Molecular targets for Targeted Radionuclide Therapy

Stephen J Mather
Barts and the London School of Medicine and Dentistry, Queen Mary University of London.
s.j.mather@qmul.ac.uk
Changes in malignancy

Levels may go up ↑ or down ↓
What are we trying to achieve?

• Selective Radiation dose delivery
  
  ↑ as high as possible to the tumour
  ↓ as low as possible to normal tissues
  ↓ as low as possible to ‘important’ normal tissues
How can we achieve this?

• Choose the best target
• Produce the best radiopharmaceutical
• Use the best delivery strategy
• Treat the best patients
Features of the best targets

- High expression in tumour
  - High density
  - High incidence
  - Good access

- Low ‘expression’ in normal tissues
Types of Targets

- **Extracellular**
- Transporters
- Neurotransmitter receptors
- Hormone receptors
- Neuropeptide receptors
- Growth Factor receptors
- Tumour-associated Antibody epitopes
- **Intracellular**
- Metabolic pathways
- DNA/RNA
- Other organelles.
Types of Targets

- Extracellular
- Transporters - Radioiodine
- Neurotransmitter receptors
- Hormone receptors
- Neuropeptide receptors
- Growth Factor receptors
- TAA epitopes
- Intracellular
- Metabolic pathways
- DNA/RNA
- Other organelles
Types of Targets

- *Extracellular*
- Transporters
- Neurotransmitter receptors – peripheral e.g. mIBG
- Hormone receptors
- Neuropeptide receptors
- Growth Factor receptors
- TAA epitopes
- *Intracellular*
- Metabolic pathways
- DNA/RNA
- Other organelles
Nor-adrenaline transporter

LeuT
Phaeochromocytoma vs neuroblastoma
LAT1 Tumour expression
Types of Targets

- Extracellular
- Transporters
- Neurotransmitter receptors
- Hormone receptors
- Neuropeptide receptors - Somatostatin
- Growth Factor receptors
- TAA epitopes
- Intracellular
- Metabolic pathways
- DNA/RNA
- Other organelles
G-protein coupled receptors

In vitro detection of somatostatin receptors in carcinoids.

A, Hematoxylin-eosin.
B, Autoradiogram.
C, nonspecific
D, Hematoxylin-eosin.
E, Autoradiogram showing sst$_2$ mRNA in the tumor by use of a $^{33}$P-labeled probe.
F, Control section

SSTR2 immunohistochemistry in ileal carcinoid

Somatostatin receptor expressing tumours

- GH-producing pituitary adenoma (sst₂, sst₅)
- Nonfunctioning pituitary adenoma (sst₃ > sst₂)
- Gut carcinoid (sst₂ > sst₁, sst₅)
- Gastrinoma (sst₂)
- Insulinoma
- Paraganglioma (sst₂)
- Pheochromocytoma (sst₂)
- Medullary thyroid carcinoma
- Small cell lung cancer (sst₂)

Meningioma (sst₂)
Neuroblastoma (sst₂)
Medulloblastoma (sst₂)
Astrocytoma
Gastric carcinoma
Hepatocellular carcinoma
Renal cell carcinoma
Prostate carcinoma (sst₁)
Breast carcinoma
Ovarian carcinoma
Lymphoma
Leiomyoma
## 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
Peptide autoradiography in breast cancer

CCKR2 radioscintigraphy

Types of Targets

- **Extracellular**
  - Transporters
  - Neurotransmitter receptors
  - Hormone receptors
  - Neuropeptide receptors
  - Growth Factor receptors
- **TAA epitopes**
- **Intracellular**
  - Metabolic pathways
  - DNA/RNA
  - Other organelles
Antibodies e.g. MUC1

- MUC1 is a protein found on the surface of epithelial cells
  - Normal epithelial cells cover the protein with sugar residues
  - Tumour cells produce MUC1 lacking normal sugar coat

- MUC1 is the target for antibodies in the HMFG1 family
  - Only accessible in tumour cells, where protein core exposed
HMFG1 - Immunohistochemistry - Breast cancer
HMFG1 vs SM3
R1549 phase II data in ovarian cancer

- Significant survival benefit vs standard care (historical controls)

R1549 in ovarian cancer – phase III ‘SMART’ trial

- Phase III ‘SMART’ study examining survival benefit
  - R1549 (Pemtumomab) 30mCi i.p. + best std care vs best std care alone
  - Patients like those shown to benefit in phase II study

- Single pivotal study including ~ 420 patients

- Results published 2004
  - No added benefit from RIT
Phase II Trial of Pretargeted Yttrium-90-DOTA-Biotin

1. NR-LU-10 Antibody/Streptavidin
2. Biotin-galactose-HSA clearing agent
3. 110mCi/m2 Y-90-DOTA-Biotin

Responses:
2 PR (8%); 4 SD (16%)

Toxicity:
Diarrhoea: 88% (up to grade IV)
Nausea and Vomiting: 70% (mostly grade I-II)
Fatigue and Anorexia: 70% (mostly grade I-II)
Haematological: 100% (mostly grade I-II)
HAMA, HASA, HACA: 100%

