Introduction to Theranostics

Michael M. Graham, PhD, MD
University of Iowa
Theranostics

Theranostics is a combination of the terms **therapeutics** and **diagnostics**. Theranostics is the term used to describe the combination of using one radioactive drug to identify (diagnose) and a second radioactive drug to deliver therapy to treat the main tumor and any metastatic tumors.
Theranostics

Theranostics is a combination of the terms **therapeutics** and **diagnostics**. Theranostics is the term used to describe the combination of using one radioactive drug to identify (diagnose) and a second radioactive drug to deliver therapy to treat the main tumor and any metastatic tumors.

*University of Iowa*
Theranostic Combinations

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Therapy</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• I-131</td>
<td>• I-131</td>
<td>• Thyroid Cancer</td>
</tr>
<tr>
<td>• Ga-68 DOTATATE</td>
<td>• Lu-177 DOTATATE</td>
<td>• Graves Disease</td>
</tr>
<tr>
<td>• Ga-68 DOTATOC</td>
<td>• Y-90 DOTATATE</td>
<td>• Neuroendocrine tumors</td>
</tr>
<tr>
<td>• Ga-68 PSMA11</td>
<td>• Lu-177 PSMA617</td>
<td>• Neuroendocrine tumors</td>
</tr>
<tr>
<td>• F-18 PSMA</td>
<td>• Ac-225 PSMA</td>
<td>• Prostate Cancer</td>
</tr>
<tr>
<td>• Tc-99m PSMA</td>
<td>• Th-227 PSMA</td>
<td>• Tumor associated fibroblasts</td>
</tr>
<tr>
<td>• Ga-68 FAPI</td>
<td>• Lu-177 FAPI</td>
<td>• Melanoma</td>
</tr>
<tr>
<td>• Pb-203 MCH</td>
<td>• Pb-212 MCH</td>
<td></td>
</tr>
</tbody>
</table>

FDA -approved In Clinical Trial
# Theranostic Combinations

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Therapy</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• I-131</td>
<td>• I-131</td>
<td>• Thyroid Cancer</td>
</tr>
<tr>
<td>• Ga-68 DOTATATE</td>
<td>• Lu-177 DOTATATE</td>
<td>• Graves Disease</td>
</tr>
<tr>
<td>• Ga-68 DOTATOC</td>
<td>• Y-90 DOTATATE</td>
<td>• Neuroendocrine tumors</td>
</tr>
<tr>
<td>• Ga-68 PSMA11</td>
<td>• Lu-177 PSMA617</td>
<td>• Neuroendocrine tumors</td>
</tr>
<tr>
<td>• F-18 PSMA</td>
<td>• Ac-225 PSMA</td>
<td>• Prostate Cancer</td>
</tr>
<tr>
<td>• Tc-99m PSMA</td>
<td>• Th-227 PSMA</td>
<td>• Tumor associated fibroblasts</td>
</tr>
<tr>
<td>• Ga-68 FAPI</td>
<td>• Lu-177 FAPI</td>
<td>• Melanoma</td>
</tr>
<tr>
<td>• Pb-203 MCH</td>
<td>• Pb-212 MCH</td>
<td></td>
</tr>
</tbody>
</table>

