Physical Bases: Which Isotopes?

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Theranostic: use of diagnostic to support therapy decisions

Nuclear medicine

**We see what we treat**
**We treat what we see**

*We need to see* → information from the specific biological function
Tumor uptake and biokinetics
→ dose exposure → **efficacy**
Normal tissue uptake and biokinetic
→ dose exposure → **safety**

*We need to treat* → deposit a localized, target specific, dose to obtain biological response
→ Tumor cell killing, induced apoptosis, stop replication, activate specific immuno-response

*We need to evaluate outcome*
Progression, stable disease, partial or complete response
Dose-response relationship
Theranostic radiopharmaceutical: basic schema

Radioisotope

Chelator

Biological Target: Tumor cell
(Genetic material: DNA)

Vector

Peptide

Antibody

Nanoparticle

microsphere

Which radioisotope?
Theranostic: basic schema

Radioisotope

Chelator

Peptide

Antibody

Nanoparticle

microsphere

Vector

Biological Target: Tumor cell

(Genetic material: DNA)

Which radioisotope?

Diagnostic

Obtain information from radiotracer specific biokinetics in patient

Gamma emitters

Therapy

We need to deliver a therapeutic radiation dose to the target

Charged particle emitters

Why not having both features together?
**We need to see (diagnostic imaging)**

Information carried by **photons** from the patient

- \( E_\gamma \) sufficient escape biological tissue (tissue attenuation)
- \( E_\gamma \) range with predominant photoelectric interaction
- Optimal detection efficacy

\[ 100 \text{ keV} < E_\gamma < 511 \text{ keV} \]

In-111

\( E_{\gamma_1} = 171 \text{ keV} \)
\( E_{\gamma_2} = 245 \text{ keV} \)

In-111 zevalin

Treatment planning of follicular lymphoma
For Radioimmunotherapy
With \(^{90}\text{Y}\)
We need to see (diagnostic imaging)

PET annihilation photons at 511 keV

Ga-68 DOTATATE PET/CT

Ga-68 Labeled Somatostatin Analogs Positron Emission Tomography/ Computed Tomography in Gastroenteropancreatic Neuroendocrine Tumors
C. Soydal. Journal of Gastroenterology, Pancreatologia & Liver Disorders
We need to see (diagnostic imaging)

Gamma emitter radionuclide are suited for diagnostic imaging

What about charged particles?
Electrons, protons and alphas

Not appropriate for functional imaging

But ideal to release a localized therapeutic dose to the target region sparing surrounding normal tissues
Theranostic: basic schema

Theranostic: basic schema

Radioisotope (radiometal)

Chelator

Peptide

Antibody

Nanoparticle

microsphere

Vector

Biological Target

Tumor cell

Which radioisotope?

Diagnostic

Obtain information from radiotracer specific biokinetics in patient

Gamma emitters

Therapy

We need to deliver a therapeutic radiation dose to the target

Charged particle emitters
We need to treat

Therapeutic outcome is dose dependent

Deposit an amount of energy in a given mass (tumor cells)

Use charge particles

- Electrons (β- emission)
- Auger electrons
- Alpha particles

Radiation dose (J/kg = Gy)

Use charge particles

- Electrons (β- emission)
- Auger electrons
- Alpha particles

Radio-immunotherapy with \(^{90}\text{Y}\)- antibody

- Local energy deposition
- High rate of deposited energy per unit or length
  → high **linear energy transfer** (LET)

Theranostics Using Antibodies and Antibody-Related Therapeutics
Beta emission:
electrons and positrons from nuclear decay
Local energy deposition vs. radiation type

Bremsstrahlung emission

Parts of:
- Electron track

2 nm
We need to treat

Ra-223

$E_\alpha = 5 \text{--} 10 \text{ MeV}$

Alpha particles

- are heavy charged particles compared to electrons
- Travels in nearly straight lines

Therapeutic radionuclides: Biophysical and radiobiologic principles
Low energy Electron (Auger emission)

Therapeutic radionuclides: Biophysical and radiobiologic principles
LET and biological effects

- Low LET (high energy $\beta$- and $\gamma$)
  - Many cells lightly wounded
  - Possible recovery
  - Global effect not important for a given D

- High LET (Auger and alphas)
  - Few cells highly injured
  - Less possibility to recover
  - Global effect important for a given D
Survival Fraction and Radio Biological Efficiency

