Targeted Radionuclide Therapy - What are the issues?

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QuickTime™ and a H.264 decompressor are needed to see this picture.
Targeted Radionuclide Therapy

The principle aim is to increase the radiation dose to the target (tumour) relative to non-target tissues
Targeted radiotherapy - considerations

- Choice of radionuclide
- Target selection
- Vector Design
- Delivery system
- Radiobiology
- Clinical applications
Choice of Radionuclide

- Physical decay characteristics
  - Mode of decay, half life
- Availability
  - Reliability, scale, cost
- Radiolabelling chemistry
  - Simplicity, stability, pharmacokinetics
Radiolabelling Chemistry

Three main categories

- **Halogens** - Iodine, Astatine
- **Group VII elements** - Technetium/Rhenium
- **Trivalent metals** - Indium, Yttrium, Bismuth
# Radionuclides - Therapy

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Type of decay</th>
<th>Energy (MeV) $E_{\beta\text{max}}$</th>
<th>Energy (MeV) $E_{\gamma}$</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{177}$Lu</td>
<td>$\beta^- \gamma$</td>
<td>0.2-0.5</td>
<td>113(6)% 208(11%)</td>
<td>6.7 days</td>
</tr>
<tr>
<td>$^{47}$Sc</td>
<td>$\beta^- \gamma$</td>
<td>0.4-0.6</td>
<td>159(68)</td>
<td>82 hours</td>
</tr>
<tr>
<td>$^{67}$Cu</td>
<td>$\beta^- \gamma$</td>
<td>0.4-0.6</td>
<td>185(49)</td>
<td>62 hours</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>$\beta^- \gamma$</td>
<td>0.61(86%) 0.33(13%)</td>
<td>0.364(80%) 0.284(6%)</td>
<td>8.04 days</td>
</tr>
<tr>
<td>$^{186}$Re*</td>
<td>$\beta^- \gamma$</td>
<td>1.08</td>
<td>137(9)</td>
<td>89 hours</td>
</tr>
<tr>
<td>$^{153}$Sm*</td>
<td>$\beta^- \gamma$</td>
<td>0.6-0.8</td>
<td>100(28%)</td>
<td>1.9 days</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>$\beta^-$</td>
<td>1.71</td>
<td></td>
<td>14.3 days</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>$\beta^-$</td>
<td>2.27</td>
<td></td>
<td>64 hours</td>
</tr>
<tr>
<td>$^{188}$Re</td>
<td>$\beta^- \gamma$</td>
<td>2.1</td>
<td>155(15)</td>
<td>17 hours</td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>$\alpha$</td>
<td>5.8 $\alpha$</td>
<td></td>
<td>7.2 hours</td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>$\gamma$</td>
<td>0.2-0.4 6-8 $\alpha$</td>
<td>440(25)</td>
<td>45 mins</td>
</tr>
</tbody>
</table>

* Not carrier free
Iodogen-diagnostic

'Iodogen' 20µg in 0.5ml Dichloromethane

2 hours R.T.

Store -20°C < 2 years.

Radioiodine (NaI) Protein

Mix Wait 10 minutes

Decant Purify

Column
Iodogen - therapeutic
Target selection

- Location of target - cell surface
- Density of expression - high
- Tissue Distribution - specific to disease
- Internalisation
  - Yes (?)
  - Nuclear trafficking
Potential targets

- Growth factor receptors
- Neuropeptide hormone receptors
- Cytokine receptors
- Transporters
- Integrins
- Differentiation markers
- Oncofoetal antigens
Vectors

- Antibodies
- Peptides
- Small molecules \((m-I(A)BG, \text{chelates})\)
- \textit{et al.}\)
HMFG1 - Immunohistochemistry
RIT-Problems with direct systemic approach

- Slow blood clearance (1-3 days)
- Low tumour uptake (0.001-0.01% per gram in solid tumours)
- High-non-target uptake (~ 30% liver, kidney)
- Immunogenicity - HAMA
  However
- There are exceptions!
Recombinant antibodies

Chimaeric

Humanised or CDR grafted

Native murine antibody

= Mouse

= Human

Minibody

Diabody

SFv

Dab

m.r.u (CDR)
Antibody pharmacokinetics -
Wu AM and Senter PD Nature Biotech 23, 1137 - 1146 (2005)
CD20 Expression

Bone Marrow

Blood, spleen, nodes

Pluripotent stem cell

Lymphoid stem cell

Pre-B cell

B cell

Activated B cell

Plasma cell

CD 20
## Tumour expression of neuropeptides

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Tumor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin</td>
<td>neuroendocrine tumors, non-Hodgkin lymphoma, melanoma, breast,</td>
</tr>
<tr>
<td>a-MSH</td>
<td>melanoma</td>
</tr>
<tr>
<td>LHRH</td>
<td>prostate, breast</td>
</tr>
<tr>
<td>VIP/PACAP</td>
<td>SCLC, colon, gastric, pancreatic</td>
</tr>
<tr>
<td>CCK-2/Gastrin</td>
<td>MTC, SCLC, pancreatic, astrocytoma, stromal ovarian cancer</td>
</tr>
<tr>
<td>Opioid</td>
<td>SCLC, neuroblastoma, breast</td>
</tr>
<tr>
<td>Neurotensin</td>
<td>SCLC, colon, exocrine pancreatic</td>
</tr>
<tr>
<td>Bombesin/GRP</td>
<td>SCLC, breast, colon, glioblastoma, prostate</td>
</tr>
<tr>
<td>Substance P</td>
<td>glioblastoma, astrocytoma, MTC, breast, intra- and peritumoral blood vessels</td>
</tr>
</tbody>
</table>

Reubi et al JNM 2005: 46: 67S
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Uptake and cellular processing of peptide analogs