**FDA-approved** | **In Clinical Trial**
Table 1. Current diagnostic PSMA ligand

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Target</th>
<th>Imaging agent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monoclonal antibody</td>
<td>$^{89}$Zr-DFO-7E11</td>
</tr>
<tr>
<td>$^{89}$Zr</td>
<td>Monoclonal antibody</td>
<td>$^{89}$Zr-DFO-J591</td>
</tr>
<tr>
<td></td>
<td>Antibody fragment</td>
<td>$^{89}$Zr-Cys-Db</td>
</tr>
<tr>
<td>$^{64}$Cu</td>
<td>Monoclonal antibody</td>
<td>$^{64}$Cu-DOTA-3/A12</td>
</tr>
<tr>
<td></td>
<td>Monoclonal antibody</td>
<td>$^{64}$Cu-DOTA-3/F11</td>
</tr>
<tr>
<td></td>
<td>Monoclonal antibody</td>
<td>$^{64}$Cu-DOTA-3/E7</td>
</tr>
<tr>
<td>$^{111}$In</td>
<td>Antibody fragment</td>
<td>$^{111}$In-JVZ007-cys</td>
</tr>
<tr>
<td>$^{99m}$Tc</td>
<td>Antibody fragment</td>
<td>$^{99m}$Tc-J591Cdia</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{99m}$Tc-MIP-1404</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{99m}$Tc-MIP-1405</td>
</tr>
<tr>
<td>$^{68}$Ga</td>
<td>Antibody fragment</td>
<td>$^{68}$Ga-THP-scFv</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{68}$Ga-rhPSMA</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{68}$Ga-THP-PSMA</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{68}$Ga-PSMA-11</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{68}$Ga-PSMA-I&amp;T</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>Small molecule inhibitor</td>
<td>$^{18}$F-SFB</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{18}$F-CTT-1298</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{18}$F-CTT-1057</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{18}$F-DCFBC</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{18}$F-DCFPyL</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{18}$F-YC-88</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{18}$F-PSMA-1007</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{18}$F-rhPSMA-7.3</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibitor</td>
<td>$^{18}$F-FSU-880</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>18F-PSMA ligands</th>
<th>Organization or company</th>
<th>Clinical phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18F-DCFPyL</td>
<td>Progenics Pharmaceuticals</td>
</tr>
<tr>
<td>2</td>
<td>18F-PSMA-1007</td>
<td>ABX</td>
</tr>
<tr>
<td>3</td>
<td>18F-CTT1057</td>
<td>Novartis (AAA)</td>
</tr>
<tr>
<td>4</td>
<td>18F-rhPSMA-7.3</td>
<td>Blue Earth Diagnostics</td>
</tr>
<tr>
<td>5</td>
<td>18F-FSU-880</td>
<td>Kyoto University</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>68 Ga-PSMA ligands</th>
<th>Organization or company</th>
<th>Clinical phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68Ga-PSMA-11</td>
<td>Telix Pharmaceuticals</td>
</tr>
<tr>
<td>2</td>
<td>68Ga-PSMA-617</td>
<td>Novartis (Endocyte)</td>
</tr>
<tr>
<td>3</td>
<td>68Ga-PSMA-I&amp;T</td>
<td>Technical University of Munich</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PSMA ligands for RLT</th>
<th>Organization or company</th>
<th>Clinical phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>177Lu-PSMA-617</td>
<td>Novartis (Endocyte)</td>
</tr>
<tr>
<td>2</td>
<td>225Ac-PSMA-617</td>
<td>Novartis (Endocyte)</td>
</tr>
<tr>
<td>3</td>
<td>177Lu-TX591</td>
<td>Telix Pharmaceuticals</td>
</tr>
<tr>
<td>4</td>
<td>177Lu-PSMA-R2</td>
<td>Novartis (AAA)</td>
</tr>
<tr>
<td>5</td>
<td>227Th-PSMA-TTC</td>
<td>Bayer</td>
</tr>
</tbody>
</table>
Gallium-68

$T_{1/2} = 68$ min

Lutetium-177

\( T_{1/2} = 6.7 \text{ d} \)

Production: Neutron activation

\( E_{\beta(\text{max})} = 497 \text{ keV (78.6 %)}, \ 384 \text{ keV (9.1 %)}, \ 176 \text{ keV (12.2 %)} \)

\( E_\gamma = 113 \text{ keV (6.6 %)}, \ 208 \text{ keV (11 %)} \)]

The mean penetration range of \( \beta^- \) particles emitted by \( ^{177}\text{Lu} \) in soft tissue is 670 \( \mu \text{m} \)

