Targeted molecular radiotherapy
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What is molecular radiotherapy?

Therapeutic approach that uses radionuclides or radiolabeled drugs to kill cancer cells.
What is molecular radiotherapy?

Delivery of radioactivity to tumor takes advantage of some aspect of tumor physiology to provide targeted accretion of radioactivity in tumor cells or in their immediate vicinity.

MRT: Interdisciplinary approach

- Radiochemistry
- Nuclear medicine
- Radiation oncology
- Internal medicine
- Medical physics
- Radiation safety
Targets for MRT

- tumor viability
- tumor proliferation
- cell membrane turnover
- antigen-antibody systems
- peptides and their receptors
- other ligands and their receptors

Radiation therapy and Targeted molecular radiotherapy: complementary modalities
RT and targeted MRT

requires knowledge of tumor location

requires knowledge of tumor biology

Targeted molecular radiotherapy

Intensity modulated radiation therapy

http://www.spectral.com/imrt.shtml

http://www.cambridgecancercentre.org.uk/users/fia20;
contributed by Dr. Franklin Aigbirhio.
Targeted MRT

Heterogeneity of cancer genome
- targeting cancer subsets
- targeting cancer mutations

Epigenetics
- targeting cancer subsets
- targeting cancer mutations

Cancer stem cells
Circulating metastasis-initiating cells

Therapeutic targeting of cancer

Hanahan and Weinberg, 2011
Merits of targeted MRT

**Targeted Molecular Radiotherapy**

Treatment can be individualized based on tumor molecular profile, confirmed by imaging, and complemented by genetic evaluation

**tMRT**

- Molecular imaging identifies the most appropriate therapeutic targets
- Theranostic approach guides the selection of radionuclides
- Dosimetry determines the best radionuclide and targeting molecule for tumor eradication while sparing normal tissues

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Merits of targeted MRT

**tMRT**

- Customized radiotherapeutic cocktails are conceivable containing radionuclides emitting different radiation molecular carriers with diverse biological properties multiple tumor-associated molecular targets
- Noninvasive monitoring of the distribution of the targeted radionuclide
- Multiple treatments with non-immunogenic radiotherapeutics
Adaptive MRT

• patient is initially treated with targeted MRT using a high-energy β-emitting radionuclide to reduce tumor volume

• molecular imaging with the same vector evaluates tumor responses and helps to adjust the next treatment to the altered molecular status of the tumor

• if response to MRT changes molecular target population, alter the molecular vector or radionuclide, as needed

• subsequent treatment for residual disease with an α-emitting radionuclide with a more focal irradiation

The U.S. FDA-approved radiotherapeutics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trade name</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>sodium $[^{131}I]$iodide</td>
<td>HICON™</td>
<td>treatment of carcinoma of the thyroid</td>
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<tr>
<td>$[^{153}Sm]$samarium lexidronam</td>
<td>Quadramet®</td>
<td>relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan</td>
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<tr>
<td>$[^{89}Sr]$strontium chloride</td>
<td>Metastron™</td>
<td>relief of bone pain in patients with painful skeletal metastases that have been confirmed prior to therapy</td>
</tr>
<tr>
<td>$[^{223}Ra]$radium chloride)</td>
<td>Alpharadin®</td>
<td>treatment of CRCP patients whose cancer has spread to the bone</td>
</tr>
<tr>
<td>$[^{32}P]$chromic phosphate</td>
<td>Phosphocol®</td>
<td>intraperitoneal or intracavitary for treatment of peritoneal or pleural effusions caused by metastatic disease</td>
</tr>
</tbody>
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| $^{90}$Y yttrium ibritumomab tiuxetan | Zevalin® | • treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin’s lymphoma  
• treatment of previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy |
| $^{131}$I tositumomab | BEXXAR® | CD20 antigen-expressing relapsed or refractory, low grade, follicular, or transformed non-Hodgkin’s lymphoma, including patients with Rituximab-refractory non-Hodgkin’s lymphoma |
| $^{123}$I-MIBG | Iobenguane® | primary or metastatic pheochromocytoma or neuroblastoma |

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When MRT is applicable?

