An Overview of Radiopharmaceutical Therapy (RPT): Past, Present, and (Primarily) Future

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Radiopharmaceutical Therapy (RPT)

- Definition: Use of a systemically or locally delivered radiopharmaceutical that either binds preferentially to or accumulates by physiological mechanisms in the intended “target”.[1]
- Is a targeted approach without use of an external beam.

Historical Perspective

- RPT is certainly not new. [e.g., P-32 for prostate cancer as early as 1936[2]; or radioiodine in the 1940's for thyroid cancer[3]]
- Other Examples:
  - Au-198 or P-32 as liquid colloid, instilled into pleural or abdominal cavity for treatment of ascites or pleural effusions
  - P-32 administered orally to treat polycythemia vera.
  - P-32 delivered locally to treat nasopharyngeoma.
  - Y-90 as liquid colloid to treat rheumatoid conditions

More recently…

- Metastron (^{89}Sr-chloride) for bone pain from metastatic cancer lesions. FDA approval 1993.
- Quadramet (^{153}Sm lexidronam pentasodium) for bone pain from metastatic cancer lesions. FDA approval 1997.
- ^{131}I-MIBG (^{131}I-metaiodobenzylguanidine). FDA approved for pheochromocytoma in 1994. [Approved for other uses subsequently.]
- ^{90}Y microspheres (SirSpheres/Theraspheres) for treatment of liver tumors. FDA approval of Sirspheres March 2002. Approval of Theraspheres 2021.
- Xofigo (^{223}Ra-dichloride) for the treatment of metastatic castration resistant prostate cancer. FDA approval May 2013.
- Lutathera (^{177}Lu-dotatate) for the treatment of somatostatin receptor–positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs). FDA approval January 2018.

What’s ahead?

Let’s defer that until later in the presentation

RPT Agents – General Categories[1]

- Elemental and unconjugated or chelated radionuclides
- Small molecule
- Peptides
- Antibodies
- Nanoconstructs (including liposomes)
- Microspheres

Elemental, unconjugated, and/or chelated[1]

- Elemental radionuclide itself (with or without another non-radioactive drug)
- Salts (e.g., iodides, chlorides, etc.)
- Chelated forms

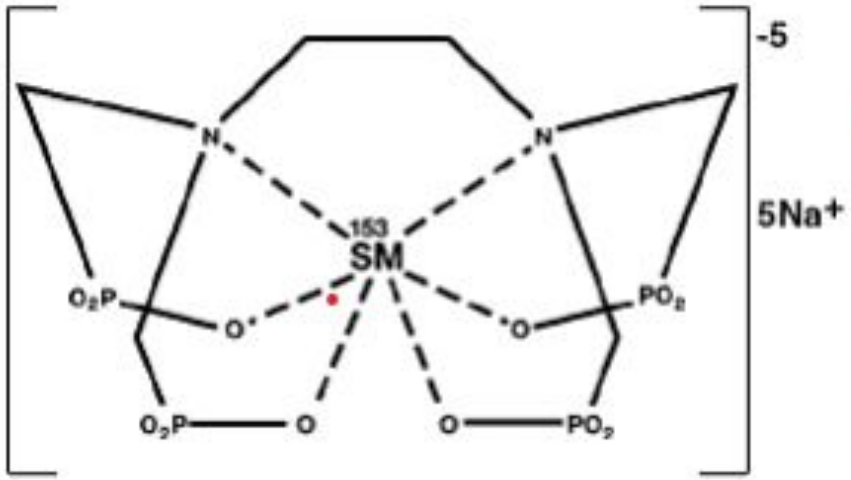
Examples (elemental, etc.)

- P-32 (with or without simultaneous administration of androgens). Non-specific targeting without androgens. Androgens improved uptake in metastatic bone lesions.[2]
- NaI-131. Iodine selectively taken up by differentiated follicular thyroid cells (normal physiological process). No uptake by cancer cells of non-follicular origin or by cancer cells that have reverted to non-differentiated forms.[1]
- Y-90, P-32, Rh-186, Erbium-169 (in Europe only), in colloidal forms (e.g., P-32 chromic phosphate). Direct intra-articular injection for synovitis.[4]
- Sm-153. As $^{153}SmCl_3$, chelated with phosphate ligands [e.g., “Quadramet”, bound to 4 phosphate ligands and 2 amines], taken up by growing bone in metastatic bone lesions.[1]
- Ra-223. As $^{223}RaCl_2$ (“Xofigo”). Calcium analog taken up by growing bone in metastatic bone lesions. [1]

“Quadramet” (chelate example)

(*image from Quadramet package insert*)

The structural formula of samarium lexidronam pentasodium is:



The ionic formula is $^{153}Sm^{+3}$ $[CH_2N(CH_2PO_3^{-2})_2]_2$ and the ionic formula weight is 581.1 daltons (pentasodium form, 696).

