Targeted Radionuclide Therapy: Practicalities and Potentials

Alan Perkins
University of Nottingham
Nottingham, UK
These Radium Rays have proved highly valuable in the treatment of the following conditions:

- Anemia
- Arteriosclerosis
- Arthritis
- Catarrhal conditions
- Diabetes
- Dental conditions
- General debility
- Goitre
- High blood pressure
- Menopause and
- Menstrual disorders
- Nephritis
- Neuralgia
- Neurasthenia
- Neuritis
- Nervous conditions
- Obesity
- Prostatitis
- Rheumatism
- Senility
- Sexual conditions
- Skin disorders
First developed in the 1950s
Unique in nuclear medicine
$^{131}$I-sodium iodide uptake by differentiated follicular thyroid cells

Proven efficacy, safety & cost
Stands as a marker against which new forms of targeted therapy can be judged.
UK Licensed Therapeutic Radiopharmaceuticals

- NaI
- MIBG
- Metastron
- Quadramet
- Zevalin
Global Perspective

- Different perception of value of nuclear medicine therapy.
- Vast discrepancy in resources between different countries.
- Difference in priorities between different countries.
- Complex relationships between practitioners, researchers, industry and regulatory authorities.
- Variable standards (efficacy/safety).
The promise of targeted molecular radiotherapy

External

Internal
The Bystander effect: Penetrating radiation minimises the problem of limited access in bulky or poorly vascularized tumours.
## Choice of Radionuclide

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>$T_{1/2}$</th>
<th>Emission</th>
<th>Mean Path Length</th>
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<td>60.0d</td>
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<td>7.2h</td>
<td>alpha</td>
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<td>50d</td>
<td>beta/gamma</td>
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<tr>
<td>Y-90</td>
<td>2.67</td>
<td>beta</td>
<td>3.9mm*</td>
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</tbody>
</table>

*Note: $^{91}I$ --> 3mm dia.  $^{90}Y$ --> 2cm dia.

Wheldon et. al. Radiother. Oncol. 1998
Rhenium-188

- Generator produced ($^{188}$W/$^{188}$Re generator).
- $^{188}$Re obtained as sodium perrhenate.
- Carrier-free.
- Same periodic group as technetium therefore Tc & Re complexes have similar chemical properties.
- Re chemistry requires validation.
$^{188}$W/$^{188}$Re generator

$^{188}$Re carrier free sodium perrhenate

Yield of Rhenium-188 Generator (3.5 GBq)
Re-188 therapy conjugates

Re-188-antibody
Re-188-lipodol for hepatoma
Re-188-HEDP

Clinical

doi:10.1038/sj.bjc.6601158

**Therapeutic efficiency of rhenium-188-HEDP in human prostate cancer skeletal metastases**

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RHENIUM-188 ANTIBODIES FOR CANCER RADIOIMMUNOTHERAPY
MARIO DE DECKER
University of Groningen NL
J HARVEY TURNER
University of Western Australia

$^{188}\text{Re} - \text{RITUXIMAB ANTI CD 20}$

$^{188}\text{Re} - \text{BASILIXIMAB ANTI CD 25}$

$^{188}\text{Re} - \text{TRASTUZUMAB ANTI HER neu 2}$

$^{188}\text{Re} - \text{CAMPATH ANTI CD 52}$
Targeting mechanisms

1. Metabolic process
   - Radioiodine
   - Radiophosphorus
   - Meta-iodobenzylguinadine

2. Extracellular mechanisms
   - Bone seeking agents
   - Radiolabelled cells

3. Cell surface receptors
   - Hormones
   - Peptides
   - Antibodies
   - Aptamers

4. Directed administration
   - Intralesional
   - Intra-arterial
   - Intracavitary
Molecular carriers?

Antibodies

Peptides

Aptamers
Antibody Targeting

Antigen combining sites

Antibody (IgG)

Linker

Cell killing moiety (Drug or radionuclide)
<table>
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<tr>
<td>CD229</td>
<td>Ly9</td>
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</table>
Do antibodies work in vivo?
Patient with bone metastases from bladder cancer.

Gamma camera image of the lower legs, 5 hours following injection of Tc-99m-C595 anti MUC1 antibody.

