more than 80% of breast cancers. PR81 is a new murine anti-MUC1 monoclonal antibody (mAb). In this study, as the first step, we have developed an efficient indirect labelling method of PR81 with ^{64}Cu (T1/2 = 12.8 h, β+ = 17%, β− = 39%, EC = 43%) through using NOTA (p- SCN-Bn-NOTA) bi-functional chelator and performed preliminary biodistribution studies in mouse bearing breast adenocarcinoma.

PR81 was conjugated with NOTA (Macrocyclics B-605), the average number of the chelator conjugated per mAb was calculated and total concentration was determined by spectrophotometrically. NOTA–antiMUC1 was labelled with ^{64}Cu then Radiochemical purity and immunoreactivity, internalization study by MCF7 cell line and serum stability of ^{64}Cu–NOTA– anti MUC1 were determined. The biodistribution studies and radioimmunoscintigraphy were performed in female BALB/c mouse bearing breast carcinoma tumour (^{64}Cu–NOTA–antiMUC1 i.v., 100 µl, 20±5 µg mAb , 6, 12, 24 and 48 h).

^{64}Cu–NOTA–anti MUC1 was prepared (RCP >98% ± 0.4, Specific activity 5.2 ± 1.2 µCi/µg). Conjugation reaction of chelator (50 molar excess ratio) to antibody resulted in a product with the average number of chelators attached to a mAb (c/a) of 4.1 ± 0.5. Labelling yield with ^{64}Cu in 400µg concentration of bioconjugate was 96.5% ± 2.1. Immunoreaction of ^{64}Cu–NOTA– anti MUC1 complex towards MUC1 antigen was determined by RIA and the complex showed high immunoreactivity towards MUC1. In vitro and in vivo stability of radioimmunoconjugate was investigated respectively in PBS and blood serum by RTLC method. In vitro stability showed more than 94% ± 1.26 in the PBS and 81% ± 2.62 in the serum over 24 hours. The Immunoreactivity of the radiolabelled PR81 towards MCF7 cell line was done by using Lindmo assay protocol. Under these conditions, the immunoreactivity of the radioimmunoconjugate was found to be 0.82. The biodistribution of ^{64}Cu–NOTA– anti MUC1 complex in the mice with normal and breast tumour at 6, 12, 24 and 48 h after intravenous administration, expressed as percentage of injected dose per gram of tissue (%ID/g). Biodistribution and imaging studies at 24 and 48 h post-injection revealed the specific localization of complexity at the site of tumours.

In conclusion, ^{64}Cu–NOTA– anti MUC_1 is a potential compound for molecular imaging of PET for diagnosis and follow up of MUC_1 expression in oncology.

S4-05

Development of a new prostate cancer theranostic radiopharmaceutical

Author: Laura Melendez-Alafort[1]

Co-author(s): Debora Carpanese[1]; Guillermina Ferro-Flores[2]; Blanca Ocampo-García[2]; Clara Leticia Santos-Cuevas[2]; Laura De Nardo[3]; Nicola Salvarese[4]; Giulio Fracaso[5]; Cristina Bolzati[4]; Antonio Rosato[3]

[1]Veneto Institute of Oncology IOV-IRCCS, Italy
[2]Instituto Nacional de Investigaciones Nucleares, Italy
[3]University of Padova, Italy
[4]Institute of Condensed Matter Chemistry and Energy Technologies ICMATE-CNR, Italy
[5]University of Verona, Italy

Corresponding author: lmalafort@yahoo.com

Prostate cancer (PCa) is the second leading cause of cancer deaths for adult men in the Western world. Although radical prostatectomy and local radiotherapy are largely successful for patients with localized cancer, available treatments for metastatic PCa have demonstrated weak curative efficacy. Consequently, new tools to improve the detection of recurrent PCa, and to identify and treat metastases, are imperatively needed. Antibody-based constructs represent a good strategy to develop theranostic agents. Currently, the murine mAb ^{111}In-capromab pendetide (ProstaScint®) is the only product that has been approved by the Food and Drug Administration (FDA) as a diagnostic radiopharmaceutical for PCa. ProstaScint® showed promising results in clinical diagnosis, but as a whole antibody exhibits low tumour targeting with a maximum uptake at 6-7 days post-injection and delayed clearance from non-target tissues. These issues limit its use as theranostic agent. Recently, preclinical studies of an anti-PSMA single-chain variable fragment of IgGD2B mAb (scFvD2B) labelled with ^{123}I, showed high tumour affinity, improved antigen-positive tumour uptake, with shorter circulatory half-life, and decreased uptake in non-target tissues. The aim of this work was to develop a new PCa theranostic radiopharmaceutical based on the scFvD2B radiolabel with ^{177}Lu.

The scFvD2B was conjugated to the chelating agent DOTA by using different stoichiometric molar ratios. The number of DOTA per scFvD2B and the affinity constant (Kd) for each construct was determined to choose the conjugated with higher specific targeting activity against PSMA receptors. The select DOTA-scFvD2B conjugate was labelled with $^{177}LuCl_3$. Stability of ^{177}Lu-DOTA-scFvD2B was studied using HPLC analysis after incubation at 37 ℃ with fresh hu- man serum, cysteine, glutathione or EDTA solutions (300-fold excess), at time points ranging from 0.5 to 192 h. In vitro cell studies were performed to determine the binding specificity and cellular internalization of ^{177}Lu-DOTA-scFvD2B. Biodistribution studies were performed in both healthy and PCa-bearing mice to evaluate ^{177}Lu-DOTA-scFvD2B pharmacokinetics and assess its tumour detection potential using SPECT imaging.

DOTA-scFvD2B Kd values showed that the construct characterized by 1:5 (scFvD2B:DOTA) molar ratio is the one with the greatest number of DOTA per scFvD2B which maintains the high specificity for the PSMA receptor. ^{177}Lu-DOTA-scFvD2B possessed high in vitro stability, the radiochemical purity of the radioconjugate accomplished at 192 hours after dilution was higher than 98%. Biodistribution studies performed in healthy mice after intravenous administration of the radioconjugate demonstrated that DOTA did not significantly change the scFvD2B pharmacokinetic properties. Indeed, ^{177}Lu-DOTA-scFvD2B showed a favourable biokinetic profile with a rapid blood clearance. Moreover, SPECT/CT imaging studies carried out in mice bearing PCa tumours in lungs proved good and specific tumour detection properties of ^{177}Lu-DOTA-scFvD2B from 6 to 192 hours post-injection.

In conclusion, ^{177}Lu-DOTA-scFvD2B high stability and specific affinity for the PSMA receptors in vitro and in vivo make this radioconjugate a promising PCa theranostic radiopharmaceutical. However, further dosimetric studies have to be performed to establish its therapeutic potential.

S5. Production of radiopharmaceuticals: SPECT

S5-01

Revising Tc-99m radiopharmaceuticals with recent advances in chemistry & imaging tools

Author: Adriano Duatti

Department of Chemical and Pharmaceutical Sciences, University of Ferrara, 44121 Ferrara, Italy

Corresponding author: dta@unife.it

Technetium-99m radiopharmaceuticals still remain the most extensively used radiodiagnostic agents covering approximately 70% of all nuclear medicine procedures carried out each year worldwide. Reasons for this success are well-known and can be traced back to the easy handling of the radionuclide in an hospital setting through the ^{99}Mo/^{99m}Tc generator, the almost ideal nuclear properties of the radionuclide ^{99m}Tc when applied in combination with the imaging modality of single photon emission tomography (SPECT) and the simplicity of the preparation of ^{99m}Tc radiopharmaceuticals carried out through the use of freeze-dried kit formulations. However, despite its relevance, in the last decades interest in the development of new imaging agents has mostly switched from ^{99m}Tc to radionuclides for positron emission tomography (PET). This change in the nuclear medicine scenario was mainly justified by the far higher sensitivity and spatial resolution of PET as compared to SPECT. Yet, this scenario is going to take a turn again mostly driven by unprecedented advancements in SPECT technology. A new generation of high-resolution, ultrafast SPECT cameras are being introduced into the field, and these new devices are expected to bring SPECT approaching almost the same performances of PET. To mention just a few of these recent technological advancements, the new SPECT cameras allow collecting a SPECT brain or cardiac scan in only 1-3 minutes, with a spatial resolution below 2 millimetres, by administering less than half of the activity currently injected in a conventional SPECT study.

Evidently, given this outstanding progress, single photon emitting radionuclides might receive a renewed attention and impetus. In particular, ^{99m}Tc radiopharmaceuticals may recover again a crucial role in nuclear imaging. Actually, it is curious to note that there exist already ^{99m}Tc analogues of some of the most celebrated PET tracers. For instance, the radiopharmaceutical ^{99m}Tc-HYNIC-TOC is a SPECT agent for the diagnosis of neuroendocrine tumours analogous to the PET tracer ^{68}Ga-DOTATATE. Similarly, the radiopharmaceutical ^{99m}Tc-Trofolastat is an analogous of ^{68}Ga-PSMA agents for the diagnosis of prostate cancer. Remarkably, a number of different derivatives of these radiopharmaceuticals are under investigation at the preclinical and clinical level. It turns out, therefore, that the arsenal of ^{99m}Tc radiopharmaceuticals is already equipped to address relevant clinical problems currently considered of exclusive domain of PET, possibly with the same, or even higher, level of diagnostic accuracy, taking advantage of the fundamental developments underway in SPECT technology.

Interestingly, it may also happen that old ^{99m}Tc radiopharmaceuticals, previously abandoned because of the difficult in handling them with current SPECT imaging devices, could be resurrected and their considerable diagnostic properties fully exploited with the novel ultrafast SPECT cameras. A typical example might be pinpointed with one of the very first cardiac tracer ^{99m}Tc-Teboroxime, which possesses almost ideal properties for myocardial perfusion, but that was given up because of its fast washout from myocardium within 5 minutes. Since a cardiac SPECT study can be completed in one-two minutes with the new ultrafast SPECT detectors, it turns out that the rapid cardiac elimination of ^{99m}Tc-Teboroxime may become an advantage rather than a disadvantage.

S5-02

Production of radiolabeled peptides for SPECT-based theranostics

Author: Guillermina Ferro-Flores

Instituto Nacional de Investigaciones Nucleares, Estado de México, Mexico

Corresponding author: guillermina.ferro@inin.gob.mx

Single-photon emission computed tomography (SPECT) cameras equipped with CT are still the systems most used in many nuclear medicine centers worldwide. The main advantage of the preparation of SPECT-based radiopharmaceuticals is the use of radiometals, which allows the development of simple, efficient, and reproducible radiolabeling procedures by using lyophilized kit formulations, without the need of further purification processes.

In this lecture, recent achievements on the design, freeze-dried kit formulations, and theranostic applications of SPECT-based radiopeptides with high affinity to cancer-associated target proteins are presented.

^{99m}Tc-HYNIC-iPSMA, ^{177}Lu-DOTA-HYNIC-iPSMA, and ^{225}Ac-DOTA-HYNIC-iPSMA. Considering that the heterocyclic ring of HYNIC interacts with the hydrophobic active sites of some enzymes and proteins, different prostate-specific membrane antigen inhibitor radiotracers (iPSMA) were prepared based on the HYNIC-iPSMA and DOTA-HYNIC-iPSMA ligands formulated as freeze-dried kits for the labeling with ^{99m}Tc, ^{177}Lu or ^{225}Ac. All radiopharmaceuticals were obtained with high radiochemical purities, which allows the availability of theranostic pairs. ^{99m}Tc-iPSMA was useful as a SPECT molecular imaging option to assist in the initial diagnosis of prostate cancer and the monitoring of disease progression. Prostate tumours are clearly visualized at three hours because of the high radiopharmaceutical affinity and low bladder activity. ^{177}Lu-iPSMA obtained from kit formulations showed high tumour uptake with good response (70%) rates in patients, including pain relief. ^{225}Ac-iPSMA prepared from lyophilized formulations also showed high *in vitro* and *in vivo* stability.

^{99m}Tc-HYNIC-CXCR-4-L, ^{177}Lu-DOTA-HYNIC-CXCR-4-L, and ^{225}Ac-DOTA-HYNIC-CXCR-4-L. As in the above case, ^{99m}Tc-,^{177}Lu- and ^{225}Ac-CXCR4-L were also prepared from lyophilized formulations with high radiochemical purity and high *in vitro* and *in vivo* stability. ^{99m}Tc-CXCR4-L was used for imaging of the chemokine-4 receptor-associated with brain tumour invasiveness. A direct relationship between the grade of differentiation and the expression of CXCR4 was found in patients.

^{99m}Tc-HYNIC-FAP-inhibitor, ^{177}Lu-DOTA-HYNIC-FAP-inhibitor, and ^{225}Ac-DOTA-HYNIC-FAP-inhibitor. Derivative ligands of the (*N*-(pyridine-4-carbonyl)-D-Alanyl)-L-Proline-boronic acid, a fibroblast activation protein (FAP) inhibitor, have also been obtained with high radiochemical purity and stability.

^{99m}Tc-HYNIC-TOC, ^{177}Lu-DOTA-TOC, and ^{225}Ac-DOTA-TOC. Lyophilized formulations have also been used for the preparation of ^{177}Lu- and ^{225}Ac-octreotide in high radiochemical yields and with excellent stability to works as theranostic pairs of ^{99m}Tc-HYNIC-TOC.

In conclusion, the use of quantitative SPECT/CT and the easy preparation of SPECT-based target-specific radiopharmaceuticals promotes the routine application of theranostics in oncological nuclear medicine, even in places where PET is not available.

Acknowledgment: this study was supported by the Mexican National Council of Science and Technology (“Laboratorios Nacionales” and CONACyT-SEP-CB-2018, A1-S-36841).

S5-03

Radiopharmacy and growth of nuclear medicine in developing countries

Author: Salah Bouyoucef
Co-author(s): Amel Fellah; Amel Taïbi

Department of nuclear medicine, Algeria

Corresponding author: salaedine@yahoo.fr

Clinical Nuclear medicine applications are growing very fast in the world. The great impact of nuclear medicine in the management of major health problems is becoming evident and visible. Many hospitals in developing countries, public and private, are interested more than before by installing a department of nuclear medicine. The approach in developing countries for supporting the expansion of nuclear medicine should be adapted to the new contest taking in consideration the development of radiopharmacy and the availability of new radiopharmaceuticals. Classically radiopharmacy in developing was limited to “hot lab” where basics preparations of technetium 99m radiolabelled cold kits are done sometimes in hot cells when available. Today those infrastructures are no longer appropriate and do not fit with the increase of clinical needs expressed daily in hospitals. This situation requires to educate train and recruit a radiopharmacist. The main responsibility of the radiopharmacist or “radiopharmaceutical scientist” in nuclear medicine is the preparation of radiopharmaceuticals to ensure their safety and efficacy. They are also responsible for the quality of the product which is essential to increase the impact on patient management through a correct interpretation of the results of the investigation, or the delivery of the correct therapeutic dose. There is a considerable scope for research and development in the field of radiopharmaceutical science. Also, the infrastructure should be adapted to the new requirements with appropriate drawing, air circulation, staff education and trackability of gross products and radiopharmaceuticals including clinical aspects.

S5-04

Selective αvβ3 integrin detection using [^{99m}Tc(N)PNP43]-tagged RGDechi Peptides: synthesis and pharmacological studies

Author: Cristina Bolzati[1]

Co-author(s): Nicola Salvarese[1]; Debora Carpanese[2]; Laura Melendez-Alafort[2]; Antonio Rosato[3]; Michele Saviano[1]; Daniela Comegna[4]; Annarita Del Gatto[4]; Laura Zaccaro[4]

[1]ICMATE-CNR, Italy
[2]Veneto Institute of Oncology IOV-IRCCS, Italy
[3]Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy
[4]IBB-CNR, Italy

Corresponding author: cristina.bolzati@cnr.it

The development of new integrin-selective molecules suitable for therapeutic or imaging purposes are currently of interest in development of effective personalized medical platforms. Recently, a bifunctional chimeric echistatin-RGD-peptide, RGDechi, has been reported as a potent and selective antagonist of αvβ3, in which the echistatin portion is essential for such selectivity 1.

Herein, RGDechi and three truncated derivatives functionalized with a cysteine (1-4), were synthetized and labelled with the [^{99m}Tc][Tc(N)PNP43]-synthon ([PNP43=(CH3)2P(CH2)2N(C2H4OCH3)(CH2)2P(CH3)2]) (^{99m}Tc1-4) as basis for selective integrin recognition.

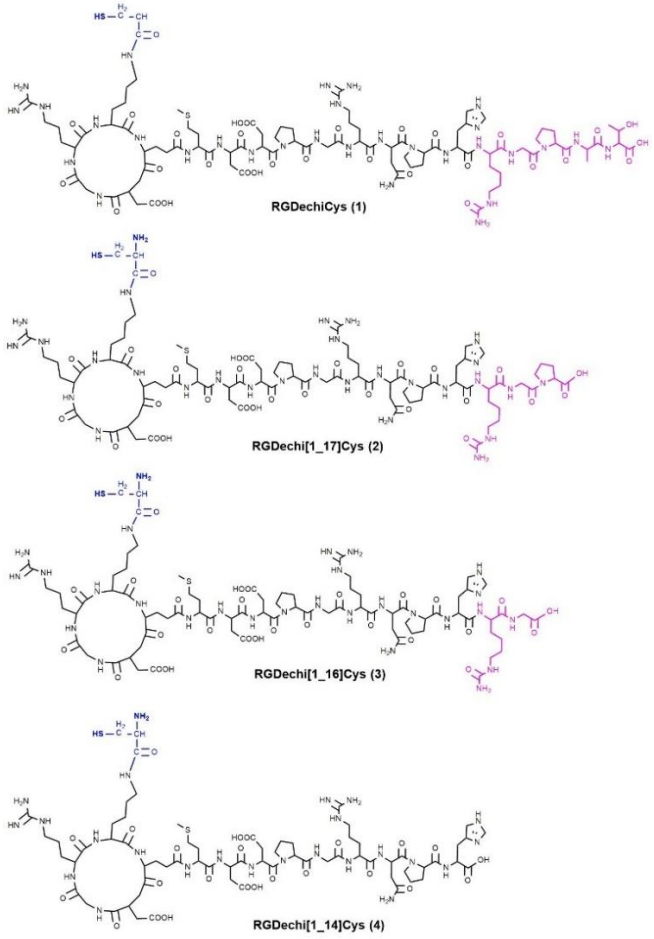


Figure 1. Schematic drawing of the peptides

RGDechi and derivatives were synthetized and conjugated to cysteine to allow the labelling with the [^{99m}Tc][Tc(N)PNP]-synthon, and characterised by HPLC. The chemical identity of ^{99m}Tc-RGDechi complexes was determined by carrier-added experiments supported by radio/UV- HPLC and LC-MS analyses. Dilution and transchelation stability studies of ^{99m}Tc-RGDechi complexes were carried out. Biological properties and binding specificity studies to the receptors were assessed on a panel of cancer cells expressing different levels of αvβ3 and αvβ5. Finally, the pharmacokinetic profiles of the more promising candidates ^{99m}Tc1 and ^{99m}Tc2 were evaluated both on healthy and melanoma-bearing mice. Their metabolism and metabolite identification were also performed.

Peptides were efficiently labelled with the [^{99m}Tc][Tc(N)(PNP)]-synthon. The compounds were stable at least for 18 hours in the reaction mixture. Dilution and transchelation studies demonstrated a high stability. In vitro binding data evidenced that the [^{99m}Tc][Tc(N)(PNP)]-synthon does not affect the biological properties of the peptides. The truncate ^{99m}Tc4, which lacks the last five C-terminal amino acid, lost the selectivity to αvβ3. Biodistribution studies conducted on ^{99m}Tc1 and ^{99m}Tc2 showed that the compounds selectively localize in tumour models expressing αvβ3 and fails to accumulate in those expressing αvβ5 receptors.

^{99m}Tc1-2 are able to discriminate between endogenously expressed integrins αvβ3 and αvβ5 and possess favourable pharmacokinetics characterized by low liver uptake and rapid elimination from non-target tissues resulting in positive target-to-non-target ratios. Results are promising; the presented construct can be considered the starting point for the development of agents for the selective detection of αvβ3 expression by SPECT.

S5-05

The past, present and future trends in radiopharmaceuticals production in Brazil

Author: Efrain Araujo Perini

Co-author(s): Sofia Nascimento Santos; Emerson Soares Bernardes; Elaine Bortoleti de Araujo; Vanessa Gomes Batista; Jair Mengatti

Nuclear and Energy Research Institute (IPEN), Brazilian Nuclear Energy Commission (CNEN), Brazil

Corresponding author: ebaraujo@ipen.br

The origins of the Nuclear and Energy Research Institute (IPEN), formerly known as the Institute of Atomic Energy (IEA), date back to the 30's with the coming of European teachers to the University of São Paulo (USP) that generated the Physics section of the Faculty of Philosophy, Sciences and Letters. The confluence of interests between the National Council for Scientific and Technological Development (CNPq) and USP, together with the donation of a nuclear research reactor by the Atoms for Peace Program, made possible the creation of the IEA of the Faculty of Physics of USP in 1956. In 1959, IPEN, through its former Department of Radioactive Material Processing, pioneered the experimental production of ^{131}I radioisotope for medical application in Brazil. With the growing interest in the nuclear medical community, in 1961, IPEN started to produce ^{42}K and ^{51}Cr radioisotopes. Over the years the demand for radioisotopes grew and in 1976 the Radiopharmacy Center (CR) was inaugurated to exclusively house the production and quality control of radioisotopes and labelled molecules. By the end of 1980, IPEN embraced the technological advancement and began the distribution of technetium generators in parallel with a growing number of freeze-dried kits for the diagnosis of several diseases. The acquisition of the Cyclone 30-IBA (1998) and CV-18-IBA (2008) and cyclotrons allowed the production of ^{123}I and ^{18}F radioisotopes and the preparation of the ^{18}F-FDG radiotracer (the gold standard radiotracer for cancer diagnosis).

Currently, IPEN stands out in the Latin America and the Caribbean for providing the highest number of radiopharmaceuticals that account for more than 1.7 million procedures per year in the nuclear medicine clinics. The CR supplies 13 lyophilized kits for labelling with ^{99m}Tc, the technetium generator and 18 ready-to-use radiopharmaceuticals for diagnostic and therapeutic purposes all over Brazil.

IPEN is presently enrolled in the creation of conditions to face up what society needs for new radiopharmaceuticals by implementing a number of initiatives in order to boost innovation. Among them, CR is pursuing active research and development aiming for radiopharmaceuticals to reach market deployment and, has settled the goal to attract and involve young people in the field, ensuring the transfer of knowledge associated with decades of radiopharmaceuticals development. Moreover, the Brazilian Multipurpose Reactor (RMB) Project, will certainly impact the radiopharmacy allowing Brazil to be self-sufficient in the production of radioisotopes, such as molybdenum-99, which are nowadays imported and depended on the foreign market and exchange rate fluctuation.

Here we provide an overview of the past achievements, the present state of radiopharmacy and the future milestones we identified to encourage young generations and universities to engage in the radiopharmaceutical production activity. We expect IPEN to keep expanding the knowledge, use and access of nuclear medicine, providing a better quality of life, to the Brazilian population.

S6. Production of radiopharmaceuticals: Therapy

S6-01

Production and quality control of bone pain palliation agents using β-emitters

Author: M.R.A. Pillai

Molecular Cyclotrons, Puthuvype, Ernakulam, Kerala, India

Corresponding author: pillai.m.r.a@gmail.com

Palliative care is an important aspect of cancer management. Bone metastasis is a major problem in lung, breast and prostate cancers. The major pain for terminally ill cancer patients is due to bone metastasis. Doctors try to improve the quality of life through palliative care. Opioid drugs are used for this purpose and have severe side effects. The use of bone seeking radiopharmaceuticals labelled with β- particles that irradiate and destroy the cancer cells is effective to reduce the pain due to bone metastasis.

Phosphorus-32 as sodium phosphate and strontium-89 as chloride were the first radiopharmaceuticals to be used for metastatic bone pain palliation. Despite having differing nuclear characteristics both the radiopharmaceuticals were found effective to reduce pain. The mechanism of action of these radiopharmaceuticals is based on the inherent property of the two elements to accumulate in bone. The production as well as the quality control of these tracers is straight forward as they are used as inorganic salts and are highly stable.

Beta particles emitting radiometals complexed with bone seeking chelating agents was a novel idea introduced by the scientists at the University of Missouri-Columbia. Over a dozen β- emitting radionuclides are tried for this purpose. Table 1 gives a limited list of bone pain palliation agents reported of which some are clinically tested. One important point to note is that the characteristics of these radionuclides vary significantly both in half life and in energy. ^{188}Re with 17-hour half-life to ^{90}Sr with half-life of 50 days is found effective. So is the case with energy of the β- particles, ^{188}Re emits high energy β- particles whereas ^{90}Sr is a medium energy β- emitter. Use of low energy β- emitters are preferred to reduce the bone marrow dose which is a limiting factor in the amount of radioactivity that can be administered.

^{153}Sm-EDTMP is a FDA approved radiopharmaceutical which is widely used and effective. ^{153}Sm can be prepared in medium flux reactors by irradiating enriched ^{152}Sm targets. Despite the logistical disadvantage of the short half-life of 46 hours, ^{153}Sm-EDTMP is available in many countries. IAEA took the initiative for the clinical implementation of ^{177}Lu-EDTMP through a coordinated research project and this product is successfully used in a few countries. The major advantage of this product is the 6.7 d half-life of ^{177}Lu and the ease of its production in large quantities by irradiating enriched ^{176}Lu targets in medium flux reactors.

The production and quality control of the radiometal based bone pain palliating agents are straight forward. Relatively large excess of the chelating agent is used and hence the products formed are stable over extended periods of time. Simple chromatographic methods such as paper and thin layer chromatography are sufficient to establish the radiochemical purity of the products.

Bone pain palliation therapy using radiopharmaceuticals has not realized its full potential despite the option of having several products.

Table 1. List of the radionuclides used for preparation bone pain palliation agents

Radionuclide	**Half-life in days**	**β- Energy in keV (%)**	**γ energy in keV (%)**	**Production**	**Chemical form used**
Rhenium-188	0.7	2120 (71.1) 1965 (25.6)	155 (14.9)	$^{188}W/^{188}Re$ Generator	^{188}Re-HEDP
Samarium-153	1.9	808 (17.5) 705 (49.6) 635 (32.2)	103 (28.3)	$^{152}Sm(n,\gamma)^{153}Sm$	^{153}Sm-EDTMP
Lutetium-177	6.7	498 (78.6) 176 (12.2)	208 (11.0) 113(6.4)	$^{176}Lu(n,\gamma)^{177}Lu$	^{177}Lu-EDTMP ^{177}Lu-DOTMP
Phosphorus-32	14.3	1711 (100)	nil	$^{32}S(n,p)^{32}P$	$Na_3{}^{32}PO_4$
Strontium-89	50.5	1497 (100)	Nil	$^{88}Sr(n,\gamma)^{89}Sr$ $^{89}Y(n,p)^{89}Sr$	$^{90}SrCl_2$
Thulium-170	128.6	968 (81.6) 883 (18.3)	84(3.26)	$^{169}Tm(n,\gamma)^{170}Tm$	^{170}Tm-EDTMP

S6-02

Comparison of promising new short-range therapeutic radiopharmaceuticals using ^{225}Ac, ^{213}Bi and ^{161}Tb

Author: Jan Rijn Zeevaart[1]

Co-author(s): Mike Sathekge[2]; Thomas Ebenhan[2]; Nick Van der Meulen[3]; Cristina Mueller[3]

[1]Necsa, Radiochemistry, South Africa
[2]University of Pretoria and Steve Biko Academic Hospital, Nuclear Medicine, Pretoria, South Africa
[3]Center of Radiopharmaceutical Sciences, Paul Scherrer Institute, Villigen-PSI, Switzerland

Corresponding author: zeevaart@necsa.co.za

Prostate-specific membrane antigen is a prominent imaging biomarker in nuclear medicine. With Gallium-68 (^{68}Ga) opportunely available to hospital radiopharmacies we recently developed a PSMA11 single kit vial radiolabelling solution which is now routinely used in the Steve Biko Academic hospital in Pretoria, South Africa. The most widely used therapeutic pendant for ^{68}Ga is ^{177}Lu but recent advances in radionuclide production methods have made ^{225}Ac, ^{213}Bi and ^{161}Tb available as alternatives to ^{177}Lu. This created interesting opportunities to treat metastases with the short-range Alpha or Auger and conversion electron emissions.

^{225}Ac is a very promising radionuclide for targeted alpha therapy. With its relatively long half-life (9.9 d) it has enough time to target also less-easily accessible tumours, and the 4 emitted alphas in the decay chain ensure effective cell killing once at the targeted site. ^{225}Ac is produced by radio-chemical extraction from ^{229}Th at the Institute for Transuranium Elements, Karlsruhe, Germany. In a recent study by the Sathekge group in Pretoria, [^{225}Ac]Ac-PSMA-617 radioligand therapy of chemotherapy-naïve patients with advanced metastatic prostate carcinoma led to a ≥ 90% decline in serum PSA in 82% of patients including 41% of patients with undetectable serum PSA who remained in remission 12 months after therapy.

In contrast the radioactive decay of ^{213}Bi (T½= 46 min) results in the emission of two high-LET α-particles releasing around 100 keV/µm. Due to the relatively short half-life of ^{213}Bi, it can deliver a high radiation dose to the target within a short period of time. ^{213}Bi is eluted from ^{225}Ac/^{213}Bi Generator (ITG, Munich, Germany). In a recent study by the Sathekge group in Pretoria a first-in- human treatment with [^{213}Bi]Bi-PSMA-617 in a patient with mCRPC that was progressive under conventional therapy, was undertaken. The patient was treated with two cycles of [^{213}Bi]Bi-PSMA- 617 and restaging with [^{68}Ga]Ga-PSMA PET/CT after 11 months showed a remarkable response w.r.t. soft tissue metastases.

The use of these short-range emitters does not go without challenges that will have to be overcome. Upon emission of an alpha particle, the daughter nuclide experiences a recoil energy which is several orders of magnitude larger than the energy of the chemical bond of the nuclide resulting in the daughter to be released from the targeting vector.

Terbium is a unique element, as it provides a quadruplet of radionuclides suited for diagnostics and therapy in nuclear medicine. ^{161}Tb (Auger/conversion electron and β–emitter, T1/2 = 6.9 d) was produced by neutron irradiation of enriched ^{160}Gd in the SAFARI-1 research reactor from which no-carrier-added ^{161}Tb was produced. In a recent study by the Müller group in Villigen-PSI, [^{161}Tb]Tb- PSMA-617 showed superior in vitro and preclinical in vivo results as compared to [^{177}Lu]Lu-PSMA- 617 confirming theoretical dose calculations with regard to a positive effect of conversion and Auger electrons.

The various options & pros and cons for these three radionuclides/radiopharmaceuticals will be discussed.

S6-03

Freeze-dried kit for quick and efficient preparation of ^{188}ReN-DEDC/lipiodol in hospital radiopharmacy

Author: Viju Chirayil[1]

Co-author(s): Madhava B Mallia[1]; Ashutosh Dash[1]

[1]Bhabha Atomic Research Centre, India

Corresponding author: vijuc@barc.gov.in

^{188}ReN-DEDC/lipiodol (DEDC – diethyldithiocarbamate) is a clinically established agent for the therapy of unresectable hepatocellular carcinoma (HCC). The original two-vial method for the preparation of ^{188}ReN-DEDC/lipiodol involved compulsory addition of stipulated amount of glacial acetic acid (GAA), which was cumbersome in a busy radiopharmacy. Moreover, an error in glacial acetic acid volume had significant impact on overall yield of ^{188}ReN-DEDC complex. Herein, we present a two-vial kit for quick, efficient and glacial acetic acid free preparation of ^{188}ReN- DEDC/lipiodol.

Sterile two-vial freeze-dried kits, vial 1 containing N-methyl-S-methyl dithiocarbazate (DTCz) (2 mg), SnCl2.2H2O (0.8 mg), oxalic acid (28 mg), sodium ascorbate (10 mg) and vial 2 containing DEDC (100 mg), were prepared in a clean room facility. In the first step, ^{188}ReN-core was prepared by adding freshly eluted sodium perrhenate (1-5 mL, ~3700 MBq), obtained from a tungsten-188/rhenium-188 generator, into kit vial 1. Vial 1 was gently shaken to dissolve the contents and incubated at room temperature for 5 min. In the second step, kit vial 2 was reconstituted with 2 mL of physiological saline. About 1 mL of the reconstituted solution was transferred into kit vial 1. Subsequently, vial 1 was sequentially incubated at room temperature for 15 min, at 65°C for 5 min and then cooled to room temperature. To extract ^{188}ReN-DEDC complex, lipiodol (2-3 mL) was added into kit vial 1 and the contents are mixed for 10 min. Clear separation of two layers was achieved by centrifugation of vial 1 at 1600g for another 10 min. Subsequently, lipiodol layer containing ^{188}ReN-DEDC was carefully separated for further use. The quality control of ^{188}ReN-DEDC/lipiodol was carried out by TLC in dichloromethane. Developed strip was analysed on a TLC scanner and radiochemical purity (RCP) was determined from peak area measurements.

The use of GAA reported in the original method of preparation of ^{188}ReN-DEDC complex was avoided by including oxalic acid/sodium ascorbate combination to provide an acidic environment conducive for ^{188}ReN formation. This modification also brought significant reduction in time required for patient dose preparation. Presence of ascorbate provided an additional protection from possible radiolytic damage to ^{188}ReN core as well as ^{188}ReN-DEDC complex. Using kit vial 1, ^{188}ReN-core could be consistently prepared in quantitative yield within 5 minutes. Upon addition of the constituents from kit vial 2 following the recommended procedure, ^{188}ReN-DEDC complex could be prepared in >85% yield. It was observed that >99% of ^{188}ReN-DEDC complex could be extracted into lipidol phase in the first attempt itself. Quality control of the lipiodol phase confirmed absence of perrhenate.

In conclusion, the two-vial freeze-dried kit presented here offer a quick and efficient way for the preparation of ^{188}ReN-DEDC/lipiodol in a hospital radiopharmacy setup and allows the use of up to five ml of radioactive solution, making a step forward from the original method in terms of ease of patient dose preparation as well as effective utilization of the ^{188}W-^{188}Re generator.

S6-04

Production of theranostic ^{153}Samarium-labelled polystyrene microparticles for hepatic radioembolization

Author: Chai Hong Yeong[1]

Co-author(s): Yin How Wong[1]; Hun Yee Tan[1,2]; Azahari Kasbollah[3]; Basri Johan Jeet Abdullah[4]

[1]School of Medicine, Taylor's University, Selangor, Malaysia
[2]Medical Radiation Surveillance Division, Ministry of Health, Malaysia
[3]Malaysian Nuclear Agency, 43000 Bangi, Selangor, Malaysia
[4]University of Malaya Medical Centre, Kuala Lumpur, Malaysia

Corresponding author: chaihong.yeong@taylors.edu.my

Hepatic radioembolization is a minimally invasive procedure involving intraarterial administration of radioembolic microparticles for the treatment of liver tumours. A biocompatible polystyrene (PS) microparticles containing Samarium-153 (^{153}Sm) were developed for hepatic radioembolization therapy. The incorporation of ^{153}Sm that possessed both diagnostic gamma energy and therapeutic beta radiation has made it a theranostic radioembolic agent for hepatic radioembolization.

The ^{152}Sm-labelled PS microparticles were prepared using solid-in-oil-in-water solvent evaporation method. The ^{152}Sm-labelled PS microparticles were neutron activated to ^{153}Sm ($E_{\beta max}$ = 807.6 keV, half-life= 46.3 hours) through ^{152}Sm(n,γ)^{153}Sm reaction in a nuclear reactor with a neutron flux of 2.0×10^{12} n.cm^{-2}.s^{-1}. Physicochemical characterization of the microparticles, gamma spectrometry and in vitro radiolabeling studies were performed to study the performance and stability of the microparticles before and after neutron activation.

The ^{153}Sm-labelled PS microparticles achieved a nominal activity of 4.0 Gbq.g^{-1} after 6 hours neutron activation. Scanning electron microscope and particle size analysis suggest the microparticles remained spherical with the diameter within 15–60 µm after neutron activation. No long half-life radionuclide impurities were found in the samples as indicated by gamma spectrum of the microparticles. The ^{153}Sm-labelled PS microparticles was found to have a radiolabeling efficiency of more than 95% in saline and blood plasma over 480 hours.

The favorable microparticles and radiation characteristics along with excellent radiolabeling efficiency have rendered the ^{153}Sm-labelled PS microparticles as potentially theranostic agent for hepatic radioembolization. This study described a safer method to prepare the microparticles for hepatic radioembolization as the preparation does not involve any harmful ionizing radiation.

S6-05

Radiolabelling and pre-clinical evaluation of Y-90-DOTATATE - formulated using Y-90-Acetate from high level liquid waste

Author: Avik Chakrabotry[1]

Co-author(s): Arpit Mitra[2]; Sangita Lad[1]; Sujoy Gaikwad[1]; Megha Tawate[1]; Sudeep Sahu[1]; Trupti Upadhye[1]; Sreeja Menon[1]; Sharmila Banerjee[2]

[1]Radiation Medicine Centre, BARC, Mumbai, India
[2]Medical Cyclotron Facility, RMC, BRIT, Mumbai, India

Corresponding author: avikbarc@gmail.com

The effectiveness of Y-90-DOTATATE as a therapeutic radiopharmaceutical for Peptide Receptor Radionuclide Therapy (PRRT) in treatment of large volume neuroendocrine lesions is well established. The high energy of β-particle emission (Emax: 2.28MeV) is suitable for treatment of neuroendocrine lesion with diameter of 5cm and more. The challenges involved in the formulation of this radiopharmaceutical is the purity of the radiochemical(Y-90-Chloride/Y-90-Acetate) used, which in turn necessitates the cost-effective extraction in clinical grade, from high level liquid waste (HLLW). Towards this, Y-90-Acetate was sourced from HLLW based on supported liquid membrane (SLM) technology. Isolated Y-90-Acetate complies with the regulatory requirement with respect to its use as a clinical grade API. This Y-90-Acetate was used in radiolabelling DOTATATE and the radiopharmaceutical was evaluated on in-vitro cell-binding and in in-vivo biodistribution studies in a suitable animal model. The present work documents the effort towards developing indigenous cost- effective Y-90-based radiopharmaceutical for PRRT of neuroendocrine tumours.

Clinical grade Y-90-Acetate sourced from two-stage Sr-90/Y-90 generator based on SLM technology. The formulation of Y-90-DOTATATE was carried out using Y-90-Acetate, 0.2N ammonium-acetate buffer(pH~5.5) and DOTATATE. The reaction mixture was incubated at 95degC for 35minutes at pH~4.0. On cooling, 60mg of gentisic acid/mL of saline was added. RCP assessed by TLC-SG {(0.1M sodium-citrate buffer(pH-5.0)} and HPLC using RP18 with gradient (0.1%TFA in water and acetonitrile). Gel-clot BET-assay and Sterility test were performed. In-vitro and serum-stability of the product on storage at -20degC was evaluated by TLC/HPLC at 24h and 48h post radiolabelling.

Pancreatic carcinoma cell-line AR42J was used for in-vitro evaluation, and it was grown in IMDM with 10%FBS at 37°C. In-vitro cell-binding was performed by incubating AR42J cells in 1mL of internalization buffer containing radioligand (~5pmol peptide) for 15, 30, 60 and 120minutes and washed with PBS. For membrane receptor binding assay, AR42J cells homogenates were incubated for above time points. Biodistribution studies carried out in AR42J cell-line xenograft tumour bearing nude mice at 6h, 24h, 48h & 72h intervals and quantified by β-spectrometer.

Using pharmaceutical-grade Y-90, formulation of 50-55 mCi of Y-90-DOTATATE prepared. Y-90- DOTATATE was clear, pale-yellow color, pH between 5.0-5.5. RAC between 8-12 mCi/mL. RCP of Y- 90-DOTATATE estimated by TLC was >98% with retention-factor 0.0-0.1. RCP derived by HPLC was >98% with retention-time of radioactive-chromatogram between 10.4-11.4minutes. EL was <6EU/mL, radiopharmaceutical was sterile. In-vitro and serum stability of the product indicated stability up to 48hrs upon storage at -20°C with stabilizer.

Y-90-DOTATATE showed rapid binding (30%) in AR42J cells, reaching a plateau after 15-30minutes. In a biodistribution study, radioactivity in the blood and most of the organs decreased after 24h post-injection. High-uptake and long-term retention of radioactivity were found in the kidney (8.01% ID/gm) and tumour (3.17% ID/gm) which corroborates scintigraphy studies.

In conclusion, the Y-90 isolated from HLLW has been approved as a clinical grade radiochemical. This has been utilized in the formulation of patient doses of Y-90-DOTATATE, and used in the treatment of large NET lesions. This development offers an affordable treatment option to many patients.

S7-A: Production of radiopharmaceuticals: PET

S7-A1

Recent advances in the development of ^{18}F and ^{11}C radiopharmaceuticals

Author: Philip H. Elsinga

University Medical Center Groningen, University of Groningen, The Netherlands

Corresponding author: p.h.elsinga@umcg.nl

PET-studies with short-lived ^{11}C and ^{18}F-radiopharmaceuticals offer advantages of low radiation burden for patients and option for repeated PET-studies. Moreover, using ^{11}C, the (bio)chemical properties of the molecules often do not change, whereas with ^{18}F steric effects of the radionuclide on pharmacological properties of radiopharmaceuticals is very small. A substantial number of ^{11}C- and ^{18}F radiopharmaceuticals have proven its clinical value with [^{18}F]FDG being the real work horse tracer for PET.

The number of radiopharmaceuticals used in humans is continuously growing with a tendency to shift from ^{11}C- to ^{18}F-radiopharmaceuticals enabling transportation to PET-sites without a cyclotron and radiochemistry lab.

Besides the increasing number of radiopharmaceuticals, also the production methods improve and expand. For production of ^{11}C-radiopharmaceuticals, the ^{11}C-methylation route is the most used method, but some other routes including use of [^{11}C]CO become more easily available. For ^{18}F-production, several late stage ^{18}F-fluorination procedures have progressed enormously.

During the presentation, new emerging ^{11}C and ^{18}F radiopharmaceuticals and production methods are highlighted.

S7-A2

Recent advances in the development of Ga-68 radiopharmaceuticals

Author: C. Decristoforo

Medizinische Universität Innsbruck, Austria

Corresponding author: Clemens.Decristoforo@tirol-kliniken.at

The worldwide interest in ^{68}Ga-radiopharmaceuticals was initiated by the clinical success of ^{68}Ga-Somatostatin analogues in the context of theranostics and the availability of ^{68}Ga from generators becoming commercially available. Automated synthesis procedures and modules were established enabling routine clinical production. An additional advancement was reached by the establishment of ^{68}Ga-PSMA11 in clinical routine. A number of alternatives to PSMA 11 have been developed and will be presented, Somatostatin antagonists have the potential to improve established PET imaging with ^{68}Ga. Besides that, a number of other targets have been investigated and in particular peptide based ^{68}Ga-radiopharmaceuticals enter the clinical area. Among the most promising candidates are Bombesin antagonists targeting the GRP receptor, RGD containing peptides targeting integrins, peptides targeting CXCR4 and most recently FAPI-analogues binding to cancer associated fibroblasts. Preparation is shifting from automated procedures to kit-based preparation also with the availability of generators with marketing authorisation.

S7-A3

Synthesis and in vitro and in vivo evaluation of iodine-124-labelled PSMA peptides: Potential theranostic radiopharmaceuticals for prostate cancer

Author: Ibrahim Aljammaz

Co-Author(S): Abdulrahman Alrabiah; Basim Alotaibi; Faisal Alrumayan; Subhani Okarvi

King Faisal specialist hospital & research centre, Saudi Arabia

Corresponding author: jammaz@kfshrc.edu.sa

Receptor-targeted radiopharmaceuticals have shown promises in the improvement of the specificity and sensitivity of nuclear medicine imaging and therapy procedures. The prostate specific membrane antigen (PSMA) is a transmembrane protein with significantly elevated expression in prostate cancer (PCa) cells compared to benign prostatic tissue. Several radiotracers have been used for molecular imaging of PCa including choline as a marker of membrane cell proliferation. However, there have been numerous studies reporting a low sensitivity and specificity of these radiotracers. Therefore, different gallium-68 and fluorine-18 PSMA-targeted PET tracers have been developed, utilized and demonstrated a high diagnostic efficacy. However, the short half-life of these radiotracers may limit distribution to distant imaging centres.

Thus, as part of our on-going research effort to develop theranostic radiopharmaceuticals, we here report the synthesis and preclinical evaluation of new $^{123/124/131}$I-PSMA conjugates. The synthetic approaches for the preparation of [$^{123/124/131}$I]iodobenzene and pyridine rhodamine conjugates entailed sequence of reactions. The key precursors N-hydroxysuccinimide 3-tri-n-butylstannyl- benzoate and 3-tri-n-butylstannyl-pyridine carboxylate were radioiodinated using classical method involving 0.1% acetic acid/methanol, iodogen and NaI ($^{123/124/131}$I, 50 MBq) at room temperature. The N-succinimidyl-p-[I]-iodobenzoate ([$^{123/124/131}$I]-SIB) and N-succinimidyl-m-[I]-iodopyridine carboxylates ([$^{123/124/131}$I]-SIP) were purified using Sep-pak silica cartridge. PSMA peptide was then reacted with [$^{123/124/131}$I]-SIB and [$^{123/124/131}$I]-SIP, then purified using C-18 Sep-pak cartridge to furnish [$^{123/124/13}$I]-SIB- and [$^{123/124/131}$I]-SIP-PSMA peptide conjugates. Radiochemical yields were >75% and synthesis times were ~45 min. Radiochemical purity was always >99% without HPLC purification. The metabolic stability of [$^{123/124/131}$I]-SIB- and [$^{123/124/131}$I]-SIP- PSMA peptide conjugates were determined in human plasma and revealed that these radioconjugates remained stable during incubation at 37^{o}C for at least 24 h. In vitro tests on LNCaP cell line has shown that the significant amount of the radioconjugate associated with cell fractions. In vivo characterization in normal Balb/c mice revealed rapid blood clearance of these radioconjugates with excretion predominantly by the renal system. Initial in vivo biological characterizations in nude mice bearing LNCaP cell line xenografts, demonstrated significant tumour uptake. The uptake in the tumours was blocked by excess injection of PSMA peptide, suggesting a receptor-mediated process. These results demonstrate that these radioconjugates may be useful as precise theranostic radiopharmaceuticals for PSMA receptor-positive cancers and their metastasis. However, further evaluation is warranted.

S7-A4

A radio-copper somatostatin analog (Cu-Sartate) for NET (neuroendocrine tumours) theranostics

Author: Vijay Kumar

Sydney Medical School, University of Sydney, Australia

Corresponding authors: vijay.kumar@health.nsw.gov.au

Radiolabelled ^{68}Ga-DOTAOctreotate or ^{68}Ga-DOTATATE was very effective PET-imaging agent for NETs and have quickly became the gold standard for diagnosis and staging of NETs. However, due to the short half-life (68min) of ^{68}Ga, there were several limitations. Therefore, ^{64}Cu was sought for this project, as its half-life is sufficiently long enough (12.7 hours) to capture the clearance kinetics required for personalized dosimetry and therapy.

Clarity Pharmaceuticals Pty Ltd (Clarity) developed ^{64}Cu-SARTATE as a PET radio-diagnostic agent for the localization of SSTR-positive NETs and "dosimetry planning" for personalized Peptide Receptor Radionuclide Therapy (PRRNT). ^{64}Cu-SARTATE was ^{64}Cu-labeled MeCOSar-Tyr3-octreotate. ^{64}Cu-SARTATE has 3 basic components; copper-64, a pure ß emitting radiometal linked via MeCOSar (a bifunctional copper chelator) to octreotate, a somatostatin analogue that targets SSTRs 2 & 5. Clarity also developed ^{67}Cu-SARTATE as a PRRNT for treatment of NETs.

^{64}Cu-SARTATE was formulated as a liquid, sterile, apyrogenous preparation. The radiochemical purity estimated by HPLC is NLT (not less than) 90% and the Radiochemical Purity by TLC was NLT 95%. Radionuclidic Purity (Gamma spec, %) was reported as 99% ^{64}Cu. Incubation of ^{64}Cu-SARTATE (radiochemical purity >99%) with fresh human serum demonstrated high metabolic stability. HPLC analysis indicated that >90% radioactivity in the non-protein bound fraction at 30mins, 1hr, 2hrs, & 24hrs was still chelator-bound representing intact radio-peptide and indicating no loss of copper or appreciable metabolic decomposition. The biodistribution of ^{64}Cu-SARTATE was investigated in tumour-bearing Balb/c nude mice. The biodistribution data was compared against ^{68}Ga-DOTATATE (data not shown). Both ^{64}Cu-SARTATE and ^{68}Ga-DOTATATE demonstrated effective blood clearance at 2 hours (0.8 ± 0.2 %ID/g and 0.1 ± 0.03 %ID/g, respectively) with further clearance shown by ^{64}Cu-SARTATE at 24 hours (0.4 ± 0.04 %ID/g, $p < 0.05$). Uptake in the liver and kidneys was higher for ^{64}Cu-SARTATE at the 2 hour time point as compared to ^{68}Ga-DOTATATE, 6.3 ± 1.5 %ID/g and 0.4 ± 0.05 %ID/g respectively. Uptake of ^{64}Cu-SARTATE in the kidneys was moderate at 2 hours (70.9 ± 5.78 %ID/g), and fell by 53% to 33.6 ± 6.8 %ID/g at 24 hours ($p < 0.05$) indicating effective clearance.

Pre-clinical biodistribution and micro-PET imaging studies indicate ^{64}Cu-SARTATE displays favourable kinetic and in-vivo stability properties of particular importance to diagnostic radiopharmaceuticals. Phase 1 first in human imaging study of ^{64}CuSARTATE showed high safety profile, excellent clearance, biodistribution, and diagnostic efficacy. The half-life of ^{64}Cu is also well suited to capture the clearance kinetics required for personalized than PRRNT dosimetry. In addition, the advantages of ^{64}Cu extend to also include logistical advantages such as centralized manufacture, GMP processes and costings that can be sufficiently lowered to become competitive once industrialized. Cu-67 Sartate was used to study biodistribution and dosimetry in patients with Meningioma. The preliminary observation was very encouraging as it localised in the lesions which are consistent with the biodistibution of Cu-64 Sartate in these patients.

S7-A5

Comparative study of [^{18}F]PSMA-1007and [^{68}Ga]PSMA-11 for prostate cancer PET imaging in Thailand

Author: Chanisa Chotipanich

Co-author(s): Jiradanai Sarasamkan; Natphimol Boonkawin; Wisakha Chintawan; Jiratthakorn Keeratipiriyakul; Nuttiya Usaha; Pannawattana Lertveerakun; Pattanapong Kongsakorn; Sukanya Yaset

National Cyclotron and PET Centre, Chulabhorn Hospital, Chulabhorn Royal Academy, Thailand

Corresponding author: chanisa.ja@gmail.com

In Thailand, PET/CT is a new technology of nuclear medicine with high efficacy for cancer diagnosing, measuring response to treatment, and guiding radiation therapy. With the advantages of PET/CT, physicians are able to accurately make treatment planning for each cancer patient toward the improved quality of life and longer survival. National Cyclotron and PET Centre was established at Chulabhorn Hospital following the aspirations of Prof. Dr. HRH Princess Chulabhorn Mahidol to serve as the first national center to produce radiopharmaceuticals in cancer research and development of new treatment modalities.

Currently, radiolabelled tracers targeting prostate-specific membrane antigen (PSMA) have become the important radiopharmaceuticals for PET-imaging of prostate cancer. The first PSMA-based radioligand in Thailand is [^{68}Ga]PSMA-11 produced by ^{68}Ge/^{68}Ga generator and a manual synthesis module, supplied by Isotope Technologies Garching (ITG). During the period of a generator, about 200 batches of [^{68}Ga]PSMA-11 should be prepared with the product stability of only 4 hours. In addition, the maximum activity is sufficient for only 3 patients at the beginning and lower at the later batches. Whereas, there is limited production capacity given by ^{68}Ga generator. In contrast, [^{18}F]PSMA-1007 from cyclotron has a longer half-life and demonstrates higher yield of activity, with outstanding tumour uptake and better diagnostic efficacy when compared to [^{68}Ga]PSMA-11. Hence, it is likely that [^{18}F]PSMA-1007 can possibly be an alternative tracer to replace [^{68}Ga]PSMA-11.

The radiosynthesis of [^{68}Ga]PSMA-11 was carried out by using ITG manual synthesis module and disposable cassettes. $^{68}GaCl_3$ from generator in 0.05 M HCl and PSMA-11 precursor in 0.25 M sodium acetate buffer were labelled at 105°C for 5 minutes, followed by the purification of a C18 cartridge and collection through a 0.22µm sterile filter. Whilst, the radiosynthesis of [^{18}F]PSMA-1007 was done on ORA NEPTIS® performed using disposable cassettes. ^{18}F from cyclotron was trapped on the QMA and eluted by 0.075 M TBAHCO3 to the reactor for radiolabelling with PSMA-1007 precursor in DMSO, followed by the purification through a series of PS-H+ and C18ec cartridges. Then, [^{18}F]PSMA-1007 passed through 0.22µm sterile filter to final product vial.

The radiosynthesis of [^{68}Ga]PSMA-11 achieved in 15 minutes with radiochemical yield of 74.69% (n=32) and maximum activity of 32.9 mCi. The radiochemical purity (RCP) was >95% for only 4 hours. Whereas, [^{18}F]PSMA-1007 was achieved in 45 minutes with a radiochemical yield of 56.64% (n=10). The obtained activity was enough for at least 8 patients and the maximum depended on the cyclotron irradiation time. The radiochemical purity was >95% for 8 hours. Additionally, PET/CT imaging of [^{18}F]PSMA-1007 showed higher uptake in liver and better lymph node pathology. Moreover, the non-urinary background overcame some limitations of [^{68}Ga]PSMA-11.

[^{18}F]PSMA-1007 possesses longer half-life than [^{68}Ga]PSMA-11 with high radiochemical yield and more accurate diagnostics, which can serve to other PET/CT centres. As a result, more patients have more chances to access effective diagnosis and better opportunity towards the improved quality of life and longer survival.

S7-B: Clinical advances in nuclear medicine

S7-B1

IAEA activities related to nuclear medicine

Author: Diana Paez

IAEA, Vienna, Austria

Corresponding author: D.Paez@iaea.org

The long-term objective of the subprogram in Nuclear Medicine focuses on enhancing Member States' capability to address health needs by the use Nuclear Medicine techniques in both imaging and therapeutic applications, complementary to conventional techniques.

Different activities are run under this subprogram: Coordinated Research Projects (CRPs); Expert Meetings to advise the Agency on specific topics; Publications and Manuals, including educational material, and creation of educational website and databases. Many projects run under Nuclear Medicine have been clearly oriented towards the clinical applications of standard and emerging technologies in Nuclear Medicine such as SPECT/CT, PET/CT for diseases related to two of the major causes of death: cancer and cardiovascular diseases. Focus is also given to therapeutic applications wherein the primary objective is to make available fundamental radiopharmaceuticals for routine clinical use in developing countries, and to develop, evaluate and standardize new diagnostic and therapeutic radiopharmaceuticals for the effective use in diagnostic and therapeutic nuclear medicine procedures. Finally, the section manages projects related to quality improvement in the clinical practice of nuclear medicine.

The IAEA supports the dissemination of quality education and strives to produce pertinent literature to better the application of nuclear medicine techniques as part of the clinical management of many diseases.

S7-B2

Recent advances in nuclear medicine: Diagnosis and therapy

Author: Homer A. Macapinlac
Co-author: Dao Le

Department of Nuclear Medicine, UT MD Anderson Cancer Center, Houston, TX USA

Corresponding author: jwmaxwell@mdanderson.org

The recent advances in the treatment of cancer patients have had imaging as a cornerstone of staging and response evaluation. Recent advances in nuclear medicine with hybrid imaging with FDG PET/CT and SPECT/CT has allowed more accurate staging and response evaluation. The multidisciplinary care of oncology patients is now supplemented by the availability and insurance coverage in the USA of theranostic agents. We will review the most frequently used diagnostic and therapeutic tracers, including applications for thyroid cancer, neuroendocrine tumours and prostate cancer. We will highlight the effect of these radio pharmaceuticals on improving disease free progression and overall survival. We will also focus on current ongoing theranostic trials to demonstrate the promising future of these diagnostic and therapeutic pairs. These advances depend of reliable clinical production of these radio pharmaceuticals which have become a valuable weapon in the effort to effectively select and treat cancer patients worldwide.

S7-B3

Production & use of cyclotron-produced radiopharmaceuticals UT MD Anderson Cancer Center

Author: Dao Le

Co-Author: Homer Macapinlac

Department of Nuclear Medicine, UT MD Anderson Cancer Center, Houston, TX USA

Corresponding author: dble@mdanderson.org

The University of Texas MD Anderson Cancer Center (UT MDACC) Cyclotron Radiochemistry Facility (CRF) is a unique facility dedicated to the production of radioistopes and radiopharmaceuticals for both research and standard patient care. Located in the Texas Medical Center in Houston, Texas; this facility is equipped with a 16 Mev Cyclotron, Nuclear Pharmacy, 34 Hot & Warm cells, 4 GMP Manufacturing Suites, 3 Development Hot Labs, a Microbiology Lab, Pk Lab, and a 2400 square foot development and analytical lab space. The CRF is located across the hall from an imaging clinic which is equipped with PET/ CT, MRI, SPECT/CT, and Hyper-Polarizer. The short distance between the GMP manufacturing facility, the radiopharmacy and imaging facility enables the utilization of short lived isotopes such as C-11 and N-13 for both research and patient care. The CRF team prepares and dispenses radiopharmaceuticals for standard of care such as Ga-68 DOTATATE, C-11 Choline and F-18 FDG, but the mission is to provide investigational radiopharmaceuticals for research use. The function of the CRF is to provide the full spectrum of development, analytical, and manufacturing services to take a radiopharmaceutical from a novel compound to an approved drug. We refer to this full process as Bench to Bedside: radioisotope production, preclinical radiopharmaceutical development, investigational new drug (IND) development and radiopharmaceutical validation.

The current focus of the MDACC CRF team is the project involving cyclotron produced ^{68}Ga. The team has successfully produced more than 1 Curie of Ga-68-chloride in a single run. This development has led to multiple innovations at the facility, including the development of fully-automated Ga-68-PSMA-11 production method. In the accepted publication, we reported the Ga-68-PSMA-11 in curie quantities that can be routinely produced. Additionally, in that publication, we demonstrated biological equivalence of PSMA-11 labelled by either generator- or cyclotron-produced ^{68}Ga. We have successfully filed a DMF for our cyclotron generated ^{68}Ga.

The future focus for the MDACC CRF is on the production of theranostic radiopharmaceuticals therefore we are building a partnership with Texas A&M University, Cyclotron Institute. Because Texas A&M Cyclotron Institute has a large cyclotron capacity, a strong nuclear physics program for target design and the CRF at MDACC has expertise in target processing and isotope purification, the joint effort is conducive for the investigation into cost-efficient procedures for producing “theranostic pairs”. The spotlight is on the production of medically important isotopes such as ^{209}At/^{211}At, ^{149}Tb/^{161}Tb, and ^{44}Sc/^{47}Sc.

S8. QA/QC/Pre-clinical

S8-01

Quality control of hospital based radiopharmaceuticals

Author: S.M. Rubow

Stellenbosch University, South Africa

Corresponding author: smr@sun.ac.za

Quality assurance plays an important role to ensure that medicines produced and dispensed in hospitals are safe, pure and effective. Radiopharmaceuticals pose special challenges due to their short shelf life and the radioactivity that is inherently part of these products. The facility, functioning and maintenance of equipment, and staff competence can all influence the quality of radiopharmaceuticals. A well-designed quality assurance programme is essential. This presentation focuses on essential quality control tests for diagnostic and therapeutic radiopharmaceuticals prepared in operational level 2 and 3 radiopharmacies. Regardless of the type of radiopharmaceutical, quality parameters include purity (radionuclidic, radiochemical and chemical), pH, particle size or absence of particles, stability, sterility and absence of endotoxins.

Radiopharmaceuticals prepared from sterile, licenced generator eluates and kits carry lower risk than those involving complex multiple step synthesis. The hospital radiopharmacy should however still test radionuclidic and radiochemical purity. The latter can be done with fast and relatively low-cost thin layer chromatography methods, provided the methods are validated.

Radiopharmaceuticals that are synthesised using more complex methods, inherently carry greater risk, especially of microbial contamination and the presence of impurities. These products require more complex analytical procedures and equipment, like HPLC (e.g. for radiochemical purity analysis) and GC (e.g. to test for residual solvents). Equipment is available that allows endotoxin testing within 20 minutes. Prior to routine production of unlicensed products, the method should be validated by proving that at least 3 production runs yield products that meet all quality criteria. This should include evaluation of the shelf-life of the product.

Sterility tests can in many cases not be completed prior to release of radiopharmaceuticals for administration to patients. These tests should nevertheless be done to ensure that the methods used will always provide sterile products. Radioactivity in sterility samples can pose a challenge, which should be addressed through methods like testing the outcome of non-radioactive dummy runs.

Radiopharmacy staff should be aware of the consequences of using poor quality radiopharmaceuticals, both from a patient safety perspective, and regarding good quality studies. It is important to have the necessary equipment, knowledge and competence to manage a quality programme that matches the level of radiopharmacy operations and nature of the radiopharmaceuticals produced at each hospital radiopharmacy.

S8-02

Development and preclinical evaluation of Cu-64 radiolabelled compounds

Author: Jeff Smith

University of Missouri School of Medicine, Columbia, United States

Corresponding author: smithcj@health.missouri.edu

In this presentation, we report investigations that describe advances and new targeting strategies using ^{64}Cu-radiolabeled peptides for molecular imaging of human cancers. Specifically, we attempt to highlight somatostatin, gastrin releasing peptide, melanocortin, and other receptor-targeting peptides and recent advances in radiolabelled, multivalent peptides for targeting and molecular imaging of cell-surface receptors via ^{64}Cu-radionuclide.

S8-03

Preclinical evaluation of ^{68}Ga-PET tracers using ^{68}Ga produced by cyclotron, a Canadian experience

Author: B. Guerin

Université de Sherbrooke, Montreal, Canada

Corresponding author: brigitte.guerin2@usherbrooke.ca

Gallium-68 (^{68}Ga, $T_{1/2}$ = 68 min) has attracted increasing interest in recent years due to the expanding clinical applications of ^{68}Ga-based radiopharmaceuticals. With this increased-demand, there is a need for improving the ^{68}Ga production capacity. The aims of this study are to enhance the production yield of ^{68}Ga using pressed targets and the purification of ^{68}Ga by using an automated cassette-based purification process. We also compare the chemical, radiochemical and biological properties of cyclotron- and generator-derived ^{68}Ga for common nuclear imaging procedures.

Using a digital hydraulic press, the pressed targets were prepared using enriched ^{68}Zn powder. They were mounted on custom-made magnetic target supports. ^{68}Ga was produced using 19 MeV and 24 MeV cyclotrons, recovered by chemical dissolution and purified by chromatography with two cation exchange resins. The radiotracers were then formulated the usual way as [^{68}Ga]-DOTA-TATE and [^{68}Ga]-PSMA-617. The PET images and distribution patterns of the cyclotron- and ^{68}Ge/^{68}Ga generator-produced ^{68}Ga radiopharmaceuticals were compared in healthy rats and mice.

Up to 140 GBq of ^{68}Ga was produced following 90 min irradiation. The overall recovery yield of $^{68}GaCl_3$ was 89% with an EMA of 77 ± 5 GBq/μmol at EOB. The outcome was a radiochemical yield >95% of [^{68}Ga]-DOTA-TATE and [^{68}Ga]-PSMA-617. Cyclotron- and generator-produced ^{68}Ga-radiopharmaceuticals were shown to be radioisotopically, chemically and biologically equivalent, giving matching images and identical kinetic and biodistribution patterns in animals.

Overall, these results show that irradiation of ^{68}Zn-pressed target is a very effective process. The cassette-based purification-process developed is rapid, simple, efficient and leads to high radiochemical yield and EMA of $^{68}GaCl_3$. Medical cyclotron can produce European Pharmacopeia-compliant ^{68}Ga-radiopharmaceuticals that can be used as substitute of generator derived ^{68}Ga.

S8-04

Ethics in animal experiments in nuclear medicine and the application of the directive 2010/63/EU

Author: Emilio Bombardieri

EANM, Italy

Corresponding author: emilio.bombardieri@gavazzeni.it

Researches on animals were carry out for a very long time. The question is: do we actually need to use animals for medical research or we simply guilty for speciesism? The general subject “Ethics in animal experimentations” has often been and still remains an area of intense debate. The final terminal of the discussions is whether the animals can or cannot be considered equal to human beings. This approach is a very complex matter, involving a lot of different matters as philosophy, religion, politics, bioethics, sociology, economy and biology. However today the big part of the scientific community and the public opinion is still in favour of animal testing due to the great benefits that humans obtain in terms of data essential for developing the scientific knowledge, treating the diseases and providing many benefits to society. The animal experimentation can be accepted if we save the concept that is morally acceptable to use animals for research only under certain conditions. These conditions drive why and how these animals should be treated. This approach in Europe has inspired the statement of a strict Legislation that transformed the meaning “Ethics in animal Experiments” in the Directive 2010/63/EU, written for the protection of animals used for scientific purposes. Under the umbrella of this Directive all the pre-clinical studies of nuclear medicine that use radioactivity are covered. The three fundamental principles, called 3Rs, are: replacement, reduction and refinement. Animal experiments must be replaced wherever possible by other methods such in vitro biological systems, or mathematical modelling. There must be a reduction in the number of animals used, by limiting the number required to obtain reliable data. The refinement requests to minimize the overall impact in animals used. According to this directive each country should have a local animal care committee, which reviews the animal research protocols, the rationale of the study, determine if animals are enough to test the hypothesis, check the appropriate sample size and procedures, in order to prevent some inappropriate use and undue suffering. These committees should control that animals are housed in appropriate facilities, have access to veterinary care, and require that personnel who work with the animals should be trained. Our personal perception about the problem of the animal experiments in the area of nuclear medicine is that in those countries where the directive is applied there are enough guarantees that the animal welfare is respected and the requests coming from 3Rs are fulfilled. To further improve this system the use of imaging instruments could be increased, the dedicated labs could be centralized, and the researches could be organized in a multidisciplinary network of information about needs and goals of the single researchers. Besides this, as far as we know, any statistics on animal experiments in Europe are not available, therefore in my opinion a general picture could be welcome in order to have a complete overview on this activity and the eventual problems.

S8-05

PET for the imaging of cerebral α7 acetylcholine receptors: from tracer development to clinical application

Author: Rodrigo Teodoro[1]

Co-author(s): Winnie Deuther-Conrad[1]; Matthias Scheunemann[1]; Barbara Wenzel[1]; Dan Peters[2]; Henryk Barthel[3]; Marianne Patt[3]; Osama Sabri[3]; Peter Brust[1]

[1]Helmholtz-Zentrum Dresden-Rossendorf, Leipzig, Germany
[2]DanPET AB, Rosenstigen 7, Malmö, Sweden
[3]Department of Nuclear Medicine, University of Leipzig, Leipzig, Germany

Corresponding author: r.teodoro@hzdr.de

Changes in the expression of homomeric α7 nicotinic acetylcholine receptors (α7 nAChR) in the human brain are widely assumed to be associated with neuropsychiatric and neuro-oncological processes. Indeed, thoroughly performed studies have shown the ability of α7 nAChR modulators to minimise the extent of cell death as well as to promote synaptic plasticity in different diseases including depression, schizophrenia, stroke and Alzheimer´s disease. Nonetheless, up to date, the clinical meaningful findings obtained with these agents were not always supported by a complete understanding of the downstream effects initiated by α7 nAChR modulators.

To help understanding these processes an extensive work has been done by our and other groups on the development of positron emission tomography (PET) α7 nAChR agents labelled with the radioisotopes fluorine-18 (^{18}F) and carbon-11 (^{11}C). So far two main classes of α7 nAChR PET tracers have been advanced to clinical trials: scaffolds composed of a three-side binding mode to the receptor (e.g., hydrogen bond acceptor, hydrophobic element and a rigid basic amine as the cationic centre), and the scaffolds containing fused functionalities belonging to the interferon inducer tilorone class of derivatives.

Structure-activity relationship studies on these two classes have been the subject of continuous research aiming at the development of highly affine and selective α7 nAChR PET tracers with suitable pharmacokinetic properties for an accurate receptor occupancy quantification and distribution of α7 nAChR in the brain. As a result, [^{18}F]NS10743, [^{18}F]NS14490, [^{11}C]NS14992, [^{18}F]DBT10 and its ortho isomer [^{18}F]ASEM emerged as the most promising α7 nAChR PET tracers developed so far. Studies in piglets were done for [^{18}F]NS10743 and [^{11}C]NS14992. Ongoing clinical trials have been reported using [^{18}F]ASEM. Efforts to translate [^{18}F]DBT10 into the clinics have been initiated with its transfer onto an automated synthesis in compliance to clinical production. The results of a successful pre-clinical imaging study, including dosimetry in piglets and evaluation in monkeys suggests the suitability of [^{18}F]DBT10 for imaging α7 nAChR. Very recently a pilot study in a large animal model of ischemic stroke in sheep revealed a high inflammation-related specific uptake of [^{18}F]DBT10 in the stroke border 14 days after permanent middle cerebral artery occlusion.

Among the receptor-specific α7 nAChR PET tracers developed so far, the dibenzothiophene isomers [^{18}F]DBT10 and [^{18}F]ASEM are under continuous investigation due to their suitable pharmacokinetics and high target-specific signal. More proof-of-concept studies are required to support the usefulness of these tracers for sensitive and specific α7 nAChR PET imaging.

S9. Health regulations: Production of radiopharmaceuticals

S9-01

A move towards harmonization of GMP regulations in radiopharmacy

Author: Sabine Kopp

World Health Organization, Geneva, Switzerland

Corresponding author: kopps@who.int

The cooperative efforts between IAEA and WHO supporting the production of high quality, safe and effective radiopharmaceuticals will be highlighted. In recognition of the longstanding request by IAEA Member States (and recommendations emerging from three technical meetings) to strengthen good manufacturing practices (GMP) for radiopharmaceuticals, the IAEA began collaborating with WHO to update its guidelines on GMP for radiopharmaceutical production.

In addition to the guidelines on GMP for radiopharmaceuticals, the IAEA has collaborated with WHO to identify, and develop, a set of specific monographs for priority radiopharmaceuticals to be included in The International Pharmacopoeia, as well as a general monograph.

The outcome of these efforts and next steps will be presented.

S9-02

The status of radiopharmaceutical regulations in Europe

Author: C. Decristoforo

Medizinische Universität Innsbruck, Austria

Corresponding author: Clemens.Decristoforo@tirol-kliniken.at

In this presentation the main rules, guidelines and guidance documents in the European Union (EU) in relation to the pharmaceutical regulatory framework are described. Radiopharmaceuticals, radionuclide generators, kits and radionuclide precursors are defined as medicinal products within the EU directive 2001/85/EC. These directives also implement the requirement for GMP and marketing authorisation for these products, unless they are exempted either as investigational medicinal products or products prepared extemporaneously. Extemporaneously prepared radiopharmaceuticals thereby are an important segment in Europe for preparation of SPECT, PET and therapeutic radiopharmaceuticals, which are regulated nationally, examples will be given. In this context, the European Pharmacopoeia with a legal status plays an important role in defining quality standards. For clinical trials the application system and regulatory framework in Europe is currently considerably changing. Whereas the current clinical trial directive requires a lengthy and complicated national application process, the new regulation 536/2014 will introduce a streamlined and unified European application process. This new regulation also takes into account the specific properties of radioactive investigational medicinal products and has introduced exceptions for good manufacturing practices (GMP) and labelling for radiopharmaceuticals. Besides the main regulatory texts, several guidelines have been published, e.g. by professional organization, in particular the EANM, in relation to GMP, documentation and toxicity studies, that support professionals in the process of radiopharmaceutical preparation. Important documents are summarized and discussed.

S9-03

The status of radiopharmaceutical regulations in the United States

Author: Serge Lyashchenko

Department of Radiology, Memorial Sloan Kettering Cancer Center, United States

Corresponding author: lyashchs@mskcc.org

The manufacture of radiopharmaceuticals in the United States is subject to specific laws, also known as regulations, passed on by the United States Food and Drug Administration. The FDA, as well as several other governmental agencies responsible for overseeing radioactive material handling, pharmaceutical production, and radiation safety, enforce compliance with the regulations through inspection. Additionally, these agencies periodically issue guidance documents that provide recommendations on how producers should comply with the relevant regulations. These guidance documents provide a more detailed description of the relevant requirements that should be followed by the radiopharmaceutical producers. In situations where a specific issue, not addressed in the regulations and guidance arises, producers have the ability to communicate with the FDA directly through meetings.

The regulatory oversite of the radiopharmaceutical manufacturing process by governmental agencies is further supplemented by manufacturing standards issued by the non-government entities such as United States Pharmacopeia or International Committee on Harmonization. The standards documents provide detailed descriptions on the requirements for particular processes related to pharmaceutical manufacture and quality control. The FDA often aligns their requirements with the requirements described in the standards documents.

Under certain circumstances (e.g. when as cold kit is used to prepare the radiopharmaceutical or when the radiopharmaceutical needs to be compounded based on the physician order for a specific patient) the process of radiopharmaceutical preparation is considered to be practice of nuclear pharmacy and medicine. In such situations, the local state agencies such as Boards of Pharmacy or Boards of Medicine are tasked with implementation of local regulations, ensuring compliance with those regulations, and actively performing inspections. However, the FDA still has the overall regulatory oversight of these activities and has the ability to become more involved in the regulation of these processes whenever required.

S9-04

GMP certification of radiopharmaceutical production facility in Kazakhstan

Author: Yelena Chakrova

Co-author(s): Yuri Bystyakov; Alexander Kulakov; Ilvira Vishnyakov; Zoya Medvedeva

Institute of Nuclear Physics, Almaty, Kazakhstan

Corresponding author: elchakrova@yandex.ru

In the end of 2018, the Institute of Nuclear Physics (INP) in Almaty became the first producer of radiopharmaceuticals in Kazakhstan certified for compliance with the GMP standard.

National Pharmaceutical Quality System, based on the recommendations of the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use, ICH Q10, was introduced in Kazakhstan in 2015. One of the major elements of the system is Good Manufacturing Practice (GMP) harmonized with GMP of European Union. GMP became obligatory for all pharmaceutical producers in Kazakhstan since the beginning of 2018 and immediately affected the operation of new radiopharmaceutical production facility commissioned at INP in 2017. This more than 700m^2 facility accommodates class A, B, C and D clean rooms and hot cells, and is intended for production of pharmaceuticals based on both cyclotron- and reactor-produced radioisotopes, including ^{99}Mo/^{99m}Tc generators, sodium iodide ^{131}I, ^{153}Sm-EDTMP, ^{18}F-FDG and others. The main stages of the establishment of GMP system and preparation for GMP certification were:

- Development of the plan of certification;
- Development of the validation master plan;
- Development of draft documents;
- Risk assessment for each technology;
- Qualification of equipment and engineering systems;
- Validation of processes;
- Production and quality control of validation batches; and
- Finalization of documents.

The developed four-level system of documents included the external documents, the documented procedures, the standard operating procedures and the records of results, altogether more than 500 documents.

Qualification of the equipment and systems required some technical modifications. It was not always possible to fully isolate the production of hot cells from the less biologically clean environment. In some cases, it was easier to provide the required cleanness outside underpressurized hot cells, to comply with both GMP and radiation safety requirements.

The application package was reviewed, and the inspection of the facility was conducted by the Pharmacy Committee of the Ministry of Public Health. After elimination of the inconsistencies revealed by the Committee, the radiopharmaceutical production facility at INP was certified for compliance with GMP.