1. Metastatic disease
2. Minimum residual disease
3. Microscopic disease
Metastatic disease

skeletal metastases

Zevalin

Radiation dosimetry results for zevalin radioimmunotherapy of rituximab-refractory non-hodgkin lymphoma.
http://onlinelibrary.wiley.com/doi/10.1002/cncr.10305/full#fig1
Zevalin: progression free survival

Morschhauser F et al. 90Yttrium-Ibritumomab Tuxetan Consolidation of First Remission in Advanced-Stage Follicular Non-Hodgkin Lymphoma: Updated Results After a Median Follow-Up of 7.3 Years From the International, Randomized, Phase III First-Line Indolent Trial JCO 2013;31:1977-1983

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223RaCl2
Alpharadin
α-emitter

- bone seeking radiopharmaceutical
- first ever FDA-approved α-emitter
- fast track designation by the FDA August 23, 2011
- 223Ra accumulates preferentially in osteoblastic metastases

©2005 by American Association for Cancer Research
Alpharadin targets new bone in metastases...

...and irradiates adjacent tumor cells

\[ ^{223}\text{RdCl}_2 \]

Discovered by Maria Sklodowska-Curie and her husband Pierre on December 21 in 1898.

Alpharadin approved 114 years later.

Used in cancer treatment in France since the 1900s, in Canada in the 1920s and 1930s

In USA, Howard Atwood Kelly, one of four founding physicians of Johns Hopkins Hospital, pioneered radium in cancer treatment in 1904

Kelly founded the privately owned Kelly Clinic in Baltimore, once the leading center for radiotherapy
Howard Kelly establishes gynecologic brachytherapy in the United States.

Alpharadin

Benefits beyond palliation

- Increases overall survival >40% (p=0.017)
- Enhanced quality of life
- Side effect profile similar to placebo
- Effective pain control
- Targets osteoblastic/sclerotic phenotype lesions induced by bisphosphonate therapy
- Provides new option for Taxotere failures
- Provides new option for Taxotere ineligible patients
- Easy to use
- Effective in patients without other treatment options
- Keeps other therapeutic options open
Alpharadin is easy to use

Simple radiopharmacy
- easy logistics
- ready to use — no complex handling
- α particles stopped by syringe or vial wall
- administered dose is very low
- dose rates are very low

Simple Administration
- outpatient procedure
- IV injection — no time-consuming infusion
- no imaging or complex pre-medications
- no limits on interactions with others

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227Th-herceptin

Microautoradiograph of individual α tracks from 227Th-Herceptin bound to BT-474 microcolonies.

Cells were incubated with 10 kBq/ml 227Th-Herceptin for 4 h.

Targeted High-LET Therapy of Bone Metastases. Ø. S. Bruland, D. Jostein, D. R. Olsen, R. H. Larsen

Dual targeted α therapy

- $^{227}$Th-Herceptin targets and penetrates into clusters of tumor cells.
- As $^{227}$Th decays, $^{223}$Ra diffuses and rapidly targets hydroxyapatite in the sclerotic parts of the macroscopic skeletal metastasis

Targeted High-LET Therapy of Bone Metastases. Ø.S. Bruland, D. Jostein, D.R. Olsen, R.H. Larsen

Minimum residual disease
after surgical debulking

Focal nodular enhancement 57 weeks after $^{211}$At-ch81C6 therapy confirmed as recurrent anaplastic oligodendroglioma.

Microscopic disease biomarkers indicate progressing disease in the absence of the macroscopic evidence.
Microscopic disease

micrometastases

neoplasms that spread as microscopically thin sheets on compartmental surfaces

- ovarian carcinoma
- neoplastic meningitis

177Lu-J591 anti-PSMA

7 days after 177Lu-J591 administration
Fractionated radioimmunotherapy with 90Y-clivatuzumab tetraxetan and low-dose gemcitabine is active in advanced pancreatic cancer

UNMC studies:
androgen receptor-targeted MRT

RISAD-P
Key points

Prostate cancer, after primary treatment, is largely driven by androgens and AR.