Small molecule[1]

- Radionuclides bound to “targeting vectors”, for example:
  - Bound to analogs of normal human molecules of physiologic importance (e.g., neurotransmitters)
  - Bound to molecules that will bind to specific receptors found on the cancer cells to be targeted (e.g., PSMA and folate receptors)
  - Bound to phospholipid ether analogs – does not target a specific receptor but targets the “overabundance of lipid rafts found on cancer cell membranes”.
  - Other(?)

Small molecule examples[1]

- [^{131}I]mIBG (^{131}I-*meta*-iodobenzylguanidine), an analog of the neurotransmitter for treatment of neuroblastomas
- Various PSMA or folate receptor agents (e.g. ^{177}Lu-labelled PSMA-617; ^{227}Th-labelled PSMA-TTC) in clinical trials
- Labelled phospholipid ether analogs targeting cancer cell-specific lipid raft microdomains (e.g. ^{131}I-labelled CLR 131; ^{131}I-labelled CLR1404) in clinical trials

“This just in:” [*from a Novartis “investor update”/press release*]

“Novartis receives FDA Breakthrough Therapy designation for investigational 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (mCRPC)

Jun 16, 2021

Novartis announced today that the US Food and Drug Administration (FDA) has granted Breakthrough Therapy designation (BTD) to ^{177}Lu-PSMA-617, an investigational radioligand therapy for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Breakthrough Therapy designation is granted to medicines being evaluated for serious conditions where early clinical evidence indicates the potential for substantial improvement over available therapy.”

Peptides[1]

- Essentially, targeting various receptors as with the “small molecules” category, but the targeting agents are larger peptides
- Frequent receptor targets include:
  - Somatostatin receptors
  - Bombesin receptors

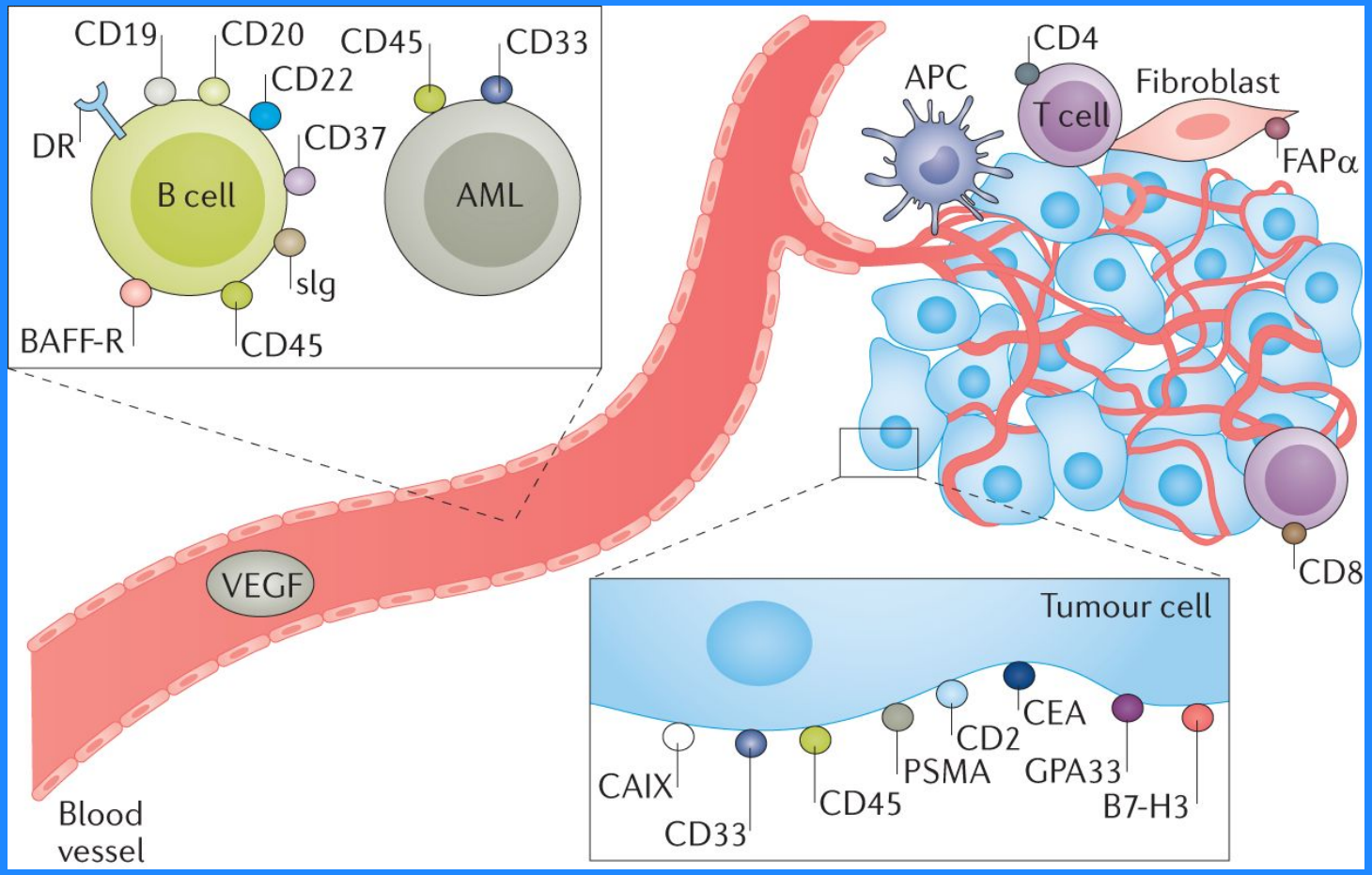
Peptide examples[1]