S9-05

Compounding radiopharmaceuticals: any regulatory difference with extemporaneous preparation?

Author: Tiina Titma

Co-Author: Sergei Nazarenko

Tallinn University of Technology, Taltech, Estonia

Corresponding author: tjjna@gmail.com

Regulation of preparation of radiopharmaceuticals, as a relatively new class of emerging medicines for human use, is carried out in different ways in the European Union member states. This may create a potential problem when the principles of free movement of services and free movement of patients are considered. Since applicable guidelines and directives consider preparing of such medicines similarly as manufacturing or compounding, different interpretation of 'compounding' could result in lower conformity with the good manufacture practice.

Traditional 'compounding' refers to the 'pharmacy compounding' or 'extemporaneous compounding', which is globally known as the practice of essential part of pharmacist' competency. The World Health Organisation (WHO) Technical Report Series states that 'Compounded preparations involve the preparation, mixing, assembling, altering, packaging and labelling of a medicine or drug-delivery device, in accordance with a licensed practitioner's prescription, medication order or initiative based on the relationship between the practitioner, patient, pharmacist and compounder in the course of professional practice'.

According to the EU Directive, radiopharmaceutical kit and radionuclides from the generator (both mother and daughter radionuclides) are considered as active substances and detailed instructions for extemporaneous preparation and quality control of radiopharmaceutical should be included in the summary of the product characteristics. Preparation of radiopharmaceuticals used as diagnostic investigational medicinal products is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals.

In Estonia, there is no specific regulation on radiopharmaceuticals. Estonian Medicinal Products Act say that the 'Act applies to radiopharmaceuticals in so far as legislation concerning radioactive substances does not provide otherwise'. In addition, it is provided that "Medicinal products prepared as magistral formulae are medicinal products prepared in a pharmacy in accordance with a medical prescription or order form." On the other hand, Estonian Radiation Act and its derivative regulative documents, do not contain provisions about preparation of radiopharmaceuticals, except for radiation safety.

In this paper, we provide an overview of the applicable regulations in case the radiopharmaceuticals are prepared in other departments of the hospital or facility.

S10. New trends in radiopharmaceuticals: Chemistry

S10-01

Development and evaluation of chelators for specific radiometals

Author: B. Guerin

Université de Sherbrooke, Montreal, Canada

Corresponding author: brigitte.guerin2@usherbrooke.ca

There was continued interest in developing more efficient new chelating agents for metal radionuclides mostly used for positron emission tomography (PET) imaging. We focused on the development of convenient syntheses and conjugation of cyclic and acyclic chelators derivatized with *N*-hydroxy-*N*-methyl succinamide pendant arms for copper-64 (^{64}Cu), gallium-68 (^{68}Ga) and zirconium-89 (^{89}Zr) complexation. The aim of this project was to assess the suitability of the new chelators for ^{64}Cu-,^{68}Ga- and ^{89}Zr -PET.

The chelators were prepared through multiple steps starting with a nonadecane, cyclen and spermine backbones to offer chelating agents with high overall yields. They exhibited strong selective coordination of ^{64}Cu, ^{68}Ga and ^{89}Zr and offered a very fast labelling kinetic at room temperature as compared to NOTA, DOTA and DFO analogs. Achievable effective molar activities for the resulting complexes are higher compared to the one prepared with commercially available chelators. The radio-complexes *were* stable in saline, serum, as well as against *transchelation* and *transmetallation.* They showed high stability in mouse plasma *in vitro* and *in vivo*. Biodistribution and imaging studies were performed in balb/C mice and the background activity in various tissues was low. Finally, the conjugation of unprotected chelators to peptides and antibodies of biological interest were complete with overall yields of 50-60%.

In conclusion, our new class of cyclic and acyclic chelators show an outstanding promise as ^{64}Cu, ^{68}Ga and ^{89}Zr chelators.

S10-02

Novel radiopharmaceuticals for clinical translation

Author: Serge Lyashchenko

Department of Radiology, Memorial Sloan Kettering Cancer Center, United States

Corresponding author: lyashchs@mskcc.org

Over the last several decades radiopharmaceuticals have emerged as a an extremely useful modality for both diagnosis and treatment of disease. Much wider availability of novel radionuclides, more advanced image collection technologies, simplified radiopharmaceutical production technologies, and, most importantly, increased clinical community interest in application of radiopharmaceuticals in patients have created a significant demand for these agents.

In the field of molecular imaging, increasingly more imaging agents are used for patient selection, therapy optimal dose finding, and patient response monitoring. Increased availability of PET radionuclides with relatively longer radioactive half-lives such as ^{124}I, ^{64}Cu, and ^{89}Zr have resulted in a much wider clinical application of diagnostic radiolabeled antibodies, molecules that were impossible to PET image with historically due to the long biological circulation and target localization time. While the application of the majority of these agents remains limited to clinical research use, there are several agents in development that may someday be used as radiopharmaceuticals approved for standard clinical care.

In parallel, the field of targeted radiotherapy with radiopharmaceuticals is undergoing a significant expansion, with ^{177}Lu and ^{131}I radiolabeled peptides and antibodies being the most common agents of interest undergoing clinical translation. More recently, targeted alpha therapy radiopharmaceuticals, containing alpha emitting radionuclides such as ^{225}Ac, ^{213}Bi, ^{212}Pb, and ^{211}At have generated great interest in the medical community. More controlled clinical studies are needed to fully elucidate the safety and efficacy of this class of agents in patients, but the available preliminary clinical studies data looks highly promising.

S10-03

Translation of new chelators for old pairs: Tc/Re NODAGA

Author: Jeff Smith

University of Missouri School of Medicine, Columbia, United States

Corresponding author: smithcj@health.missouri.edu

In this presentation, we report diagnostic (^{99m}Tc) and therapeutic (^{186}Re) agents for targeting somatostatin receptor (SSTR) and gastrin releasing peptide receptor (GRPR) positive tumours. We have evaluated *in vitro* complexes of the general formula [M(CO)$_3$(L-sst$_2$-ANT)] and [M(CO$_3$)(L-C6-BBN-ANT)] (M = ^{99m}Tc, ^{186}Re), where L denotes NODAGA or NOTA and sst$_2$-ANT denotes the potent SSTR2 antagonist 4-NO$_2$-Phe-c(DCys-Tyr-DTrp-Lys-Thr-Cys)-DTyr-NH$_2$. For the GRPR targeting agent, C6 is an aminohexanoic linker conjugated to BBN-ANT, a powerful GRPR peptide antagonist (H-DPhe-GIn-Trp-Ala-Val-Gly-His-Sta-Leu-NH$_2$). Moreover, we have assessed the *in vivo* properties of the ^{99m}Tc-complexes in animal SSTR-positive or GRPR-positive tumour models.

S10-04

Radioactive Gold-198 nanoparticles in nanomedicine: green nanotechnologies in digital and molecular agents for innovative cancer diagnosis and therapy approaches in oncology

Author: Kattesh Katti[1]

Co-author(s): Kavita Katti[1]; Menka Khoobchandani[1]; Ademar Lugao[2]

[1]University of Missouri, United States
[2]IPEN, Sao Paulo, Brazil

Corresponding author: kattik@health.missouri.edu

Cancer alone continues to kill more people than AIDS, malaria, and tuberculosis combined. According to the International Agency for Research on Cancer, there were 12.7 million new cancer cases in 2018. The World Health Organization projects that without major breakthroughs in cancer prevention, discovery of new and accurate diagnostic modalities and development of highly effective therapeutic approaches, the global number of deaths from cancer will increase by nearly 80% by 2030, with most occurring cases in low- and middle-income countries. There are over 100 pharmaceutical formulations approved by the US Food and Drug Administration (FDA) in order to combat this deadly pandemic. Although surgery and radiation treatments are the initial treatments for most cancers, a large number of oncological approaches are being used to control or cure cancer. Today, cancer patients have more choices in which treatment or combination of treatments may be used, encompassing three areas of emphasis: (a) Chemotherapy, (b) Hormone therapy; (c) Biological treatment. Despite the currently available choice of established anticancer agents for first-line of activity against cancer, effective delivery of chemotherapeutic, hormonal and biological pharmaceuticals to the tumour tissue and cancer cells selectively continues to be the most vexing problem in cancer oncology. Problems associated with effective delivery of cancer drugs pose severe oncological challenges especially when treating solid tumours (sarcomas, carcinomas, and lymphomas) which account for over 85% of all human cancers. Circumventing these problems is not easy because molecular and cellular biology of neoplastic cells alone has failed to explain the non-uniform uptake of these agents in solid tumours. Repeated delivery of cancer drugs leads to systemic toxicity creating major collateral adverse effects where cancer cells mutate making them resistant to chemotherapeutic treatments. Therefore, the discovery of new drug delivery approaches that effectively penetrate extracellular compartments consisting of vascular and interstitial valves within solid tumours is of profound importance.

Radioactive nanoparticles with diagnostic and therapeutic capabilities provide intelligent drug delivery systems to maximize therapeutic activity and to minimize undesirable side effects. For example, the radioisotope of gold metal, Au-198, provides a desirable beta energy emission and half-life that destroys tumour cells/tumour tissue (βmax = 0.96 MeV; half-life of 2.7 days). Its penetration range (up to 4 mm in tissue or up to 1100 cell diameters) is sufficiently long to provide cross-fire effects to destroy tumour cells/tissue, but short enough to minimize radiation exposure to adjacent tissues. One particularly attractive feature of radioactive gold nanoparticles is that it does not have to be incorporated into every tumour cell to have a therapeutic effect. The path length of the emitted radiation is sufficient to allow effective therapy following uptake into a subpopulation of tumour cells. It is this feature that has attracted recent attention to apply nanotechnology for the effective delivery of therapeutic doses of beta emitting nanoparticles selectively to tumour tissue and tumour cells. We have reported the synthesis of novel radioactive gold nanoparticles using the trimeric phosphine (referred to as 'Katti Peptide' discovered in our laboratory.

In our continued efforts to apply green nanotechnology for the development of therapeutic radioactive gold nanoparticles, recently we have discovered that the high antioxidant capacity of Epigallocatechin gallate (EGCG), which is the most abundant catechin polyphenol in tea, can be used to convert radioactive Gold-198

precursor to the corresponding biocompatible radioactive gold nanoparticles. Most recently, we have shown that Mangiferin—a glucose functionalized xanthanoid, found in abundance in mango peels, serves dual roles of chemical reduction and in situ encapsulation, to produce gold nanoparticles with optimum in vivo stability and tumour specific characteristics. Interaction of mangiferin with Au-198 gold precursor affords MGF-^{198}AuNPs as the beta emissions of Au-198 provide unique advantages for tumour therapy while gamma rays are used for the quantitative estimation of gold within the tumours and various organs. Laminin receptor specificity of mangiferin affords specific accumulation of therapeutic payloads of this new therapeutic agent within prostate tumours (PC-3) of human prostate tumour origin induced in mice which overexpress this receptor subtype. Detailed in vivo therapeutic efficacy studies, through the intratumoural delivery of MGF-^{198}AuNPs, shows retention of over 80% of the injected dose (ID) in prostate tumours up to 24 h. In order to estimate the tumour and local tissue doses in MGF-198-AuNPs for prostate cancer radiotherapy, we have undertaken Monte-Carlo N-Particle code calculations. The overall objective of this investigation was to estimate the dose distribution delivered by radioactive gold nanoparticles (^{198}AuNPs or ^{199}AuNPs) to the tumour inside the human prostate as well as to the normal tissues surrounding the tumour using Monte-Carlo N-Particle code (MCNP-6.1.1 code). This lecture will provide: (a) scope and prospects of beta emitting radioisotopes in nanomedicine; (b) details in the intervention of nuclear activation analysis and various radioanalytical approaches for the production of tumour specific radioactive gold-198 nanoparticles; and (c) full in vivo investigations on therapeutic properties of MGF-198-AuNP agent in treating prostate tumours and (d) the overall implications of green nanotechnology of therapeutic beta emitting nanoparticles in oncology.

According to the MCNP results, ^{198}AuNPs are a promising modality to treat prostate cancer and other solid cancers and the gamma of ^{198}AuNPs, as well as ^{199}AuNPs could be used for imaging purposes. In summary, the preclinical therapeutic efficacy studies and the detailed toxicity studies of MGF-198-AuNPs provide compelling evidence for the clinical translation of this innovative nanotherapeutic agent for use in treating prostate and related solid tumours in human patients. Therefore, future studies will focus on clinical trials of MGF-198-AuNPs, in prostate tumour bearing patients, in order to seek approval from regulatory agencies (FDA) for the utility of this new nanomedicine agent in oncology.

S10-05

New strategies for imaging brain cancer with radiopharmaceuticals

Author: Peter Brust

Helmholtz-Zentrum Dresden-Rossendorf, Germany

Corresponding author: p.brust@hzdr.de

Brain cancer is a challenge for the health care system because of major problems for treatment. Radical surgery is not possible. Radiation treatment is restricted by missing borderlines, and drug treatment is limited by the blood-brain barrier. Therefore, glioblastoma multiforme, the most aggressive type of primary brain tumour, has a median overall survival of only ~12 months. Although new molecular pathways are being constantly discovered, translation of basic science into clinical practice is rather slow. Major obstacles in the resistance to therapy are heterogeneity of brain tumours, multiple genetic alterations, and their diffuse, infiltrative behaviour. Hence, monitoring of pathways related to tumour etiology and growth are highly important.

Positron emission tomography (PET) offers the potential to identify key signalling and metabolic pathways in tumours and to discover drugs for targeted therapy. An important prerequisite for PET is the development of radiolabelled molecules (radiotracer) to investigate impaired brain functions in living human subjects. Fluorine-18 is currently the most favourable radionuclide that is routinely used for radiolabelling because of its half-life of 109.8 min. The presentation will focus on the development of fluorine-18 labelled radiotracers bridging from basic science to biomedical application and focusing on four targets of major importance for brain cancer.

Cannabinoids are known to induce apoptosis of glioma cells and the extent of cannabinoid CB2 receptor expression is related to tumour malignancy. The challenge in radiotracer development is the high expression of CB1 receptors. Therefore, our strategies will be presented to achieve highly selective PET radiotracers for CB2 receptors.

The immunosuppressive effects of adenosine and the adenosine-triggered activation of catabolic energy production account for pro-cancer roles of extracellular adenosine. Accordingly, plasma-membrane-bound adenosine receptors were identified as new targets in the immunotherapy of brain tumours. Currently, we have PET radiotracers for A2A and A2B receptors under development, which are regarded as potential tools for therapy monitoring.

Sigma receptors, previously regarded as opioid receptors, are comprised of the σ1 and σ2 subtypes and represent orphan receptors of different families. While the σ1 receptor is a molecular chapter one, which interacts with various ion channels and G-protein coupled receptors, the σ2 receptor (TMEM97) is an intracellular protein located at the endoplasmic reticulum that binds numerous drugs. There is evidence that both subtypes are important for glioblastoma growth thus facilitating the ongoing development of selective PET radiotracers for both subtypes in our department.

Furthermore, as other cancers, glioblastoma is characterized by metabolic reprogramming to preferentially undergo aerobic glycolysis. The elevated production of lactate is accompanied by the increased expression of monocarboxylate transporters (MCTs). Accordingly, a therapeutic approach targeting MCTs is a promising strategy in brain cancer treatment. A PET radiotracer for peripheral MCT1/MCT4 imaging has already been developed by us and will be discussed concerning its suitability for glioblastoma imaging.

Numerous attempts are ongoing for molecular characterization of brain cancer with PET radiopharmaceuticals. It is expected that they will support in the future patient stratification and hence individualized therapy.

S11-A. Production of alpha emitters and radiopharmaceuticals

S11-A1

Production and quality control of radiopharmaceuticals labelled with Actinium-225 and Bismuth-213

Author: Alfred Morgenstern

European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany

Corresponding Author: Alfred.morgenstern@ec.europa.eu

Alpha emitters are highly effective radionuclides for targeted alpha therapy of cancer. The remarkable clinical results obtained in the last years for treatment of advanced prostate cancer with ^{225}Ac-PSMA617 have strongly stimulated the global interest in targeted alpha therapy. The supply of suitable alpha emitters in enough quantity and purity is a main pre-requisite for a widespread application. This presentation will give an overview of methods for the production of the alpha emitters Actinium-225 and Bismuth-213 and describe methods for the labelling of biomolecules.

S11-A2

US DOE Tri-Lab Effort to Produce Ac-225

Author: Cathy S. Cutler

Collider Accelerator Department, Brookhaven National Laboratory, Upton, NY, United States

Corresponding author: ccutler@bnl.gov

There is growing interest in using alpha emitters for targeted therapy particularly in cases where the disease has metastasized. A major limitation to this approach has been the limited availability of the alpha emitters themselves. The US DOE isotope program has made its top research priority developing production capability to meet the quantities and quality of Ac-225 needed to support clinical applications. After evaluating multiple production pathways, the DOE chose to concentrate on the high energy accelerator route through the proton bombardment of Th-232. This effort utilizes the high energy accelerators housed at BNL and LANL along with the Ac-225 chemistry separation and experience contained at ORNL. Over the past two years over 22 thorium targets have been irradiated at BNL and LANL and then shipped to ORNL for processing and distribution. The material has been thoroughly characterized and then sent out to external users for evaluation. Actinium-225 can either be directly used for targeted therapy applications or as generator feedstock for Bismuth-213. Thus, the development of Ac-225 provides two alpha emitters with different nuclear properties expanding the library of radionuclides that can be utilize for targeted therapy. The project has successfully completed the first stage of the effort demonstrating the feasibility of developing targetry which can be irradiated at high energies and developing the chemistry that enables the separation of the Ac-225 from over 100 other radionuclides that are produced from the irradiation. Stage 2 is ongoing which involves scaling up production to 100 mCi quantities and developing facility plans to allow for curie level production at multiple sites. Submission of a drug master file for the accelerator material by the end of the 2019 calendar year. Material is being produced with up to 30-50 mCi being routinely put into inventory for external stakeholders. Details regarding the Tri-Lab production effort for Ac-225 will be provided.

S11-A3

Recent results of the joint CNL and TRIUMF project on the production of Ac-225

Author: Mark Lesinki[1]

C-author(s): Patrick Causey[1], Kathryn Hayashi[2], Keith Ladouceur[2], Kevin McDuffie[2], Andrew Robertson[2], Paul Schaffer[2]

[1]Canadian Nuclear Laboratories (CNL), Canada
[2]TRIUMF Innovations, 4004 Wesbrook Mall, Vancouver, BC, Canada

Corresponding author: patrick.causey@cnl.ca

CNL has a history spanning more than 70 years in the application of nuclear technology toward the betterment of human health. Pioneering accomplishments include megavoltage radiation therapy for the treatment of cancer, and the implementation of large-scale production of several critical isotopes, including the global supply of ^{99}Mo (molybdenum-99) for ^{99}Mo/^{99m}Tc (technetium-99m) generator manufacture and distribution. In total, an estimated one-billion medical treatments and scans were conducted using isotopes produced at CNL's Chalk River Laboratories. Presently, CNL has expanded its research capabilities and continues to serve as a world-leader in the development and delivery of medical isotope technology andnuclear health sciences.

Recently, CNL has developed a thorium-229 (^{229}Th)/actinium-225 (^{225}Ac) generator to enable both internal and collaborative research at TRIUMF, the University of Saskatchewan, the Fedoruk Center; to further develop known and novel radiopharmaceuticals for treatment of various cancers. ^{225}Ac is an alpha-emitting radioisotope, and when radiolabeled to a targeting vector, it has attracted worldwide attention in the medical community for its potential to treat and cure cancers. Known as targeted alpha therapy (TAT), various drugs incorporating alpha emitting isotopes are in clinical trials and pre-clinical research for an array of cancers,as well as viral and bacterial infections, including infectious diseases. However, anticipated demand for225Ac far exceeds supply as producers work to overcome the many challenges associated with scaled-up production. TRIUMF houses a high energy (520 MeV) accelerator that allows for the production of both radium-225 (^{225}Ra) and ^{225}Ac via 232Th spallation. CNL and TRIUMF have partnered on a project thataims to produce isotopically pure ^{225}Ac in quantities needed to support clinical studies, preclinical researchand multiple drugs once approved for human use. The joint project begins at TRIUMF's Isotope Production Facility, with the high energy proton spallation of ^{232}Th, producing a wide range of isotopes, including appreciable and scalable quantities of ^{225}Ra. The irradiated targets are shipped to CNL for ^{225}Ra separation using standard separation techniques, modified by proprietary improvements, to yield a ^{225}Ra generator. Milking the ^{225}Ra generator produces pure ^{225}Ac, free of long-lived impurities, including ^{227}Ac and other spallation products.

Multiple processing runs have been completed with processing yields for ^{225}Ra and ^{225}Ac of greater than 70% decay corrected to End-of-Bombardment (EOB). This material, devoid of ^{227}Ac, performs identical to material produced via ^{229}Th decay when subjected to radiolabeling, and has passed all internal quality control release tests. A key challenge to this work is the disposition of waste generated during processing, an area of expertise CNL is known for and developing further. With promising results to date, the CNL-TRIUMF partnership is part of a critical path to ultimately demonstrate a supply route for significant quantities of clinical-grade ^{225}Ac.

The results, significance and key challenges of the joint project will be discussed during the presentation.

S11-A4

Argentinian project for developing production of Ac-225 and Bi-213 in cyclotrons for targeted therapy

Author: Oscar Pozzi

Co-author(s): Valentina Vercelli; Celeste Iljadica; Carmen Ali Santoro; Sandra Siri; Carmelo Rocco; Hector Cols

Ezeiza Atomic Center, Argentina

Corresponding author: pozzi@cae.cnea.gov.ar

The Alpha Project of the National Atomic Energy Commission of Argentina is a local project for developing the production of Ac-225 and Bi-123 from Ra-226 targets via Ra-226(p,2n)Ac-225 reaction in medium-low energy cyclotrons. The main goal of the Alpha Project is to secure the regional supply of Ac-225 in order to provide future treatment of cancer patients and to support the R&D for new applications. To fulfil the goals of the project, a new dedicated nuclear facility is being built in Argentina and expected to become fully operational in 2020-2021. It will have several radiochemical labs containing one multipurpose hot cell, five hot cells dedicated to Ac-225 processing, and one GMP hot cell. This installation will also have a pilot plant for radiopharmaceutical production, initially under local GMP condition but capable to be upgraded to international GMP regulation.

The irradiation of the Ra-226 target will be made in the cyclotron “Cyclotron Corporation CP42” (25- 42 MeV) located at the Ezeiza Atomic Center of CNEA, using the fully automated irradiation station for solid target with a new target holder specifically designed to work with sealed Ra-226 targets and 4 pi water for cooling. Theoretical models predict the cooling time to be at least 240 hours (one T1/2 of Ac-225) before processing the target. This will decrease the Ac-226 activity to < 0.3% of its initial value and provide Ac-226/Ac225 ration to be < 0.005. This cooling time will also result in a decay of the Ac-226 daughters. According to the yield calculations for the preliminary target designed to run at lower density current <100 microampere/cm^2, with 58 mg $RaCl_2$ irradiated 4 hrs. x 50 microampere/cm^2 at 24-10 MeV will be able to produce 335 mCi EOB per batch, and 167.5 mCi after cooling time of 240 hrs. A production target capable to withstand 200 microamperes will require a bigger amount of $RaCl_2$ (230mg for 2 cm^2) with 24 hrs. x 50 microampere irradiation at 24-10 MeV will result in 1.34 Ci of Ac-225 EOB per batch, and 670 mCi after 240 hrs. of cooling. Assuming an average dose of 0.5 mCi/patient, this amount will be enough for 1340 patient (losses for purification are not considered). Based on this assumption, one cyclotron running once a week, 4 weeks/month, 11 month/year will be able to produce 29.5 Ci/year of Ac-225, which is enough for almost 59,000 patients per year.

This production method based on the Ra-226(p,2n)Ac-225 based in cyclotrons have several advantages. It produces Ac-225 of high radionuclide purity; it is suitable for local and regional markets where Ac-225 production can be adjusted depending on the needs; it can produce on demand up to ~30 Ci/year using only one non-dedicated cyclotron working once a week; and it fulfils the goals set for the Alpha Project to secure the Ac-225 supply for our country and the region.

S11-B Technical cooperation success stories

S11-B2

Sustainable production of Tc-99m generators and radiopharmaceuticals an IAEA/Cuban experience

Author: René Leyva Montaña

Isotope Centre, Cuba

Corresponding author: leyvamontanarene4@gmail.com

Through collaboration with the IAEA, CENTIS has managed to establish a system for the sustainable production of generators and radiopharmaceuticals. Radionuclide generator systems continue to play a key role in providing both diagnostic and therapeutic radionuclides for various applications in nuclear medicine. The generators represent important in-house production systems that can provide daughter radioisotopes generated by parent decay on-demand without the need for local access to an accelerator or nuclear reactor. Cuba has not had accelerators or reactors for many years, so its radionuclide and radiopharmaceuticals production is based mainly on importation or local generators production. Our presentation resumes the Cuban experience in the production of radionuclide generators and radiopharmaceuticals.

In CENTIS facilities, the production of ^{99}Mo/^{99m}Tc generator began in 2003 using the column chromatography method as separation technology. More than 4 000 generators have been produced in different presentations (8 GBq, 20 GBq, 37GBq, 55,5 GBq and 74 GBq) during this years. However, long before in the 90s, CENTIS already manufactured cool kits to form radiopharmaceuticals from imported generators. Starting with generator production in 2003 allowed us to guarantee the sustainability of nuclear medicine services in the country.

Among many other requirements one of the main challenges for our radionuclide generators production has been the need to manufacture and operate under the conditions of good manufacturing practices (GMP) guidelines since these products represent final product or active pharmaceutical ingredients (APIs) which will be incorporated into radiopharmaceutical products prepared for human use. In this presentation, we included the necessary modifications performed to our ^{99}Mo/^{99m}Tc generators production and the conditions established to comply with the current GMP guidelines supported by a Technical Cooperation Project with the IAEA (CUB/6/023).

S11-B3

IAEA support of $^{99}Mo/^{99m}Tc$ gel generator production project in Kazakhstan

Author: Yelena Chakrova

Co-author(s): Denis Afanasyev; Vladimir Kutepov; Igor Fetssov; Zoya Medvedeva

Institute of Nuclear Physics, Almaty, Kazakhstan

Corresponding author: elchakrova@yandex.ru

The Institute of Nuclear Physics (INP) in Almaty for more than 18 years produces and supplies all nuclear medicine organizations of the Republic of Kazakhstan with the most used radiopharmaceutical for radionuclide diagnostic ^{99m}Tc solution.

For production of generators activation ^{99}Mo is used, obtained by irradiation of natural molybdenum oxide at the WWR-K research reactor with a thermal neutron flax $2 \cdot 10^{14}$ $n \cdot s^{-1} \cdot cm^{-2}$. The “gel” technology, the basis of which have been developed by scientists from Australia and the United States, applied on an industrial scale in India is used to produce $^{99}Mo/^{99m}Tc$ gel generators at the Institute. Specialists of the Institute of Nuclear Physics have improved this technology by developing unique technological equipment for the production of generators in hot cells and creating a new generator design, as well as implementing GMP principles in production.

The project of creation of $^{99}Mo/^{99m}Tc$ gel generator production was implemented within the framework of budget programs aimed at the development of new technologies in the Republic of Kazakhstan and the success of the project is largely due to the significant support provided by IAEA through Technical Cooperation and Coordinated Research Projects.

S11-B4

Strengthening capacities for the development of radiotracers labelled with fluorine-18, different from Fluordesoxyglucose in the FCDN

Author: Adrian Duran[1]

Co-author(s): Fabiana Rodriguez[2]; Jonathan Santiñan[2]; Erica Heringer[3]; Rebeca Vargas[2]; Sabrina Seidel[3]; Jaime Palatnik[3]; Alicia Coronel[2]

[1] Comision Nacional de Energia Atomica, Argentina
[2] FCDN, Argentina
[3] FCDN/CNEA, Argentina

Corresponding author: aduran@fcdn.org.ar

The “Fundación Centro Diagnóstico Nuclear (FCDN)” has a large experience in Argentina as a FDG producer with more than 3500 batches, distributing a large part of the production to other sites as well as to our own patients. Besides, the institution produces routinely ^{11}C, ^{68}Ga and ^{13}N radiopharmaceuticals. Do to the expansion of applications related with PET and specially with ^{18}F, the institution has decided to apply to an IAEA’s TC program in order to get the input to strengthen our capacities to produce ^{18}F radiopharmaceuticals other than FDG. The program consists of fellowships, expert missions and procurement of equipment. In the first year we have installed an automatic synthesis module, two fellowships have been granted and one expert mission was completed.

With the help of this program in the first year the radiopharmacy department was able to produce ^{18}F-Cholina, ^{18}F-PSMA1007, ^{18}F-FMISO and ^{18}F-FAZA with all the required quality controls. ^{18}F-Choline is in clinical use for internal patients and ^{18}F-PSMA1007 documentation has been presented to the regulatory agencies in order to apply to a clinical trial. Regarding ^{18}F-FMISO and ^{18}F-FAZA, we are defining which of them is the best candidate for the clinical applications.

In conclusion, the program has proven to be helpful to train staff and implement new technologies aimed to help Argentina´s community.

S12. Emerging radioisotopes for radiopharmacy

S12-01

Development of production strategies for new emerging research radionuclides using cyclotrons

Author: Valery Radchenko

TRIUMF/UBC, Canada

Corresponding author: vradchenko@triumf.ca

Targeted Radionuclide Therapy (TRT) with Auger emitters has great potential due to the low energy (eV-KeV) and high Linear Energy Transfer (LET) that is ideal for local damage on the cellular level. Auger emitters in combination with selective delivery systems may maximize damage of tumour cells with minimal effect on surrounding healthy tissues. However, dosimetry of Auger emitters for nuclear medicine application is still relatively unexplored and mostly performed with commercially available radionuclides which are not necessarily the most suitable for Auger therapy (e.g. ^{111}In, ^{99m}Tc, ^{125}I). Therefore, production and testing of alternative radionuclides is important to realize the full potential of Auger emitters for therapy.

TRIUMF (Canada's Particle Accelerator Centre) has unique infrastructure to produce a broad pallet of promising radionuclide candidates for TRT research. This includes a number of cyclotrons with operating energies between 13 and 520 MeV and radiochemical facilities to perform radiochemical separations and radiolabeling. In this work, production, radiochemical separation and radiolabeling of potent radionuclides for Auger therapy namely antimony (^{119}Sb), erbium (^{165}Er) and mercury ($^{197m+g}$Hg) will be presented.

Sb and Hg isotopes were produced by irradiation of natural tin and gold targets respectively at TR-13 cyclotron. Liquid-liquid extraction was applied for Sn/Sb separation and previously published procedure based on Ln resin was applied for Hg purification.

For production of ^{165}Er, the ISAC facility at TRIUMF. Radiochemical purification from co-produced no-carrier added lanthanides was performed using solid phase extraction chromatography on a Ln resin.

Irradiation of natural tin resulted in a variety of Sb isotopes including ^{119}Sb, but due convenient for detection gamma lines, ^{120m}Sb was used as a tracer for antimony to establish radiochemical separation and chelation yields. Liquid-liquid extraction with dibutyl ether yielded over 95% of Sb recovery and >10^3 of Sn/Sb. Irradiation of monoisotopic gold provide mixture of $^{197m+g}$Hg which was further purified with Ln resin with recovery yield over 90%.

Detection of produced ^{165}Er and ^{165}Tm was performed with gamma spectroscopy. Radiochemical separation from co-produced ^{165}Tm results in efficient separation and purified erbium was tested for chelation with DOTA and macropa. Results showed over 99% radiolabelling efficiency with DOTA for using in combination with selective delivery systems for microdosimetry studies.

S12-02

Emerging clinical applications of [^{64}Cu]$CuCl_2$ radiopharmaceutical

Author: Miguel A. Avila-Rodriguez

Unidad Radiofarmacia-Ciclotrón, Universidad Nacional Autónoma de México, Ciudad de México, Mexico

Corresponding author: avilarod@uwalumni.com

Over the last two decades there has been a growing interest in Copper-64 (Cu-64) and important advances have been achieved in preclinical and clinical applications with this emerging radionuclide. Given its favorable physical properties (half-life and decay scheme), Cu-64 has the potential to be used for PET molecular imaging and targeted radionuclide therapy (TRT) in oncology. Among the positron emitters of copper, Cu-64 is by far the most commonly used for PET molecular imaging, in part given by the versatility of its half-life of 12.7 h that allows the imaging of peptides and small molecules with fast clearance, and macromolecules with slow pharmacokinetics. However, in recent years, Cu-64 in the chemical form of copper dichloride ([^{64}Cu]$CuCl_2$) has been identified as a potential agent for PET molecular imaging and TRT, using the copper transporter protein CTR1 as molecular target.

CTR1, a 190-aminoacid protein of 28 kDa with three transmembrane domains, is expressed in many normal tissues but most interestingly it has been found that this copper transporter is overexpressed in a variety of cancer cells, converting it in a molecular target for tumours overexpressing CTR1, characteristic that has been employed for PET imaging with promising results in both, preclinical applications in animal models, and clinical applications in humans. The potential of [^{64}Cu]$CuCl_2$ as theranostic agent have also been evaluated in animal models, but to date, no clinical trials have been performed in humans, only case reports have been described.

In this talk an overview on the emerging clinical applications of [^{64}Cu]$CuCl_2$ radiopharmaceutical will be presented.

S12-03

Towards large-scale Cu-67 cyclotron production

Author: Petra Martini[1]

Co-author(s): Gaia Pupillo[1]; Liliana Mou[1]; Micòl Pasquali[1]; Alessandra Boschi[2]; Carlos Rossi Alvarez[1]; Férid Haddad[3]; Adriano Duatti[2]; Juan Esposito[1]

[1]INFN-LNL, Italy
[2]UNIFE, Italy
[3]ARRONAX, Italy

Corresponding author: psqmcl@unife.it

Among the most promising radionuclides for cancer therapy, Cu-67 is worldwide under the spot- light thanks to its potential application in theranostics, by itself or in pair with Cu-64. The main advantage of Cu-67 and theranostic radionuclides in general, is their peculiar possibility to perform diagnosis and therapy with the same radiopharmaceutical, allowing the selection of patients with a significant chance of responding to the specific treatment by performing low-dose imaging studies prior therapy. Currently, the use of Cu-67 in preclinical and clinical trials is curtailed by its short availability. The production of Cu-67 still presents considerable challenges because of some unfavourable parameters characterizing the nuclear reactions that have been investigated. In particular, the most intensively studied reaction has been the ^{68}Zn(p,2p)^{67}Cu nuclear process. The efforts of the international community are thus focused on technological improvements allowing larger and reliable productions.

At the INFN Legnaro National Laboratories (LNL, Padua), a new high-performance particle accelerator (i.e. BEST 70p cyclotron) has been installed in 2015 and a dedicated research facility called LARAMED (laboratory of radionuclides for medicine) is currently under completion. Cu-67 has been a top priority of LARAMED project in the last years: in 2016 the project COME (Copper Measurement), funded by INFN (CSN3), was carried out and research activities were presented at the CRP No. F22053 by the IAEA. The aim of the COME project was to experimentally determine the cross-section of the Zn-70(p,x)Cu-67 reaction in the still unexplored proton energy region above 35 MeV. Irradiation runs were performed at the ARRONAX facility (Nantes, France), by using the 70 MeV proton beam and stacked-foils targets, composed by a set of thin metal foils. An added value of this project was the development of a high-yield chemical separation procedure of Cu from Zn and Ga elements, optimized for the cross-section measurement.

We successfully measured the Zn-70(p,x)Cu-67 cross section in the energy range 45-70 MeV, applying a radiochemical process to irradiated targets and by using gamma-spectrometry. The optimal experimental conditions to maximize the Cu-67 yield were identified and compared to the well-known reaction on Zn-68 targets.

Results of this study brought us to the idea of a special target design that allows the maximization of Cu-67 production while minimizing the Cu-64 contamination, by using 70 MeV proton beams. This result led in 2018 to the INFN patent entitled “A method and a target for the production of Cu-67”. The experience gained on the technologies for target realization and processing so far is the starting point for developing and optimizing the large-scale Cu-67 cyclotron-production chain.

S12-04

Production of ^{47}Sc from ^{47}Ca – comparison of four separation methods

Author: Izabela Cieszykowska

Co-author(s): Dariusz Pawlak; Wioletta Wojdowska; Małgorzata Żółtowska; Józef Leon Parus; Piotr Garnuszek; Renata Mikołajczak

National Centre for Nuclear Research, Radioisotope Centre POLATOM, Poland

Corresponding author: izabela.cieszykowska@polatom.pl

Scandium-47 with a half-life of 3.35 days is a promising low-energy β- emitter (Eβ- (max) = 600 keV) suitable for targeted radionuclide therapy. It also emits radiation (E = 159 keV, 68.3%), which could be utilized for imaging by using SPECT technique for tracing the radiopharmaceutical administered for therapy. Together with positron emitter ^{44}Sc, it can create the pair of radionuclides proposed for theranostic application. Scandium-47 can be produced by irradiation of ^{46}Ca with thermal neutrons in ^{46}Ca(n,g)^{47}Ca→^{47}Sc nuclear reaction. The aim of this work was to find the best procedure of ^{47}Sc separation from ^{46}Ca irradiated in a nuclear reactor enabling multiple separation of ^{47}Sc from ^{47}Ca/^{47}Sc generator system and the production of ^{47}Sc of high radionuclidic and chemical purity suitable for radiolabelling of radiopharmaceuticals.

Scandium-47 was produced by irradiation of ^{46}Ca targets (48.5 mg of $CaCO_3$, 5.2% enrichment in ^{46}Ca) for 150 h in thermal neutron flux of 1.2 1014 cm-2s-1 in Maria research reactor. Four different methods of ^{47}Sc separation from Ca were investigated and compared: the precipitation of scandium hydroxide with ammonia, the solid phase extraction chromatography using UTEVA resin, extraction chromatography with TBP resin and extraction chromatography with DGA resin. In ^{47}Sc solutions obtained from precipitation, UTEVA and TBP methods were necessary to decrease their acidity. It was done on the cation exchange columns in H+ form. The solutions after ^{47}Sc separation were used for next recoveries of ^{47}Sc after about 4 days. Four cycles of separation were carried out. Target material was recovered via precipitation of calcium carbonate.

Irradiation of targets containing 48 mg of [^{46}Ca]$CaCO_3$ resulted in ^{47}Sc activity up to 660 MBq at EOB. The separation yields of ^{47}Sc obtained with the use of four methods for 4 consecutive separation runs were as follows: for hydroxide precipitation: 99%, 54%, 24%, 16 %, for extraction of UTEVA resin: 79%, 42%, 27%, 16%, for extraction of TBP resin: 80%, 55%, 83%, 62%, for extraction of DGA resin: 96%, 91%, 87%, 93%. The only radionuclidic contaminant in separated ^{47}Sc was ^{47}Ca with concentration below 0.1%.

Out of the four evaluated separation methods the highest separation yield was achieved for DGA resin. Also, the radiolabelling yield of DOTATATE was the highest when using ^{47}Sc obtained by this method. In addition, it was demonstrated that multiple separations of ^{47}Sc from irradiated enriched ^{46}Ca target material are efficient until 15 days after the end of irradiation in nuclear reactor.

Acknowledgements: This project was supported with the funds awarded by the Ministry of Science and Higher Education in Poland within the agreement No. 3639/FAO/IAEA/16/2017/0, IAEA Research Contract No. 20496 and CERAD project, financed under Smart Growth Operational Programme 2014-2020, Priority IV, Measure 4.2.

S12-05

Accelerator-based production of Sc-47: results of the PASTA project

Author: Gaia Pupillo[1]

Co-author(s): Hanna Skliarova[1]; Sara Cisternin[1]; Petra Martini[2]; Micòl Pasquali[2]; Alessandra Boschi[3]; Luciano Canton[1]; Andrea Fontana[1]; Férid Haddad[4]; Carlos Rossi Alvarez[1]; Adriano Duatti[3]; Juan Esposito[1]; Liliana Mou[1]

[1]INFN, Italy
[2]INFN-LNL and University of Ferrara, Italy
[3]University of Ferrara, Italy
[4]Arronax-Subatech, University of Nantes, Italy

Corresponding author: gaiapupillo@hotmail.com

^{47}Sc is an emerging theranostic radionuclide included in the CRP No. F22053 by the IAEA, together with ^{67}Cu and ^{186}Re. The long half-life of ^{47}Sc (about 3.35 days) is suitable to follow the slow biodistribution of monoclonal antibodies and large molecules, while its β- and γ radiation are useful to deliver cytotoxic dose to small-medium size tumours and to perform SPECT imaging studies to select patient prior therapy. In addition, ^{47}Sc can be paired to β+ emitters such as ^{44}Sc or ^{43}Sc to perform low-dose PET with the same radiopharmaceutical, to tailor the dose to the specific patient before therapy. The critical issue in the use of ^{47}Sc is the lack of availability in sufficient quantities and at a reasonable cost. In the framework of the LARAMED program, the PASTA project (acronym of Production with Accelerator of Sc-47 for Theranostic Applications) was funded at INFN-LNL. The goal of the PASTA project is to measure several nuclear cross sections, comparing them with previous experimental data and theoretical predictions, in order to find out the best irradiation conditions for ^{47}Sc production.

Data in literature regarding nuclear reactions induced by proton beams were analysed in detailed, finding that the most interesting materials for ^{47}Sc production are ^{nat}V and the enriched ^{48}Ti, ^{49}Ti and ^{50}Ti targets. Highly pure ^{nat}V foils are easily available on the market, while the enriched titanium targets were obtained by using metal powder deposited on an aluminium substrate by using the high-energy Vibrational Powder Plating (HIVIPP) technique (E_PLATE project). Irradiation runs were performed at the ARRONAX facility by using stacked-foils targets and low-intensity pro- ton beams. Gamma-spectrometry measurements were performed up to 5 days after the End of Bombardment (EOB), in order to follow the decay of all the radionuclides of interest (^{47}Sc, ^{46}Sc, ^{44}Sc, ^{44m}Sc, ^{43}Sc, ^{48}Sc, ^{48}V, ^{43}K, ^{48}Cr, ^{49}Cr, ^{51}Cr). Cross section calculations were carried out by considering the reference monitor reactions proposed by the IAEA Nuclear Data section. Experimental values were compared with data in literature and with theoretical estimations obtained by using different nuclear codes: Fluka, Talys and Empire. In addition to this, a radiochemical procedure aimed at the Sc/Ti separation was developed in collaboration with the University of Ferrara, by using the Solid Phase Extraction chromatography (tests performed with cold material).

We successfully measured the ^{nat}V(p,x)^{47}Sc and ^{48}Ti(p,x)^{47}Sc cross sections and the co-production of contaminant radionuclides (i.e. ^{46}Sc). Results, compared with previous data and theoretical estimations, are shown in this work. Experimental runs with ^{49}Ti and ^{50}Ti targets are scheduled in 2019; considering the high-cost of the enriched materials used, the energy ranges of major interest were identified by comparing the predictions of the different nuclear codes.

Results of this study will indicate the best nuclear reaction and the optimal irradiation conditions to produce ^{47}Sc by using proton beams, avoiding the co-production of contaminant radionuclides, especially ^{46}Sc. Further work is needed to establish a reliable ^{47}Sc production based on particle accelerators.

S13. Radiopharmacy installations

S13-01

How to set up a medium size ^{99m}Tc generator facility: IAEA experience

Author: Adriano Duatti

Department of Chemical and Pharmaceutical Sciences, University of Ferrara, 44121 Ferrara, Italy

Corresponding author: dta@unife.it

The transportable ^{99}Mo/^{99m}Tc generator is still the major global source of ^{99m}Tc, one of the most widely used diagnostic radionuclides. According to many Pharmacopoeias (*e.g.*, FDA, PhEur, PhInt), this generator is classified as a medicinal product and not as a medical device. The reason for this choice originates from the fact that the eluate withdrawn from the generator contains the pertechnetate anion, [^{99m}Tc][TcO_4], which in turn can be used, under this chemical form, as diagnostic agent for assessing thyroid's function. Because of this classification, the production of a ^{99}Mo/^{99m}Tc generator should be accomplished strictly following the principles of Good Manufacturing Practice (GMP) elaborated to produce injectable drugs. It should be noted that GMP rules only dictate that, to ensure the quality of the final product always complies with the standards usually described in Pharmacopoeia's monographs, the most efficient approach is to design and build up a robust production process that must be fully traceable and reproducible. GMP principles provide a guidance for rationally designing such a process and establishing a GMP production facility, but the adopted technical solutions can vary depending on the local conditions and, therefore, should be tailored to each specific situation. Usually, a rigorous and rational approach, supported by technological advancements as well as a correctly designed quality management system, would suffice to delineate the most appropriate solutions. In this short overview, the key steps involved in the production of a ^{99}Mo/^{99m}Tc generator and a few possible layouts for setting up a medium-size GMP facility are presented and discussed.

S13-02

Design and successful operation of SPECT hospital radiopharmacy

Author: Vijay Kumar

Sydney Medical School, University of Sydney, Australia

Corresponding author: vijay.kumar@health.nsw.gov.au

Essential elements of Radiopharmacy SPECT laboratory should address the following aspects: selecting appropriate staff and training, provide adequate facilities and infrastructure, develop SOPs (Standard operating procedures), properly documented purchase of materials, labelling procedures, standard quality control and quality assurance measures, waste management and systematic documentation.

The ultimate objective of the professional SPECT hospital Radiopharmacy is to provide “Best Patient Care”. All operations should be carried out under the supervision of the nuclear physician in charge and a radiopharmacist/radiochemist will be responsible for the setting up of the suitable quality control and quality assurance programme. There is a large diversity of diagnostic & therapeutic NM procedures in an ever-changing field. Increasing levels of competence & knowledge are required to maintain high quality practice.

At an international level standardization and harmonization is difficult due to diverse practice environment. Therefore, IAEA developed “operational guidance on hospital radiopharmacy: a safe and effective approach”. The publication is not intended to over-ride local guidance or provide comprehensive advice on all aspects of radiopharmacy practice. There are different levels of operations in Radiopharmacy and were classified into 3 levels. Operational level 1a-Rady to use approved products. Dispensing radiopharmaceuticals purchased in their final form from centralised radiopharmacy. This includes unit doses required no compounding but preferably it is dispensed within a Laminar flow cabinet. The cabinet is an essential equipment, as it protects the product from the operator. Operation at level 1b involves dispensing radioiodine (I-131) and other ready to use radiopharmaceuticals for radionuclide therapy. Handling of beta-emitting volatile radioisotopes should be performed within a “Fume cupboard” as it protects the operator from volatile radiation (eg. I-131).

Operation at level 2a involves preparation of radiopharmaceuticals from approved reagent kits and radionuclide, e.g. ^{99m}Tc. The procedures should be performed within clean room equipped with Isolators with built-in space for preparation, dispensing, and dose-calibrator. The level-2b involves radiolabelling of autologous blood cells. This operation requires specialised training on the methodology and infection control. Operation at level-3 mainly involves in-house compounding of radiopharmaceuticals from ingredients and 3b is on Synthesis of PET radiopharmaceuticals and long-lived PET generators. It is beyond the scope of this abstract to cover details on these operations.

New chapter on radiopharmaceuticals (International Pharmacopeia) is developed by IAEA, which gives detailed information on methods of analysis, sterility and pyrogen testing, monographs and networking with manufacturers, drug regulators and reference centres.

S13-03

Cyclotron and PET radiopharmacy installation: experience in setting up a commercial centre

Author: M.R.A. Pillai

Molecular Cyclotrons, Puthuvype, Ernakulam, Kerala 682 508, India

Corresponding author: pillai.m.r.a@gmail.com

Molecular Cyclotrons is a private PET radiopharmaceuticals manufacturing and distribution facility operating in Kerala, a southern state of India with a population of 35 million. The facility is built as part of a hospital which will specialize in cancer care with focus on targeted radionuclide therapy. The Cyclotron-PET radiopharmaceuticals production facility is licensed by the Atomic Energy Regulatory Board and is in commercial operation since 2017.

Prior to the commissioning of this facility there were only 2 PET-CT operating in the state of Kerala and the radiopharmaceuticals were brought by air freight. Thanks to the local production of PET radiopharmaceuticals the number of PET-CT in Kerala has increased to 15 or 0.4 PET-CT per million inhabitants. The state also has one of the three PET-MRIs available in India.

The Cyclotron Centre is planned as per the IAEA TRS 471: Cyclotron Produced radionuclides: Guidance for setting up a new facility. The facility is compliant with EU good manufacturing practices and is GMP certified. The cyclotron is a self shielded Siemens Eclipse HP machine with 11 MeV proton beam and dual target having 2 x 60 μA beam current. The hot cells were procured from Von Gahlen. It consists of a twin Class C hot cell with 100 mm lead shielding, another twin Class C hot cell with 75 mm shielding, a Class A dispensing hot cell with 75 mm lead shielding and a bio-safety cabinet. A comprehensive radiation monitoring system supplied by Rotem Industries Ltd is installed in the Cyclotron Centre. This is an online system with possibility of retrieval of data as and when needed.

Three synthesis modules are installed of which the Siemens Explora FDG 4 can do four consecutive batches on FDG in a row without opening the hot cell. There are two Neptis Mosaic LC modules which are capable of making several F-18 radiopharmaceuticals using fluoride chemistry. During synthesis, the air from the hot cell is collected in delay-decay tanks which are located in the cyclotron vault. The quality control laboratory is equipped with GC, TLC and Endosafe equipment for estimation of chemical, radiochemical and pharmaceutical purity. The finished products are packed in Type A lead and tungsten packages and transported by road.

The Cyclotron Centre is supervised by the centre manager, who is a qualified radiochemist and an independent AERB approved Radiation Safety Officer. Other operating personnel include M.Sc medical physicists (2), M.Sc Chemists (3) and a pharmacist. Cyclotron operation is done during night and packages are despatched at different lots with the last batch leaving the Centre prior to 7 in the morning. About 850 batches of FDG are produced thus far and there was no quality failure in any of the batches. FDOPA, FLT, FET, F-choline and FPSMA-1007 are the other radiopharmaceuticals prepared regularly in the Centre. The centre is catering to 15 nuclear medicine departments and FDG is also exported to Sri Lanka.

The model developed at Molecular Cyclotrons is an ideal commercial centre and can be readily adapted by new comers entering the fascinating field of PET radiopharmaceuticals production.

S13-04

How to set up a PET radiopharmaceutical facility IAEA experiences

Author: Uday Bhonsle

Director of Radiopharmacy, Gulf International Cancer Center, Al Bahia, Abu Dhabi, United Arab Emirates

Corresponding author: udaybhonsle@gmail.com

Nuclear Medicine Imaging plays a significant role in diagnosis and management of cancer as well as many other diseases. Diagnostic imaging depends on injection of a radiopharmaceutical followed by a scanning using either SPECT CT or PET CT system depending on the organ and disease under investigation. The radiopharmaceutical distribution, accumulation within the body provides much needed information regarding diagnosis of the disease or management of the disease. The SPECT-CT or PET-CT scanners are based on physical principles of radiation detection and image formations. Therefore, the diagnostic accuracy of the procedure depends on the quality of radiopharmaceuticals. Radiopharmaceuticals are unique pharmaceutical products due to their short shelf life. Certain aspects of quality of a radiopharmaceutical cannot be assessed due to the short life of the product therefore the quality of the radiopharmaceutical products needs to be built in the design of radiopharmaceutical production and use processes. The IAEA, professional organizations and regulators have published detailed guidelines for setting up radiopharmaceutical production facilities. However, mainly due to the lack of specific project management experience, many IAEA member states, particularly belonging to the lower and middle income group, find it difficult to implement the guidance that is currently available due to lack of detailed project implementation plan. This presentation will explain with examples different steps that need to be taken to ensure timely completion of radiopharmaceutical production facility that is compliant with both pharmaceutical and radiation protection regulations.

S13-05

An effort to develop? diagnostic and therapeutic nuclear medicine practice at Fukushima Medical University using two medical cyclotrons

Author: Kohshin Washiyama

Co-author(s): Miho Aoki; Taiki Joho; Naoyuki Ukon; Ken-ichi Nishijima; Kazuhiro Takahashi; Songji Zhao; Noboru Oriuchi

Advanced Clinical Research Center, Fukushima Medical University, Japan

Corresponding author: kwashi@fmu.ac.jp

The Advanced Research Clinical Center (ACRC) was established at Fukushima Medical University in June 2016 as a symbol of rehabilitation of the disaster held in 2011. Radioisotope production using two cyclotrons and equipment for producing labelling compounds have been introduced, providing medical services generated from them to Fukushima citizens and re-activating Fukushima. The center has the mission to advertise our current status of the recovery process through the activity of our clinical R&D and application.

The ACRC has installed two cyclotrons created by Sumitomo Heavy Industries, Ltd. Two types of cyclotrons can manufacture various types of radionuclides for diagnosis and treatment. There are five laboratories for making radiopharmaceuticals, some of which are cGMP grade. One PET/CT and one PET/MRI are installed for daily diagnosis. A nine-bed section has been set up in the treatment ward to perform radionuclide therapy which requiring hospitalization (i.e. thyroid cancer treatment with ^{131}I). The maximum dose approved in a bed is 37 GBq (1 Ci).

The compact cyclotron MP-20S-V is used for producing positron emitting radionuclides such as ^{11}C, ^{13}N, ^{15}O, ^{18}F for diagnosis. Among these nuclides, ^{18}F is routinely manufactured and labelled as ^{18}F-FDG for cancer screening of patients. This cyclotron can also be used for research, and so far, it has been producing 64Cu, ^{89}Zr, ^{124}I, which is promising for radioimmunoscintigraphy. On the other hand, the cyclotron MP-30 is an accelerator newly developed by Sumitomo as a new type of cyclotron capable of accelerating alpha particles. The MP-30 can accelerate proton, deuteron, and alpha particles, and is mainly used for research and development to make novel radiopharmaceuticals. So far, ^{65}Zn, ^{99m}Tc, ^{68}Ge, ^{177}Lu, and ^{211}At radioisotopes have been manufactured. Among them, ^{211}At has been focusing on research at our facilities especially because of the growing interest in targeted alpha therapy globally. Last year, we made 34 runs of ^{211}At production via ^{209}Bi(a,2n)^{211}At nuclear reaction and the sum amount of produced radioactivity reached 13.8 GBq. Most of them have been used for our research and development, and some have been transported to other facilities for chemical experiments and preclinical studies under collaboration.

The activity of our facility has just begun. We will contribute to patients in Fukushima and nearby areas through daily screening with radiopharmaceuticals for diagnosis. And we aim to be one of the global R&D and application centres for cancer treatment through the development of new alpha and beta emitting radiopharmaceuticals.

S14. IAEA databases and apps

S14-01

The medical isotope browser

Author: Arjan Koning
Co-Author: Marco Verpelli

Nuclear Data Section, IAEA, Vienna, Austria

Corresponding author: A.Koning@iaea.org

A new web tool has been developed which allows to directly predict the production yield of a medical isotope on the basis of user input. The first version is restricted to isotopes produced by charged-particle accelerators.

The user can specify the characteristics of the accelerator, such as the projectile (proton, deuteron, triton, Helium-3 or alpha particle), current in mA, the incident and exit energy, and specify the target material and the desired produced radioisotope. After a simple mouse click the required isotopic yield as a function of irradiation and cooling time, as well as a complete description of all the produced impurities is obtained, virtually instantaneous.

The medical isotope browser is based on 4 essential ingredients, which will be discussed in some detail:

- A web-based Graphical User Interface
- An efficient solution of the production and depletion equations
- A radioactive decay data library
- A complete cross section library

A live demonstration of the Medical Isotope Browser will be given for some important examples as Tc-99m, Ac-225 and Ga-68.

S14-02

The IAEA's research reactor database (RRDB)

Author: Nuno Pessoa

Physics Section, IAEA, Vienna, Austria

Corresponding author: N.Pessoa-Barradas@iaea.org

The IAEA's research reactor database (RRDB) is an authoritative database containing technical information on over 800 research reactors, including critical and sub-critical assemblies in 67 countries. The information in the database, provided by facility focal points nominated through official channels, also includes utilization and administrative information. The presentation will focus on the information provided by the RRDB on production of medical radioisotopes with research reactors worldwide.

S14-03

Introduction to new IAEA database “cyclotrons used for radionuclide production”

Author: Amir R Jalilian[1]

Co-author(s): Mohammad Haji-Saeid[2], David Schlyer[3], Aliz Simon[1], Joao Osso Jr.[1]

[1]Department of Nuclear Sciences and Applications, International Atomic Energy Agency (IAEA), Austria
[2]Consultant, Vienna, Austria
[3]Scientist Emeritus at Brookhaven National Laboratory, Upton New York, United States

Corresponding author: A.Jalilian@iaea.org

The number of cyclotrons has expanded in the last decade due to advances in medical imaging applications leading to increased radiopharmaceutical demand worldwide. With the development of sophisticated molecular imaging techniques (PET, SPECT, PET/CT and PET/MRI); introduction of user friendly compact medical cyclotrons from manufacturer companies has become possible. On the other hand, in many Member States, several PET radiopharmaceuticals are eligible for reimbursement by government or insurance companies.

An online interactive directory of cyclotrons that are used for radionuclide production in Member States is launched recently and contains information supplied to the IAEA. This directory was prepared through information collected by reports from the major manufacturers and information taken from previous directories. Best efforts were made to include only those cyclotrons in current operation or under testing, but this was not always possible and therefore, there may exist entries in the database which are no longer valid, or not yet associated with an institution. These entries need to be updated.

The directory includes a significant number of the cyclotrons world-wide that are used, at least in part, for radionuclide production. Some institutions reported that older cyclotrons had been shut down and replaced with newer cyclotrons (In an effort to keep the database as up-to-date as possible, please follow the instructions on the website to update details regarding your new or existing facility).

The database is organized alphabetically by Member State and by city but can be downloaded and sorted in any manner desired. There are individual entries for each cyclotron even for institutions having more than one cyclotron. The contact person and email address were entered where available. Again, every effort was made to update this list, but some of the people listed have changed positions and so may no longer be associated with an institution.

There are more than 1300 entries for cyclotrons operating in Member States of the IAEA. This is an increase of more than 40% over those reported in the 2013 cyclotron directory. The increase has been in the number of cyclotrons in developed countries, but even more so in the developing countries. Large concentrations of cyclotrons for radionuclide production are in the United States of America, Japan and Germany. The largest number of cyclotrons for a single country is in the United States of America. However, taken collectively there are more cyclotrons located in the Far East including China and Japan that are used for medical radionuclide production. Please visit the following website for your overview:

https://nucleus.iaea.org/sites/accelerators/Pages/Cyclotron.aspx

S15. Education in radiopharmacy

S15-01

Development and performance of a radiopharmacy platform certification, EANM experience

Author: Philip H. Elsinga

University Medical Center Groningen, University of Groningen, The Netherlands

Corresponding author: p.h.elsinga@umcg.nl

EANM organizes radiopharmacy courses within the Framework of ESMIT (European School of Molecular Imaging and Therapy). Besides several e-Teaching modules designated as a level 1 activity, ESMIT organizes training on level 2 and level 3.

Regarding level 2, the EANM Radiopharmacy committee has established a European Postgraduate Specialization Certificate in Radiopharmacy. This certificate is available to anyone who completes a defined program of education and a two-year period of practical experience in the field. The program addresses chemists, pharmacists and other natural scientists working in the small-batch production or quality control of radiopharmaceuticals. The program is coordinated by members of Radiopharmacy Education Board in collaboration with ETH Zurich Switzerland. The program consists of 3 blocks of 2 weeks and includes Module 1: Pharmacy and Legislation; Module 2: Radiopharmaceutical Chemistry and Module 3: Radiopharmacology and Clinical Radiopharmacy.

This certificate is valid for a duration of 5 years. For the (re)certification process each certificate holder is asked to upload documents to the EANM Area on the EANM-website. Each document will be reviewed by the Radiopharmacy Education Board and if accepted, 5 points will be received per document. The recertification obligation has been started start Jan 1st 2019. Candidates who apply for the first time will receive the certificate as soon as they have all the documents needed and they fulfill all the requirements. Applicants who ask for a recertification of the existing certificate have to wait until the old certificate has expired before a new one will be issued. This counts also when the total of 20 points have been reached before the expiry date. A new certificate will then be issued – valid for another 5 years.

Regarding level 3, the EANM Radiopharmacy committee organizes an interactive high-end course on GMP. The course focuses from the basics and fundamentals of Good Manufacturing Practice (GMP) through User Requirement Specification (URS), Validation, Deviations and Facility Planning. Moreover, Radiation Safety, the question how to build up and manage a quality risk management system will be covered in the course. Additionally it explains the increasing regulatory demands from laboratory work to clinical trials, going from laboratory notes to an Investigational Medicines Product Dossier (IMPD). The target audience includes Radiochemists and Radiopharmacists with the interest to increase the understanding of GMP and the consequences of different GMP related activities (e.g. persons who have attended the EANM Radiopharmacy Courses) but as well Pharmacists who wants to gain a better understanding for GMP in the context of Radiopharmaceuticals.

S15-02

Education and qualification of radiopharmacists in Latin America

Author: Ana Rey Ríos

Universidad de la República Oriental del Uruguay-UdelaR university, Montevideo, Uruguay

Corresponding author: arey@fq.edu.uy

Radiopharmacy is an area with increasing development and technological complexity. According to WHO´s official documents (WHO Annex 2, Report 48 -TRS 986 and Annex 3 Report37 - TRS 908) the production of radiopharmaceuticals requires the supervision of qualified personnel with postgraduate training and appropriate experience in their function. Although most countries in Latin America have adopted these documents in their legislation the real situation is highly heterogeneous. Almost all countries have clear regulations regarding radioprotection. Many countries require a pharmacist for centralized and industrial radiopharmacies. However, specific qualification in radiopharmacy is not clearly specified in the national regulations and the adequate educational offer is very restricted. In Radiopharmacies operational level 1 or 2 (according to IAEA´s Operational guidance on Hospital Radiopharmacy) technicians are frequently in charge without proper qualification or supervision of a Radiopharmacist.

The overall situation regarding regulations on educational requirements for radiopharmacy is as follows: Argentina, Bolivia, Chile, Cuba, Ecuador, México, Paraguay, Perú and Uruguay have no legal requirements for radiopharmacies at operational level 1 and 2. On the other hand Colombia, Costa Rica and Brazil require a responsible pharmacist in all types of radiopharmacies and also some kind of postgraduate specific education in radiopharmacy as well as continuous education of all personnel.

The educational offer is also very heterogeneous in Latin America: only Brazil and Uruguay have specific pre- and postgraduate university options in radiopharmacy. Countries like Argentina, Mexico and Cuba have some elective pre-graduate courses or postgraduate in specific courses on nuclear techniques, while the rest of the countries have no educational offers at all, and professionals are trained either abroad or in the working place.

Brazil offers postgraduate courses (480 hours or more) depending from which universities mostly in Sao Paolo. Uruguay offers since 2016 a postgraduate diploma of specialization in radiopharmacy having 300 hours of theoretical and practical lessons and 300 hours of supervised professional practice both in conventional and PET radiopharmacy. This programme is available not only for pharmacists but also for other professionals (chemists, biochemists) and for professionals coming from other countries due to the flexibility and personalized curricula.

In conclusion, the educational offer in radiopharmacy in the region is insufficient and should be drastically incremented in the near future to fulfil international recommendations. Regional networking with support from IAEA is the way to achieve the internationally accepted standards.

S15-03

Master's degree in radiopharmaceutical sciences: step forward to enhance regional capacities in nuclear medicine in Africa

Author: Naoual Bentaleb

Department of Radiopharmaceuticals Production, National Centre for Nuclear Energy, Sciences and Technologies (CNESTEN) Rabat, Morocco

Corresponding author: naoualbentaleb@yahoo.fr//bentaleb@cnesten.org.ma

Nuclear medicine is a multidisciplinary specialty in which medicine, physics and radiopharmacy are involved. The preparation of high-quality radiopharmaceuticals is the base for a high-quality nuclear medicine examination. Radiopharmaceutical science is a rapidly expanding field and there is strong demand for qualified professionals. To address the gap in human resources, and to enhance national and regional capabilities in nuclear medicine in Africa, a master's degree in Radiopharmaceutical Sciences was developed in Morocco by CNESTEN in collaboration with the Faculty of Medicine and Pharmacy of Rabat and the INSTN- France with the support of the IAEA and AFRA.

The master's degree developed attempts to address the shortage of suitably trained radiopharmacists and professional radiopharmaceutical scientists in Morocco and French-speaking African countries by providing the knowledge and skills required in the field of diagnostic and therapeutic radiopharmaceuticals.

In the framework of the AFRA project RAF6054 relating to Strengthening and Improving Radiopharmacy Services, several meetings were organized to prepare the Curriculum of the master's project which was initiated in 2018. These meetings were attended by representatives of the IAEA, CNESTEN, the Faculty of Medicine and Pharmacy of Rabat and the INSTN- France to ensure that the program is in accordance with IAEA standards and reviewed for their technical and scientific integrity. After the accreditation of the program by the Ministry of Higher Education of Morocco, the courses were open for pharmacists, chemists, biochemists and biologists and were started officially in October 2019. The most theoretical courses will be done at the faculty of medicine and pharmacy of Rabat and also in CNESTEN. For practical sessions, CNESTEN's radiopharmaceuticals production facilities as well nuclear medicine hospital facilities in Rabat and Casablanca will be used. The two industrial PET facilities would be also supportive to ensure practical training.

The duration of the program entitled "Radiopharmaceutical Sciences" is two years. Each academic year consists of two semesters. The course is made up of 18 required modules and a research project on any aspect of Radiopharmacy. The modules are covering the fundamentals of development, preparation, testing and stability of radiopharmaceutical preparations, radiolabelled drug synthesis, scientific and regulatory issues in radiopharmacy, as well as providing a solid foundation in medical applications of radiopharmaceuticals.

Radiopharmaceutical science and nuclear medicine are expanding fields and there is strong demand for qualified professionals in Africa. Education of radiopharmacists and professional radiopharmaceutical scientists is necessary at the University level to allow nuclear medicine and molecular imaging in Africa to reach its potential regarding their benefits and usefulness in the management of cancer and other diseases.

The development of master's degree in radiopharmaceutical sciences in Morocco is a big step forward to enhance regional capacities in nuclear medicine in Africa.

S15-04

Developing, testing and installing e-learning system for radiopharmacy as a tool to harmonize education in a developing country

Author: Emilija Janevik-Ivanovska

Faculty of Medical Sciences, Goce delve University Stip, North Macedonia

Corresponding author: emilija.janevik@ugd.edu.mk

The main goal of our work is to create e-learning platform for master students (pharmacist, chemist, biologist physicist, physician and other with academic postgraduate diploma) and post graduate degree (PGD) for technologists working in the field of radiopharmacy and nuclear medicine.

Basic education in radiopharmacy is an essential component of the scientific and technical background of a radiopharmacist and the inescapable route by which quality assurance in radiopharmacy can be implemented. The purpose of this study was to evaluate e-learning as a method to improve worldwide education in radiopharmacy and increase the awareness about concepts pertaining the quality of radiopharmaceuticals.

To establish an e-learning platform designed as an innovative learning apparatus that, working alongside conventional teaching methods, integrates education in all aspects of radiopharmacy into the curricula being offered by universities at existing education and training institutions is the next step forward to the global recognition of the unified standards.

In this study, a few lines of analysis for developing a suitable e-learning platform in radiopharmacy were as follows:

- Course flexibility to improve access and personalization by students,
- Rigorous definition of basic concepts and methods according to international standards,
- Significantly decrease costs for education in radiopharmacy,
- Enable fast practical implementation of theoretical concepts through virtual laboratory,
- Building up a worldwide available, virtual repository of learning resources in radiopharmacy.

Findings:

- Each module is designed as a “basic unit of knowledge”, comprising a group of minimum competencies and knowledge about a specific subject and used independently or in combination with other modules or training resources;
- Students can select the module and the time that best suits his/her professional needs for accessing the materials;
- Diversity and interactions between different educational contexts are exploited to increase harmonization and integration.

Practical implications: two categories of practical implications important for implementation of the successful sustainable system of quality assurance could be envisaged as follows.

Infrastructural:

- A new hardware infrastructure dedicated to radiopharmacy,
- Novel and upgradable e-learning solutions for education in radiopharmacy, Database and soft material repository:
  - Basic concepts, definitions, theoretical models and analytical methods, Virtual training in radiopharmacy practice,
  - Quality standards and quality assurance,

- Translational tools to adapt the e-learning platform to various educational systems.

Originality and value: the present work is the first analysis to assess the feasibility of a global e-learning platform for education in radiopharmacy. It is expected that this approach would contribute to (a) overcome local differences in the interpretation of radiopharmacy practice and standards, (b) to spread worldwide knowledge in radiopharmacy, (c) to help harmonization of regulatory systems through education and (d) to implement good standard for quality assurance system.

S15-05

The World Nuclear University's WNU's 7 approaches to enhance professional performance

Author: Patricia Wieland

Co-author(s): Sarah Cullen, Silke Klassen

World Nuclear University, London, UK

Corresponding author: pat.ita.w@hotmail.com

Building the next generation of experts in nuclear energy and the applications of nuclear science and technology is not an easy task. Identifying potential leaders in an expanding nuclear industry is even more challenging. The World Nuclear University (WNU) addresses these challenges by engaging educational institutions, nuclear industries, international organizations, professional associations and nuclear professionals of all ages in an ever expanding long lasting educational global network. WNU develops leadership and communication skills with dynamic methods in a unique international environment. It provides the 'big picture' necessary to work in the nuclear sector at any level and promotes up do date and tacit specific knowledge transfer.

WNU has contributed to the development of human resources in the nuclear area since its creation in 2003, in a relevant way. It has attracted participants to pursue careers in the nuclear area, has motivated many to gain more visibility in their field of expertise, engage with their peers, and to pursue more formal leadership roles.

This paper describes the approaches WNU uses to enhance professional performance from selection of participants to long term evaluation, in a continuous improvement process.

PS1: Poster Session 1

Track: Production of PET- and SPECT-based diagnostic, therapeutic, and theranostic radiopharmaceuticals

PS1-01

Tc-99m octreotide in neuroendocrine tumours: a different radiotracer from traditional ^{111}In: our experience

Author: Mariela Agolti

Co-author(s): Camila Aruga; Lucrecia Solari

Centro Medicina Nuclear Clinica Modelo, Parana, Argentina

Corresponding author: marielsmednuc@hotmail.com

Tumours deriving from cell types expressing somatostatin receptors may be imaged by somatostatin receptor scintigraphy. The most common radiotracer to bind octreotide is ^{111}In, which is not produced in our country, as well as in other Latin American countries. Its cost is very high, its half-life is very long, and its availability is rare. We have started labelling Octreotide with Tc-99m, which is a more available and cheaper, and its short half-life let us work more easily. The basic mechanism is the union to receptors SST 2 and 5, is conserved. We have studied 27 cases during 4 years with this method, and the objective of this work is to share the results of our experience. We had cases of carcinoid small bowel tumour, ileocecal carcinoid tumour, stage IV paranglioma, Meckel type carcinoid tumour, pulmonary carcinoid tumour and septal appendectomy, carcinoid tumour of the cecum and terminal ileum, insular and trabecular carcinoid ovarian tumour and thymoma.

We analysed 27 cases during January 2014 until March 2019 with Tc-99m Octreotide. The dose administered was 30 mCi, three hours after the injection, we made whole body images, SPECT the thorax and abdomen. After 20 hours we performed a second round of images with a single-headed GE Gamma Camera. Of the 27 cases studied, we ruled out 5 cases because we could not do the correct follow- up. We divided the results into 18 positives and 4 negatives for the studies of neuroendocrine tumours. We correlated our results with the biopsy, when possible (21 studied cases) and the clinical follow-up of 5 cases (especially in the negative studies for active neuroendocrine tumours).

Results showed that out of the 4-negative scintigraphy, 2 were negative at the close of this study. Out of the 18 positive cases, 18 were confirmed by biopsy and follow-up, where 1 patient died of this disease or it' s complications. These results show 18 true positives, and 2 true negatives, with a method that shows a sensitivity of 94.5% and a specificity of 100%.

In conclusion, Tc-99m Octreotide appears to be cheaper, more available, and with less radiation dose for patients. It was performed during a day and more easily performed (with low energy and high-resolution collimator) as an alternative to ^{111}In octreotide scintigraphy. With a very good sensitivity and specificity.

PS1-02

Preparation and preclinical evaluation of ^{64}Cu-Nota-Anti Muc1 as a radioimmunoconjugate for diagnosis of Muc1+ breast cancer by pet

Author: Behrouz Alirezapour[1]

Co-author(s): Saeed Rajabifar[1]; Miad Hashemizadeh[2]; Ehsan Maadi[2]; Javad Mohamadnejad[3]

[1]Radiation Application Research School, Nuclear Science and Technology Research Institute, Tehran, Islamic Republic of Iran

[2]Pars Isotope Company, Tehran, Islamic Republic of Iran

[3]Department of Life Science Engineering, Faculty of New Sciences & Technologies, University of Tehran, Tehran, Islamic Republic of Iran

Corresponding author: balirezapour@aeoi.org.ir

Radioimmunoscintigraphy (RIS) has attracted considerable clinical applications in tumour detection. Underglycosylated MUC1 antigen is one of the early hallmarks of tumour genesis and is overexpressed in more than 80% of breast cancers. PR81 is a new murine anti-MUC1 monoclonal antibody (mAb). In this study, as the first step, we have developed an efficient indirect labelling method of PR81 with 64Cu (T1/2 = 12.8 h, β+ = 17%, β− = 39%, EC = 43%) through using NOTA (p- SCN-Bn-NOTA) bi-functional chelator and performed preliminary biodistribution studies in mouse bearing breast adenocarcinoma.

PR81 was conjugated with NOTA (Macrocyclics B-605), the average number of the chelator conjugated per mAb was calculated and total concentration was determined by spectrophotometrically. NOTA–antiMUC1 was labelled with 64Cu then Radiochemical purity and immunoreactivity, internalization study by MCF7 cell line and serum stability of 64Cu–NOTA– anti MUC1 were determined. The biodistribution studies and radioimmunoscintigraphy were performed in female BALB/c mouse bearing breast carcinoma tumour (64Cu–NOTA–antiMUC1 i.v., 100 µl, 20±5 µg mAb, 6, 12, 24 and 48 h).

^{64}Cu–NOTA–anti MUC1 was prepared (RCP >98% ± 0.4, specific activity 5.2 ± 1.2 µCi/µg). Conjugation reaction of chelator (50 molar excess ratio) to antibody resulted in a product with the average number of chelators attached to a mAb (c/a) of 4.1 ± 0.5. Labelling yield with ^{64}Cu in 400µg concentration of bioconjugate was 96.5% ± 2.1. Immunoreaction of ^{64}Cu–NOTA– anti MUC1 complex towards MUC1 antigen was determined by RIA and the complex showed high immunoreactivity towards MUC1. In vitro and in vivo stability of radioimmunoconjugate was investigated respectively in PBS and blood serum by RTLC method. In vitro stability showed more than 94% ± 1.26 in the PBS and 81% ± 2.62 in the serum over 24 hours. The Immunoreactivity of the radiolabelled PR81 towards MCF7 cell line was done by using Lindmo assay protocol. Under these conditions, the immunoreactivity of the radioimmunoconjugate was found to be 0.82. The biodistribution of ^{64}Cu–NOTA– anti MUC1 complex in the mice with normal and breast tumour at 6, 12, 24 and 48 h after intravenous administration, expressed as percentage of injected dose per gram of tissue (%ID/g). Biodistribution and imaging studies at 24 h and 48 h post-injection revealed the specific localization of complexity at the site of tumours.

^{64}Cu–NOTA– anti MUC1 is a potential compound for molecular imaging of PET for diagnosis and follow up of MUC1 expression in oncology.

