Innovations in cancer treatment

Matthias D'Huyvetter

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Matthias D’Huyvetter is a co-Founder of Camel-IDS SA/NV
Targeted radionuclide therapy

• Tumor cells with a specific protein over-expressed on their surface
• Accessible for circulating agents
• Guide a therapeutic radionuclide to the expressed protein using a target-specific vehicle
• Disproportional interaction of the vehicle between normal and tumor cell
• Promotes tumor cell death
Targeted radionuclide therapy

(a) Conventional radiation beam therapy works well for localized cancer but not for cancer that has metastasized.

(b) With targeted radionuclide therapy, the proven effectiveness of radiation in curing cancer can be extended to metastatic and residual cancer.
Targeted radionuclide therapy

*Theranostic* approach of TRNT

The goal of TRNT is to selectively deliver radiation to cancer cells and/or diseased tissue with minimal toxicity to surrounding normal tissues.

The basis for successful TRNT is a theranostic approach that integrates diagnostic testing for the presence of a molecular target for which a specific treatment/drug is intended.

Early diagnostic scans would therefore serve as support for dose estimation and impact the rationale of treatments based on dose-effect relationships.
Targeted radionuclide therapy
TRNT mode of action

- Alpha particle
- Beta particle
- Auger electron

- Antibody (-fragments)
- Peptide
- Substrate

Potency
Range of action

Size
Stability

Stability
Tumor cell retention

Halogenation
Chelation

Target cell retention

Molecular Vehicle

Concentration
Tumor cell specificity

Receptor
Antigen
Enzyme
Targeted radionuclide therapy
TRNT mode of action: radionuclides

- **Radionuclides of interest for imaging:**
  - $\beta^+$ (positron) decay: PET imaging
  - $\gamma$ decay: SPECT imaging

- **Radionuclides of interest for TRNT:**
  - $\beta^-$ decay
    Mainly explored for TRNT
    Path length 0.05-12 mm
    Larger tumor volume
  - Auger electron decay
    Path length < 1 μm
    Cascades of auger electrons
    Intracellular/intranuclear delivery
  - **$\alpha$ decay**
    Path length 50-100 μm
    Metastatic/residual disease
Each type of radiation emitted during atomic decay can be classified by means of its **linear energy transfer (LET)**.

LET corresponds to the energy released over a certain distance. For the same absorbed dose, high LET is more cytotoxic than low LET radiation.

- $\beta^-$: low LET (about 0.2 keV/μm)
  - Reparable damage
- Auger: intermediate LET (4-26 keV/μm)
  - Poorly reparable damage
- $\alpha$: high LET (50-230 keV/μm)
  - Poorly reparable damage

Pouget J.-P. et al. (2011) Clinical radioimmunotherapy—the role of radiobiology
Targeted radionuclide therapy

Selection of radionuclides

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Daughter isotopes*</th>
<th>Physical half-life</th>
<th>Maximum energy (keV)</th>
<th>Associated emissions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-particle emitters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>-</td>
<td>64.1 h</td>
<td>2.284</td>
<td>NS</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>-</td>
<td>193.0 h</td>
<td>606</td>
<td>Gamma</td>
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<tr>
<td>$^{177}$Lu</td>
<td>-</td>
<td>161.0 h</td>
<td>497</td>
<td>Gamma, LEE</td>
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<tr>
<td>$^{67}$Cu</td>
<td>-</td>
<td>61.9 h</td>
<td>575</td>
<td>Gamma, Auger</td>
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<td>$^{186}$Re</td>
<td>-</td>
<td>90.6 h</td>
<td>1077</td>
<td>Gamma, LEE</td>
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<tr>
<td>$^{188}$Re</td>
<td>-</td>
<td>17.0 h</td>
<td>2120</td>
<td>Gamma, EC</td>
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<tr>
<td><strong>Alpha-particle emitters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>-</td>
<td>7.21 h</td>
<td>5.867</td>
<td>Gamma, LEE</td>
</tr>
<tr>
<td>$^{211}$Po</td>
<td>-</td>
<td>516 ms</td>
<td>7.450</td>
<td>NS</td>
</tr>
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<td>$^{225}$Ac</td>
<td>-</td>
<td>240 h</td>
<td>5.830</td>
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<tr>
<td>$^{221}$Fr</td>
<td>-</td>
<td>4.9 min</td>
<td>6.341</td>
<td>Alpha, Gamma, Auger</td>
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<tr>
<td>$^{217}$At</td>
<td>-</td>
<td>32.3 ms</td>
<td>7.069</td>
<td>Alpha</td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>-</td>
<td>45.6 min</td>
<td>6.051</td>
<td>Alpha, Gamma, Auger, Beta-</td>
</tr>
<tr>
<td>$^{213}$Po</td>
<td>-</td>
<td>4.2 μs</td>
<td>8.377</td>
<td>NS</td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>-</td>
<td>45.6 min</td>
<td>6.051</td>
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<td>8.377</td>
<td>NS</td>
</tr>
<tr>
<td>$^{212}$Bi</td>
<td>-</td>
<td>61 min</td>
<td>5.870</td>
<td>Gamma, Auger, Beta-</td>
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<tr>
<td>$^{212}$Po</td>
<td>-</td>
<td>298 ns</td>
<td>8.785</td>
<td>NS</td>
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<tr>
<td>$^{227}$Th</td>
<td>-</td>
<td>18.72 d</td>
<td>6.038</td>
<td>Gamma, Auger</td>
</tr>
<tr>
<td>$^{223}$Ra</td>
<td>-</td>
<td>11.4 days</td>
<td>5.871</td>
<td>Gamma, Auger, Beta-</td>
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<tr>
<td>$^{219}$Rn</td>
<td>-</td>
<td>4 s</td>
<td>6.819</td>
<td>Gamma</td>
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<td>$^{215}$Po</td>
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<td>1.8 ms</td>
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<td>NS</td>
</tr>
<tr>
<td>$^{211}$Bi</td>
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<td>2.14 min</td>
<td>6.623</td>
<td>Gamma</td>
</tr>
</tbody>
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D'Huyvetter et al., Curr Opin Drug Deliv, 2014
Targeted radionuclide therapy
Effects of radiation

