Impact of radiopharmaceutical development on the management of cancer

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Acknowledgments

IAEA

Morgenstern A, Bruchertseifer F, Betti M
Vorster M, Lawal I, Knoesen O, Lengana T, Mahapane J,
Davis C, Boshomane T, Mokoala K, Mokgoro N, Kaoma C,
Corbert C, Kratchowil C, Giesel F, NTP

NM UP/SBAH

Nonjola L, Ebenhan T, Mahlangu Z, D Van Wyk, L Boshoff,
C van Raven, AM Koegelenberg, M Mekwa, Kleynhans J,
Zeevaart JR & NECSA radiochemist staff, Maes A, Van de
Wiele C, Buscombe J
Radiopharmaceuticals: Targeting of the Hallmarks of Cancer

- Metabolism
  - Glucose
  - Cell membrane
  - Proteins
  - Bone
- Tumor specific agents
- Proliferation
- Angiogenesis
- Apoptosis
- Vascularization
- Hypoxia

- Characterization of tumor biology - image-based “biomarker”
- Identification of therapy targets - Theraonostics and treatment planning
- Early Indicator of Tumor Response - patient-specific effect on outcome
Process of New Drug Development

Duration of new drug development: 12 years
Cost of new drug development: R800 million
Successful compounds: only 8% of candidate compounds

 Seeds
- Pharmacodynamics
- Pharmacokinetics
- Toxicity

**Preclinical**
- Candidate compounds
- In vitro
- Animal study

**Clinical trial**
- Phase 1: Safety
dose
- Phase 2: Safety
effect
- Phase 3: Safety
effect

**Clinical use**
- Application
- Review
- Approval
- Phase IV
- Side effects
  in patients

**Screening of compounds**
- Pharmacokinetics
  - Urinary or biliary
  - Excretion
  - Unexpected accumulation
- Dose setting
- Effectiveness

Clinical use
- Effectiveness
- Screening of patients

Jun Hatazawa – Drug Development
Schematic Representation of a Drug for Imaging and Targeted Therapy

**Molecular Address**
- Antibodies, minibodies, Affibodies, aptamers
- Regulatory peptides (agonists & antagonists)
- Amino Acids

**Targets**
- Antigens e.g. CD20, HER2
- GPCR e.g. SSTR
- Enzymes & inhibitors e.g. PSMA
- Transporters

**Reporting Unit**
- $^{99m}$Tc, $^{111}$In, $^{67}$Ga
- $^{64}$Cu, $^{18}$F, $^{68}$Ga
- Gd$^{3+}$

**Cytotoxic Unit**
- $^{225}$Ac, $^{177}$Lu, $^{213}$Bi, $^{131}$I
- $^{105}$Rh, $^{67}$Cu, $^{188}$Re, $^{90}$Y

**THERANOSTIC PAIRS**
Targeted Molecular Imaging and Therapy
The Key-Lock Principle

**Lock**
**Target**

**Key**
**Ligand**
**Linker**
**Chelator**

$^{68}$Ga, $^{225}$Ac, $^{177}$Lu

Modified form: Helmut Mäcke & Rich Baum
Androgen Receptors
PARP inhibitors
Glucose metabolism
Prostate Cancer
Somatostatin Receptor
Cancer-Fibroblasts

Proteins metabolism
Cell Membrane
Bone
Proliferation
Angiogenesis
Estrogen Receptors

Tumor
• Detection
• Staging
• Recurrence

Lee et al. Sem Nucl Med 2019
Fibroblast activation protein (FAP) is overexpressed in cancer associated fibroblasts of several tumor entities (15).

90% of the gross tumor-mass can consist from stromal but not tumor cells

FAPI-tracers contain the universal DOTA-chelator: theranostic approach
68Ga-PSMA PET/CT Replacing Bone Scan in the Initial Staging of Skeletal Metastasis in Prostate Cancer: A Fait Accompli?

Thabo Lengana,1 Ismaheel O. Lawal,1 Tebatso G. Boshomane,1 Gbenga O. Popoola,2 Kgomotso M.G. Mokoala,1 Evelyn Moshokoa,3 Alex Maes,1,4 Neo P. Mokgoro,1 Christophe Van de Wiele,1,5 Mariza Vorster,1 Mike M. Sathekge1

Planned clinical management altered in 52%
Theranostics

Find

Fight

Follow-up

68Ga-DOTATATE/PSMA

Lu-177/Bi213 DOTATATE/PSMA

68Ga-DOTATATE/PSMA

M Sathekge: CME 2013
<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Radioconjugate</th>
<th>Patients</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>$^{213}$Bi-HuM195mAb</td>
<td>49</td>
<td>[38,39]</td>
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<tr>
<td></td>
<td>$^{225}$Ac-HuM195mAb</td>
<td>36</td>
<td>[40]</td>
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<tr>
<td>Lymphoma</td>
<td>$^{213}$Bi-anti-CD20-mAb</td>
<td>12</td>
<td>[41]</td>
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<tr>
<td>Melanoma</td>
<td>$^{213}$Bi-9.2.27mAb</td>
<td>54</td>
<td>[42-44]</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>$^{213}$Bi-anti-EGFR-mAb</td>
<td>12</td>
<td>[32,45]</td>
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<tr>
<td>Glioma</td>
<td>$^{213}$Bi-Substance P</td>
<td>68</td>
<td>[46-48]</td>
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<tr>
<td></td>
<td>$^{225}$Ac-Substance P</td>
<td>19</td>
<td>[48]</td>
</tr>
<tr>
<td>Neuroendocrine tumors</td>
<td>$^{213}$Bi-DOTATOC</td>
<td>25</td>
<td>[4]</td>
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<td></td>
<td>$^{225}$Ac-DOTATOC</td>
<td>39</td>
<td>[49]</td>
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<tr>
<td>Prostate cancer</td>
<td>$^{225}$Ac-PSMA-617</td>
<td>190</td>
<td>[5,50,51]</td>
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</tbody>
</table>
Remission for 26 Months

Post-Tx

Pre-Tx
Radiopharmaceuticals: Targeting of the Hallmarks of Cancer

<table>
<thead>
<tr>
<th>Pretoria cohort</th>
<th>Heidelberg cohort</th>
<th>Munich cohort</th>
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</thead>
<tbody>
<tr>
<td>Castrate-resistant</td>
<td>70% (51/73) 29% CR PFS 15.2 mo</td>
<td>8/8/8 MBq 63% (24/38) 13% CR PFS 7.0 mo</td>
</tr>
<tr>
<td>Chemo naive</td>
<td>88% (15/17) 41% CR 8/6/4-6 MBq</td>
<td>63% (19/30) 10% CR 6/6/6 MBq 44% (7/16) 12% CR</td>
</tr>
<tr>
<td></td>
<td>4 GBq Lu / 4 MBq Ac</td>
<td>76% (13/17) 0% CR 4 GBq Lu / 4 MBq Ac 76% (13/17) 0% CR</td>
</tr>
<tr>
<td></td>
<td>Ac post Lu 62% (21/34) 3% CR PFS 4.0 mo</td>
<td>Ac post Lu 33% (5/15) 0% CR</td>
</tr>
</tbody>
</table>

Sathekge........................................Kratochwil .................................Heck.................................
Morgenstern & Bruchertseifer

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