PS1-03

In house preparation and biodistribution of ^{64}Cu-ATSM, ^{64}Cu- PTSM and ^{64}Cu-DOTATATE for theranostic application

Author: Thaer Assaad

Co-author(s): Abdul. H Al Rayyes; Mahmoud Al-Ktaifani

AECS, Syrian Arab Republic

Corresponding author: thassaad@aec.org.sy

In this work the radiolabelling and biodistribution of ^{64}Cu-ATSM, ^{64}Cu-PTSM and ^{64}Cu-DOTATATE were carried out. A routine production method of no-carrier-added $^{64}CuCl_2$ was performed through the nuclear reaction ^{68}Zn(p,αn) ^{64}Cu from high current solid target. By using suitable proton energy, the amount of ^{67}Cu had been neglected the end of synthesis which constitutes about 1%. High quality ATSM, PTSM and DOTA-TATE were synthesized in our laboratory and then characterized by NMR, FTIR spectroscopies and MS spectrometer. All compounds were successfully labelled with ^{64}Cu and the radiolabelling yields of the labelled compounds were greater than 98%. Biodistribution of ^{64}Cu- DOTATATE were performed at 0.5, 1 and 1.5 hours. Whereas the biodistribution of ^{64}Cu-ATSM and ^{64}Cu-PTSM were carried out at 1, 2 and 3 hours. The results show that ^{64}Cu-DOTATATE, ^{64}Cu- ATSM and ^{64}Cu-PTSM are rapidly and efficiently cleared from the blood. Only less than 1% of the injected activity/g remains in blood pool. Normal ^{64}Cu-DOTATATE biodistribution in kidneys increase and stabilize at 10% of the injected dose per gram at one-hour post injection. Whereas stabilize at 2.5 % of injected dose per gram in the liver healthy cells. ^{64}Cu-ATSM shows a lower uptake in the myocardium than ^{64}Cu-PTSM.

PS1-04

Trends and perspectives in prostate-specific membrane antigen based radiopharmaceuticals in Mexico: the experience of the National University

Author: Miguel A. Avila Rodriguez

National Autonomous University of Mexico, Mexico

Corresponding author: avilarod@uwalumni.com

The Positron Emission Tomography (PET) Center of the National Autonomous University of Mexico (UNAM) is a state-of-the-art molecular imaging facility. It was the first PET center in Mexico and nowadays it continues at the forefront in this field in the country. The cyclotron radiopharmacy facility of this centre produces a broad palette of radiopharmaceuticals for PET-based molecular imaging applications in oncology, neurology, and cardiology, maintaining for almost two decades the forefront of innovation in the field of PET imaging in Mexico. In 2014 we introduced in the country the use of ^{68}Ga-labelled prostate-specific membrane antigen (PSMA) and given its high demand, and the exponential rise in the cost of the ^{68}Ge/^{68}Ga generators, it was recently decided to move to ^{18}F-labelled PSMA. Currently, a research project is under way to evaluate the clinical use of ^{64}Cu-labelled PSMA, a better imaging option when considering theranostic applications. The aim of this work is to highlight the versatility and possibilities to prepare PSMA binding agents labelled with different radionuclides with high yields and radiochemical purity (RCP), suitable for routine clinical applications.

The preparation of ^{68}Ga-PSMA-11 (^{68}Ga-PSMA) was performed in an iQS module (ITG GmbH) using a generator of the same brand. Briefly, an aliquot of 100 µl containing 12.5 µg of PSMA-11 (ABX GmbH) was diluted with 900 µl of 0.25 M NaOAc, mixed with 4 ml of $^{68}GaCl_3$ (0.05 M HCl), and incubated for 10 min at room temperature. Purification was made by SPE using a Sep-Pak C18 cartridge. ^{18}F-PSMA-1007 (^{18}F-PSMA) was synthetized in a cassette-based automated synthesizer (Trasis GmbH). Briefly, the aqueous ^{18}F-trapped on an ion-exchange cartridge is eluted with an ethanolic solution of tetrabutylammonium bicarbonate and evaporated to dryness. The trimethylammonium PSMA-1007 precursor is added to the residue and labelled by nucleophilic substitution to yield the crude ^{18}F-PSMA, which is then purified by SPE. For the preparation of ^{64}Cu-NOTA-Benzoil-NCS-HYNIC-iPSMA (^{64}Cu-iPSMA), the iPSMA-conjugate was synthetized at the National Laboratory of Research and Development of Radiopharmaceuticals (LANIDER), and labelled with $^{64}CuCl_2$ produced via the ^{64}Ni(p,n)^{64}Cu nuclear reaction, using a labelling kit approach.

The non-decay-corrected yields for ^{68}Ga-PSMA and ^{18}F-PSMA were 70±10% (n=10) and 40±5% (n=3), respectively, obtaining in both cases a RCP≥98%. The labelling yield of ^{64}Cu-iPSMA was almost quantitative with a RCP≥97% (n=5), without the need of purification.

Over the past few years PSMA-PET has become the gold standard method for the diagnosis of prostate cancer and it is especially useful to evaluate recurrent disease with low PSA levels. The introduction of ^{18}F-PSMA will mitigate the “ups and downs” in the availability of ^{68}Ga-PSMA because of the radioactive decay of generators, while ^{64}Cu-iPSMA will be of great value to obtain late images that better suit theranostic approaches using PSMA binding agents.

PS1-05

Membrane interacting peptides as Positron Emission Tomography (PET) based infection imaging probes

Author: Jyotsna Bhatt Mitra[1]

Co-author(s): Archana Mukherjee[1]; Kumar Mukesh[1]; Dash Ashutosh[1]

[1]Bhabha Atomic Research Centre, India

Corresponding author: jyob59@gmail.com

Ubiquicidin (UBI) or ribosomal protein S30 (RS30) is a result of post-translational processing of a 133-amino-acid fusion protein Fau, consisting of an N-terminal 74-amino-acid polypeptide FUBI and the C-terminal 59 amino acid RS30 polypeptide also known as Ubiquicidin. Fragments derived from the RS30/ubiquicidin are known to detect bacteria in-situ. UBI (29-41) has been labelled with ^{99m}Tc as well as ^{68}Ga and ^{18}F in order to develop single photon emission computed tomography (SPECT) agent and positron emission tomography (PET) based infection imaging agents respectively. A smaller fragment UBI (31-38) is also reported to show uptake in infectious foci. We set out to compare the potential of radiolabelled UBI (29-41) and UBI (31-38) fragments as PET based infection imaging probes with the aim of improving the sensitivity of detection.

To facilitate ^{68}Ga labelling, 1,4,7-triazacyclononane-1-glutaric acid-4,7-diacetic acid (NODAGA) conjugated peptide fragments UBI (29-41) and UBI (31-38) were utilized in the current study. Interaction of peptide conjugates was studied with bacterial as well as mammalian membranes models using isothermal titration calorimetry (ITC) and circular dichroism (CD). These peptide conjugates were labelled with ^{68}Ga in order to develop PET based infection imaging agent and tested for radiochemical purity (RCP), serum stability and in-vitro association with bacteria. Bio-distribution of the ^{68}Ga labelled peptides was carried out in mice bearing infection to understand the pharmacokinetics of these agents.

Both peptides selectively interacted with bacterial membrane model (anionic) and not with mammalian (neutral) membrane models. UBI (29-41) interacted more strongly with bacterial membrane model as compared to the octapeptide UBI (31-38). Stronger interaction of UBI (29-41) with bacterial membrane model could be explained by greater propensity to form helix in a “membrane like environment”. Both peptide conjugates could be labelled with ^{68}Ga, with high RCP. ^{68}Ga labelled peptide conjugates were found to be comparable in terms of in-vitro association with bacteria and biodistribution in mice bearing infection.

In conclusion, our results indicate that NODAGA-UBI (29-41) was superior to NODAGA-UBI (31-38) with respect to binding bacterial membranes.

PS1-06

^{99m}Tc(N)(DASD)(pnpn)]+ (DASD=1,4-dioxa-8-azaspiro[4,5]decandithiocarba pnpn=bisphosphinoamine) for myocardial imaging

Author: Cristina Bolzati [1]

Co-author(s): Nicola Salvarese[1]; De Nardo Laura[2]Laura Melendez-Alafort[3]; Valentina Gandin[4]; Davide Carta[5]; Cristina Marzano[4]

1 ICMATE-CNR, Italy
2 Dipartimento di Fisica e Astronomia, Università di Padova, Italy
3 Veneto Institute of Oncology IOV-IRCCS, Italy
4 Department of Pharmaceutical Sciences, University of Padua, Italy
5 Department of Pharmaceutical Sciences, University of Padua, Italy

Corresponding author: cristina.bolzati@cnr.it

^{99m}TcN-DBODC5 ([DBODC = bis(N-ethoxyethyl)-dithiocarbamate; 5 = bis(dimethoxypropylphosphinoethyl)-ethoxyethylamine]) is the lead candidate of a series of heteroleptic monocationic proposed compounds, for their favourable biodistribution profile, as myocardial perfusion imaging agent (MPIA). Phase I clinical studies clearly showed that its clinical properties were comparable to those of the commercially available agents. Therefore, direct modification of ^{99m}TcN-DBODC(5) to increase its pharmacokinetic profile, by obtaining an ideal myocardial imaging without interference from the adjacent organ activities, would be desirable. This work describes the synthesis, characterization and the biological evaluation of four new cationic 99mTc-nitrido complexes, of general formula [^{99m}Tc(N)(DASD)(PNPn)]+(DASD=1,4-dioxa-8-azaspiro[4,5]decan dithiocarbamate; PNPn=bisphosphinoamine), abbreviated to ^{99m}TcN-DASD(n), proposed as improved MPIAs.

^{99m}TcN-complexes were synthetized by a two-step reaction. The chemical nature of the compounds was determined by carrier-added experiments supported by radio/UV-HPLC and LC-MS analyses. Mechanistic studies were performed in-cellulo by using drug sensitive human cancer cell lines and the corresponding drug resistant sublines and in-vivo. Biodistribution studies were performed in rats and compared with the distribution profiles of ^{99m}TcN-DBODC(5) and ^{99m}Tc-Sestamibi. The in-vitro and in-vivo metabolisms of the best compounds were evaluated by chromatographic methods.

^{99m}TcN-DASD(n) compounds were obtained in high yield. Biological studies revealed that the complexes have a fast high initial and persistent heart uptake with rapid clearance from non-target tissues. Among the tested compounds ^{99m}TcN-DASD(5) and ^{99m}TcN-DASD(7) showed improved heart uptake with respect to the gold standard, with a rapid liver washout and superior heart-to-liver ratio. Cellular and in-vivo studies demonstrated that the compounds are membrane potential responsive and are avidly transported by Pgp-MRP1. Metabolism studies evidenced a remarkable in-vivo stability of these agents.

^{99m}TcN-DASD(5) and ^{99m}TcN-DASD(7) are promising MPIAs. The rapid pharmacokinetic profiles might shorten the duration of imaging protocols below 30 min allowing the early acquisition of images with high quality. In oncological field, the advantage of the in-vivo pharmacokinetic profile can also be applied to tumour imaging.

PS1-07

Clinical indications and labelling procedures influencing in vitro stability and early myocardial uptake of ^{99m}Tc-tetrofosmin

Author: Salah Eddine Bouyoucef[1]

Co-author(s): Amel Fellah[2]; Amel Taïbi[2]

[1]Department of Nuclear Medicine CHU Bab El Oued, Algeria
[2]Nuclear medicine department, Algeria

Corresponding author: as.taibi@yahoo.fr, salaedine@yahoo.fr, benbetka.amel@yahoo.com

^{99m}Tc tetrofosmin is a lipophilic cationic agent (diphosphine group) used for imaging myocardial perfusion during stress and at rest. The myocardial uptake of [^{99m}Tc] tetrofosmin appears to occur by a passive diffusion process. However, the uptake and retention curve models of ^{99m}Tc tetrofosmin by myocardial tissue are not well established. Particularly early images for myocardial perfusion imaging and stability of [^{99m}Tc] tetrofosmin are not well defined. 15 preparations of [^{99m}Tc] tetrofosmin and 40 patients have been used to study the different parameters that are part of the process of labelling in order to study the stability of [^{99m}Tc] tetrofosmin and its early uptake at 5 minutes by myocardial muscle. The studied parameters were the pH, temperature of storage, time of agitation and the way of intravenous injection. Radiochromatography was performed at different times during 6 hours and early myocardial uptake was estimated by the ratio heart/mediastinum uptake. Early results confirm that constant agitation and storage temperature are influencing the in vitro stability of [^{99m}Tc] tetrofosmin meanwhile clinical indications and the PH of the injected solution of [^{99m}Tc] tetrofosmin are influencing the early uptake of [^{99m}Tc] tetrofosmin by the myocardium.

PS1-08

Development, characterisation and in vivo evaluation of two ^{68}Ga- labelled NPY analogues as potential tracers for breast cancer imaging

Author: María Elena Cardoso Moreno[1]

Co-Authors[1]: Kevin Zirbesegger; Leticia Fernández; Eduardo Savio; Mariella Teran Gretter; Ana Maria Rey Rios

[1]Universidad de la República Oriental del Uruguay-UdelaR, Montevideo, Uruguay

Corresponding author: mariaelenacardosom@gmail.com

Receptor targeting with radiolabelled peptides has gained attention in nuclear medicine since these are over-expressed in many proliferative processes. In particular, researchers found that Neuropeptide Y (NPY) type 1 receptor is over-expressed in 90% of breast carcinomas.

The aim of the present study was to develop and characterise two ^{68}Ga-labelled NPY analogues with potential application in breast cancer imaging. Two peptides were used (L1, L2), both having the active sequence (Tyr-Arg-Leu-Arg-BPA-Nle-Pro-Asn-Ile-OH), NOTA as a chelator and a molecule of lysine as a spacer.

The amino acid sequences of both peptides are identical but L2 has an acetyl group (–COCH3) in the amino residue of the spacer (L1: H-Lys(NOTA)-Tyr-Arg-Leu-Arg-BPA-Nle-Pro-Asn-Ile-OH) (L2: Ac-Lys(NOTA)-Tyr-Arg-Leu-Arg-BPA-Nle-Pro-Asn-Ile-OH).

Each peptide (100 µg, 5.85x10-5 mmol) was incubated with [^{68}Ga]$GaCl_3$ (60-100MBq,0.2 mL), at pH 4.5 and 95ºC for 10 minutes. Physicochemical characterisation included: radiochemical purity (RCP) assessed by RP-HPLC, lipophilicity (through partition coefficient between octanol and phosphate buffer pH 7.4), plasmatic protein binding (PPB) by size exclusion. Stability in plasma and in labelling milieu was assessed up to 2 hours. Challenge with 100 molar excess of diethylenetriaminepentacetic acid (DTPA) was performed by HPLC. Biological behaviour was evaluated in accordance to the University Ethics Committee regulations, in female nude mice bearing MCF7 cancer xenograft induced with 1x106 cells injected subcutaneously into the right hind leg. Tumour was allowed to grow 4 weeks up to an average mass of (0.07+0.02)g. Biodistribution was determined one hour post injection of each tracer.

Both complexes were obtained with RCP higher than 95% and were stable in plasma and in reaction milieu. Log P values were (^{68}Ga-L1=- 3.2+0.1) and (68Ga-L2 =-2.6+0.1). Protein binding values were (31.7+0.4) % for ^{68}Ga-L1 and (20.1+0.3)% for ^{68}Ga-L2. Challenge with DTPA, in both cases showed high stability and no trans-chelation of the gallium for up to 2 hours.

Both complexes showed low blood and muscle uptake and high renal excretion, ^{68}Ga-L2 higher uptake in liver and kidneys compared to ^{68}Ga-L1. The target/non target ratio expressed as % of injected dose/gram) was (3.5+0.4)% for ^{68}Ga-L1 and (4.7+0.4)% for ^{68}Ga-L2.

Labelling strategy was adequate for obtaining both complexes with high RCP and remarkable in vivo stability. Even though both complexes showed similar behaviour, ^{68}Ga-L2 was less hydrophilic and had lower PPB value compared with ^{68}Ga-L1, probably due to the addition of the acetyl group to the amino group of the spacer. Biodistribution studies showed that renal elimination is the main route of excretion in both cases. Although tumour uptake is moderate favourable T/nT ratio encourages performing further studies in cell lines in order to conclude about the potentiality of both tracers as promising radiopharmaceutical for breast cancer imaging.

Acknowledgements: ANII (POS_NAC_2016_1_130455), Pedeciba-Química.

PS1-09

[^{89}Zr]ZrOx/Cl preparation based on commercial cassette base, synthesis module

Author: Emiliano Cazzola[1]

Co-author(s): Jonathan Amico[1]; Daniele Peruzzi [1]; Giancarlo Gorgoni[1]; Giorgio Keppel[2]; Giorgio Azzolini[2]

[1]Sacro Cuore Hospital, Italy

[2]INFN-LNL Istituto di Fisica Nucleare-Legnaro National Laboratories, Italy

Corresponding author: emilianocazzola@me.com

^{89}Zr is one of the emergent isotopes due to the favourable PET imaging characteristics (β+max 0.395 MeV; 22.7%) and half-life (T½78.4h) ideals to label antibodies. Monoclonal antibodies (MAbs) are the most approved biopharmaceutical in the word with a multiple and selective target. The immune PET can facilitate the approval for new MAbs and can help on patient selection. Due to needs of a robust production, purification and labelling procedure, it should be optimized on automatic modules in order to minimize the operator dosimetry and increase the reproducibility.

The aim of this work is based on an easy modification of automatic, cassette base, and commercial module in order to dissolve and purify the ^{89}Zr, in both formulations currently used from sputtered target. The single use cassette reduces the possibility to accumulate metal impurities in the purification step due to missing mandatory cleaning steps on synthesis modules, based on fixed tubes technology.

An Eckert&Ziegler cassette base module were used to set up an automatic dissolution and purification procedure. The Sputtered ^{89}Y targets were bombarded on TR-19 cyclotron at 12.5 MeV without degrader at different current 20-60 μA for a variable time 30-240 minutes. The coins were transferred on dedicated coated hot cells and finally inserted on a EZAG module in order to dissolve and purify the [^{89}Zr]/[^{89}Y] material in a single use cassette. A 2 N HCl solution was used to dissolve the target material, the solution was transfer to ZR resin (Triskem) and recovered on vial in oxalate or chloride form.

Ten sputtered targets were processed after bombardment and final impurities profile were evaluated by γ-spectrometry and by ICP-MS.

In conclusion, what we described on this work is one of the possible ways to optimize the ^{89}Zr production starting from ^{89}Y sputtered target, with a simple and single use cassette recovery process based on EZAG module to minimize the impurities.

PS1-10

[^{18}F]-FPSMA1007 synthesis HPLC free on FASTLAB platform QC evolution

Author: Emiliano Cazzola

Co-author(s): Paolo Colombo; Daniele Peruzzi; Armando D'Angelo; Alberto Purgato; Jonathan Amico; Matteo Malachini; Giancarlo Gorgoni

[1]*Sacro Cuore Hospital, Italy*

Corresponding author: emilianocazzola@me.com

Over the past years, many different PET agents have been developed to investigate on prostate cancer (PC) to make the non-invasive approach a reality, in order to replace the biopsy and the related complications. The PC is the most common cancer that affect the male population. Due to the high incidence of this pathology, is mandatory to investigate on a fluorine-18 tracer that gives the possibility to overcome the gallium-68 tracers' limitations.

During the last year we have optimize a [^{18}F]FPSMA1007 synthesis HPLC free on Ge FASTLab® module and related HPLC control. The aim of this study is to show the results of the routine productions in terms of yield and quality control by evaluation of two elution solutions (TBAHCO3/ACN or K222/ACN/K2CO3) and two HPLC methods. The reference one, based on Eclipseplus C-18 and a new one based on Ascentis express Peptide Es C-18 column.

The synthesis method is based on one step synthesis using a new precursor commercialized by ABX and is tuned on Ge FASTLab® synthesizer. All the reagents are included on a single use cassette. The ^{18}F was trapped on QMA and eluted with a mixture of TBAHCO3/ACN or K222/ACN/K2CO3. After drying at 125℃ on synthesis reactor, the dissolved ABX precursor in DMSO was added to proceed with the nucleophilic [^{18}F]-Fluorination. The reaction mixture was heated up at 95℃ for 10 min the reaction step, then the mixture was cooled at 35℃ to start the purification step followed by formulation. The total process takes place on 37 minutes.

HPLC analysis was performed on an Agilent 1260 Infinity HPLC equipped with an Agilent 1260 UV detector and a Raytest gamma-ray detector, controlled with OpenLAB. The analysis was performed on a 4,6x100 Eclipse Plus C18 3,5µm (Agilent) in isocratic conditions using CH3CN and 0.1 % TFA (70/30 run time 15 min) flow 0.8 ml/min and on 4,6x150 Ascentis express Peptide Es C-18 2,7um flow 1.3 ml/min in gradient methods using CH3CN and a solution of dihydrogen phosphate and phosphoric acid.

Two different elution solutions were used to compare the final process yields, at the same time, high activity runs were performed, in different inlet activity range, to evaluate the yield and product stability in final formulation. For stability study a range of 1-2.5 GBq/ml radioactive concentration was evaluated at room and at 40℃ for up to 12h. According to the final product formula specifications, the synthesis yield was stable in a range 35-55 % at the inlet activity range (55-185 GBq) with a very high Am (800-3500 GBq/µmol) at EOS.

The radiochemical purity for all the runs were always higher than 95%. The chemical HPLC profile shows differences in separation for the FPSMA1007, OHPSMA1007 HPSMA1007 and reaction precursor that make a difference in the chemical purity evaluation.

All the performed synthesis by using the K222 elution solution shows slightly lower yield compared to TBA. At the same time only the HPLC methods based on Ascentics column allow to have a right chemical purity evaluation due to more efficient peak resolutions.

PS1-11

Preparation of single patient dose of Lu-177-DOTA-Rituximab – using low specific activity Lu-177-chloride

Author: Avik Chakrabotry[1]

Co-author(s): Arpit Mitra[2]; Sangita Lad[1]; Sujoy Gaikwad[1]; Megha Tawate[1]; Sudeep Sahu[1]; Swati Bagul[1]; Sreeja Menon[3]; Sharmila Banerjee[4]

[1]Radiation Medicine Centre, BARC, Mumbai, India
[2]Medical Cyclotron Facility, RMC, BRIT, Mumbai, India
[3]Health Physics Division, BARC, Mumbai, India
[4]Radiation Medicine Centre, BARC, Mumbai, India & Medical Cyclotron Facility, RMC, BRIT, Mumbai, India

Corresponding author: sharmila@barc.gov.in, arpitmitra@gmail.com, avikbarc@gmail.com

Limited access to high specific activity Lu-177 in India and its cost provides necessary impetus for the present work on the development of Lu-177-DOTA-Rituximab by using low specific activity Lu-177. Based on the advantageous/favourable nuclear properties of Lu-177 over the I-131, the development of Lu-177-DOTA-Rituximab was obviously pertinent. Towards this we attempted to optimize the radiolabelling of Lu-177-DOTA-Rituximab using low specific activity (<15 mCi/µg) and carrier added Lu-177-Chloride. The physicochemical, biological quality control parameters, in vitro stability, immunoreactivity and cell binding studies were carried out in Daudi cell-lines. In vivo biodistribution studies were also carried out in suitable animal models.

Lu-177-Chloride was produced at our research reactor. Rituximab(10mg/mL) pre-concentrated from 500µL to 100µL using 30kDa MW cut-off filtration device at 5000rpm for 22minutes. Coupling of rituximab (5mg/100µL, 34.75nM) with p-NCS-benzyl-DOTA (240µg/24µL, 347.56nM) carried out at 1:10 molar ratio incubating at 37degC for 22hr. The conjugated reaction mixture purified using preconditioned PD-10. The DOTA-benzyl-Rituximab eluted from PD-10 using 0.2M sodium-acetate buffer(pH~5.5) and its concentration was estimated by Bradford's assay at 570nm. Prior to radiolabelling, pH of Lu-177-Chloride (285-300mCi in 250-275µL) adjusted to 6.5-7.0 using 0.2M sodium-acetate solution. Lu-177-Acetate incubated with 124µL of DOTA-benzyl-Rituximab at 37degC for 80 minutes. After incubation the radiolabelled reaction mixture was purified using PD10 (pre-conditioned with 0.2M sodium-acetate solution). In-vitro stability of the Lu-177-DOTA-Rituximab was ascertained by adding ascorbic acid (40mg/0.5mL of 0.2M sodium-acetate solution). The RCP was evaluated using TLC-SG {(0.1M sodium-citrate buffer(pH-5.0)}and HPLC (size-exclusion column, 0.05M phosphate- buffer, pH~6.8). Gel-clot BET-assay and sterility test were performed.

Human Leukemia cell-line Daudi expressing CD20, used for in-vitro evaluation, grown in IMDM with 10%FBS at 37°C. In-vitro cell-binding studies performed by incubating Daudi cells in 1mL of internalization buffer (IMDM, 0.2%BSA) containing radioligand (~5pmol peptide) for 15, 30, 60 & 120 minutes and washed with PBS. Non-specific internalization assessed by addition of cold rituximab (5nmol). For membrane receptor binding assay, cells homogenates were incubated at above time points. Biodistribution studies carried out in Daudi cell-lines xenograft tumour bearing nude mice at 6h, 24h, 48h & 72h intervals and quantified by γ-spectrometer.

Using Lu-177 of low specific activity (< 15 mCi/µg), 60-65mCi of Lu-177-DOTA-Rituximab (single patient-dose) was prepared using ~300mCi of Lu-177-Chloride. Lu-177-DOTA-Rituximab was found to be clear, colourless, pH between 5.5-6.0 and RAC between 8-10 mCi/mL. The RCP of Lu-177-DOTA- Rituximab estimated by TLC was >98% with retention-factor 0.00-0.10. RCP derived by HPLC was >95% with retention-time of labelled product between 14.5–15.5minutes. EL <6EU/mL, radiopharmaceutical was sterile. In-vitro and serum stability of the product indicated stability up to 96hr upon storage at -20°C with stabilizer.

Lu-177-DOTA-Rituximab showed rapid binding in Daudi cells (25%), reaching a plateau after 30 - 60 minutes. In biodistribution study, radioactivity decreased from most organs after 24h post-injection. High uptake and long-term retention of radioactivity found in tumour model which corroborates with scintigraphy studies.

Single patient dose of Lu-177-DOTA-Rituximab could be produced in optimum yield using 12-15 mCi/µg Lu-177. The product compares well with the preparation documented using NCA Lu-177. Further studies towards clinical translation of this promising radiopharmaceutical in patient are underway.

PS1-12

Synthesis of m-Iodobenzylguanidine (m-IBG) by solid phase method and its evaluation

Author: Ammar Charef

Co-author(s): Samia Boudjemai; S.Neffafa; A.Benzaid

Draria Nuclear Research Centre, Algiers, Algeria

Corresponding author: ammarcharef@yahoo.fr

Meta-iodobenzylguanidine (MIBG) radioiodinated with ^{123}I, and ^{131}I is one of the most important radiopharmaceuticals used in nuclear medicine. It is used for diagnosis and treatment of pheochromacytoma and neuroblastoma, imaging of adrenal medulla, and for studying heart sympathetic nerves. Almost described methods of synthesis of cold meta-iodobenzylguanidine hemisulfate are performed in accordance to Wieland and al procedure (1980), by condensation for 4 hours of meta-iodobenzylamine hydrochloride with Cyanamid into an oil bath heated at 100℃. This method seems to be long and difficult to implement for routine production.

The objective of this study was to develop an efficient and rapid method for preparing MIBG. Various experiments in order to reduce the time of the synthesis were carried out by heating in an oven a mixture of meta-iodobenzylamine Hydrochloride and cyanamide at 120℃ during several times. The second step was done according to Wieland's method. We have also studied the effect of the reaction time on the yield of meta-iodobenzylguanidine bicarbonate.

Physicals and chemicals properties of synthetized MIBG was evaluated by the determination of melting point, UV-Visible spectrophotometry, spectroscopy IR and HPLC.

Results showed high purity of synthesized molecule with yields similar to those obtained by Wieland and al (70%) and purity over 98 % after 30 min of reaction at 120℃. The HPLC analysis of MIBG gives a good retention time.

A procedure for radioiodinated of cold m-iodobenzylguanidine with iodine-125 has been developed in our laboratory. Freeze-dried kits prepared from MIBG (synthesized and reference), ascorbic acid and copper nitrate were reconstituted in deaerated distilled water and labelled with 9-18 MBq of sodium iodide (NaI-125). The vials were heated in an oil bath at 100 °C for 20 minutes.

The labelled MIBG kit presents a very high radiochemical purity and a high labelling efficiency.

PS1-13

In-house radiocolloid development for sentinel lymph node detection

Author: Putthiporn Charoenphun[1];

Co-author(s): Kittipong Thongklam[1]; Siripong Wittayachokkitikhun[1]

[1]Ramathibodi Hospital, Mahidol University, Thailand

Corresponding author: ps4436@hotmail.com

Currently sentinel lymph node (SLN) dissection is an important procedure alongside to the tumour removal surgery especially for breast cancer. In general, SLN can be localised with blue dye or radiocolloid. In nuclear medicine, several types of radiocolloid have been utilised such as ^{99m}Tc sulfur colloid, ^{99m}Tc nanocolloid including ^{99m}Tc dextran. One of the critical factors that influence the detection is the particle size of the radiocolloid because kinetic of the lymphatic system is strongly dependent on the size of colloid. The appropriated size should be less than 100 nm. Regarding costs of the commercial radiocolloid, the in-house radiocolloid has been required. Then, aims of this study were to develop and characterise the in-house radiocolloid kit for SLN detection.

The in-house dextran kit was developed in a kit form which was contained dextran and reducing agent. Then 0.5 mL of the solution was dispensed into the evacuated vials and stored at -20^{o}C until use. Approximately 3, 5 and 10 mCi $Na^{99m}TcO_4$ was labelled with the dextran kit in triplicate before the radiochemical purity (RP) was determined at 15 min, 3 h and 6 h post radiolabelling by instant thin layer chromatography (ITLC). The ITLC-silica gel and methyl ethyl ketone was used as a stationary and mobile phase, respectively. The size of the ^{99m}Tc dextran was evaluated by using transmission electron microscope. To examine the shelf life, 3 frozen dextran kits were labelled with $Na^{99m}TcO_4$ 5 mCi at 1, 3, 6 and 12 months after kit production and analysed for the RP. SLN detection using ^{99m}Tc dextran in breast cancer patients was retrospectively enrolled and compared with the blue dye technique.

The radiochemical purity of 3, 5 and 10 mCi ^{99m}Tc dextran were not altered after radiolabelling for 15 min, 3 h and 6 h which were greater than 98%. The transmission electron microscope result showed the non-uniformity of aggregation to form colloid with the diameter range of 15 nm to 40 nm offering the advantage for SLN detection. At the different storage times of 1, 3, 6 and 12 months, the RP results were 97.58 ± 0.33, 97.79 ± 0.52, 97.88 ± 0.33 and 98.09 ± 0.43, respectively. The concordance between blue dye and ^{99m}Tc dextran to detect SLN was comparable.

The in-house dextran kit showed a greater radiochemical purity than 98% over 6 hours post radiolabelling with the $Na^{99m}TcO_4$ activity up to 10 mCi. The optimum particle size was revealed. Its shelf life was up to 12 months. SLN detected by in-house radiocolloid was comparable to that of blue dye in breast cancer patients. Therefore, low cost in-house kit could be used in the routine service for sentinel lymph node detection.

PS1-14

Comparative preclinical evaluation of ^{68}Ga-labelled Neuromedin N and B for targeting glioblastoma malignant tissues

Author: E. Livia Chilug[1]

Co-author(s): Dana Niculae[2;] Radu Anton Leonte[1]; Gina Manda[3]; Cosmin Mustaciosu [1]; Vasile Lavric[4]

[1]*Horia Hulubei National Institute for R&D in Physics and Nuclear Engineering, Radiopharmaceutical Research Center, Romania*

[2] *University Politehnica of Bucharest, Faculty of Applied Chemistry and Materials Science, Romania*

[3] *"Victor Babes" National Institute of Pathology, Romania*

[4]*University Politehnica of Bucharest, Faculty of Applied Chemistry and Materials Science, Romania*

Corresponding author: livia.chilug@nipne.ro

Neuromedin N is a hexapeptide that shares the 4 amino acid Pro-Tyr-Ile-Leu homology with neurotensin and exhibits neurotensin-like effects in malignant glioma cells. Neuromedin B is a bombesin like peptide which specifically binds to BN receptors widely expressed in central nervous systems and in peripheral tissue and organs. This study was aimed to select and characterize the most effective Neuromedin peptide to target glioblastoma U87MG cancer cells.

DOTA-Neuromedin N and B were labelled with ^{68}Ga obtained from a ^{68}Ge/^{68}Ga generator, in order to quantify their ability to bind to their specific receptors expressed on glioblastoma U87MG cancer cells. The selective binding of peptides was characterized and their binding capacity towards NT receptors and BN receptors previously reported on U87MG cell line was tested. The influence of synthesis parameters like reaction time, evaporation time and pH upon overall process indicators and quality parameters of the final product were studied. The synthesis method has been translated to an automated synthesis module, which lead to a shortening of the process time, consistent high yields (>85%) and radiochemical purity greater than 90% for both radiotracers. The stability of the radiolabelled peptides was assessed up to 4h post-synthesis. Comparative preclinical in vitro assay of the cellular uptake–retention curves on U87MG cancer cells was performed in order to determine the time from incubation and peptide concentration at which the receptors are saturated, and to evaluate the retention profile over time. Specific binding of both peptides was characterized by selectively antagonized receptors blocking with SR 142948/48692 and NTRC 824 antagonists for neurotensin receptors and PD 176252/ML18 for bombesin receptors respectively. The results showed over 60% retention of ^{68}Ga-DOTA-Neuromedin B stable up to 80 minutes from incubation and more than 50% retention for ^{68}Ga-DOTA-Neuromedin N. The preliminary in vivo investigations (biodistribution and PET imaging) using both ^{68}Ga-DOTA-Neuromedin B and ^{68}Ga-DOTA-Neuromedin N on glioblastoma bearing mice, at 30 min and 60 minutes post-injection, have shown promising results for glioma malignant tissues imaging.

Acknowledgements: this work was supported by a grant of the Romanian Ministry of Research and Innovation UEFISCDI project number 64PCCDI/2018.

PS1-15

Development of ready-to-use ^{177}Lu-PSMA-617 formulation for treatment of inoperable metastatic prostate cancer

Author: Vrinda Chouthkanthiwa[1];

Co-author(s): Ajish Kumar KS[2]; Navin Sakhare[1]; Anupam Mathur[1]; Chanda Arjun[1]; Ravi Seshan[1]; Sandip Kumar Nayak[2]; Venkatesh Rangarajan[3]

[1] Board of Radiation and Isotope Technology, India
[2]Bhabha Atomic Research Centre, India
[3] Tata Memorial Hospital, India

Corresponding author: vrinda@britatom.gov.in

Prostate cancer is the second most prevalent cancer worldwide. ^{177}Lu-PSMA-617 has emerged as a useful therapeutic modality in the management of metastatic castration-resistant prostate cancer. The present work describes a ready-to-use ^{177}Lu-PSMA-617 injectable formulation of the produced therapeutic radiopharmaceutical by using medium specific activity ^{177}Lu (> 15 Ci/mg) and evaluated for its integrity and performance three days post its preparation.

The radiolabelling procedure was optimised typically for 10.0 GBq dose; by heating $^{177}LuCl_3$ (corresponding 0.1-0.2 mL; Sp. Act. > 555 GBq/mg) with commercially available (CMR, Russia) or indigenously synthesized PSMA-617 peptide (2.0-2.5 equiv.) in sodium acetate buffer (pH 5.0; 0.6 mL) containing sodium ascorbate (2 mg) at 95℃ for 15-20 min. The crude radiolabelled product was then passed through Sep-Pak C18 purification assembly to yield the final product in ethanol which was diluted with 0.1 M sodium acetate buffer containing 2% sodium ascorbate to reduce the final ethanolic content below 10%. The diluted radiopharmaceutical was then sterilized by membrane filtration and dispensed as a single patient dose (7.4 GBq) with activity calibration of 2 days. The preparation was then stored at -20℃ and shipped under dry ice conditions.

Peptide to metal ratio and pH of the reaction mixture are key factors responsible to achieve high radiolabelling yields (> 95%) and hence recoveries of the radiolabelled product post C18 purification. Out of 15 batches, only one batch, recovery yield observed was less than 95%. The labelled product, at a radiochemical concentration of the range of 740 ±74 MBq/mL (0.1 M sodium acetate buffer with 2% sodium ascorbate) was found to be stable for 9 days when stored at -20℃. Ten clinical studies were carried out in diseased patients with activities in the range of 5.55-7.40 GBq by using ready-to-use formulation. 1- 3 days post its formulation, it showed an affinity towards the lesions with symptomatic relief to the patients.

A new ‘ready-to-use’ ^{177}Lu-PSMA-617 formulation has been developed and validated for its end-use up to three days post its formulation. Clinical effectiveness studies showed a positive response in a limited number of diseased patients.

PS1-16

Impact of hospital production vs commercial kits purchase of ^{68}Ga-DOTA peptides

Author: Julien Costes[1]

Co-author(s): Kilian Casagrande[1]; Judith Delage[1]; Olivier Fabre[1]; Joelle Caputo[1]; Joelle De Figuereido[1]; Nicklaus Schaefer[1]; John Prior[1]; Farshid Sadeghipour[1]

[1] *Pharmacie, Centre Hospitalier Universitaire Vaudois, Switzerland*

Corresponding author: julien.costes@chuv.ch

^{68}Ga-DOTA peptides, somatostatin analogs, are used for neuroendocrine tumours diagnosis. Commercial kits of ^{68}Ga-DOTATATE are available for this indication with an expansive supply. The aim of this study is to evaluate the impact of a switch from commercial kits to a hospital production of ^{68}Ga-DOTATOC.

To synthetize this radiopharmaceutical in our laboratory, a quality dossier has to be submitted to the local authority, Swissmedic. In this dossier, we must describe the synthesis and quality control (QC) methods and validate them on three batches. Synthesis was done with Mini AiO® synthesis module (TRASIS, Belgium). For each batch, all QC required by European Pharmacopeia (8th edition) were performed. Moreover, an additional filter integrity test was done with Mini AiO® to assess the sterility of the synthesis process. Then, the synthesis of ^{68}Ga-DOTATOC was compared to ^{68}Ga-DOTATATE kits in regard to costs and time of production.

On validation batches, activity yields were 84.4% ± 6.31%. All QC parameters were in conformity with the limits prescribed by the pharmacopeia monography. Calculated radiochemical purity was 99.36% ± 0.15% and residual ethanol measured was 7.77% ± 0.83%. Microbiological analyses (sterility and endotoxin) showed that the entire synthesis process allows sterility conditions. Furthermore, filter integrity test was successful for all batches.

Synthesis module is in a hotcell with a microbiological class A with a regular microbiological monitoring. Sedimentation plate and filter integrity test are also performed before pharmaceutical release. Based on these parameters, sterility and endotoxin analyses will be performed only on validation batches and every 6 months.

On one hand, synthesis and QC control of ^{68}Ga-DOTATOC are longer than ^{68}Ga-DOTATATE kits respectively 60 minutes vs 30 minutes and 130 minutes vs 15 minutes. Indeed, more QC are needed for ^{68}Ga-DOTATOC (HPLC, GC) whereas only PRC determination by TLC and pH measurement are required for ^{68}Ga-DOTATATE kits. Thus, additional human resources and materials are necessary for hospital production.

But, on the other hand products for ^{68}Ga-DOTATOC synthesis are cheaper than ^{68}Ga-DOTATATE kits. Based on a number of 130 synthesis per year scheduled by the nuclear medicine department, hospital production allows to obtain human resources and an important saving for the institution.

^{68}Ga-DOTATOC is conveniently prepared in sterile conditions by using Mini AiO® synthesis module with high radiochemical purity (> 99.3%) and enough final activity for 2-3 patients in a single batch. The advantageous costs saving compared to the commercial kits available in Switzerland prompt to extend this work to other ^{68}Ga radiotracers.

Moreover, radioprotection benefits of automatized synthesis vs manual preparation of commercial kits could be assessed in a future study.

PS1-17

Optimization of labelling α,γ–mangosteen isolated from mangosteen cortex fructus (garcinia mangostana l) with radionuclide technetium-99m for cancer detection

Author: Isti Daruwati[1]

Co-author(s): Dwina Indriani Putri[2]; Aang Hanafiah Ws[2]

[1] *National Nuclear Energy Agency of Indonesia (BATAN), Indonesia*
[2] *Indonesian College of Pharmacy (STFI), Indonesia*

Corresponding author: isti@batan.go.id

There are usually no complaints and symptoms in the early-stage of cancer where the patient is not aware of the presence cancer in their body. The spread of cancer cells could be prevented if known earlier. One of the early methods of cancer detection which is currently being developed is a technique in nuclear medicine by using radiopharmaceuticals. A radiopharmaceutical has two components: a radionuclide and a pharmaceutical. Technetium-99m has a half-life of 6 hours and a pure gamma ray transmitter (140 KeV) for diagnosis. Mangosteen is isolated from the pericarp of Garcinia mangostana L which is a widely developed anticancer activity. α-mangosteen, and γ-mangosteen compounds have anti-cancer effects in cancer cell proliferation disorders; so α, γ-Mangosteen is expected to be a carrier that will bind technetium-99m to cancer cells. This study has aimed to determine optimal labelling conditions α, γ-mangosteen with technetium-99m radionuclides. Determination of pH conditions, the number of reducers, the number of ligands used, and the variation of incubation time is essential to produce optimal labels. We labelled α, γ-mangosteen with technetium-99m by using a directed method. The result showed that the optimum condition for ^{99m}Tc-mangosteen were 500 µg mangosteen, 20 µg SnCl2.2H2O, 20 µL tween 80 (0,1%), pH 8 and 5 minutes incubation time at room temperature. ^{99m}Tc-mangosteen has a radiochemical purity of 99.41 ± 0.04% with stability for 3 hours which has fulfilled the requirements (more than 90%). Based on the results of ^{99m}Tc-mangosteen compounds above are expected to be used for early detection of cancer.

PS1-18

Radiopharmaceutical production of ^{68}Ga-PSMA at the National Cancer Institute, Bogotá, Colombia

Author: Nidia Esperanza Delgado Lopez

Co-author(s): Javier Antonio Rada; Jonathan A Sanchez; Carlos Perez; Amelia De Los Reyes; Carlos Granados; Augusto Llamas; Cesar Sanchez; Jairo Otalora; Wilson Cardenas; Alejandro Barrera

[1] *Instituto Nacional de Cancerologia, Colombia*

Corresponding author: ndelgado@cancer.gov.co

^{68}Ga-prostate-specific membrane antigen (PSMA) radioligand diagnostic is a novel diagnostic option in patients with metastatic prostate cancer. The aim of this work was to standardize an efficient automated synthesis method for radiolabelling radiopharmaceutical-grade ^{68}Ga-PSMA for PET/CT diagnosis of prostate cancer.

We employed PSMA-HBED-CC (PSMAHBED) peptide manufactured according to GMP requirements (purity >96%) obtained from ABX (Advanced Biochemical Compounds) and 1850 MBq ITG ^{68}Ge/^{68}Ga generator consisting of organic-matrix column metal free. Sodium acetate, ascorbic acid, NaCl, HCl Ultrapur and EtOH was obtained from Merck.

Automated synthesis module “Taddeo” from COMECER was installed in a shielded Hot cell and used for radiolabelling. The ^{68}Ga solution was eluted from the generator with 7mL of 0.1M HCl at a flow rate of 2.5mL/min and transferred to a PS-H+ column and eluted with 5M NaCl (1.8mL). The total ^{68}Ga activity (1400MBq) were transferred directly into the reaction vessel containing 5µg PSMA-HBED-CC peptide, dissolved in 1mL of Acetate buffer 1.0M with pH 4 and Ascorbic acid 10µL, heated to 92°C per 8 min. To process the radiolabelling product Strata-X-tubes pre-conditioned (Phenomenex) were used. The ^{68}Ga-PSMA-HBED-CC was retained and unreacted ^{68}Ga passed through into a waste vial. The Strata-X-tubes were then washed with 5mL of pure water and the ^{68}Ga-PSMA HBED-CC was recovered with 1.2mL EtOH/Water (1:1) followed by 10 mL of 0.9% saline. Finally, the product was sterile-filtered under aseptic conditions through 0.22µm membrane filter (Milex-GV, Millipore) and the activity was measured in a Capintec-CRC-15R dose calibrator.

The radiochemical purity and identity of the ^{68}Ga-PSMA solution was assessed by RP-HPLC equipped with a UV and ɣ detector. A Lichospher-100 column C-18 (25mm x 4.6mm, 5µm) was used as a stationary phase. The mobile phase was as follows: 0-0.5min: 95%B; 0.5-10min: a linear gradient 80% A, flow rate 2ml/min (6). Retention times were 1.5- 2.0 min for free ^{68}Ga (III) and 4.9- 5.1 the themodynamically more stable diastereomer (RR), 5.2- 5.4 the thermodynamically less stable.

An indicator strip was used for the pH analysis of the ^{68}Ga-PSMA dose and the Bacterial endotoxin content was analysed using an Endosafe R system (LAL test), the values limit was <175/IU/ml. The sterile filter integrity test of the ^{68}Ga-PSMA solution was performed with a limit value >50psi ^{68}Ge-contamination was detected and quantified using a gamma counter (at full open window and at a 1min measurement time) retaining the preparation for at least 48h to allow ^{68}Ga to decay to a level allowing the detection of the impurities. The total radioactivity due to ^{68}Ge must not be >0.001% referred to the original activity.

Radionuclidic identity and purity tests were performed by gamma-ray spectrometry and the principal gamma peaks analysed, energies of 511Kev and 1077Kev were only allowed. The physical half-life was measured 3 times using a Capintec-CRC-15R Radioisotope Dose Calibrator. The half-life must be 62-74min.

Sterility test was performed by an external laboratory, according to the current US-pharmacopoeia.

The synthesis of ^{68}Ga-PSMA-HBED-CC parameters were optimized as described previously with 75% +/- 5% decay corrected radiochemical yield. The production of ^{68}Ga-PSMA-HBED-CC was within 28 min+/-1. Over the study period we made 52 synthesis of ^{68}Ga-PSMA-HBED-CC. The radiochemical purity was >99.7% as two diastereomers, with pH range 5.5-7.0. The ^{68}Ge impurities was found to be <0.0010% in the radiolabelled compounds. All samples passed the bacterial endotoxin test at values <10IU/mL and the sterility test. The residual solvent of the final product was ethanol in less than 10%. Up to date we have injected 45 patients.

We have shown that it is possible to perform an automated synthesis to ^{68}Ga-PSMA-HBED-CC using an automated synthesis module “Taddeo” from COMECER ensuring a quality and high radiochemical yields and radiochemical purity > 99.7%.

PS1-19

Complexes of copper and bismuth cations with acyclic and macro- cyclic polyamines bearing picolinic pendant arms

Author: Bayirta Egorova[1]

Co-author(s): Taisia Kalmykova [1]; Daria Likhosherstova[1]; Anastasia Zubenko[2]; Anna Bakhareva[2]; Anna Priselkova[1]; Yury Fedorov[2]; Olga Fedorova[2]; Stepan Kalmykov[1]

[1]Lomonosov Moscow state university, Russia

[2]A. N. Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences, Russia

Corresponding author: bayirta.egorova@gmail.com

By this time acyclic and macrocyclic ligands with picolinate moieties became very attractive for binding of Pb2+, Bi3+, REE3+ and Cu2+. As soon as linear and cyclic ligands are already used in radiopharmaceuticals and characterized by different benefits and drawbacks, we decided to evaluate both types with the same set of picolinic arms. Here we present our first results on complexation of cations with new ligands possessing picolinate arms L1-L4.

All ligands were characterized by using NMR-spectroscopy, elemental analysis and potentiometric titration. For complex stability study with Bi3+, Cu2+ and Pb2+ potentiometric titration and competitive extraction technique with radioactive tracer were used. Labelling experiments with radioisotopes of ^{61,64}Cu and ^{207}Bi were performed for leading compounds. Dissociative stability of formed complexes in presence of biologically relevant cations as well as re-chelation of radionuclides by serum proteins were studied. Control of labelling efficiency and dissociation of complexes was carried out by thin layer chromatography and protein precipitation accompanied by gamma-spectrometry.

Obtained results show lower protonation constants of macrocyclic ligands obviously because of the presence of carbamide groups. However, complexation constants with Cu2+ and Bi3+ for L4 reach quite high values logK=14.6 and 19.6 respectively. Leading complexes with Cu2+ and Bi3+ possess logK=18.7 and 27.7 for L3. The latter characterized by the largest number of donor atoms and absence of amide groups in contrast to L4 demonstrates the most promising complexation ability. Conditions for effective labelling of L3 by ^{61,64}Cu and ^{207}Bi were determined and synthesized complexes were challenged with excess of Ca2+, Fe3+, Zn2+, stable Cu2+ and serum proteins. It was shown that for >95% radiolabelling yield of L3 and L4 by ^{207}Bi is achieved at c(L)=0.4 mM and 1mM and by ^{61,64}Cu at c(L)=0.2 mM for both ligands. BiL3 and BiL4 in presence of serum proteins have shown slow trans-chelation up to 40% in 1 hour and to 50-60% in 16 hours. It should be noted that acyclic ligand L3 releases cation much faster and it could be the sequence of well-known tendency of linear ligands to form kinetically unstable complexes. After summarizing all obtained results, we can conclude that novel picolinate-containing ligands form complexes almost immediately at room temperature and formed complexes demonstrate stability in vitro.

Acknowledgement: this work was supported by Russian Foundation for Basic Research project №18-33-20152.

PS1-20

Synthesis and preclinical evaluation of ^{64}Cu-NOTA-HYNIC-iPSMA

Author: Guillermina Ferro-Flores

Co-author(s): Blanca Ocampo-García; Myrna Luna-Gutierrez; Clara Leticia Santos-Cuevas

Institutito Nacional de Investigaciones Nucleares, Mexico

Corresponding author: guillermina.ferro@inin.gob.mx

Because of its beta-negative (negatron) and beta-positive (positron) particle emissions, ^{64}Cu is useful for PET imaging and therapy 1. ^{99m}Tc-HYNIC-iPSMA has demonstrated high ability to target tumours over-expressing the prostate specific membrane antigen (PSMA) useful for SPECT imaging. One critical aspect of this molecule is the presence of the HYNIC group acting as an additional lipophilic location for the coupling to the hydrophobic structure of the PSMA enzyme. Taking the advantage of HYNIC-iPSMA to detect prostate tumours, in this research we added NOTA to the molecule to obtain a new ^{64}Cu radiopharmaceutical with theranostic potential.

The objective was to synthesize and characterize biochemically ^{64}Cu-DOTA-HYNIC-iPSMA as well as to evaluate in mice its potential as a PET imaging agent for PSMA-positive tumours.

The p-SCN-Bn-NOTA (Macrocyclics, USA) was conjugated to the HYNIC-iPSMA ligand (molar ratio 0.95:1) by dissolving the compounds in 0.1 mL of 0.2M $NaHCO_3$ (pH 9.5) and incubated at 37°C for 1 h. After reaction, the sample was diluted to 50 mL using injectable grade water. The solution was filtered by membrane (0.22µm) and fractionated in sterile vials (2 mL and 100 µg of the conjugate per vial). Finally, samples were lyophilized and analysed by HPLC. The lyophilized vials containing NOTA-HYNIC-iPSMA (purity of 95%) were reconstituted with 1 mL of acetate buffer (1M, pH 5.0) plus 0.5 mL of $^{64}CuCl_2$ (pH 4) and incubated at 95°C for 10 min. The in vitro evaluation of the obtained radiopharmaceutical was carried out in human serum (stability) and in human prostate LNCaP cancer cells (cancer cell uptake). For PET images a lung in LNCaP micro-metastases model in athymic mice was used.

HPLC analyses of NOTA-HYNIC-iPSMA showed a high yield of the reaction (99%). Only 5% of HYNIC-iPSMA remained as a chemical impurity. Radio-HPLC analysis showed the formation of ^{64}Cu NOTA-HYNIC-iPSMA with a radiochemical purity of >98%. In vitro studies demonstrated high stability in human serum and a LNCaP cell uptake of 8.3±1.6 % (of the total activity) at 1 h. PET images showed a clear visualization of LNCaP metastases.

^{64}Cu NOTA-HYNIC-iPSMA obtained from kit formulations showed high in vitro an in vivo stability in human serum and specific uptake in LNCaP cells with potential as a new theranostic radiopharmaceutical.

Acknowledgment: This study was supported by the Mexican National Council of Science and Technology (“Laboratorio Nacional de Investigación y Desarrollo de Radiofármacos CONACyT”).

PS1-21

Bioconjugates of barium ferrite as a Ra-223 carrier in alpha-radioimmunotherapy

Author: Weronika Gawęda

Co-author(s): Aleksander Bilewicz

Institute of Nuclear Chemistry and Technology, Poland

Corresponding author: wu.maliszewska@gmail.com

Among all alpha particle emitters, only a few nuclides are of considerable interest for alpha-radioimmunotherapy because of their properties, such as half-live, high cytotoxicity and short path length. One of the most important issues, which affects the wider use of alpha-radioimmunotherapy in nuclear medicine, is the availability and price of the radionuclides. At-211 is produced by alpha irradiation at high-energy cyclotrons, which are available only in a few scientific centers in the world. Resources of Ac-225 and Bi-213 radioisotope are quite small. On the contrary to Ac-225, Ra-223 (T1/2=11.4d) is already easily (commercially) available. Ra-223 is easily obtained from the Ac-227/Ra-223 generator.

Unfortunately, Ra-223 as a member of Alkaline Earth metals, forms very weak complexes. Therefore, there is a lack of chelators which can effectively bind Ra-223, retain its daughter radionuclides and be coupled to targeting vectors. We propose to use barium ferrite (BaFe12O19) nanoparticles as multifunctional carriers for Ra-223 radionuclide for alpha-radioimmunotherapy and magnetic hyperthermia.

Barium ferrite nanoparticles labelled with Ra-223 were synthesized with a hydrothermal synthesis method in the autoclave. The reaction mixture of $FeCl_3$, $BaCl_2$ and $^{223}RaCl_2$ was alkalized with NaOH solution. Next, the reaction mixture was stirred in autoclave at 210^{o}C for 6 h. Obtained radioactive, magnetic [Ra-223] BaFe12O19 nanoparticles were washed with distilled water and hydrochloric acid (1 mM HCl). Yield of labelling was about 70% (for 100kBq Ra-223). Stability of the obtained radioactive nanoparticles was tested in various biological solutions: 1 mM PBS, 0.9% NaCl and in human blood serum. It is confirmed that Ra-223 was highly retained inside nanoparticles in every tested solution. Only about 25% of Pb-211 (decay product of Ra-223) was released to the solution. Obtained magnetic BaFe12O19 nanoparticles were characterized by transmission emission microscopy and dynamic light scattering. The diameter of synthesized nanoparticles was about 15-30 mn and the determined saturation magnetization of obtained nanoparticles in room temperature was about 42 emu/g.

In order to synthesize a radiobioconjugate having affinity to HER2 receptors, the monoclonal antibody trastuzumab was conjugated to the obtained barium ferrite nanoparticles. Firstly, the surface of barium ferrite nanoparticles was modified with 3-phosphonopropionic acid linker, and then, the monoclonal antibodies were coupled to the barium ferrite nanoparticles using the carbodiimide chemistry.

Synthesized bioconjugate was characterized by thermogravimetric analysis, dynamic light scattering and was tested for stability in biological fluids. The obtained [Ra-223]BaFe12O19-CEPA-trastuzumab radiobioconjugate almost quantitatively retains Ra-223 and the majority of the daughter products. Radiobioconjugate has high receptor affinity towards HER2 receptors expressing on ovarian cancer cells and exhibits high cytotoxic effect in vitro (SKOV-3 cell line).

Acknowledgement: this work was supported by National Science Centre of Poland (Grant OPUS 2016/21/B/ST4/02133).

PS1-22

Comparison of ^{68}Ga-NOTA-Bisphophonate with ^{99m}Tc-MDP in 34 patients with skeletal metastases in various type of cancers

Author: Roni George

Co-author(s): Raviteja Nanabala; Samuel Raja; Tony Alex; Bindhu S; Ajith Joy; Frank Roesch; MRA Pilllai

Doctors Diagnostic Nuclear Medicine and Research Centre, Medical College Ulloor Rd, Kerala, India

Corresponding author: ronigeorge88@gmail.com

There is an increasing preference of PET-CT over SPECT for evaluation of metastasis as the former is able to identify more lesions thanks to the higher resolution. Bisphosphonate ligands conjugated to chelates and labelled with ^{68}Ga are good choice as radiopharmaceuticals for PET-CT imaging in patients suffering from metastatic cancer. We present the comparison of ^{68}Ga-NOTA-Bisphosphonate (NOTA-BP) with ^{99m}Tc-MDP in 34 patients suffering from different types of cancer.

^{68}Ga-NOTA-BP was prepared by adding 4 ml of ^{68}Ga (555- 925 MBq) in 0.01 M HCl to 50 µg of NOTA-BP dissolved in 1 ml of 0.25 M sodium acetate buffer and heating at 95°C for 10 minutes. The product is passed through a 0.22 micron Millipore filter and radiochemical purity was estimated by TLC in 0.1 M trisodium citrate buffer.

Thirty four patients suspected to be suffering from metastatic bone cancer were administered with ^{68}Ga-NOTA-BP (185-260 MBq) in saline. Imaging was done one-hour post injection in a Siemens Biograph PET-CT machine. A low dose CT from head to toe was acquired prior to PET. PET images were done in 2 min per bed. ^{99m}Tc-MDP image was acquired in a GE SPECT-CT camera post 3-hour injection of ~740 MBq of activity. A visual comparison of the PET-CT and SPECT images were done.

Direct comparison was performed between both the scans which were interpreted by a nuclear medicine physician and a detailed analysis was done qualitatively regarding the number of lesions and quality of the images. The number of lesions detected by ^{68}Ga-NOTA-BP PET-CT was significantly higher when compared to the ^{99m}Tc-MDP bone scan. Tracer accumulation was seen both in lytic lesions as well as in sclerotic lesions with latter being higher. The uptake of ^{99m}Tc-MDP was less in lytic lesions, making them difficult to identify. The 2D planar acquisition gathered less information and decreased the specificity especially in suspicious vertebral and rib lesions, which required SPECT-CT acquisition and further clarification. This process made it more time consuming and tedious, whereas ^{68}Ga-NOTA-BP PET-CT obviated the need for it. The image quality of PET-CT was far more superior compared to the planar bone scan. The low dose diagnostic CT for anatomical correlation and attenuation correction that was performed increased the specificity of the study. Better lesion characterization and overall lesion detection was noted in the ^{68}Ga-NOTA-BP scan. Patients could be imaged within 50 to 60 minutes after injection significantly lower than Tc bone scan proving to be more pleasant to the patient.

In conclusion, PET-CT imaging using ^{68}Ga-NOTA-BP is superior to ^{99m}Tc-MDP for evaluation of metastatic bone cancer. PET-CT identified significantly a greater number of lesions as compared to ^{99m}Tc-MDP. Routine clinical use of ^{68}Ga based tracers for bone imaging will help in enhancing the utility of ^{68}Ge/^{68}Ga generator.

PS1-23

Methods of integration of radio Cu-64 label in luminescent copper nanoclusters for pre and intra operative imaging and therapy of pancreatic cancer

Author: Sony George

Department of Chemistry, University of Kerala, India

Corresponding author: emailtosony@gmail.com

This study illustrates our attempt to integrate radioimaging modality via incorporating radio Cu-64 on to luminescent Cu nanoclusters synthesized by using BSA (Bovine Serum Albumin) and HSA (human serum albumin). The Cu-64 [Cu nanoclusters] are further conjugated with Erlotinib, a EGFR receptive drug to attribute targeting ability to the tracer cluster towards pancreatic cancer cells. In addition, the radioactive copper moiety Cu-64 is a dual edged sword by virtue of being a positron as well as an electron emitter (deliver a selective cytotoxic dose of beta radiation) there by acting as theranostic agent. Cu nanocluster enveloped by BSA circumvents the challenges created by trans chelation and detachment of Cu-64. The affinity of the probe on the targets was assessed in in vitro studies with PAN C 1 cell lines. The developed integrated imaging dual modality is expected to improve intraoperative assessments of pancreatic tumour demarcation. Cu-64 PET probes can be employed for preoperative assessment of pancreatic cancer lesions. PET probes coupled with luminescent copper nanoclusters can be employed for enhanced visual imaging modalities which are quite requisite for accurate delineating cancer lesions in the emerging era of robotic surgery.

PS1-24

Potential radiotracers based on the 4'-O-methylhonokiol structure for PET visualization of neuroinflammation

Author: Natalia Gomzina

Co-author(s): Daria Vaulina; Olga Kuznetsova

N.P. Bechtereva Institute of Human Brain, Russian Academy of Science, Russia

Corresponding author: gomzina@ihb.spb.ru

Neuro-inflammatory processes are known to underlie the mechanism of neuronal damage and play a key role in the neurodegenerative disease progression. The cyclooxygenase 2 (COX-2) enzyme is one of the most studied neuroinflammatory biomarkers and an attractive target for PET imaging. Neolignan 4'-O-methylhonokiol (MH) isolated from Magnolia officinalis, has high anti-inflammatory activity and selectively inhibits the expression of COX-2 with IC50=0.062 μM, as was recently shown by Kim H.S. et.al., 2015. Here we report the synthesis of novel labelled MH derivatives ([^{11}C]MPbP and [^{18}F]FEtPbP) and their preliminary evaluation on the lipopolysaccha- ride (LPS)-induced neuroinflammation rat model.

The MH derivatives [^{11}C]MPbP (4'-[^{11}C]methoxy-5-propyl-1,1'-biphenyl-2-ol) and [^{18}F] FEtPbP (4'-(2-[^{18}F]fluoroethoxy)-2-hydroxy-5-propyl-1,1'-biphenyl) were obtained by 11C-methylation and

^{18}F-fluoroethylation of the precursor with Boc-protecting group using synthons [^{11}C]CH3I and [^{18}F] FCH2CH2Br, respectively. After HCl hydrolysis of intermediates the crude reaction mixtures were purified by semi-preparative HPLC. Neuroinflammation in rats was induced by an intraperitoneal injection of LPS from E.coli (2 mg/kg) before 24 h the administration of [^{11}C]MPbP, [^{18}F]FEtPbP, celecoxib or placebo into the tail vein (0.1-0.2 mCi/0.5 ml of phosphate buffer pH 7.4, containing ethanol (5-7%, v/v)). Celecoxib, a well-known non-steroid anti-inflammatory drug and a selective inhibitor of COX 2 was used as a reference. Ex vivo radioligand biodistribution was performed by direct radiometry of organs and tissues samples. The uptake of radioactivity was determined by the dose administered per gram of tissue (% ID/g).

[^{11}C]MPbP and [^{18}F]FEtPbP were obtained in decay-corrected isolated radiochemical yields 20 and 35 % based on the activity of the corresponding alkylating agent. The biodistribution data showed that the observed uptake in the brain of neuroinflammatory rats was 4 times higher than it was in intact animals. In addition, it was shown that [^{11}C]MPbP or [^{18}F]FEtPbP increased uptake occurred in the parts of rat brain where COX-2 expression was observed (pons&medulla).

A decrease in the radiotracer uptake by 2-3 times in these regions with the celecoxib pre-treatment may serve as evidence of this hypothesis. Synthesis of [^{11}C]MPbP and [^{18}F]FEtPbP, labelled MH analogues has been developed. On the rat neuroinflammation model, it has been shown that these radiotracers have the potential for PET imaging of neuroinflammation.

Acknowledgement: this study was funded by RFBR according to the research project 17-04-02119 A.

PS1-25

Direct production of ^{68}Ga using ^{68}Zn pressed target

Author: Brigitte Guérin[1]

Co-author(s): Aiman H. Alnahwi[1]; Sebastien Tremblay[1]; Samia Ait-Mohand[1]; Jean-François Beaudoin[1]; Véronique Dumulon-Perreault[2]; Étienne Rousseau[1]; Jean-Mathieu Beauregard[3]; Frédéric Pouliot[4]

[1] Université de Sherbrooke, Montreal, Canada
[2] CRCHUS, Canada
[3] CHU de Québec – Université Laval, Canada
[4] Centre de recherche du CHU de Québec - Université Laval, Canada

Corresponding author: brigitte.guerin2@usherbrooke.ca

Gallium-68 (^{68}Ga, T1/2 = 68 min) has attracted increasing interest in recent years due to the expanding clinical applications of ^{68}Ga-based radiopharmaceuticals. With this increased demand, there is a need for improving the ^{68}Ga production capacity. The aims of this study are to enhance the production yield of ^{68}Ga using pressed targets and the purification of ^{68}Ga by using an automated cassette-based purification process. We also compare the chemical, radiochemical and biological properties of -cyclotron and generator- derived ^{68}Ga for common nuclear imaging procedures.

Using a digital hydraulic press, the targets were prepared using enriched ^{68}Zn powder and were mounted on custom-made target supports. ^{68}Ga was produced using 19 MeV and 24 MeV cyclotrons, recovered by chemical dissolution and purified by chromatography with two cation exchange resins. The radiotracers were then formulated the usual way as [^{68}Ga]-DOTA-TATE and [^{68}Ga]-PSMA-617. The PET images and distribution patterns of the cyclotron and ^{68}Ge/^{68}Ga generator produced ^{68}Ga radiopharmaceuticals were compared in healthy rats and mice.

Up to 140 GBq of ^{68}Ga was produced following 90 min irradiation. The overall recovery yield of $^{68}GaCl_3$ was 89% with an EMA of 77 ± 5 GBq/µmol at EOB. The outcome was a radiochemical yield >95% of [^{68}Ga]-DOTA-TATE and [^{68}Ga]-PSMA-617. Cyclotron and generator produced ^{68}Ga radiopharmaceuticals were shown to be radioisotopically, chemically and biologically equivalent, giving matching images and identical kinetic and biodistribution patterns in animals.

Overall, these results show that irradiation of ^{68}Zn-pressed target is a very effective process. The cassette-based purification-process developed is rapid, simple, efficient and leads to high radiochemical yield and EMA of $^{68}GaCl_3$. Medical cyclotron can produce European Pharmacopeia compliant ^{68}Ga radiopharmaceuticals that can be used as substitute of generator derived ^{68}Ga.

PS1-26

Preparation of ^{177}Lu-DOTA-Trastuzumab: an insight into the in-house optimized radiochemistry procedures employed for patient dose preparation

Author: Mohini Guleria

Co-author(s): Tapas Das; Jeyachitra Amirdhanayagam; Ashutosh Dash

Bhabha Atomic Research Centre, India

Corresponding author: mohini@barc.gov.in

Trastuzumab (Herceptin®), a humanized monoclonal antibody, is an approved agent used for immunotherapeutic treatment of metastatic breast cancer as it targets HER2 (human epidermal growth receptors 2) receptors over-expressed in such cancer cells. Therefore, radiolabelled Trastuzumab is expected to have significant potential as a radioimmunotherapeutic agent for the treatment of cancer breast patients over-expressing HER2 receptors. The aim of the present study is to standardize the formulation protocol of ^{177}Lu-Trastuzumab and scale-up the preparation for administration in patients.

Trastuzumab was conjugated with a suitable bi-functional chelating agent (BFCA) namely, p-NCS-benzyl-DOTA by incubating Trastuzumab (5 mg, 35 nmol) and p-NCS-benzyl-DOTA (190 µg, 350 nmol) in sodium carbonate buffer (pH=9.5, 0.2 M) at 37 ℃ for 17 h. Post-incubation, the reaction mixture was purified using Amicon ultra-centrifugal units (MW cut off 10kDa) using NaOAc buffer (pH=5.0, 0.2 M). Determination of average number of p-NCS-benzyl-DOTA molecules attached per antibody moiety was carried out by UV-Vis spectrophotometry as well as by mass spectrometry using the MALDI-TOF technique. ^{177}Lu-Trastuzumab complex was prepared by incubating the purified Trastuzumab-BFCA conjugate (2 mg, 13 nmol) with $^{177}LuCl_3$ [150 µL, 80 mCi (2.96 GBq)] at 37 ℃ for 90 min at pH ~5.5. Percentage radiolabelling yield (%RCY) of the radiolabelled formulation was determined by paper chromatography (PC) using 0.1M sodium citrate solution as the mobile phase and high performance liquid chromatography (HPLC) using 0.05 M phosphate buffer with 0.05% sodium azide as the mobile phase. The radiolabelled preparation was purified by PD10 desalting columns using 0.2 M NaOAc buffer as the eluting solvent. The stability of the purified ^{177}Lu-Trastuzumab complex was determined till 4 days post-preparation by incubating the complex in phosphate buffered saline (PBS) at room temperature and carrying out the quality control analyses following the procedures mentioned above at various time intervals. The purified ^{177}Lu- Trastuzumab formulation was administered in 08 cancer breast patients [~5 mCi (185 MBq) in each patient] for studying preliminary pharmacokinetics and biological distribution of the agent.

An average of 7.5±1.2 p-NCS-benzyl-DOTA molecules were found to be attached per Trastuzumab moiety. HPLC studies showed that the ^{177}Lu-Trastuzumab conjugate could be prepared with a %RCY of 75.78±3.56 (Rt = 15.5 min and 21.5 min for ^{177}Lu-Trastuzumab and free $^{177}LuCl_3$, respectively), which was subsequently improved to >95 by purification through PD10 column (with average recovery of 72.8±1.2%). In-vitro stability studies showed that the %RCY of ^{177}Lu-Trastuzumab decreased to 84.15±1.57 after 4 days of storage at room temperature in PBS. Clinical studies in cancer breast patients revealed the accumulation of the radiolabelled antibody at breast cancer lesions with slow but gradual clearance of activity from blood and other non-target organs. An in-house procedure for the formulation of patient dose of ^{177}Lu-Trastuzumab was optimized. Preliminary clinical imaging studies revealed the retention of affinity of Trastuzumab towards the disease after functional modifications and radiolabelling procedures.

PS1-27

In vitro NK1R affinity evaluation of novel radioconjugates based on peptide antagonist SPANTIDE I and Ga-68/Lu-177 theranostic like isotopes for glioma cancer

Author: Paweł Halik[1]

Co-author: Ewa Gniazdowska[1]; Przemysław Koźmiński[1]; Piotr Lipiński[2]; Joanna Matalińska[2]

[1] *Institute of Nuclear Chemistry and Technology, Poland*

[2] *Mossakowski Medical Research Centre, Polish Academy of Sciences, Poland*

Corresponding author: p.halik@ichtj.waw.pl

The NK-1 receptor and its endogenous agonist Substance P (SP) is a system that have been connected with many physiological processes like angiogenesis, wound healing and activation of inflammation state mediator's synthesis. Moreover, the overexpression of NK-1 receptor is observed on certain types of cancer cells especially glioma, astrocytoma, melanoma, neuroblastoma and some types of lymphomas. This makes NK-1 receptor a potential target for cancer diagnosis and anti-tumour agents' therapy. Presently there are some known glioblastoma treatment trials with labelled derivatives of SP but none of them is effective enough.

High affinity to NK-1 receptor exert also antagonists of this receptor. SPANTIDE I [D-Arg1,D-Trp7,9, Leu-11]SP is a SP-analogue peptide antagonist designed with higher in vivo stability than natural SP (half-life of 2-3 minutes in human blood). There are also reports that inhibition action on NK-1 receptor can be correlated with antitumour activity of the inhibitor. That is why our goal is to synthetize novel radioconjugates based on peptide antagonist SPANTIDE I and evaluate their affinity and toxicity against glioma cancer cell lines.

In the course of this research we have synthesized two types of conjugates consisting of DOTA chelator and full peptide SPANTIDE I (1-11) or shorten peptide SPANTIDE I (5-11). Afterwards, we have obtained desired radioconjugates by labelling with Ga-68 or Lu-177 and performed an assessment of physicochemical parameters like lipophilicity and stability in human serum. Later, prepared radioconjugates have been evaluated on in vitro assay with chosen NK-1 overexpressed cell lines to determine their affinity to the receptor after structural modification. In the next step cytotoxicity assay has been performed.

We have successfully obtained high specific activity in all four radioconjugates: shorten SPANTIDE I (5-11)-DOTA and full SPANTIDE I (1-11) - (DOTA)2 labelled with Ga-68 or Lu-177. Presence of two DOTA chelators in full SPANTIDE I radioconjugates affects significantly on lower radioconjugates logP parameter in comparison with shorten SPANTIDE I (5-11) radioconjugates with one chelator. All four radioconjugates show full stability in human serum for more than 4 times of applied isotope half-life. In vitro assays confirm maintenance of receptor affinity of obtained radioconjugates on glioma cell line.

In conclusion, obtained radioconjugates fulfil many crucial aspects for the potential radiopharmaceuticals strictly required from the clinical application point of view. Gallium labelled radioconjugates may show a usefulness in diagnosis of NK-1 receptor overexpression and lutetium labelled SPANTIDE I peptides may complement the therapeutic application by similar in vivo action in theranostic idea of designed radioconjugates. Application concept of peptide NK-1 receptor antagonists may be a helpful reference in further development of tumour treatment solutions.

PS1-28

Synthesis, characterization and radiolabelling of iminodiacetic acid derivative with technetium-99m

Author: Walid Hamouda[1]

Co-author(s): Mohamed A. Motaleb[1]; Mahmoud El-Tawoosy[2]; Mohamed Abdallah[3]; Abdallah Hassan[3]

[1]Atomic Energy Authority, Egypt
[2]AEA, Egypt
[3]Zagazig University, Egypt

Corresponding author: waleedhamoda@yahoo.co.uk

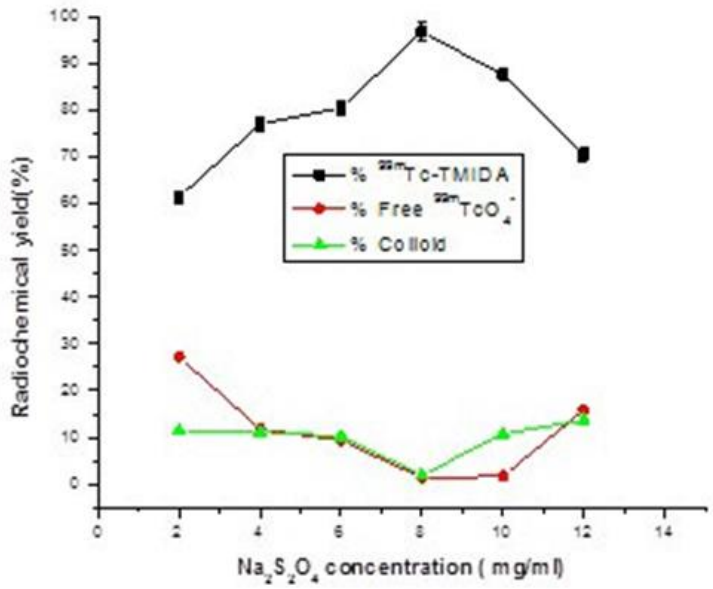
This study aimed to synthesize and characterize N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid (TMIDA) and then radiolabel it with technetium-99m by direct technique using sodium didithionite as reducing agent. The labelling parameters including TMIDA concentration, sodium didithionite concentration, pH of the reaction mixture, reaction temperature and reaction time were optimized.

The synthesis N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid (TMIDA) was prepared in two steps. The first one involves the synthesis of ω-chloro-2,4,6-trimethylacetanilide and the second step involves the synthesis of TMIDA by reaction of ω-chloro-2,4,6-trimethylacetanilide (10 mmol) and iminodiacetic acid (10 mmol) in 50% aqueous ethanol was refluxed for 5 h at 85℃ and adjusted to pH 11-12 with 10% NaOH every hour. The mixture was cooled to room temperature and the ethanol was removed using rotary evaporated. The mixture was extracted three times with diethyl ether. The aqueous layer was then adjusted to pH 2-3 with HCl and the precipitate was formed on cooling. The precipitate was filtered off, dried and recrystallized with ethanol to give TMIDA (Yield: 23.5 % and Mp: 218-221 ℃).