AC Perkins QMC Nottingham
Patient with arterial thrombus in the right femoral artery.
Right: In-111-P256 Fab’ platelet specific antibody showing focal uptake at 3 sites.
Left: X-ray contrast angiogram confirming sites of thrombus in femoral artery.

AC Perkins, QMC Nottingham
Antibody-directed therapies for hematological malignancies

Michael L. Linenberger, David G. Maloney and Irwin D. Bernstein


THE EMERGING ROLE OF RADIOIMMUNOTHERAPY IN HAEMATOLOGICAL MALIGNANCIES
T. M. Illidge
P. W. M. Johnson

Cheson BD - J Clin Oncol 2001;19:3908-3911
Rationale for Radioimmunotherapy in NHL

- NHL is inherently sensitive to radiation.

- Radiotherapy *can* be curative in early stage NHL but is less easily applied to advanced stage disease.

- Synergistic activity between naked Mab and radionuclide.
Zevalin (Ibritumomab Tiuxetan)
Murine parent of rituximab

Suitable for outpatient administration

**CD20 antigen**
- Hydrophobic, 35 kD phospho-protein
- Expressed only on B lineage cells
- Important for cell cycle initiation and differentiation
- Does not shed, internalize or modulate
Bexxar - Iodine-131 Tositumomab

Tositumomab

- murine IgG2\textsubscript{a} anti-CD20 MAb
- B-cell specific
- triggers apoptosis
- antibody-dependent cellular cytotoxicity

Iodine-131

- gamma emission - allows individual dosimetry
- restricts outpatient use.
Antibody Targeted Therapy

**Systemic administration**
Largely limited to diffuse refractory lymphomas
Design of treatments can be improved
Pretargeting strategies

**Intracavitary administration**
Suitable for solid tumours
Direct intralesional injection e.g. glioma
IP administration for ovarian carcinoma
Intravesical administration for superficial bladder cancer
Intravesical Therapy

- Simple procedure
- Well tolerated
- No systemic effects
- Can be easily repeated
Patient 10 (PK): 40MBq Re-188-C595

Re-188-C595 Post washout

Large superficial TCC
Tumour to normal tissue ratio = 79:1
What are aptamers?

- Aptamers derived from the Greek word *aptus*, meaning “to fit”

- Aptamers are single or double stranded RNA or DNA oligonucleotide ligands selected for high affinity and the specific molecular fit with targets of interest.
Molecular size

- Intact antibody: 150kDa
- Fab fragment: 50kDa
- Single chain fragment: 27kDa
- Aptamer: 8-12kDa
- Small peptide: 0.5-2kDa
Aptamer production
Systematic Evolution of Ligands by Exponential enrichment SELEX

• SELEX is a method of combinatorial chemistry employing libraries of nucleic acids for the recognition of a variety of biological and chemical targets
• It is a technology for the identification of high affinity and specificity oligonucleotide ligands (aptamers) based on consecutive rounds of selection and amplification
What is SELEX made of?

SELEX Libraries

- Libraries may be:
  - Synthetic oligonucleotides (ds or ss, RNA or DNA)
  - Digested genomic DNA

- Library size:
  $4^n$ where $n=$number of degenerate bases, eg for an oligonucleotide with 25 degenerate bases:

$$4^{25} = 10^{15}$$

different ligands

25 degenerate bases will allow formation of all common secondary structural motifs
Selection Procedure

1. Add Library
2. Selection
3. All unbound species are washed away
4. Elution and Desalting
5. Freeze-drying
6. PCR amplification
7. Successive Selection rounds
8. Cloning
9. Analysis of Positive clones
10. Sequencing
Aptamer binding

Aptamers have proved to be highly selective high affinity-binding ligands.

The binding characteristics of aptamers can be influenced by the experimental system used for their selection (modified bases, pH changes, or salt concentrations).

- **Affinity of aptamers for:**
  - Antibodies: $K_d = 1 \text{nM}$
  - Growth Factors: $K_d = 0.2 \text{nM}$
  - Hormones: $K_d = 60 \text{nM}$
  - Enzymes: $K_d = 10 \text{nM}$
  - Amino acids: $K_d = \sim 10 \text{nM}$
Why use Aptamers?