Pouget J.-P. et al. (2011) Clinical radioimmunotherapy—the role of radiobiology
## TRNT in clinical practice

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<thead>
<tr>
<th>Indication</th>
<th>Product</th>
<th>Physical half-life of the radionuclide (days)</th>
<th>Emission</th>
<th>Maximum Path length (mm)</th>
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<tr>
<td>Thyroid cancer</td>
<td>$^{131}$I</td>
<td>8.04</td>
<td>$\beta,\gamma$</td>
<td>4</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>$^{177}$Lu-octreotide</td>
<td>6.72</td>
<td>$\beta,\gamma$</td>
<td>1</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>$^{90}$Y-octreotide</td>
<td>2.7</td>
<td>$\beta$</td>
<td>12</td>
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<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>$^{90}$Y-ibritumomab tiuxetan</td>
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<td>Liver metastases</td>
<td>$^{90}$Y-microspheres</td>
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<td>Phaeochromocytoma/neuroblastoma</td>
<td>$^{131}$I-MIBG</td>
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<td>$\beta,\gamma$</td>
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<tr>
<td>Bone metastases</td>
<td>$^{153}$Sm-EDTMP</td>
<td>1.95</td>
<td>$\beta,\gamma$</td>
<td>3.1</td>
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<td>Bone metastases</td>
<td>$^{89}$Sr-chloride</td>
<td>50.5</td>
<td>$\beta$</td>
<td>8</td>
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<tr>
<td>Bone metastases</td>
<td>$^{223}$Ra-chloride</td>
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* D'Huyvetter et al., Curr Opin Drug Deliv, 2014
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D'Huyvetter et al., Curr Opin Drug Deliv, 2014
TRNT in clinical practice

$^{223}$Radiumchloride (Xofigo)

- Previous therapies for bone metastases did not improve survival
- Multiple metastatic lesions, which make XRT treatment difficult
- Bone metastases are a major cause of death, decreased QOL and increased cost of treatment
- More than 90% with metastatic prostate cancer have bone metastases

$^{233}$Ra ($\alpha$ emitter) is preferentially absorbed by bone by virtue of its chemical similarity to calcium
- When not taken up by bone it is cleared, primarily via the gut, and excreted
- The very short path length reduces damage to surrounding healthy tissues, producing an even more localized effect than the $\beta^-$ emitter $^{89}$Sr
TRNT in clinical practice

$^{223}$Radiumchloride (Xofigo)

- **Toxicity Rationale:** Minimizes bone marrow irradiation compared with $\beta$-emitters

- **Efficacy Rationale:** Maximizes irradiation of adjacent tumor cells
TRNT in clinical practice

$^{223}$Radiumchloride (Xofigo)

ALSYMPCA Phase III: Overall Survival (*Parker et al., 2012*)

![Graph showing overall survival](image)

- **HR 0.695; 95% CI, 0.552-0.875**
- **$P = 0.00185$**

- **Radium-223, n = 541**
  - Median OS: 14.0 months
- **Placebo, n = 268**
  - Median OS: 11.2 months
Targeted radionuclide therapy
Molecular vehicles on the road to clinic

- Peptides ($^{68}$Ga/$^{177}$Lu-PSMA peptide)
- Protein scaffolds (affibody)
- Monoclonal antibodies
- Antibody-fragments (diabody, minibody, nanobody)
Targeted radionuclide therapy
Molecular vehicles on the road to clinic

- Peptides ($^{68}$Ga/$^{177}$Lu-PSMA peptide)
- Protein scaffolds (affibody)
- Antibody fragments (diabody, minibody, nanobody?)
Molecular vehicle
Nanobody (VHH, sdAb)

Classic Monoclonal Antibody

- heavy and light chains
- both necessary for antigen-binding

Single chain antibodies

- only heavy chains
- functional for antigen-binding
- Camelidae species

Nanobody

- nanomolar affinity
- produced in bacterial system
Molecular vehicle
Nanobodies as imaging tools