In the labelling procedure study TMIDA was labelled with technetium-99m by the direct technique using sodium dithionite (Na2S2O4) as a reducing agent as shown in scheme 2. To 100 µl of freshly eluted $^{99m}TcO_4$- (400 MBq), the required concentration of solid sodium dithionite was added directly with continuous stirring followed by immediate addition of the required TMIDA concentration, which dissolved in 0.1 M NaOH. The pH of the preparation was adjusted followed by incubation at room temperature at a specific reaction time. TMIDA concentration, $Na2S_2O_4$ concentration pH, reaction time and temperature were studied as factors affecting labelling efficiency. Each factor studying experiment was repeated three times.

Synthesis of N-(2,4,6-trimethylphenylcarbamoylmethyl)iminodiacetic acid (TMIDA). Synthesis of TMIDA was accomplished according to the reaction sequence in two steps. The first one involves the reaction between 2,4,6-trimethylaniline derivative and chloroacetyl chloride to give ω-chloro-2,4,6-trimethylacetanilide. The second step involves condensation reaction between ω-chloro-2,4,6-trimethylacetanilide and iminodiacetic acid at alkaline pH in ethanol for 5 h to give TMIDA.

The synthesized compound, TMIDA, was confirmed by IR, mass and 1H-NMR spectra. Factors affecting the percent radiochemical yield of ^{99m}Tc–TMIDA complex:



Biodistribution of ^{99m}Tc–TMIDA complex

In conclusion, TMIDA can be synthesized and radiolabelled using an easy and cheap method, considering the biodistribution data results, ^{99m}Tc-TMIDA can be used as a hepatobiliary imaging agent for an evaluation of the functional status of the hepatocytes and the patency of the biliary duct.

PS1-29

Radiosynthesis of 1-{4-[4-(2-[^{18}F] Fluoroethoxy)-phenyl] Piperazine- 1-yl} ethenone and its evaluation in animal models bearing C57BL6 melanoma xenograft

Author: Somnath Kar[1]

Co-author(s): Lakshminarayanan N.[1]; Avik Chakraborty[1]; Yogita Pawar[1]; Sutapa Rakshit[1]; Sharmila Banerjee[2]

[1] BARC, Mumbai, India

[2]Homi Bhabha National Institute, Trombay, Mumbai, India

Corresponding author: somnath.chem2013@gmail.com

Sigma receptors were initially described to be a subtype of opioid receptor, but later due to its unique characteristics it has been postulated as a distinguished receptor system. It is divided into Sigma 1 and Sigma 2 subtypes. Sigma receptors are well known for their over-expression in high density, in different types of tumours as in those of breast, melanoma, non-small-cell lung carcinoma, prostate, glioma and tumour of neural origin. Literature study shows that piperidine or piperazine moiety is an important pharmacophore showing binding affinity with the sigma receptors overexpressed on specific tumours. The present effort is directed towards the radiosynthesis of [^{18}F]fluoroethylated analogue of 1-Acetyl-4(4-Hydroxyphenyl) piperazine and evaluation of its potential as a tumour marker.

^{18}F-fluoride production and radiosynthesis were performed using GE PETtrace cyclotron and GE TRACERlab module (Configured for 2-[^{18}F]FDG production) respectively. [^{18}F] radiofluorination was carried out using dry [^{18}F] tetrabutylammonium fluoride. The radiosynthesis was carried out by a one-pot, two-step process. In the first step, [18F]fluoroethyl tosylate was synthesized by fluorination of ethylene ditosylate. In the second step, [^{18}F]fluoroethyl tosylate was tagged with piperazine analogue to form [^{18}F]fluoroethylated-piperazine analogue. The reaction mixture was purified using neutral alumina and Light C18 cartridges. The final product was eluted from the column with 10% ethanol. In-vitro cell uptake study was done by using melanoma cell line (B16F10). Bio-distribution in tumour xenograft model was carried out in C57BL6 mice with melanoma. Towards this B16F10 cell line (5x105 cells per mice) were injected in C57BL/6 mice. After 15 days the size of tumour was found to be 0.75-1 cm3. The size was considered to be sufficient for carrying out the studies. [^{18}F] activity of 200 µCi per mice was injected through tail vein. Mice were sacrificed at 30, 60, and 120, min post injection for biodistribution studies. The same mice which was used for bio-distribution after 120 min pi was used for imaging using PET-CT camera at 60 min pi.

As a result, the reaction conditions were optimized in order to obtain maximum yield of the radiolabelled product. The purity of the product was evaluated using Radio-TLC and radio-HPLC analysis and found to be more than 99%. A bed volume of 4 g neutral alumina and two Light C18 cartridges were found to be sufficient for efficient purification. A non-decay corrected radiochemical yield of 30% (n=4) was obtained with the reaction time of 60 min. In-vitro cell binding study shows good uptake in B16F10 cell line. Biodistribution study shows the compound to have good in-vivo stability and a significant tumour uptake till two hours. Tumour/blood ratio was found to increase with time. Hepatic and renal clearance pattern was observed at 120min pi.

In conclusion, [^{18}F]fluoroethylated piperazine analogue was successfully synthesized and purified, with a radiochemical purity of 99%. The radiotracer showed enough in-vivo stability. Biodistribution studies shows significant tumour uptake. Further uptake studies with different tumour xenograft models are underway.

PS1-30

Correlation between the yield of produced [^{18}F]FDG and the activity retained during synthesis

Author (s): Katerina Kolevska; Maja Chochevska; Maja Velichkovska;

Co-author(s): Filip Jolevski; Marija Atanasova-Lazareva; Jasmina Razmoska; Nikolche Doshlakoski; Zlatko Filipovski; Sasho Nikolovski; Marina Zdraveska-Kochovska; Ana Ugrinska

University Institute for Positron Emission Tomography, Skopje, North Macedonia

Corresponding author: kolevskakaterina@gmail.com

The radiosynthesis of 2-[^{18}F]fluoro-2-deoxy-D-glucose [^{18}F]FDG is a routine automated process at the University Institute for Positron Emission Tomography, Skopje, which is performed by using an IBA Synthera V2 synthesis module. [^{18}F]FDG is synthesized by nucleophilic fluorination followed by base-catalysed hydrolysis. The purification of the final product is accomplished by passing the hydrolysed reaction mixture through purification cartridges (strong cation exchange column, aluminium oxide column and C-18 bonded silica column). The objective of our study is to define whether there is a correlation between the production yield and the activity retained during synthesis.

The analysis include 63 batches of [^{18}F]FDG performed on the same module. The IFP cassettes and reagents kits were from the same manufacturer (ABX). In all the syntheses were used Waters

Sep-Pak cartridges (QMA, Alumina B, C18) and SPure SCX cartridge. The radiochemical purity was determined by thin layer chromatography using Raytest miniGITA TLC scanner. The radioactivity retained on the cartridges, reaction vessels, v-vials, tube connections and [^{18}O]H2O recovery vials, was measured using Biodex Atomlab 500 Dose Calibrator.

The results of the radiochemical purity show that the [^{18}F]FDG content is more than 99% of the total radioactivity in all of the batches. To interpret the results of the measured retained activity, we made five subgroups of the batches, depending on the yield (decay-corrected): less than 50%, 50-55%, 55-60%, 60-65%, more than 65%. One-way analysis of variance shows that there is no statistically significant correlation between the yield variability and the activity retained on the C18, QMA, SCX cartridges, tubes, reaction vessel, v-vial and recovery vial ($p>0.05$, for all seven correlations). The regression analysis of the activity retained on the alumina cartridge indicates negative linear regression (Fig.1).

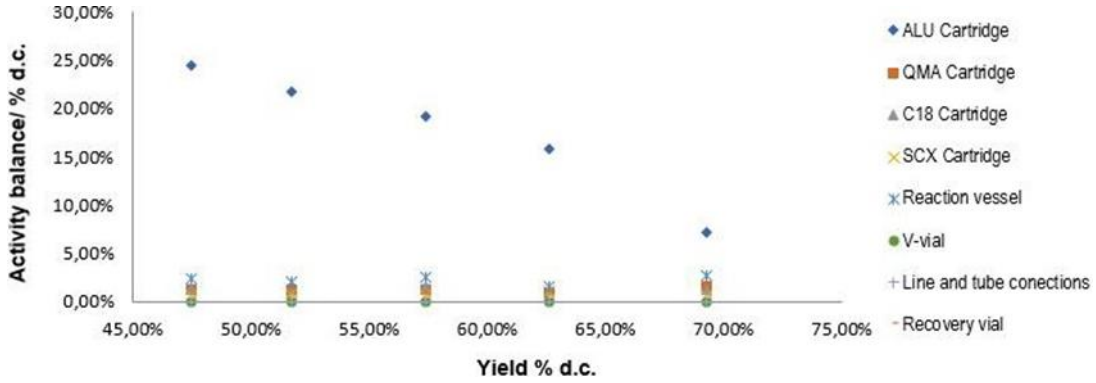


Figure 1: Regression analysis of the retained activity and the yield

A conclusion is made that in our automated [^{18}F]FDG synthesis process, there is statistically significant correlation only between the [^{18}F]FDG yield and the amount of radioactivity retained on the alumina cartridge, which adsorbs the unreacted [^{18}F] fluoride.

PS1-31

Nucleophilic synthesis of 6-[^{18}F]fluoro-L-DOPA via copper mediated radiofluorination

Author: Raisa Krasikova[1]

Co-author(s): Olga Fedorova[1]; Olga Kuznetsova[1]; Orlovskaya Victoria[1]

[1]N.P. Bechtereva Institute of Human Brain, Russian Academy of Science, Russia

Corresponding author: raisa_krasikova@inbox.ru

Radiopharmaceuticals for positron emission tomography (PET) bearing electron rich [^{18}F]fluorinated arenes are still in limited use as the direct introduction of [^{18}F]fluoride via commonly used SNAr is not suitable. Recently, several transition metal-mediated labelling strategies have been introduced to address this problem. Among them, radiofluorination of pinacol esters of arylboronic acids (ArylBPin) mediated by copper triflate complex with pyridine (Tredwell at al., 2014) is one of the more promising synthetic avenues under development. This new methodology allows to facilitate access to clinically relevant radiotracers, ^{18}F-ring fluorinated aromatic amino acids, drug-like molecules and others. However, implementation of the copper-mediated fluorination in automated synthesizers remain a challenging task. Several studies indicated that the choice of phase-transfer catalyst (PTC) and corresponding base used for the generation of reactive [^{18}F]fluoride species has a profound impact on the ^{18}F-fluorination fluorination of base-sensitive ArylBP in precursors. Here we introduce a new ^{18}F-processing protocol using tetrabutylammonium triflate (TBAOTf) as a neutral PTC and its application in the preparation of 6-[^{18}F]fluoro-L-DOPA via copper-mediated fluorination of commercially available ArylBPin precursor.

Radiolabelling precursor, 3,4-OMOM-6-(BPin)DOPA(Boc2)-OtBu, was kindly provided by ABX, Germany. Aqueous [^{18}F]fluoride was loaded onto QMA carb SepPak cartidge (46 mg) from the male side, the cartridge was rinsed by 1.5 mL of i-PrOH and dried with helium. ^{18}F was eluted in the opposite direction using a solution of 12.5 µmol of TBAOTf in 0.6 mL i-PrOH directly to a solution of 5 µmol of Cu(OTf)2Py4, 8 µmol of labelling precursor in 0.3 mL DMA. The mixture was heated in a sealed vial at 110℃ for 15 minutes under air. After intermediate purification (two C18 SepPak cartridges in a series) and acid hydrolysis the crude 6-[18F]fluoro-L-DOPA was purified by HPLC: RP-Amide, Supelco, 250 x 10 mm, NaOAc 10 mM + AcOH 50 mM + 0,1 g/l ascorbic acid; flow 4 ml/min; Rt 9 min.

Results showed: first, developed ^{18}F-processing protocol allowed to eliminate conventional azeotropic drying step and to facilitate automation. The use of TBAOTf as a PTC provides a high ^{18}F elution efficiency (up to 90%) and a radiochemical conversion of 83±6 (n=7) as determined by radioTLC. The desired tracer was obtained in a RCY of 20% (non-optimized, corrected for decay), radiochemical purity > 97% and enantiomeric purity > 98% within 80 min synthesis time. Notably, the suggested procedure employed reduced amounts of expensive precursor (8 µmol) and Cu-catalyst (8 µmol). Work is now in progress to optimize hydrolysis and purification conditions to increase isolated radiochemical yield.

In conclusion, the suggested novel ^{18}F-processing protocol enables the simple and efficient production of 6-[^{18}F]fluoro-LDOPA from commercially available ArylBPin precursor avoiding time consuming solvent evaporation steps. This method can be further extended for the preparation of other ^{18}F-ring fluorinated amino acids.

PS1-32

Evaluation of oxygen-18 water enriched for the production of fluorine-18 in a medical cyclotron

Author: Anees Muhammed K

Co-author(s): Raviteja Nanabala; Dilshad Kottuparamban; Ajith Joy; M.R.A Pillai

Molecular Cyclotrons, Kerala, India

Corresponding author: aneesk@moleculargloba l.com

PET-CT imaging using flourine-18 radiopharmaceuticals more specifically [^{18}F]FDG is an integral part of cancer management. Fluorine-18 is produced by bombarding ^{18}O enriched water with high energy proton beam. The quality of ^{18}O water and its enrichment ratio are very important to ensure higher yields. However, there are a number of other factors that influence the production of ^{18}F ions such as energy of cyclotron beam, beam current, volume of target and irradiation time. In a cyclotron which is routinely used for commercial production, the above factors are varied depending on the production needs. Hence, it is very difficult to do a direct comparison of the quality of different enriched water used. We have done a retrospective analysis of 18O enriched water supplied by two different vendors, the results are presented below.

These studies were done in a 11 MeV Siemens Eclipse HP self-shielded medical cyclotron. The cyclotron system has dual beam providing 11 MeV having beam current up to 60 µA in each beam line. Negative hydrogen ion (H-) is accelerated in quasi-spiral orbits and converted to proton beam by using extracting foil and impinged to water targets filled with ^{18}O enriched water to produce ^{18}F-ions by the nuclear reaction, ^{18}O(p, n)^{18}F. The cyclotron has two tantalum water targets having 2.6 ml capacity fitted for each beam line.

Oxygen-18 enriched water supplied by two vendors were, ABX advanced biochemical compounds, Germany and Taiyo Nippon Sanso Corporation, Japan were used in these studies. While the beam current was kept constant at 60 µA irradiations were done for different timings, 120,150, 165 and 180 min. The amount of radioactivity produced was transferred to Capintec CRC-55t PET dose calibrator for measurement.

The fluorine-18 activity formed was found to be different with the two different supplies of enriched ^{18}O water and as expected the 98% enriched water gave about 300 mCi higher activity as compared to 97% enriched water when irradiated for 120 min at 60 µA. The results were consistent at 150,165 and 180 minutes of irradiation, the average yield enhanced up to 5% in each target. Due to high demand of the ^{18}F radiopharmaceuticals, the higher the quantity of fluoride-18 produced, the economy of production improves with higher enriched water.

It is important to evaluate each, and every input used in a commercial site used for the preparation of F-18 radiopharmaceuticals. A judicious selection of enriched water from different vendors will help in achieving higher production yields, thereby improving the economy of operation of the machine.

PS1-33

Radiolabelled TATE functionalized gold nanoparticles for potential use in imaging and therapy of neuroendocrine tumours

Author: Dheeraj Kumar[1]

Co-author(s): Navin Sakhare[1]; Anupam Mathur[1]; Shubhangi Mirapurkar[1]

[1]Board of Radiation and Isotope Technology, India

Corresponding author: dheeraj.kum@britatom.gov.in

Peptide receptor radionuclide theranostics is a targeted approach for imaging and therapy of cancers. In this purview, a number of peptide-based derivatives such as octreotide analogues, are in clinical use utilizing $^{68}Ga/^{177}Lu$ radionuclidic pair. The octreotide peptide such as 3-Tyr-Octreotate (TATE) used for peptide receptor targeting is an agonist peptide which enters the tumour cell via somatostatin receptor mediated transport across the cell membrane. However, rapid elimination of the radiopharmaceutical from blood limits the uptake of the radiopharmaceutical in the tumours. To effect improved target uptake, there is an interest to explore the performance of radiolabelled TATE functionalized gold nanoparticles, as the later are known to have higher blood residence period. Surface modified gold nanoparticles are known to enter living cells and are an excellent candidate for utilization in biomedicines, mainly in cancers and carcinomas. The objective of the present work is to functionalize gold nanoparticles with TATE peptide along with DOTA chelator so as to radiolabel them with $^{68}Ga/^{177}Lu$ radionuclides and evaluate them for their theranostic potential.

Commercially available DOTA-TATE was directly used to functionalize Gold nanoparticles. Briefly, DOTA-TATE (0.7 mM, 0.5 mL) solution in water was added and mixed with a solution of $HAuCl_4$ (1mM) in TWEEN 80 (1mM). The resulting solution was then reduced rapidly with ice-cold NaBH4 (0.5 M, 1mL) to obtain the required 'TATE along with DOTA functionalized gold nanoparticles. The obtained gold nanoconjugates were purified by dialysis, characterized and then used for labelling studies. The labelling protocol involved direct addition of purified gold nanoparticles to $^{68}GaCl_3/^{177}LuCl_3$ activity (185 MBq) in 0.1M acetate buffer (pH 4-5), and the resulting reaction mixture was heated at 60℃ for 15-30 min to yield the radiolabelled TATE functionalized gold nanoparticles.

TATE having a disulphide linkage is expected to have affinity towards Au surface under reducing conditions. Such a formation was observed in the present experimental conditions and gold nanoparticles in wine red colour were obtained. The nanocolloidal solution using UV/Vis Spectroscopy gave a prominent peak at 512nm, thus confirming the nanocolloidal nature of the particle synthesized with size in the range 10-20 nm. The radiolabelling yield as determined by paper chromatography in 0.5M citrate buffer [Rf free MCl3 ($M=^{68}Ga/^{177}Lu$) =0.8-1.0; TATE functionalized Au-nanoparticle = 0-0.2] was observed to be >90% for both the radiometals. In vitro experiments in AR42J cell lines are underway to evaluate the potential of the functionalized gold nanoparticles in comparison with the DOTA-TATE metal complexes in clinical use.

Water dispersible Gold NPs functionalized with TATE peptide along with DOTA chelator has been successfully synthesized. These have been successfully labelled with radiometals in reasonable yields. Further cell experiments are underway to evaluate the efficacy of the labelled Au nanoparticles.

PS1-34

Recent advances in Ga-68 radiopharmaceuticals and Ga-68 bisphosphonates for the theranostic management of neuroendocrine tumours

Author: Vijay Kumar[1]

[1]Westmead Hospital, The Children's Hospital at Westmead & Sydney Medical School, Sydney University, Australia

Corresponding author: vijay.kumar@health.nsw.gov.au

Renaissance of ^{68}Ga-labelled peptides has given a new dimension to theranostic imaging of neuroendocrine tumours and prostate cancer. The outstanding success of ^{68}Ga-labelled agents in the last decade is primarily due to the availability of reliable, long-lived ^{68}Ge/^{68}Ga generators, extensive automation, development of new macrocyclic linker based ^{68}Ga chemistry, and a huge amount of clinical data in a short time.

Somatostatin receptors are over-expressed in neuroendocrine tumours such as pituitary adenoma, neuroblastoma and small cell lung carcinoma etc. These tumours are diagnosed with ^{68}Ga-DOTA-TATE and are effectively treated with ^{177}Lu-DOTA-TATE. The huge success in the management of neuroendocrine tumours led to rapid development in theranostic approach for prostate cancer management, as there was no specific diagnostic or treatment tool available prior to this agent. Urologists, endocrinologists and oncologists were very excited, and they passed on the benefits to the patients, the ultimate winners.

Availability of ionic ^{68}Ga from the ^{68}Ge/^{68}Ga generator is the key to the recent developments. Equally important is the development of macrocyclic linkers such as DOTA, NOTA etc. The ability of these linkers enabled the scientists to radiolabel a large number of ligands for clinical applications. The most extensively used agents are ^{68}Ga-DOTA-TATE for neuroendocrine tumours, and ^{68}Ga-PSMA for prostate cancer. The bifunctional chelators such as DOTA and NOTA were shown to bind ^{68}Ga and ^{177}Lu with equal efficiency and offered kinetic stability and thermodynamic stability, which is the under-pinning success for theranostic developments in the last decade.

New approaches are developed for therapy, which include combined PRRT (with other treatment modalities) such as chemotherapy (capecitabine, doxorubicin), kinase inhibitors (sunitinib, sorafenib), intraoperative use of probes after PRRT with ^{177}Lu and applications. Alpha emitters (eg. ^{225}Ac, ^{213}Bi, and ^{223}Ra) were shown to be highly effective. Frank Roesch's group has shown that bisphosphonates were good theranostic agents to deliver beta radiation to the bones and soft-tissues to augment therapeutic efficacy.

Recent developments in "theranostic approach" are the best thing to happen in nuclear medicine in the past decade. They have created extensive enthusiasm around the world to apply this technology for the benefit of the patients.

PS1-35

An automated synthesis method for Ga-68 labelled ubiquicidin 29-41

Author: Jannie Le Roux[1]

Co-author(s): Sietske Rubow [1]; Thomas Ebenhan [2]; Carl Wagener[3]

[1]Stellenbosch University, South Africa
[2]University of Pretoria, South Africa
[3]South African Nuclear Energy Corporation, South Africa

Corresponding author: jsleroux@sun.ac.za

Published methods for radiolabelling of ubiquicidin (UBI) 29-41 to date describe manual processes. Manual labelling of 1,4,7-triazacyclononane-1,4,7-triacetic acid ubiquicidin (NOTA-UBI) with Gallium-68 (Ga-68) has several disadvantages, including unnecessary radiation exposure to operators, and difficulty to meet Good Manufacturing Practice (GMP) requirements. The aim of this study was to develop an automated synthesis method for the labelling of Ga-68 NOTA-UBI.

Ga-68 activity was eluted from an iThemba Labs Ge-68/Ga-68-generator using 0.6 M HCl. This approach of developing an automated method first duplicated the manual method developed by Ebenhan et al. (2014) using the generator, eluant and consumables available at our PET Centre, followed by adaptations of the radiosynthesis to suit the automated module. Radiolabelling yield and radio- chemical purity were determined after each labelling experiment to compare the efficiency of each method and changes to the protocols.

Ga-68 NOTA-UBI was labelled using the following three generator eluate preparations: the Ge- 68/Ga-68 generator was eluted using fractional elution and 1.5 M 4-(2-hydroxyethyl) piperazine-1- ethanesulfonic acid (HEPES) was added as a buffering agent (method 1); fractional generator elution was done and 1.0 M sodium acetate solution was added as a buffering agent (method 2); and a cationic exchange-based pre-purification step was utilized to clean-up the full-scale generator eluate from any possible metal impurities and combined with 1.0 M sodium acetate solution as buffering agent (method 3). The pH of all labelling mixtures was adjusted to range between 3.5 – 4.0. Following radiolabelling, a C18-cartridge based separation of Ga-68 NOTA-UBI was performed to free the labelled product from impurities including colloidal Ga-68. This step was performed on all methods. Regardless of the methods applied, Ga-68 NOTA-UBI stability and further tests were performed after each radiosynthesis to justify the product validity for human administration.

NOTA-UBI was successfully labelled (n = 23) with Ga-68 using automated procedures for fractional elution and cationic pre-purification and sodium acetate as buffer. The best percentage of labelling efficiency (78.9 ± 3.6, n = 7) was obtained using the cationic pre-purification method. The average radiochemical purity for the cationic pre-purification method was 99.0 ± 1.7 (n = 7). When method 1 was used, the HEPES content in the final labelled product exceeded the limit prescribed in the European Pharmacopoeia which limited further use of HEPES buffer in these labelling methods. Stability and validation studies performed on the Ga-68 NOTA-UBI indicated that both, the fractional elution and cationic purification methods comply with specifications for batch release of radiopharmaceuticals intended for human use.

An automated synthesis protocol using a Scintomics GRP Module has been successfully developed and tested for robustness and repeatability. Both fractional elution and cationic purification automated methods using sodium acetate as a buffer can be utilised for the routine synthesis of Ga-68 NOTA-UBI under GMP conditions, demonstrating high radiochemical yield and purity. An automated cationic pre-purification method using sodium acetate resulted in the best labelling efficiency. HEPES as a buffer was however found not suitable for routine labelling of Ga-68 NOTA-UBI.

PS1-36

Formulation and radiolabelling of ethambutol with technetium-99m for detection of extrapulmonary tuberculosis

Author: Wening Lestari

Co-author(s): Anna Roselliana; Enny Lestari; Mujinah Mujinah; Witarti Witarti; Agus Ariyanto; Widyastuti Widjaksana

Center for Radioisotope and Radiopharmaceutical Technology, National Nuclear Energy Agency, Indonesia

Corresponding author: wening@batan.go.id

According to the World Health Organisation (WHO) tuberculosis (TB) is one of the top 10 causes of death worldwide. It was also reported in the world in 2017 that 10 million people fell ill with TB and 1.6 million died from the disease. TB is an infection caused by the bacterium Mycobacterium tuberculosis. TB usually attacks lungs, but it can also spread to other organs; this TB is commonly called extrapulmonary TB. This type of TB is relatively difficult to be detected by conventional methods, therefore a proper and specific method is needed. The Center for Radioisotope and Radiopharmaceutical Technology (CRRT) at the National Nuclear Energy Agency of Indonesia (BATAN) has been developing single-vial ethambutol radiopharmaceutical kits which can be used to detect this type of TB. The single-vial ethambutol kit is an improved form of the previous developed two-vial ethambutol kits.

Lyophilized ethambutol kits were aseptically prepared in the clean room and consisted of ethambutol, SnCl2.2H2O, mannitol and sodium pyrophosphate. Lyophilization of ethambutol kits was performed by using a freeze dryer with freezing step, primary drying and secondary drying for 42 hours, 3 hours and 3.5 hours respectively. Evaluation of single-vial ethambutol kit included clarity, pH, radiochemical purity, sterility and endotoxin. Radiochemical purity, sterility and endotoxin tests were performed using thin layer chromatography, direct inoculation and Tachypleus Amebo- cyte Lysate (TAL) respectively. Radiolabelling of ethambutol with technetium-99m was prepared by incubating the kit erials dissolved in 1.5 mL of Tc-99m at room temperature for 10 minutes.

Freeze-dried and sterile ethambutol kit has been prepared. Each ethambutol kit vial comprised a lyophilized mixture of 3.5 mg ethambutol, 1 mg SnCl2.2H2O, 5 mg mannitol and 17.5 mg sodium pyrophosphate. Radiolabelling of single-vial ethambutol was carried out by using 1.48 GBq of Tc-99m to result in a clear ^{99m}Tc-ethambutol complex with radiochemical purity of above 85% and pH 9. Endotoxin test which was performed by using TAL, gave a concentration of Lysate < 0.25 EU/mL. The sterile lyophilized single-vial ethambutol kits, radiolabelled with Tc-99m, have been clinically tested for diagnosis of extrapulmonary TB in adults as well as children patients at the Hasan Sadikin Hospital, Bandung, Indonesia. The results showed that ^{99m}Tc-ethambutol can be used as a safe, effective and non-invasive alternative modality for diagnosis of extrapulmonary TB.

In conclusion, freeze-dried ethambutol kit, a sterile product, has been developed and suitable for diagnosis of extrapulmonary tuberculosis.

PS1-37

Radioconjugates based on the monoclonal antibody Nimotuzumab® for use in radioimmunotherapy

Author: Rene Leyva Montaña[1]

Co-author(s): Alejandro Perera Pintado[1]; Angel Raimundo Casacó Parada[2]

[1]Centro de Isótopos, Cuba
[2]Centro de Inmunología Molecular, Cuba

Corresponding author: rene@centis.edu.cu

Target-specific radiopharmaceuticals are becoming increasingly utilized in the management of cancer because they provide the unique tool for target-specific delivery of radionuclides to the diseased tissues. The encouraging results observed in the radioimmunotherapy of hematologic tumours have not yet been translated to solid tumours. The investigation of new radionuclides, new molecular constructs and better targeting strategies to prevent or overcome host toxicities will translate to progress in the therapy of solid tumours. For tumours associated antigens like EGFR, molecules that are overexpressed in tumours but are also expressed in normal tissues, monoclonal antibodies with intermediate affinity might have preferential uptake in target tissues overexpressing target antigen, while might decrease toxicity in normal tissue. In this work the preparation and preclinical evaluation of radioconjugates based on Nimotuzumab monoclonal antibodies with intermediate affinity and selected trivalent radiometals are described.

Nimotuzumab is radiolabelled with selected trivalent radiometals using bifunctional chelators. The cell-binding characteristics and toxicity of the radioimmunoconjugates was assessed using radioimmunoassay in cultured cell lines. Tumour targeting properties of Nimotuzumab labelled with ^{177}Lu, ^{90}Y and ^{188}Re were evaluated in mice bearing human carcinomas xenografts with varying EGFR expression levels.

The radiolabelling procedures yielded a high and reproducible radiometal complexation suitable for the practical preparation of radiopharmaceuticals. Radioconjugates with high radiochemical purity and specific activity without significant loss in the targeting function were obtained. Radioimmunoconjugates showed higher cell growth inhibition in cultured cell lines (overexpressing EGFR or HER2) than unmodified monoclonal antibodies. Optimized preparation of Nimotuzumab labelled with n.c.a. ^{177}Lu showed high stability in vivo. ^{177}Lu-Nimotuzumab showed high specific tumour uptake accompanied by low uptake in normal tissues in mice bearing EGFR-overexpressing human epidermoid (A431) tumour xenografts. Preparation of radioimmunocojugate with 90Y and its preclinical evaluation is also described. The results using ^{188}Re in a Phase I clinical trial are also included in the present investigation.

PS1-38

Preclinical evaluation of the theranostic ^{68}Ga/^{177}Lu-[DOTA-CXCR4- L] pair

Author: Myrna Luna-Gutiérrez

Co-author(s): Guillermina Ferro-Flores; Nallely Jiménez-Mancilla; Blanca Ocampo-García; Marcela Ávila-Sánchez; Clara Santos-Cuevas; Erika Azorín-Vega

Instituto Nacional de Investigaciones Nucleares, Mexico

Corresponding author: myrna.luna@inin.gob.mx

The chemokine-4 receptor (CXCR4) is overexpressed in more than 23 types of human cancers that metastasize to distant organs. In the progression of breast cancer and its metastases, the overexpression of CXCR4 has been demonstrated in 90% of triple-negative breast cancer tumours.

To prepare and evaluate the in vitro and in vivo ability of ^{68}Ga-CXCR4-L and 177Lu-CXCR4-L ligands to target the CXCR4 protein in glioblastoma and triple-negative breast cancer cells.

^{68}Ga labelling was performed by adding 1 M acetate buffer (pH 4.0) and gallium-68 chloride obtained from a ^{68}Ge/^{68}Ga generator (ITG, Germany) to a lyophilized formulation containing the cyclo(D-Tyr-D-[NMe]Orn(HYNIC-DOTA)-Arg-Nal-Gly) ligand [DOTA-CXCR4-L] followed by incubation at 95℃ for 10 min. For ^{177}Lu labelling, 1 M acetate buffer (pH 5.0) and lutetium-177 chloride (ITG, Germany) were added to a lyophilized vial containing the DOTA-CXCR4-L following by incubation at 95℃ for 30 min. The radiochemical purity was evaluated by reversed-phase HPLC and ITLC-SG analyses. Stability studies in human serum were performed by size-exclusion HPLC. In vitro and in vivo cell uptake was tested using human breast cancer cells (triple-negative DU-4475) and human glioblastoma cells (U87MG) with blocked and non-blocked receptors. Images were obtained in athymic mice with induced DU 4475 or U87MG pulmonary micrometastasis by using a micro- SPECT/PET/CT system.

^{68}Ga-DOTA-CXCR4-L and ^{177}Lu-DOTA-CXCR4-L obtained with radiochemical purities of 95% and 99%, respectively, showed high stability in human serum and specific in vitro and in vivo recognition in glioblastoma and triple-negative breast cancer cells. Using pulmonary micrometastasis DU-447 and U87MG models, a clear uptake of both radiopharmaceuticals was observed.

The results obtained in this study warrant further preclinical studies to evaluate therapeutic efficacy of ^{177}Lu-DOTA-CXCR4-L, as well as dosimetry and clinical studies to determine the specificity and sensitivity of ^{68}Ga-DOTA-CXCR4-L to target the chemokine-4 receptor in different kind of tumours. Acknowledgment

Acknowledgment: this study was supported by the Mexican National Council of Science and Technology (“Laboratorios Nacionales” and CONACyT-SEP-CB-2018, A1-S-36841).

PS1-39

Study of the physicochemical stability of HMPAO-Technetium (^{99m}Tc)

Author: Anis Majoul[1]

Co-author(s): Asma Toumi[2]; Najla Ayachi[2]; Kaouthar Chatti[1]

[1] *Hopital Sahloul, Sousse, Tunisia*
[2] *Ministère de la santé, Tunisia*

Corresponding author: majoul.anis@gmail.com

^{99m}Tc-labelled hexamethylpropylene amine oxime (HMPAO) is used in cerebral perfusion scintigraphy. The manufacturer recommends its utilization within 30 minutes after preparation. Each reconstituted vial allows us to perform 2 scintigraphy scans. However, some circumstances (preparation of patient, duration of acquisition per patient, availability of the γ-camera), make the use of the ^{99m}Tc-labelled HMPAO within 30 minutes hard to reach.

Our aim is to study the stability of this product beyond the period of recommended use by the manufacturer. We used Ceretec® as a cold kit and a fresh eluate of ^{99m}Tc (Ultratechnekow® generator).

The preparation was carried out under the direct control of the radiopharmacist, respecting the manufacturer's instructions. The control of Radiochemical Purity (RCP) was made by thin layer chromatography (TLC) from the 30th minute of reconstitution.

We used a silica plate (Macherey-Nagel®) as stationary phase and two types of solvents (methylethyl keton, sodium chloride 0.9%) as a mobile phase in order to separate respectively: free ^{99m}Tc ([TcO]_4^-) and reduced-^{99m}Tc associated with a secondary complex ^{99m}Tc-HMPAO ([TcO]_2+CII). The TLC plates were read by γ-camera (Ecam®).

We carried out quality controls on several HMPAO preparations at times: t0=30 min; t1=60 min; t2=90 min.

At t0, the average of the RCP was 86.5% (average of the impurities [TcO]_4^-=4% [TcO]_2+CII=11%). For t1, there was an increase in the percentage of the mixture ([TcO]_2+CII) from 11% to 16.5%, resulting in a decrease in the average of the RCP (82%).

After 90 min, the RCP further decreased to an average of 76% ([TcO]_4^-= 4.5%, [TcO]_2+CII= 19.5%).

According to the manufacturer's recommendations, the preparation of ^{99m}Tc-HMPAO can only be used if the RCP ≥ 80%.

In conclusion, the stability study showed that the ^{99m}Tc HMPAO is stable beyond 30 min up to 60 min after preparation. Thus, the product is stable for 60 min allowing flexibility of usage. Further tests are needed to validate these results.

PS1-40

Synthesis and biodistribution of 1-((2-methoxyphenyl) piperazine)ferrocenecar labelled with technetium-99m as a potential brain receptor imaging AG

Author: Nadia Malek[1]

Co-author(s): Najoua Mejri[1]; Mouldi Saidi[1]; Radhia ELAissi[2]; Eric Benoit[3]

[1]CNSTN, Tunisia
[2]National Institute of Applied Sciences and Technology, INSAT, Tunisia
[3]Universitè Paul Sabatier, France

Corresponding author: nadia.malek@gmail.com

The goal of this study is to develop a novel brain receptor imaging agent. This study reports the synthesis, characterization and the biological evaluation of 1-((2-methoxyphenyl) quickly (radiolabelling time <5 min.), in 90% yield. The ^{99m}Tc-complex, characterized piperazine)ferrocenecarboxamide labelled with technetium-99m (^{99m}Tc-MP). The ^{99m}Tc-MP was obtained by HPLC (20 to 50% ACN of 0 at 5 min then 50% ACN of 5 at 17 min to finally with 50 at 20% ACN of 17 at 20 min). It was stable, neutral and lipophilic enough to cross the blood-brain barrier which was confirmed by octanol/water partition coefficient (LogP = 1.82). In vivo biodistribution indicated that this complex had exceptional brain uptake (2.47% ID/g at 5 min and 0.75% ID/g at 60 min). The distribution of the activity at 15 minutes post-injection in various rat brain regions showed a higher accumulation in the hippocampus area. After blocking with 8-hydroxy-2-(dipropylamino) tetralin, the uptake of hippocampus was decreased significantly from 0.87% ID/g to 0.21% ID/g at 15 min p.i., while the cerebellum had no significant decrease.

The new ^{99m}Tc-cyclopentadienyltricarbonyl technetium complex reported here showed promising biological results, making it an interesting starting point for the development of a new ^{99m}Tc complex as brain receptor imaging agent.

PS1-41

A practical method for the preparation of ^{18}F[TFB] labelled with sodium fluoride, using a ITG IQS fluidic labelling module

Author: Juan C Manrique Arias

Co-author(s): Vanessa Izquierdo-Sánchez; Esteban Barrera; Paulina Munguia; Osvaldo García Pérez; Hector Valdovinos

Falcultad de Medicina, UNAM, México

Corresponding author: juancmanriquea@unam.mx

^{18}F-Tetrafluoroborate (^{18}F-TFB) is a radiotracer, promising iodide analog for PET imaging of thyroid cancer and sodium/iodide symporter (NIS) reporter activity in viral therapy applications. The aim of this study was to standardize y characterize a new radiosynthesis method of ^{18}F[TFB] in facilities with little infrastructure.

^{18}F was produced in a cyclotron via the ^{18}O(p,n)^{18}F reaction with 18 MeV protons and then delivered to the hot cell and trapped in a QMA and plus accell CM cartridges. The cartridge was rinsed with 10 mL of water and dried with nitrogen for 3 minutes. After this step, the QMA was eluted with 1.2 mL of NaCl 0.9 % ([^{18}F]-NaF 740-1850 MBq) in the reactor where it contains 100uL of NaBF4 dissolved in water (10ug) were mixed. The mixture was left to react at 120°C for 20 minutes venting the reactor every 5 minutes.

The crude ^{18}F-TFB product was purified by SPE using a Sep-Pak Alumina Light and plus cartridge and washed with 1 mL of water. Then, it was diluted with 5 ml of isotonic sterile saline and filtered through a hydrophilic 0.22 µm Millex. Radiochemical purity was determined by TLC using SG strips as a stationary phase methanol as a mobile phase. TLC-strips were analysed by autoradiography.

Results: Labelling and formulating took about 30 minutes, where the radiochemical purity of ^{18}F[TFB] was higher than 98%. The radiochemical yield of ^{18}F-TFB was 31.0% ± 0.7% (n=10) uncorrected in a synthesis time of 20 min (Fig 1). The final product ^{18}F-TFB was analysed for radiochemical purity by both radio-TLC (MeOH, Rf=0.23 for fluoride, 1.04 for ^{18}F-TFB) and anion chromatography HPLC with a radioactivity detector (retention times, 3.7 min for ^{18}F-fluoride, 7.8 min for ^{18}F-TFB).

Based on the results of radiochemical purity and quality control, we can determine that this method is possible to adapt in facilities where there is little equipment infrastructure. A solid-phase supported synthesis of ^{18}F-TFB was developed via [^{18}F]-NaF. With the optimized condition, the radiochemical yield of ^{18}F-TFB was 31.0% ± 0.7% (n=10) uncorrected in a synthesis time of 20 minutes.

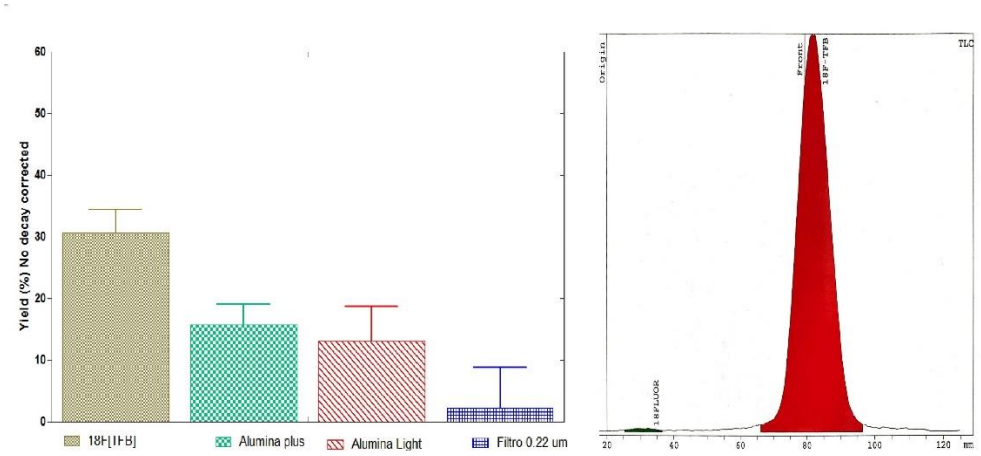


Figure.1 Radiochemical purity and yield (%) undecae corrected of [18F]-TFB (n=10).

PS1-42

Radiation dosimetry in healthy subjects of ^{68}Ga-DOTA-BBN, a potential theranostic tracer in oncology

Author: Juan C Manrique-Arias

Co-author(s): Cristian Alejandro Cabezas Ortíz; Geiser Damian Rodríguez Mena; Osvaldo García Pérez; Quetzali Pitalua Cortes; Roberto Pedrero Piedras

Instituto Nacional de Cancerología, Mexico

Corresponding author: juancmanriquea@unam.mx

^{68}Ga-Labelled peptides have become relevant for diagnostic imaging because of their favorable pharmacokinetics and their usefulness as radiotracer of PET. Gastrin-releasing peptide receptor (GRPR), also known as bombesin (BBN) receptor subtype II, is a member of the G protein- couple receptor family of BBN receptors, its expression has been reported in various cancer types, including prostate cancer, breast cancer, colorectal cancer, pancreatic cancer, glioma, lung cancer and gastrointestinal stromal cancer. Therefore, GRPR became an interesting target for receptor mediated tumour imaging and treatment. The aim of this research was to evaluate the biodistribution and radiation dosimetry of ^{68}Ga-Lys1, Lys3-DOTA-BBN (1,14) based on whole body (WB) PET imaging in healthy human subjects.

Twelve healthy volunteers were included and underwent WB PET/CT (from the apex through the feet) at 5 time points (1, 10, 30, 60, 90 minutes) after intravenous injection of the tracer (190 ±28 MBq). Subjects did not void the bladder until the entire series of images was completed. Images were analyzed using Syngo.via VB10B software by drawing volume of interest in source-organs to determine radiotracer uptake. OLINDA/EXAM software was used to estimate human radiation doses using the reference adult model.

The dosimetry results indicate that the critical organ is the Pancreas, and urinary bladder, where the absorbed doses reached 206.5±35.7,210±57.1, 120±20.9, 390.23±61.6 µGy/MBq, the (women and men, respectively) and the effective doses were estimated as 73.2±6.0, 49.8±7.3 µGy/MBq

In conclusion, ^{68}Ga-DOTA-BBN is rapidly cleared from the body by urinary excretion. The mean effective dose (all subjects, men and women) for a typical injected activity of 185 MBq is on the order of 4 mSv, which is a like other ^{68}Ga-labelled radiopharmaceuticals.

PS1-43

Technetium-99m labelled Human immunoglobulin G polyclonal antibody – different approach for better results

Author: Aschalew Alemu Marie[1]

Co-author(s): Yohannes Jorge Lagebo[1]; Paulina Apostolova[2]; Toni Tripunoski[3]; Emilija Janevik Ivanovska[2]

[1]Addis Ababa University, Ethiopia
[2]Faculty of Medical Sciences, Goce Delcev University Stip, North Macedonia
[3]University Ss Cyril and Methodiuous, Skopje, North Macedonia

Corresponding author: aschuradio@yahoo.com

The aim of the study was to compare the radiochemical purity of ^{99m}Tc-human immunoglobulin G using direct and indirect methods of labelling.

Radiopharmaceuticals used for infection and inflammation imaging have significant use for good patient management outcomes especially in developing African countries. Several radiopharmaceuticals have been used for the diagnosis of infection and inflammation disorder. Even though none of them is ideal, each one has its own strengths and weaknesses. Human immunoglobulin G as a ligand labelled with technetium-99m radionuclide that provides an important characteristic since there is commercially introduced injectable form of human immunoglobulin (IgG). It is suitable for intravenous administration for the treatment of immunodeficiency syndrome, and the availability of technetium-99m radionuclide has the ideal radiation characteristics for diagnostic imaging from the Mo- 99/Tc-99m generator.

Human immunoglobulin G polyclonal antibody can be labelled with technetium using direct and indirect method. Direct method of labelling uses a weak ligand to facilitate the labelling process. Sodium pyrophosphate and sodium glucoheptone are the most commonly used weak ligands. Indirect labelling uses HYNIC that can serve us a bifunctional agent that can bind both the antibody and the radionuclide.

We compared the labelling efficiency including radiochemical purity of directly labelled and indirectly labelled human immunoglobulin G polyclonal antibody for infection and inflammation disorder imaging and we found out that direct labelling method provide better labelling efficiency than indirect labelling method. In addition, it was realized that there is no difference in the labelling efficiency to use sodium pyrophosphate and sodium glucoheptonate as a weak ligand.

PS1-44

Radiolabelled peptidomimetic inhibitor of the VEGF/NRP-1 complex for the imaging of malignant tumours - preliminary research

Author: Katarzyna Masłowska[1]

Co-author(s): Ewa Witkowska[2]; Jędrzej Predygier[2]; Beata Wileńska[2]; Aleksandra Misicka[2]; Paweł Halik[3] ; Ewa Gniazdowska[3]

[1]Institute of Nuclear Chemistry and Technology, Poland
[2]Faculty of Chemistry, University of Warsaw, Poland
[3]Institute of Nuclear Chemistry and Technology, Poland

Corresponding author: p.halik@ichtj.waw.pl, maslowskakatarzyna@o2.pl

The widest possible range of available molecular targets and their vectors is a crucial key for targeted diagnosis and cancer therapy problems. The present work is concerned with a vector: the peptidomimetic inhibitor, the molecular target of which is neuropilin-1 (NRP-1). NRP-1 is a receptor for the vascular endothelial growth factor-165 (VEGF165), playing an important role in pathological angiogenesis and in tumour development and progression. It has been observed that NRP-1 overexpression is associated with tumour aggressiveness in several types of cancers. The demonstrated involvement of VEGF165/NRP-1 complex in pathological angiogenesis has catalysed interest in searching for inhibitors of such interaction to combat angiogenesis dependent diseases. It was shown before that a heptapeptide Ala-Thr-Trp-Leu-Pro-Pro-Arg (A7R) is a good inhibitor of the VEGF165/NRP-1 interaction.

The work involved the labelling of the Lys-(hArg)-Dab-(Ahx-DOTA)-Pro-Arg peptide (working name KM1) and preliminary physicochemical studies of obtained radiobioconjugate. KM1 is an analog of the A7R peptide what is stronger inhibitor of VEGF165/NRP-1 complex than A7R.

Peptide KM1 was synthesized in the Peptides Laboratory of the University of Warsaw using the SPPS method on Wang resin using the Fmoc strategy. The labelling was performed with ^{68}Ga (95°C, 10 min) and the obtained radiobioconjugate was purified by HPLC (semi-preparative Jupiter® Proteo column). Lipophilicity (logP value) was determined in a standard biological system (PBS solution and n-octanol) and the stability of the compound was tested in human serum.

The labelling yield was about 72%. The determined logP value equal to -4.16 ± 0,02 indicates that ^{68}Ga-DOTA-KM1 radiobioconjugate is a strongly hydrophilic compound. Stability studies in human serum showed that about 85% of the radiobioconjugate remains in the free form in the serum solution (about 15% is combined with the protein present in the serum).

The present studies are the first step on the new VEGF/NRP-1 radioisotopically labelled peptidomimetic inhibitors for cancer diagnostics and therapy. In the next steps, the syntheses of new peptidomimetics are planned as well as the using of a long-lived isotope, e.g. ^{177}Lu or a ^{43,44}Sc/^{47}Sc theragnostic pair.

PS1-45

The critical parameters of Ga-68 labelling of POLATOM's PSMA- 11 kit

Author: Michal Maurin

Co-author(s): Piotr Garnuszek; Marcin Radzik; Renata Mikołajczak

National Centre for Nuclear Research, Radioisotope Centre POLATOM, Poland

Corresponding author: m.maurin@polatom.pl

Development of the universal radiopharmaceutical kit, which would contain the active ingredient, i.e. PSMA-11 (nazwę chemiczną tutaj), and excipients allowing its efficient radiolabelling with ^{68}Ga eluate regardless the type of ^{68}Ge/^{68}Ga generator used, remains a challenge. The aim of the study was to determine the critical quality parameters of our earlier developed kit for ^{68}Ga labelling of PSMA-11 and the investigation of limitations in the radiolabelling conditions.

The study was performed using sterile and endotoxin free dry kits, which have been developed in our lab, each containing 20 µg of PSMA-11 and 60 mg of sodium acetate. To investigate the labelling conditions (pH, radioactivity, volume) the kits were labelled with ^{68}Ga eluted from different ^{68}Ge/^{68}Ga generators (manufactured by ITG, Eckert & Ziegler and IRE) in volumes ranging from 1 to 5 ml and radioactivity from 200 MBq up to 1.2 GBq. The labelling yield and radiochemical purity were checked by HPLC (Kinetex C18 150mm; A: 0.1%TFA/H2O, B: 0.1%TFA/CAN, 5-50% B in 10 min) and TLC (ITLC SG; 10% NH4OAc/MeOH 50/50 v/v). In the second part of study the influence of potential metallic impurities originating in the ^{68}Ge/^{68}Ga generator eluate or other reagents were tested by spiking the labelling mixture with the Zn(II), Cu(II), Fe(III), Al(III), Ti(IV), Ge(IV) and Sn(IV) ions. The formation of the PSMA-11 metal complexes was confirmed by HPLC-MS. The stability of the kits was studied in lowered temperature (2-8℃), room temperature (25℃) and in transport conditions (at 35℃ for two weeks). In the stability study, the main parameters controlled were the radiochemical purity of the labelled PSMA-11 and the radiolabelling yield after using low and high volumes of the eluate.

It was observed that 20 µg of PSMA-11 in the kit is enough to obtain high radiolabelling yield (>99%) even if high radioactivity of ^{68}Ga eluate (> 1GBq) was used. Also, the varying volume of the radiolabelling does not affect the radiochemical yield. The most critical parameter of labelling is the pH, which should be maintained < 5. In the pH range of 4.5-5.0 the labelling yields were >98% or between 95 and 98%, depending on the batch, and the type of ^{68}Ge/^{68}Ga generator. These differences in the labelling yields could be attributed to the presence of metallic impurities in the eluates. The collected stability data indicated that manufactured kits are very stable during storage at 25℃ as well as at elevated temperature (up to 35℃).

PS1-46

Development of synthesis method for the automated production of ^{177}Lu-EDTMP with ML-EAZY and PHARM-tracer modules

Author: Gudem Mercanoglu[1]
Co-author(s): Kurtulus Eryılmaz[2]

[1]University of Health Sciences, Faculty of Pharmacy, Turkey
[2]Moltek Health Services Production and Marketing Inc, Turkey

Corresponding author: guldemiko@gmail.com

The symptomatic treatment of skeletal pain due to metastases is complex. Especially in patients with multiple skeletal lesions and osteoblastic lesions on skeletal scintigraphy, systemic radiotherapy with radionuclides linked to a bone-seeking agent is preferred because of its efficacy, low cost, and comparatively low toxicity. Various radiopharmaceuticals are available for this radiotherapy including ^{32}P, ^{89}Sr, and ^{186}Re labelled hydroxyethylidene diphosphonate and ^{153}Sm and ^{177}Lu labelled ethylene diamine tetramethylene phosphonate (EDTMP). Because of its use in many Nuclear Medicine protocols including peptide radionuclide therapy and radioimmunotherapy, the clinical experience is higher with ^{177}Lu. Therefore, ^{177}Lu-EDTMP is the most preferred among these radio- pharmaceuticals. However, in contrast to other peptide radionuclide therapy agents (^{177}Lu-PSMA, ^{177}Lu-DOTATATE, ^{177}Lu-DOTANOC) there is no standard and optimized method for the synthesis process in routine practice, and clinics use their own manual methods. The aim of this study was to develop the automated ^{177}Lu-EDTMP synthesis for routine use.

The study was conducted in 3 main groups: 1) to determine and optimize the synthesis conditions of EDTMP and ^{177}Lu to be complexed in maximum ratio 2) Development of automated standardized production method by transferring manually determined synthesis parameters to automatic synthesis device (ML-Eazy and Pharmtracer, EZAG GmBH, Germany) 3). Development of the radiochemical purity analysis of method ^{177}Lu-EDTMP.

Determined synthesis conditions were: EDTMP: 40 mg, ^{177}Lu: 10-100 mCi, buffer: $NaHCO_3$ (1M), time15-30 min, temperature: 80 C°

Synthesis parameters:

1. Pre-heating of reaction vial at 50 ℃ (60 sec)
2. Transfer of ^{177}Lu to reaction vial by elution with radiolabelling solution (90 sec)
3. Radiolabelling at 80 ℃ (1500 sec)
4. Cooling with 4 mL saline
5. Transfer by passing through Sep Pak CM cartridge
6. Filtration from 0.22 µm filter

Developed analysing method parameters were: Device: Shimadzu LC-20A

Column: C-18 perfectbond ODS-H 5µm (100x4 mm)

Mobile phase: A: water:ethanole (90:10); B: water:TFA (100:0.1)

Elution: Gradient 100% A (0-5min), 100% B (5-5.30min), 100% B (5.30-16 min), 100 % A (16-20min) Sample chromatogram was presented.

In this study, the method for automated synthesis of ^{177}Lu-EDTMP with PharmTracer and ML-Eazy synthesis modules was developed. Repeatable production of this agent in pharmaceutical grade can be achieved in hospital setting.

PS1-47

Preparation, characterization and in-vitro studies of [^{68}Ga]NODAGA- Pamidronic acid for PET bone imaging

Author: Zarif Naim Mohd Ashhar[1];

Co-author(s): Nor Azah Yusof[1]; Wan Hamirul Bahrin Wan Kamal[2]; Hishar Hassan[1]; Hazlina Ahmad Hassali[2]; Fathinul Fikri Ahmad Saad[1]; Siti Mariam Mohd Nor[1]

[1]University Putra Malaysia & National Cancer Institute, Putrajaya, Malaysia
[2]Malaysian Nuclear Agency, Malaysia

Corresponding author: azahy@upm.edu.my, zarifnaim@gmail.com

For years, bisphosphonates (BP) were known for their role in reducing the risk of skeletal related event in patients with bone metastases by accumulating and inhibiting the osteoclastic activity. Hence, since the emergence of germanium-68/gallium-68 generator for positron emission tomography (PET) imaging, developments in gallium-68 labelled BP for bone imaging have been looked into. Through the conjugation of a stable bifunctional chelator to a BP namely 2,2'-(7-(1-carboxy- 4-((2,5-dioxopyrrolidin-1-yl)oxy)-4-oxobutyl)-1,4,7-triazonane-1,4-diyl)diacetic acid (NODAGA) and Pamidronic acid, this research aims to study the preparation, characterization, and in-vitro studies of [^{68}Ga]NODAGA-Pamidronic acid ([^{68}Ga]NODPAM) for PET bone imaging.

NODAGA was conjugated to Pamidronic acid via NHS ester strategy. The conjugated precursor was characterized using tandem mass spectrometry (MS/MS) and purified using high performance liquid chromatography (HPLC). The conjugated NODAGA-Pamidronic acid was radiolabelled with gallium-68 in acetate buffer forming [^{68}Ga]NODPAM complex. The percentage radiochemical purity (%RCP) was assessed using radio-thin layer chromatography scanner (stationary phase: TLC-SG 60; mobile phase: acetonitrile:0.4M Phosphate (7:3)). The human plasma stability was studied 0.5 hourly for 2.5 hours. The bone binding assay of [^{68}Ga]NODPAM was performed using synthetic hydroxyapatite (HA) and was compared with [^{99m}Tc]MDP. To visualize the retention of [^{68}Ga]NODPAM on bone, a preliminary PET image of fresh bone incubated in [^{68}Ga]NODPAM was performed.

The MS/MS analysis of conjugated NODAGA-Pamidronic acid produced expected mass-to-charge ratio (calculated [M-H]- m/z: 591, obtained [M-H]- m/z: 591). Based on the fragments produced, the structure of NODAGA-Pamidronic acid was confirmed ([M-H-H2O]- m/z: 573, [M-H-H2O-HPO2]- m/z: 509). The %RCP of radiolabelled [^{68}Ga]NODPAM was above 90% within 15 minutes at pH 4-4.5. The [^{68}Ga]NODPAM proves to be stable in human plasma throughout the study. The in-vitro percentage HA bone binding assay performed showed significant difference between [^{68}Ga]NODPAM 82.25%±1.72% and [^{99m}Tc]MDP of 53.21%±0.28% (p-value <0.05). The superiority of [^{68}Ga]NODPAM in bone binding assay may be due to its indirect chelation ([^{68}Ga]-chelate-BP) effect as compared to direct chelation ([^{99m}Tc]-BP) which may hinder its affinity of BP towards HA. Preliminary assessment using animal PET proves good bone uptake.

[^{68}Ga]NODPAM was prepared and characterized accordingly and the in vitro bone binding assay was assessed. From previous studies, radiolabelled gallium-68 bisphosphonates showed convincing animal biodistribution results. Though the data obtained may not reflect overall clinical potential, preliminary data suggests that further [^{68}Ga]NODPAM experiments on animal model, especially to determine the biodistribution and bone-to-blood ratio, must be performed in order to prove its clinical indication.

PS1-48

Nucleophilic synthesis of [^{18}F]FDOPA by using an automated module: a summary of the results of 18 batches

Author: Raviteja Nanabala

Co-author(s): Anees Muhammed K; Dilshad Kottuparamban; Junais Pokkat; Arun PK; Bhuvaneswari Gopal; Ajith Joy; M.R.A Pillai

Molecular Cyclotrons Pvt Ltd, India

Corresponding author: raviteja@moleculargloba l.com

6-[^{18}F]Fluoro-L-DOPA, ([^{18}F]FDOPA) or simply FDOPA is a radiopharmaceutical used for targeting dopamine receptors by using positron emission tomography. FDOPA is useful for different diagnosis of Parkinson's disease and other degenerative disorders of the central nervous system. FDOPA PET is also useful for the detection and staging of endocrine and brain tumours. FDOPA is conventionally produced via electrophilic substitution by using fluorine-18 prepared by irradiating neon gas using deuteron beam. However, results in the production of low specific activity tracer. Nucleophilic substitution reaction using fluoride has been developed for the synthesis of FDOPA which results in the production of high specific activity tracer. Cassette based synthesis in automated module using novel precursors are now commercially available. Considering the high demand for FDOPA, we are routinely carrying out the production of FDOPA under GMP. The results are presented in this paper.

No carrier added ^{18}F was produced by 11 MeV Siemens HP cyclotron. Production of FDOPA was carried out using NEPTIS automated synthesizer procured from Neptis, which Belgium installed in a clean room with class B area. Radioactivity measurements were done using a capintec dose calibrator. Oxygen-18 enriched water and FDOPA cassettes, including all chemicals were procured from ABX, Germany. The precursor (S)–N-Trityl–5–formyl-4-methoxy-methylene-2-nitro-phenylalanine tert-butyl ester is used in the cassette in addition to all other chemicals and purification cartridges. TLC was performed using AR2000 TLC scanner procured from Erkect and Ziegler. The mobile phase used for TLC is glacial acetic acid and methanol (9:1). Residual solvents were analysed by Agilent Gas chromatography.

The FDOPA was prepared in a four-step synthesis in a Neptis synthesizer. Followed by the steps of nucleophilic fluorination, oxidation of intermediates and hydrolysis, FDOPA was trapped on HR-P cartridge and eluted with phosphate buffer, passed through a C-18 and Oasis Wax cartridges to remove non-polar and solid impurities. The product is collected in a 30 mL vial connected to a 0.22µm millipore filter. The above series of purification avoids the need for HPLC purification. The total duration of FDOPA production was 90 minutes. The radiochemical yields of FODPA (n=18) are 6 ± 1.2% (decay uncorrected) and 10.5 ± 2.2% (decay corrected). The radiochemical purity was always >94 % and 97.2±1.6 % (n=18) and was retained > 92% up to 7 hours. FDOPA was used in multiple nuclear medicine departments for PET-CT and PET-MR studies. The images were found to be highly useful for clinical evaluation of patients suffering from neurological disorders as well as for neuroendocrine tumours.

Consistent production of FDOPA was achieved using a cassette based nucleophilic synthesis in a Neptis automated synthesizer under GMP conditions. Even though the final decay uncorrected yields were low (~6%), the product was found to be clinically useful for PET-CT and PET-MR studies.

PS1-49

Synthesis of [^{18}F]PSMA-1007 for imaging prostate cancer by using an automated module and clinical studies

Author: Raviteja Nanabala

Co-author(s): Anees Muhammed K; Dilshad Kottuparamban; Junais Pokkat; Arun PK; Arun Sasikumar; Johny Joseph; Ajith Joy; MRA Pillai

Molecular Cyclotrons Pvt Ltd, India

Corresponding author: raviteja@moleculargloabl.com

Radiopharmaceuticals targeting the enzyme, PSMA over expressed in prostate and other cancers are now widely used in nuclear medicine. ^{68}Ga-PSMA-11 has become a widely accepted tracer for imaging prostate cancer. The nuclear medicine centres which do not have access to ^{68}Ge/^{68}Ga generator are interested in using ^{18}F tracers for imaging prostate cancer. PSMA-1007 is a ligand having molecular structure similar to PSMA-617, which is widely used for ^{177}Lu/^{225}Ac therapy of prostate cancer. We describe here the production of [^{18}F]PSMA-1007 using Neptis Syntheziser and a commercially available cassette.

No carrier added ^{18}F was produced in a 11 MeV Siemens HP cyclotron. Production of [^{18}F]PSMA-1007 was carried out using NEPTIS mosaic RS automated synthesizer procured from Neptis, Belgium, installed in clean room with class B area. Radioactivity measurements were done using Capintec dose calibrator. Oxygen-18 enriched water and [^{18}F]-PSMA cassettes that include all chemicals were procured from ABX, Germany. The precursor PSMA-1007 was used in the production, which was supplied along with cassette by ABX. TLC was performed using AR2000 TLC scanner procured from Eckert and Ziegler. The mobile phase used for TLC is Acetonitrile and Water 60/40 (V/V). Residual solvents were analysed by agilent gas chromatography. Clinical studies were done in patients referred to the nuclear medicine department for PET imaging of prostate cancer.

The [^{18}F]PSMA-1007 was prepared in two step synthesis. Followed by labelling, [^{18}F]PSMA-1007 was trapped on a preconditioned C-18 cartridge and eluted with 30% ethanol and passed through Chromafix PS-H+ cartridge. The final product was collected through a 0.22 µ Millipore filter connected to a 30 mL vial. The total duration of [^{18}F]PSMA-1007 production was 45 minutes. The radiochemical yields of [^{18}F]-PSMA-1007 are 28 ± 8% (decay uncorrected, end of the synthesis) and 38 ± 10% (decay corrected to start of the synthesis). The radiochemical purity was always >98 %. [^{18}F]PSMA-1007 was used in multiple nuclear medicine departments. PET-CT images are acquired 2 hour post injection of 200-300 MBq of the radiopharmaceutical in prostate cancer patients. The images were reconstructed with standard software and evaluated by nuclear medicine physicians. PET-CT images were comparable to [^{68}Ga]PSMA-11. Compared to ^{68}Ga-PSMA-11 images, some differences in physiological uptake sites of the tracer were noted with [^{18}F]PSMA-1007 images; eg. the consistent tracer uptake in gall bladder owing to the hepatobiliary route of excretion of [^{18}F]PSMA-1007. However, the reporting nuclear medicine physicians appreciated the image quality of [^{18}F]PSMA-1007 images and judged the image quality of [^{18}F]PSMA-1007 images at par with ^{68}Ga-PSMA-11 for imaging prostate cancer.

[^{18}F]PSMA-1007 was prepared in higher yields and in Curie quantities using a cassette based nucleophilic synthesis in a Neptis automated synthesizer under GMP conditions. The synthesis yields were sufficient to deliver the activity to multiple nuclear medicine centres. [^{18}F]PSMA-1007 is a tracer that can be routinely prepared in a cyclotron and distributed to NM centres for assessment of prostate cancer.

PS1-50

Fully automated radiosynthesis of ^{18}F-16-α-Fluoroestradiol ([^{18}F]FES) with solid phase extraction cartridge purification by Sep Pak® Plus ALOX N

Author: Saikat Nandy

Co-author: Sharmila Banerjee

[1]RMC, BARC, Mumbai, India

Corresponding author: sharmila@barc.gov.in, saikatnandy1976@gmail.com

The utility of [^{18}F]Fluoroestradiol ([^{18}F]FES), a fluorinated steroidal tracer for determining the tissue estrogen receptor level of breast cancer patients is clinically proven. This radiotracer is thus used in prior prediction of the response of antiestrogen therapy of primary, recurrent or metastatic breast cancer. A fully-automated, high-yield synthesis procedure is the key requirement for its availability in large scale, ensuring its wide-spread clinical use.

The radiosynthesis of [^{18}F]FES is carried out starting from MMSE (3-methoxymethyl-16α, 17β-epiestriol- O-cyclic sulfone) precursor. The low yield of [^{18}F]FES obtained from this precursor is attributed to difficulties in the hydrolysis and purification steps after the first step radiofluoriation.

Herein, we report an improved fully automated and optimized radiosynthesis procedure of ^{18}F-16-α-Fluoroestradiol ([^{18}F]FES) from MMSE precursor, involving hydrolysis with 2N HCl and subsequent purification using SepPak® Plus ALOX-N cartridge. The method is reliable, with considerably improved yield of the product with acceptable radiochemical purity.

^{18}F produced in the medical cyclotron [^{18}O (p, n) ^{18}F] was trapped in perfectly conditioned and dried QMA cartridge and TBA^{18}F was eluted by 0.6 ml 75mM $TBAHCO_3$. 1.2 ml dry acetonitrile was added followed by azeotropic distillation for obtaining extra dry TBA^{18}F. MMSE precursor (2mg/0.8 ml dry MeCN) was added and radiofluorination was carried out at 120˚C for 15 minutes. Hydrolysis of the radiofluorinated MMSE precursor was carried out at 115˚C for 12 min using 0.7 ml of HCl (2N). The reaction mixture was cooled and around 2ml of pharmacopeia grade ethanol was added into the reaction vessel, under stirring condition. The reaction mixture was then passed through a stand of four perfectly conditioned SepPak® Plus ALOX-N cartridges discarding the eluent and subsequently dried by-passing helium. Finally, [^{18}F]FES was eluted with 12 ml of 15% ethanol containing water in the product vial. 1.5 ml of 10% NaCl and 0.5 ml of 1(M) NaH_2PO_4 were added at the beginning of the synthesis in order to maintain acceptable pH and isotonicity of the product.

[^{18}F]FES was then dispensed through 0.2µ filter into sterile and bacterial endotoxin free vials. Including its physical properties, radiochemical purity was ascertained by radio-TLC. The product formation is confirmed by comparison of its TLC with that of the authenticated reference standard [^{19}F]FES.

The non-decay corrected radiochemical yield was found to be ~ (35±5) % (n = 3) within 60±2 mins. The radiochemical purity (> 95 %) was confirmed by radio-TLC using freshly prepared 95/5 MeOH/NH_3 solvent. While [^{18}F]FES has Rf of 0.7, free [^{18}F]F- exhibits Rf of 0.01 and that of the radiofluorinated MMSE precursor is around 0.15. The radiochemical purity of [^{18}F]FES was confirmed by comparing with the authenticated reference standard [^{19}F]FES. [^{18}F]FES obtained was clear, colourless and free of any suspended particle, with pH ~ 6.

In conclusion, [^{18}F]FES has been successfully synthesized and purified in good yield using the fluorination module in the medical cyclotron under optimized condition which is identical in principle with GE TRACERLABFX-FDG.

PS1-51

Development and evaluation of ^{18}F-radiolabelled acetaminophen (paracetamol) for tumour imaging based on COX-2 overexpression

Author: Saikat Nandy

Co-author(s): Yogita Pawar; Sutapa Rakshit; Avik Chakraborty; Rajesh Chinagandham; Somnath Kar; Sharmila Banerjee

RMC, BARC, Mumbai, India

Corresponding author: saikatnandy1976@gmail.com

Overexpression of COX-2 receptors is observed in a variety of tumours. Therefore, development of suitable ^{18}F-labelled PET radiotracers of selective COX-2 inhibitors is an attractive option to target selective and specific inhibitors of COX-2. The binding free energy [ΔG(-KCal/mole)] of Ac- etaminophen and F-18 labelled derivative of Acetaminophen has been calculated by using AUTODOCK 4.2 and crosschecked using www.swissdock.ch against the PDB code 3LN1 and has been found to be comparable in both cases. This encouraging result provides the necessary impetus towards the development of F-18 labelled derivative of Acetaminophen based on its property of selective COX-2 inhibition in designing PET radiopharmaceutical for tumour imaging.

Herein, we report the fully automated radiosynthesis of the novel F-18 Fluoroethylated paracetamol by direct radio-fluoroethylation of paracetamol and subsequent purification with SEP-PAK® cartridge purification. The evaluation of the PET radiotracer has been carried out by PET/CT imaging, bio-distribution in mice tumour model and histopathological studies.

The fully automated radiosynthesis of ^{18}F-Fluoroethylated paracetamol using general purpose synthesis module which, in principle, is similar to GE TRACERlab FXFDG, has been carried out in three steps: (i) Radiosynthesis of the fluoroethylating agent, [^{18}F]Fluoroethyl tosylate (ii) Coupling of [^{18}F]Fluoroethyl tosylate with paracetamol in DMSO solvent and (iii) purification by SPE using Sep Pak® Plus ALOX N cartridges. Pharmacokinetic studies were evaluated by PET/CT imaging study in healthy rabbit at two different time points. Biodistribution study was carried out in nude mice bearing tumour (MDA-MB-231). COX-2 overexpression in tumours was confirmed by histopathological studies.

The non-decay corrected radiochemical yield is around (25±3) % (n = 3) within 60±2 mins (total synthesis time). The radiochemical purity is >95 % as confirmed by radio-TLC and radio-HPLC coupled with UV (λ=276 nm). Biodistribution study demonstrated significant tumour accumulation and retention over a period of two hours post injection. COX-2 overexpression in tumour was confirmed by histopathological studies using mouse anti-COX2 antibody. One-hour post injection PET/CT imaging study in healthy rabbit showed very fast clearance from liver and blood, however, with high accumulation of the tracer in highly proliferating regions like bone marrow and sub-mandibular jaws. The thick leg joints showed significant uptake which can be attributed to age related inflammation in aged rabbit and the well-known fact that COX-2 is overexpressed in inflammation. Both the kidneys as well as urinary bladder showed very high tracer accumulation indicating clearance via renal route.

The PET/CT image of two-hours post injection showed complete blood clearance with elimination via renal route, however with bone marrow accumulation. No bone uptake other than the thick joints was observed throughout the period of PET/CT study confirming in vivo stability of the tracer. Thick joint uptake can be attributed to age-related inflammation of the aged rabbit and the well-known fact that COX-2 is overexpressed in inflammation. F-18 labelled Paracetamol has successfully been designed, developed and evaluated as a PET tracer for tumour imaging agent based on COX-2 overexpression in a variety of tumours.

PS1-52

Comparative evaluation of Tc-99m octreotide, synthesized by different labelling methods: for diagnostic accuracy assessment in neuro-endocrine tumours

Author: Naseer Naseer Ahmed[1]

Co-author(s): Shazia Fatima[1]; Muhammad Faheem[1]; Adnan Saeed [1]; Zain Khurshid [1]

[1] *Department of Nuclear Medicine, AECH-NORI, Islamabad, Pakistan*

Corresponding author: naseernori@gmail.com

Neuro-endocrine tumours (NETs) are ranked among uncommon tumours but owing to their multicentric origin, often pose a clinical challenge for their diagnosis and treatment. In developing countries like Pakistan, where PET based tumour's somatostatin receptor (SSR) imaging are limited, Tc-99m is the key imaging tool for diagnosis, management and assessment of therapy response.

The aim is for two HYNIC-TATE radiopharmaceuticals (RP-1 & RP-2) of different origin, methods of labelling and excipient as RP-1(a single vial) while RP-2 (two vial-(HYNIC Conjugate + co-ligand) were used to compare their in-vitro quality and clinical diagnostic efficacy in histopathologically known NETs and others for the imaging of SSR avidity, evaluated for utilization in PRRT therapy. The clinical sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of SSR scintigraphy were calculated and compared.

The used methods included freshly eluted sodium pertechnetate for radiolabelling. The radiochemical purity was checked as per specifications and injected to 75 patients (43 Male, 32 Female: Age: 87-22) of known primary and secondary neuro-endocrine tumours (known histopathology and prognostic markers i.e. synaptophysin, chromogranin and Ki-67 Index). Their Tc-99m-OCT scans were correlated with histopathology, CT and/or MRI reports.

It was found that RP-1 average radiolabelling efficiency was 96.4±0.2% as complex, 2.4±0.2% as hydrolysed and 2.6±0.3% free pertechnetate, while in RP-2 was 98.3 ±0.5% labelled, 1.82±0.4 % hydrolysed and 0.9±0.1% as free pertechnetate. Out of 75 in 39 patients, where imaging was performed with RP-1, 23 were found to be true positive, 7 as true negative (T/P), while 9 as false negative (F/N), with sensitivity, specificity, and PPV, NPV of 71.87%, 100%, 100% and 43.75%. While in 36 scans screened with RP-2, 22 were T/P, 6 as T/N, 8 as F/N, with 75.8%, 100%, 100% and 50% sensitivity, specificity, PPV and NPV. For assessment of lesion site specificity, 14 patients with hepatic lesions were imaged with RP-1, showing 71.4% T/P, 21.4 % T/N, while with RP-2, 81.8% as T/P, 18.18% as T/N. Similarly, in NET of lung, both had 100% T/P result. 1 patient of pheocromocytoma was conducted with RP-2 and was found to be T/P. 1 Patient of papillary urothelial carcinoma found as T/P with both radiopharmaceuticals and 1 patient of small cell NET-Gall Bladder, where baseline scan and post chemotherapy scan with time interval of 6 months, showed progression in disease.

In conclusion, the SSR scintigraphy of NET with RP-2 as compared to RP-1 had better labelling efficiency with more sensitivity but equal specificity, having similar positive and negative predictive values. Both can be used for staging and follow-up assessment of patients. Developing countries where accessibility of PET-CT and gallium derived diagnosis is not very feasible, gamma camera for scintigraphy augmented by SPECT-CT can enhance the diagnostic accuracy and assessment of treatment response via these radiopharmaceuticals. Keeping this in view, in future the study can be performed by enhancing the number of patients imaged by SPECT-CT and thus further assessing the diagnostic capabilities of these kits.