Survival Fraction \( SF = \frac{N \text{ cells survived to } D}{N \text{ initial cells}} \)

\[-\ln(SF) = \alpha D + \beta D^2\]

- **Linear part**
  → cell killing due to single hit mechanism
- **Quadratic part**
  → cell killing due double hit mechanism

\[ D = \frac{\alpha}{\beta} \] : dose at which cell killing due to linear and quadratic component are equal

\( \alpha/\beta \) is peculiar of specific radiation type delivered to a given cell population

**X-ray beam with 250 keV photons.**

\( \text{RBE} = 1 \)

**RBE** = D that result in a given SF applying a reference radiation

D that result in the same SF with the test radiation considered
Relative biological effect (RBE)

\[
RBE = \frac{\text{dose that produces a given effect with a reference radiation}}{\text{dose that produces a given effect with a given radiation}}
\]

The more damaging is the radiation type \(\rightarrow\) The higher RBE

X-ray beam with 250 keV photons. \(\text{(RBE} = 1)\)
Table 3 Beta-Particle Emitters: Physical Properties

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-Life</th>
<th>$E^{\beta^-}_{\text{max}}$ (keV)</th>
<th>$R^{\beta^-}_{\text{max}}$ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{33}$P</td>
<td>25.4 days</td>
<td>249</td>
<td>0.63</td>
</tr>
<tr>
<td>$^{177}$Lu</td>
<td>6.7 days</td>
<td>497</td>
<td>1.8</td>
</tr>
<tr>
<td>$^{67}$Cu</td>
<td>61.9 hours</td>
<td>575</td>
<td>2.1</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>8.0 days</td>
<td>606</td>
<td>2.3</td>
</tr>
<tr>
<td>$^{186}$Re</td>
<td>3.8 days</td>
<td>1077</td>
<td>4.8</td>
</tr>
<tr>
<td>$^{169}$Dy</td>
<td>2.3 hours</td>
<td>1285</td>
<td>5.9</td>
</tr>
<tr>
<td>$^{89}$Sr</td>
<td>50.5 days</td>
<td>1491</td>
<td>7.0</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>14.3 days</td>
<td>1710</td>
<td>8.2</td>
</tr>
<tr>
<td>$^{166}$Ho</td>
<td>28.8 hours</td>
<td>1854</td>
<td>9.0</td>
</tr>
<tr>
<td>$^{188}$Re</td>
<td>17.0 hours</td>
<td>2120</td>
<td>10.4</td>
</tr>
</tbody>
</table>

$^{90}$Y: 64.1 hours, 2284 keV, 11.3 mm

Table 2 Alpha-Particle Emitters: Physical Properties

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>$E_{av}$ (MeV)</th>
<th>$R_{av}$ (μm)</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{211}$At</td>
<td>6.79</td>
<td>60</td>
<td>7.2 hours</td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>8.32</td>
<td>84</td>
<td>46 min</td>
</tr>
</tbody>
</table>

$^{223}$Ra: 5.64 MeV, 45 μm, 11.43 days
$^{225}$Ac: 6.83 MeV, 61 μm, 10 days

Decay

<table>
<thead>
<tr>
<th>Particles (#)</th>
<th>$E_{(\text{min})}$-$E_{(\text{max})}$</th>
<th>Range</th>
<th>LET</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha^{++}$-particle</td>
<td>He nuclei (1)</td>
<td>5 to 9 MeV†</td>
<td>40 to 100 μm</td>
</tr>
<tr>
<td>$\beta^-$-particle</td>
<td>Energetic electrons (1)</td>
<td>50 to 2300 keV‡</td>
<td>0.05 to 12 mm</td>
</tr>
<tr>
<td>EC/IC</td>
<td>Nonenergetic electrons (5 to 30)</td>
<td>eV to keV†</td>
<td>2 to 500 nm</td>
</tr>
</tbody>
</table>

Therapeutic radionuclides: Biophysical and radiobiologic principles
Dosimetry
Dosimetry assessment based on imaging

Biokinetics of therapeutic radiotracers should be evaluated to assess Absorbed dose to:

- Tumor dose (efficacy) ideal large $T_{\text{eff}, \text{tum}}$
- Normal tissue dose (safety) ideal small $T_{\text{eff}, \text{NT}}$

\[ A(t)/A_0 \]

\[ \text{AUC} \sim \text{N decays} \]
Dosimetry assessment based on imaging
Biokinetics of therapeutic radiotracers should be evaluated to assess
Absorbed dose to:
- Tumor dose (efficacy)
- Normal tissue dose (safety)