• Cheap, efficient, reproducible and rapid production

• Stable: - long term storage
  - transportation in ambient temperatures

• Versatile and easy to modify

• Small size - less immunogenicity,
  - good tumour penetration

• Good as inhibitors, antagonists or regulators of pathways
  (VEGF, NX1838)

• Carrier/reporter molecules
  (Fluorophores, radionuclides etc)

• Excellent molecular probes and sensor recognition units
Applications

• DNA ligands as inhibitors or antagonists

• Diagnostic assays

• Sensors (biosensors/chemosensors)

• Targeted therapeutics:
  • Delivery system for non-specific inhibitors
  • Drug attached to aptamer
  • Radionuclide attached to aptamer
Macugen™

- The first pharmaceutical aptamer formulation, Macugen® (pegaptanib sodium injection) was approved in the United States in 2004.
- Anti-VEGF aptamer formulation.
- Used for the treatment of Neovascular age-related macular degeneration.
- Pegaptanib sodium is a covalent conjugate of twenty-eight nucleotides in length terminating in a pentylamino linker, to which polyethylene glycol (PEG) is attached via the two amino groups on a lysine residue.
- It is formulated as a sterile, aqueous solution for intravitreous injection.
**Macugen™ Mode of action**

**VEGF** binds to its receptors on the cell surface and stimulates angiogenesis.

**Macugen** binds to **VEGF**. This prevents **VEGF** from binding to the receptors on the cell surface. As a result, angiogenesis is not stimulated.
intravitreous injection

Macugen Injection

Leaking blood vessel
Aptamers as imaging agents

1. Thrombus

2. Inflammation

3. Alzheimer’s Disease
In 2000 Hicke and Stephens used the term “escort aptamers” indicating that aptamers offered a delivery service for diagnosis and therapy.

- Aptamer (TTA1) produced against extracellular matrix protein Tenascin-C.
- Radiolabelled with $^{99m}$Tc using mercapto-acetyl glycene ($\text{MAG}_2$) and DTPA.
- Biodistribution studies were undertaken in nude mice bearing either U251 glioblastoma or MDA-MB-435 breast tumour xenografts.
Tc-99m-TTA1 aptamer directed against Tenascin-C

U251 glioblastoma xenografts
Selected aptamers against MUC1
MCF-7 tumour imaging

Poor tumour visualisation due to high amount of activity in the kidneys and bladder resulting from the rapid clearance of the aptamers due to their small size.
Electronic autoradiography

MCF-7 Tumour Slides

Imaging of tumour slides in a microchannel plate detector

Tumour penetration of aptamers superior to Mab!
Tumor Therapy with Targeted Atomic Nanogenerators

Michael R. McDevitt,¹ Dangshe Ma,¹ Lawrence T. Lai,¹ Jim Simon,² Paul Borchardt,¹ R. Keith Frank,² Karen Wu,¹ Virginia Pellegrini,¹ Michael J. Curcio,¹ Matthias Miederer,¹ Neil H. Bander,³ David A. Scheinberg¹*

A single, high linear energy transfer alpha particle can kill a target cell. We have developed methods to target molecular-sized generators of alpha-emitting isotope cascades to the inside of cancer cells using actinium-225 coupled to internalizing monoclonal antibodies. In vitro, these constructs specifically killed leukemia, lymphoma, breast, ovarian, neuroblastoma, and prostate cancer cells at becquerel (picocurie) levels. Injection of single doses of the constructs at kilobecquerel (nanocurie) levels into mice bearing solid prostate carcinoma or disseminated human lymphoma induced tumor regression and prolonged survival, without toxicity, in a substantial fraction of animals. Nanogenerators targeting a wide variety of cancers may be possible.
Merits of and radiation

- The mass is 7000 x that of (4 mass units versus 1/1800)
- The 's energy is 30 x that of (typically 6 MeV versus 200 keV)
- The electric charge is double (+2 versus -1)
- LET ~100 times greater (range 50-90 m)
- Typically 0.25Gy in 10 m cell diameter
- The effective range of particles in tissue is approx 5 cell diameters compared with hundreds/thousands for particles.
Some $\beta^-$-emitting radionuclides of interest to nuclear medicine