PS1-53

Utility of gamma camera as an effective non-invasive imaging modality for docetaxel loaded liposomal chitosan nanoparticles: synthesis and the in-vivo trafficking in animal model

Author: Naseer Naseer Ahmed

Co-author(s): Ayesha Ayesha Ammar; Noreen Noreen Marwat; Shazia Shazia Fatima; Zain Zain Khurshid

Oncology and Radiotherapy Institute AECH-NORI, Islamabad, Pakistan

Corresponding author: ayesha-ammar@hotmail.com, naseernori@gmail.com

The physicochemical properties of drug loaded nanoparticles in physiological system are important determinants for their in vivo distribution and drug delivery efficiency. Stability of nanoparticles in blood serum remains a significant challenge for successful delivery to target tissue. Analysis of intra-biliary infusion of nanoparticles within two-compartmental pharmacokinetic modelling revealed efficient retention in the liver and minimal leakage from the liver to the blood stream. Our aim was to demonstrate the utility of gamma camera as an effective non-invasive imaging modality for the biodistribution of docetaxel loaded liposomal chitosan nanoparticles.

Folic acid thiolated chitosan was synthesized via EDAC coupling at pH-5.0 and purified by a dialyzing membrane. NPs were partially oxidized 1h with stirring at room temperature, tween 80 was added to make an emulsion. Folic acid was grafted to TCS. The docetaxel was loaded as a cross linkage using TPP (1%) solution in 500ml DCM, the weighed number of lyophilized liposomes were suspended in 1mg/ml solution of FA-TCS and stirred for 4 hours for proper coating through electrostatic interaction between liposomes and FA-TCS. The coated liposomes were separated through ultracentrifugation. The Docetaxel loaded liposomal Thioglycolated chitosan were characterized for hydrodynamic diameter and surface zeta potential and their Surface morphology was studied with electron microscope (FEI Nova NanoSEM 450). The encapsulation efficiency was calculated by ACN: MeOH: buffer and quantified by HPLC-PDA. The in-vivo pharmacodynamic study was prepared with docetaxel loaded liposomal thioglycolated chitosan (FORM-A) with freshly eluted Tc-99m and docetaxel labelled alone with Tc-99m. Then, it was loaded afterwards on liposomal thioglycolated chitosan (FORM-B), by an optimized protocol to retain their favourable physicochemical properties. Radiolabelling efficiency was measured by TLC-SG and methanol using BIOSCAN-TLC scanner coupled with PMT detector. The radiolabelled nanoparticle complexes (avg. dose = 58±10MBq) were orally given to the animal model. Planer and static gamma images were acquired at the interval of 30 minutes, 1, 2, 3, 4, 24 and 36 hours for the localization of drug absorption and delivery site. The docetaxel drug absorption rate was quantified by HPLC.

The drug loaded liposome was successfully coated with FA-TCS, confirmed by change in zeta potential. Encapsulation efficiency indicated that liposomal formulations showed higher value above 70% as compared to chitosan-TGA. The radiolabelling efficiency of both formulations measured by TLC was 99.2%. Gamma camera acquisition quantified as activity versus time curve indicated that the form A was localized in gut after 2 hours of administration, and HPLC quantification confirmed that 63% of the drug was absorbed at 2 hours of administration. Form–B images showed that 68.2% of the drug was localized in the lungs, 23.2 % in liver and 8.6% was excreted through kidney. Confirmation by HPLC quantification indicated slow release of drug till 36 hours.

The use of gamma imaging can help to locate the specific site of absorption of nanoparticles and drug release while HPLC helps to quantify accurate assessment of drug release in general body circulation.

PS1-54

Radiolabelling and preliminary biodistribution study of Samarium-153-Zoledronic acid as a novel bone pain palliative agent

Author: Yen Ng

Co-author(s): Azahari Kasbollah; Wan Hamirul Bahrin Wan Kamal; Khei Choong Khong

Malaysian Nuclear Agency, Malaysia

Corresponding author: yen@nm.gov.my

There are a large number of advanced stage breast cancer, prostate cancer and lung cancer patients suffering from severe bone pain due to the metastases of the disease. The conventional therapy which includes oral analgesics and localised external radiotherapy has been associated with various unwanted side effects. Targeted radiotherapy using radiolabelled bisphosphanate complexes are known to be the most effective agent. These compounds bind avidly to the bone and the radiation emitted from the radionuclides can substantially reduce the formation of bone tumour. Zoledronic acid (ZOL), a bisphosphonate agent, is currently being widely used in clinical as osteoclast bone resorption inhibitor. ZOL has proven to be an effective agent to prevent the manifestation/occurrence of skeletal-related complications in patient with bone metastases.

The aim of this study was to develop ZOL-Samarium-153 as a potential radiotherapy agent. The ^{153}Sm-ZOL complexes were assessed for its radiolabelling efficiency, in vitro stability, and bone uptake visualized by whole body scintigraphic images using Sprague Dawley rats.

Production of ^{153}Sm was performed using ^{152}Sm(n,gamma)^{153}Sm reaction at TRIGA PUSPATI reactor located at Agensi Nuklear Malaysia. Enriched ^{152}Sm (purity>98%) was used to produce Sm-153. ITLC-SC strips were used for radiochemical purity studies. Radiochromatography were performed by using BIOSCAN scanner, connected with NaI(Tl) detector. Scintigraphic images of the whole body were acquired using T-Quest gamma camera integrated with the NuQuestTM software to produce 2D whole body image. The rat was placed on a flat hard surface with both legs spread out and all legs fixed with surgical tape, then an aliquot of 0.2-0.3 ml containing 18.5-37MBq of ^{153}Sm-ZOL was injected intravenously via the tail vein. Ketamine/xylene were used as anaesthesia for the rats before recording the scintigraphy images. All others activity measurements were made with Na(I) gamma counter.

The labelling yield was found to be greater than 99.1+0.07. 153Sm-ZOL moves with solvent front with Rf value of 0.89+0.01, while free samarium-153 remained at the point of origin. Biodistribution and localization of free Samarium-153 cation solution and ^{153}Sm-ZOL were studied using Sprague Dawley rats as animal model. It was observed that for ^{153}Sm cation, the biodistribution was mainly accumulated in the liver, as expected. The uptake of ^{153}Sm-ZOL in rat's bone was visualized after accumulation of injected ^{153}Sm-ZOL. Our preliminary study showed that free ^{153}Sm-ZOL was excreted via the kidney. The tracer was clearly visible in bone at 2d, 4d and 7d post administration and the uptake in bone increased with time and accumulated in the bone as expected for bone avid radiopharmaceuticals.

Radiolabelling of ^{153}Sm-ZOL was successful with radiochemical purity (>99%). The complex also exhibited significant stability in room temperature for up to 24h in vitro. Scintigraphy imaging in rats shows high uptake of complex in skeleton up to 7 days, the duration of studies. The biodistribution results of ^{153}Sm-ZOL demonstrated that this tracer has great potential to be a new candidate for clinical applications for bone pain palliation therapy.

PS1-55

Development and evaluation of a ^{68}Ga-labelled angiotensin peptide coupled to rhodamine for diagnostic imaging of heart

Author: Subhani Okarvi
Co-author: Ibrahim Aljammaz

King Faisal Specialist Hospital and Research Centre. Riyadh 11211, Saudi Arabia

Corresponding author: sokarvi@kfshrc.edu.sa

Rhodamine (Rh) is a lipophilic cation, same as ^{99m}Tc-MIBI that specifically accumulates in the myocardium. In an attempt to formulate a PET-based cardiac agent with enhanced targeting efficiency, we linked Rh to angiotensin II (Ang II), an 8 amino acid peptide that has been known to play an important role in cardiovascular function. Here we evaluate the ^{68}Ga labelled Rh-Ang II conjugate for its potential as a cardiac imaging agent.

Rh-Lys(DOTA)-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-CONH2 was prepared conveniently by solid-phase peptide synthesis according to Fmoc/HBTU chemistry. Rh-NHS ester was coupled to the peptide through the amino group of Lys residue and radiolabelled with ^{68}Ga via DOTA chelator. Metabolic stability of the radiotracer was determined in human plasma and in vivo biodistribution and pharmacokinetics was conducted on Balb/c mice and Sprague Dawley rats.

Results showed that The Rh-Ang II conjugate was radiolabelled efficiently with ^{68}Ga (>75%) as determined by radio-HPLC analysis and showed sufficient metabolic stability in human plasma. In mice, the radiotracer displayed efficient clearance from the blood and excreted from the body mainly through the renal route with some elimination by the hepatobiliary system. The radiotracer uptake in the heart was found to be 1.85±0.59% ID/g as early as 30 min post-injection. The accumulation in other major organs including liver, lungs, stomach, intestines and kidneys was below 8% ID/g. A high uptake by these organs may interfere with the efficient visualization of the heart. In case of rats, the radiotracer showed better pharmacokinetic characteristics, with low uptake of radioactivity in the major body organs/tissues (<4.0% ID/g). The uptake of ^{68}Ga-Rh-Ang II in the heart, 1.91±0.65% ID/g, was higher than the uptake found in the blood and muscle resulting in good heart-to-blood and heart-to-muscle ratios. Additionally, the radiotracer exhibited cardiac extraction values comparable to ^{99m}Tc-MIBI in rat hearts.

These results suggest that the combination of two biomolecules is an attractive approach to enhance targeting efficiency and for rapid and efficient diagnostic imaging of heart. Further studies are in progress to determine the full potential of this cardiac imaging agent.

PS1-56

Total solid-phase synthesis of DOTA-Functionalized tumour targeting peptides for PET imaging and therapy

Author: Subhani Okarvi
Co-author: Ibrahim Aljammaz

King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Corresponding author: sokarvi@kfshrc.edu.sa

The convenient synthesis of metal chelating agents couple with tumour targeting peptides is needed to accelerate the research and clinical translation in molecular imaging. DOTA has been one of the most widely used macrocyclic ligands for the development of new metal based imaging and therapeutic agents, owing to its ability to form stable and inert complexes under physiological conditions making these radiopharmaceuticals useful for imaging and therapy. DOTA-tris-t-butyl ester is commercially available, but it is expensive and contain impurities of both the dialkylated and tetra-alkylated cyclen. There is a need to explore new methods for preparation of DOTA-tri-tert-butyl ester, which are less expensive and provide a high purity DOTA product. The aim of this study was to develop a convenient and cost-effective synthetic approach for the preparation of DOTA peptides directly on solid support for tumour imaging and therapy.

The tumour targeting peptide (i.e. bombesin 7-14) was synthesized by Fmoc-based solid- phase peptide synthesis. For coupling with DOTA, bromoacetic acid after activation with HOBt/DIC was coupled to free amino group of peptide resin. This was followed by the monoalkylation of bromoacetylated peptide resin with cyclen (tetraazacyclododecane). The cyclen peptide was then alkylated with tertbutylbromoacetate to afford the desired DOTA peptide. Additionally, the same peptide was prepared from commercially available tris-tert-butyl-DOTA for comparison. These peptides after labelling with ^{68}Ga were evaluated for their ability to bind bombesin receptors over-expressed on human breast and prostate cancer cells. In vivo tumour targeting was examined in nude mice implanted with MDA-MB-231 xenografts.

The identity and purity of DOTA peptides was confirmed by mass spectrometry and HPLC. The peptides radiolabelled efficiently with ^{68}Ga (>90%) and exhibited high binding affinity to BN positive MDA-MB-231 and PC3 cancer cell lines (kd=<20 nM). In nude mice with MDA-MB-231 xenografts, ^{68}Ga-labelled peptides displayed efficient clearance from the blood and uptake/retention in all the major organs was found to be low to moderate (below 5%ID/g). The accumulation in the BN positive tumours was ~2% ID/g at 1 h p.i., with good tumour to blood and muscle ratios. The main route of excretion was renal pathway. Both peptides displayed comparable in vitro and in vivo behaviour.

In conclusion, we have described the preparation and in vitro and in vivo activity of two DOTA coupled peptides. The synthesized peptides hold good tumour affinity and tumour targeting potential. This successful and economical synthetic strategy can be applied to the facile synthesis of various tumour targeting peptides which ultimately can be translated into clinical settings.

PS1-57

Use of tetrabutylammonium tosylate in conjunction with chiral NiII complex precursor for automated synthesis of [^{18}F]FET

Author: Viktoriya Orlovskaya

Co-author(s): Olga Fedorova; Raisa Krasikova

N.P.Bechtereva Institute of Human Brain RAS, Russia

Corresponding author: orlovskaya@ihb.spb.ru

Due to favourable characteristics in in-vivo applications, high specificity and long half-life of ^{18}F (109.8 min), the O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) has become an important tool for molecular imaging of cerebral tumours. In our previous studies we presented a convenient synthesis of [^{18}F]FET via direct nucleophilic fluorination of a chiral NiII complex of an alkylated (S)-tyrosine Schiff base, Ni-(S)-BPB-(S)-Tyr-OCH_2-CH_2OTs (I) in the presence of K2.2.2 and K_2CO_3. After acidic hydrolysis, [^{18}F]FET was purified using reverse phase and strong cation exchange cartridges. Tfhe process was automated on the Scintomics Hotboxone synthesis module. However, when transferring this procedure to TRACERlab FX N Pro, commonly used ^{18}F radiolabelling platform, we observed two radiolabelled by-products that were not amendable to SPE purification procedure. Their formation may be a consequence of reaction vessel design (high volume/surface vs small amount of reaction mixture) and possible over-heating during vacuum drying of ^{18}F-fluoride complex. As the construction of the heating block was amendable to modification, we have focused on improving fluorination process, substituting the K2.2.2/K_2CO_3 mixture with an alternate PTC- tetrabutylammonium tosylate (TBAOTs). The SPE purification protocol was also adjusted to better suite TRACERlab FX N Pro.

Aqueous [^{18}F]fluoride solution (1.3 ml) was loaded on Waters QMA carbonate Plus light Sep-Pak cartridge (46 mg). The cartridge was rinsed with 5 ml of MeOH and dried using gas flow; the [^{18}F]Fluoride was eluted with 700 µl of MeOH with 4 mg of TBAOTs. After solvent removal 4 mg of I in 700 µl of MeCN was added, and reaction mixture heated to 80^{o}C for 7 min. After acidic hydrolysis (0.5M HCl, 110^{o}C, 5 min) the reaction mixture was diluted with 11 ml of water and 2.5 ml of 0.1M NaOH. Resulting basic solution (pH 9) was passed through small filtration column and three tC18 Light cartridges connected sequentially. [^{18}F]FET was eluted with 10 ml of sodium acetate solution (5 mM, pH 4) containing 3% of EtOH and further purified by passing through CM Plus cation exchange cartridge to removal any residual nickel.

As a result, replacement of K2.2.2/K_2CO_3 with TBAOTs allowed us to substantially increase radiochemical conversion (RCC > 85%, radioTLC). Formation of radiolabelled by-products discussed earlier was not observed using gradient HPLC analysis. [^{18}F]FET was obtained with radiochemical purity >99% and enantiomeric purity of 94-95%. Decay corrected radiochemical yield was 50%, synthesis time ca. 35 min.

In conclusion, using non-aqueous solution of TBAOTs as an inert PTC allowed for substantial increase of fluorination efficiency while avoiding formation of radiolabelled by-products. The radioactivity loss on the inner surfaces, which is critical for the reaction vessel on the TRACERlab FX N Pro, was minimized. The proposed synthesis methodology appears to be well-suited to transfer to other automated synthesizers for nucleophilic synthesis of ^{18}F-labelled radiotracers.

Acknowledgments: this research supported by RFBR grant 18-29-01015-mk.

PS1-58

Optimization of the automatic synthesis of ^{16}α-[^{18}F]fluoroestradiol in the SYNTHRA RNplus Research Module

Author: Maria Pía Pereira[1]

Co-Author(s): Maia Zeni[2]; Javier Giglio[2]; Ana Rey[1]

[1]Facultad de Química, UdelaR, Uruguay

[2]Centro Uruguayo de Imagenología Molecular (CUDIM), Uruguay

Corresponding author: qf.mppereira@gmail.com

16α-[^{18}F]-fluoroestradiol ([^{18}F]FES) is used for estrogen receptors imaging in breast cancer diagnosis and follow up. Although reported methods use similar labelling procedures, optimal hydrolysis and purification conditions may be different according to the used module. No data referring SYNTHRA RNplus Research Module were found in the literature.

The aim of the present study was the optimization of the automatic synthesis of [^{18}F]FES using the SYNTHRA RNplus Research platform.

Synthesis of ([^{18}F]FES) was achieved by reaction of 1 mg of 3-O-methoxy-methyl- 16β-epiestriol-O-cyclic sulfone in 1 ml of anhydrous acetonitrile with 37 GBq of [^{18}F]F at 100°C for 10 min. The product was hydrolysed at 100°C for 12 minusing different conditions: 1) 1.0N HCl, 2) 2.0N HCl in acetonitrile: water (3.0 ml, 9:1 v/v) and 3) 0.5N H2SO4 in ethanol: water (3.0 ml, 9:1 v/v). Purification was performed by HPLC using a C18 column (VP250/10 SynthraReeperbahn, 5 µm) flow rate: 2.0 ml/min, λ=280 nm, using either a) Ethanol: water 50:50 or b) Water: Etanol: Acetonitrile (50:25:25) as mobile phases. The peak was either diluted with 0.9% NaCl (a) or with 50ml of water and purified with a Sep-Pak C18 Plus-Light cartridge (b).

The radiochemical purity (RCP) was determined by HPLC using a Phenosphere column (ODS 80 A, 250x4.6 mm, 5 µm), flow 1.5 ml/min. and a gradient of acetonitrile in water (acetonitrile 10% to 90% from 0 to 10 min) and λ=280 nm.

Results show that the module contain a reduced volume reactor (7 mL, conical shape) to perform the labelling and a standard reactor for the hydrolysis.

Synthesis of ([^{18}F]FES) was developed by a standard procedure and the labelling yield (aprox. 25%) was similar to the reported data.

Hydrolysis and purification are critical steps and different conditions were assayed in order to optimize the RCP of the product. Hydrolysis can be performed either using HCl or H2SO4. The use of H2SO4 led to the formation of less impurities and consequently was selected for further experiments. Purification was developed by preparative HPLC. The selection of ethanol as the only organic solvent offers the advantage of the simplicity of the final conditioning. However, this condition led to poor RCP (<90%). The use of a mixture of ethanol and acetonitrile, on the other hand, required an additional step of solid phase extraction but rendered a RCP of approximately 100%. In all the syntheses, the pH was in the range of 5.0-6.0, the residual Kryptofix® was below the limit and the residual solvents (acetone, acetonitrile and ethanol) met the specifications.

In conclusion, the synthesis of [^{18}F]FES was optimized in a SYNTHRA RNplus research platform. The best hydrolysis condition was the use of 0.5N H2SO4 in ethanol: water (3.0 ml, 9:1 v/v) and the purification by HPLC using Water: Etanol: Acetonitrile (50:25:25) as mobile phase followed by solid phase extraction to remove acetonitrile. Acknowledgments: ANII (POS_FCE_2018_1_1007787).

PS1-59

Labelling of anti-cd20 monoclonal antibody cimabior with ^{90}Y

Author: Madian Pino Peraza[1]

Co-author(s): Alejandro Perera Pintado[1]; René Leyva Montaña[1]; Magdiel Góngora Bravo[1]; Anais Prats Capote[1]; Alejandro Alberti Ramírez[1]; Denise Dorvignit Pedroso[2]; Ignacio Hernández González[1]; Mariela León[1]

[1]Centro de Isótopos (CENTIS), Cuba
[2]Centro de Inmunología Molecular (CIM), Cuba

Corresponding author: madian@centis.edu.cu

Radioimmunotherapy of non-Hodgkin lymphomas with anti-CD20 monoclonal antibodies (Mabs) labelled with b-emitter radionuclides has resulted promising. The aim of this work was to establish a method for the labelling Cuban chimeric anti-CD20 MAb CIMABior with ^{90}Y.

The influence of 3 BCA (NHS-DOTA, p-SCN-CHX-A"-DTPA and p-SCN-Bn- DOTA) was studied. Conjugation reaction was performed in bicarbonate buffer 0.1mol/L pH=8.5-9.0 at room temperature, varying molar ratio Mab:BCA and incubation times. After conjugation, the antibody was purified by gel filtration and by ultrafiltration through Amicon 30 kDa and changing to ammonium acetate buffer 0.1mol/L pH=6.0-6.5. Labelling reactions were performed at room temperature and 42 ºC, when DTPA and DOTA derivatives were employed, respectively. A challenging assay against 300-fold molar excess of EDTA was used to assess the stability of radioconjugates. Immunoreactivity was assayed by flow cytometry. To assess the in vivo behaviour of ^{90}Y- CIMABior, 9 male healthy rats received 50 µg of the Mab (37 MBq, 0.2 mL) through marginal vein of the tail. Blood samples were drawn, and organs collected up to 72 h.

Results showed that depending on the BCA and the molar ratio Mab:BCA, the number of chelating groups bound to the antibody varied in the range from 2 to 13. The same way, the labelling yield also depended on the employed BCA and the number of the chelating groups in the IgG molecule. The conjugates with p-SCN-CHX-A"-DTPA and p-SCN-Bn-DOTA showed the best results of labelling efficiency (>95%). Radioimmunoconjugate CIMABior-Bn-DOTA-^{90}Y showed the highest stability (>90% after 96 h). The affinity of Mab CIMABior for the antigen CD20 was affected by the increasing of the molar excess of BCA in the conjugation reaction. Besides, the affinity for the antigen was significantly lower in case of NHS-DOTA, with regard to the other two immunoconjugates. Immunoreactive fraction of CIMABior-Bn-DOTA-^{90}Y was (95.27 ± 6.21) %. Labelled Mab showed a satisfactory in vivo stability. The main target organ was the spleen (1.2-2.0 %ID/g). Product had an elimination pathway through kidneys and liver. PK study showed a monoexponential with a T1/2 = 7.0 ± 3.1 h.

In conclusions, according with the outcomes of the present work, a methodology for the satisfactory labelling of anti-CD20 monoclonal antibody was established. Radioimmunoconjugate CIMABior- Bn-DOTA-^{90}Y showed the most adequate initial characteristics to be used in the future for the radioimmunotherapy of NHL.

PS1-60

Influence of the source of Lu-177 on radiopharmacy waste management – an estimate

Author: Sietske Rubow[1]

Co-author(s): Janke Kleynhans[2]; Jannie le Roux[1]

[1]Stellenbosch University, South Africa
[2]University of Pretoria and Stellenbosch University, South Africa

Corresponding author: jsleroux@sun.ac.za

When radiopharmaceuticals are procured, it is tempting to select based on the cost of the product. In the case of Lutetium-177 for radiopharmaceutical therapy, this may have considerable practical consequences. The radionuclide can be produced using a direct (NCA Lu-177) or an indirect method (CA Lu-177), yielding products with different specific activities and different levels of contamination with Lu-177m, which has a half-life of 160 days. We asked ourselves what the implications for waste management would be if we switched from NCA to CA Lu-177.

Data from 73 Lu-177 therapy doses prepared and dispensed in our hospital were reviewed. Doses were individually prepared, starting with approximately 7.4 GBq Lu-177. The activity of waste from the radiosynthesis procedure (production waste, P) and from dispensing and administration of the patient dose (dispensing waste, D) were calculated. These values were used to estimate potential levels of Lu-177m in waste.

Waste P contained an average of 885 ± 336 MBq and waste D 183 ± 106 MBq Lu-177. Assuming that 0.05 kBq Lu-177m is present per 1 MBq CA Lu-177 (Bakker et al, 2006), the waste contents of the longer-living isotope would be 44 kBq and 9 kBq respectively (Table 1).

In South Africa, radioactive substances with activities less than 100 Bq/g and total activity less than 4 kBq can be disposed as normal waste. On the day of synthesis and administration, all our production waste would have exceeded the 4 kBq limit, while only 10 lots of dispensing waste would fall below that level. In our worst-case scenario, even if a facility were to receive a ready-to-use Lu-177 radiopharmaceutical containing Lu-177m, waste from dispensing may have to be stored almost 2 years before disposal.

In this study we only considered waste and we excluded patient excreta. For radiosynthesis and therapy, other aspects of the radionuclide, like the effect of low specific activity, should also be carefully considered.

In conclusion, the decision regarding Lu-177 procurement should not be based on cost only. If long-living contaminants are likely in a radiopharmaceutical product, waste management and storage facilities will be an important consideration.

PS1-61

Synthesis and biodistribution study by rats of two new ^{99m}Tc-Tricarbonyl complexes as potential brain imaging agents

Author: Mouldi Saidi

CNSTN, Tunisia

Corresponding author: mouldibenlamari@gmail.com

Many radiolabelled PET tracers, which can specifically bind to 5HT1A receptors, have been developed for in vivo imaging of 5HT1A receptors in living brain with positron emission tomography. However, due to the high cost of cyclotron-produced radionuclides such as ^{18}F, ^{11}C and a lack of availability in most nuclear medicine departments (very short half-life), these tracers have limited use in clinical practice. Up to the present technetium-99m is still the most widely used radionuclide in diagnostic nuclear medicine by virtue of its ready availability, low cost and optimal radiation properties (t 1/2= 6 h, 89% photon yield of 140 keV).

The development of ^{99m}Tc cyclopentadienyltricarbonylpiperidine derivatives, in which Tc+1 is coordinated to cyclopentadienide (C5H5-) and three carbonyl groups, have been reported. These complexes have shown high uptake in the brain of rats and rabbits, as well as high affinity to the 5HT1A receptors in rats 20 min after i.v. administration.

In order to better understand the structure/biodistribution relationship of piperidine derivatives and to improve brain retention, two new substituted piperidine derivatives were synthesized, radiolabelled and evaluated by biodistribution studies in the rat brains. As Ref. we used a previously published complex. This complex has showed a high affinity to the hippocampus rich in 5HT1A receptors but a rapid wash out from the brain.

Methodology: three piperidylferrocencarboxylats were synthesized by reaction of the piperidine alcohol with ferrocenecarbonyl chloride to give the corresponding esters (1, 2 and 3.)

Radiochemical synthesis is carried out in a microwave according to the following scheme: we replaced the Wenzel method which suffers from inadequate conditions (high temperature and long reaction time) by a microwave method. This new method allowed us to achieve a higher yield (90%) for a very short time of 2 min and allowed us to avoid heating at 150 °C.

Biodistribution studies: in order to increase the brain uptake of tricarbonyl complexes, substituted piperidinol were used for the synthesis of complex 2a and 3a. Both substituted cyclopentadienyl

Piperidine can cross easily the blood brain barrier. However, the in vivo studies in rats showed a lower uptake of complex 3a carrying a butyl group in position 4 as compared to previously published data for the reference compound (complex 4a). On the other hand, the complex 2a carrying a methyl group in position 4 has shown the highest brain uptake.

With the increase of the carbon chain in position 4 a camouflage of the functional group that interacts with the receptors could explain the decrease of the retention

In conclusion, labelled complexes in the presence of a sterically hindered ester do not affect the time of brain retention.

PS1-62

Freeze-dried kit formulation of ^{177}Lu- and ^{90}Y-labelled immuno-conjugates of Trastuzumab – formulation and characterization

Author: Marija Sterjova Arev[1]

Co-author(s): Predrag Džodić[2]; Petre Makreski[2]; Katarina Davalieva[3]; Drina Janković[4]; Marija Mirković[4]; Sanja Kiprijanovska[3]; Magdalena Radović[4]; Aleksandar Dimovski[2]; Emilija Janevik-Ivanovska[5]

[1]University of Niš, Nis, Serbia
[2]Ss. Cyril and Methodius University, Skopje, North Macedonia
[3]Macedonian Academy of Sciences and Arts, Skopje, North Macedonia
[4]University of Belgrade, Serbia
[5]Goce Delcev University Stip, North Macedonia

Corresponding author: marija.arev@ugd.edu.mk, emilija.janevik@ugd.edu.mk

Trastuzumab is a monoclonal antibody for treatment of HER2 positive breast cancer. Immunoconjugate of this antibody labelled with lutetium-177 and yttrium-90 has been investigated as potential radiopharmaceutical for radioimmunotherapy. In our study, the labelling was done via DOTA, DTPA and 1B4M-DTPA as a chelator in a molar ratio of 1:20.

Several techniques have been used to characterize the stability and retained immunoreactivity of the antibody in the formulated immunoconjugates. A protein integrity and purity were accessed by Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE). Vibrational (infrared and Raman) spectroscopy provided molecular structure information and was found convenient for verification of possible changes in the secondary structure. The number of chelating groups per one trastuzumab molecule was obtained by MALDI-TOF-MS. After conjugation, the freeze-drying process was performed to obtain stable immunoconjugates for further labelling. Quality control and stability were examined by ITLC using a three different mobile phases (0.9% saline solution, 0.4 M methanol:sodium acetate (1:1) and 0.1M acetic buffer).

The same intensity of the fragments (25 kDa for light chain and 50 kDa for heavy chain) of lyophilized immunoconjugates and pure trastuzumab indicated that there is no degradation of the antibody. The presence of characteristic amide bands in infrared spectra (amide I (1700-1600 cm-1), amide II (1480-1575 cm-1) and amide III bands (1255-1244 cm-1) and Raman spectra (amide I band at ~1670 cm-1 and amide III band at 1230-1300 cm-1) have also indicated that all samples have retained native secondary structure. An average of 3.92 p-SCN-Bn-DTPA, 3.69 p-SCN-Bn-DOTA and 4.43 1B4M-DTPA groups could be randomly conjugated to an antibody molecule, which represent promising result for successful labelling.

After labelling with ^{177}Lu and ^{90}Y (specific activity of 200 µCi/mL), radiochemical purity and stability studies were performed using ITLC method in 0.9% NaCl and 0.4 M methanol:sodium acetate (1:1) as an appropriate mobile phase. The stability studies after 72 h have revealed that ^{177}Lu labelled trastuzumab is more stable (<10% of the released 177Lu) than ^{90}Y-labelled one (<25% of released ^{90}Y).

In conclusion, our study shows successful formulation of stable radioimmunoconjugates which makes this proposed freeze-dried kit as a potential radiopharmaceutical in vivo investigations.

PS1-63

A novel therapeutic phthalimide derivative for cancer: synthesis, radioiodination and biological evaluation

Author(s): Hesham Shamsel-Din[1]

Co-author(s): Mohamed Abd El-Motaleb[1]; Ibrahem Abd El-Ghaney[1]; Hamed Abd El-Bary[2]

[1]Egyptian Atomic Energy Authority, Cairo, Egypt
[2]Faculty of Science, Menoufiya University ,Cairo, Egypt

Corresponding author: hisham86@yahoo.com

Developing novel agents for tumour diagnosis and therapy is relevant in the attempt to improve prognosis and to increase patient survival. The target of this study is the synthesis of a new phthalimide derivative and radiolabel with one of the most important therapeutic radioisotopes; iodine-131 is to be investigated as a novel therapeutic agent for cancer.

Synthesis of biologically active novel phthalimide derivative containing pyrimidine moiety, N-(6-(2-hydroxyphenyl)-2-mercaptopyrimidin-4-yl)phthalimide (HSPMPTH), in two steps from the intermediate chalcone by the claisen-schimidt condensation of N-acetylphthalimide with salicaldhyde, and then chalcone undergo a subsequent cyclization reaction with thiourea. The synthesized compounds were characterized by IR, mass and 1H-NMR spectra. New synthesized phthalimide derivative was radiolabelled with iodine-131 by direct electrophilic substitution reaction using chloramine-T as an oxidizing agent. The radiochemical yield was determined by using different chromatographic techniques (HPLC, paper chromatography and paper electrophoresis). Factors affecting labelling yields were optimized and a biological evaluation in solid tumour bearing mice was studied in detail.

The synthesized phthalimide derivative was prepared in excellent yield (about 86 %) and its structure was confirmed by IR, mass and 1H-NMR spectra. The radioiodination study of HSPMPTH showed high radiochemical yield of 95.20 ± 1.30 and good in vitro and in vivo stability of the ^{131}I-HSPMPTH. Biodistribution study for radioiodinated HSPMPTH in solid tumour bearing mice showed high solid tumour uptake and T/NT ratio (8.45 ± 0.08 at 30 min. post- injection) compared with many new tracers which have been developed in recent years.

In conclusion, ^{131}I-HSPMPTH accumulated specifically in the solid tumour with high T/NT ratio suggesting that this tracer could be considered as a potential lead for its development as a new therapeutic agent for cancer.

PS1-64

The first proof-of-concept theranostic radiopharmaceutical in Thailand

Author: Shuichi Shiratori[1];

Co-author(s): Supatporn Tepmongkol[1]; Kanaungnit Kingpetch[1]; Kitiwat Khamwan[1]; Suree Nimitwongsin[2]; Tawatchat Chaiwatanarat[1]

[1]Chulalongkorn University, Bangkok, Thailand

[2]King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Bangkok, Thailand

Corresponding author: chumpolt@yahoo.com

Theranostic concept was coined first by John Funkhouser in the last two decades utilizing the combination of a high specific drug that targets diagnostic and therapeutic tools for a specific disease. As a part of personalized medicine, theranostics was practically established in oncology as well as applied to nuclear medicine by labelled gamma emitter diagnostic imaging agent before initiating treatment of labelled beta emitter targeted therapeutic drug. Currently, theranostic applications are used in neuroendocrine tumour (NET) and prostate cancer which have been investigated in many countries around the world. Especially in European countries, where thousands of combinations of ^{68}Ga and ^{177}Lu-labelled PRRT (Peptide Receptor Radionuclide Therapy) together with PSMA (Prostate-Specific Membrane Antigen) have been successfully used in clinics. We aim to establish theranostic radiopharmaceuticals in clinically routine use in our facility.

Four theranostic radiopharmaceuticals of ^{68}Ga-PSMA, ^{177}Lu-PSMA, ^{68}Ga-HADOTATATE and ^{177}Lu-HADOTATATE were manually labelled under sterile techniques. Briefly, PSMA and HADOTATATE ligands were added with acetate buffer 1.5 ml before mixing to ^{68}Ge/^{68}Ga generator eluted $^{68}GaCl_3$ 4 ml, then heated at 100^{o}C, 15 minutes. After cool down to room temperature, ^{68}Ga-PSMA, ^{68}Ga-HADOTATATE were purified via C-18 column, filtrated through 22 µ membrane filter. In the other hands, PSMA and HADOTATATE ligands were added with ascorbic buffer 1.5 ml before mixing to commercially available non-carrier added Lutetium-177, then heated at 100^{o}C, 15 minutes. After cool down to room temperature, ^{177}Lu-PSMA, ^{177}Lu-HADOTATATE were filtrated through 22 µ membrane filter. All theranostic radiopharmaceuticals were subjected to quality control process before injection to patients. ^{177}Lu-DOTATATE was co-infused with amino acid solution for renal protection. Post-treatment SPECT scan time for the patients who were injected with ^{177}Lu- PSMA, ^{177}Lu-HADOTATATE, were 0, 1, 4, 14, 48 hrs, respectively. Absorbed dose in kidneys was determined following the MIRD method.

From February 2018 to February 2019, we performed ^{68}Ga-PSMA 35 doses, ^{68}Ga-HADOTATATE 7 doses, ^{177}Lu-PSMA 13 does and ^{177}Lu-HADOTATATE 5 doses. No nephrotoxicity of ^{177}Lu-HADOTATATE and ^{177}Lu-PSMA was found in all cases of our patients according to joint IAEA, EANM and SNMMI protocol guidance.

The first proof-of-concept theranostic in Thailand has been successfully established in King Chulalongkorn Memorial Hospital without nephrotoxicity. In very near future, two new theranostic radiopharmaceuticals, ^{225}Ac-HADOTATATE and ^{225}Ac-PSMA, will be introduced to provide better effective result and enhance our patients' benefit.

PS1-65

Exploring Ga-68 Trastuzumab Fab for noninvasive PET imaging to detect HER2 expressing lesions

Author: Jaya Shukla[1];

Co-author(s): Yogesh Rathore[1]; Priya Bhusai[1]; Ishita Laroiya[2]; Rajender Kumar[1]; Harmandeep Singh[1]; Amanjit Bal[3]; Gurpreet Singh[2]; Bhagwant R Mittal[1]

[1]Department of Nuclear Medicine, India
[2]Department of General Surgery, India
[3]Department of Histopathology, India

Corresponding author: shuklajaya@gmail.com

HER 2 is a transmembrane protein expressed in a variety of tissues involved in cell development, proliferation and differentiation. Amplification of HER2 gene leads to over expression of HER2 receptors and uncontrolled growth. HER2 expression is associated with aggressiveness of tumours. The anti HER2 monoclonal antibody, Trastuzumab (145 kDa), binds to domain IV of HER2 receptor and inhibits the tumour growth. The fragment of trastuzumab bearing antigen binding site, Fab (45 kDa), is explored for imaging HER2 expression in breast cancer patients.

The Trastuzumab Fab was generated with papain digestion and conjugated with a bifunctional chelating agent NOTA. The NOTA conjugated Ga-68 trastuzumab Fab was separated and was radiolabelled with freshly eluted Ga-68 from Ge-68/Ga-68. Radiolabelled Ga-68 NOTA- Ga-68 trastuzumab Fab (Ga-68 trastuzumab Fab) was separated using PD-10 column and passed through 0.22 µm filter for sterility. The radiochemical purity of Ga-68 Fab was assessed by paper chromatography using sodium-citrate (pH-5.5) as mobile phase, apyrogenicity with PTS and sterility in culture broth for 7 days. The patients (n=7) with immunohistochemistry (IHC) proven HER 2 expressing breast cancer (n=7) and HER 2 negative (n=2) were recruited. The F-18 FDG PET/CT was done in all patients. After obtaining permission from the Institute and informed written consent forms from patients, Ga-68 trastuzumab Fab (3-5 mCi) was injected and PET/CT was acquired after 1.5, 3.0 hour. Scans were analysed by two nuclear medicine physicians and compared with ^{18}F- FDG findings.

The Fab region of trastuzumab is responsible for binding with HER2 ligand binding domain. Fab was generated by papain digestion and separated by desalting (P-10 column). The NOTA conjugation was standardized at 4°C from 22 to 24 hours incubation time and average 1.5 NOTA molecules per Fab (MALDI-TOF) were conjugated at 25:1 molar ratio of NOTA:Fab. The labelling efficiency of Ga-68 trastuzumab Fab was more than 50% and after purification, the radiochemical purity was >95%. The Ga-68 trastuzumab Fab was found sterile and pyrogenic. Ga-68 trastuzumab Fab MIP PET image showed high blood pool activity at 1.5 h, which was decreased at 3h. However, high kidney and bladder activity demonstrated clearance by the renal route. The uptake at primary and metastatic lesions was visualized at 1.5 h and increased at 3 h, in terms of SUV max, in all HER2 expressing patients. However, no uptake was observed in HER 2 negative patients. The liver uptake was noted in all patients. The lesions detected on Ga-68 trastuzumab Fab PET/CT were comparable with F-18 FDG PET/CT. To the best of our knowledge this is the first human study using Ga-68-Fab.

In conclusion, the Ga-68 Fab has been formulated and demonstrated to be potential for targeting HER2 positive lesions. In the future, this imaging could be utilized to demonstrate the pattern of HER2 receptor throughout the body before and after trastuzumab and trastuzumab radioimmunotherapy therapy.

PS1-66

Improvement of synthesizing material and method for an in-house production of [^{18}F]-florbetapir PET tracer for imaging beta amyloid deposition in the brain

Author: Tossaporn Siriprapa[1]

Co-author(s): Sadashiro Naka[2]; Tanyaluck Thientunyakit[1]

[1] Faculty of Medicine Siriraj Hospital, Thailand
[2]Osaka University Hospital, Thailand

Corresponding author: tossaporn.sip@mahidol.ac.th

Recently, the (E)-2-(2-(2-(2- [18F]-fluoroethoxy)ethoxy)ethoxy)-5-(4-methylaminostyryl) pyridine) (a.k.a. [^{18}F]-florbetapir) was developed in our laboratory as a radiotracer to detect β amyloid deposition in the brain using PET scan assisting for diagnosis of Alzheimer's disease. In this research, we aimed to compare the production yield of [^{18}F]-florbetapir obtained from the newly adapted synthesizing materials with an optimized method and that of the original method.

[^{18}F]-florbetapir was produced at Siriraj Cyclotron Centre using HM-20S cyclotron with CFN-MPS200 module (Sumitomo, Tokyo, Japan). The activated fluoride (^{18}F) was combined to AV-105 precursor by substituting the tosylate leaving group in a fluorination step. Then, 1N hydrochloric acid was added and pH-adjusted with 1N sodium hydroxide to remove the boxylic protecting group with deprotection process or hydrolysis. During synthesizing steps, in the original method (Method A) we used FLT cassette (Sumitomo, Tokyo, Japan) with installed silicone tubes. In the new method (Method B), we replaced all original tubes in FLT cassette with PharMed® BPT tube (Saint-Gobain, Akron Ohio, United States), which was further sent for sterilization at local central sterile supply department (CSSD) before use. Following purification via HPLC semi-preparative, the products from both methods were neutralized with 0.5% sodium ascorbate/water (non-diluted in method A and diluted 1:8 in method B), purified with Sep-Pak tC18 reverse phase column, eluted into the vial containing normal saline and filtrated with 0.22 µm Millex GV filter.

The quality control of [^{18}F]-florbetapir was done by standard methods for the determination of basic characteristics of radiopharmaceuticals including appearance, acid-base range, radiochemical purity, residual solvent, pyrogenicity, half-life, chemical impurities, sterility, nuclidic purity and assay of ascorbic acid. The remaining radioactivity inside the tubes, overall yield, specific activity, radiochemical purity and other physical properties from both methods were compared. The remaining radioactivity inside the tubes of method B was 3.23±1.4 (n =4), which was 32.57% decreased from 9.93±1.52% remaining radioactivity in the tubes of method A (n = 3). The recovery rate from tC18 after neutralization with 0.5% sodium ascorbate/water (Method B) was 94.72±6.00%, which was higher than 76.71±4.58% from method A.

The overall yield, specific activity and radiochemical purity of [^{18}F]-florbetapir produced by method B were 21.4±0.2% (not decay corrected), 5.24±2.25 TBq/mmol and 96.1±3.2%, respectively, which were higher than 5.7±1.50%, 1.26±0.28 TBq/mmol and 95.84±0.80% obtained from method A. Other physical properties including appearance, acid-base range, half-life, residual solvents (acetonitrile and DMSO), total chemical impurities, assays of ethanol and assays of sodium ascorbate, and bacterial endotoxins of [^{18}F]florbetapir produced by both methods were within standard criteria.

We successfully improved [^{18}F]florbetapir production by optimizing a new type of tubing cassette material to use with the automated synthesizer and minor adjustment of neutralization method. This new method provides higher production yield and higher radiochemical purity as compared to our previous method. In addition, this applied cassette is able to reduce production cost, easy to operate and suitable for Siriraj Cyclotron facility.

PS1-67

Evaluating quality control of ^{18}F-FDG: experience in Sultan Qaboos University Hospital, Oman

Author: Naima Tag

Co-author(s): Jawa Zabah; Noura Al Makhmari; Aziza Al Jabr

Sultan Aaboos University Hospital, Muscat, Oman

Corresponding author: naima.tag@gmail.com

The use of ^{18}F-FDG for PET/CT imaging is relatively new in Oman with only two centres, Sultan Qaboos University Hospital (SQUH) and Royal Hospital. At the onset, ^{18}F- FDG was imported from Dubai which is about an hour. flight from Muscat, however, in 2015, a cyclotron was installed at the Royal Hospital, which now supplies both centres. To ensure patients and staff safety, as well as good image quality, a continuous and rigorous quality control (QC) of ^{18}F-FDG is necessary.

The aim of this study is to highlight the potential value of continuous surveillance of the quality of ready to use ^{18}F-FDG, to share our initial experience in this area, and finally to highlight the importance of a radio-pharmacist in a nuclear medicine department.

A review of the quality control release form for each new batch of ^{18}F-FDG which includes, radionuclide and radiochemical identity, radiochemical purity, chemical purity, pH, sterility, and bacterial endotoxin level as well as patient preparation before ^{18}F-FDG injection, and any patient complaints after injection and image quality.

We receive ^{18}F-FDG only after all the tests are passed, patient injection and release after scan is always after all QC has been completed, however, there may be challenges associated with using ^{18}F-FDG in our institution without a qualified radio pharmacist. These will be presented at the conference.

In conclusion, a continuous and rigorous quality control of ^{18}F-FDG by the qualified persons is important for patients and staff safety, as well as good image quality. This study highlights the critical role and the importance of an in-house radio pharmacist in a NM department.

PS1-68

Design, synthesis and evaluation of a family of ^{99m}Tc estradiol derivatives for breast cancer imaging

Author: Maria Emilia Tejeria
Co-author(s): Javier Giglio; Ana Rey

Área Radioquímica, Facultad de Química, Universidad de la República (UdelaR), Montevideo, Uruguay

Corresponding author: etejeria@fq.edu.uy

With the objective to develop a potential radiopharmaceutical for estrogen receptors imaging we present the design of a family of ^{99m}Tc complexes derived from estradiol, using different oxidation states of the metal and chelating units and studying their influence on the overall properties of the resulting products. Ligands were synthesized starting from ethinylestradiol, derivatizing the triple bond to incorporate different donor atoms to coordinate the ^{99m}Tc.

The selected labelling strategies were the formation of a Tc (I) tricarbonyl complex (C1) with an N,N,O donor atom set, a Tc (V) nitride symmetric complex (C2) with two units of estradiol and dithiocarbamate as bidentade chelator and a Tc (III) 4 + 1 complex (C3) using a ligand bearing an isonitrile moiety and an NS3 tridentate coligand. Characterization stability studies, lipophilicity, protein binding, in vitro cell binding and in vivo overall biodistribution.

Results show that synthesis of the ligands was successful in all cases, although the difficulty level is remarkably different. The selected labelling strategies rendered the desired ^{99m}Tc complexes with high radiochemical purity. However, HPLC purification was required for C3.

All complexes showed high stability in labelling milieu and in human serum for at least 3 hours. Lipophilicity expressed as log P (partition coefficient between octanol and phosphate buffer 0.1M, pH = 7.4) was 1.3 ± 0.1 for C1, 0.8 ± 0.1 for C2 and 0.48 ± 0.06 for C3. C3 exhibited the lowest lipophilicity which agrees with the bibliography which indicates that the preparation of Tc(III) 4+1 complexes could be a good strategy to reduce the overall lipophilicity .

A moderate protein binding in comparison to ethynilestradiol (98%) was observed in all the three cases with values of 33 ± 11%, 41 ± 9% and 46 ± 6, respectively.

Binding to MCF7cells was 2.0 ± 0.2%, 6.8 ± 0.9% and 3,33 ± 0,12% respectively, while tritiated estradiol (Estradiol [6.7-3H (N)]) exhibited a binding of 6.6±1.4%. C2, a symmetric Tc(V)-nitrido complex bearing two units of the pharmacophore has the highest binding. Our findings are in agreement with reports that indicate the positive effect of dimerization or multimerization in receptor binding. Biodistribution in normal rats for C1 and C2 showed low blood activity (0.70 ± 0.26% and 5.13 ± 2.49% at 2 hours, respectively). However, liver uptake was very high for C1 (40.8 ± 2.4%) and moderate for C2, (13.0 ± 1.3%). Excretion occurred mainly through the hepatobiliary system with only a minor fraction excreted in the urine. C2 has the properties in vitro and in vivo properties. In vivo studies for C3 are being performed.

In conclusion, influence of the chelating system in the physicochemical and biological properties of Tc-labelled in biomolecules is clearly demonstrated by our experimental results. Consequently, the design of the suitable chelator is crucial in obtaining the biological stability and pharmacokinetics desired for a radiopharmaceutical.

Acknowledgments: ANII (FCE_1_2017_1_136416), CAP, PEDECIBA-Química, Bayer Schering Pharma AG, Hans-Jürgen Pietzsch.

PS1-69

Labelling of PSMA-11 with ^{68}Ga in $NaHCO_3$

Author: Kamila Urbanová
Co-author(s): Daniel Seifert; Ondřej Lebeda

Nuclear Physics Institute of the Czech Academy of Sciences, Husinec, Czech Republic

Corresponding author: urbanova@ujf.cas.cz

Prostate specific membrane antigen (PSMA) is a type II membrane protein which is widely expressed on the surface of prostate cancer cells. One of the functions of PSMA is to be receptor mediating the ligand internalization. This feature of PSMA is employed in the diagnostic and therapeutic procedures that use PSMA as an antigen target.

Over the years, small molecules with high affinity for PSMA have been developed and labelled with positron emitters (e.g. ^{68}Ga, ^{18}F, ^{11}C, ^{64}Cu, or ^{86}Y). One of these radiolabelled ligands, [^{68}Ga] PSMA-11, is the most frequently used tracer for PET imaging of the prostate cancer. PSMA-11 has a strong binding affinity for the PSMA protein and is effectively internalized in the prostate cancer cells.

The aim of this work is to test a new approach to the labelling of the PSMA-11 ligand with ^{68}Ga eluted from the Galli Eo generator (IRE Elit) in slightly alkali milieu.

The ^{68}Ga-eluate was loaded to the Oasis MCX cartridge. The cartridge was activated before use and thoroughly washed with water after the loading ^{68}Ga. The radionuclide ^{68}Ga was eluted from the cartridge with 0.1M $NaHCO_3$ (pH = 8.5). The precursor PSMA-11 was mixed directly with the eluate. Activities were determined using an ionizing chamber, pH was measured for all samples that were further analysed by LC-MS and HPLC systems.

A total of 18 experiments of labelling PSMA-11 with ^{68}Ga were performed. In these experiments, altogether 34 samples of PSMA-11 were labelled and subjected to radiochemical purity test. All the samples were compared with the standard for [^{68}Ga]PSMA-11. In more than 20 samples radiochemical yields (RCY) exceeded 90 % and in only 5 samples the RCY dropped below 50 %.

Table 1 shows average values of pH, activity, retention times (RT) and radiochemical yields (RCY) with standard deviations (STDEV) for samples of ^{6}8Ga-labelled PSMA-11 in 0.1M NaHCO3.

	Average values for 34 samples of PSMA-11
pH	8.3 ± 0.5
A (MBq)	72.7 ± 55.4
RT (min)	3.3 ± 0.1
RCY (%)	83.4 ± 27.4

Tab. 1. Results for labelling of PSMA-11 – average values of pH, activity, retention times (RT) and RCY with standard deviations (STDEV)

In conclusion, a new method of labelling PSMA-11 ligand with ^{68}Ga in 0.1M $NaHCO_3$ (pH = 8.5) using Oasis MCX cartridges was developed and tested. The results demonstrated that the method is straightforward, rapid (the whole process of labelling takes 10–15 min) and reproducible.

PS1-70

Influence of ^{99m}Tc-chelation at N-terminal and/or C-terminal on receptor binding affinity of NGR peptides

Author: Kusum Vats

Co-author(s): Rohit Sharma; Mythili Kameswaran; Haladhar Dev Sarma; Drishty Satapati; Ashutosh Dash

Bhabha Atomic Research Centre, India

Corresponding author: vkusum@barc.gov.in

The NGR peptide has high affinity towards aminopeptidase receptors (APN or CD13 receptors) upregulated in tumour angiogenic blood vessels as well as in melanoma, ovarian, prostate, lung, and breast tumours. This study aimed at determining the influence of modification of NGR peptide at either N- or C-terminal on the receptor binding affinity. Tridentate ligand scaffolds were introduced at N- or C-terminal of NGR peptide via click chemistry for radiolabelling with $^{99m}Tc(CO)_3$-precursor. In vitro and in vivo evaluation of N- and C-terminal radiometalated peptides was performed to determine the effect on receptor binding affinity.

The N- and C-terminal azide-functionalized NGR peptides, K(N^3)c(CNGRC)G-$CONH_2$ (1a) and c(CNGRC)K(N_3)G-$CONH_2$ (2a) were synthesized manually by standard Fmoc solid phase peptide synthesis protocol. For N-terminal modification CNGRCG sequence was first assembled on the solid phase followed by coupling of Fmoc-Lys(N_3)-OH at the N-terminus. The C-terminal modification of NGR peptide was performed by loading Fmoc-Gly-OH as the first amino acid on the solid phase followed by Fmoc-Lys(N_3)-OH. Further CNGRC sequence was assembled and disulphide bridge was formed by cyclization of cysteine sulphides. Subsequent to cleavage from the solid phase and purification by semi-preparative HPLC, the azide peptides were subjected to click reaction with propargyl glycine in solution phase to synthesize peptide constructs K(Pra-Tz)c(CNGRC)G- $CONH_2$ (1b) and c(CNGRC)K(Tz-Pra)G-$CONH_2$ (2b) respectively, containing a tridentate chelating unit for radiolabelling with [$^{99m}Tc(CO)_3$]+ core. Peptide constructs were characterized by mass spectroscopy. The radiotracers, $^{99m}Tc(CO)_3$-K(Pra-Tz)c(CNGRC)G-$CONH_2$ (1c) & $^{99m}Tc(CO)_3$-c(CNGRC)K(Tz-Pra)G-CONH2 (2c) were analysed by HPLC and evaluated for in vitro receptor affinity in murine melanoma B16F10 cells and in vivo pharmacokinetic behaviour was determined in C57BL/6 mice bearing melanoma tumour.

The N- and C-terminal azide-NGR peptides (1a and 2a) synthesized manually by solid phase peptide synthesis were obtained in an overall yield of 27% and 31% respectively; with >98% purity. Radiometalation of peptide constructs 1b and 2b resulted in formation of neutral $^{99m}Tc(CO)_3$-NGR complexes, 1c and 2c respectively with >95% radiochemical purity. The C- terminal modified peptide exhibited higher binding affinity towards B16F10 cells in comparison to N-terminal modified peptide (IC50 values 1b: 136 @ 2.3 nM; 2b: 65 @ 1.7 nM). The C-terminal con- struct 2c exhibited higher uptake in murine melanoma B16F10 cells during in vitro studies. In vivo tumour uptake of 2c was higher than of N-terminal modified peptide construct 1c at 2 h p.i. (2.4 @ 0.5 vs 1.9 @ 0.3% ID/g respectively). Blocking studies carried out by co-injection of cNGR peptide led to ~50% reduction in the tumour uptake at 2 h p.i. suggesting receptor-mediated uptake of radiotracers. Both the radiotracers exhibited rapid urinary excretion and cleared from all the major organs (heart, lungs, spleen, stomach and blood) at 4 h p.i. (<1% ID/g).

The N- and C-terminal modified peptide constructs could be radiometalated with $^{99m}Tc(CO)_3$ core in good radiochemical yield (>95%). However, higher in vitro cell uptake and in vivo tumour uptake was observed for the C-terminal construct illustrating the preferred conjugation of drugs, dyes, radiometals etc. at C-terminus of NGR peptide.

PS1-71

Development of automatic system for production of small batches of radioiodine capsules

Author: Aleksandar Vukadinovic[2]

Co-author(s): Miroslav Ravlic[1] ; Milovan Matovic[3]; Sanja Vranjes-Djuric[2]

[1]Prizma company, Serbia
[2]Vinca Instutute of Nuclear Sciences, Serbia
[3]University of Kragujevac, Faculty of Medical Sciences, Serbia

Corresponding author: vukadinovic@vin.bg.ac.rs

Preparation of small batches of custom ordered ^{131}I capsules in hospitals and institutes is often done manually. Operators could be exposed to a significant level of radiation exposure doses during manual preparation of capsules with high activities of ^{131}I. There are few commercial solutions for automatic capsule filling, but those devices are very expensive. We developed a simple and affordable automatic system for this purpose. The goal of this publication is to present and shortly describe the function of our system. The system consists of PC controlled device which is dedicated to precise dosage of ^{131}I solution and filling of capsules with different amount of radioiodine activities. The whole device is located into a dedicated chamber, shielded by lead bricks. It is known that the solution volume in microliters closely correlates with the activity in mCi, which is a basic principle of our system. The first step in the whole process is filling of the known volume of ^{131}I solution into the syringe. The next step is filling-out the needed volume (i.e. activity) in the capsule and closing it with appropriate cap. The third step includes measuring ^{131}I activity in the capsule (dose calibrator) and printing its value on the self-adhesive label. The final step is to transport the capsule to a lead container. The whole process is automated, controlled by PC, which is equipped by an appropriate software. The advantage of this system is that it is suitable for custom ordered capsules because every produced capsule can be of desirable activity and calibration date. The list of capsules with their activities and calibration dates can be easily uploaded to the system as an Excel file. Our system reduces the unnecessary radiation exposure of personnel and also prevents errors caused by subjective or objective reasons, which are often the case during manual capsules filling.

PS1-72

^{111}In-labelled bifunctional agents for dual targeting of breast cancer cells

Author: Filipe Vultos

Co-author(s): Lurdes Gano; Célia Fernandes; Filipa Mendes; João D. G. Correia

Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa, Portugal

Corresponding author: lgano@ctn.tecnico.ulisboa.pt

Breast cancer (BC) is the most common invasive cancer diagnosed in women worldwide. The estrogen receptor (ER) is a well-established biomarker for prognosis and guiding treatment of patients, and it is a good target for molecular imaging and radionuclide therapy. The objective of this study was to improve the theranostic value of previously studied ^{111}In-labelled ER-targeting moieties (e.g. estradiol derivatives/LXXLL-based peptides) by enhancing the delivery of the radionuclide into BC cells' nucleus in close proximity to DNA. To achieve this goal, we have explored an approach that combines into a single ^{111}In-hybrid compound two different biological targeting moieties for dual targeting of BC cells. Hybrid compounds containing an ER ligand conjugated to a DOTA derivative functionalized with a nuclear-targeting moiety (DNA-intercalating agent, AO, or a peptidic nuclear localizing sequence, NLS) were synthesized. The bifunctional compounds were radiolabelled with the Auger electron emitter Indium-111 that has simultaneous emissions of gamma radiation aiming the selected delivery into ER plus breast cancer cells.

Synthesis of a DOTA- based pre-chelator that could allow double vectorization with two different molecular entities was achieved by following an orthogonal strategy. The versatility of this chelator to prepare radiolabelled hybrid compounds was demonstrated by the synthesis of three different conjugates containing an ER-binding molecule and a nuclear-targeting agent. Radiolabelling with ^{111}In was performed at 95ºC, pH=5 acetate buffer. Radiochemical purity and in vitro stability of the radiolabelled compound was evaluated with HPLC. Cellular uptake of ^{111}In conjugates were assessed in MCF-7 (ER+) and MDA-MB-231 (ER-) human BC cells. The subcellular localization, in particular the internalization into the cell nucleus was also evaluated. The ability of ^{111}In-compounds to induce DNA damage in-vitro was tested by incubation with double-stranded plasmid DNA for 140 hours. The biodistribution was assessed in female mice with MCF-7 xenografts.

The synthesis of dual-conjugates comprising an ER-targeting and a nucleus targeting moieties was successfully achieved by following an orthogonal strategy. The In-/^{111}In- complexes of the hybrid conjugates were successfully prepared and the radiolabelled conjugates demonstrated high stability. The prepared dual-targeting radiolabelled probes [^{111}In]ER3AO, [^{111}In]E2NLS and [^{111}In]E2AO demonstrated high nuclear internalization (higher than 50%) in MCF-7 cells, proving the efficacy of the applied nuclear-targeting approaches. Moreover, [^{111}In]ER3AO demonstrated ability to cause direct damage in DNA. Preliminary biodistribution studies of [^{111}In]ER3AO in tumour-bearing mice were also encouraging since high in-vivo stability, fast blood clearance from blood and uptake in the ER-rich organs and in the tumour, as well as high target tissue/ non-target tissue radioactivity ratios were obtained.

A straightforward and versatile synthetic approach was used for the synthesis of bifunctional radioconjugates bearing two different molecular entities. The favourable biological results of the ^{111}In conjugates in cellular and animal models represent promising properties for the development of radiopharmaceuticals for Auger therapy.

Acknowledgments: F. Vultos thanks FCT for PhD grant (SFRH/BD/84509/2012). The work was supported by UID/Multi/04349/2013.

PS1-73

Cancer drugs and ^{99m}Tc-glutation radiopharmaceutical interaction to achieve optimal result of cancer diagnostics in nuclear medicine

Author: Teguh Hafiz Ambar Wibawa

Co-author(s): Yudi IswahyudiNone; Ahmad Kurniawan; Isti Daruwati

National Nuclear Energy Agency, Jakarta, Indonesia

Corresponding author: teguh.haw@gmail.com

Cancer is one of the leading causes of death in the world, including Indonesia. By 2030, it is estimated that cancer sufferers reach 26 million people and 17 million dies from cancer, with a faster increase in developing countries. The application of nuclear techniques in nuclear medicine plays an important role in diagnosing cancer, measuring therapy responses, and identify an optimal therapy. PSTNT - BATAN has contributed to the development of diagnostic kits, one of which is ^{99m}Tc-Glutathione. By utilizing these diagnostic kits, there is a tendency to increase the risk of drug interactions consumed by cancer patients with diagnostic kits that can lead to misinterpretation of data. This study aims to investigate the possible alteration in the pharmacokinetics profiles and biodistribution of ^{99m}Tc-Glutathione when given in combination with cancer drugs in Balb/C strain mice (Mus musculus). The study was divided into four groups of normal and model animals test. Each group is differentiated by treatment, i.e. control (I), animals test with doxorubicin treatment (II), 5-fluorouracil (III), and methotrexate (IV). Each drug is intravenously, after 5 minutes it is injected with ^{99m}Tc-Glutathione intravenously. Furthermore, the pharmacokinetics and biodistribution studies were carried out. Study of pharmacokinetics and biodistribution interaction showed that the administration of cancer drugs before administration of ^{99m}Tc-Glutathione reduces the elimination half-life and target / non-target organ ratio significantly. The target / non-target ratio of ^{99m}Tc-Glutathione (control) and ^{99m}Tc-Glutathione that combined with cancer drugs doxorubicin, 5-fluorouracil, and methotrexate in normal mices are:7.01, 1.47, 1.43, and 5.61 respectively. Whereas, the target / non-target ratio of ^{99m}Tc-Glutathione (control) and ^{99m}Tc-Glutathione that combined with cancer drugs doxorubicin, 5-fluorouracil, and methotrexate in cancer model mices are: 2.94, 1.33, 0.42, and 2.11 respectively. The results can certainly cause misinterpretation of diagnosis data. Therefore, the phenomenon of drugs and radiopharmaceutical interactions must be considered by clinicians in nuclear medicine.

PS1-74

In vivo study of radiolabelled flavonoid ^{99m}Tc-quercetin as cancer radiotracer on normal balb/c mice

Author: Eva Maria Widyasari

Co-author(s): Rizky Juwita Sugihari; Maula Eka Sriyani; Iim Halimah; Endah Rosyidiah; Ahmad Kurniawan; Iswahyudi Iswahyudi

National Nuclear Energy Agency BATAN, West Java, Indonesia

Corresponding author: evamaria@batan.go.id

Cancer is a major health problem and it is estimated that more than 10 million new cases of cancer diagnosed worldwide with more than 4 million deaths, annually. Chemotherapy is still the primary choice in cancer modality that uses chemotherapeutic drugs to eradicate and inhibit the growth of cancer cells. This treatment has excellent reliability and is effective to kill cancer cells, but its cost is high. Therefore, patients tend to seek alternative treatment such as consuming traditional herbal medicine. Abundant presence of flavonoid in natural products used as traditional herbal medicines that have an interesting bioactivities need to be studied. Quercetin (3,3',4',5,7- pentahydroxyl-flavone) is a flavonoid compound found in many fruits and vegetables that have antioxidant activity. As an antioxidant compound, quercetin will protect the body from free radical that can increase the risk of disease. However, as a traditional herbal medicine, its effectiveness is not yet been fully established due to the lack of scientific information. Many in-vitro studies have proven the effectiveness of quercetin as an anticancer compound, but the data from in-vivo study is still limited. In recent years, several radioisotopes have been utilized for biodistribution studies of biologically important natural products because nuclear medicine techniques provide some advantages over conventionally used methods in term of detection sensitivity and availability. This study was conducted as a preliminary study to understand the biodistribution pattern of ^{99m}Tc-quercetin on normal balb/c mice. In vivo data from this study would provide meaningful biological and pharmacological information of ^{99m}Tc-quercetin for understanding its effectiveness as for development of quercetin as anticancer agent.

^{99m}Tc-quercetin was prepared by addition of 30 µl (1 mg/ 1 mL) of solution $SnCl_2$. 2H2O into a glass vial containing 320 µL quercetin solution (0,5 mg/320 µL) and 200 µL 0.2 M phosphate buffer pH 7.5. pH of the mixture was adjusted to 7.5 by addition of NaOH 0,1 N and final volume of the mixture was carried out into 600 µL by addition of bidistilled water. Thereafter, 400µL (± 0,5 mCi) of freshly eluted $^{99m}TcO_4$ was added into the vial and incubated within 5 minutes in room temperature.

Radiochemical yield of ^{99m}Tc-quercetin was determined by using a thin layer chromatography using TLC-SG F254 strips with two solvent systems to distinguish and quantify the amounts of radioactive contaminants (free $^{99m}TcO_4$, $^{99m}TcO_2$). Chromatography system of TLC-SG F254 / acetone was used to separate impurities of $^{99m}TcO_2$, while TLC-SG F254/NaCl 0.9 % was used to separate free $^{99m}TcO_4$. Radioactivity on chromatograms strips was measured using TLC-scanner (AR-2000, BIOSCAN).

Animal studies were conducted in accordance with our institutional guidelines and were approved by the Ethics Committee for Care and Use of Experimental Animal - National Nuclear Energy Agency. Biodistribution studies were performed by intravenous administration of a 0.1 mL ^{99m}Tc-quercetin (2.6 µCi/100 µL) to 5-week-balb/C mice (BIOFARMA). Groups of three mice were used for the experiments. Organs of interest were removed, weighed, and the radioactivity was determined with an automatic-well γ counter (2470 Wizard, PERKIN ELMER) at 15 minutes, 1, 3, and 24 h post-injection. Urine and faeces were collected for 24 h post injection, and the radioactivity counts were determined.

Labelling efficiency of the ^{99m}Tc-quercetin was assessed by thin layer paper chromatography. In TLC-SG F254 using saline as the solvent, free ^{99m}Tc moved with the solvent front, while ^{99m}Tc-quercetin and ^{99m}TcO2 remained at the spotting point. $^{99m}TcO_2$ was determined by using TLC-SG F254 / acetone as the mobile phase where the $^{99m}TcO_2$ at the point of spotting while free ^{99m}Tc and ^{99m}Tc-quercetin moved with the solvent front. The radiochromatogram of ^{99m}Tc-rutin was presented. ^{99m}Tc-quercetin had labelling efficiency > 90 % and can be used to carry out in vivo test.

Biodistribution study in normal mice showed that the radioactivity levels in the stomach were below 1%ID up to 24 h post-injection, indicating that ^{99m}Tc-quercetin was stable in vivo. The uptake of ^{99m}Tc-quercetin in kidney in 15 minutes was 6.13±1.05 %ID/g and remain 3.31±0.29 %ID/g at 24 hour post injection. After 15 minutes, 1 hour, 3 hour and 24 hour post injection the radioactivity levels on the blood was 3.39±0.21 %ID/g, 1.81±0.54 %ID/g 1.59±0.30 %ID/g and 0.46±0.07 %ID/g respectively. These results suggested that ^{99m}Tc-quercetin had fast rate of plasma clearance after administration. The biodistribution study of ^{99m}Tc-quercetin also demonstrated that high radioactivity accumulation was found in the liver at all post injection time points, indicating that ^{99m}Tc-quercetin was lipophilic compound. Moreover, the radioactivity was observed in the intestine for 15 minutes, 1 hour, and 3 hours that is 1.63±1.96 %ID/g, 1.53±0.33 %ID/g, and 1.44±0.53 %ID/g. Then, the uptake value was decreased after 24 hours to 0.54±0.20 %ID/g. This study also showed that ^{99m}Tc-quercetin was excreted through urinary and faecal excretion. These results in the current study demonstrated that intravenously injected of ^{99m}Tc-quercetin was metabolized in the liver and moved to intestine via the bile duct.

This study gave preliminary biodistribution data of ^{99m}Tc-quercetin in normal mice. Further studies on target accumulation of ^{99m}Tc-quercetin in animal model with cancer would provide a good basis for developing radiolabelled flavonoid as radiotracer to understand the mechanisms of quercetin as anticancer.

PS1-75

The synthesis and cytotoxicity of ^{64}Cu/NOTA-terpyridine platinum conjugate, as a novel theranostic agent

Author: Brigitte Guérin

Co-author(s): Meysam Khosravifarsani; Samia Ait-mohand; Léon Sanche

Université de Sherbrooke, Sherbrooke, QC, Canada

Corresponding Author(s): brigitte.guerin2@usherbrooke.ca

Currently, theranostics for both imaging and concomitant chemoradiotherapy is widely used in the treatment of cancerous patients. In this regard, defining the optimal timing between Pt-drugs injection and radiation delivery to the patients is an important issue. Recent advances in the field of nuclear medicine can potentially solve this problem by selective delivery of Pt-based compounds labelled with a positron/Auger-emitting radionuclide to cancer cells. In this study, we designed and validated for the first time a ^{64}Cu-NOTA terpyridine platinum conjugate as a novel Pt-based positron/Auger emitting agent targeting G-quadruplexes DNA structure. This project is aimed to demonstrate that such theranostic agent could give rise to a synergistic effect with a greater selectivity toward cancer cells.

The in-vitro cytotoxic and synergistic effects of the conjugate were assessed by Presto-blue assay. The cellular uptake, internalization and efflux of ^{64}Cu-NOTA terpyridine platinum conjugate was measured for colorectal cancer cell (HCT116) as well as a normal fibroblast cell line (GM05757) at 24, 48 and 72 h after initial incubation time.

As a result, natCu-conjugate showed 3.4, 1.7 and 2.3 times higher cytotoxicity against HCT116 cells relative to GM05757 fibroblast normal cells. However, natCu-conjugate exhibited 9.6, 11.5, 14.1 folds lower cytotoxic effects on HCT116 cells than cisplatin at 24, 48 and 72 h, respectively. The internalization of 64Cu-conjugate in HCT116 cells increased from 15 min (0.04±0.021%) to 24h (18.7±2.8%) and followed by a plateau at 48h (18.6±1.5%), post-administration. The percentages of internalization were significantly higher in HCT116 cancer cells as compared to GM05757 normal cells at 24h, 48h and 72h post-administration (Pvalue<0.001), which is associated with higher cytotoxicity of the conjugate toward HCT116 cells. More importantly, the efflux profile of HCT116 cells showed that a considerable amount of ^{64}Cu-conjugate was retained throughout the time course from 15 min (100±7 %) to 72h (48±6%). Additionally, there was a little percentage of the conjugate (<1%) internalized at 4 ℃ and all time points, indicating that passive uptake of the compound is not primarily responsible for internalization. A synergistic (radiosensitizing) effect was measured for the ^{64}Cu-conjugate (5 and 8MBq) at low concentrations (<100µM). Conversely, cell viability (%) started to increase steadily exhibiting an infra-additive (radioprotective) effect at the highest concentration (500µM) on the HCT116 cells.

These results support the potential use of ^{64}Cu-labelled terpyridine platinum conjugate as a novel theranostic agent to diagnose and treat cancers.

POSTER SESSION 2

Track: Design of industrial, hospital and centralized radiopharmacy facilities

PS2-01

Creation of the first public PET unit at Sahloul hospital in Sousse, Tunisia

Author: Najla Ayachi[1]
Co-author: Asma Toumi[2]; Anis Majoul[2]; Kaouthar Chatt[2]

[1]Ministère de la santé, Tunisia
[2]Hopital Sahloul, Tunisia

Corresponding author: ayachinajla@gmail.com

The International Atomic Energy Agency has established programs and cooperation with developing countries to promote applications in nuclear medicine.

The objective of this work is to report the progress of the first public PET unit in Tunisia and to raise the difficulties encountered in launching its operation.

The PET unit has been designed in compliance with the regulations in force regarding radiation protection and manipulation of injectable drugs.

It includes a "hot" zone formed by a room designed for the PET- CT camera, a control room with lead glass, an interpretation room for exams, a hot laboratory or radiopharmacy, an injection room divided into three individual boxes and a room for the storage of radioactive waste until decay.

The "cold" zone includes the space reserved for the reception and registration of patients, a waiting room for non-injected patients and offices.

The local of radiopharmacy is intended to hold, prepare and control radiopharmaceuticals. It is classified in controlled atmosphere zone (class D) and includes a ventilated hot cell in depression, adapted to the handling of the high energies thus respecting the recommendations of the good practices of preparation.

The creation of the unit is subject to an authorization regime.

The PET unit is ready to receive the PET- CT Camera but the reception has not yet taken place. This delay is mainly due to the heavy administrative tasks. Indeed, the complexity of the procedures is causing a delay in the start of the activity.

PET- CT activity, in the public sector in Tunisia, will see soon the light of day. However, the willingness of the various parties involved is necessary to speed up the start of this activity. A revision of the procedures is also desirable in order to reduce the time of reception of the next two public units.

PS2-02

A new compact high power e-beam accelerator for radiotherapeutic production: a first evaluation

Author: Samy Bertrand

Co-Author: Jeremy Brison; Jean-Michel Geets; Cristiana Gameiro

IBA, Belgium

Corresponding author: samy.bertrand@iba-group.com

Recent developments in the theranostics field have put actinium-225 (^{225}Ac) under the spotlight. Its historical supply from ^{229}Th generators will rapidly be limited (yearly supply of 1-2 Ci), which has led to the development of other viable alternatives. Production of radiotherapeutics such as ^{225}Ac, ^{67}Cu and ^{47}Sc from photoreaction with gamma beams have already been demonstrated. This production route is relatively safe when compared to proton irradiation and results in good purity of the final product. However, the low intrinsic reaction yield is a showstopper, especially when combined with the low power of the most available electron accelerators.

This paper will present a new high-power industrial electron accelerator capable of producing several curies of ^{225}Ac from photoreaction on ^{226}Ra.

The Rhodotron® TT300 is a well-known electron accelerator for industrial applications. The new high energy version (Rhodotron® TT300 HE) with high current and continuous beam capacity can therefore be used for efficient radiotherapeutics production.

Based on theoretical models and on experiments, a production of 0.0093 µCi / (h.mg of ^{226}Ra.µA) EOS (end of synthesis) of ^{225}Ac can be extracted after 18 days of decay.

Several parameters can be adjusted to increase its production capacity (electron energy, mean current, quantity of ^{226}Ra irradiated, and geometry)

The estimated yield is of 147.85µCi of ^{225}Ra/(h.mg of ^{226}Ra) or 65µCi of ^{225}Ac/(h.mg of ^{226}Ra). Considering an irradiation of 150h of 1g of ^{226}Ra, one could weekly produce up to 9.7Ci of ^{225}Ac after 18 days of decay. In this approach, the target capsule containing large quantities of radium is totally decoupled from the accelerator and beam line vacuum and can be designed to avoid radium release.

The following technical challenges are under evaluation: converter electron-gamma, target container, target cooling, and shielding.

Extrapolation from experiments on ^{225}Ac production shows that the Rhodotron® TT300 HE could provide sufficient levels of production to respond to the increasing demand of ^{225}Ac. The challenges to integrate such an accelerator in a radioisotope production line have been highlighted. Appropriate design of the facility could allow to produce other therapeutic isotopes such as ^{67}Cu and ^{47}Sc using the same photonuclear route.

PS2-03

Optimized non-conventional radioisotopes production with industrial mid-energy cyclotron

Author: Samy Bertrand[1]

Co-author(s): Benoit Nactergal[1]; Jean-Michel Geets[1]; Eric Kral[1]; Sebastien de Neuter[1]; Jozef Comor[2]; Francisco Alves[3]

[1] IBA, Belgium
[2] Elex Commerce, Serbia
[3] Coimbra University, Portugal

Corresponding author: samy.bertrand@iba-group.com

While F-18 is still one of the most used radionuclides in PET procedures, other metallic non-conventional radioisotopes, such as copper-64, zirconium-89, scandium-44 and undeniably gallium- 68 are gaining interest. The production of these radioisotopes usually requires more sophisticated infrastructure and their intrinsically low reaction yields often limit the levels of activity produced. This paper presents the solutions developed in order to increase the production rates and facilitate production processes of non-conventional radioisotopes in an industrial mid-energy cyclotron, while preserving its compactness and simplicity. A proton only optimized cyclotron with fixed energy has been designed using the well-known internal ion source, negative ions acceleration (H-) and stripping extraction 1.