Preclinical imaging

$^{99m}$Tc-labeled anti-HER2 nanobody

Clinical imaging

$^{68}$Ga-labeled anti-HER2 nanobody
Molecular vehicle

*Theranostics* in nanobody-based TRNT

The strategy whereby related molecular vehicles are used for both diagnosis and therapy.
HER2\text{pos} breast cancer

Background: HER2

- More than 1.676.000 new cases diagnosed in 2012
- 20-30\% of breast cancer identified with HER2-protein overexpression

- Significant number of systemic disease recurrence after standard care
- There is a need for systemic adjuvant therapy strategies
Radio-lanthanide $^{177}$Lu

- $\beta^-$ particles
- $\gamma$ for imaging purposes
- $T_{1/2} = 6.72$ days

- Choice of bifunctional chelator!
- Impact on radiopharmaceutical functionality

$^{177}$Lu labeling of anti-HER2 Nanobody

$D’Huyvetter$ et al., 2012; Contrast media & Mol imaging
$D’Huyvetter$ et al., 2014; Theranostics
$^{177}$Lu-labeled anti-HER2 nanobodies
Preclinical biodistribution

$^{177}$Lu-labeled anti-HER2 monoclonal antibody
$^{177}$Lu-labeled anti-HER2 nanobody
$^{177}$Lu-labeled anti-HER2 nanobodies

Targeted radionuclide therapy

Saline

Non-targeting nanobody

Anti-HER2 nanobody

![Graph showing tumor volume over time](image)

- Tumor volume (mm$^3$)
- Time, days
- Saline
- Non-targeting nanobody
- Anti-HER2 nanobody
177Lu-labeled anti-HER2 nanobodies
Targeted radionuclide therapy

Events
1. Mortality
2. 20% weight loss
3. Ulcerating tumor
4. Tumor volume > 250mm³
177Lu-labeled anti-5T2 nanobodies
Background: multiple myeloma

- 114,000 new cases of myeloma worldwide in 2012
- Blood cancer that starts in plasma cells, inside bone marrow

- Production of M-protein (paraprotein)
  - Secreted into blood and (often) associates with the MM cell surface

- Incurable disease (chemotherapy)
  - Residual chemoresistant MM cells in bone marrow

Plasma cells
  - Produce mAbs
  - Fight infections
$^{177}\text{Lu}$-labeled anti-5T2 nanobodies

Imaging multiple myeloma

- SPECT/micro-CT images of mice using $^{99}\text{Tc}$-labeled anti-5T2 nanobody
$^{177}$Lu-labeled anti-5T2 nanobodies
Targeted radionuclide therapy

(A) SPECT/micro-CT scans of $^{99m}$Tc-anti-5T2 nanobody after 5 weeks of treatment

(B) Weight of spleen after 7 weeks of treatment
Novel target
Targeting the tumor stroma

Cancer cells
Structural cells
Immune cells:
T cells
Granulocytes
Monocytes
Dendritic cells
Macrophages

M1 type
M2 type
Tumor promotion
Novel target
Function of TAM

1. Invasion
2. Angiogenesis
3. Immuno-suppression
4. Metastasis
Macrophage Mannose Receptor (MMR, CD206) is a marker expressed on subset of TAM’s

- MMR >>> TAM’s
- Progressed disease
- Hypoxic regions

Production of single-domain antibody fragments (sdAb) or Nanobodies (Nbs) against MMR

Labeling of lead compound with radioisotopes

NEW prognostic tracer for imaging

NEW Potential target for TRNT
Novel target
Lead compound M2TARGET

- Phase I clinical trial with $^{68}$Ga-labeled M2TARGET in head and neck, breast and lung cancer patients is under preparation.
- These type of tumors are known for high infiltration of macrophages and severe hypoxic regions.
- Poster Anneleen Blykers.

$^{99m}$Tc-labeled

Movahedi et al., 2012
Future perspectives

• The road to clinical translation of radiolabeled nanobodies for TRNT
  ➢ successful nb-based TRNT in two distinct preclinical disease models

• Further investigation of kidney retention of nanobodies
• Identifying the optimal combination of nanobody >> radioisotope

New targets and disease models
➢ targeting tumor-supporting macrophages in tumor-stroma (MMR-target)

New radiochemistry procedures
➢ further augment target accumulation and reduce aspecific accumulation

Additional radioisotopes
➢ α-emitters
VHH-based TRNT (1)
Industrial valorization

Specific delivery of intense radiation to cancer cells using camelid derived antibody fragments

Clinical Trial Phase 1 in HER2-positive breast cancer begins in September 2015
VHH-based TRNT (2)
Industrial valorization

- Radiolabeled monoclonal antibody
  - Rapid and specific tumor uptake: therapeutic effect
  - Faster elimination from healthy tissues: low toxicity

- Radioiodinated VHH

Camel-IDS
Strikethecancer,notthepatient
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