## Some Molecular Targets for RIT in Haematology

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Radionuclide</th>
<th>(Specificity antigen)</th>
<th>Target cell/disease</th>
<th>Isotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-B1 (Tositumomab) (Bexxar™)</td>
<td>I-131</td>
<td>CD-20 antigen</td>
<td>NHL</td>
<td>Murine IgG2a</td>
</tr>
<tr>
<td>LYM-1</td>
<td>I-131</td>
<td>HLA-DR antigen</td>
<td>NHL</td>
<td>Murine IgG2a</td>
</tr>
<tr>
<td>LL2 (Epratuzumab)</td>
<td>I-131, Y-90</td>
<td>CD22 antigen (transferrin R)</td>
<td>NHL</td>
<td>Murine IgG2a</td>
</tr>
<tr>
<td>Anti-CD33 (Hu-M195)</td>
<td>I-131, Bi-213</td>
<td>CD-33 antigen</td>
<td>Acute/chronic myelogenous leukemia</td>
<td>Humanized murine Mab</td>
</tr>
<tr>
<td>Ibritumomab Tiuxetan, (Zevalin™ IDEC-Y2B8)</td>
<td>Y-90</td>
<td>CD20 antigen</td>
<td>NHL</td>
<td>Murine IgGI</td>
</tr>
</tbody>
</table>
Figure 1.3 CD20 is expressed only by B-cell precursors and mature B-cells
CD20

- Restricted to B-cell lineage
- >90% of B-cell malignancies
- Highly expressed (100 - 200,000 copies per cell)
- Not shed/modulated
- No clonal selection
- Direct induction of apoptosis
Non-Hodgkin’s Lymphoma
CT before and after Radioimmunotherapy
90Y Zevalin Versus Rituximab Therapy: Response

- **Patients (%)**
  - 90Y Zevalin: 80 (P=0.002)
  - Rituximab: 56 (CR: 16, ORR: 40)

*P-values indicate statistical significance.*
Figure 1.1 Multiple mechanisms contribute to the cytotoxic activity of MabThera
# Type I and II antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Type</th>
<th>Apoptosis</th>
<th>CDC</th>
<th>ADCC</th>
<th>adhesion</th>
<th>Lipid rafts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>I</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>B1</td>
<td>II</td>
<td>+++</td>
<td>-</td>
<td>++</td>
<td>+++</td>
<td>-</td>
</tr>
</tbody>
</table>
Contributions of radiation and cell signalling

• Radiation:
  – External
  – 131-I anti MHC(II)

• Signalling:
  – Anti-Id
  – Anti-CD19

Yong Du et al, Blood (2004) 103, 1485-1494
EBRT + anti-Id

BCL1

A31
I-131 + anti-Id

A

B

BCL1

A31
I-131 + CD19

- Control
- 18.5 MBq $^{131}$I Anti-MHCII
- 18.5 MBq $^{131}$I Anti-MHCII + anti-CD38
- 18.5 MBq $^{131}$I Anti-MHCII + anti-CD19
- 18.5 MBq $^{131}$I Anti-MHCII + anti-Id

% surviving vs Time after tumor inoculation (d)
HER receptor family
EGF receptor
Table 1: Effect of Gefitinib on Binding, Internalization, and Nuclear Localization of $^{111}$In-DTPA-hEGF in MDA-MB-468 Human Breast Cancer Cells

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion (%)</th>
<th>Proportion of cell-bound $^{111}$In-DTPA-hEGF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radioactivity</td>
<td>Cell-bound radioactivity internalized by cells</td>
</tr>
<tr>
<td></td>
<td>bound to cells</td>
<td></td>
</tr>
<tr>
<td>$^{111}$In-DTPA-hEGF</td>
<td>54.7 ± 8.6</td>
<td>76.9 ± 5.9</td>
</tr>
<tr>
<td>$^{111}$In-DTPA-hEGF + gefitinib</td>
<td>58.1 ± 2.8</td>
<td>81.1 ± 1.0</td>
</tr>
</tbody>
</table>

* $P < 0.05$. 

Epidermal Growth Factor Receptor Inhibition Modulates the Nuclear Localization and Cytotoxicity of the Auger Electron–Emitting Radiopharmaceutical $^{111}$In-DTPA–Human Epidermal Growth Factor. 
Journal of Nuclear Medicine (2007); 48: 1562-1570 
Kristy E. Bailey, Danny L. Costantini, Zhongli Cai, Deborah A. Scollard, Zhuo Chen, Raymond M. Reilly and Katherine A. Vallis
Conclusions

• A variety of targets have been successfully exploited for TRT
• Many interesting targets remain
• Expression on normal tissues may not be a limiting factor - non-receptor mediated mechanisms may dominate
• Intrinsic radiosensitivity of tissues is important
• Synergistic effects of radiation and cell-signalling may be advantageous
Thank you