Custom energy: some novel radioisotopes require lower energy in order to limit the co-production of impurities. As an alternative to degrade foils, the industrial cyclotron proposes one or two exit ports that can be operated at lower fixed energy (typically between 13 MeV and 15 MeV). This feature helps to overcome the beam current limitation of the degrader foils and allows to safely increase the current in the target.

High current: the cyclotron has been designed to improve performance of ion sources, beam transmission and beam extraction. This state-of-the-art cyclotron is able to produce and sustain over an extended lifetime a total beam current of up to 300 µA.

High power solid target: solid target low reaction yields often requires increasing the target current in order to reach higher production capacity. A high-power solid target station has been designed to match the performance of the optimized cyclotron (i.e. maximum current acceptance for 64Ni targets up to 300 µA without energy degrader). It can accommodate various target materials to produce ^{64}Cu, ^{89}Zr, $^{123/124}$I. Suitable chemistry system for separation and purification are also available.

^{68}Ga Liquid target technology: many recent developments in the production of radiometals with liquid targets have been published. Production rates and purity levels reached for ^{68}Ga showed that this technology is a perfect viable alternative to the ^{68}Ge/^{68}Ga generators. The same process philosophy was successfully applied in the production of ^{64}Cu and ^{61}Cu. In conclusion, the selection of a production mode for a given radioisotope will require the careful assessment of the pro's and con's of each process and the production capacity that they offer.

Results: The custom energy feature has been successfully tested in a factory. Two beam exit ports (out of a total of 8) can be modified to accommodate lower proton energy on target for more effective non-conventional radioisotope production. The high current 300 µA cyclotron was fully installed, commissioned, and accepted in 2017. The liquid target technology has now proven records and it benefits from an increasing popularity. In conclusion, combining the cyclotron, its dedicated features, the different target technologies and the chemistry solutions, a whole range of possibilities are given to easily produce non-conventional radioisotopes. These integrated attractive solutions can be implemented in a PET radiopharmacy without compromising the large-scale production of conventional PET radioisotopes.

PS2-04

Research and development initiatives on radiopharmaceutical production in the Philippines

Author: Adelina Bulos

Co-author(s): Rommel Mascarinas; Ivy Angelica Nunez; Joanna Michelle Chua

Philippine Nuclear Research Institute, Philippines

Corresponding author: admb_79@yahoo.com

In response to the increasing demand for radioisotopes and radiopharmaceuticals in nuclear medicine sector in the Philippines, the Philippine Nuclear Research Institute (PNRI) initiated the establishment of a Tc-99m generator production facility. Technetium-99m or Tc-99m is still the most commonly used radioisotope for diagnosis and imaging of various organs and determining physiological functions.

The Tc-99m generator production facility was established at the Philippine Nuclear Research Institute (PNRI) through the assistance of the Department of Science and Technology (DOST) and of the International Atomic Energy Agency (IAEA). The facility aims to make locally available the Tc- 99m generator for medical applications as well as for research initiatives for radiopharmaceutical applications. The facility is envisioned to meet the country's requirements for all the major medical radioisotopes, starting with the local production of Tc-99m and the most commonly used Tc-99m radiopharmaceuticals. At present, all radioisotope supplies in the country are sourced overseas at prices that vary accordingly.

With the establishment of the PNRI's laboratories, we now have a GMP-grade Tc-99m generator facility capable of producing 50 Tc-99m generators per batch. Instead of Tc-99m being imported, it will be the parent Mo-99 that will be transferred to PNRI facility from Mo-99 processing facilities overseas, contained in specialized transport containers, and via airfreight arrangements so it can be processed locally to make Tc-99m generators. But, to make Tc-99m radiopharmaceuticals, the other non-radioactive components also needed to be sourced from abroad. Thus, it has become imperative to also locally produce the non-radioactive components or the kits.

The PNRI is currently vigorously conducting research and development activities for producing locally the most common Tc-99m radiopharmaceuticals such as MDP, DTPA and sesta-MIBI, initially. Through the IAEA TC program, the Institute was also able to establish a clean room facility for aseptic manufacturing of these kits.

This poster presentation describes the PNRI Mo-99/Tc-99m generator production facility, its technical specifications, generator process flow and radiation safety measures. The benefits, opportunities, challenges, and issues related to its establishment and operation will also be presented. Furthermore, the radiopharmaceutical kit facility will also be described and the different on-going research initiatives and activities including capacity building on radiopharmaceutical production technology will be discussed.

PS2-05

A comparative study of passive air sampling in different radiopharmacies

Author: Fany Pricile Ekoume[1]

Co-author(s): Hendrikus Boersma[2]; Sietske M. Rubow[3]

[1]Yaoundé General Hospital, Cameroon
[2]University Medical Centre Groningen, The Netherlands
[3]Stellenbosch University, South Africa

Corresponding author: ekoumefanypricile@gmail.com

Assessing air quality in areas where radiopharmaceuticals are prepared and dispensed should be a routine to ensure product safety. Passive microbiological sampling is a relatively simple and affordable method for evaluation of air quality. This study compared air sampling results from two African radiopharmacies (noted as “Y” in Cameroon and “T” in South-Africa) and one European radiopharmacy, “G” in the Netherlands.

Tryptic soy agar settle plates were opened for 2 to 4 hours at predetermined locations in sites where radiopharmaceuticals were produced, either during work or while work stations were not used (“rest”). After exposure, the plates were incubated at 30 to 35℃ for 72 hours and the number of colonies forming units (CFU) per exposure hour was determined. Based on the GMP grade of the sampling location and the corresponding recommended action limits, the percentage of settle plate results exceeding limits were recorded. We compared data from “Y” to “T” data and routinely collected samples from “G” (Fischer’s exact test with $P<0.05$ considered significant).

456 samples at rest and 198 samples during work were collected in 6 different sampling sites over a 6-month period at radiopharmacy “Y”. At “T”, 184 samples were collected during work versus 87 at rest during a 12-month sampling period. “G” provided results of 315 samples collected over one year during work.

Table 1: Colony counts exceeding relevant limit

		“Y”		“T”		“G”
Site	Limits	Rest	Work	Rest	Work	Work
Area where RP are prepared	< 1	35* #	39%* #	7%	8%	3%
Other Class A area	< 1	8%	16%	0%	20%	10%
Open Bench (class C)	50	14%* #	15%* #	0%	3%	0%
Floor (class D)	100	43%*	45%*	-	-	0%

* differs significantly from “G” # differs significantly from “T”

Results for all sampling sites at radiopharmacies “Y” differed significantly from those at “G”. The highest number of CFU/h in the Tc-99m radiopharmaceutical preparing cabinets were 58 at “Y”, 6 at “T” and 1 at “G”. The results reflect the facility design and practice. Radiopharmacy “Y” does not have clean rooms. The closed cabinet used for radiopharmaceutical preparations runs without maintenance or filter replacement. Radiopharmacy “T” has a dedicated shielded laminar air flow cabinet with a regular maintenance programme. The room is however not a designed clean room. Radiopharmacy “G” is a GMP certified site.

Despite recent improvements in staff training and cleaning procedures at “Y”, further steps are required. “T” should also investigate means to improve air quality in the radiopharmacy.

Conclusion: Compared to “G,” both “T” and “Y” radiopharmacies need some improvement in the air quality of their respective units to reach GMP compliant performance levels. More corrective actions are needed at “Y” for reducing the risk of microbial contamination of radiopharmaceuticals.

PS2-06

Studying and assessment of clean area for Tc-99m production in radioisotope production facility

Author: Hesham Elkhatib

Egyptan Atomic Energy Authority, Egypt

Corresponding author: heskhatib1966@yahoo.com

Clean rooms nowadays have high technology solutions with very high demands on the air cleanliness level. Not only particulate matter but also airborne molecular contaminants (AMC) are addressed in more and more applications. Therefore, it is important to estimate the level of air cleanliness in the cases of new production of, or reconstruction of a clean room. Radioisotopes production facility (RPF) is a facility that needs clean room to produce technetium (Tc-99m) for medical purposes. The air cleanliness level in a clean room is dependent on the quality of the air supply, contamination sources, design of the ventilation system as well as strict procedures to sterilize available surfaces on the area and commitment to follow precautions in the area. Three classes are available in production area, A, C and D according to ISO 14644-1. Measurements are also taken to verify the particle counts in areas of technetium loading as well as prediction of these counts by a computer program, which predicts the particles and necessary time required to achieve the standard particle counts. Biological tests also are conducted to control and assess sterility of the area to assure cleanliness and validity for medical radioisotope production. High efficiency particulate air filters with class H14 are dedicated for the clean area and equipped with pressure drop manometers to decide its replacement in case of blockage. The prediction results are verified by measurements.

This program estimates the cleanliness class in clean rooms or in other spaces (offices, etc.) using different types of air filters. Depending on the number of people, the activity in the room, the ventilation system and the filter selection the clean room class is calculated.

PS2-07

Survey on arduous challenges and possible tracks of heightening the radiopharmacy and nuclear medicine services in Africa

Author: Yohannes Jorge Lagebo
Co-author: Aschalew Alemu Marie

[1] *Addis Ababa University, Ethiopia*

Corresponding author: jorgelagebo@yahoo.com

Radiopharmacy is the backbone of the nuclear medicine services. Without radiopharmaceuticals, it would be impossible to imagine services for nuclear medicine patients. Strengthening the radiopharmacy services within an institution, country or in a region, implicitly means strengthening the corresponding nuclear medicine patient services. These services have meaningfully advanced in several continental regions of the globe in the last two to three decades. Unfortunately, this contemporary global developmental momentum in radiopharmacy and nuclear medicine is yet to be attained generally in Africa. This global scientific and technological advancements in radiopharmacy and nuclear medicine have in turn brought undeniably remarkable contributions to other diversified disciplines of clinical medicine, by enhancing their roles in effective diagnosis and management of various debilitating diseases including cancer. The objective of this survey is to identify some of the possible reasons attributing to the comparative backwardness of the radiopharmacy and nuclear medicine services being rendered in many African countries. Based on the findings, there is an emphasis to give relevant recommendations to change the existing professional status quo in radiopharmacy and nuclear medicine patient services, such as in African countries. Unlike most countries in the other continental regions of the globe, there are several African countries where there have not even been initiated radiopharmacy units and nuclear medicine patient services. The started services in some of the countries are not satisfactory and not in pace with the accepted scope and standard level of patient services. The survey was conducted through literature review, questionnaire, review of countries reports, one to one interview administered to professionals and via critical personal observations of experienced professionals. The results of the survey findings will be discussed thoroughly, and the possible service heightening recommendations will be forwarded. The survey showed that the practicality of radiopharmacy and the associated nuclear medicine patient services are unacceptably low in Africa, and several African countries are not yet to start these services for the benefit of patients in their respective countries.

PS2-08

Parametrical study for iodine plate out theoretical model in fission radioisotope production plant ventilation pipes

Author: María Cecilia Maneiro

Co-author: Alexis Maître; Fabiana Molli; Hernán Meier; Ricardo Rey; Sandra Matzkin

INVAP S.E., Argentina

Corresponding author: mmaneiro@invap.com.ar

The radioisotope production plants aim to select, extract, purify and condition fission product radioisotopes for medical use. ^{99}Mo and ^{131}I are the radioisotopes that are the most widely worldwide produced by fission in nuclear research reactors by irradiation plates made of Al-U. After irradiation, the plates, which contain ^{99}Mo and ^{131}I, are transferred to the radioisotope production plant for separation, conditioning, quality control and dispatch of radioisotopes and radiopharmaceuticals products. Some of these stages take place in an enclosed shielded place called “Hot Cell”. Radioactive gases as iodine and noble gas are emitted in the enclosure. Radioactive iodine can be deposited on the inner side of ventilation pipes. This phenomenon is called plate out.

This work studies variations in many parameters in order to determine which ones have the most impact on shield thickness to minimize the dose rate to workers. When the plate out in ventilation pipes is estimated, a transport calculation is done to determine the shield needed to protect the workers. The dose rate to an operator during hot cell operation depends on many parameters as:

- Neutron flux
- Decay time
- Emission of radioactive iodine
- Decay time process system
- Diameter and length of ventilation pipes
- Air velocity in the ventilation pipes
- Iodine molecular forms
- Shield thickness

For each parameter, a deviation from a base case, based on INVAP experience, is proposed. The iodine plate out in the exhaust ducts is calculated and the lead thickness needs to have a dose rate inferior to 0.1mSv/h that is calculated with MICROSHIELD®. The following results were obtained related to the shielding thickness:

- Parameter Result
- Initial Inventory Limited impact
- Length duct Limited impact
- Airflow Limited impact
- Iodine Emission Significant impact
- Decay time Negligible
- Chemical form Significant Impact in Fraction of I2

This work shows that the parameters that have the most significant impact on the thickness of the shield needed to protect the plant personnel from the gamma radiation coming from radioactive iodine deposited in the exhaust ducts of the hot cells of a radioisotope production plant by fission are:

- The fraction of iodine emitted during the process, and
- The chemical form of the iodine released

PS2-09

An overview of commercial nuclear pharmacy in the US-safely delivering 35,000 patient-ready radiopharmaceuticals doses each day

Author: Jeffrey Norenberg

University of New Mexico, USA

Corresponding author: norenberg@nanp.net

This presentation will describe the current pharmacy practice model for commercial nuclear pharmacies which safely deliver over 35,000 patient-ready radiopharmaceuticals to hospitals and clinics throughout the US. These short-lived drugs enable over 10 million nuclear medicine procedures each year in the US.

The first commercial nuclear pharmacy was established in 1972 at the University of New Mexico by Dr. Richard Keesee, a true pioneer who recognized the need for standardization and uniformity of radiotracers used for nuclear medicine imaging. Applying pharmacy principles together with resource consolidation and just-in-time inventory management, is how commercial nuclear pharmacy was born.

Today, nuclear pharmacies embrace the highest standards of quality and professionalism to ensure that patients have access to safe and effective radiopharmaceuticals for diagnostic imaging and therapy. Founded in 1984, the National Association of Nuclear Pharmacies (NANP) is a non-profit industry association of over four hundred nuclear pharmacies, comprising most nuclear pharmacies in the United States. The membership of the NANP includes chain, independent, and academic/institutional nuclear pharmacies. NANP also has Associate Members, who are companies primarily involved in manufacturing or operating support in nuclear pharmacy. NANP serves its members in three main areas: business issues, legislation and regulation, and education.

PS2-10

Saskatchewan centre for cyclotron sciences: a new multi-user research and production facility

Author: D Schick-Martin; Jacqueline Cawthray
Co-author: J MacKenzie; D Frattinger; L Matei

Saskatchewan Centre for Cyclotron Sciences, Saskatoon, Canada

Corresponding author: d.schickm@fedorukcentre.ca

The Saskatchewan Centre for Cyclotron Sciences (SCCS), located at the University of Saskatchewan, in Saskatoon, Canada, is a multi-user radioisotope and radiopharmaceutical production and research facility operated by the Sylvia Fedoruk Canadian Centre for Nuclear Innovation (Fedoruk Centre). The SCCS supports an interdisciplinary program to develop and produce radioisotopes, radioprobes and radiopharmaceuticals for use across the life sciences including medical, veterinary and agriculture. The facility is outfitted with recently renovated state-of-the-art cGMP production clean rooms, QC laboratories, packaging rooms, and research hot labs, facilitating innovative radiopharmaceutical research and development. The recently renovated Innovation Wing serves as a world-class multi-user research facility equipped with a pre-clinical imaging suite, animal housing and support capabilities, radiopharmaceutical development, radiochemistry, analytical and tissue culture laboratories, and the PhytoSuite - a nuclear imaging suite dedicated to plants and soils including a molecular imaging system for plants, based on PET technology.

The paper will provide a perspective of the renovation process and lessons learned regarding the project requirements to address the needs of different types of users.

PS2-11

Development of radiopharmaceutical production in Bangladesh

Author: Momtaz Fatima Waheed

Bangladesh Atomic Energy Commission, Bangladesh

Corresponding author: momtaz_waheed@yahoo.com

The production of radioisotopes for medical diagnosis and treatment are the important activities of Bangladesh Atomic Energy Commission (BAEC). Tc-99m generator is in regular production line, which is extensively used in 15 Nuclear Medicine Centres of the BAEC and all other private & government run nuclear medicine departments of the country. RIPD has installed a cGMP compliant facility in May 2005 with the technical cooperation of IAEA (BGD2010). This plant can produce 50 generators per batch by processing maximum 30Ci of fission Mo-99. Since 2005 BAEC has fulfilled the entire demand of the country for Tc-99m generator by using imported Molybdenum-99. Iodine-131 is currently imported to treat patients. The Radioisotope Production Division (RIPD) of BAEC has established an ISO certified clean room facility to produce Tc-99m cold kits to meet the country's demand. BAEC is trying to establish a Lu-177 production plant. The country's only cyclotron is run by a private hospital. The second cyclotron is going to be installed under BAEC very soon. Two SPECT/Computerized Tomography (CT) and two Positron Emission tomography (PET)/CT scanners have been installed. A linear accelerator has been installed to treat cancer patients. In therapeutic related services, beta ray therapy is now given by Strontium-90 for pterygium treatment at different centres. A new research reactor (20 MW) dedicated for medical radioisotope production is planning to be installed. BAEC is trying to serve the patients of the country to achieve a healthy life and to substitute import of radioisotopes and radiopharmaceuticals by homegrown production.

Track: Education, including e-learning, certification and training methodologies for professionals involved in radiopharmacy

PS2-12

Education/Awareness-2

Author: Boima Darju

Ministry of Education, Liberia

Corresponding author: bdarju2013@gmail.com

Education, including e-learning certification and training methodologies for professionals involved in radiopharmacy can establish a good foundation and create several opportunities in this important field. Education and awareness are very cardinal in the area of radiopharmacy. This field is quite essential in the area of improving human health as it provides a valuable diagnostic information It is important to adequately capacitate professionals to be able to cope with major challengers in the coming decade, where new concepts will be developed in dealing with new trends of humans illness, like in the case of Ebola, a pressing illness in Africa. This virus infects the reproductive organ of male and female in macaques, so human could be similarly infected in this manner.

The IAEA should organize a periodic training for young radiopharmacy professionals, empowering universities/institutions in under privilege countries through scholarships to encourage more young students in the field and to create a workable system and collective efforts in awareness for all. Through radiopharmacy, professionals will adequately be informed, grape new visions about the growing challenges and put into place a resilient solution mechanism.

Institutions will be empowered, and many young students will grow their interest in the field. In conclusion, a good level of education for these professionals will positively correlate a breakthrough and new discovery in the interest of the global population in health advancement. Followed by an in-depth multi-dimensional analysis of credible research activities.

PS2-13

Relevance of the study of radiopharmacy at San Francisco Xavier University

Author: Elizabeth Huanca

Universidad SFXCH, Bolivia

Corresponding author: ehuancasardinas@hotmail.com

The objective of the present work was to evaluate the pertinence of maintaining the subject of radiopharmacy in the curriculum of the chemical pharmaceutical career in the Faculty of Pharmaceutical and Biochemical Sciences at the Universidad Mayor Real and Pontificia de San Francisco Xavier de Chuquisaca. A questionnaire was applied to graduates of this career who performed their rotatory internship at the Institute of Nuclear Medicine. The results reflect that: 100% needed knowledge about the management of radioactive material; 100% consider that for their training it is necessary to study the subject of radiopharmacy; 100% indicate that the presence of the pharmaceutical chemists are fundamental in the laboratory of radiopharmacy; and 60% indicate that they have a low level of management of laboratory material and biosecurity techniques. Hence, it is necessary to develop professional criteria through practices throughout the training in the Race, considering that from the fourth-year students have a real vision of what will be their professional work, and also bearing in mind that the formation of the pharmaceutical chemist must respond to science and technology. In conclusion, since the subject of radiopharmacy does not count in the curriculum, the graduated students from the faculty do not have sufficient knowledge in the matter; therefore, the inclusion of said matter is important.

PS2-14

Development of nuclear pharmacy training module in Malaysia

Author: Noratikah Mat Ail

Co-author(s): Suharzelim Abu Bakar; Zaitulhusna Md Safee

National Cancer Institute, Malaysia

Corresponding author: atikah2257@gmail.com

Clear, transparent and updated guidelines are the driving force for improving the quality of services provided by medical institutions in the Ministry of Health Malaysia (MOH) to prioritize the interests of the patient for appropriate and optimal diagnosis and therapy. Human capacity building is crucial for optimizing human resources to meet the vision and mission in delivering excellent Nuclear Pharmacy Services. Credentialing of a nuclear pharmacist through a structured training course is obligatory to ensure the individual pharmacist qualifies and is competent before he/she is capable to manage and use the controlled radioactive drugs or radiopharmaceuticals.

Nuclear Pharmacy Training Module (NPTM) was developed by the Pharmacy Services Programme, MOH to provide standardization of nuclear pharmacists training and to encourage Good Radiopharmacy Practices when preparing radiopharmaceuticals.

The training module consists of two parts; Hospital Nuclear Pharmacy practice and PET Manufacturing Practice. It also covers the radioactive relevant legislation in complying with the requirements under local Atomic Energy Licensing Regulations (Basic Radiation Safety Protection 2010) which requires the employer and nuclear medicine facilities to provide training, retraining and updating the skills and knowledge of their personnel.

This module is divided into two components, didactic (Section 1) and experiential (Section 2) for the training programs in Part A: Hospital Nuclear Pharmacy and Part B: PET Manufacturing Nuclear Pharmacy. The didactic component involves 66 hours of lectures given by selected speakers such as nuclear medicine consultants/physicians, physicists, and nuclear pharmacists while the experiential component provides the trainees with hands-on experience in handling radiopharmaceuticals. This component requires to be completed while working in a nuclear pharmacy for 12 weeks and with the assistance of a senior qualified nuclear pharmacist serving as a preceptor. Preceptors are responsible to evaluate the trainees. Each part (Part A and Part B) consists of four (4) components: tutorial, examination, experiential and soft skills. Trainees will be assessed on exercise questions, which carry 20% of total marks. Trainees are required to achieve at least 50% from written examination and 80% in the experiential component. Any trainee who fails to pass the minimum requirement in the written examination will need to sit for a viva examination to evaluate his/her knowledge and skills. Certification is awarded to a trainee who has successfully completed the program and demonstrated their knowledge and competency by examination.

In conclusion, thirty individuals have successfully completed the NPTM over the past nine years with the improvement in productivity and adherence to quality standards. The development of individual skills allows them to undertake a greater variety of work which not only focuses on the technical handling of radiopharmaceuticals but also gets them to be involved in the clinical team.

PS2-15

Diploma of radiopharmacy specialist in Uruguay: a flexible tool to achieve a certificated postgraduate education in radiopharmacy

Author: Ana Rey Ríos

Co-author(s): Mariella Terán; Eduardo Savio; Henia Balter; Alba León

Facultad de Química, Universidad de la República, Uruguay

Corresponding author: arey@fq.edu.uy

One of the key aspects of Good Manufacturing Practices is the education and training of personnel. According to WHO´s official documents the production of pharmaceutical products requires enough qualified personnel to perform all necessary tasks. In the specific case of radiopharmaceuticals, technical staff should have a postgraduate training or technical training as well as an appropriate experience in their function. However, radiopharmacy education at university level is not accessible in most Latin-American countries and professionals in this area continue to be trained in the working place without sufficient theoretical background.

In this context a new postgraduate Diploma in Radiopharmacy offered by the Faculty of Chemistry in Uruguay has started in 2016, with the objective to offer specific education to professionals working in the field. The programme is open to professionals with a university degree in Chemistry, Pharmacy or Biochemistry, both from Uruguay and other countries. The syllabus include: i) 300 hours of lessons (theoretical and practical) and 300 hours of a supervised professional practice in conventional Radiopharmacy (at the Nuclear Medicine Centre in the University hospital) and PET (at the Uruguayan Centre for Molecular Imaging. The Diploma can be obtained in one year. The curricula include basic topics of nuclear physics, radiation detection, radiation biology and radioprotection, as well as updated information on labelling chemistry, clinical application of radiopharmaceuticals, GMP, regulations and guidelines and research and developments in the area. The candidates can also select complementary courses according to their background between a wide range of options including analytical, inorganic or organic chemistry, microbiology, pharmaceutical technology or clinical assays.

Flexibility is a key feature of our Diploma. The recognition of the previous education and working experience of the candidates and the option of performing the professional practice in an accredited Radiopharmacy in their own country offer the possibility to shorten the curricular time and reduce the cost.

The Diploma has until now four graduates from Colombia (1), Costa Rica (2) and Uruguay (1). We also have 4 other students from Uruguay who will finish by December 2019.The profile of our graduates and students is very different. Some of them have been working in the area before but needed to increase their knowledge to adjust to the increasing requirements of the regulations or to catch up with the new developments. Others are completely new in the field and either have working proposals in Radiopharmacy or are interested in opening the possibility to work in the area in the near future.

According to the opinion of our students “the Diploma has a broad range of topics, solid professionals with deep knowledge in the field and very good didactic materials”. “The Diploma offered an enlightening experience that lead to the achievement of new professional goals”

However, the implementation of the Diploma is still in an initial phase and further modifications and improvement will be introduced to better suit the necessities of the professionals of Radiopharmacy in Latin America.

PS2-16

Accelerators of Ural Federal University as a base for student education and stuff training

Author: Oleg Riabukhin

Ural Federal University, Russia

Corresponding author: ryaboukhin@mail.ru

The Ural Federal University (UrFU) is one of the largest higher educational institutions in Russia bringing together fundamental education and innovative approach towards the challenges of modern times. As a part of UrFU, the Institute of Physics and Technology (IPT) has more than 55 years' experience in acceleration technique exploitation (R&D mostly) and education of students in a field of Nuclear Physics and Technologies including questions of nuclear reactors, isotopes production, dosimetry and radiation detection. From 2015 the IPT was equipped by new accelerators: 18-24 MeV TR-24 proton cyclotron and 10 MeV E-beam LINAC. On the basis of these installations, centres of nuclear medicine (for radiopharmaceutical production and implementation) and radiation sterilization (for radiation processing) were organized. Taking into account IPT's background in the field of radiation application and education, install equipment was the objective of the Education and Training Center (ETC).

For organizing ETC, it is planned:

- To employ teachers' staff from Experimental Physics and Radiochemistry departments, Nuclear Medicine and Radiation Sterilization Centers, Medical University with experience in international collaboration in the fields of accelerator operation, radiation interaction with matter, dosimetry, radiation detection, isotopes and radiopharmaceutical production, and using radiopharmaceuticals;
- To attract specialists in the quality control and assurance (QC/QA) procedures in the field of radiation technologies;
- To elaborate educational and training programs including theoretical and practical exercises on topics of radiation processing of materials and radiopharmaceutical production and implementation;
- To obtain an international experience through participating in Regional Training Courses of IAEA TC projects on subjects related with nuclear physics and radiation technologies.

As a result of our activity in ETC organizing at the present day we have elaborated international training course programs on the subject of "Multipurpose Irradiation Centre as a Component of Centre of Nuclear Science and Technology" supported by the State Corporation Rosatom. It aims to train foreign participants, inside this country training course program on the subject of "Radiation sterilization at E-beam facility" for Russian participants.

On the operating base of radiation sterilization center, numbered IAEA RER1017 and RER1019, the regional training course "Dosimetry at E-beam and Gamma- Facility" was carried out in 2017 and 2019. The staff of ETC regularly takes part in IAEA meetings, workshops and training courses in RER 1019, RER 9149 and plans to take part in RER 1020 related with radiation technologies, radiation safety and radiotracers. The nuclear medicine center will be commissioned during 2019 and will start radiopharmaceutical production.

The IPT of Ural Federal University is in the beginning phase of developing an education and training center on the base of proton and electron accelerators and it has all the premises to become an international multifunctional center of education and training.

PS2-17

Status of radiopharmacy practices in Sudan

Author: Mohammed Ahmed Siddig

National Cancer Institute (NCI), University of Gezira, Sudan

Corresponding author: siddig@email.com

Radiopharmacy is a branch of nuclear medicine (NM), which was started in Sudan in 1962 at RICK (Khartoum), 1995 at NCI, Wad Medani. Later, Shendi came to the picture as a third public centre. Now there are 6 NM centres, 3 out of them are public and 3 are private. The public ones are located in Khartoum (capital of Sudan), Wad Medani (NCI is ~196 km south Khartoum) and Shendi (~200km north Khartoum). There are two more centres are coming up, one in Marawe (north Sudan) and the other is in Alobaid (west Sudan).

Instruments available, functions and size: all the centres are equipped with SPECT gamma cameras, dose calibrators. The functions and size of radiopharmacy units in Sudan are different from one to another. In RICK, there are an oncology department, NM department, and medical laboratories for general investigations. In NCI there are 6 departments on oncology, NM, radiology, medical physics, laboratories and blood bank, and molecular biology. In Shendi there are oncology and NM departments.

The ^{99}Mo-^{99m}Tc generators come from Monrol – Turkey twice a month through (national medical supply fund – NMSF). Performed investigations include but are not limited to bone scan, hepatobiliary, thyroid, renal studies, and perfusion lung scan. In RICK, in addition to the above, the cardiology gated blood pool scan has been carried out. In NCI, we performed 99mTc-PYP hot spot scans, parathyroid scan using ^{99m}Tc-MIBI. Training received: thanks goes to the IAEA for providing the man power with fellowships, scientific visits and training courses, as well as equipment and experts.

Challenges: there are challenges facing the radiopharmacy practices in Sudan: high cost for running and maintaining radiopharmacy services, and brain drain of trained radiopharmacists. They go to other countries with better infrastructure in radiopharmacy and better payment; with high salaries and incentives, leading to the survival of workers abroad. Other challenges also include lack of funding and high cost of equipment and radiopharmaceuticals, lack of understanding of radiopharmacy and NM by health administrators. Careful management of resources and information drives have helped to sustain the radiopharmacy and NM service despite economic problems in the country. Still there is a severe shortage of trained staff in NM and radiopharmacy in Sudan.

The pharmaceutical requirements of good radiopharmacy practice (e.g. suitable facilities for sterile preparations) in most radiopharmaceuticals laboratories still need further improvements (public and private).

Training and education needed: Any procedure in radiopharmacy laboratories should be done in the right way to maintain the sterility and pyrogenicity. Therefore, radiopharmacy professionals should have adequate training in all aspects of sterile preparation, quality control, radiation safety and radiochemistry to ensure that they are competent to handle radioactive materials and that can take responsibility for their level of practice.

Impact evaluation of IAEA assistance: Standards of radiopharmacy practice have been improved to some degree with continuous training by holding the previous training courses and hoping they will continue through upcoming projects. We hope continuation of these training courses for radiopharmacists, both hospital based as well as regulators. Exposure of technologists for external training has had effective impact.

Risk towards the patients has been decreasing, and there is an increased awareness of radiopharmacy. The improvement in documentation of training and procedures will improve safety and efficacy of radiopharmaceuticals to the benefit of patients and staff safety.

PS2-18

Assessment of training needs for radiopharmacists in Africa

Author: David Wata

Kenyatta National Hospital, Kenya

Corresponding author: dwata@knh.or.ke

African countries are at various levels in radiopharmacy practice. Cyclotrons are only available in few countries. Other countries have technetium based radiopharmacy practice. Staff hired to work in the institutions that have nuclear medicine practice may not necessarily have the requisite qualifications and competencies of radiopharmacy practice. The IAEA through the AFRA projects has funded some short courses for radiopharmacy for various African participants working in radiopharmacy. However, participants from different countries have different needs depending on their background degree and their current and future levels of radiopharmacy practice. Thus, it is important to have the bassline data on competencies in radiopharmacy so as to design radiopharmacy courses that would suit the varied participants from Africa.

There was a survey on radiopharmacy competencies. A data collection form was used to collect the required data and to be sent out to radiopharmacy practitioners working in several countries in Africa. The received data was analysed.

20 Participants from 10 African countries responded. The practice involved research in radiopharmacy (30%), procurement and supply chain of radiopharmaceuticals (16.7%), PET radiopharmaceuticals production (8.3%), technetium based radiopharmaceutical preparations (40%), dispensing of radiopharmaceuticals including radio iodine (60%), blood cell labelling (8.3%) and quality assurance and quality control (16.7%). Note that participants were involved in more than one practice area.

The participants were mostly Bachelor of Pharmacy graduates (80%) and 20% had additional MSc in radiopharmacy. Less than 10% had other degree qualifications such as a Bachelor of Science in radiography or biology. For the Bpharm graduates, 60% did not have any additional radiopharmacy training. 30% of these had done some short courses in radiopharmacy. None had done any online course in radiopharmacy. The short courses done in radiopharmacy had provided competencies in the following areas: quality control procedures, fluorodeoxyglucose preparation, preparation of technetium-based radiopharmaceuticals, health worker safety, and radiation risk assessment and radiation dose calculation.

Based on the current practice, participants mentioned the following areas where there are skills gaps and would require further training: dose calculations, peptide and protein PET radiopharmaceutical production, blood cell labelling, radiation protection, GMP in radiopharmacy, quality control for radiopharmaceuticals and safe handling of iodine 131.

In conclusion, African countries are at various levels of radiopharmacy practice with only limited number of cyclotrons (in South Africa, Morocco, Egypt and Kenya). Most of other countries are only involved in technetium based radiopharmaceutical preparations and dispensing of iodine. Fewer still do blood cell labelling. It is important to set standards on the qualifications for practice of radiopharmacy. It is also imperative to include radiopharmacy modules in the Bachelor of Pharmacy programs. Some of the knowledge gaps mentioned can be fulfilled by having an online course with various modules. The IAEA can focus some of the radiopharmacy training where there are knowledge gaps.

Track: Health regulatory aspects related to the production of radiopharmaceuticals

PS2-19

Regulatory aspects related to good practices of preparation of radiopharmaceuticals in Colombia

Author: Maria Cristina Baracaldo Cortes

Ministry of Health and Social Protection, Colombia

Corresponding author: mbaracaldo@minsalud.gov.co

Nuclear medicine in Colombia involves a set of diagnostic and therapeutic procedures through sources of open radiation, consisting of radioactive isotopes, radiopharmaceuticals and radionuclides for human use, which is currently developed in the country in 82 licensed nuclear medicine services.

The regulatory authorities of this subject are combined between the Ministry of Mines and Energy, in terms of radiological protection and by the Ministry of Health and Social Protection, regarding the health issue, issuing regulations according to their competence. The Ministry of Mines and Energy authorizes the entry and handling of radioactive material in the country, and the Ministry of Health and Social Protection regulates its applications in medical services.

Therefore, in 2015, Colombia issued regulations for radiopharmacies, their products and their certification in Good Practices for the Preparation of Radiopharmaceuticals, issued by the National Institute for Surveillance of Medicines and Foods -INVIMA for a term of 5 years, in order to guarantee quality, safety and efficacy of this type of products, as well as their availability and access to the population. This regulation does not apply to Good Manufacturing Practices, clinical trials or industrial production of radiopharmaceuticals.

This regulation defined requirements that include personnel issues, staffing, infrastructure, equipment, return of materials and radiopharmaceuticals, documentation, quality management system, quality control analysis, pharmaceutical quality water collection system, validation, preparation of radiopharmaceuticals and analysis (by contract, agreement and / or quality agreement), materials, distribution and transportation, processing, dispensing and administration of radiopharmaceuticals and pharmacovigilance.

To date, according to information from the Ministry of Mines and Energy sent by INVIMA to this Ministry, there are 116 radiopharmacies in the country (hospital and centralized), of which only 6 meet the requirements and are certified in Good Practices for the preparation of radiopharmaceuticals. Additionally, there are no industrialized radiopharmacies in the country that produce radiopharmaceuticals, which means that all products (cold kits, generators and some radionuclides) are imported, since there is no nuclear reactor in the country.

Taking into account the above, it is necessary to review, analyse and modify, if deemed appropriate, the requirements of the current regulation, in critical aspects that have presented problems for the implementation of the regulation, mainly in terms of staff availability and training, infrastructure, endowment, quality control, quality management system, validation, preparation, dispensing and administration of radiopharmaceuticals and pharmacovigilance.

PS2-20

Optimization of ^{18}F-radiopharmaceutical production with a new platform, in accordance with GMP

Author: Javier Giglio

Co-author(s): Ingrid Kreimerman; Florencia Zoppolo; Pablo Buccino; Andrea Boné; Lucía Tajám; Eduardo Savio

Centro Uruguayo de Imagenología Molecular, Uruguay

Corresponding author: javier.giglio@cudim.org

The installation of a new platform in a radiopharmacy unit represents a challenge to adapt the labelling techniques with GMP requirements. It is a great opportunity to improve radiosynthetic conditions and it involves the introduction of new procedures into the Quality Management System of The Uruguayan Center of Molecular Imaging (CUDIM) Centre.

Our purpose was to optimize the production of different ^{18}F-radiopharmaceuticals in accordance with GMP quality requirements in the new automated radiosynthetic platform RN Plus Research (Synthra).

CUDIM has recently acquired a radiosynthetic module RN Plus® Research (Synthra) to replace a TRACERlab® Fx FN (General Electric). The new platform enables more versatility due to the presence of two reactors and a major number of interconnections. The module was installed in a hot cell Comecer MIP1 LAF (air quality Class A). To perform the acceptance test, the following radiopharmaceuticals were synthetized: [^{18}F]AlF- PSMA-11, [^{18}F] Fallypride, [^{18}F]FMISO. Since two reactors are available, the labelling steps were performed in the first one and the hydrolysis steps (if necessary) in the second one. The reaction volume for labelling of the new module is 7 mL, whereas the TRACERlab® Fx FN (GE) is 11 mL. Therefore, it was necessary to adjust the amount of the solvent in order to carry out the labelling reactions. Another advantage of the new module is the fact that the preparative HPLC allows to perform the purification steps using solvents gradient.

Table 1 – Radiochemical yield obtained for each module (mean ± SD, n = 3)

Radiochemical Yield (No decay corrected)	**Tracerlab FxFN (General Electric)**	**RNplus Research (Synthra)**
[^{18}F]AlF-PSMA-11	18 ± 2 %	23 ± 3 %
[^{18}F]Fallypride	11 ± 1 %	20 ± 5 %
[^{18}F]FMISO	22 ± 4 %	40 ± 5 %

Table 1 shows a comparison of the radiochemical yield obtained in each module for the radiopharmaceuticals. Physicochemical and microbiological controls were performed according to quality control specifications established by CUDIM for the different radiotracers. Besides this, a production under clinical trial was also optimized in this module ([^{18}F]-FPR-04-MZ). The quality system documentation was updated to introduce the procedures of the new platform.

The introduction of a new radiosynthesis module into the radiopharmacy unit was carried out in accordance with the quality system of CUDIM. The new established methodologies enabled us to optimize the production procedures and thus increase the radiosynthetic yields.

PS2-21

Optimization of ^{18}F-radiopharmaceutical production with a new platform, in accordance current status of radiopharmaceuticals production in Brazil: licensing and radioprotection aspects

Author: Samira Marques de Carvalho

Co-author(s): Alessandro Facure; Walter Fritz; Claudia Silveira

Brazilian Commission of Nuclear Energy, Brazil

Corresponding author: samira.carvalho@cnen.gov.br, facure@cnen.gov.br

In Brazil, as it has been occurring worldwide, the number of procedures using radiopharmaceuticals are increasing. The production and selling of short half-life radioisotopes are monopolized by the Brazilian Government. In 2006, a Constitutional Amendment revoked the state monopoly due to the need for the use of short half-life radioisotopes in nuclear medicine centres very far from government production facilities. The aim of this study is to describe the current status of radioisotope production and sales in Brazil and discuss some licensing process. Currently, there are 14 radiopharmaceuticals production facilities and 4 radiopharmacies operating in Brazil. The type of licensing process conducted in Brazil does not take into account the population density of each state, with a free competition model being adopted. Because of this, there are a lot of equipment concentrated in the Southeast while no cyclotrons or radiopharmacy operating in the Northern part of the country. One of the biggest obstacles during the licensing process is the designation of qualified personnel in radiopharmacy or accelerator for radiopharmaceutical production as operation workers and radiation safety officers. Currently, there are only 17 qualified workers in these fields. Regarding regulatory inspection in Brazil, during the facilities licensing process two types of inspections are usually performed: one to monitor the radiopharmaceutical production (usually overnight) and another to verify records and to test security systems. The number of facilities for radiopharmaceuticals production and sales are increasing. However, several external factors such as the distance from the nuclear medicine centres, and qualified personnel have proved crucial for the economic viability of this type of facility, and a rigorous licensing process is necessary to ensure radiological protection.

PS2-22

[^{68}Ga]PSMA PET/CT: which HTA tools can be used in local or regional reimbursement decision?

Author: Lorena Pozzo [1]

Co-author: Lucilena Rebelo Monteiro[1]; Juliano Julio Cerci[2]; Stefano Fanti[3]; Antonella Negro[4]; Evelinda Trindade[5]

[1]IPEN - CNEN/SP
[2]Quanta Diagnósticos Nucleares
[3]University of Bologna
[4]Agenzia Sanitaria e Sociale Regionale - Emilia Romagna
[5]Coordenadoria de Ciência, Tecnologia e Inovação em Saúde, Secretatia de Saúde do Estado de São Paulo

Corresponding author: lorena.pozzo@ipen.br

Up to date, [^{68}Ga]PSMA has been used in a clinical research context. Sales authorization for a new radiopharmaceutical or imaging equipment alone does not support the continuity and increase of the role of nuclear medicine. Each country and health system have their own set of requirements and priorities. Health Technology Assessments (HTA) tools could and should be considered. Mostly, to base and to help decision-makers to spread or not any new technology in local or regional levels. Efficacy and accuracy of [^{68}Ga]PSMA PET/CT in the real world could be assessed in primary and in secondary studies. Only after that any consideration on local or regional use and economical aspects could be applied by health systems. The present study discusses how HTA tools on the use of [^{68}Ga]PSMA PET/CT can help health systems.

Test/imaging accuracy, detectability, positivity and change of management were some of the diverse comparators and outputs used in primary and secondary studies using [^{68}Ga] PSMA PET/CT, that the present study evaluated under HTA requirements. The selection criteria, applicability and association to the treatment efficacy of the comparators and outputs were assessed and discussed.

The selection of a variable as an outcome in secondary studies can vary from the detectability of the lesion, (indicators of) positivity, sensitivity and specificity, change of management, etc. HTA guidelines for diagnostic procedures consider only accuracy as an outcome. However, costs of imaging diagnostics procedures are considerably high compared to other kinds of tests. Then, clinical outputs, considering effective change of management and consequent therapy results are necessary. Secondary studies are frequently associated with critical weaknesses, such as risk of bias, publication bias, true effect, and study heterogeneity. HTA requires a more integrative information assessment of the diagnostics and treatment. Investments and costs associated with change of management should be evaluated by considering patient prognosis/response and not only the imaging test specification. Nuclear medicine and HTA integrated goals can enlarge significantly the number of studies and patients to accelerate the approval procedure.

The use of [^{68}Ga]PSMA PET/CT, as many other procedures in nuclear medicine, still needs a broad approach considering HTA requirements. HTA needs to evaluate the procedure by diagnostic accuracy and the resulted patient treatment efficiency. While SR/ MA evaluate a procedure single outcome, multicentric and integrative studies, capable of collect and assess multivariate data seem to be the way to identify true effects over the patient prognosis.

PS2-23

Regulation of radiopharmaceuticals in Uganda current situation

Author: Robert Ssekajjugo[1]
Co-author: Richard Sseggane[2]

[1]*Uganda National Drug Authority, Uganda*
[2]*Atomic Energy Council Uganda, Uganda*

Corresponding author: sricmut@gmail.com, bob4yesus@gmail.com

Uganda has had a steadily growing cancer burden (1) and rapid population growth (2) in the last few decades. There has been an overall increase in the incidence of cancers in both males and females, with incidence rates of major cancers such as breast and prostate showing particularly marked in- creases (3.7% and 5.2% annually, respectively). Nuclear medicine is a key weapon in the arsenal against neoplastic diseases, among its other applications in medicine. There is thus to a steadily increasing demand for Radiopharmaceuticals in the country and thus a need for a progressive strengthening of the systems that provide assurance of their safety and efficacy.

For the last few decades, the country has had one nuclear medicine facility which is under the Mulago National Referral Hospital in the nation's capital - Kampala. The said nuclear medicine facility has for the past three years been closed as the hospital was undergoing renovations and infrastructural upgrades. The works in the department are near completion and the nuclear medicine practice will soon resume.

Aga-Khan university hospital, a private hospital in Uganda has declared intentions of opening a nuclear medicine department and has publicly stated that a cyclotron will be installed soon among others for use in their nuclear medicine practice. This will raise the number of nuclear medicine facilities in Uganda to two and with the resumption of Mulago National Referral Nuclear Medicine Department, there will be regular import, possible production, hospital compounding / preparation and use radiopharmaceuticals in the country.

The Atomic Energy Act No. 24 of 2008 mandates the Atomic Energy Council to regulate all peaceful uses of ionizing radiation in Uganda for the protection of people and the environment from the harmful effects of ionizing radiation. The National Drug Policy and Authority Act of 1993 mandated the National Drug Authority to regulate the import, production, sale and use of drugs within Uganda for the protection of the public from possible effects of substandard or low-quality drugs.

As it is already known, radiopharmaceuticals used in nuclear medicine are a combination of both drugs and radioactive sources. The laws and organizations respectively mentioned above regulate the two components of radiopharmaceuticals independently, yet they are combined their production or import and their production and use considers them as one.

There is thus the need to harmonise the legal and regulatory frameworks to implement sound interfaces between both regulatory systems in order to address the gaps and overlaps in the regulation radio-pharmaceuticals in Uganda. The paper will identify and propose fixes to the gaps and overlaps in Uganda's regulatory framework for radiopharmaceuticals.

Track: Nanosized radiopharmaceuticals

PS2-24

Synthesis of radioactive gold nanoparticles and bimetallic gold nanoparticles for cancer therapeutic application

Author: Fazizulafizi Madin[1]

Co-author(s): Wan Nordiana Rahman[2]; Azahari Kasbollah[2]; Khairunisak Abdul Razak[1]; Julia Abdul Karim; Siti Selina Abdul Hamid[1]

[1] Universiti Sains Malaysia, Kelantan, Malaysia
[2]Malaysian Nuclear Agency, Selangor, Malaysia

Corresponding author: fazizulafizimadin@hotmail.com

This study was conducted to synthesise radioactive gold nanoparticles (^{198}AuNPs) and bimetallic gold nanoparticles (AuHgNPs) for application in cancer therapy. The β^- particles emitted by ^{198}AuNPs can be used for cancer therapy while AuHgNPs is a promising nanoparticle for radiosensitization effect in radiotherapy. Gold nanoparticles (AuNPs) in liquid form was synthesized by reducing Tetrachloroauric acid with Trisodium citrate (Turkevich Method), producing particles with sizes of 10, 40 and 80 nm. The neutron bombardment of AuNPs was carried out at TRIGA PUSPATI Reactor yielding ^{198}AuNPs. Then, the neutron activation analysis (NAA) was performed on the ^{198}AuNPs to analyse its composition. The ^{198}AuNPs was then let to decay completely before the Inductively Coupled Plasma – Mass Spectrometer (ICP-MS) was being used to confirm the presence of mercury and gold (AuHgNPs). This study confirmed a suitable method of producing ^{198}AuNPs and AuHgNPs from AuNPs synthesized by the Turkevich Method.

PS2-25

Radiation crosslinked protein-based nanoparticles as delivery system for radiopharmaceuticals

Author: Aryel Heitor Ferreira[1]

Co-author(s): Fabio Luiz Navarro Marques[2]; Gustavo Henrique Costa Varca[3]; Caroline Cristiano Real[4]; Daniele de Paula Faria[4]; Mara de Souza Junqueira[5]; Ademar Lugao[6]

[1]Instituto de Pesquisas Energéticas e Nucleares, Brazil
[2]Faculdade De Medicina, Universidade De Sao Paulo, Brazil
[3]IPEN/CNEN-SP, Brazil
[4]Universidade de Sao Paulo, Sao Paulo, SP, Brazil
[5]Instituto do Câncer do Estado de São Paulo (ICESP), Brazil
[6] IPEN, Brazil

Corresponding author: aryelhf@gmail.com

Protein-based nanoparticles have been used as vehicles to deliver radioactivity to tumour cells for external imaging and targeted radiotherapy, also used as drug delivery for chemotherapeutics. The development of these nanocarriers holds the potential to overcome some of the current problems associated with the existing traditional nuclear medicine agents. A nanosized vector can be administered using minimally invasive techniques (e.g., by intravenous or intratumour injection), penetrate across tumour vasculature and improved tumour uptake if compared to common labelled radiopharmaceuticals. The aim of the present work was the study of radiolabelling of bovine serum albumin (BSA-NPs) and papain (P-NPs) nanoparticles, synthesized by gamma ray irradiation, with ^{99m}Tc and characterize their in vitro and in vivo properties towards potential novel nanoradiopharmaceuticals. The nanoparticles were synthesized with an average diameter of 9.3 ± 1.9 and 25.1 ± 2.9 nm, P-NPs and BSA-NPs respectively. The direct labelling of protein nanoparticles with 99mTc was optimized using different concentration of reducing agent SnCl2, pH and reaction time. Radiochemical evaluation was performed using TLC and by high performance liquid chromatography (SEC-HPLC). Ex vivo biodistribution studies and SPECT/CT imaging were performed in male AG129 mice and female spontaneous breast cancer model (MMTV-PyMT mice), respectively. Excised tumour of 4T1 xenograft model was used to perform autoradiography and immunohistochemistry assays. The radiolabelling reached around 95% yield, and the ^{99m}Tc-BSA-NPs showed stability for 24 h in all assayed conditions, while ^{99m}Tc-P-NPs presented stability for 6 h in human serum. Radiolabelled P-NPs were mainly identified in the spleen, lungs and featured a renal excretion profile. On the other hand, the ^{99m}Tc-BSA-NPs were found in the liver and spleen to a larger extent, undergoing hepatic excretion. Ex vivo biodistribution also showed good tumour uptake for both nanoparticles, and SPECT/CT images corroborated these results. The autoradiographic studies and immunohistochemistry assays revealed a high density of both papain and BSA nanoparticles in peripheral regions of tumour tissue and confirmed the efficacy of the developed nanoradioparmaceuticals for targeting breast cancer.

PS2-26

Multimodal radiobioconjugate Octreotide-PEG-^{198}AuNPs-PEG-DOX for targeted cancer therapy

Author: Agnieszka Majkowska- Pilip; Magdalena Kaliszczak

Co-author(s): Emilia Górzyńska; Monika Łyczko; Aleksander Bilewicz;

Institute of Nuclear Chemistry and Technology, Warsaw, Poland

Corresponding author: a.majkowska@ichtj.waw.pl

Recently, radioactive nanoparticles have attracted intense interest in medicine, both in diagnostics and therapy. Among various β– emitters, ^{198}Au radionuclide exhibits very attractive properties for its application in targeted radionuclide therapy (t1/2 = 2.7 d, βmax = 0.96 MeV). Unfortunately, both Au+ and Au3+ cations do not form stable complexes and it is impossible to attach them to biomolecules, therefore an interesting approach would be the synthesis of gold nanoparticles (AuNPs) containing ^{198}Au. Additionally, employing AuNPs allows the simultaneous use of a number of therapeutic methods, such as chemo and radiotherapy in one agent, which is extremely important due to the high resistance of cancer cells. To increase the efficiency and selectivity of the therapy as a novel targeted brachytherapy is required to apply radioactive gold nanoparticles for the treatment of locally-advanced neuroendocrine cancer.

The aim of our research is to obtain a multimodal radiobioconjugate containing simultaneously a chemotherapeutic, radionuclide and biomolecule in a one structure. To achieve this goal, we proposed that the radioactive gold nanoparticles (^{198}AuNPs) as a β- emitter and a carrier for doxorubicin (DOX) are used in chemotherapeutic and octreotide as guiding vectors with an affinity to SSTR2 receptors overexpressed in neuroendocrine tumour cells.

Synthesis of radioactive gold nanoparticles (^{198}AuNPs) was performed by using a radioactive ^{198}Au precursor, which was obtained in ^{197}Au(n,γ)^{198}Au reaction in the reactor. To determine the shape, size, size distribution, zeta potential TEM (Transmission Electron Microscopy) and DLS (Dynamic Light Scattering) techniques were applied. The chromatography methods such as HPLC (High Performance Liquid Chromatography) and SEC (Size Exclusion Chromatography) were used to analyse the efficiency of the obtained DOX-PEG-SS-PEG-DOX, Octreotide-PEG-SS- PEG-Octreotide conjugates and the final product -Octreotide-PEG-^{197}AuNPs-PEG-DOX.

To avoid radioactivity contamination of used equipment, the analysis of physicochemical parameters of nanoparticles were carried out on non-radioactive ^{197}AuNPs. The DLS and TEM measurements confirmed the expected average size (~5 nm) and spherical shape of the synthesized nanoparticles. The zeta potential value showed the high stability of ^{197}AuNPs without a tendency to agglomeration. The ^{197}AuNPs were modified with bifunctional hydrophilic polymer polyethyleneglycol (PEG) in different molar ratios to optimize a degree of surface coverage. The synthesis of DOX-PEG-SS-PEG-DOX and Octreotide-PEG-SS-PEG-Octreotide conjugates were carried out with the use of triethylamine and DMF as a solvent. The products were successfully purified by HPLC using semi-preparative C18 column and finally analysed with the MS method. Bioconjugates of radioactive nanoparticles ^{198}AuNPs with doxorubicin and octreotide were obtained by spontaneous attachment of the DOX-PEG-SS-PEG-DOX and Octreotide-PEG-SS-PEG-Octreotide compounds to the gold nanoparticles through the sulphide bond.

Based on the strong affinity of sulphur to gold, the synthesized DOX-PEG-SS-PEG- DOX and Octreotide-PEG-SS-PEG-Octreotide conjugates were attached to the ^{198}AuNPs surface. The obtained multimodal radiobioconjugate Octreotide-PEG-^{198}AuNPs-PEG-DOX containing in its structure doxorubicin, radionuclide and octreotide could be a promising radiopharmaceutical for the treatment of neuroendocrine tumours.

PS2-27

Gold-198 coated superparamagnetic iron oxide nanoparticles (SPION) for cancer radiotherapy and magnetic hyperthermia

Author: Michał Żuk[1]

Co-author(s): Agnieszka Majkowska-Pilip[2]; Aleksander Bilewicz[2]; Magdalena Osial[2]; Paweł Krysiński[1]

[1]University of Warsaw, Warsaw, Poland
[2]Institute of Nuclear Chemistry and Technology, Warsaw, Poland

Corresponding author: a.bilewicz@ichtj.waw.pl

In modern world cancer is the second cause of death after cardiovascular diseases, making it a serious threat to human life. The World Health Organization estimates that every sixth deaths are due to cancer. To counteract these unfavourable statistics novel methods of cancer treatment are needed. Due to the high resistance for the single treatment, the synergistic approach shows great promise in cancer therapy. Especially, combining external radiotherapy with hyperthermia showed great promise in treating locally advanced head and neck cancer in comparison to radiotherapy alone. Also, a combination of hyperthermia with radiotherapy may be much more effective against hypoxic cancers through radiosensitization. Currently in our group, we propose the use of a combination of internal radionuclide therapy in combination with magnetic hyperthermia.

Superparamagnetic iron oxide nanoparticles (SPIONs) which show high heating efficiency in the alternating magnetic fields and can be easy coated with radioactive layer of ^{198}Au. ^{198}Au ($\tau 1/2=27d$) is obtained by neutron irradiation of high purity gold in n,y reaction. As a soft energy B-emitter, ^{198}Au could be used in radionuclide therapy of small tumours or tumours metastasis.

The modified method developed by Lee et. al. was used for synthesis of ^{198}Au coated SPIONs Briefly, SPIONs were synthesized through precipitation from solution containing Fe(II) and Fe(III) ions with 25% NH3 aq. After synthesis, nanoparticles were coated with sodium citrate as a stabilizing agent preventing against SPIONs agglomeration and added to boiling gold-198 solution for core-shell coating reaction which was performed under reflux. Finally, the product was purified by magnetic sedimentation and centrifugation and resuspended in deionized water.

Preliminary results indicate that obtained SPION-198Au nanoparticles show satisfactory stability in 0,9% NaCl, PBS solutions and additionally in human serum. Despite the existence of the gold coating, the nanoparticles retain comparable magnetic properties to unmodified SPIONs. Studies on modification by attachment of the targeting vector and the in vitro tests are planned to be made.

Acknowledgments: the contribution of M.T. Żuk was realized within Project No POWR.03.02.00-00-I009/17-00 (Operational Project Knowledge Education Development 2014-2020 co-financed by European Social Fund).

Track: Pre-clinical evaluation of radiopharmaceuticals

PS2-28

Dosimetric model based on the distribution of PSMA targeted radiopharmaceuticals to bone metastasis

Author: Erika Azorin-Vega[1]

Co-author(s): Eva Rojas-Calderón[1]; Guillermina Ferro-Flores[1]; Liliana Aranda-Lara[2]; Nallely Jiménez-Mancilla[1]; Rigoberto Oros-Pantoja[1]

[1]Instituto Nacional de Investigaciones Nucleares, Estado de México, Mexico
[2]Facultad de Medicina. Universidad Autónoma del Estado de México, Mexico

Corresponding author: erica.azorin@inin.gob.mx

Targeted radiopharmaceuticals based on PSMA inhibitors (iPSMA) have been proved as suitable agents for the detection and treatment of advanced metastatic prostate cancer (PCa) 1. Recent clinical studies have shown that the therapeutic application of iPSMA labelled with ^{177}Lu produce a decrease of more than fifty percent in the prostate antigen (PSA) levels, as well as a significant survival increase. However, bone metastases appear to respond less to treatment with ^{177}Lu-iPSMA than visceral or lymph nodal disease. Due to their destructive power, alpha particle emitters have been proposed as an ideal option for targeted radiotherapy of resistant bone metastases. Dosimetric models are needed for a personalized alpha particle targeted radiotherapy.

The objective is to obtain a dosimetric model based on a subcellular distribution of targeted radiopharmaceuticals in an animal bone metastases model generated from prostate cancer cells embedded in ectopic bone plaques.

In the present study the radiation absorbed dose produced by ^{177}Lu-iPSMA and ^{225}Ac-iPSMA to prostate cancer cell nuclei was assessed by using in vivo biokinetic data obtained from experimental measurements of radiopharmaceutical distribution at a cellular level considering the influence of bone microenvironment. For this purpose, LNCaP cells embedded in ectopic bone plaques were grown in adult mice during 20 days, radiopharmaceuticals were administered and their biokinetics were analysed under a fluorescence microscope to determine the distribution of the radiopharmaceutical in the bone matrix and in the mesenchymal tissue. In order to calculate the absorbed dose in LNCaP cell nuclei, Monte Carlo simulation with the MCNPX code was used and a dosimetric model was obtained.

Results show that ^{225}Ac-iPSMA releases a nine hundred-fold radiation dose greater than ^{177}Lu- iPSMA. The obtained dosimetric model considers these differences in order to calculate the absorbed dose in LNCaP cell nuclei, needed for the elimination of prostate cancer cells in a bone metastasis without damaging adjacent tissues (such as bone marrow). ^{225}Ac-iPSMA has potential dosimetric and radiobiological advantages over ^{177}Lu-iPSMA in the treatment of bone metastases in patients with advanced prostate cancer.

Since the biological effect of beta emissions are significantly different to that of alpha particles and due to the recent attention that alpha particle radiopharmaceutical therapy has been acquired for the successful treatment of bone lesions, the developed dosimetric model is useful for the personalized and safe application of ^{225}Ac-iPSMA.

Acknowledgment: This study was supported by the Mexican National Council of Science and Technology (“Laboratorios Nacionales” and CONACyT-SEP-CB-2018, A1-S-36841).

PS2-29

In-vitro and in vivo pre-clinical evaluation for Lu-177, Y-90 and Ga-68-DOTATATE in SSTRII positive AR42J cell line and negative HCT116 and MCF7 cell line

Author: Avik Chakraborty

Co-author: Megha Tawate; Sujay Gaikwad; Arpit Mitra; Sangita Lad; Sudip Sahu; Trupti Upadhye; Srija Menon; Sharmila Banerjee

BARC, Mumbai, India

Corresponding author: avikbarc@gmail.com

Abundant expression of somatostatin receptors (SSTR) in differentiated neuroendocrine tumours (NET) serve as a potential target for designing agents for diagnostic imaging and treatment. In this study, the theranostic concept has been utilized by choice of SSTR-targeting compounds, Ga-68-DOTATATE and Lu-177/Y-90 DOTATATE towards diagnosis and treatment of NET. In-vitro and in-vivo evaluation of the efficacy of these NET specific diagnostic and therapeutic radiopharmaceutical pair was performed using SSTRII positive (AR42J) and negative (HCT116 and MCF7) cell lines.

Y-90-DOTATATE was produced from Carrier free, clinical grade Y-90-Acetate, sourced from a two- stage Sr-90/Y-90 generator system based on supported liquid membrane (SLM) technology. Lu-177- Chloride were produced in our research reactor using enriched Lutetium-177-oxide {Lu-176 (n,γ) Lu-177}. Ga-68-DOTATATE was synthesized using Gallium-68-Chloride obtained from Ge-68/Ga- 68 generator. The endotoxin limit was quantified by gel-clot BET assay and sterility test done by direct inoculation.

Pancreatic carcinoma cell-line AR42J (expressing SSTRII), Human colon carcinoma cell-line HCT- 116 (with SSTRII expression) and MCF7 (with negative SSTR II expression) were used for the in vitro evaluation. The cells were grown in IMDM medium with 10% FBS in 5% CO2 at 37 °C. In vitro cell-binding and receptor binding studies were performed by incubating AR42J cells and cell homogenate respectively with radioligand (~5x10–12 mol DOTATATE) up to 120 min followed by washing with PBS. Non-specific binding was assessed by addition of cold DOTATATE (5x10–9 mol). The degree of receptor mediated uptake of the radio-conjugate was determined by biodistribution studies in tumour bearing athymic nude mice. The Lu-177/Y-90 DOTATATE (50µCi-100µCi/mice) was injected in xenografted mice through tail vein. Planar scintigraphy/ PETCT images were obtained for comparative analysis.

Radiopharmaceuticals showed rapid cell binding (in the range of 25-40%) in AR42J cell line, reaching a plateau after 30 min with Ga-68, Lu-177 and Y-90-DOTATATE. Compared to AR42J, the HCT116 and MCF7 cell line showed 8-10% and 5-6% respectively. Yttrium showed marginally higher percentage of internalization in AR42J in cell line as compared to Ga-68 and Lu-177. In PET/CT imaging study, Ga-68 showed precise localization of tumour in nude mice xenograft. 177Lu-DOTATATE showed localization in tumour by SPECT scanning. Biodistribution analysis of the tumour bearing mice revealed that radioactivity in the blood and most of the organs decreased after 24hour post-injection. High uptake and long-term retention of radioactivity were found in kidney (8.01% ID/gm), and tumour (3.17% ID/gm) which is in concordance with our scintigraphy studies.

The indigenously produced Ga-68, Lu-177 and Y-90-DOTATATE presented here is sustainably refined and advanced with respect to targeting large volume NET lesions. Pre-clinical evaluation of Lu-177/Y-90 DOTATATE theranostic pairs show optimal targeting properties for treatment of neuroendocrine cancer patients. PET/CT imaging using Ga-68-diagnostic counterpart provide essential information about SSTR density, which is relevant for treatment decisions, and selecting patients for treatment with peptide receptor radionuclide therapy (PRRT) with the therapeutic pairs.

PS2-30

Evaluation of Rhenium and ^{99m}Technetium of tamoxifen derivatives as potential breast cancer radiopharmaceuticals

Author: Tesnim Dallagi[1]

Co-author(s): mouldi Saidi[1]; Siden Top[2]; Gèrard Jaouen[2]

[1]CNSTN, Tunisia

[2]Sorbonne University, France

Corresponding author: tesnim.dallegi@gmail.com

Breast cancer is the most common cause of death from cancer overall. Breast tumours are traditionally classified according to their estrogen receptor status: Hormone-dependent tumours (ER+), and hormone-independent tumours (ER-). These receptors serve as targets for endocrine therapies of these cancers. But they also can be used as targets for diagnostic imaging and radiotherapy. For example, antiestrogens, such as tamoxifen, are largely used for the treatment of women suffering of ER breast cancer. It is known that prolonged treatment with tamoxifen develops drug resistance. Radioimaging methods for early diagnosis are attractive because they simultaneously and non-invasively provide information on all tumour sites and allow treatment at an early stage. For radiotherapy, a non-penetrating radiation is needed. ^{99m}Tc presents very favourable characteristics to be used in nuclear imaging medicine. Just below technetium in the periodic table, rhenium has two radioactive isotopes suitable for therapeutic use: Since rhenium occurs naturally as a mixture of non-radioactive isotopes ^{185}Re and ^{187}Re, it is possible to work on the non-radioactive rhenium compounds first to predict the behaviour of technetium compounds. Their interest could thus be evaluated, before tackling the radioactive $^{186/188}$Re and ^{99m}Tc derivatives. Their ultimate use in vivo and their availability in aqueous solutions make it necessary to find water-stable rhenium and technetium compounds. The stable piano stool CpM(CO)3 core (M = Re, Tc) is one of the most promising moieties for this purpose. The preparation of radiopharmaceuticals should ideally allow the incorporation of the radionuclide at the final step of synthesis. It also requires a rapid and simple isolation and purification of the final product. Therefore, it is important to find a suitable stable precursor for the synthesis of rhenium and technetium compounds bearing the cyclopentadienyl tricarbonyl motif. We were interested in using the ferrocenyl derivatives as precursors for rhenium and technetium ligands of the Estrogen Receptor. Many rhenium and technetium estradiol derivatives have been proposed, but most of them fail to have a strong enough affinity for the estrogen receptor. The search for improved or more tunable radiopharmaceuticals is still currently undertaken and recent research has been directed to radiopharmaceuticals based on compounds containing the CpTc(CO)3 group or Tc(CO)3core because of the high stability of these moieties. Consequently, we sought to explore this field, by proposing suitable ferrocenyl tamoxifen-type molecules for the double metal exchange reaction. We had interest in preparing several compounds and examining their potential as a radiopharmaceutical. Therefore, the development of such hormone receptor ligands for diagnostic imaging is a promising area of research.

PS2-31

Biological evaluation of ^{177}Lu-DOTA-PSMA(inhibitor)-RGD in LNCaP and PC3 prostate cancer cells

Author: Alondra Escudero-Castellanos[1]

Co-author(s): Blanca Ocampo-García[2]; Guillermina Ferro-Flores[2]; Clara Leticia Santos-Cuevas[2]; Enrique Morales-Avila[3]; Keila Isaac-Olivé[3]

[1]Universidad Autónoma del Estado de México (UAEM); Instituto Nacional de Investigaciones Nucleares (ININ), Mexico

[2]Instituto Nacional de Investigaciones Nucleares, Mexico

[3]Universidad Autónoma del Estado de México, Mexico

Corresponding author: ealondrac@gmail.com

The objective of this study was to evaluate the in vitro potential of the ^{177}Lu-PSMA(inhibitor)-RGD radiopharmaceutical to bind PSMA and α(v)β(3) integrins overexpressed in LNCaP (lymph node metastasis-derived) and PC3 (bone metastasis-derived) prostate cancer cell lines.

The LNCaP (PSMA-positive) and the PC3 (α(v)β(3) integrin-positive) cells were grown in RPMI 1640 supplemented with 10% of fetal bovine serum and 1% of antibiotics. For evaluating the cell uptake, 1x10^5 cells were incubated (45 min, 37°C) with the treatments (^{177}Lu-PSMA(inhibitor)-RGD 60 nM and their monomers as controls:^{177}Lu-PSMA-617 and ^{177}Lu-RGD, 30 nM). Then, cells were washed with glycine buffer (pH 2.8, 50 mM) followed by the addition of NaOH 0.3 M to determine the cell uptake and internalization fraction. For binding affinity, 1x10^5/well were incubated (1h, 37°C) in the presence of a constant concentration of the ^{177}Lu-PSMA(inhibitor)-RGD with cold peptide at 12 different concentrations (from 0 to 5,000 nM, n=3). After washing the cells, the bound activity was counted in a gamma NaI(Tl) detector. The 50% inhibitory concentration (IC50) was estimated by fitting the competitive binding curves to the Hill function (Origin OriginLab 8.0). To determine IC50 for ^{177}Lu-PSMA-617 and ^{177}Lu-RGD the same procedure was performed. The cell viability was assessed with the XTT assay kit (Roche, Germany). LNCaP or PC3 cells (8x103 cells/well, 96 well plates) were incubated with each treatment for 4 h (~2 Bq/cell) and cell viability was evaluated in 24hours and 48hours. The control group represents 100% of viability with untreated cells. The cell absorbance was measured at λ=450 nm. The differences between the ^{177}Lu-PSMA(inhibitor)-RGD radiopharmaceutical and their monomers were evaluated using Student's t-test.

Cell uptake studies for PC3 cells showed a statistically-significant higher uptake of ^{177}Lu-PSMA(inhibitor)- RGD (3.64±0.58%) compared with ^{177}Lu-PSMA-617 (0.32±0.08%,$p<0.05$), and not statistically significant when compared with ^{177}Lu-RGD (3.02±0.34%,$p>0.05$). For LNCaP cells, there was statistically significant differences in the ^{177}Lu-PSMA(inhibitor)-RGD (6.24±0.32%) compared with the ^{177}Lu-PSMA-617 (5.35±0.16%,$p<0.05$) and ^{177}Lu-RGD (1.01±0.05%,$p<0.05$). The affinity of ^{177}Lu-PSMA(inhibitor)-RGD for PSMA (5.7±1.3nM) was 1.6 times higher than PSMA-617 (8.9±0.9nM,$p<0.05$). In terms of α(v)β(3) integrins, the binding affinity of 177Lu-RGD was 6.2±1.2nM and 4.5±0.7nM for ^{177}Lu-PSMA(inhibitor)-RGD, with a statistically significant difference between them ($p<0.05$). After expo- sure to ^{177}Lu-PSMA(inhibitor)-RGD, the effect on cell viability was 2.5 times higher in LNCaP cells (18.61%) compared with the observed viability in PC3 cells (47.07%).

The radiotracer showed specific recognition for PSMA and α(v)β(3) integrins, and the capability to inhibit cancer cell proliferation with suitable affinity to be used as a radiotheranostic agent. These pre-liminary results warrant future preclinical studies to establish the potential of ^{177}Lu-PSMA(inhibitor)- RGD for the treatment of prostate cancer.

PS2-32

[^{99m}Tc]Tc labelled levonorgestrel derivative as potential ER+/PR+ imaging agent

Author: Leticia Fernández

Co-author(s): Ana Maria Rey Rios; Mariella Teran Gretter

UdelaR, Montevideo, Uruguay

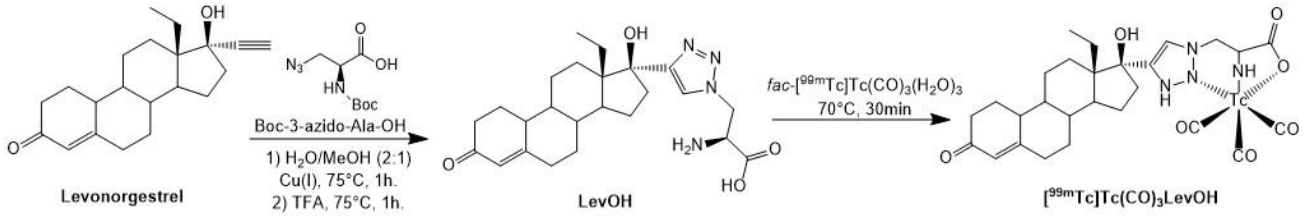
Corresponding author: lfernandez@fq.edu.uy

Breast cancer is a very important health problem. More than 60% of breast tumours that are positive for estrogen receptor (ER+) are also positive for progestogen receptor (PR+), and almost 75% of these tumours (ER+/PR+) respond positively to endocrine therapy. However, a radiotracer directed to PR has potential advantages over one aimed at ER. There is a better correlation between the PR status and the response to hormone therapy. Additionally, a radiotracer capable of recognizing PR could be used after the initiation of anti-estrogenic hormone therapy, while an ER-directed one may not be useful when the ER tumour is saturated by the hormonal agent.

The aim of this work was the preparation of a [^{99m}Tc]Tc labelled levonorgestrel derivative (LevOH) and its physicochemical and biological evaluation as a potential agent for imaging breast cancer by gamma scintigraphy.

LevOH bearing functional groups to coordinate Tc through the formation of a tricarbonyl complex was synthesized by a 1,3-dipolar cycloaddition of Huisgen, catalysed by Cu(I) between the azide group of N-Boc-3-azido-L-alanine and the terminal alkyne of levonorgestrel. Labelling was performed in 2 steps by involving the synthesis of the fac-[^{99m}Tc]Tc(CO)$_3$(H2O)$_3$ precursor and the subsequent substitution with LevOH. The physicochemical characterization included: stability in reaction milieu, in plasma, lipophilicity and plasma protein binding. In-vivo evaluation was performed in athymic mice with human xenograft tumours obtained by inoculation of MCF-7 cells (ER+, EP+) at 1, 4, 12 and 24 hours post-injection.

Figure 1



The derivatization of levonorgestrel was achieved by one of the so-called “click chemistry reactions” which are very specific and avoid the necessity of complicated purification and isolation processes. The ligand bears 3 electron-donor groups that can be used for coordination of Tc through the formation of a tricarbonyl complex (Fig. 1). The radiolabelling was performed in the same pot that the derivatization leading to a main product, [^{99m}Tc]Tc(CO)$_3$LevOH, that was isolated by HPLC, with radiochemical purity > 95%. The complex remained stable in the reaction milieu at least for 3 hours and in plasma for 2 hours. The Log P value was (0.67 ± 0.01), suitable for the passage through biological membranes. Plasma proteins binding was (85.4 ± 2.3)%, which is reasonable when taking into account that levonorgestrel is transported in plasma by the sex hormone binding globulin in 70%. In-vivo biodistribution was very favourable, with low blood activity (4 % at 1 hour post- inj.),

high urinary elimination (60±2% at 24 hours) and a tumour /muscle ratio ranging from 2.8 to 6 (from 1 to 24 hs. post-injection).

The physicochemical and biological evaluation of the complex [^{99m}Tc]Tc(CO)$_3$LevOH showed a promising profile for a potential imaging agent of ER+/EP+ breast cancer by gamma scintigraphy. Nevertheless, further studies with cell lines and isolated receptors will be done in order to assess the potentiality of this approach.

Acknowledgments: ANII FCE_1_2017_1_136416, CAP, CUDIM, CMNIM Hospital de Clínicas.

PS2-33

In vitro kinetics property evaluation of ^{11}C-acetate in real time

Author: Hadis Honarvar

Co-author(s): Regula Naresh Kumar; Jens Sörensen

Department of Surgical Sciences, Radiology, Uppsala, Sweden

Corresponding author: hadis.honarvar@ridgeview.eu

Prostate cancer cells show great demand of cell membrane lipids for growth and proliferation. Acetate as an important intermediary substrate is the main carbon source for fatty acid and lipid synthesis. The lipogenic phenotype of prostate cancer can be imaged, among others, with ^{11}C-acetate PET. Cancerous cells govern the use of acetate for de novo lipogenesis wherein fatty acid synthase (FASN) is the rate limiting enzyme. Earlier studies have shown that there is a direct correlation between ^{11}C-acetate uptake and FASN expression.

Several clinical studies have evaluated the potential clinical role of ^{11}C-acetate for PET imaging of prostate cancer. The information on the uptake and retention rates of ^{11}C-acetate on a cellular level is, however, limited. Therefore, a study was performed to evaluate the in vitro kinetics of ^{11}C-acetate in prostate cancer in real-time.