Y-90
$\beta^-$

Organ dose assessment in Y-90 radioimmunotherapy
$\beta^-$ ($E_{\gamma,\text{max}} = 2.3$ Mev)
$T_{\text{phys}} = 64.1\text{h} = 2.67\text{d}$

In-111
$\gamma$

Use of diagnostic activity of In-111
$\text{In-111}$
$E_{\gamma 1} = 171$ keV
$E_{\gamma 2} = 245$ keV
$T_{\text{phys}} = 67.2\text{h} = 2.8\text{d}$

Emission Imaging possible
Production
Dedicated facilities $\rightarrow$ isotopes commercially available
Examples of isotopes
For theranostic

Therapeutic Radiometals Beyond 177Lu and 90Y: Production and Application of Promising α-Particle, β–Particle, and Auger Electron Emitters
C. Müller et al., Nucl Med 2017; 58:91S–96S
Y-90, half-life: 2.67d

Used for radio immunotherapy of follicular lymphoma
Radioembolisation of HCC and liver metastases
PRRT with DTPA and DOTA chelators in NET

Antibody: Diagnostic pair: In-111  →  Pre-treatment dosimetry
Radioembolisation with microsphere : Diagnostic pair: Tc-99m MAA
Bremsstrahlung → post TTT deposition:
β+ emission (32ppm) → post TTT PET → post-TTT dosimetry

Lu-177, half-life: 6.65d

PRRT with DTPA and DOTA chelators in NET

Prostate Specific Membrane Antigen (PSMA) in prostate cancer

Gamma emission → post-TTT dosimetry (SPECT)
Cu-67, half-life: 2.58 d

<table>
<thead>
<tr>
<th>$\alpha$ (keV)$^*$</th>
<th>$E_{\beta^-}$ average (keV)</th>
<th>$E_y$ or $E_{\beta^+}$ (keV)$^*$</th>
<th>Production method</th>
<th>Chelator</th>
<th>Diagnostic match</th>
</tr>
</thead>
<tbody>
<tr>
<td>141</td>
<td>$y$: 91 (7.0)$^{+}$</td>
<td>$^{68}$Zn(p,$2p$)$^{67}$Cu (7)</td>
<td>NOTA, NODAGA, TETA, $^{64}$Cu (PET)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$y$: 93 (16.1)$^{+}$</td>
<td>$^{68}$Zn(y,$p$)$^{67}$Cu (76)</td>
<td>CPTA, (DOTA), $^{62}$Cu (PET)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$y$: 185 (48.7)$^{+}$</td>
<td>$^{70}$Zn(p,$\alpha$)$^{67}$Cu (77)</td>
<td>cross-bridged macrocycles (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{70}$Zn(d,$\alpha$)$^{67}$Cu (78)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SPECT post-TTT possible

Need of high energy accelerators

Labeled with antibody in radioimmunotherapy (bladder cancer, lymphoma)

Cu-64 half life = 12.7 h

Sc-47, half-life: 3.35d

<table>
<thead>
<tr>
<th>$E_{\beta^-}$ average (keV)</th>
<th>$E_y$ or $E_{\beta^+}$ (keV)$^*$</th>
<th>Production method</th>
<th>Chelator</th>
<th>Diagnostic match</th>
</tr>
</thead>
<tbody>
<tr>
<td>162</td>
<td>$y$: 159 (68.3)$^{+}$</td>
<td>$^{47}$Ti(n,$p$)$^{47}$Sc (18, 19)</td>
<td>DOTA (17), $^{43}$Sc (PET)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{46}$Ca(n,$y$)$^{47}$Ca $\rightarrow 47$Sc (17, 19)</td>
<td>AAZTA (24), $^{44}$Sc (PET)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{48}$Ca(y,$n$)$^{47}$Ca $\rightarrow 47$Sc (21)</td>
<td>DO3AP (23)</td>
<td></td>
</tr>
</tbody>
</table>