- Binding
- Internalization
- Metabolism
- Recycling
- Externalization
- Lysosome
- Nucleus
- Nuclear binding
- Endosome
- Receptor
- radionuclide
- peptide analog

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Radiolabelled somatostatin analogues

(D) Phe  
Cys ——— Cys  
123-Iodine → Tyr - (D)Trp - Lys - Thr  
123-I-Tyr-3 - Octreotide
Octreoscan

Indium-111- DTPA
(D) Phe
Cys
Thr(ol)
Cys
Phe - (D)Trp - Lys - Thr

Neospect

Tyr - (D)Trp - Lys - Val

Queen Mary
University of London

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## Antibodies vs Peptides

<table>
<thead>
<tr>
<th>ANTIBODIES</th>
<th>PEPTIDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Immunogenic</td>
<td>Non-immunogenic</td>
</tr>
<tr>
<td>‘Biologicals’</td>
<td>Synthetic</td>
</tr>
<tr>
<td>Expensive</td>
<td>‘Inexpensive’</td>
</tr>
<tr>
<td>Non-toxic</td>
<td>Pharmacological</td>
</tr>
<tr>
<td>Stable</td>
<td>‘Unstable’</td>
</tr>
</tbody>
</table>
Delivery systems

• Direct systemic
• Loco-regional
• Indirect (pretargeted)
Locoregional Therapy of glioblastoma

Before

And

After

4x 25mCy Y-90 labelled antibody

From Riva et al
EJNM 2000 27:601
Antibody Pre-targeting

Step 1: Antibody-streptavidin

BLOOD → TUMOUR
Antibody Pre-targeting

Step 1: Antibody-streptavidin

Step 2: Clearing agent
Antibody Pre-targeting

Step 1: Antibody-streptavidin
Step 2: Clearing agent
Step 3: Radiolabelled biotin
Effect of clearing agent on antibody blood clearance

Courtesy NeoRx
Biodistribution of non-pretargeted DOTA-Biotin.

Courtesy NeoRx
200µCi Non-pretargeted 90-Y Labeled antibody

800µCi Pretargeted 90-Y Labeled DOTA-Biotin

A

AUC\text{tumor} = 3314
AUC\text{blood} = 2724
Ratio T/B = 1.22

B

AUC\text{tumor} = 16,200
AUC\text{blood} = 572
Ratio T/B = 28.3

■ = tumour

○ = blood

Courtesy NeoRx

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Pre-targeting of anti-CD20 antibodies

A, C = directly labelled antibody

B, D = pre-targeted antibody

Krishnan Subbiah et al
Pre-targeting of anti-CD20 antibodies

- Directly labelled antibody
- Pre-targeted antibody

Data 24 hours after injection of radioactivity

Krishnan Subbiah et al
Pre-targeted therapy of SCLC xenografts with ● 200µCi 90-Y antibody, □ 200, ▲ 600, ▼ 800µCi pre-targeted Y-90-DOTA Biotin

Radiobiology

- Complex
- Largely unexplored
- Very important
Radiation doses in TRT

• Radioimmunotherapy ~ 10-20 Gy
• Radiopeptide therapy ~ 50-500 Gy
• Dose rates: Typically 2-20 Gy/day (0.1-1 Gy/hr)
• cf. External beam radiotherapy ~ 10-70 Gy in ~ 2 Gy fractions@100’s Gy/hr.
Heterogeneity of dose distribution

- Macro (tissue) level
- Micro (cellular) level
Tissue penetration of electrons/alphas/betas

- 20keV I-125/In-111
- 30keV I-125
- 84keV Ga-67
- 145keV In-111
- 219keV In-111
- 6MeV alpha Bi-213
- 0.6MeV beta I-131
- 2.3MeV beta Y-90

Cell diameter (10um)

(um)  0  100  200  300  400  500  600  700  800  900  1000
Radiation induced damage

Direct effect

Indirect effect

single-strand break
intra-strand cross-link
base modification
double-strand break
base loss

DNA-protein cross-link

photon

H₂O

4 nm
# Alphas vs Betas

<table>
<thead>
<tr>
<th></th>
<th>Energy</th>
<th>Path-length (µm)</th>
<th>LET(KeV/µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y-90</td>
<td>2MeV</td>
<td>3960</td>
<td>0.2</td>
</tr>
<tr>
<td>At-211</td>
<td>6MeV</td>
<td>70</td>
<td>97</td>
</tr>
</tbody>
</table>
Low vs. High LET
The threshold effect

Survival %

High LET radiation
Low LET radiation

More radiosensitive
Less radiosensitive

Dose (Gy)
Clinical applications

- Not destined for ‘Universal’ utility.
  - Some ‘niche’ applications
    - Non-Hodgkins Lymphoma
    - Neuroendocrine tumours
Non-Hodgkins Lymphoma

- Very radiosensitive tissues
- Relatively high antibody uptake
- Non-radiation mediated effects
  - ADCC (antibody-dependent cell cytotoxicity)
  - Receptor (specific) stimulation
  - Apoptosis
$^{90}$Y Zevalin Versus Rituximab Therapy: Response

<table>
<thead>
<tr>
<th></th>
<th>90Y Zevalin</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>CR</td>
<td>30</td>
<td>16</td>
</tr>
</tbody>
</table>

 Patients (%)

$P = 0.002$

$P = 0.04$
Non-Hodgkin’s Lymphoma
CT before and after Radioimmunotherapy
Neuroendocrine tumours

- High target expression
- “High” radiation doses
- Excellent radiopharmaceutical
177Lu-DOTA-TATE

CT of metastasized nonfunctioning endocrine pancreatic tumor before treatment (left) and 3 months after the last treatment (right)

Thank you