In a kinetic assay, the ^{11}C-acetate uptake and retention rates by PC3 and DU145 (low and high aggressive) cell lines were evaluated under the same conditions. In order to check the uptake saturation of ^{11}C-acetate, two assays were performed where the uptake was monitored over time using LigandTracer White. In a blocking assay, two experiments were performed in parallel on PC3 cells. Another in vitro study was performed on DU145 and PC3 cells to compare their uptake per cell.

The uptake was linear and proportional to the ^{11}C-acetate concentration in solution indicating the continuous consumption of the latter by the cells for lipogenesis. The relative uptake rate of ^{11}C-acetate was significantly ($p=0.002$) higher for PC3 cells than that for DU145 cells indicating that ^{11}C-acetate is taken up in proportion to fatty acid synthesis. There was a significant difference ($P=0.001$) between the retention rates for DU145 and PC3 cell lines showing that PC3 has a 2 times faster anabolic metabolism than DU145. In a titration assay, it could be seen that ^{11}C-acetate uptake by DU145 and PC3 cells in vitro was characterized by a steady uptake (figure 1). The ^{11}C-acetate uptake was strongly reduced when excess of non-labelled acetate was added, indicating the specific uptake of ^{11}C-acetate. The uptake of ^{11}C-acetate by PC3 cells was about three times higher than that by DU145 cells. The ^{11}C-acetate concentration was gradually increased by subsequently adding 200, 600, 1800, and 3000 kBq, respectively. ^{11}C-acetate retention was monitored after replacement of the incubation solution with medium after 125 min.

In vitro studies demonstrated higher uptake and retention ($p<0.01$) of ^{11}C-acetate in the more aggressive PC3 cells. Thus, faster kinetics of ^{11}C-acetate might reflect the level of aggressiveness of the cancer cell lines.

PS2-34

Application of the Cerenkov radiation produced by ^{177}Lu radiopharmaceuticals in preclinical studies

Author: Nallely Jiménez-Mancilla[1]

Co-author(s): Keila Isaac-Olivé[2]; Eugenio Torres García[2]; Miguel Angel Camacho López[2]; Gerardo Julian Ramirez Nava[1]; Héctor Javier Mendoza Nava[1]

[1]CONACyT. Instituto Nacional de Investigaciones Nucleares, Mexico
[2]Universidad Autónoma del Estado de México, Mexico

Corresponding author: nallely_jimenez@yahoo.com.mx

Cerenkov radiation (CR) is the energy produced in the ultraviolet-visible region of the electromagnetic spectrum. It is produced when charged particles are travelling faster than the speed of light in the same medium. This effect produces polarization of the molecules, which relaxes by releasing energy in ultraviolet and/or visible radiation form. When β particles travel through tissue with energies higher than 219 keV, CR occurs. Spectral optical window of the tissue is from 600 nm to 1100 nm, consequently, the amount of CR within this range could be useful for quantitative preclinical studies from optical images. ^{177}Lu is a radionuclide with a half-life of 6.71 d and a βmax emission of 0.497 MeV (78%), and it has been used successfully for radiopeptide therapy. Some β particles emitted by ^{177}Lu are in relativistic limited because they travel faster than the speed of light in different mediums. The in vivo evaluation of ^{177}Lu radiopharmaceuticals could be used in preclinical studies by CR imaging. The objective was to determine the experimental emission spectrum of CR-^{177}Lu and to evaluate their transmission properties in tissue.

Theoretical and experimental characterization of the emission and transmission spectra in tissues of the ^{177}Lu-CR within the Vis-NIR region (350-900 nm), were carried out by using the Frank-Tamm and relativistic theory, Monte Carlo simulation (MCLTmx code) and light spectroscopy. The acquisition of ^{177}Lu-CR images of mice was performed by using a CCD camera. The total number of image photons/second/mm2 was quantitatively analysed. The total number of disintegrations and the biokinetic models in the kidneys and tumour regions were obtained using the image quantitative analysis.

Results showed a good agreement between theoretical and experimental ^{177}Lu-CR emission spectra. At 1.9 cm of tissue depth, there is still a signal in the spectral range. The total number of disintegrations obtained by ^{177}Lu-CR image analysis showed a good agreement when compared with reported ex-vivo studies of ^{177}Lu (<3%).

In conclusion, preclinical CR images demonstrated that the biokinetics of ^{177}Lu-radiopharmaceuticals in the main organs of mice can potentially be acquired from CR optical images.

PS2-35

Evaluation of biological properties of radiolabelled nanogel-bombesin conjugates

Author: Michał Maurin[1]

Co-author(s): Urszula Karczmarczyk[1]; Monika Orzelowska[1]; Piotr Garnuszek[1]; Renata Mikołajczak[2]; Clelia Dispenzaa[2]; Maria Antonietta Sabatino[3]; Lorena Anna Ditta[3]

[1]National Centre for Nuclear Research Radioisotope Centre POLATOM, Poland
[2]Dipartimento dell'Innovazione Industriale e Digitale, Viale delle Scienze, Italy
[3]Istituto di Biofisica (IBF), Consiglio Nazionale delle Ricerche, Italy

Corresponding author: m.maurin@polatom.pl

Poly-N-vinyl pyrrolidone-co-acrylic acid nanogels have been developed as nanocarrier systems. Their small size (80 nm), minimal toxicity, stability in serum and easiness of their surface modification (by attachment of targeting molecules, fluorescent probes or chelators for radiolabelling) make them interesting candidates for innovative drug delivery systems. The aim of the presented work was the evaluation of biological properties of 177Lu radiolabelled nanoparticles modified by conjugation of DOTA-bombesine.

DOTA-bombesin-nanogels and DOTA-bombesin alone were labelled with $^{177}LuCl_3$ (LutaPol) and $^{90}YCl_3$ (ItraPol). The labelling yield was assessed by TLC (iTLC SG plates/0.2M KCl pH 2.4). Purification of radiolabelled preparations was conducted by size exclusion chromatography (mini PD10 columns eluted with saline) and ultrafiltration (amicon ultra centrifuge filters 3kDa). In vitro binding studies in AR42J cell line (rat's pancreatic cancer cells) were performed to assess the biological activity. Standard procedures for assessing specific and non-specific binding and internalization were employed. Biodistribution was evaluated in two animal models: normal Wistar rats and the tumour model - female BALB/c Nude (CAnN.Cg-Foxn1nu/Crl). To grow the tumours, the AR42J cells (106 cells in 200 µL PBS) were inoculated on the left or right shoulder. The radiolabelled nanogels were administrated intravenously and intratumourally in the dose of 10 MBq/animal. The animals were sacrificed at different time points after injection and the radioactivity distribution was measured ex vivo after organ dissection.

The radiolabelling yield of nanogels was in the range of 50-70% and after purification by size exclusion and ultrafiltration the radiochemical purity was more than 95%. [^{177}Lu]-DOTA-bombesin-nanogel conjugates showed high affinity to the AR42J cells at the level of 8.4% of specific binding and 80% internalisation rate, which was comparable to that of [^{177}Lu]- DOTA-bombesin. In vivo biodistribution in normal rats revealed that the liver is the critical organ with over 80% of accumulation of injected dose (%ID). Biodistribution after iv. injection to tumour bearing animals revealed increasing accumulation of labelled nanoconjugates in the tumour from 0.2% ID/g at 2 h p.i. to 2.3% ID/g at 24h p.i. and high accumulation in the liver. After intratumourall injection no leakage of radioactivity was observed over 48h.

The specific membrane binding and internalization to the AR42J cells of the radiolabelled DOTA- bombesin-nanogel was comparable to that of DOTA-bombesin which confirmed the targeting properties of the nanoconjugate in vitro. However, the biodistribution revealed that radiolabelled DOTA- bombesin-nanogels highly accumulate in the liver with rather small fraction taken up by the tumour. Further studies are needed to modify the size or/and surface of these nanoconjugates in order to improve the biodistribution pattern. Importantly, retention of [^{177}Lu]-DOTA-bombesin-nanogel in the tumour after intratumourall administration confirmed its stability in vivo and indicates the potential of the particles in direct therapy of primary tumours.

Acknowledgements: the study was performed within the International Atomic Energy Agency co-ordinated research project. F22064 „Nanosized Delivery Systems for Radiopharmaceuticals."

PS2-36

Comparative radiobiological evaluation of intracellular effects induced by $^{64}CuCl_2$ in different tumour cells

Author: Dana Niculae[1]

Co-author(s): Livia Chilug; Radu Serban; Cosmin Mustaciosu; Mihaela Temelie; Ramona Dusman; Radu Leonte; Doina Draganescu; Dragos Niculae; Anca Dinischiotu

Horia Hulubei National Institute for Physics and Nuclear Engineering, University of Bucharest, Romania

Corresponding author: dana.niculae@nipne.ro

Copper, as a natural bioelement in the human body, incorporated into a variety of proteins, is involved in key biological processes based on its redox properties. Its trafficking, accumulation and clearance are tightly controlled in normal health but often disturbed in disease states. These mechanisms can be exploited for both imaging and therapy, based on several radioisotopes of copper which are of certain medical interest. $^{64}CuCl_2$ has recently been proposed as a promising agent for cancer theranostics, based on preclinical studies. The use of $^{64}CuCl_2$ for therapy raises important radiobiological questions, therefore this study proposes a comparative radiobiological evaluation of the intracellular effects induced in different tumour cells.

An automated process for the production and purification of copper-64 produced by irradiating solid targets in a variable energy (14-19 MeV) cyclotron has been employed, by using a commercially available automated solid target system comprising modules for electrodeposition, pneumatic transfer, irradiation, dissolving and purification. To comparatively evaluate the biological effects, we used a panel of tumour cell lines: U87MG (glioblastoma), AR2J (pancreatic cancer cells), HT29 (colon adenocarcinoma), A431 (epidermoid carcinoma) and DU-145 (prostate cancer cells) in comparison with non-tumoural, control cell lines (monocytes ATTC). We performed cytogenetic and radio-cytotoxicity assays to evaluate the significant changes at cellular level induced by the exposure to $^{64}CuCl_2$: cell viability by MTT/MTS, micronuclei testing genotoxicity and morphologic apoptosis and H2AX, when relevant.

Results showed that tumour cells were found to exhibit increased $^{64}CuCl_2$ uptake comparing to normal cells; early DNA damage, higher cytotoxicity and genotoxicity were also observed in tumour cells, with different intensities for different cancer cells tested. Double strain breakages were observed, which correlate with deficient DNA-damage repair capacity. The results contribute to elucidation of mechanisms involved, to quantify radiobiological effects and to sustain the use of $^{64}CuCl_2$ for theranostic applications.

Acknowledgement: this work was supported by a grant of the Romanian Ministry of Research and Innovation CCCDI - UEFISCDI project number 64PCCDI/2018, PNCDI III.

PS2-37

In-vitro study of therapeutic radionuclides' impact on selected tissue and tumour cell lines

Author: Lukáš Ondrák

Co-author(s): Martin Vlk; Ján Kozempel; Marie Davídková; Jana Vachelová

Czech Technical University in Prague, Prague, Czech Republic

Corresponding author: lukas.ondrak@fjfi.cvut.cz

Beta emitters are widely used in treatment of various oncological diseases for a long time. Alpha emitters belong to new and perspective candidates for therapeutic use and some of them have been already introduced into clinical practise. Targeted alpha-particle therapy (TAT) is a rapidly evolving field of cancer treatment. Nevertheless, there are some severe issues that prevent TAT from being a leading modality in radionuclide therapy. The nuclear recoil effect that causes the daughter nuclei release from the original radiopharmaceuticals is a critical problem for alpha emitters. Moreover, targeting and proper dosimetry is still an issue. Therefore, we focused on the dosimetry on cellular and subcellular level with an aim to quantitatively and qualitatively compare the effect of alpha and beta emitters on living cells.

For our study we used Ra-223, Sm-153 and Re-186 as a model radionuclides. All radionuclides were used in the range 0-8 kBq/mL. Studied cell lines were V79 (Chinese hamster lung fibroblasts), DU145 (human adenocarcinoma cell line) and U87 (human primary glioblastoma cell line) obtained from American Type Culture Collection (ATCC). All cells were cultivated in humidified atmosphere under standard culture conditions (37°C, 5 % CO2). Chines hamster cell line (V79) was cultivated in Dulbecco's Modified Eagle's Medium (Sigma-Aldrich, Germany) supplemented with 10% of Fetal Bovine Serum South America Origin (Biosera, France) and 1% of Penicillin-Streptomycin (Biosera, France)). Human adenocarcinoma cell line (DU145) and human glioblastoma cell line (U87) were cultivated in Eagle's minimum essential medium (Sigma-Aldrich, Germany) supplemented with 10% of Fetal Bovine Serum of South America Origin (Biosera, France), 1 % of Penicillin-Streptomycin (Biosera, France)), 1 % of L-glutamine (Sigma-Aldrich, Germany), 1 % of Non-essential amino acids (Sigma-Aldrich, Germany) and 1 % of pyruvate (Sigma-Aldrich, Germany). All cell lines have been cultivated in the presence of Ra-223, Sm-153 or Re-186 for 24 hours after the monolayer of the cells was created. After the cultivation with Ra-223, Sm-153 or Re-186, the clonogenic survival test was performed and survival curves for all cell lines were constructed.

All obtained survival curves correspond to the linearly quadratic model. Sensitivity of both human carcinoma cell lines (adenocarcinoma and glioblastoma cell line) to treatment by all used radionuclides is higher than the sensitivity of the Chinese hamster pulmonary fibroblast cell line. Sensitivity of tested carcinoma or tissue cell lines is higher to alpha treatment than to beta treatment using the same applicated activities of alpha or beta emitters. The achieved results enabled further progress in enhancing the alpha dosimetric studies.

Acknowledgment: this work was supported by the Health Research Agency of the Czech Republic (grant No. NV16- 30544A).

PS2-38

Factors and drug interactions that cause altered biodistribution of radiopharmaceuticals

Author: Graciela Rabiller

CNEA, Argentina

Corresponding author: rabiller@gmail.com

The role of the specialist in radiopharmacy is important in the medical interpretation of images obtained in nuclear medicine studies. One of the most common problems associated with radiopharmaceuticals is an unexpected or altered biodistribution, which can have a significant clinical impact on dosimetry, interpretation of the scan and the precision of the images for diagnosis. In its most extreme manifestations, the results of images with altered biodistribution may compromise the usefulness and precision of nuclear medicine studies. The biochemical and pharmaceutical interpretation of the molecular mechanisms involved must be considered.

Studies carried out will be analysed in order to consider important factors that affect the biodistribution of radiopharmaceuticals that can be the following main categories and include:

- Problems in preparation methods or in the formulation of radiopharmaceuticals;
- Problems caused by radiopharmaceutical administration techniques;
- Previous Medical procedures, such as biopsy puncture, surgery, radiotherapy or dialysis;
- Due to changes in biochemistry and physiopathology of the patient and also by pharmacological interactions.

The altered biodistribution of ^{99m}Tc radiopharmaceuticals is generally associated with increased amounts of ^{99m}Tc radiochemical impurities, such as $^{99m}TcO_4$ free, impurities and particles, such as ^{99m}Tc colloids or reduced ^{99m}Tc hydrolyzed species, or other radionuclides.

Failure in the function of excretory organs and systems, such as the hepatobiliary and genitourinary systems can contribute to the altered biodistribution of radiopharmaceuticals.

Incidental findings perfusion artefacts that commonly occur may have clinical significance and/or may affect the interpretation of the study, and should be considered and reported appropriately.

An important factor, not always considered, is dose infiltration or contamination with antiseptics and aluminium during dose administration, which can cause significant artefact.

In conclusion, new molecular radiopharmaceuticals for diagnostic or therapeutic use, should be considered, since pharmacological interactions should be evaluated and in the same way, the techniques of labelling and administration.

PS2-39

^{99m}Tc-CXCR4-L: biokinetics and radiation dosimetry in humans

Author: Clara Santos-Cuevas[1]

Co-author(s): Guillermina Ferro-Flores[1]; Angelica Arellano-Zarate[2]; Osvaldo Garcia-Perez[2]; Paola Vallejo-Armenta[3]; Rosa Maria Villanueva[3]; Jorge Gonzalez-Diaz[3]

[1]Instituto Nacional De Investigaciones Nucleares, Mexico
[2]Instituto Nacional De Cancerologia, Mexico
[3]Centro Medico Nacional Siglo XXI, Mexico

Corresponding author: clara_letici@yahoo.com.mx

The receptor for chemokines CXCR4 is mainly expressed in cells of the central nervous and immune systems, hematopoietic stem cells, endothelial and epithelial cells. The ability of CXCR4 to mediate the metastasis of a variety of cancers has been studied because it is associated with angiogenesis, tumour progression and survival. Several CXCR4 antagonist peptides have been used to reduce tumour growth and angiogenesis in preclinical studies. Recently our group has radiolabelled a new chemokine-4 ligand (CXCR4-L) with Tc-99m for specific imaging of tumours with CXCR4 expression. The objective is to estimate the biokinetics and radiation dosimetry of ^{99m}Tc-CXCR4-L in six healthy subjects and to evaluate its ability to target CXCR4 in one patient with medulloblastoma.

The radiopharmaceutical ^{99m}Tc-CXCR4-L was obtained with radiochemical purity >98% from lyophilized formulation. The complete body anterior and posterior gamma images from six healthy humans (three women and three men) were acquired at different times after radiopharmaceutical administration (20 min, 1, 2, 4, 6 and 24 h). Images of each time frame were corrected by attenuation and scattering. The geometric mean of the anterior and posterior images was obtained and regions of interest (ROI) were selected (source organs). ROI's time-activity curves of ^{99m}Tc-CXCR4-L were used to set the biokinetic models and estimate the total number of disintegrations (N) that took place in the source regions. Using OLINDA/EXM and N data the internal radiation doses were calculated.

A brain SPECT/CT image was acquired in a medulloblastoma tumour 3 h after administration of ^{99m}Tc-CXCR4-L.

The half-life value of blood activity had one fast and two slow components of 0.81 min (T1/2α=ln2/51.01), 12.19 min (T1/2β=ln2/3.41) and 2.03 h (T1/2γ=ln2/0.34), respectively. The equivalent doses calculated for a study using 740 MBq in females for brain, breast, kidneys, liver, lungs, and spleen were 0.0025 ± 0.0002, 0.2235 ± 0.0474, 0.0232 ± 0.0042, 0.1046 ± 0.0265, 0.3236 ± 0.0650 and 0.0054 ± 0.0006 mSv, correspondingly, and in males for brain, kidneys, liver, lungs and spleen were 0.0026 ± 0.0007, 0.0764 ± 0.0655, 0.1078 ± 0.0115, 0.3483 ± 0.0423 and 0.0052 ± 0.0014 mSv, respectively. The average effective dose for the six subjects was 3.91E-3 ± 3.25E-4 mSv/MBq. The ^{99m}Tc-CXCR4-L uptake in medulloblastoma of the patient was significantly higher in respect to the background of the lesion.

In conclusion, the ^{99m}Tc-CXCR4-L radiation absorbed doses in source organs was comparable to those recommended for Tc-99m imaging studies. The radiopharmaceutical uptake in tumour of medulloblastoma in the brain was significantly higher than the background brain uptake, which demonstrated the ability of the new ^{99m}Tc-labelled CXCR4 ligand to detect tumours with CXCR4 expression.

Acknowledgment: this study was supported by the Mexican National Council of Science and Technology (LANIDER, CONACyT-ININ).

PS2-40

In vitro cell binding detection of novel radiopharmaceuticals: a radionuclidic evaluation

Author: Mine Silindir Gunay
Co-author: A. Yekta Ozer

Faculty of Pharmacy, Hacettepe University, Turkey

Corresponding author: mines@hacettepe.edu.tr

The development of novel radiopharmaceuticals is a labour intensive, time consuming and expensive period similar to novel drug delivery systems. The targeting ability to the desired disease site should be evaluated for the assessment of the specificity of radiopharmaceuticals. Therefore, in vitro cell culture studies are becoming widespread all around the world due to being easy to apply, and a rapid and safe method for the development of novel radiopharmaceuticals. In vitro cell culture studies gained a significant role in preclinical studies depending on obeying the three R concepts (replacement, reduction and refinement) and animal welfare. By this way, unnecessary laboratory animal use in research has reduced significantly.

Cell culture studies comprise the studies after growing under controlled conditions after removing cells from the tissues. Cell culture studies can be used in molecular biology as model systems, cancer research, toxicity tests, virology, vaccine production, monoclonal antibody production, organ and tissue production, gene therapy and as preclinical studies in drug development. Similar to novel drug development studies, radiopharmaceutical development studies benefited from cell culture studies in tumour modelling, BBB modelling, permeability, cytotoxicity, cell binding and uptake and targeting.

This research comprises a series of different studies evaluating cell binding studies of novel radiopharmaceuticals for tumour imaging. In vitro cell culture model, property, culture conditions, and applications of radiopharmaceuticals were maintained, and specific cell binding and uptake of radiopharmaceuticals were evaluated by obtaining microscopy images, fluorospectroscopy and counting radioactivity in gamma counter. For this purpose, either tumour binding or BBB penetration of radiolabelled, active targeted liposomes were evaluated and compared with unmodified, PEGylated liposomes in different cell culture lines.

According to cell culture studies, significantly higher uptake was observed with radiolabelled tumour specific ligand modified liposomes in cell binding and surface association of different tumour cell lines, when compared with unmodified conventional liposomes. Successful cell culture studies are thought to mimic in vivo conditions and live tissue functions more properly.

This research gives an overview to a series of different studies performed by our group evaluating cell binding and cell surface association studies of novel radiopharmaceuticals for different diseases. Therefore, in vitro cell culture studies are essential for the development of novel radiopharmaceuticals similar to drug development by reducing unnecessary animal utilization, more rapidly and safer.

PS2-41

The advantage of using radiotracers for pre-clinical assays with conventional drugs: the case of meglumine antimoniate

Author: Samanta Etel Treiger Borborema[1]
Co-author: Joao Alberto Osso[2]

[1]Center for Parasitology and Mycology, Adolfo Lutz Institute, Sao Paulo, SP, Brazil
[2]International Atomic Energy Agency, Vienna, Austria

Corresponding author: samanta.borborema@ial.sp.gov.br

The process of drug discovery and development requires substantial resources and time. A good understanding of the pharmacokinetics of the existing drugs could lead to a more successful strategy. The application of pharmacokinetic principles is one of the tools available for optimizing drug therapy, including drugs whose concentration-pharmacological response relationship is well established. Leishmaniases are mosquito-borne infectious diseases caused by protozoan parasites of the genus Leishmania. The mainstay of treatment remains pentavalent antimonial agents in the form of sodium stibogluconate (Pentostam®) or meglumine antimoniate (MA, Glucantime®). Despite the pharmacokinetics of pentavalent antimonials having been already reported, the available data are conflicting due to the different methodologies employed to measure antimony (Sb), the sample numbers, and the treatment schedules. In this review, we discussed the use of the radiolabelled compound to provide a sensitive and powerful tool to determine their pharmacokinetic properties. Radioisotopes of Sb were prepared to follow the biodistribution of MA and its liposomal formulations, also to evaluate the amount of Sb incorporated inside the liposomes. Samples of free MA and MA-liposomes in clean polypropylene tubes were placed together with Sb standards inside the aluminium container. Irradiations were carried out at a thermal neutron flux of 0.8 x 1012 n.cm-2.s-1 for 15 minutes inside the nuclear reactor. Two Sb tracers, ^{122}Sb and ^{124}Sb, were produced through the reactions ^{121}Sb(n,γ)^{122}Sb and ^{123}Sb(n,γ)^{124}Sb. Studying the biodistribution of MA is easier and faster when the drug is radioactive when compared to conventional analytical techniques. Because there are no antimony radioisotopes commercially available, irradiating the MA was the best choice for the in vivo evaluation studies. The advantage of this procedure is that neutron irradiation of the stable antimony isotopes present in the MA formulation enables the detection and quantification of total antimony, but without distinguishing between the pentavalent and trivalent antimony species. We also found that there was no difference in the antileishmanial activity in the irradiated MA compared to the non-irradiated MA in both in vitro and in vivo evaluations. The use of radiotracers as a tool to evaluate the biodistribution of drugs in animal models is a feasible approach and these results could contribute to the development of new pharmacological studies using drug delivery systems for leishmaniases. This work emphasizes the importance of antimony pharmacokinetic profile in finding better therapeutic protocols as to its dosage, administration interval, and the duration of therapy. The use of radiotracer has great potential for improving the efficiency in the drug development process.

Track: Quality control and quality assurance of medical radioisotopes and radiopharmaceuticals

PS2-42

An experimental study on radiochemical purity (RCP) of ^{99m}Tc- tetrofosmin compounded outside manufacturer's guideline using TEC-control™ chromatography system

Author: Ahmad Bazli Ahmad Zikirleh
Co-author: Siti Khadijah Mohammad Fawzi

Nuclear Medicine Department, Hospital Sultanah Aminah Johor Bahru, Malaysia

Corresponding author: bazlizikrileh@gmail.com

Myoview™ (Tetrofosmin) is a pharmaceutical agent which needs to be radiolabelled with technetium-99m according to manufacturer's guideline to become ^{99m}Tc-Tetrofosmin. It then needs to undergo a radiochemical purity (RCP) test to determine that the percentage RCP is within acceptable limit. This is defined according to WHO Pharmacopeia (≥90%), before being used for nuclear cardiology imaging. Myoview™, which is quite expensive in Malaysia (€950 / 5 vials), is supposed to be reconstituted with 12GBq of technetium-99m with final volume of 8mL (radioactivity concentration of 1.5GBq/mL) and it can be used for approximately 8 one-day protocol patients. Using a new cardiac dedicated gamma camera (GE Discovery NM 530c), the department anticipates an increased number of patients and scans per day resulting the enlarged usage of Myoview™; and thus, an increase in operational costs. Increasing radioactivity concentration per vial may be done to cater this issue.

To determine RCP percentage of ^{99m}Tc-Tetrofosmin compounded outside manufacturer's guidelines at radioactivity concentration of 2.0GBq/mL, 2.5GBq/mL and 3.0GBq/mL at time 0, 4, and 8 hours post-reconstitution with null hypothesis: RCP percentage of ^{99m}Tc-Tetrofosmin is ≥ 90% and alternative hypothesis: RCP percentage of ^{99m}Tc-Tetrofosmin is < 90%.

Five batches of ^{99m}Tc-Tetrofosmin were prepared at each radioactivity concentration of 2.0GBq/mL, 2.5GBq/mL and 3.0GBq/mL. Each batch underwent 9 RCP tests using TEC-Control™ chromatography system; 3 tests for each sampling time at 0, 4, and 8-hour post-reconstitution. Data were analysed using one-sample T-Test and Repeated Measures ANOVA.

RCP's mean percentage of each sampling time (0hr, 4hr and 8hr): at a concentration of 2.0GBq/mL were 94.52%, 96.24% & 95.72%; at concentration of 2.5GBq/mL were 96.15%, 95.86% & 95.21%; and at concentration of 3.0GBq/mL were 95.80%, 95.71% & 93.41%. A one-sample t-test was run to determine whether RCP percentage in samples was different as compared to the acceptable limit. RCP's mean percentage of ^{99m}Tc-Tetrofosmin (95.41% ±1.86) was higher than the acceptable limit of 90%, which is statistically significantly higher by 5.41 (95% CI, 5.97 to 4.85), $t(44) = 19.5$, $p < 0.0005$. As there was a statistically significant difference between mean ($p < 0.0005$) and the mean is more than the acceptable limit, we can accept the null hypothesis and reject the alternative hypothesis. Repeated measures ANOVA was used to determine whether there is significant difference of RCP percentage of each radioactivity concentration at different sampling time. Result shows there was no statistically significant effect of sampling time (0hr, 4hr and 8hr post-reconstitution) on radioactivity concentration of 2.0GBq/mL, (Wilks' Lambda = .39, $F(2,3) = 2.32$, $p>0.05$), on radioactivity concentration of 2.5GBq/mL (Wilks' Lambda = .53, $F(2,3) = 1.3$, $p > 0.05$) and on radioactivity concentration of 3.0GBq/mL (Wilks' Lambda = .31, $F(2,3) = 3.29$, $p>0.05$).

The RCP percentage of ^{99m}Tc-Tetrofosmin that were compounded at a radioactivity concentration of 2.0GBq/mL, 2.5GBq/mL and 3.0GBq/mL were acceptable regardless of sampling time. This study may be used to save approximately €47,500 per year of the departmental in operational costs.

PS2-43

Development of a new method for the microbiological analysis of Iodine-131

Author: Abdelmjid Aiboud

Co-author(s): Abdellah Ettabia; Aziz Fllaoui; kadddour Benhamou; Mouhssine Ait said; Naoual Bentaleb; Younes Ghamad; Zine el abidin Ayaz

National Center for Energy Sciences and Nuclear Techniques, Morocco

Corresponding author: aiboud.abdelmjid@gmail.com

The main aim of this study is to develop a new microbiological control method for the solution of iodine 131 in a closed system for radiopharmacy services not equipped with a class of A Hot Cell dedicated to microbiological analysis according to GMP requirements.

The method is based on the preparation of perforated petri dishes containing three culture media. The perforation of the Petri dishes was realized under a class A laminar flow hood using a heated metal cylindrical rod. A sterile magnetic stir bar was then placed in each Petri dish before closing the hole and sealing Petri dishes with autoclaving adhesive.

First, the method was tested inside a class C room then inside an unclassified area by perforating the adhesive with a sterile syringe and injecting a volume of sterile water before the perforation was closed by a second sterile adhesive. Seeding was performed by moving each Petri dish on a magnet. Then the Petri dishes were incubated inside the Hot Cell at room temperature for yeasts and molds at 32.5 ℃ and for Total Aerobic Microbial and Total Coliform. A positive control (bacterial suspension) and a negative control (sterile water) were performed for each culture medium. Finally, the method was tested inside a class C Hot Cell for three production batches of sterile iodine- 131.

Results showed that after 5 days incubation at 32,5℃ and 7 days at room temperature, The Petri dishes were sterile for both tests performed in class C room and for the unclassified room. The same result was obtained with the solution of iodine-131 in the three production batches.

This new method has shown good efficiency to keep the sterility of culture medium during the microbiological analysis independently of the environmental class. It could be adopted by radiopharmacy services for the control of the solution of iodine-131 and other radiopharmaceuticals. This method would make it possible to carry out the microbiological analysis of radiopharmaceuticals quickly without waiting for the decay. Moreover, it allows to minimize the risk of exposure of the laboratory technicians by iodine inhalation.

PS2-44

User-friendly sterility testing method for injectable radiopharmaceuticals – feasibility study and validation

Author: Chanda Arjun [1]

Co-author(s): Aaditya Shah[1]; Barakha Karkhanis[1]; Pramila Jog[1]; Chetan Kothalkar[1]; Aruna Korde[2]; Arun Dey[1]

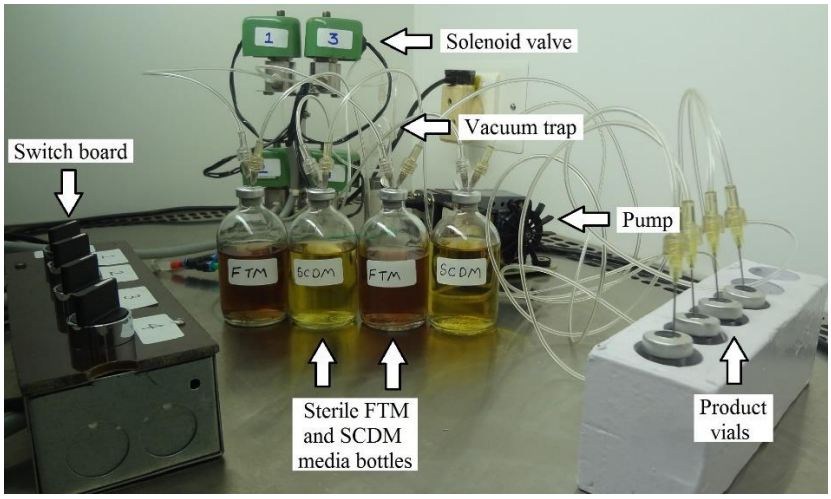
[1] Board of Radiation and Isotope Technology (BRIT), Navi Mumbai, India

[2]Division of Physical and Chemical Sciences, International Atomic Energy Agency, 1400 Vienna, Austria

Corresponding author: chanda@britatom.gov.in

Various diagnostic and therapeutic radiopharmaceuticals are regularly supplied for clinical use across India by BRIT. BRIT QA/QC monographs and Indian Pharmacopeia approve parametric release of short lived injectable radiopharmaceuticals as it is not feasible to complete the Sterility Test (ST) before the product is released. However, as a good manufacturing practice, it is mandatory that the test be commenced at the earliest. Conventional methodology for ST involves manual transfer of test samples - minimum four vials per batch - into sterile growth media under aseptic conditions. This method is time-consuming, requires skilled persons and results in considerable radiation exposure to analyst in routine testing facilities. We describe here a simple vacuum-based manifold system which was designed in house, validated and tested in routine use to circumvent these problems.

The vacuum-based manifold system consisted of four silicone tubings (Masterflex) connected to a vacuum pump and attached to sterile needles (Fig. 1). These needles were introduced into Fluid Thioglycollate Medium (FTM) and Soyabean Casein Digest Medium (SCD) bottles (HiMedia Laboratories). A sterile assembly containing a spinal needle (^{18}G) connected to a sterile needle (23G) via silicone tubing was used. The spinal needles were introduced into the sample vials such that their tip touched the base of the vials. Individual vacuum control for each of the four sets was done using solenoid valves placed between the media bottles and the vacuum trap. Switching on the vacuum and respective solenoid valve ensured withdrawal of the entire sample volume through the spinal needle and tubing into the media vial. Test samples were housed in slotted lead stand of appropriate thickness. The whole assembly was set up inside a Biosafety Cabinet (Class III). The inoculated media were incubated at 30-35°C and 20-25°C respectively for 14 days and examined for microbial growth by visual examination.



Sterile saline was used to inoculate the media in the same manner and used as controls. The radiopharmaceuticals tested by this method included: ^{153}Sm-EDTMP, ^{131}I-mIBG and Na^{99m}TcO$_4$ eluates from ^{90}Mo-^{99m}Tc generators (04 batches each, RAC ~20mCi/mL (740MBq/mL) per vial).

Results shows that all the injectable radiopharmaceutical products tested passed the ST as indicated by absence of microbial growth on completion of the 14 days incubation period.

In conclusion, the adaptation of the ST method using a vacuum manifold, besides being safe and time saving, provides a reliable quality control testing option for radiopharmaceuticals and decreases personal errors. This method can result in a significant reduction in the radiation dose received by the analyst and provides a feasible alternative to the conventional method.

PS2-45

Feasibility of a green analytical method for radiochemical purity determination of sodium [^{99m}Tc] pertechnetate

Author: Chanda Arjun; Sanjeev Kumar Basude
Co-author(s): Padmanabhan Dharmarajan

Board of Radiation and Isotope Technology (BRIT), DAE, India

Corresponding author: chanda@britatom.gov.in

Green Analytical Chemistry (GAC) is a branch of Green Chemistry based on the principles of sustainable development through eco-friendly analysis in laboratories. This employs techniques which replace or modify organic solvents, corrosive and toxic reagents, hazardous pollutants and carcinogens with safer ones, making it possible to reduce the amounts of reagents consumed and generated waste.

^{99m}Tc-radiopharmaceuticals are most widely used for radionuclide imaging of various organs. ^{99m}Tc-based radiopharmaceuticals are produced using sodium[^{99m}Tc]pertechnetate ($Na^{99m}TcO_4$) and cold kits generally procured from commercial sources. $Na^{99m}TcO_4$ is eluted from $^{99}Mo/^{99m}Tc$ generator systems and the quality of radiopharmaceuticals in turn depends on the quality of the $Na^{99m}TcO_4$.

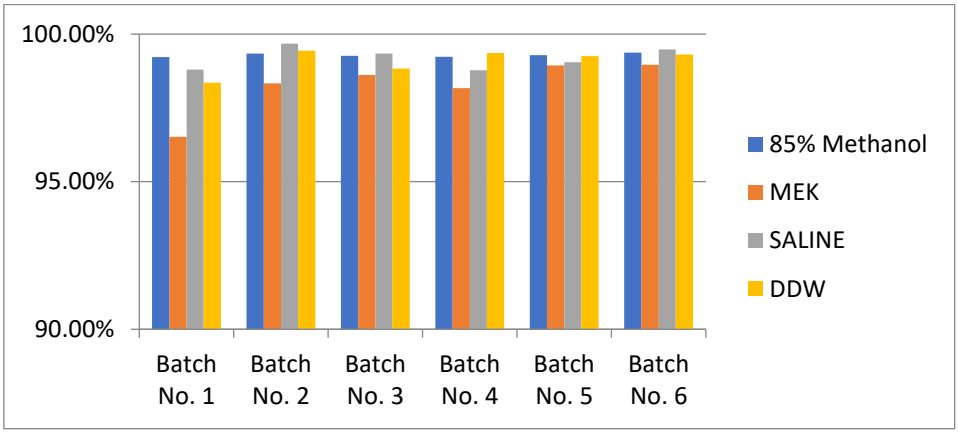
Radiopharmaceuticals are required to undergo Quality Control (QC) testing as it is important to have a product with acceptable QC specifications described in the Pharmacopoeias. Radiochemical purity (RCP) is a very important parameter which reflects the integrity and stability of radiopharmaceuticals. RCP of $Na^{99m}TcO_4$ is done by paper chromatography and should be > 95%. RCP determination of $Na^{99m}TcO_4$ eluates from $^{99}Mo/^{99m}Tc$ generators is done by using paper chromatography (PC) followed by scanning for radioactivity using radiochromatogram scanner. The chromatograms are developed in any one of the solvent systems:

1. 85% Methanol
2. Methyl ethyl ketone (MEK)
3. 0.9% Sodium chloride (Saline).

The aim of this work was to standardise an eco-friendly, alternative method for assessing RCP of $Na^{99m}TcO_4$ using Double Distilled Water (DDW) as the mobile phase (MP).

$Na^{99m}TcO_4$ was eluted from a $^{99}Mo/^{99m}Tc$ Column (alumina) generator (BRIT). Paper chromatography of $Na^{99m}TcO_4$ was done in duplicate by ascending chromatography by using strips of Whatman No.3 (3x23cm). Determination of Reduced Hydrolysed Technetium (RHT) (impurity) in these eluates (06 batches) was done in the same manner by adding 10% $SnCl_2$ in 0.1N HCl to the eluates and heating for 10 minutes at 100℃. The chromatography strips were scanned in a radiochromatogram scanner and the RCP data was computed.

Table 1: % RCP values of $Na^{99m}TcO_4$ and RHT in four different solvent systems



The percentage RCP of $Na^{99m}TcO_4$ & RHT (Table 1) by using the alternative procedure (DDW) is in good agreement with the other three standard chromatography procedures. Hence, this method can be used as an alternative method as it is compatible with routine nuclear medicine practices and can be easily adopted in hospital radiopharmacies.

RCP determination using DDW is very convenient to use in hospital radiopharmacies as DDW is inexpensive and easily available. The method was standardized by us; hence, it provides an opportunity for utilizing the GAC techniques in the field of QC, besides offering significant ecological and economical merits.

PS2-46

Bacterial endotoxin testing of injectable radiopharmaceuticals: BRIT experience

Author: Chanda Arjun[1];Barakha Karkhanis[1]
Co-author(s): Aruna Girish Korde[2]

[1] Board of Radiation and Isotope Technology (BRIT), Mumbai, India
[2] International Atomic Energy Agency, Vienna, Austria

Corresponding author: chanda@britatom.gov.in

Diagnostic and therapeutic injectable radiopharmaceuticals are regularly supplied by BRIT to use in Nuclear Medicine Centres all over India. It is mandatory to perform Bacterial Endotoxin Test (BET) before releasing these products. Bacterial endotoxin is the only significant pyrogen of concern in parenteral drug preparations due to its potency and ubiquity in nature. The adverse effects of bacterial endotoxins are dependent on dose, route and rate of administration. For BET based on gel-clot formation, Limulus Amoebocyte Lysate (LAL) reagent is commercially a viable option for routine testing. However, attention to test conditions are important as the method is both time and temperature sensitive. We describe here the optimisation of BET by gel clot method of various injectable radiopharmaceuticals based on test dilution, preparation of samples/controls, maintenance of test conditions and acceptance criteria.

BET was carried out in accordance with the Indian Pharmacopeia using standard kit reagents (Charles River, India). It is required to calculate the Maximum Valid Dilution (MVD) for radiopharmaceutical products to establish the extent of dilution to avoid interfering test conditions. MVD = EL/ (EL is the Endotoxin Limit of injectable radiopharmaceuticals and is the sensitivity of LAL reagent used). The EL is 25 EU/mL (EU= Endotoxin Units) based on 7 mL being the maximum volume for the most injectable radiopharmaceuticals and the of the lysate used is 0.125 EU/mL. Hence, the permitted MVD works out to be 1:200. The exceptions are ^{177}Lu-DOTATATE and ^{68}Ga labelled DOTATATE and PSMA, the former being unstable at higher radioactive concentrations and the latter formulated in a higher volume due to logistical reasons (Table 1). For the test, diluted samples (MVD) were incubated with LAL reagent at 37±1℃ for 60±2 minutes. At the end of the incubation period, the tube was inverted by 180° to detect gel–clot formation. The results were compared with negative and positive water control tests and product control tests. The former contained endotoxin free water and the latter contained the radiopharmaceutical product in the absence and presence of standard endotoxin, respectively.

Table 1: MVD values of in house produced injectable radiopharmaceuticals

	Product	No. of Batches tested	Volume (mL)	EU/mL	MVD
1	^{131}I-mIBG	440	7	25	200
2	^{153}Sm-EDTMP	395	7	25	200
3	^{32}P-sodium orthophosphate	223	7	25	200
4	^{32}P-Sm-Phosphate Colloid	47	7	25	200
5	$Na^{99m}TcO_4$	310	7	25	200
6	^{177}Lu-EDTMP	14	7	25	200
7	^{177}Lu-PSMA	10	7	25	200
8	^{177}Lu-DOTATATE	26	12	14	120
9	^{68}Ga-DOTATATE	18	10	17.5	140
10	^{68}Ga-PSMA	34	10	17.5	140

All the injectables, diluted as per the optimised protocols, passed the BET when tested by the gel- clot method thus verifying the suitability of the test protocol under actual conditions of use. The consistent results observed during the testing of these considerable numbers of batches proved the validity of the test.

In conclusion, BET testing of in-house produced injectable radiopharmaceuticals, as per the protocols standardised by us, has proved to be a reliable and reproducible quality control method in our experience in BRIT.

PS2-47

"^{99}Mo/^{99m}Tc Radionuclide Generators" optimization: new quality control standards of alumina columns and kinetic study of molybdenum adsorption on α alumina

Author: Mohammed Rabie Bricha[1]

Co-author(s): Kaddour Ben Hamou[1]; Naoual Bentaleb[1]; El Mahjoub Chakir[2]; Abdelhalim Mesfioui[2]

[1]CNESTEN, Morocco

[2] Ibn Tofail University, Faculty of Sciences, Kenitra, Morocco

Corresponding author: bricharabie@gmail.com

Radiopharmaceutical preparations (RP) or radiopharmaceuticals are medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a medicinal purpose (diagnostic or therapeutic). In the nuclear medicine department, the reconstitution of a radiopharmaceutical is done by labelling a chemical molecule, the vector, with known pharmacokinetic and pharmacodynamics properties by a radionuclide, the marker. In vivo monitoring after administration of the RP is achieved usually by detecting the gamma radiation emitted by the radionuclide (scintigraphy). Technetium-99m (^{99m}Tc) is the most used radionuclide in 99% of nuclear medicine prescriptions. ^{99m}Tc is obtained by elution from "^{99}Mo/^{99m}Tc radionuclide generators" delivered once or twice a week in each nuclear medicine department. This system allows the separation of the daughter radionuclide (^{99m}Tc) from the parent radionuclide (^{99}Mo) fixed on a chromatographic column loaded with aluminium oxide ($Al2O_3$). The amount of ^{99m}Tc recovered (Elution yield) depends on the efficiency of this system relative to the physicochemical interactions of the eluent (Isotonic Sodium chloride) with the adsorbate (^{99}Mo/^{99m}Tc) and the stationary phase ($Al2O_3$).

In this study, we worked on the optimization of the "^{99}Mo/^{99m}Tc Radionuclide Generators". First, we characterized the chemistry surface of α alumina used as stationary phase according to particles sizes distribution, contact time and pH ranges. Therefore, we identify new quality control parameters and specifications for α alumina powder in order to produce homogenous batches of alumina columns and finally more reproducible yield generators.

The main parameters checked were: particle size, specific surface and surface chemistry. We evaluated alumina's charge density by identifying four parameters: active sites number (SN), alumina surface charge (Q), zero charge point (ZCP) and isoelectric point (IEP).

Then, we studied the adsorption of molybdenum on this alumina in order to optimize the efficiency of the ^{99}Mo/^{99m}Tc generators.

It emerges from this study that alumina having particle sizes distribution between 63 and 200µm offers optimal acid-base properties, and that the mechanism of adsorption of molybdenum on $Al2O_3$ is by electrostatic type in the range of pH < 5. Between pH 5 and 7 the molybdenum is adsorbed molecularly, while it is carried out by ion exchange at pH higher than 7.

The maximum adsorption level is carried out at pH 4.

The columns filled with alpha alumina conditioned at pH=4 offer the best performance in terms of yield generators.

PS2-48

Effect of autoclaving, activity concentration and ethanol on the stability of [^{18}F]-FDG

Author: Adrian Duran[1]

Co-author(s): Jaime Palatnik[1]; Erica Heringer[1]; Sabrina Seidel[1]; Rebeca Vargas[2]; Jonathan Santiñan[2]; Fabiana Rodriguez[2]; Alicia Coronel[2]

[1]FCDN/CNEA, Italy
[2]FCDN, Italy

Corresponding author: aduran@fcdn.org.ar

The molecule of [^{18}F] -FDG decomposes over time due to different factors. Among these are the following: pH, temperature of storage and the phenomenon of radiolysis that intensifies when the radiopharmaceutical is produced in high concentrations. In the facility where this study has been carried out, concentrations of up to 110 mCi / ml of [^{18}F]-FDG are usually produced and a sterilization cycle is applied by autoclaving. Under these conditions the degradation process of the molecule is increased. It has been documented that the control of pH, temperature and the use of free-radical scavengers such as ethanol are strategies that slow down this process. In this work, the effect of autoclaving, the activity concentration and the incorporation of ethanol were studied on the stability of the [^{18}F] -FDG molecule by periodically determining the radiochemical purity for nine hours. These studies verified that the application of a cycle of autoclaving and a high concentration of activity produce a greater degradation of [^{18}F]-FDG molecule over time. On the other hand, ethanol fulfilled the role of stabilizer by significantly increasing the stability of the radiopharmaceutical over time. In conclusion, a 0,3% of ethanol was added, and the final product was stable up to 9 hours after EOS.

PS2-49

Enantiomeric purity of radiolabelled amino acids is influenced by the type of chiral column

Author: Olga Fedorova[1]

Co-author(s): Michail Nadporojskii[2]; Raisa Krasikova[1]

[1]Bechtereva Institute of the Human Brain Russian Academy of Sciences
[2]St. Petersburg State Institute of Technology

Corresponding author: fedorova@ihb.spb.ru

The amino acid based radiotracers labelled with ^{11}C or ^{18}F are of significant importance for imaging cerebral tumours with PET. Both biodistribution and kinetics of L-isomers of amino acids are known to be different from those for D-isomers, and the L-configuration is generally preferred for brain

tumours imaging. Therefore, the enantiomeric purity (EP) test is an important part of quality control of L-[^{11}C-methyl]methionine ([^{11}C]MET), O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) and other clinically relevant PET radiotracers. Despite of the use of enantiomerically pure precursors, racemization may occur during radiolabelling process by lowering the EP. In common practice, the EP control is performed by chiral radioHPLC by using two types of columns: Crownpak CR(+) (Daicel) containing crown ether stationary phase or Chirobiotic T (Astec) with sorbent based on covalently binding glycoproteins to silica gel. Quality control (QC) analysis with Crownpak column required an aqueous perchloric acid, pH 1-2, as an eluent; care must be taken for the use of organic solvents destroying the column capacity. On the contrary, Chirobiotic column is compatible with any type of buffers and organic solvents facilitating its use and handling during QC routine. However, when transferring our QC routines from Crownpak CR(+) to Chirobiotic T, we observed some discrepancy in the results. Therefore, we decided to perform a systematic study of the above mentioned columns via analysis of the same batches of [^{11}C]MET and [^{18}F]FET.

HPLC analysis was performed by using Dionex ISC-5000 system equipped with a gradient pump, Rheodyne type injector with a 20 µL loop, UV absorbance detector with variable wavelength connected in series with a radiodetector, Carrol and Ramsey Associates, CA, USA, model 105-S. The system 1 consists of Crownpak CR(+) column, Daicel (150x4,0 mm), eluent HClO4, pH 2 for [^{11}C]MET and $HClO_4$, pH 2 +10% MeOH for [^{18}F]FET. The system 2 includes Chirobiotic T, Astec (250x4,6 mm), eluent 20% aqueous EtOH for [^{11}C]MET and 0,1% TEA acetate, pH 4, containing 20% of EtOH, for [^{18}F]FET.

For both radiotracers the use of Crownpak (+) gives a lower EP value comparing with Chirobiotic T column. The difference in the EP value between the columns was in range of 2,4-4,0% for the same sample of the radiotracer. Interestingly, for both columns the five-fold dilution of the analytical sample resulted in 1.5% increased content of L-isomer. In addition, we analyse a series of cold methionine solutions prepared with different ratios of L- and D- enantiomers. We observed the overestimated value for D-isomer for Crownpak (+), whereas its content was underestimated by using Chirobiotic T. The deviation from the calculated (theoretical) value of D-isomer was from 0,67 to 1,92%.

Our results showed that determination of the EP of amino acids radiotracers may be influenced by the type of chiral column and the analytical sample dilution. This study will be continued to include different amino acids.

PS2-50

Quality control of ^{68}Ga radiopharmaceuticals: pitfalls and solutions

Author: Anton Larenkov

Co-author(s): Alesya Maruk; Galina Kodina

Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, Russia

Corresponding author: anton.larenkov@gmail.com, amaruk@list.ru

Gallium-68 is a generator produced radionuclide with optimum nuclear physical characteristics which makes it an important isotope for positron-emission tomography.

Radiochemical purity (RCP) is an extremely important parameter for radiopharmaceuticals (RPs) and its determination is a critical point of QC in routine clinical practice. Knowing the exact value of content of every radiochemical impurity is very important during R&D of [^{68}Ga]Ga-RPs as well. The results of evaluation of [^{68}Ga]Ga-RPs using various TLC and HPLC procedures were compared and presented previously and it was shown that HPLC results do not always match TLC results. In a number of cases results of HPLC analysis of ^{68}Ga conjugates were performed according to 9th Ph. Eur., whoever its recommendations do not reflect the real unbound gallium-68 content in radiopharmaceutical preparations. This uncertainty comes from nonspecific sorption of unbound gallium-68 on C18 phase. The aim of this study was to fix the weakness of HPLC analysis procedure, since in some cases it can be difficult to replace.

It was found that in pH range from 3 to 6, there is a significant capture of the gallium-68 ionic forms on the reversed phase of the HPLC column. The value of the capture also depends on the nature and concentration of the buffer agent in the preparation. The nature of this phenomenon is a subject of pure radiochemistry. New data shedding light on this effect will be presented.

It is highly probable that the same effect can occur when analysing other metal-based RPs (such indium-111, lutetium-177, etc.). To date some very interesting correlations between chromatographic behaviour during QC of gallium-68 and zirconium-89 were found and will be presented.

In order to avoid the capture of unbound gallium-68 on the column during HPLC analysis new procedure of sample processing and analysis was developed. The procedure involves usage of chelators in order to prevent gallium-68 sorption on the column. For this purpose, DTPA, DOTA, NOTA and HBED were evaluated. The details of their influence on the course of analysis will be presented.

PS2-51

^{89}Sr and ^{90}Sr/^{90}Y activity by Cherenkov counting in medical ^{99}Mo quality control

Author: Lucas Piola

Co-author(s): Alexis Dukart; Claudia Osuna; Juan Merino

1INVAP S.E., Av. Cmte. L. Piedrabuena 4950, S. C. de Bariloche, Río Negro, Argentina

Corresponding author: LPiola@invap.com.ar

Medical Molybdenum-99 (^{99}Mo) is a fission product of uranium ^{235}U, process in which more than 200 different radionuclides are produced. Strontiun-90 (^{90}Sr) and strontium-89 (^{89}Sr) are byproducts of this fission and their activity must be quantified to meet the quality standards required by the European Pharmacopoeia 9.0. Total radioactivity due to ^{90}Sr and ^{89}Sr must not exceed 6 x 10-5 per cent of the total radioactivity.

^{89}Sr and ^{90}Sr decay by β emission solely and their activities can be measured by Cherenkov counting, with counting efficiencies of 42 % and 1 % respectively. Yttrium-90 (^{90}Y), the daughter nuclide of ^{90}Sr, is useful for the indirect measurement of the ^{90}Sr activity by Cherenkov counting (counting efficiency 72%).

The goal of this study is to obtain separate ^{89}Sr and ^{90}Sr activities by Cherenkov counting after chromatographic separation of Sr from Y.

Known activities of radionuclide standards (^{89}Sr and ^{90}Sr) were mixed together and treated as real samples. Eichrom Sr® resin, 2 mL packed cartridges were used to separate the strontium mixture from yttrium prior to Cherenkov counting using Triathler Liquid Scintillation Counter (Hidex).

The time of separation of the Sr mixture was recorded as the start of yttrium ingrowth and cartridges placed in sealed bags for use in ^{90}Y separation following ingrowth period. After chromatographic separation, the elution containing Sr (10 mL) was measured for 30 minutes. One week later, Sr strip solution used for Cherenkov counting was transferred to the appropriate Sr resin cartridge. Time of separation of yttrium was recorded as stop time for yttrium ingrowth and samples were prepared for Cherenkov counting.

Strontium nitrate ($Sr(NO_3)2$) was used as yield tracer and measured using a Agillent 5110 ICP-OES Instrument.

The chemical yield of Sr for the chromatographic separation was 97.2 ± 2.5 % while the Cherenkov counting efficiencies for ^{89}Sr, ^{90}Sr and ^{90}Y were 40.5 ± 2.2 %, 0.5 ± 0.1 % and 71.5 ± 2.9 % respectively. ^{89}Sr activity was calculated considering: Sr and background count rates, ^{89}Sr and ^{90}Y Cherenkov counting efficiency, Sr yield, ^{90}Y in-growth factor, ^{89}Sr and ^{90}Sr decay correction.

The difference between the activity of ^{89}Sr standard added and Cherenkov activity of Sr measured was 7.7 ± 4.9 %.

^{90}Sr activity was calculated based on ^{90}Y Cherenkov counting, considering: ^{90}Y and background count rates, 90Y Cherenkov counting efficiency, Sr and Y yields, ^{90}Y in-growth factor and decay correction. The difference between the activity of ^{90}Sr standard added and Cherenkov activity of Sr calculated was 9.4 ± 5.2 %.

Cherenkov counting turned out to be very useful for the activity determination of ^{89}Sr and ^{90S}r when both are present in a sample.

PS2-52

Implementation of a quality assurance program and quality control results of radiopharmaceuticals

Author: Kirill Skovorodko
Co-author: Rūta Urbanavičiūtė

Vilnius University Hospital Santaros Klinikos, Lithuania

Corresponding author: kirill.skov@gmail.com

In accordance with international guidelines and recommendations, the quality assurance (QA) program should cover all clinical aspects of nuclear medicine related to the smooth operation, including quality control (QC) of radiopharmaceuticals. In order to reduce risk of repeated studies, misinterpretation of the images and to protect patient from unnecessary radiation exposure due to poor quality radiopharmaceuticals, QC procedures should always be performed on a daily basis prior to radiopharmaceutical administration by appropriately trained personnel. The objective of this study was to evaluate quality control results of technetium (^{99m}Tc) based radiopharmaceuticals and to determine the molybdenum (^{99}Mo) content in a ^{99}Mo/^{99m}Tc generator eluate.

The data was collected from November 2017 till February 2019 in Vilnius University Hospital Santaros Klinikos nuclear medicine department. In this study, two methods of quality control were conducted: radionuclidic and radiochemical purity. For estimating radionuclidic purity of a ^{99}Mo/^{99m}Tc generator (manufacturers: POLATOM POLGENTEC and GE Drytec) ^{99}Mo breakthrough test in a pertechnetate solution of ^{99m}Tc was done. ^{99}Mo assayed was measured with Veenstra VDC- 405 radionuclide activity calibrator. The dose calibrator QA and QC were performed routinely according to local and international recommendations including intercomparison measurements that performed Centre for Physical Sciences and Technology, Ionizing radiation metrology laboratory with secondary standard radionuclide calibrator Capintec CRC-15R. For ^{99m}Tc (^{99m}Tc-MIBI; ^{99m}Tc-MAA; ^{99m}Tc-MDP; ^{99m}Tc-MAG3; ^{99m}Tc-DTPA; ^{99m}Tc-DMSA) labelled radiopharmaceuticals, radiochemical purity Biodex Tec-Control thin-layer chromatography (TLC) system was used. The Sigma-Aldrich Chemie solvents and reagents were used to perform each chromatography test. All the radiopharmaceutical preparations were performed according to manufacturer instructions.

^{99}Mo breakthrough tests of radionuclidic purity (n=192) were 0.0028 ± 0.011%. According to inter- national guidelines and vendors recommendations the limit allowed is 0.1% for contamination by ^{99}Mo. Radiochemical purity results for ^{99m}Tc-MAA was 99.11 ± 1.49% (n=14); for ^{99m}Tc-MIBI was 90.87 ± 5.01% (n=41); for ^{99m}TC-MDP was 98.51 ± 2.55% (n=24); for ^{99m}Tc-MAG3 was 98.11± 1.29% (n=21); for ^{99m}Tc-DTPA was 97.46 ± 2.93% (n=19); for ^{99m}Tc-DMSA was 95.73 ± 3.85% (n=8), respectively. For most radiopharmaceuticals, the lower limit of radiochemical purity is 95%. In our department, the results of QC for almost all radiopharmaceuticals were at the acceptance level, only for ^{99m}Tc-MIBI tests the values were slightly lower than European Pharmacopoeia limits (≥94%). In daily practice we use thin-layer chromatography and radionuclide activity calibrator.

In nuclear medicine, an administration of correct radiopharmaceuticals activity to the patient is strongly dependent on the accuracy of the QC measurements of all equipment. It is important to have a product with acceptable quality control parameters in order to make the study of nuclear medicine effective and to protect the patient from unnecessary radiation exposure. In our daily practice we successfully implement thin-layer chromatography method for ^{99m}Tc labelled radiopharmaceuticals and radionuclidic purity in a ^{99}Mo/^{99m}Tc generator eluate. In order to improve our QA program, in the future we need to start QC procedures with TLC-scan systems.

Track: Production of radionuclide generators

PS2-53

Production of radionuclide generators: the Cuban experience

Author: Alejandro Alberti Ramírez[1]

Co-author(s): Jorge C. Cruz Arencibia[1]; Amed Cruz Morales[1]; René Leyva Montaña[1]; Jozef Comor[2]; Madian Pino Peraza[1]; Rolando Serra Aguila[1]; Marilín Castro Isaac[1]; Miguel A. Soria Guevara[1]

[1]Centro de Isótopos (CENTIS), Cuba
[2]Electrónica Commerce, Cuba

Corresponding author: alberti@centis.edu.cu

Radionuclide generator systems continue to play a key role in providing both diagnostic and therapeutic radionuclides for various applications in nuclear medicine. The generators represent important in-house production systems that can provide daughter radioisotopes generated by parent decay on-demand without the need for local access to an accelerator or nuclear reactor. Cuba has not had accelerators or reactors for many years, so its radionuclide and radiopharmaceuticals production is based mainly on importation or local generators production. The present work resumes the Cuban experience in the production of radionuclide generators.

As it is known, the most widely used generator for clinical applications is the ^{99}Mo/^{99m}Tc generator system. In CENTIS facilities, the production of this product began in 2003 using the column chromatography method as a separation technology. More than 4 000 generators have been produced in different presentations (8GBq, 20GBq, 37GBq, 55,5GBq and 74GBq) during these years. A summary of the production process parameters and quality control results of the last five years is reported. Based on the data, it is concluded that a stable production process has been established.

On the other hand, the success in the development of therapeutic radiopharmaceuticals has driven the development of generators that provide therapeutic radionuclides. In 2010, Cuba received the first prototype of ^{90}Sr/^{90}Y generator based on an electrochemical separation for its evaluation and setting up as a part of a Technical Cooperation Project with the IAEA (Project CUB/2/015). Several parameters for the separation of ^{90}Y with the required quality were evaluated and the results are reported here. In consequence, the final technological procedure was established and the first national authorization to produce radiopharmaceutical quality grade of ^{90}Y was issued in December of 2011.

Among many other requirements one of the main challenges for our radionuclide generators production has been the need to manufacture and operate under the conditions of good manufacturing practices (GMP) guidelines since these products represent final product or active pharmaceutical ingredients (APIs) which will be incorporated into radiopharmaceutical products prepared for human use. In the present work, we included the necessary modifications performed to our ^{99}Mo/^{99m}Tc generators production and the conditions established for the production of ^{90}Y to comply with the current GMP guidelines.

PS2-54

Design and development of an automated mini-plant for ^{99m}Tc production

Author: Eleazar Aliaga[1]; Pablo Mendoza[1]

Co-author(s): Rafael Urquizo[1]; Jorge Rojas[1]; Julio Santiago[1]; Yon López[2]

[1]Instituto Peruano de Energia Nuclear IPEN, Lima, Peru
[2]UNM San Marcos, Peru

Corresponding author: ealiaga@ipen.gob.pe

A mini plant has been designed and developed to obtain ^{99m}Tc from irradiated MoO_3 pellets. This mini plant has a maximum capacity of 37 GBq and is constituted by three modules where the operations of dissolution of MoO_3, extraction of ^{99m}Tc and evaporation of the solvent are carried out. The mini plant is completed with a module for the injection of the necessary chemical reagents and a module for obtaining an isotonic solution of ^{99m}Tc with the required activity. All the modules except for the separator and evaporator are communicated by Serial RS485 with a main control panel. They operate independently through a set of interconnected electrovalves, which are activated sequentially to execute each stage during the process of obtaining ^{99m}Tc. The mini plant has a vacuum pressure system necessary to carry out the transport of radioactive material between the various modules. It also has a SCADA system displayed on a touch screen HMI, which allows the control and monitoring of each stage. The implementation of the entire main control system was carried out in a PLC programmable logic controller and the modules under microcontrollers.

PS2-55

Recovery of highly pure ^{99m}Tc from low specific activity (n,g)^{99}Mo using activated charcoal column

Author: Sankha Chattopadhyay

Co-author(s): Sujata Saha Das; Madhusmita; Md. Nayer Alam; Shayantani Ash; Umesh Kumar; Sharmila Banerjee

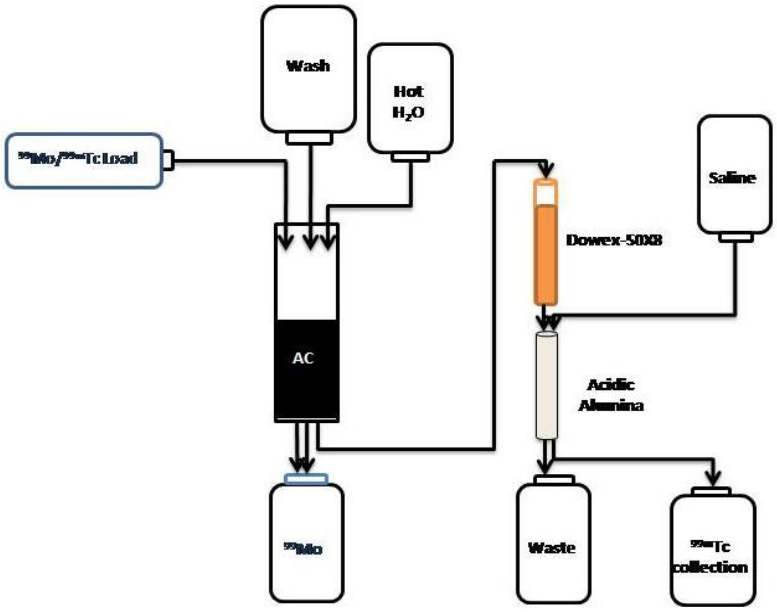
BRIT, DAE, Mumbai, India

Corresponding author: sankha@vecc.gov.in

Technetium-99m [t1/2= 6.02h; 140.51 keV (89%)] continues to be the workhorse isotope in diagnostic nuclear medicine till today. Therefore, various methods of sourcing this isotope constitute a relevant field of research. The methods which are exposed to produce ^{99}Mo are ^{98}Mo (n, g) ^{99}Mo in a research reactor, ^{100}Mo (p, x) ^{99}Mo or ^{99m}Tc directly through ^{100}Mo (p, 2n) ^{99m}Tc, in a cyclotron,100/natMo(g,n)^{99}Mo, in a linear electron accelerator. Herein we report a new ^{99}Mo/^{99m}Tc generator based on column chromatographic technique using activated charcoal in tandem with a small cation exchanger column and an alumina column utilizing (n,g)^{99}Mo, to produce highly purified Na[^{99m}Tc]TcO_4.

Molybdenum-99 produced from irradiation of natural MoO_3 through ^{98}Mo(n,g)^{99}Mo reaction was supplied as [^{99}Mo]Na_2MoO_4 in 0.5 M NaOH (150 mg Mo/ml:1.11–2.22 GBq/ml), by the Radiochemical Section, Radiopharmaceutical Division, Bhabha Atomic Research Centre (BARC) and Board of Radiation & Isotope Technology (BRIT), Mumbai, India. The pH of the [^{99}Mo]Molybdate solution was adjusted to pH-3 using dilute nitric acid and the solution was loaded to a preconditioned powdered charcoal column (500mg) with a flow rate of 1.5ml/min. The column was washed with H2O followed by a dilute of NaOH to remove ^{99}Mo. The adsorbed ^{99m}Tc was then eluted from the charcoal column with hot H2O. The ^{99m}Tc eluate was further purified by passing the ^{99m}Tc solution through a tiny Dowex-50X8 column (500mg) connected in tandem with a small acidic alumina column (1g). Finally, highly pure sodium ^{99m}Tc-pertechnetate was recovered from acidic alumina column with 3-5 ml saline. The whole process flow diagram is shown in Fig. 1. The performance of the new ^{99}Mo/^{99m}Tc generator based on activated charcoal column chromatography was evaluated by studying recovery yield of ^{99m}Tc, physicochemical qualities of ^{99m}Tc-pertechnetate and radiolabelling of ^{99m}Tc-pertechnetate with kits like MDP, DTPA & MIBI obtained from BRIT, Mumbai, India.

Fig. 1. Flow diagram of charcoal column chromatography based $^{99}Mo/^{99m}Tc$ generator



It was found that the adsorption of ^{99m}Tc on charcoal column from $^{99}Mo/^{99m}Tc$ solution (pH-3) was around 90-95% (n=5) in comparison to that of alkaline or neutral $^{99}Mo/^{99m}Tc$ solution where it was 35-60%. The average yield of recovery of ^{99m}Tc was above 80%. The quality control studies showed that ^{99m}Tc-pertechnetate has the following characteristics: i) Clear solution; ii) pH: 6-7; iii) ^{99}Mo breakthrough: <0.002%; iii) Mo and Al impurities: < 10 ppm; iv) RC Purity: >99% and v) RN Purity: >99.9%. The RC purities of ^{99m}Tc-compounds like ^{99m}Tc–MDP, ^{99m}Tc–DTPA and ^{99m}Tc-MIBI were found to be above 95% (n=6).

In conclusion, an efficient technique has been developed to recover ^{99m}Tc as $Na[^{99m}Tc]TcO_4$ formulation in good yield and high quality from a research reactor produced (n, g)^{99}Mo.

PS2-56

Development of Ge-68/Ga-68 radionuclide generator for nuclear medicine

Author: Kateřina Fialová

Co-author(s): Kryštof Adámek; Martin Vlk; Ján Kozempel; Ferdinand Šebesta

Faculty of Nuclear Sciences and Physical Engineering, Czech Technical University in Prague, Czech Republic

Corresponding author: katerina.fialova@fjfi.cvut.cz

The Ge-68/Ga-68 radionuclide generator has a big perspective to become one of the most important sources of radionuclides for PET. Recently, available generators inorganic ion exchangers, especially titanium and tin oxides, are used as a stationary phase and diluted hydrochloric acid as eluent. Even though they provide Ga-68 in convenient chemical form, some of them do not provide it in a sufficient radionuclidic purity in one separation step as the Ph. Eur. limit for the mother radionuclide is 0.001%. This work was focused on the development of Ge-68/Ga-68 generator system based on the nanocomposites of cerium(IV) and zirconium(IV) in the polyacrylonitrile matrix. These perspective stationary phases should provide eluate in excellent quality.

Cerium(IV), zirconium(IV) and titanium(IV) oxides and hydroxides were studied as potential active ion-exchanger components. All materials were characterized by X-ray powder diffraction, transmission and scanning electron microscopy, FT-IR and Raman spectrometry. Sorption properties of these materials were examined by the measurement of equilibrium distribution coefficients, Dw, of Ge-68 and Ga-68 in the presence of diluted hydrochloric acid (concentrations: 1 mol/l; 0.1 mol/l; 0.01 mol/l and 0.001 mol/l). On the basis of the separation factor, α, the optimal concentration of hydrochloric acid was determined and two materials with the best separation factor, cerium(IV) oxide and zirconium(IV) hydroxide, were granulated into the polyacrylonitrile matrix. Prepared composites were used for the construction of two model generators with bed volume of 0.57 ml and 1.6 MBq of Ge-68 and 1 MBq of Ge-68 for cerium(IV) oxide and for zirconium(IV) hydroxide, respectively. Elution curves, yields of elution and contamination percentages were determined for both prepared model generators.

Considering the separation factor, α, of Ge-68 and Ga-68 for individual acid concentrations, the optimal medium for separating these radionuclides is 0.1mol/l hydrochloric acid (α = 26 857 for cerium(IV) oxide and α = 4 949 for zirconium(IV) hydroxide).

The model generator containing cerium(IV) oxide as stationary phase provided Ga-68 with yields over 90 % in 1.6 ml of eluate and the contamination by Ge-68 was under 0.0004 %. Used flow rate was 0.32 ml/min. Even after 6 months of usage, the yield did not decrease under 60 % and the contamination remained under 0.0002 %. These observations probably relate to the increasing affinity of both radionuclides to the stationary phase over time and the radiation degradation of the composite can also play its role.

However, for the case of model generator based on zirconium(IV) hydroxide, the yield of Ga-68 elution was considerably lower than in the case of cerium(IV) oxide generator under the same conditions of elution and also the contamination by Ge-68 exceeded the limit of 0.001 %.

Experiments with model generators gave us some very promising results and in the upcoming study the separation qualities and radiation stability of cerium(IV) oxide composite has to be confirmed using higher activities of Ge-68.

Acknowledgements: this work was supported by Technology Agency of The Czech Republic, grant no. TJ01000334 and the Health Research Agency of the Czech Republic, grant no. NV16-30544A.

PS2-57

Selective separation of no carrier added Sc-47 from reactor irradiated Ca using zirconium vanadate gel for nuclear medical applications

Author: Mohamed El-Gizawy

Co-author(s): Mohamed Aydia; Hesham Shamsel-Din; Khaled Al-Azony

Egyptian Atomic Energy Authority, Cairo, Egypt

Corresponding author: dr_mgizawy@yahoo.com

In recent decades, great efforts have been paid for the development of radiopharmaceuticals which can be used for combined imaging and therapy or briefly, for radiotheragnostics. This approach of employing one molecular vector to render diagnosis beside targeted radiotherapy claim the parallel expansion in the production and separation of radioisotopes of dual purposes. One of these radioisotopes which received great attention, scandium-47, due to its favourable nuclear and chemical properties [T½ = 3.35 d, Eβ-(max.) = 600 keV, Eγ = 159 keV]. In this context, it seemed of interest to study the production and separation of Sc-47 and this work spotlights on the rapid and effective separation of no-carrier-added (NCA) Sc-47 from natural Ca targets using inorganic ion exchanger.

A target of 1 gm of natural calcium carbonate was irradiated in the ETRR-2 Research Reactor, Egypt, at a thermal neutron flux of 1.8 x 1014 n cm-2 s-1 for 24 h. zirconium-vanadate gel was prepared following the method published by Roy, et al. and studied as a sorbent material for the separation of ^{47}Sc(III) from ^{47}Ca(II). The Influence of HCl and HNO_3 concentrations on the distribution coefficients of ^{47}Sc(III) and ^{47}Ca(II) ions was investigated by batch technique. Chromatographic column separation of ^{47}Sc(III) from ^{47}Ca(II) was carried out using the prepared zirconium vanadate gel. Finally, the radionuclidic and radiochemical purities of the eluted ^{47}Sc(III) were examined.

The results obtained from the batch adsorption studies revealed that the adsorption efficiency of ^{47}Sc(III) ions is strongly dependent on the initial acid concentration and high adsorption can be obtained at 0.001 M HCL and HNO_3. Conversely, the change in acid concentration not affect the ^{47}Ca(II) ions adsorption. These results are in concordance with numerous studies in which the ionic radius of one ion is smaller than the other. This finding made us consider the possibility of radiochemical separation of ^{47}Sc(III) from ^{47}Ca(II) using zirconium vanadate gel ion exchanger packed column, where ^{47}Sc(III) is substantially retained at 0.001 M HNO_3 without any remarkable adsorption of $_{47}$Ca(II) ions. 1 M HNO_3 directly eluted the retained ^{47}Sc at a flow rate of 1 ml/min with elution yield of 75%. The eluted ^{47}Sc with high radiochemical and radionuclidic purities.

In summary, Zirconium vanadate gel is an effective material for separation of ^{47}Sc(III) from irradiated Ca target with high yield and high purity and our results thus hold a great promise for the use of ^{47}Sc(III) in the preparation of radiopharmaceuticals for theranostics applications.

PS2-58

Evaluation of alternatives for the removal of heat within the Mo-99 production cell by fission from the estimation of the radionucleidic composition and power of filters with uranium precipitate

Author: Maria Victoria Gonzalez

Co-author(s): Agustin Marticorena; Luis Gonzalez; Fernando Braun

INVAP SE, Argentina

Corresponding author: mvgonzalez@invap.com.ar

Mo-99 is the most widely used radionuclide in the field of nuclear medicine.

The Mo-99 production facilities must be designed by taking into account the minimization of fission gas emissions, complying with the regulations in force according to the regulatory authority of each country.

It is important to know the stages of the production process that generate the greatest amount of fission gases to take the necessary precautions to reduce their emissions in the facility.

The production process of Mo-99 begins with the irradiation of uranium mini-plates in a research reactor originating more than 250 radioactive species among which is the Mo-99.

The separation process of Mo-99 consists of several separation and purification stages that are carried out in shielded hot cells, due to the high activity contained in the irradiated plates coming from the reactor.

One of the first steps is the dissolution of the plates in an alkaline medium and filtration. During this stage, large quantities of radioactive gases are released, where the most important are radioiodines and radioxenons accompanied by a large amount of heat generated.

The resulting uranium precipitate is stored in the production of hot cells for months to decay.

The removal of the heat generated by the uranium precipitate holders is very important because it is necessary to maintain the temperature inside the cell below 45 ° C, in order to prevent damage of the sealing gasket material used in the containment box. In addition, each uranium precipitate holder must be sealed in order to contain the fission gases.

The present work describes the evaluation of alternatives for the heat removal in the cell whose purpose is to converge in the design of the ventilation of the plant to avoid the emission of these gases outside the facility.