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<th>energy (MeV)</th>
<th>Range (m)</th>
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<td></td>
<td></td>
<td>5.9</td>
<td>58</td>
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</table>
Radium-223 treatment of skeletal metastases

Cations of the heavy alkaline earth elements naturally seek bone!

\[ ^{223}\text{Ra} \quad (\text{T}_{1/2} = 11.4\text{d}) \]
\[ \rightarrow ^{219}\text{Ra} \quad (\text{T}_{1/2} = 3.96\text{s}) \]
\[ \rightarrow ^{215}\text{Po} \quad (\text{T}_{1/2} = 1.78\text{ms}) \]
\[ \rightarrow ^{211}\text{Pb} \quad (\text{T}_{1/2} = 36.1\text{m}) \]
\[ \rightarrow ^{211}\text{Bi} \quad (\text{T}_{1/2} = 2.17\text{min}) \]
\[ \rightarrow ^{207}\text{TI} \quad (\text{T}_{1/2} = 4.77\text{min}) \]
\[ \rightarrow ^{207}\text{Pb} \quad \text{(stable)} \]
Preclinical studies employing $^{223}$Ra ($T_{1/2} = 11.4$ d) in a skeletal metastases model of human breast cancer revealed a strong affinity for the skeleton and demonstrated significant anti-tumor activity.


Phase I clinical trial in patients with skeletal metastases from breast and prostate cancer.

Dose range 46-250kBq/kg

Algeta is conducting trial BC1-02 as part of its Phase II clinical trial of Alpharadin(TM), a novel radiopharmaceutical based on the alpha particle emitter radium-223, which naturally targets and attacks skeletal metastases. The double-blind placebo-controlled trial involves 64 patients with painful skeletal metastases as a consequence of HRPC and is in its follow-up phase at 11 centers in Norway, Sweden and the UK. The trial was fully enrolled in May 2005. Algeta believes that Alpharadin may offer an anti-tumor effect and significant advantages over existing palliative treatments, improving life expectancy and quality of life based on the following key properties: Demonstrated anti-tumor effects, Minimal side-effects, Ready-to-use formulation of radium-223 chloride, Administered on out-patient basis, Intrinsic targeting of skeletal tissues, Selective accumulation in skeletal metastases, Optimal half-life of 11.4 days, Photo emission enables concurrent imaging, Safe and easy produce, delivery, handling and disposal.
Practicalities of targeted therapy
Radiopharmaceutical Laboratory

Sterile pharmaceutical production area

Radiation laboratory

Regulatory certificates and licences
  e.g. UK  MHRA
  Environment Agency
  Heath and Safety
  Dept of Health.
Radiation Protection Standards

- Registration and Authorisation Certificates
- Local rules dated and reviewed
- Warning signs for Controlled/Supervised areas
- Staff monitoring
- Appropriate use of shielding
- Calibration of contamination monitors
- Storage of radioactive materials
- Disposal of radioactive waste
- Safe to clean/permit to work
- Radiation audit
References

5. Medical and dental guidance notes. IPEM York 2002
Therapeutic radiopharmaceuticals

- Dispensed in the radiopharmacy as sterile products.
- Use licensed products when possible.
- Written procedures for all preparations.
- Batch manufacturing records,
  lot No, staff names etc.
- QC and sterility tests
  Essential for therapeutics
  (some tests may be retrospective)
- Adverse reactions reported.
Administration to patients

Checklist

1. Full patient history including home circumstances
2. Patient identification
   - Name / d.o.b. / address
3. Any patient questions?
4. Check radiopharmaceutical,
   - Radionuclide & chemical form.
5. Amount of radioactivity prescribed for the procedure.
   - Administration set
   - Gloves and syringe shield.
6. Route and speed of injection.
7. Flushing of the line.
Breast feeding patients

*(Physical and chemical characteristics of emitted radiation)*

Interrupt breast feeding and monitor activity in milk.

*(Pharmacokinetics and excretory path of radiopharmaceutical)*

Obtain advice from:

Publications and Notes for Guidance.

*(For table of excretion data see J Nucl Med 2000;41:863-873)*

Nuclear Medicine Department.

RPA/MPE.