AR signaling remains the dominant growth pathway in prostate cancers that progress in the setting of low serum androgens.

AR-targeted MRT

RISAD-P

\[ R = {}^{123}\text{I}, {}^{124}\text{I}, {}^{125}\text{I} \]

5-RadioIodo-3’-O-(17β-Succinyl-5α-Androstan-3-one)-2’-Deoxyuridin-5’-yl monophosphate
AR binding

RISAD-P

Lock-in mechanism

RISAD-P
Biodegradable linker

DNA co-targeting
Theranostic approach

RISAD-P

\[ R = ^{123}\text{I}, ^{124}\text{I}, ^{125}\text{I} \]
Why AR targeted drug?

“...AR - targeted therapies will remain a central part of the treatment of advanced stage prostate cancer...”

16β-[\textsuperscript{18}F]fluoro-5α-dihydrotestosterone
67-year-old man with CRPC and PSA of 789 ng/mL
FDHT-predominant nodal disease

16β-[\textsuperscript{18}F]fluoro-5α-dihydrotestosterone
69-year-old man with CRPC and PSA of 213 ng/mL
FDHT-predominant bone disease
Why DNA targeted drug?

S-phase fraction is significantly higher in tumors with high AR density.

Recurrent prostate tumors with AR amplifications are highly proliferative.

Mechanism of uptake
AR and proliferation in PCa

- AR NOT amplified
- one copy of chromosome X: cyan
- and AR gene: purple
- Ki-67
- only a few positive cells are present

- AR amplified
- one copy of chromosome X: cyan
- with multiple copies of AR gene: purple
- Ki-67
- AR amplification is associated with high Ki-67 labeling index

- the higher the levels of AR in the tumor, the higher the proliferative activity
- biopsies from 475 patients

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125IRRISAD-P SPECT-CT

- CT
- fused
- SPECT

- transverse
- coronal

- arrowheads: red – prostate cancer; yellow – stomach content; blue – ID transponder
$^{125}$IRISAD-P necropsy

Folate receptor

good target for MRT
Folate receptors are overexpressed by:
• ovarian cancer
• breast cancer
• colon cancer
• lung cancer
• prostate cancer
• nose and throat cancers
• brain tumors

Folate receptors are also overexpressed on hematopoietic malignancies of myeloid origin, including chronic and acute myelogenous leukemia.

Folate receptor TMRT

- targeting: seeks folate receptor
- albumin-binding: prolongs blood circulation time


NETs peptides
NET peptides

<table>
<thead>
<tr>
<th>Peptide</th>
<th>hSSTR1</th>
<th>hSSTR2</th>
<th>hSSTR3</th>
<th>hSSTR4</th>
<th>hSSTR5</th>
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<tr>
<td>(^{111}\text{In})-octreotide</td>
<td>&gt;10,000</td>
<td>22±3.6</td>
<td>182±13</td>
<td>&gt;1,000</td>
<td>237±52</td>
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<tr>
<td>(^{90}\text{Y})-DOTATOC</td>
<td>&gt;10,000</td>
<td>11±1.7</td>
<td>389±135</td>
<td>&gt;10,000</td>
<td>114±29</td>
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<tr>
<td>(^{90}\text{Y})-DOTALAN</td>
<td>&gt;10,000</td>
<td>23±5</td>
<td>290±105</td>
<td>&gt;10,000</td>
<td>16±3.4</td>
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<tr>
<td>(^{90}\text{Y})-DOTA-OC</td>
<td>&gt;10,000</td>
<td>20±2</td>
<td>27±8</td>
<td>&gt;10,000</td>
<td>57±22</td>
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<tr>
<td>(^{111}\text{In})-DTPA-Tyr3-octreotate</td>
<td>&gt;10,000</td>
<td>1.3±0.2</td>
<td>&gt;10,000</td>
<td>433±16</td>
<td>&gt;1,000</td>
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<tr>
<td>(^{90}\text{Y})-DOTA-Tyr3-octreotate</td>
<td>&gt;10,000</td>
<td>1.6±0.4</td>
<td>&gt;1,000</td>
<td>523±239</td>
<td>187±50</td>
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</tbody>
</table>

Affinity profiles (IC\(_{50}\))\(_a\) for human somatostatin receptors SSTR1–SSTR5 (hSSTR1–hSSTR5) of a series of somatostatin analogues.