The radionuclide composition of the uranium precipitate contained in the filters and the power generated were simulated by using the NUCLEONICA® software paying attention to these fission gases and their evolution inside the filter holder, highlighting the importance of ensuring tightness in the filter holder in the first 8-10 weeks.

For the removal of the heat in the dissolution cell, two cases were studied using the computational fluid dynamics code (CFD) ANSYS FLUENT®; cooling of the filters with air outside the enclosure and cooling of the filters with ventilation air inside the enclosure.

The input data for the simulation in FLUENT were those obtained in NUCLEONICA.

As a conclusion, it is proposed to refrigerate the filters with forced ventilation outside the enclosure; in this way the refrigeration of the filters is not interrupted, keeping below the required temperature inside the enclosure during the 8-10 weeks for the decay of the gases nobles avoiding their emission to the ventilation system.

PS2-59

Fluorine-18 production yield in an 11 MeV medical cyclotron: comparison of theoretical and practical yields

Author: Dilshad Kottuparamban

Co-author(s): Anees Muhammed K; Raviteja Nanabala; Ajith Joy; M.R.A. Pillai

Molecular Cyclotrons Pvt Ltd, India

Corresponding author: dilshadk@moleculargloba.com

Fluorine-18 is one of the important positron emitting radionuclides that is used for the preparation of an array of diagnostic radiopharmaceuticals. Low energy (11-18 MeV) cyclotrons are used for this purpose in which oxygen-18 enriched water is irradiated with 11-18 MeV protons. The yield of production depends on several factors including beam current, beam energy and time of irradiation. A systematic assessment of fluorine-18 production in a newly installed 11 MeV Siemens Eclipse HP cyclotron is presented in this paper.

Siemens Eclipse HP cyclotron, having a dual beam with current up to 60 µA, each beam line is used for the production of fluorine-18. 2.6 mL of 97% oxygen-18 enriched water where it was loaded to one of the tantalum targets. The loaded oxygen-18 water in the target was then pressurized using argon gas up to 375-385 psi. 11 MeV proton beam was extracted from negative hydrogen beam using a carbon extraction foil and it was directed to the tantalum target. The proton beam traversed through a copper hex grid, 25 µm target window (Havar foil) and the water target, respectively. The formed activity was measured in a dose calibrator and compared with the theoretical yield calculated as described below.

Energy reduction of the proton beam in the Havar foil and in the water was calculated using Stopping and Range of Ions in Matter (SRIM). Stopping power and range of proton in water are calculated in the PSTAR programme of the National Standards and Technology (NIST). Cross-section data of $^{18}O(p,n)^{18}F$ are referred from the IAEA EXFOR library. The total range of the proton beam in water was divided into smaller segments of micrometre level and the production rate of fluorine-18 was calculated for each segment. Integration of these segments gave the total fluorine-18 production rate. For more accurate approximation of the calculation, proton scattering with hydrogen nuclei was also considered.

Fluorine-18 yields were calculated by two means. In the first method, yields were calculated by taking the standard equation accounting for the proton flux, cross section and the number of target nuclei. These values were significantly lower than the experimental values. In the second method, scattering of the protons with the hydrogen nuclei in water was also considered to calculate the theoretical yield of fluorine-18 formed. The yield calculated by this modified method was comparable with the practical yield obtained. Elastic scattering of proton with the hydrogen nuclei in water molecule provided a significant contribution to the fluorine-18 production providing better theoretical approximation that are comparable to the practical measurements of fluorine-18 production. Since the literature about the elastic scattering of proton with the hydrogen nuclei in water are only a few, this study adds as a proof for the p-p scattering in water.

PS2-60

Production, separation and purification of In-111 from irradiated natural CD: produced In-111 quality evaluated after radiolabeling with pentetreotide

Author: Kanchan Kushwaha

Co-author(s): Arpit Mitra; Sangita Lad; Rahul Bhoite; Sudeep Sahu; Milan Dey; Pravind Maletha; Ashis Satpati; Sharmila Banerjee

Medical Cyclotron Facility, Radiation Medicine Centre, BARC, Mumbai, India & HBNI, Mumbai, India

Corresponding author: kkanchan-pari@gmail.com

In-111-Pentetreotide (OCTREOSCAN®) is a commercially available FDI approved SPECT agent for imaging of neuroendocrine tumours (NET). However, production of the medically important In-111 in a medical cyclotron for formulation of In-111 Pentetreotide metallic radioisotope, using prototype semi-automated indigenously developed solid-target assembly, and its radiochemical separation from irradiated natural Cd possess is a considerable challenge.

Towards this, we explored the possibility of producing In-111 using natural Cd targets (electroplated on copper discs) via Cd-111 (p, n) In-111 nuclear reactions, in the 16.5 MeV medical cyclotron. Column chromatography separation of In-111 from target matrix and other radionuclides formed as activation products were performed to obtain purified In-111-chloride. The purity of the separated In-111-chloride was established after radiolabelling with pentetreotide. Consistent yield of pure In-111-Pentetreotide provided support to the formation of In-111 of required purity.

The present work thus envisages cost-effective and pharmaceutical grade production of In-111-chloride in the 16.5 MeV cyclotron as a cost-effective diagnostic radiopharmaceutical for patients with neuro endocrine tumours.

Natural cadmium was electrodeposited over circular copper disc (diameter: 25 mm and 2 mm thick) using non-cyanide bath. Electrodeposited natural cadmium target was irradiated by 15.5 MeV (after attenuation from havar foils) proton beam for 1h at 5µA current using indigenously developed solid target assembly. The irradiated disc was decayed for 24h prior separation to remove other short-lived radioisotopes. Radiochemical separation was carried out by co-precipitation with 8M HCl and concentrated HBr and column-based ion exchange chromatography using acidic alumina oxide and Dowex-50W-X-4, 200-400 dry mesh, H+ form. RCP of purified In-111-chloride was evaluated by HLPC using RP18 in gradient mode (0.1%TFA in water and acetonitrile) coupled with NaI(Tl) and UV(220 nm) at 1mL/min. Radionuclidic purity assessed by γ-spectrometry in 64K-MCA coupled with HPGe detector. The purified In-111-chloride (220 µCi/mL) were radiolabelled with pentetreotide using citrate buffer containing gentisic acid as stabilizer. RCP of In-111–Pentetreotide assessed by HPLC.

Non-cyanide electroplating bath yielded 200µm thick electrodeposition of natural cadmium (diameter 15mm) on copper disc. Our route for producing In-111, using 200µm thick natural cadmium target offers maximum yield of 128 µCi/µAh at EOB(n=3). The radiochemical yield (RCY) of the purified In-111-chloride after radiochemical separation was ~45-50 %. The recorded γ spectrum of purified In- 111-chloride shows only two prominent characteristics peak (171 and 245 KeV) of In-111.

The RCP of In-111-chloride derived by HPLC was >98% with retention-time between 2.40–3.40minutes.

The RCP of the radiolabelled In-111-Pentetreotide(n=3) was >98% with retention-time between 30.5-31.5minutes. EL <6EU/mL and product were sterile. Retention of RCP on storage at -20degC, at 72h post-preparation was confirmed by the single radioactive peak (Rt: 31.4minutes) in HPLC chromatography.

In conclusions, the quality control parameters of the produced In-111-chloride from natural Cd target, using indigenously developed solid-target system were validated and compared to the pharmacopeia standard. The radiolabelling studies of pentetreotide, yielding the product in acceptable RCP establishes the quality of the In-111-chloride used and adds support to its use as a pharmaceutical grade radiochemical.

PS2-61

Worldwide ten-year trend analysis of the scientific literature on therapeutic radiometals (2008 - 2018)

Author: Petra Martini[1]

Co-author(s): Licia Uccelli[2]; Alessandra Boschi[2]; Corrado Cittanti[3]; Aldo Carnevale[3]; Loretta Missiroli[3]; Melchiore Giganti[3]; Mirco Bartolomei[2]

[1]INFN-LNL and University of Ferrara, Italy
[2]University of Ferrara, Italy
[3]UNIFE, Italy

Corresponding author: petra.martini@lnl.infn.it

Despite in the last decade a large number of papers on therapeutic radiometals (TRMs) have been published, a worldwide ten-year trend analysis of the scientific literature on this topic has never been made before. The aim of the present study is therefore to quantify and identify the global trend of scientific literature and emphasize the interdisciplinary nature of this research field by analysing the TRMs research output (2008-2018).

The Bibliometric data search, focused on conventional (^{131}I, ^{90}Y, ^{177}Lu, ^{188}Re, ^{186}Re, ^{153}Sm, ^{89}Sr, ^{169}Er) and emergent (^{67}Cu, ^{47}Sc, ^{223}Ra, ^{166}Ho, ^{161}Tb, ^{149}Tb, ^{212}Pb/^{212}Bi, ^{225}Ac, ^{213}Bi, ^{211}At, ^{117}Sn) TRMs, has been performed on Scopus database and elaborated with Excel. The data-analysis has been performed in terms of years of publication and TRMs category (conventional vs emergent) in order to illustrate the trend of the last decade. Moreover, with the aim to underline the multidisciplinary character of this research field, data have been categorized in terms of Journal-Subject-Areas. Finally, the authors' country provenience has been analysed with the aim to map the worldwide interest and investment of resources on TRMs. The 81.3% and 18.7% of the total number of publications, 12.717, regards conventional and emergent TRMs respectively. Among conventional, ^{131}I, ^{90}Y and ^{177}Lu while, among emergent, ^{223}Ra, ^{117}Sn, ^{213}Bi, and ^{225}Ac resulted as the most investigated TRMs.

The multidisciplinary character of the publications differs from conventional TRMs, where most contributions come from preclinical and clinical fields, to emergent TRMs. Thus, the major interest in their production studies makes the contribution unbalanced mainly for Physics, Engineering and Material Science fields. From the geographical analysis, it appears that almost half of the total number of works, on both conventional and emergent TRMs, have been published by European researchers. It is also evident the high collaboration grade between countries, characteristics in line with the multidisciplinary of this medical sector. Top 20 countries have also been drawn up. On the podium of conventional TRMs, there are USA, Germany, and China, while the USA, Germany, and the United Kingdom are on the podium of emergent TRMs. The overall conclusion is that the success of NM has been intimately linked to the availability of new TRMs. In recent years a particular focus on the production and application of emergent TRMs, such as ^{67}Cu, ^{47}Sc, has been encouraged by the interest in the theranostics personalized approach. ^{223}Ra and ^{225}Ac alpha emitters are also gaining attention particularly in the USA and Germany. Among conventional radionuclides, instead, the research on ^{177}Lu is constantly growing. In conclusion, the radiopharmaceuticals field is constantly evolving thanks to the contribution of specialists coming from different disciplines and the collaboration between countries.

PS2-62

Preparation of zirconium molybdate gel as material for $^{99}Mo/^{99m}Tc$ chromatographic column generator

Author: O. Odintsov

Co-author(s): V.V. Tryshyn; V.A. Ageyev

Institute for Nuclear Research NAS, Kyiv, Ukraine

Corresponding author: ooodin@ukr.net

The goal of present investigations is the implementation and optimization of the technological process for the synthesis of Zr-Mo gel from the high-active Mo samples after an irradiation in the WWR-M research reactor Institute for Nuclear Researches NAS of Ukraine. Production of the radiopharmaceutical sodium pertechnetate (^{99m}Tc) by means of the portable ^{99}Mo-^{99m}Tc generator. The Mo oxide (MoO_3) of 10 - 20 g in the sealed quartz ampoule was used as the target material; it has been irradiated by the neutron flux of 5×1013 n/cm2×s in the wet channel of the WWR-M reactor. The irradiate Mo oxide dissolves in the sodium hydroxide solution. The zirconyl chloride solution is prepared in advance, and then it is sterilized. The molybdenum solution was added to the zirconyl chloride solution by drops at the intensive mixing with heating. The temperature of mixture was equal to 50 °C. The gel draining is considered completed when it is possible to see the small gel pieces (the size less than 5 mm) of yellow-green colour. For the disintegration of pieces (i.e. transformation to the particles with the sizes from 100 to 500 μm) the hot sodium chloride isotonic solution is supplied from the sterilizing module. The filtration of excess water from the Zr-Mo gel was performed by means of the Shotta filter with the hole size up to 40 μm. Taking into account the big number of factors influencing the Zr-Mo gel synthesis, we have used the results of previous investigations, which have been used as the input data for the development of installation for the Zr-Mo gel synthesis.

The chromatography column with Zr-Mo gel (^{99m}Tc) is the Teflon tube equipped by the protruded outer grooves to close with rubber stoppers and the aluminium caps for the flasks. The glass wool tampon and the aluminium oxide for the chromatography are located in the column. In all cases the amount of aluminium oxide for the cleaning of ^{99m}Tc eluate from admixtures of ^{99}Mo and for the reaching of solution required acidity was equal to 2.0 g. The amount of Zr-Mo gel was in the range from 2 to 4 g. The elution of sodium pertechnetate ^{99m}Tc solution is carried out by means of the sterilized solution of sodium chloride 0,9 %. The efficiency of ^{99m}Tc elution is more than 70 %. The investigation of the elution efficiency was carried out by the radiometry method on the gamma-spectrometer. In all cases ^{99m}Tc was obtained by means of the portable generators. The ^{99m}Tc activity in the eluate was measured several days later after production. The remotely manipulated devise for the production of the Zr-Mo gel has been made, which will allow the treatment of the irradiated Molybdenum (MoO_3) samples. The design of ^{99}Mo-^{99m}Tc generator has been developed and constructed.

The physical and chemical parameters of the radiopharmaceutical sodium pertechnetate (^{99m}Tc) have been determined by means of the inductively coupled plasma methods, the gamma-spectrometry and the potentiometry. The radionuclide purity of sodium pertechnetate ^{99m}Tc exceeded the value of 99.9% during whole time of the generator availability. The radiochemical purity of sodium pertechnetate ^{99m}Tc is 99,4 %. The eluate acidity of the radiopharmaceutical sodium pertechnetate ^{99m}Tc is in the range from 4.6 to 6.3. The total activity of ^{99}Mo in the prepared generators was between the range from 10 to 13 GBq for the moment of supply to the medical institution in dependence on the Zr-Mo gel amount, which was putted into a chromatography column of generator. It was determined that the parameters are complying with the requirements of the Terms of Reference and the European Pharmacopoeia.

PS2-63

Photonuclear production of ^{67}Cu radionuclide using “one-stage” setup

Author: Alex Tsechanski [1]

Co-author(s): Valeriia Starovoitova[2]; Dmytro Fedorchenko[3]; Alexander Galperin[1]

[1]Ben-Gurion University of the Negev, Israel
[2]International Atomic Energy Agency, Vienna, Austria
[3]NSC Kharkov Institute of Physics and Technology, Poland

Corresponding author: atsechanski@gmail.com

^{67}Cu is one of the most promising beta-emitters for cancer treatment. It is also a gamma-emitter and thus can be used as a theranostic radioisotope either by itself or together with positron-emitting ^{64}Cu. One of the most efficient production routes for ^{67}Cu is photonuclear method based on the ^{68}Zn(γ,p)^{67}Cu reaction. Typically, a 30-40 MeV electron accelerator is used with Ta or W converter to generate bremsstrahlung X-rays, which irradiate the zinc target. However, relatively low reaction cross section (11 mb at 22 MeV) impedes obtaining high specific activities of the irradiated target. To improve the efficiency of the production and to increase the specific activity we propose a “one-stage” approach with zinc acting both as a converter and a target.

To evaluate ^{67}Cu production yield in the “one-stage” setup, we used the transport code PHITS (Particle and Heavy Ion Transport Code System). First, the spectral density of the bremsstrahlung photons flux was simulated; then it was convoluted with the ^{68}Zn(γ,p)67Cu reaction cross section from the IAEA Handbook on Photonuclear Data. Such approach reduces the statistical uncertainty of the calculated values and eliminates problems concerning the simulation of (γ,p) reaction using built-in PHITS models. Spatial distribution of the produced ^{67}Cu in a large zinc target was found and used to determine the optimal target dimensions to maximize ^{67}Cu specific activity. The results were compared to the conventional “two-stage” approach which uses a 2 mm thick tungsten converter and proved to yield higher specific activity. Depending on the target size, absolute values for the “one-stage” approach were found to range from 1.22 to 5.28 MBq/g for natural zinc target assuming 1-hour irradiation with 40 MeV 1 kW beam.

Monte Carlo simulation showed that the “one-stage” setup provides higher specific activity of the produced ^{67}Cu due to better utilization of the electron beam power. The drawback of this approach is high heat deposition into the target. Thermomechanical analysis of the system was performed to find maximum electron beam power the target can withstand.

Track: Production of PET- and SPECT-based diagnostic, therapeutic and theranostic medical radioisotopes

PS2-64

Fully automated liquid target production of [^{68}Ga]$GaCl_3$ in line with GMP requirements

Author: Antero Abrunhosa[1]

Co-author(s): Vitor Alves[1]; Angela Neves[1]; Cristiana Gameiro[2]; Jean-Michel Geets[2]; Francisco Alves[1]

[1]ICNAS/University of Coimbra, Portugal
[2]IBA, Belgium

Corresponding author: antero@pet.uc.pt

The increasing interest in the use of ^{68}Ga for theranostic application continues to grow requiring more sources of this radioisotope. Nowadays, due to the high demand and limited availability of (GMP) ^{68}Ge/^{68}Ga generators there is a long waiting list limiting the access to 68Ga-radiopharmaceuticals worldwide. IBA and ICNAS/University of Coimbra have developed a GMP liquid target process for the production [^{68}Ga]$GaCl_3$. At the same time, to support this initiative, the EDQM has accepted to work on a new monograph for the production of this isotope with a cyclotron. The first draft of this monograph (Gallium (^{68}Ga) chloride (accelerator-produced) solution for radiolabelling (3109)), was published for public consultation in the end of 2018 in Pharmaeuropa 30.4.

In this study, we will provide the quality control methods and results for the [^{68}Ga]Cl_3 produced from a liquid target and we will demonstrate that the quality obtained meets all the requirements set forth in the Eur. Ph. draft. We will also explain how to establish the shelf-life considering the regulatory aspects.

The process herein described is fully automated and employs commercially available systems: a dedicated liquid target system, where a solution enriched ^{68}Zn is irradiated; and a Synthera® Extension module for the post-process step to obtain purified and ready-to-use [^{68}Ga]Cl_3 for further labelling. The whole process can be put in a GMP environment. The quality control methods are based on the Eur. Ph. draft and the results will be reported. Most of the new monograph is based on the existing Eur. Ph. Gallium (^{68}Ga) Chloride solution for labelling 07/2013:2464, except for the radionuclidic purity. The major radionuclidic impurities are ^{67}Ga and ^{66}Ga, mainly because of isotopic impurities in the target material and the competing (p,2n) and (p,n) reactions. The new Eur ph. requires radionucludic purity (RNP) of > 98% and this RNP must be guaranteed over the entire shelf-life of the labelled compound. Another critical requirement (for the efficiency of the labelling) is the metallic impurities (Fe and Zn in µg/GBq), which is also challenging since the starting target material is zinc solution.

All of these parameters have been tested and validated against the current Eur. Ph. draft. Several batches have been produced and consistently meet the requirements with shelf-life ranging from 3-5 hours end of post process ($GaCl_3$) giving enough time for the labelling on site or even the possibility of some distribution to nearby radio pharmacies.

PS2-65

Study of the optimization of the use of the reducing agent in the formulation and production of Sodium Iodide-^{131}I oral solution

Author: Naoual Bentaleb

Co-author(s): Kaddour BENHAMOU; Aziz Fllaoui; Youssef Boudraa; Ayaz Zine elabiddine

National Centre for Nuclear Energy, Sciences and Technologies (CNESTEN) Rabat, Morocco

Corresponding author: naoualbentaleb@yahoo.fr//bentaleb@cnesten.org.ma

Iodine-131, with a half-life of 8.02 days, is one of the most widely used radionuclides in medical diagnosis and therapy for a variety of thyroid disorders. Sodium iodide [^{131}I] has been produced on 2018 by CNESTEN. The manufacturing process and the formulation of the product have yielded a high quality finished product. The formulation is an aqueous solution of the active substance sodium iodide [^{131}I] containing sodium thiosulphate as a reducing agent to inhibit radiolytic oxidation of sodium iodide [^{131}I] and liberation of free iodine [^{131}I]. The current formulation use 0,08 ± 10%mg/mCi of sodium thiosulphate.

The objective of the present study is to provide data on optimum quantities of sodium thiosulphate used in the manufacture of Sodium iodide [^{131}I] and also to follow the impact of variation of its concentration throughout the period of validity of the product.

The study was performed on three batches with two types of samples: dispensing solution (without reducing agent) and finished product containing sodium thiosulphate. Relating to the finished product two different activities, a low activity (10 mCi/ 5 ml) and a high activity (100 mCi /5 ml) were chosen. Testing was performed on four time points after production (J0, J+8, J+15, J+22 (expiry date)). Only pharmacopoeial methods were used. Identification and concentration of thiosulfate are determined by HPLC.

Results showed that for dispensing solution, the stability indicating factor (radiochemical purity and pH) remained nearly constant throughout the shelf life. For finished product, Sodium thiosulphate concentration decreased throughout the shelf life. Specification for appearance, radioactivity, radiochemical purity and pH were always met.

No significant difference was found between low (10 mCi) and high (100 mCi) activities comparing with the proposed specifications. The radioactive concentration remains constant throughout the shelf life. This is an indication that no volatile iodine is formed by oxidation of the iodide.

The pH remains constant because the formulation contains a buffer.

Under normal condition, a formulation without sodium thiosulphate would still render a product of the same high radiochemical purity. However, there is a risk that air might be introduced accidentally into the solution when multi-doses are withdrawn hence the need to use sodium thiosulphate as a reducing agent.

From the results above it can be concluded that despite the drop in the concentration of sodium thiosulphate, no effect is observed on the other parameters throughout the shelf life. The presence of sodium thiosulphate throughout the shelf life is necessary as a safety precaution. For this reason, it is proposed to maintain the current formulation with 0,08 ± 10%mg/mCi of sodium thiosulphate which also has demonstrated its quality throughout the shelf life. Higher concentration of sodium thiosulphate is not necessary.

PS2-66

Long-lived radionuclic impurities in the production of ^{18}F-labelled radiopharmaceuticals

Author: Sviatoslav Brinkevich[1]

Co-author(s): Vadzim Krot[2]; Dmitry Brinkevich[3]; Alexander Ivaniykovich[4]

[1]Alexandrov's National Cancer Centre of Belarus for Oncology and Medical Radiology, Minsk, Belarus
[2]NN Alexandrov National Cancer Center of Belarus, Belarus
[3]Belarusian State University, Belarus
[4]Belarusian State Institute of Metrology, Belarus

Corresponding author: brinkevich@bsu.by

Long-lived radionuclides with half-lives from 5 to 312 days are common radionuclide impurities in ^{18}F-labelled radiopharmaceuticals. They are produced along with [^{18}F]fluoride under the action of high-energy protons, neutron and γ-quants on target body and ion window foil during irradiation of [^{18}O]H2O. Subsequent elution of the impurities to a synthesis module results in the contamination of radiopharmaceutical products, as well as radioactive waste accumulation.

In the present study the isotopic composition and partition of long-lived radionuclides between recovered [^{18}O]H2O, solid state extraction cartridges, as well as the final pharmaceutical preparations were studied by means of HPGe γ-spectrometry and liquid scintillation technique.

It was shown that ^{51}Cr, ^{52}Mn, ^{54}Mn, ^{56}Co, ^{57}Co, ^{58}Co, ^{7}Be, ^{57}Ni are the major γ-emitting radionuclides in irradiated water coming from Cyclone 18/9 HC with niobium target and Havar window foil. The activities of ^{65}Zn, ^{92m}Nb, ^{95}Nb, ^{184}Re, ^{183}Re, ^{95}Tc and ^{96}Tc are at least three orders of magnitude lower. Reactions for the formation of the named nuclides are proposed.

Over 90% of chromium and beryllium radionuclides precipitate on QMA light cartridge, while 65- 80% of cobalt, 65-70% of manganese and over 92% of nickel radionuclides are removed to recovered [^{18}O]H2O. Only minor percentage of cobalt, manganese, chromium and beryllium isotopes (1-7%) is eluted from QMA light cartridge by carbonate solution. Whereas technetium, rhenium, niobium radionuclides existing in anionic forms in water-acetonitrile solution in the presence of [^{18}F]fluoride are eluted quantitatively in the reactor vessel. Further purification from γ-emitting long-lived radionuclides strongly depend on the synthesis scheme implemented. High specific activity of 3H was found in irradiated [^{18}O]H2O resulting from side reaction ^{18}O(p, T)16O. Since in production process ^{18}F is separated from the water by ionic exchange on QMA light cartridge over 90% of 3H is segregated into recovered [^{18}O]H2O. Residual tritium is washed along with ^{18}F into reactor vessel and further goes to gaseous effluents during the fluoride drying step. In most ^{18}F-labelled radiopharmaceuticals, except sodium fluoride, tritium activity is comparable with natural levels.

In the present work it was shown that activities of long-lived radionuclides in ^{18}F-labelled radiopharmaceuticals were much below the pharmacopeia levels. Leaching of activated Havar foil window was found to be the main source of γ-emitters and should be minimized in order to decrease the amount of radioactive wastes and overexposure of patients. Attention should be paid to the accumulation of tritium-containing liquids and gaseous effluents worldwide from multiple PET cyclotron radiochemistry facilities.

PS2-67

Analysis and model of radioactive noble gases and iodine emissions from a fission Mo-99 production process

Author: Santiago Campos

Co-author(s): Maria Cecilia Maneiro; Juan Jose Merino

INVAP S.E, Argentina

Corresponding author: scampos@invap.com.ar

Molybdenum-99 (^{99}Mo) is the most important isotope because its daughter isotope, technetium-99m (^{99m}Tc), has been the most widely used medical radioisotope for more than 50 years, accounting for > 80% of total nuclear diagnostics worldwide.

The design of ^{99}Mo production facilities must consider and not exceed the maximum limit of emissions required by the corresponding regulatory authority for each country where plants of this type are installed. For this, it is important to have knowledge of the production process and analyse which are the stages of the process that generate the release of a greater inventory of radioactive gases and, in this way, to be able to take measures to reduce the emissions of the installation.

This work is based on the study of the different stages of the production process of ^{99}Mo through low enrichment Uranium (LEU) and the analysis of those stages of the process that involve the release of radioactive gases into the environment in the hot cells.

The stages of the process that are analysed are those that have controlled releases of radioactive gases and those stages that have uncontrolled releases and whose emissions are more difficult to be treated, which are product of openings in the production system of ^{99}Mo.

In addition, a theoretical model is presented to estimate the emissions at each stage of the process, using the Nucleonica software as a calculation support software, in order to obtain an analysis of emissions from hot cells to the ventilation system in each of the stages of ^{99}Mo production process. These values are compared with those obtained during the start-up of a production plant, relating the maximum values of emissions in normal operation with the stages of the process associated with these releases, focusing attention on ^{133}Xe and ^{135}Xe.

Finally, this work provides estimated values of iodine and xenon emissions in each stage of the process and the fractions of these gases released into the hot cell environment, providing a detail of the analysis to determine the stage of the process responsible for these emissions.

The analysis showed how the release of ^{133}Xe are products that have a significant decay time, while ^{135}Xe emissions are due to equipment openings in the production process.

PS2-68

Nuclear reaction calculations applied to cyclotron production of emerging radiopharmaceuticals

Author: Luciano Canton; Andrea Fontana

Co-author(s): Mario Carante; Gaia Pupillo; Liliana Mou

INFN, Italy

Corresponding author: luciano.canton@pd.infn.it

In the framework of the LARAMED program (laboratory of radionuclides of medicine) at the INFN-Legnaro National Laboratories (LNL), we have carried out a study of nuclear reaction calculations using different nuclear codes: Fluka, Talys and Empire. The calculations were directed to aid experimental investigations in finding efficient routes and conditions for the production of emerging theranostic radionuclides. The calculation involved not only cross-section evaluations but also yields, activities, isotopic and radionuclidic purities. We have studied in particular the cyclotron-based production of ^{47}Sc in the framework of the experimental PASTA project. This project aims to measure various production cross sections, to seek for the best irradiation conditions for ^{47}Sc production. The radioisotope is also included in the CRP No. F22053 by the IAEA, together with ^{67}Cu and ^{186}Re, as emerging theranostic radionuclides. The use of ^{47}Sc as a theranostic agent is hindered by the fact that there is not yet an established economical route for the production in sufficient quantities and purity. The goal of this theoretical study is to support the PASTA experiment in the search of efficient routes for the production of ^{47}Sc.

The study initiated by considering existing experimental production data involving proton beams. These data have been integrated later with the results obtained in the PASTA project at the ARRONAX facility and compared with theoretical estimations obtained by using different nuclear codes. Starting from the theoretical cross-sections we have calculated yields and activities produced, together with isotopic and radionuclidic purity.

We have calculated production of the theranostic ^{47}Sc by proton collision with targets of natTi, ^{48}Ti, ^{49}Ti, ^{50}Ti and natV. Analysis has been performed with nuclear reaction codes Talys 1.9, Empire 3.2 and Fluka dev 2018.0. Considering the co-produced Sc-isotopes and their half-lives, the main contaminant is ^{46}Sc and its production had to be avoided or minimized. The use of natTi and ^{48}Ti targets appears not to be suitable for the production of ^{47}Sc with high purity in the range E<100 MeV, while, with targets made of enriched ^{49}Ti, ^{50}Ti and natV, it was possible to identify energy regions suitable for the production of ^{47}Sc with high level of purity. The selected regions are 25-40 MeV for the enriched ^{49}Ti target, 10-20 MeV for the enriched ^{50}Ti target, and 20-30 MeV for natV. For natV we have calculated the activity produced for given beam current and impinging energy and target thickness. For the specific parameters considered, we predicted significant production of ^{47}Sc with a high level of purity.

The results of this phenomenological study appear very promising and should stimulate thick target yields measurements in the corresponding irradiating conditions to substantiate the predictions.

PS2-69

Measurement of excitation functions of proton-induced nuclear reactions on gold

Author: Jaroslav Červenák
Co-author(s): Ondřej Lebeda

Nuclear Physics Institute, Řež, Czech republic

Corresponding author: yaro.cervenak@gmail.com

The isomers Hg-197m/Hg-197g represent a new potential theranostic radionuclide pair. The shorter lived Hg-197m (T½ = 23.8 h) emits a dominant 134 keV γ-line (Iγ = 33.5 %) suitable for SPECT imaging, while the ground state Hg-197g (T½ = 64.6 h) provides therapeutic low energy β particles with maximum energy of 523 keV. Moreover, the well-known chemical properties of mercury allow for rapid and efficient separation and later for straightforward labelling using appropriate chelators.

The Hg-197m/Hg-197g pair production is possible either via proton-induced, or via deuteron-induced nuclear reactions on naturally monoisotopic gold targets. The choice of projectile and its energy allows for changing the isomeric ratio in the product. That is why precise knowledge of the excitation functions is highly desirable. Currently available data are scarce and sometimes inconsistent.

The excitation functions were measured using the stacked foils technique on the cyclotron U-120M of the Czech Academy of Sciences in the energy interval of 6.4–35.3 MeV. After the irradiation, the foils were measured using a γ-ray spectrometer equipped with an HPGe detector in order to determine precisely the activity of radionuclides born in the target. Subsequently, cross-sections and their uncertainties were calculated.

The measured cross-sections for the nuclear reactions Au-197(p,x)Hg-197m, Hg-197g, Hg-195m, Hg- 195g, Au-196m, Au-196g, Au-194g in the energy range of 6.4–35.3 MeV were compared with previously published experimental data and with theoretical prediction of the excitation functions adopted from the nuclear reaction model code TALYS (library TENDL2017). Thick target yields were calculated. All activities of the ground-state isomers were corrected for the contribution of the metastable isomeric nuclei. Our data are generally in a good agreement mainly with the majority of recently published data sets. Inconsistencies were observed mainly in the case of Hg-197g, for the older data and sometimes with the TALYS prediction.

We provided a detailed cross-section data for the nuclear reactions Au-197(p,x)Hg-197m, Hg-197g, Hg-195m, Hg-195g, Au-196m, Au-196g, Au-194g covering the energy range of 6.4–35.3 MeV. The thick target yields calculated from the experimental data allow for reliable prediction of the activities at the EOB and the isomeric ratio Hg-197m/Hg-197g as the function of energy.

PS2-70

Separation of ^{99m}Tc from low specific activity ^{99}Mo

Author: Izabela Cieszykowska

Co-author(s): Małgorzata Żółtowska; Dariusz Pawlak; Wioletta Wojdowska; Tomasz Janiak; Parus Józef Leon; Piotr Garnuszek; Renata Mikołajczak

National Centre for Nuclear Research, Radioisotope Centre POLATOM, Poland

Corresponding author: izabela.cieszykowska@polatom.pl

Technetium-99m is the most widely used radionuclide for medical imaging. It is generally obtained by elution of commercially available ^{99}Mo/^{99m}Tc generators. Research reactors have been the main source of ^{99}Mo, the parent of ^{99m}Tc, for several decades. Due to their aging, the numerous alternative production modes of ^{99}Mo or directly ^{99m}Tc were investigated. One of them is the photonuclear reaction ^{100}Mo(g,n)^{99}Mo with bremsstrahlung irradiation obtained by the use of an electron accelerator. This method offers a less-expensive alternative to fission-made ^{99}Mo, but with lower yield resulting in low specific activity (LSA) of ^{99}Mo. This requires efficient methods of ^{99m}Tc separation from large excess of molybdate and the application of new adsorbents with high capacity for Mo. The International Atomic Energy Agency initiated the Coordinated Research Project No. F22068 (2017-2020) on “New Ways of Producing Tc-99m and Tc-99m Generators” in order to promote this technology in Member States. POLATOM is participating in this project since the last year. The main goal of our work is to develop a practically useful separation method of pharmaceutical grade ^{99m}Tc.

The separation of ^{99m}Tc will be performed in so called reverse generator system. Investigation on resins selective for ^{99m}Tc and allowing to pass Mo through the column are under way. The experiments with AnaLig-Tc-02 resin (IBC Advanced Technologies, Inc.) were performed to optimize ^{99m}Tc separation from molybdenum. The sorption yield of ^{99m}Tc on this resin as a function of NaOH concentrations was studied. We used various resin amounts at different flow rates. The same process using ^{99m}Tc as tracer and natural molybdenum with different ratios of both metals is studied in detail. The TRU resin (Triskem International) and other solid phase extraction systems are also tested to obtain the highest yield of ^{99m}Tc with the lowest Mo contamination.

In conclusions we believe that this study will be a good starting point for the design of the new ^{99}Mo/^{99m}Tc generator suitable to use LSA ^{99Mo}.

Acknowledgements: This project was supported with the funds awarded by the Ministry of Science and Higher Education in Poland within the agreement No. 3969/IAEA/2018/0, IAEA Research Contract No. 22652 and CERAD project, financed under Smart Growth Operational Programme 2014-2020, Priority IV, Measure 4.2.

PS2-71

Yttrium cyclotron solid target preparation for Zirconium-89 production

Author: Sara Cisternino[1]

Co-author(s): Hanna Skliarova[1]; Emiliano Cazzola[2]; Giancarlo Gorgoni[2]; Vincenzo Palmieri[1]; Juan Esposito[1]; A. Baldini[3]; U. Anselmi-Tamburini[3]

[1]INFN-LNL Istituto Nazionale di Fisica Nucleare - Legnaro National Laboratories, Italy
[2]Sacro Cuore Hospital, Italy
[3]University of Pavia, Italy

Corresponding author: sara.cisternino@lnl.infn.it

The interest in ^{89}Zr radioisotopes is increasing in the last years due to its half-life that allows to label biomolecules, such as monoclonal antibodies, for pharmacokinetic studies and clinical trials to trace slow biological process. Due to the availability of the target material in natural form, the ^{89}Y(p,n)^{89}Zr is considered the best nuclear reaction for the production of ^{89}Zr in medical cyclotrons. Nowadays, the design and manufacturing of appropriate cyclotron solid targets for the production of large amounts of ^{89}Zr with high specific activity remain a technological challenge.

The LNL-INFN group, in the framework of the LARAMED (laboratories for radioisotopes of medical interest) project, has developed two methods for ^{89}Y targets realization for the production of ^{89}Zr. The targets have been tested in collaboration with IRCCS Sacro Cuore-Don Calabria Hospital in Negrar (VR).

The first proposed method is Magnetron Sputtering (MS) deposition of yttrium material directly onto niobium backing (chosen due to its chemical inertness). MS is a physical vapour deposition technique that takes place in a vacuum by means of inert gas plasma (Ar). The material of interest is attached to the cathode, and plasma is created when a difference of potential is applied between the cathode and the substrate (anode). The positive ions of the inert gas are accelerated towards the cathode. When the ions collide with the atoms of the sputtering target, the energy transfer causes the detachment of some atoms, which are then deposited on the substrate. Magnetron sputtering is characterized by elevated plasma utilization efficiency thanks to its magnetic confinement.

The yttrium MS process parameters have been optimized in order to obtain thick (~70 µm), dense film, adherent to niobium backing, thanks to minimizing the intrinsic stress, which can compromise the performance of produced cyclotron target.

Spark Plasma Sintering (SPS) was chosen as a second target preparation technique. SPS combines simultaneous application of uniaxial pressure with pulsed direct electrical current (DC) under vacuum. In this work, commercially available 150 µm thick yttrium foil has been bonded to niobium backing to realize the targets.

In order to realize a comparison, targets obtained by both described methods, MS and SPS, were irradiated at 12.7 MeV, increasing proton beam current in steps using TR19 cyclotron at IRCCS Sacro Cuore-Don Calabria Hospital in Negrar (VR). The visual inspections of the targets after irradiations and the radionuclide purity after the dissolution process in HCl and standard radiochemical separation procedure were taken into account.

The comparison of the two methods, MS and SPS, from the technological point of view (target thickness, realization time, density, efficiency, backing material, beam current supported), has been done.

PS2-72

Production of actinium-225 at JRC Karlsruhe

Author: Alban Kellerbauer

Co-author(s): Frank Bruchertseifer; Rikard Malmbeck; Alfred Morgenstern

European Commission, Joint Research Centre, Nuclear Safety and Security

Corresponding author: alban.kellerbauer@ec.europa.eu

The targeted treatment of cancerous tumours by alpha-emitting radionuclides has shown remarkable efficacy in recent clinical trials. It is likely that this treatment option will ultimately be applicable to a wide range of cancers and other diseases, subject to the development of specific carrier molecules. Currently Ac-225 is mainly produced from natural ingrowth in existing stocks of Th-229. An anticipated wider application for radiotherapy will require many orders of magnitude of more radionuclide than can currently be produced. Consequently, following up on earlier experimental work at JRC, we are pursuing alternative production methods. In particular, the production by irradiation of Ra-226 with medium-energy protons at cyclotrons will be investigated. In this talk, past experience with proton irradiation of Ra-226 at JRC Karlsruhe will be reviewed. In addition, short- and medium-term plans for future work in this direction will be presented.

PS2-73

Technetium-99m production by medical cyclotron

Author: Alessandra Boschi[2]

Co-author(s): Petra Martini[1]; Adriano Duatti[3]; Hanna Skliarova[4]; Licia Uccelli[5]; Micòl Pasquali[6]; Gaia Pupillo[7]; Liliana Mou[4]; Gianfranco Cicoria[7]; Sara Cisternino[4]; Carlos Rossi-Alvarez[4]; Juan Esposito[4]

[1]Department of Morphology, Surgical and Experimental Medicine, University of Ferrara, Italy; INFN – LNL, Viale dell'Università, Italy
[2] Legnaro, Padova, Italy
[2]Department of Morphology, Surgical and Experimental Medicine, University of Ferrara, Italy
[3]Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Italy
[4]INFN-LNL Istituto Nazionale di Fisica Nucleare - Legnaro National Laboratories, Italy
[5]University of Ferrara, Italy
[6]INFN-LNL, Italy
[7]Nuclear Medicine S. Orsola Hospital, Bologna, Italy

Corresponding author: alessandra.boschi@unife.it

^{99m}Tc (T1/2=6.06 h, Eγ =140 keV (89%)) is the most used radionuclide worldwide for Single Photon Emission Computed Tomography scans (SPECT). It is commonly obtained from the decay of its parent nuclide ^{99}Mo (T1/2=66 h), by eluting compact and transportable ^{99}Mo/^{99m}Tc generator systems that makes it available directly in nuclear medicine departments. The majority of ^{99}Mo is produced in a few ageing nuclear reactors around the world, using highly enriched uranium (HEU) targets. The unexpected worldwide Technetium-99m (t1/2=6h, Eγ=140keV) shortening occurred on the radioisotope market in 2009-2010, due to the reactor-produced parent nuclide ^{99}Mo production crisis. It has prompted new ideas about alternative production routes of this important gamma emitter radionuclide used in 85% of diagnostic nuclear medicine procedures.

In the framework of INFN-funded (National Scientific Committees 5-CSN5, (2012-2017) research programs APOTEMA/TECHN-OSP, and of a Coordinated Research Project (CRP Code: F22062) promoted by the International Atomic Energy Agency (IAEA), we developed in collaboration with other Italian Universities and Research Institutions, a technology to produce GBq amount of ^{99m}Tc by the existing medical cyclotron network in Italy, through the (p,2n) nuclear reaction on a ^{100}Mo enriched metal target.

Several ^{100}Mo metal target configurations were developed based on the prototype solid target station of a TEMA Sinergie assembled at the GE PETtrace (16MeV) cyclotron. Among them, the SPS (spark plasma sintering) technique, allowing to utilize an inert backing plate, has been chosen as the most efficient.

A remotely controlled module for the fast and efficient extraction and purification of ^{99m}Tc from the irradiated ^{100}Mo enriched metallic target, by exploiting the high efficiency of the Solvent Extraction (SE) technique, has been developed. The automatic module assembly was based on pre modular units (Modular-Lab Standard, Eckert & Ziegler) and was customized by adding a handmade glass column vial (length =25 cm, ø =1cm) and a home-made reactor heater. Quality controls have been conducted on the final products following the monograph specifications. Radiolabelling and imaging studies with a clinical gamma camera, have been conducted as well. Finally, an efficient procedure for the recovery of expansive ^{100}Mo was developed.

The developed technology allowed to obtain cyclotron-produced [^{99m}Tc]TcO_4 suitable for clinical application with a Quality Assurance (QA) process in compliance with the European Pharmacopoeia recently issued. Local nuclear medicine departments equipped by medical cyclotrons and our technology will be able to self-produce sufficient amount of ^{99m}Tc for their daily diagnostics needs.

PS2-74

Assessment of dose increase after administration of radiopharmaceuticals prepared with cyclotron-produced ^{99m}Tc

Author: Laura Melendez-Alafort[1];

Co-author(s): Guillermina Ferro-Flores[2]; Laura De Nardo[3]; Michele Bello[3]; Marta Paiusco[1]; Alessandra Zorz[1]; Nikolay Uzunov[4]; Juan Esposito[5]; Antonio Rosato[3]

[1]Veneto Institute of Oncology IOV-IRCCS, Italy
[2]Instituto Nacional de Investigaciones Nucleares, Italy
[3]University of Padova, Italy
[4]Faculty of Natural Sciences, University of Shumen, Bulgaria
[5]INFN-LNL Istituto Nazionale di Fisica Nucleare - Legnaro National Laboratories, Italy

Corresponding author: lmalafort@yahoo.com

Technetium-99m (^{99m}Tc) is currently available from ^{99}Mo/^{99m}Tc generators as the β-decay product of ^{99}Mo (T½=66 h). Nowadays, ^{99}Mo is mostly obtained as a fission product in nuclear reactors by neutron-induced reactions on highly enriched uranium. Alternative production routes, such as direct production of ^{99m}Tc via ^{100}Mo(p,2n)^{99m}Tc reaction using medical cyclotrons has the potential to be both reliable and relatively cost-effective. However, results showed that the extracted ^{99m}Tc from the proton-bombarded ^{100}Mo-enriched target contains small quantities of several Tc radioisotopes (^{93m}Tc, ^{93}Tc, ^{94}Tc, ^{94m}Tc, ^{95}Tc, ^{95m}Tc, ^{96}Tc and ^{97m}Tc).

The aim of this work was to estimate the dose increase (DI) due to the contribution of Tc radioisotopes generated as impurities, after the intravenous injection of four radiopharmaceuticals prepared with cyclotron-produced ^{99m}Tc (CP-^{99m}Tc) using 99.05% ^{100}Mo-enriched metallic targets.

Four ^{99m}Tc radiopharmaceuticals (pertechnetate, sestamibi (MIBI), hexamethylpropylene- amine oxime (HMPAO) and disodium etidronate (HEDP)), were considered in this study. The biokinetic models reported by the International Commission on Radiological Protection (ICRP) for each radiopharmaceutical were used to define the main source organs and to calculate the number of disintegrations per MBq that occurred in each source organ (Nsource) for each Tc radioisotope present in the CP-^{99m}Tc solution. Then, target organ equivalent doses and effective dose were calculated for each Tc radioisotope with the OLINDA/EXM software versions 1.1 and 2.0, using the calculated Nsource values and the adult male phantom as program inputs. Total effective dose produced by all Tc isotopes impurities present in the CP-^{99m}Tc solution was calculated using the fraction of total activity corresponding to each radioisotope generated by the bombardment of ^{100}Mo-enriched (99.05%) metallic target. Finally, the effective obtained dose was compared with the effective dose delivered by the generator-produced ^{99m}Tc.

The total effective dose increases of CP-^{99m}Tc radiopharmaceuticals, calculated with both versions of the OLINDA software, remained within the 10% limit in all cases, from 6 up to 12 hours after end of bombardment (EOB). The Tc radioisotopes with the highest concentration in the CP-^{99m}Tc solution at EOB are ^{94m}Tc and ^{93m}Tc. However, their contribution to DI 6 hours after EOB is minimal, due to their short half-lives. ^{96}Tc is the radioisotope with the largest contribution to the effective DI, followed by ^{95}Tc and ^{94}Tc, although their concentration in the CP-^{99m}Tc solution is 5 times less than ^{94m}Tc and ^{93m}Tc at the EOB. This is due to the types of their emissions and relatively long half-lives. The increase in the radiation dose caused by the other Tc radioisotopes contained in produced CP-^{99m}Tc, as described here, is quite low. Although the concentrations of the ^{94}Tc and ^{95}Tc radioisotopes in the CP-^{99m}Tc solution exceed the limits established by the European Pharmacopoeia, CP-^{99m}Tc radiopharmaceuticals could be used in routine nuclear medicine diagnostic studies if administered from 6 to 12 hours after the EOB; thus, maintaining the effective DI within the 10% limit.

PS2-75

Development of a copper oxide reactor to convert hydrogen to water in the dissolution of radioisotopes production targets

Author: Juan Merino

Co-author(s): Claudia Osuna; Sebastián Sevillano; Fernando Braun

INVAP S.E., Argentina

Corresponding author: jmerino@invap.com.ar

The development of a CuO – wires form - reactor at laboratory scale is carried out to convert on line H2 gas into H2O vapour and to avoid the handling of explosive gas. The process of regeneration of CuO is also developed in order to reuse the reactor a large number of cycles.

2 CuO + H2 —–> Cu2O + H2O Reaction 1 (CuO reduction or H2 conversion) 2 Cu2O + O2 —–> 4 CuO Reaction 2 (Cu2O oxidation or CuO regeneration)

The objective is to have a unit operation that meets the safety requirements in the management of H2 that is produced when the irradiated targets in a research reactor, of aluminium cladding base, are dissolved in alkaline solution, for the production of fission radioisotope of medical use (^{99}Mo, ^{131}I, ^{133}Xe, etc.).

2 Al + 2 NaOH + 2 H2O —–> 2 NaAlO2 + 3 H2 Reaction 3 (Irradiated target dissolution)

If the H2 gas is not properly managed, it can reach concentrations above the lower flammability limit, and under favourable conditions of oxygen index and activation energy can be produced by ignition and consequent deflagration and/or explosion of the H2.

The experimental tests were made in a CuO fixed-bed tubular stainless-steel reactor heated by electrical heaters. The CuO used is Merk catalogue 102765, p.a. grade, wire fine about 0.65 x 3 mm for elementary analysis, (surface: CuO, core: Cu2O, CuO: minimum 55%). The dimensions of the reactor are: 70 mm diameter and 300 mm length with a 3.5 kg CuO capacity.

Conversion and regeneration experiments are carried out at different temperatures and flow rates to find the optimal conversion and regeneration conditions. Effect of temperature and residence time on CuO-H2 and Cu2O-O2 reactions are evaluated.

The experiment is complemented by the analytical determination of Cu, Cu2O, CuO and O species, plus the measurement of the CuO weight variation and the produced mass of water.

The CuO wires fixed-bed reactor preheated to 250-350 Celsius degree is a passive equipment where the H2-CuO reaction has an efficiency exceeding 99%. The hysteresis in the regeneration stage - loss of CuO which is available for conversion reaction- is minimal and ensures a rate of reuse of the reactor exceeding 100 cycles.

With each conversion / regeneration cycle a slight degradation of the CuO bed is observed due to the decrease of the exposed superficial area of the CuO wires due to the collapse of some of them by local heating. This is largely avoided by performing at the beginning of the process the pre-treatment of the CuO to reduce the CuO concentration from 55 to 30%.

PS2-76

The LARAMED project at INFN-LNL: laboratory of radionuclides for medicine

Author: Liliana Mou[1]

Co-author(s): Adriano Duatti[1]; Juan Esposito[1]; Alessandra Boschi[2]; Sara Cisternino[1]; Giovanni Fiorentini[2]; Giorgio Keppel[1]; Petra Martini[1]; Micòl Pasquali[1]; Gaia Pupillo[1]; Gabriele Sciacca[1]; Hanna Skliarova1; Diego Bettoni[1]

[1]INFN-LNL, Italy
[2]University of Ferrara, Italy

Corresponding author: liliana.mou@lnl.infn.it

The great advancement of nuclear medicine (NM) held in the last decades mainly relies in the development and use of a wide range of different and more effective radiopharmaceuticals. This goal has been achieved by combining the biological behaviour of new ligand molecules, selective for the specific tumour target, and the main nuclear properties of novel radioisotopes, specific for diagnostic, therapy and theranostic applications. The use and availability of a variety of radionuclides has experienced a great development as a result of the increase of technologies related to their production, even based on cyclotrons.

At INFN-LNL a BEST 70p high performance cyclotron was installed in 2015, to be dedicated not only to the new frontiers of nuclear physics studies (SPES project), but also to the interdisciplinary and medical physics investigations, through the LARAMED project, acronym for LAboratory of RADionuclides for MEDicine. Albeit the facility is currently under development (installation of beam-lines, laboratories etc), since 2012 the team started working on the production of conventional and innovative radionuclides for NM applications.

LARAMED activities have started with TECHN-OSP and APOTEMA projects, aimed at the direct production of Tc-99m with small cyclotrons already installed in hospitals. The focus is now devoted on studying new emerging radionuclides such as Cu-67 (COME project), Sc-47 (PASTA project) and Mn-52 (METRICS project). These studies have allowed the development of new techniques for producing thin solid targets by using High Energy Vibrational Powder Plating (HIVIPP) method (E- PLATE project) and high-power target (TERABIO premium-project).

The collaboration with NM radiopharmacies holding a PET cyclotron (e.g. the Sant'Orsola Hospital in Bologna and the Sacro Cuore Don Calabria Hospital in Negrar), as well as with national and international research institutes, such as several INFN sections, the University of Ferrara, the CNR in Milan and the ARRONAX facility (Nantes, France), made all this effort possible.

An up-dated overview of the on-going projects regarding different radiometals, produced by using proton cyclotrons, is the purpose of this poster. Results from cross-section measurements, target production, irradiation runs, target processing and recovery, that was carried out by the LARAMED research group will be presented.

PS2-77

Production of ^{89}Zr and radiolabelling of phosphatidylserine liposome

Author: Fabio Luiz Navarro Marques[1]; Caroline Cristiano Real[1]

Co-author(s): Larissa Estessi de Souza[1]; Daniel Henrique Uzueli[1]; Rubens Abe[1]; Ulisses Lacerda Figueiredo Sa[1]; Daniele de Paula Faria[1]; Giovani Marino Favero[2]; Roger Chammas[1]; Carlos Alberto Buchpiguel[1];

[1]Universidade de Sao Paulo, Sao Paulo, Brazil

[2]Departamento de Biologia Geral, Universidade Estadual de Ponta Grossa, Parana, SP, Brazil

Corresponding author: fabio.marques@fm.usp.br

The application of ^{89}Zr as a diagnostic radionuclide in PET is of increasing interest, due to easy production, from natural ^{89}Y target and chemical separation. Furthermore, the physical t1/2 = 3.27 days is appropriated for long-term metabolic investigations, such as observed in antibodies or nanomaterials. Recently we had studied the use of liposomes composed phosphatidylserine (PS) to delivery chemotherapeutics for cancer treatment, based on the property of PS to be recruited by cells, adsorbed in their surface, followed by endocytosis. To measure in vivo drug delivery or liposome biodistribution we decide to label liposome with the isotope ^{89}Zr. Since liposomes are structures composed by a hydrophobic phospholipid bilayer, containing an inner and external hydrophilic core, we studied different labelling procedures. The aim was to optimize the production of ^{89}Zr in our cyclotron and evaluate the conditions for radiolabelling the PS liposome.

^{89}Zr was produced by ^{89}Y(p,n)^{89}Zr nuclear reaction in a GE cyclotron PETtrace 880, using a homemade target built in aluminium. High purity (> 99 %) ^{89}Y sheet (16.6x16.6x0.125 mm) was bombarded with 12.8 MeV protons, at a current of 10 uA, by 180 min. Activated ^{89}Y sheet was dissolved in 6 M HCl and ^{89}Zr was purified by filtration in hydroxamate column, eluted with oxalate solution (0.1 M). Liposome formulation was prepared dissolving 10 mg of commercial PS in chloroform/methanol (10:1) and dried under vacuum, then it was dissolved in saline and sonicated by 10 min. Radiolabelling was performed by three different methods: 1) sonicated formulation was reacted with SNC-Bn-DFO overnight followed, concentration in Amicon 10 kD and reaction with [^{89}Zr(oxalate)] at 37 oC/1 h; 2) sonicated compound was incubated with 8-hydroxyquinoline (8HQ) at 37 oC/1h; 3) [^{89}Zr(SNC-Bn-DFO)] was mixed in saline and used to dissolve dried PS, followed by sonication during 10 min. [^{89}Zr(liposome)] purification and labelling efficiency was performed in PD-10 column eluted with PBS 0.1 M pH 7.4. ^{89}Zr yield at EOB/acid digestion was 444 ± 74 MBq, and activity was recovered in 80-85% from hydroxamate column. The relevant formation of undesired ^{88}Zr (t1/2 83 d; 393 keV gamma line) was not observed by gamma spectrometry. Radiolabelling yield was lower than 1 % for methods 1 and 2, and method 3 gave 53 % of labelled product.

The conditions to produce ^{89}Zr on a PETtrace cyclotron using a homemade target was optimized. Liposome radiolabelling conditions still in development, having the method 3 [^{89}Zr(SNC-Bn-DFO)] the most promising results regarding radiolabelling yield.

PS2-78

Towards multimodal PET/MRI imaging with cyclotron-produced $^{52/51}$Mn

Author: Micòl Pasquali[1]

Co-author(s): Petra Martini[1]; Gaia Pupillo[2]; Hanna Skliarova[3]; Juan Esposito[3]; Alessandra Boschi[4]; Liliana Mou[3]; Adriano Duatti[5]; Sara Cisternino[3]; Carlos Rossi Alvarez[2]; Gabriele Sciacca[3]; Licia Uccelli[4]

[1]INFN-LNL and University of Ferrara, Italy
[2]INFN-LNL, Italy
[3]INFN-LNL Istituto Nazionale di Fisica Nucleare - Legnaro National Laboratories, Italy
[4]University of Ferrara, Italy
[5]University and INFN of Ferrara, Italy

Corresponding author: psqmcl@unife.it

Multimodality imaging is a diagnostic technique that combines morphological and functional information for improving the power of current imaging methods. PET or SPECT with CT are currently the most popular multimodal imaging technologies in this field while the combination of PET or SPECT with MRI (magnetic resonance imaging) is a newly-established technology. This multimodal technology usually involves the use of two different compounds, a contrast agent for MRI (i.e. Gadolinium-based molecules) and a radioactive tracer for PET/SPECT, generating a mismatch in the diagnostic information content.

In this regard, we want to investigate the possibility and the effect of having a molecular fusion between PET and MRI by using a bimodal probe, a molecule able to be detected by both techniques. The same compound will act as a contrast and as a radioactive agent, preserving both the paramagnetic and nuclear characteristics. Manganese is the only transition element having paramagnetic properties suitable for MRI and two manganese isotopes, ^{52}Mn and ^{51}Mn, positron emitters that could be employed as PET tracers.

The scope of the METRICS project (METRICS: Multimodal pET/mRi Imaging with Cyclotron-produced $^{52/51}$Mn iSotopes), funded by INFN (CSN5 2018–2020), aims to develop a perfect molecular matching between PET and MRI using paramagnetic and radioactive manganese isotopes to afford an unprecedented type of PET/MRI hybrid imaging and to develop the technology, target, and separation module to self-produce by cyclotron the $^{51/52}$Mn. So far, natural chromium targets have been successfully produced and tested under a proton beam up to 50 µA (~ 1 kW) for thermomechanical tests, manganese paramagnetic complexes have been synthesized and characterized, while dosimetric studies and Cr/Mn radiochemical separation are currently under development.

In this work we present the preliminary results of the METRICS project. The possible efficacy of having a real molecular fusion between PET and MRI by using a new bimodal probe, based on the use of manganese paramagnetic complexes, labelled with $^{51/52}$Mn radionuclides will be underlined.

PS2-79

Effect of radiolysis produced by high levels of radiation dose (Gy) delivered by alpha particles on the production and supply of Ac-225, and the labelling of radiopharmaceutical for therapy

Author: Oscar Pozzi[1]

Co-author: Michael Zalutsky[2]

[1]National Atomic Energy Commission, Ezeiza Atomic Center, Argentina
[2]Duke University, United States

Corresponding author: pozzi@cae.cnea.gov.ar

The development of therapeutic radiopharmaceuticals labelled with radioisotopes emitting alpha particles provides additional challenges compared with beta-minus radioisotopes in terms of radiation safety but also with regard to the deleterious effects of high radiation fields over the labelling chemistry and shelf life because alpha particles deposit large amounts of energy in a highly focal manner producing a well-known deleterious effect mostly related to the radiolysis produced by the high LET alpha particles.

These problems for labelling at high activities for therapeutic purpose and distribution of the radioisotope to locations distant from the production site for industrial applications have been the most comprehensively investigated for At-211, and similar difficulties probably exist with others alpha particle emitters like Ac-225.

The radicals, ion and molecular species produced by radiolysis process might produce profound changes on the labelling process in several ways including producing changes in the oxidation state of the radioisotope (observed for At-211), degradation of the labelling precursor, or side-reactions by having a potential impact on labelling yields, purity of the radiopharmaceutical products or shelf life. For At-211 serious problems were already found for labelling at high activities but also for delivering activities.

Given the excellent results already observed on the treatment of patients with prostate cancer with ^{225}Ac-PSAM-167, currently several countries are working in developing new production technology in order to secure the supply of Ac-225, like Argentina. Given the half-life of Ac-225 that allows supply to distant location the radiolysis issue might become critical for producers planning to deliver Ac-225 kilometres away from the production site because the radiation doses delivered by at least five alpha particles coming Ac-225 and its daughters, Fr-221, At-217, Bi-213 and Po-213 will make the situation potentially worst and worth to be studied.

This presentation will show in detail that the level of radiation dose delivered on several scenarios for Ac-225 and its daughters are even much higher than the ones delivered for At-211 and extremely much higher that with beta minus emitters like Lu-177. Due to the radiolysis, water solutions of Ac-225 will produce very high concentration of radicals and molecular products like hydrogen and hydrogen peroxide, producing a reaction media for labelling is extremely harsh. For example, delivering 50 mCi at a location distant 10 hours away will arrive a delivery radiation dose (Gy) into the Ac-225 solution astonishing high, 7.5 times more that for At-211 with a concentration of H2O2 200 times higher than the prototypical concentration used for labelling PSMA-167 (200 micrograms). This labelling environment might preclude achieving good labelling yields or even making impossible to avoid severe side reaction. It might require not also a systematic study about this potential issued but also to find new strategies for delivering activity to make possible the supply of Ac-225 to distant locations.

PS2-80

High energy vibrational powder plating for cyclotron solid target preparation for radiopharmaceuticals production

Author: Hanna Skliarova[1]

Co-author(s): Sara Cisternino[1]; Lorenzo Pranovi[1]; Piergiorgio Antonini[1]; Pierantonio Facco[2]; Valentino Rigato[1]; Gaia Pupillo[1]; Gabriele Sciacca[1]; Liliana Mou[1]; Matteo Campostrini[1]; Carlos Rossi-Alvarez[1]

[1]INFN-LNL Istituto Nazionale di Fisica Nucleare - Legnaro National Laboratories, Italy
[2]University of Padua, Italy

Corresponding author: hanna.skliarova@lnl.infn.it

Cyclotron solid target realization is often crucial for radioisotope production. A set of most standard techniques for target preparation is often inefficient for the refractory metals, like Ti, Mo, W, Zr. In the case of enriched isotopes, a technique that causes minimal material losses is absolutely essential. The High Energy Vibrational Powder Plating (HIVIPP) method, based on the motion of material powders in an electric field, provides a solution to minimize losses and deposition of “problematic” refractory metals. The deposition process is carried out in a vacuum inside a quartz cylinder with electrodes mounted at its top and bottom. A high voltage (>2 kV) applied to the electrodes causes the powder motion towards the electrode of the opposite charge on which particles are deposited. The HIVIPP method allows preparation of targets with areal densities ranging from µg/cm2 up to mg/cm2, with a very high yield and of excellent thickness homogeneity, superior to the one obtained by conventional evaporation.

In order to guarantee a reliable and reproducible application of the HIVIPP method for other enriched materials, a deep study of the process is required. The “E-PLATE: Electrostatic Powder Plating for Accelerator Targets” project of INFN (2018-2019) is devoted to R&D on HIVIPP technique aimed to depose optimization and overcoming thickness limitation (evident from previous works of I. Sugai). This is done to allow the preparation of the targets as for nuclear cross-section measurements (program-minimum), as for medical radionuclides production (program-maximum).

The E-PLATE project includes the use of the appropriate Design of Experiment (DOE) approach, to understand the influence of further factors on the deposited thickness: electric field, powders size, powders oxidation level, the distance between electrodes. Since the cyclotron-based production of ^{99m}Tc high-efficiency ^{100}Mo target deposition is of great interest, Mo powder deposition onto Cu target backing was defined as a modelling system for HIVIPP process study. To assure the reproducibility of the experiments, the automation of the deposition system was realized. In order to guarantee no additional powders oxidation, the system has been equipped with dedicated Ar glove-bag. The powders size is defined by sieving ^{nat}Mo powders with certified sieves in Ar atmosphere. The experiments corresponding to the DOE plan are ongoing.

The obtained process model after statistical analysis of the experimental data of the deposit thickness (using both measurements: weighting of the samples and Rutherford backscattering spectrometry analysis) will be used to optimize the deposition parameters.

First results showed that an HIVIPP deposition system was installed at INFN-LNL and was successfully used for the production of ^{48}Ti targets (0.1-2 mg/cm2 thick) for the nuclear cross section measurements aimed to verify ^{47}Sc production.

Several HIVIPP deposited ^{nat}Mo on copper backing targets have been tested for thermomechanical stability under TR19 cyclotron proton beam at “Sacro Cuore Don Calabria” Hospital. The targets withstood the heat powder density up to 1kW/cm2 without any visible alterations.

PS2-81

The yield of ^{47}Sc at photonuclear production

Author: Vyacheslav Uvarov

Co-author(s): Nikola Dikiy; Yury Lyashko; Valentin Shevchenko; Alexandr Zakharchenko

Kharkov Institute of Physics & Technology, Poland

Corresponding author: uvarov@kipt.kharkov.ukraine

^{47}Sc is considered as a promising beta-emitter for cancer radioimmunotherapy. Its practical application is hampered by the absence of a technology that could provide sufficient yield of the target isotope at a tolerant content of admixtures. A possible approach to settle this issue is a carrier-free ^{47}Sc production using a soft technology on the basis of the ^{48}Ti(gamma,p)^{47}Sc reaction in the field of high-energy bremsstrahlung radiation of an electron accelerator. In this work, the analysis of the key factors that determine the photonuclear yield of ^{47}Sc in a thick titanium production target is carried out.

An analytical model providing the description of isotope generation in a thick target exposed to a spatially nonuniform flux of high-energy X-ray photons is developed. A set of main parameters of the process determining the total yield and distribution of activity in a target has been established. It is shown, that those parameters are the normalized coefficient of photonuclear conversion, the rms radius of photon flux density at a target, and also average annular divergence of the photon flux. The proposed approach is used for the optimization of geometry and activation mode of a cylindrical target from titanium. An independent study was conducted using a simulation technique on the basis of a GEANT4 transport code. The conditions of activation of targets from natural titanium in the electron energy range 30-95MeV are experimentally studied as well.

It is established, that within the stated range of electron energy the yield of main scandium admixtures ^{48}Sc and ^{46}Sc are respectively by one and two order of values less than the yield of ^{47}Sc.The dependence of the ^{47}Sc gross and specific activity of a cylindrical target on its dimensions and electron energy has been calculated.

In the case of a target from titanium enriched in ^{48}Ti and activation mode (40MeV; 0.3mA), the capacity of the photonuclear method amounts up to 1GBq/h ^{47}Sc at low content of by-products.

PS2-82

Cyclotron production of scandium-44

Author: Wioletta Wojdowska

Co-author(s): Dariusz Pawlak; Izabela Cieszykowska; Małgorzata Żółtowska; Tomasz Janiak; Tadeusz Barcikowski; Józef Leon Parus; Piotr Garnuszek; Renata Mikołajczak

National Centre for Nuclear Research, Radioisotope Centre POLATOM, Poland

Corresponding author: izabela.cieszykowska@polatom.pl

Scandium-44 emitting β+ particles (Eβ+= 1474 keV) with a gamma radiation component of 1157 keV is becoming interesting as a PET radionuclide. Due to its half-time of 3.35 h it can be complementary to ^{68}Ga or ^{18}F. On the other hand, the ^{47}Sc, an isotope with potential for radionuclide therapy, gives the possibility for employment of ^{44}Sc/^{47}Sc isotopic pair in disease diagnosis, therapy dose estimation and assessment of therapeutic response. Scandium-44 can be produced from ^{44}Ca via ^{44}Ca(p,n)^{44}Sc nuclear reaction. The aim of this study was to develop a working procedure for separation of ^{44}Sc of sufficient purity and specific activity to be used for medical needs.

Calcium targets, natural and enriched (99.2%), were prepared by pressing calcium carbonate powder or metallic calcium dendritic chunks into pellets. Typical irradiation conditions were from 45 min to 3 h at 13 - 23 μA of the proton beam current. After irradiation the calcium targets were dissolved in 3 M hydrochloric acid and ^{44}Sc was separated from excess of calcium by precipitation of scandium hydroxide using ammonia. The targets were also dissolved in 11 M hydrochloric acid and ^{44}Sc was separated by extraction chromatography on UTEVA resin. The ^{44}Sc was further purified and concentrated on a cation exchange resin. Gamma spectrometry with a high purity germanium detector when used to determine the separation efficiency and radionuclide purity.

Results showed that twenty two irradiation and separation runs were performed using both natural and enriched calcium targets. As result of 1hour proton activation s of $^{44}CaCO_3$ pellet with 99.2% enrichment more than 4.8 GBq of ^{44}Sc activity at EOB was obtained.

The recovery yield of ^{44}Sc in both investigated separation methods was comparable and amounted to above 90%. The working procedures were developed and the quality of separated ^{44}Sc solution was determined by labelling the bioconiugates. The chemical purity of the product was sufficient for preclinical experiments.

In conclusion, Scandium-44 can be produced inexpensively with adequate yields and radionuclide purity via ^{44}Ca(p,n)^{44}Sc nuclear reaction in medical cyclotrons. The obtained ^{44}Sc is pure in terms of radionuclide and chemical purity, as shown by the results of peptides radiolabelling.

Acknowledgements: This project was supported with the funds awarded by the National Centre for Research and Development in Poland within the Applied Science Program, grant no PBS3/A9/28/2015 and CERAD project, financed under Smart Growth Operational Programme 2014-2020, Priority IV, Measure 4.2.

PS2-83

Biodistribution of Nanoradiopharmaceuticals in Internal Organs

Author: Baode Zhang[1]
Co-author: Ali Nabipour Chakoli[2]

[1]Liaoning Shihua University, Fushun Liaoning, China
[2]Nuclear Science and Technology Research Institute, AEOI, Tehran, Iran

Corresponding Author: zhangbaode@aliyun.com

Conjugation of nanomedicine and radiopharmacy treats a new research and technology area that is named nanoradiopharmacy. It has great advantages in disease diagnosis and control and subsequent therapy, due to the ability to develop molecular diagnostics for the early detection of disease as well as the ability to develop increasingly personalized and individualized treatments. Nanostructured materials attracted considerable attention because of their high surface area to volume ratio resulting from their nanoscale dimensions. This class of sorbents is expected to have a potential impact on enhancing the efficacy of radioisotope generators for diagnostic and therapeutic applications in nuclear medicine. Radiolabelled nanoparticles represent a novel class of radiopharmaceutical agents with great potential in cancer research. The radiolabelled nanoparticles can be used for specific tumour imaging or for effective tumour treatment by specific radiation. Various kinds of nanoradiopharmaceuticals, such as Tc-99m nanogels, have been industrialized and applied for disease diagnosis purposes. But, nanoradiopharmacy like other technologies has its own limitations that must be considered.

Nanoparticles have several orders of magnitude larger than classical drugs and represent an important advancement in drug therapy because they can be assembled as multimolecular complexes including not only pharmacologically-active molecules, but also molecules for selective targeting to specific tissues. The Liver and spleen have important roles in nanoparticles pharmacokinetics. The spleen has a mechanism for sequestrating nanoparticles. A preferential accumulation in the liver and in the spleen was observed by researchers. It was found that unmodified nanoparticles disappear from the blood in seconds or minutes after their injection. Renal filtration has a significant role in this process if their size is smaller than 15 nm, whereas for nanoparticles larger than 40 nm, their disappearance from the blood is mainly dependent on their accumulation in cells of the reticuloendothelial system. This significantly reduces nanoparticle half-life and represents a major barrier for the implementation of their clinical use. Nanoparticle uptake is mainly operated by liver Kupffer cells, but splenic macrophages also have a significant role. Splenic capture can be used to selectively deliver old drugs to the spleen. Additionally, researchers found that spleen capture is a limiting factor in nanoparticle pharmacokinetics and that it has to be overridden in order to optimize its therapeutic effects.

In most cases after injection of nanoradiopharmaceuticals, due to the pharmacokinetics role the radioactivity is detected in the liver and spleen. Hence, increasing the internal radiation dose in liver and spleen may initiate the creation of some kind of diseases for the liver and spleen. Radiation induced toxicities in non-tumourous liver tissues are associated with the development of numerous symptoms or have serious chronic side effects (Fig. 1).

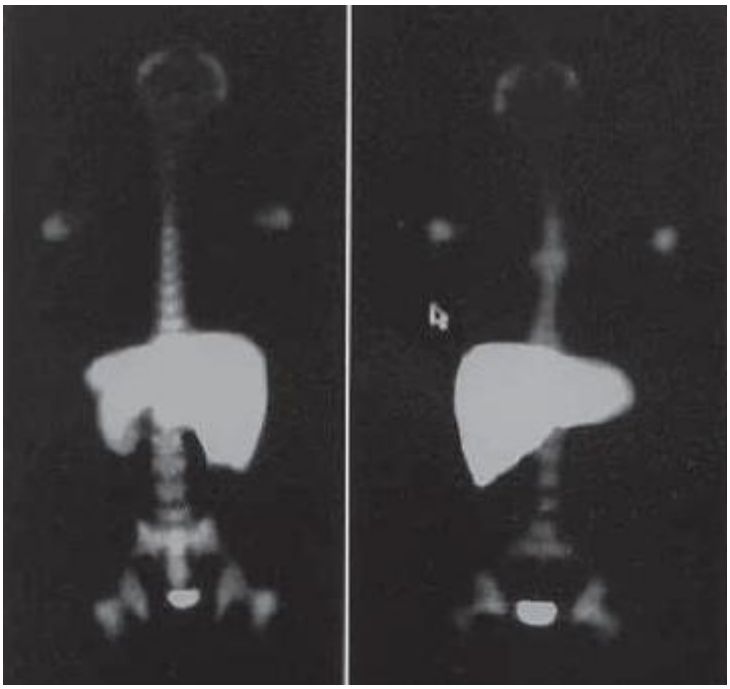


Figure 1. In planar images of liver after injection of Technetium-99m nanocolloid.

IAEA Recent Publications Related to this Symposium

1-Gallium-68 Cyclotron Production
Details: IAEA-TECDOC-1863; (ISBN978-92-0-100819-0); 66 pp
https://www.iaea.org/publications/13484/gallium-68-cyclotron-production

2-Quality Control in the Production of Radiopharmaceuticals
Details: IAEA-TECDOC-1856; (ISBN:978-92-0-107918-3); 148 pp.; 5 figures; € 18.00; Date Published: 2018
https://www-pub.iaea.org/MTCD/Publications/PDF/TE-1856web.pdf

3-Cyclotron Based Production of Technetium-99m
Details: STI/PUB/1743; (ISBN:978-92-0-102916-4); 59 pp.; 48 figures; € 33.00; Date Published: 2017
https://www-pub.iaea.org/MTCD/Publications/PDF/P1743_web.pdf

4- Cyclotron Produced Radionuclides: Emerging Positron Emitters for Medical Applications: 64Cu and 124I
Details: STI/PUB/1717; (ISBN:978-92-0-109615-9); 63 pp.; 38 figures; € 38.00; Date Published: 2016
https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1717Web-25315812.pdf

5- Radiopharmaceuticals for Sentinel Lymph Node Detection: Status and Trends
Details: STI/PUB/1674; (ISBN:978-92-0-109714-9); 162 pp.; 43 figures; € 39.00; Date Published: 2015
https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1674web-3264500.pdf

6- Yttrium-90 and Rhenium-188 Radiopharmaceuticals for Radionuclide Therapy
Details: STI/PUB/1662; (ISBN:978-92-0-103814-2); 301 pp.; 164 figures; € 52.00; Date Published: 2015
STI/PUB/1662; (ISBN:978-92-0-103814-2); 301 pp.; 164 figures; € 52.00; Date Published: 2015
https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1662web-89688003.pdf

7- Good Practice for Introducing Radiopharmaceuticals for Clinical Use
Details: IAEA-TECDOC-1782; (ISBN:978-92-0-111215-6); 80 pp.; 6 figures; € 18.00; Date Published: 2015
https://www-pub.iaea.org/MTCD/Publications/PDF/TE-1782_web.pdf

8- Cyclotron Produced Radionuclides: Operation and Maintenance of Gas and Liquid Targets
Details: STI/PUB/1563; (ISBN:978-92-0-130710-1); 104 pp.; € 35.00; Date Published: 2012
https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1563_web.pdf

9- Cyclotron Produced Radionuclides: Guidance on Facility Design and Production of Fluorodeoxyglucose (FDG)
Details: STI/PUB/1515; (ISBN:978-92-0-117310-2); 153 pp.; 11 figures; € 55.00; Date Published: 2012
https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1515_Web.pdf

10-Operational Guidance on Hospital Radiopharmacy, A Safe and Effective Approach
English STI/PUB/1342 978-92-0-106708-1 75 9 32.00 2008
https://www.iaea.org/publications/7708/operational-guidance-on-hospital-radiopharmacy