Used with DOTATATE, PSMA, FAPI
Yttrium-90

$T_{1/2} = 64.6 \text{ h}$

Production: decay from Sr-90

$E_{\beta(\text{max})} = 2.28 \text{ MeV (99.98 \%)}$

$E_{\gamma} = 1.76 \text{ MeV (0.017 \%)}$

The mean penetration range of $\beta^-$ particles emitted by $^{90}\text{Y}$ in soft tissue is 2.5 mm

Positron emission = 32 ppm

Used with DOTATOC
Imaging following intra-arterial administration of $^{90}$Y resin microspheres

Bremsstrahlung SPECT/CT

PET-CT

DOTATOC and DOTATATE

The untapped potential of Gallium 68-PET: The next wave of $^{68}\text{Ga}$-agents
D.L. Smith et al. / Applied Radiation and Isotopes 76 (2013) 14–23
67 year old with episodic flushing, loose stools, documented liver mets, elevated chromogranin A. Primary NET site not established.
Ga-68 DOTATOC
FIGURE 4. Whole-body images acquired after administration of $^{177}$Lu-DOTATATE in different therapy cycles. (200 mCi (7.4 GBq) per dose)
116 patients treated with Lu-177 DOTATATE plus low dose long-acting octreotide
113 patient treated with high dose long-acting octreotide

41 centers in 8 countries were involved

Neuroendocrine tumors

Incidence of NETs Increasing

Radiotracers for Prostate Cancer

- **Bone Scan (Sr-85)** 1964
- **Bone Scan (Tc-99m)** 1972
- **In-111 Prostascint** 1996
- **In-111 J591** 2003
- **Ga-68 Bombesin** 2013

- **Bone Scan (F-18) NaF** 1999
- **F-18 FDG** 1993
- **C-11 Choline** 1998
- **F-18 Fluoro-choline** 2000
- **C-11 Acetate** 2002
- **F-18 FACBC** 2007
- **F-18 FDHT** 2004
- **PSMA small molecules** 2012

**Dates are first reports of imaging in humans**

**Green agents are approved**
Most widely studied
Prostate-Specific Membrane Antigen (PSMA)
Radiopharmaceuticals

Ga-68 PSMA-11

Lu-177 PSMA-617

F-18 PSMA Targeted Radiopharmaceuticals

\[ ^{18}\text{F}-\text{PSMA-1007} \]

\[ ^{18}\text{F}-\text{DCFBC} \]

\[ ^{18}\text{F}-\text{DCFPyL} \]

Ac-225-PSMA617 - a single center experience of 40 patients receiving PSMA-targeted Alpha therapy

C. Kratochwil¹, F. L. Giesel¹, F. Bruchertseifer², M. Rius², C. Apostolidis², U. Haberkorn¹, A. Morgenstern²

(1) Department of Nuclear Medicine, University of Heidelberg, Heidelberg, Germany
(2) Institute for Transuranium Elements, European Commission, Joint Research Centre, Karlsruhe, Germany
Ac-225-PSMA617 - a single center experience of 40 patients receiving PSMA-targeted Alpha therapy

C. Kratochwil¹, F. L. Giesel¹, F. Bruchertseifer², M. Rius², C. Apostolidis², U. Haberkorn¹, A. Morgenstern²

(1) Department of Nuclear Medicine, University of Heidelberg, Heidelberg, Germany
(2) Institute for Transuranium Elements, European Commission, Joint Research Centre, Karlsruhe, Germany

Poster at SNMMI 2016 annual meeting

177Lu-PSMA  225Ac-PSMA
Ac-225 PSMA

**FIGURE 2.** TTP vs. duration of clinical benefit. After favorable initial PSA and imaging response to complete remission, patient 14 had TTP of only 1 y (January to December 2015). However, duration of clinical benefit was more than 1 y longer: because of asymptomatic disease and slow growth velocity, treatment-free interval could be prolonged until April 2017. Whether patient will again respond to second series of $^{225}$Ac-PSMA-617 is not yet known. (Images courtesy of Prof. Felix Mottaghy, Rheinisch-Westfälische Technische Hochschule Aachen.)