SPECT post-TTT possible

Generator production

Sc-47-DOTA-folate

Sc-43 and Sc-44 half life :3.9h
Ho-166 half-life: 1.11d

<table>
<thead>
<tr>
<th>$E_\alpha$ (keV)*</th>
<th>$E_{\beta^-}$ average (keV)</th>
<th>$E_y$ or $E_{\beta^+}$ (keV)*</th>
<th>Production method</th>
<th>Chelator</th>
</tr>
</thead>
<tbody>
<tr>
<td>665</td>
<td>y: 81 (6.6)$^\dagger$</td>
<td>$^{166}$Ho(n,$\gamma$)$^{166}$Ho (26)</td>
<td>DOTA (32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>y: 1,379 (0.9)</td>
<td>$^{164}$Dy(2n,$\gamma$)$^{166}$Dy $\rightarrow$ $^{166}$Ho (31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SPECT post-TTT possible

Incorporated microspheres (neutron bombardment activation)
→ Radioembolisation of liver metastases
Paramagnetic → Possible MRI
Percutaneous injection of Ho-166/chitosan in small HCC
Bone metastasis (breast primary) and myeloma

Tb-161 half-life: 6.89d

<table>
<thead>
<tr>
<th>$E_\alpha$ (keV)*</th>
<th>$E_{\beta^-}$ average (keV)</th>
<th>$E_y$ or $E_{\beta^+}$ (keV)*</th>
<th>Production method</th>
<th>Chelator</th>
<th>Diagnostic match</th>
</tr>
</thead>
<tbody>
<tr>
<td>154</td>
<td>y: 49 (17.0)$^\dagger$</td>
<td>$^{160}$Gd(n,$\gamma$)$^{161}$Gd $\rightarrow$ $^{161}$Tb (35)</td>
<td>DOTA (37)</td>
<td></td>
<td>$^{152}$Tb (PET)</td>
</tr>
<tr>
<td></td>
<td>y: 75 (10.2)$^\dagger$</td>
<td>$^{155}$Tb (SPECT)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+ Auger electrons

Combined use of Tb-161-folate and Lu-177-Folate
Tb-161 superior to Lu-177 ?
Possible pre-TTT diagnostic
Possible post-TTT dosimetry ?
Tb-149 half-life: 4.118h

<table>
<thead>
<tr>
<th>Ea (keV)*</th>
<th>Eβ− average (keV)</th>
<th>Ey or Eβ+ (keV)*</th>
<th>Production method</th>
<th>Chelator</th>
<th>Diagnostic match</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,967 (16.7)</td>
<td>β+: 730 (7.1)</td>
<td>y: 165 (26.4)†</td>
<td>Nd(12C,5n)149Dy → 149Tb (42)</td>
<td>DOTA (37)</td>
<td>152Tb (PET)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>y: 352 (29.4)</td>
<td>Spallation of tantalum target (37,42)</td>
<td></td>
<td>155Tb (SPECT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>y: 389 (18.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

α emitter

Both PET pre-TTT and post-TTT quantitative assessment can be considered

Ongoing pre clinical study on mice

Pb-212 (Bi-212) half-life: 10.64h (60.6min)

<table>
<thead>
<tr>
<th>Ea (keV)*</th>
<th>Eβ− average (keV)</th>
<th>Ey or Eβ+ (keV)*</th>
<th>Production method</th>
<th>Chelator</th>
</tr>
</thead>
<tbody>
<tr>
<td>6,050 (25.1)†</td>
<td>100</td>
<td>y: 238 (43.6)</td>
<td>224Ra/212Pb generator (48)</td>
<td>DOTA (48), TCMC (48)</td>
</tr>
<tr>
<td>6,089 (9.75)†</td>
<td></td>
<td>y: 300 (3.3)†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

α emitter
Multiple alphas

Ac-DOTA-antibody or small molecules
-leukemia
-lymphoma
-Breast. Ovarian
-and prostate cancers

Mice studies
Phase II studies in humans

68Ga-PSMA-11 PET/CT

Alpha with very short half life

P-substance Glioma
lintuzumab → leukemia
Take Home Messages

Isotopes for theranostics:

- Combined gamma and charge particle emission is desired
- Diagnostic $\to$ gamma emission (low LET)
- Therapy $\to$ $\alpha$, $\beta^-$, Auger (high LET)

Possible pre-TTT and post-TTT dosimetry

With PET or SPECT data

Diagnostic pairs (ex In-111 for Y-90 in radio-immunotherapy):
Diagnostic isotope half-life comparable to therapeutic isotope half-life

Enable pre-TTT dosimetry

Isotope production
Safe
Economic

New radiopharmaceuticals for theranostic are coming
Thank you for your attention

Questions?