All values are IC\(_{50}\)±SEM in nM.

\[\text{[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]\text{Octreotate}}\]

Patient with a NET of unknown origin with multiple liver and bone metastases

Treatment: 1 GBq of \(^{177}\text{Lu}\)-octreotate.

A. CT before treatment with \(^{177}\text{Lu}\)-octreotate, with no evidence of bone metastases.

B. CT 6 wk after treatment with \(^{177}\text{Lu}\)-octreotate, showing bone metastasis located at L2 and shrinkage (pseudocirrhosis) of liver.

C. \([^{111}\text{In-DTPA}^0]\)octreotide scintigraphy before treatment with \(^{177}\text{Lu}\)-octreotate showing uptake in multiple liver and bone metastases.

D. \([^{111}\text{In-DTPA}^0]\)octreotide scintigraphy 4 months after last treatment with \(^{177}\text{Lu}\)-octreotate, showing reduction of liver and bone metastases and shrinkage of liver.

E. Serum alkaline phosphatase, \(\gamma\)-glutamyl transpeptidase, and chromogranin A levels during and 3 months after treatment.
[\textsuperscript{177}Lu-DOTA\textsuperscript{0,}Tyr\textsuperscript{3}]Octreotate

Patient with gastro-entero-pancreatic neuroendocrine tumor.
Plot shows serum chromogranin A concentrations (red symbols, closed line) and patient’s weight (black symbols, dotted line).

[\textsuperscript{177}Lu-DOTA\textsuperscript{0,}Tyr\textsuperscript{3}]Octreotate

\textbf{Patients}: 76 patients with neuroendocrine gastro-entero-pancreatic tumors
\textbf{Doses}: 100 mCi were injected in 20 min; 150 and 200 mCi injected in 30 min
\textbf{Interval between treatments}: was 6–9 weeks
\textbf{Cumulative dose}: 750–800 mCi (27.8–29.6 GBq)
\textbf{Complete remission}: one patient
\textbf{Partial remission} 22 patients (29%),
\textbf{Minor remission}: 9 patients (12%)
\textbf{Stable disease}: 30 patients (40%)
\textbf{Progressive disease}: 14 patients (18%)
Six out of 32 patients who had stable disease or tumor regression after the therapy and were also evaluated after 12 months (mean 18 months from therapy start) developed progressive disease.
In the other 26, the tumor response was unchanged.
Median time to progression was not reached at 25 months from the beginning of therapy.
**[177Lu-DOTA⁰,Tyr³]Octreotate**

Scintigraphy after each cycle

- Decreased uptake of [177Lu-DOTA⁰, Tyr³]octreotate on the last scan; black arrows = index lesion

At 3 and 6 months after four cycles of therapy, the patient had a partial remission (>50% decrease in tumor volume on CT); white arrows = index lesion.

**[90Y-DOTA-D-Phe¹-Tyr³]octreotide**

- Contrast enhanced

Cancer

Volume 118, Issue 11, pages 2915-2924, 21 OCT 2011 DOI: 10.1002/cncr.26616

http://onlinelibrary.wiley.com/doi/10.1002/cncr.26616/full#fig1
90Y-DOTA-D-Phe1-Tyr3 octreotide

SPECT Images
Letters A through C mark metastases

177Lu-Octreotate vs chemotherapy

In conclusion...

- Targeted molecular radiotherapy eradicates cancer cells by targeting specific receptors or antigens, e.g., Bexxar or Zevalin, or physiological processes, e.g., Xofigo (formerly alpharadin).
- Typically, the design of targeting moieties allows the incorporation of imaging radionuclides for PET or SPECT as well as therapeutic radionuclides for molecular radiotherapy (theranostic approach).
- Most molecular radiotherapeutics allow for the adoptive approach.
Co-investigators

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