FIGURE 5. Waterfall graphs of PSA response. Patients who died before week 8 (red) or discontinued because of xerostomia (yellow) were classified as progression.
The Need for Dosimetry

“The high dose to kidney, bone marrow, and other nontarget tissues, as well as the large variability in biodistribution and tumor uptake among patients, should be addressed. Thus, precise and reliable dosimetry of normal organs and tumor with these agents is needed, and its achievement is challenging.”

Dosimetry requires determination of (MBq - Hrs)/gm in tissue (quantitative imaging) and appropriate software

Other uncertainties in dosimetry arise from the unknown micro-distribution and the possible mobility of the daughter nuclides.
Astatine - 211

\[ ^{211}\text{At} \quad 7.2 \text{ hr} \]

- \( \alpha \) 5.87 MeV
- 42% electron conversion
- 58% electron conversion

\[ ^{207}\text{Bi} \quad 38 \text{ yr} \]

- electron conversion

\[ ^{211}\text{Po} \quad 0.5 \text{ sec} \]

- \( \alpha \) 7.45 MeV
- Po K X-rays 77-92 keV

\[ ^{207}\text{Pb} \quad \text{stable} \]
Lead – 212 and Lead - 203

- $^{212}\text{Pb}$: $\beta$ 570 keV, 10.6 hr, $\gamma$ 239 keV 43%
- $^{212}\text{Bi}$: $\alpha$ 6.2 MeV 36%, $\beta$ 2.25 MeV 64%, 61 min
- $^{208}\text{Tl}$: $\beta$ 5.0 MeV, 3 min
- $^{212}\text{Po}$: $\alpha$ 8.95 MeV, 0.3 μsec
- $^{208}\text{Pb}$: stable

- $^{203}\text{Pb}$: Electron Capture, 51.9 hr, $\gamma$ 279 keV 95%, $\gamma$ 401 keV 3%
- $^{203}\text{Tl}$: stable

M. M. Graham
Radium - 223

\[
\begin{align*}
223^{\text{Ra}} & \quad \text{11.4 days} \\
\downarrow \alpha & \quad \text{5.8 MeV} \\
219^{\text{Rn}} & \quad \text{3.96 sec} \\
\downarrow \alpha & \quad \text{6.9 MeV} \\
215^{\text{Po}} & \quad \text{1.8 msec} \\
\downarrow \alpha & \quad \text{7.5 MeV} \\
211^{\text{Pb}} & \quad \text{36 min} \\
\downarrow \beta & \quad \text{450 keV} \\
211^{\text{Bi}} & \quad \text{2.2 min} \\
\downarrow \alpha & \quad \text{6.6 MeV} \\
207^{\text{Tl}} & \quad \text{4.8 hr} \\
\downarrow \beta & \quad \text{490 keV} \\
207^{\text{Pb}} & \quad \text{stable}
\end{align*}
\]
Alpha Emitters Gamma Spectra

Ra-223


Ac-225

Current status
• Ga-68 and Lu-177 DOTATATE are currently approved in clinical use for treating neuroendocrine tumors
• Current approach is 200 mCi x 4 at monthly intervals
• Some patients get too much, many could get more

Near future
• Several PSMA agents are in clinical trial and will be approved in the next few years, including alpha-emitting agents

The challenge and opportunity
• Develop convenient, user-friendly methodology to provide
  • A-priori dosimetry to determine the appropriate 1st administered dose
  • Based of 1st dose dosimetry, determine appropriate next doses
  • Dosimetry for alpha-emitting radiopharmaceuticals

This needs to be developed for Lu-177 DOTATATE first, then for the prostate agents.
Theranostics

END