- ^{177}Lu-DOTATATE (“Lutathera”) for treatment of neuroendocrine tumors. FDA approved.
- ^{177}Lu-labelled NeoBOMB1 (for gastroenteropancreatic cancer). In clinical trials.
- ^{177}Lu-labelled RM2 (for gastroenteropancreatic cancer). In preclinical development.
- ^{90}Y-octreotide (^{90}Y-DOTA-Tyr^{3}-octreotide) for neuroendocrine tumors. In clinical trials.

Antibodies[1]

- Labelled antibodies, target multiple receptors
- Antibodies mostly in the “IgG” class have been studied for RPT
- Specific monoclonal antibodies used
- To date, mostly studied for hematological and lymphoid cancers

Target antigens that have been used in antibody-based radiopharmaceutical therapy.
From: Radiopharmaceutical therapy in cancer: clinical advances and challenges[1]



Antibodies to a variety of tumour-associated targets may be raised, including leukaemia-associated and lymphoma-associated targets (for example, CD20, CD45 and CD33), targets expressed on solid-tumour cancer cells (for example, carcinoembryonic antigen (CEA), prostate-specific membrane antigen (PSMA) and GD2) and targets expressed on their supporting microenvironment (for example, fibroblast activation protein-α (FAPα)). AML, acute myelogenous leukaemia; APC, antigen-presenting cell; BAFF-R, B cell-activating factor receptor; CAIX, carbonic anhydrase 9; DR, death receptor; slg, secretory immunoglobulins. Adapted from ref.[305], Springer Nature Limited.

Antibody-based (examples) [1]

- ^{225}Ac-labelled aCD38 (for multiple myeloma). In clinical trials.
- ^{225}Ac-labelled aCD33 (for leukemia; myelodysplastic syndrome). In clinical trials.
- ^{212}Pb-labelled aCD37 (for leukemia/lymphoma). In preclinical development.
- ^{227}Th-labelled aCD22-TTC (for lymphoma). In clinical trials.

Nanoconstructs[1,5]

- Nanomaterials may be:
  - Inorganic
  - Polymeric
  - Carbon-based
  - Liposomes
- Nanomaterials may radiolabeled by:
  - Chelation
  - Entrapment
  - Sorption
  - Covalent bonding
- One advantage of nanoconstructs is that each nanoparticle may incorporate multiple radioactive atoms

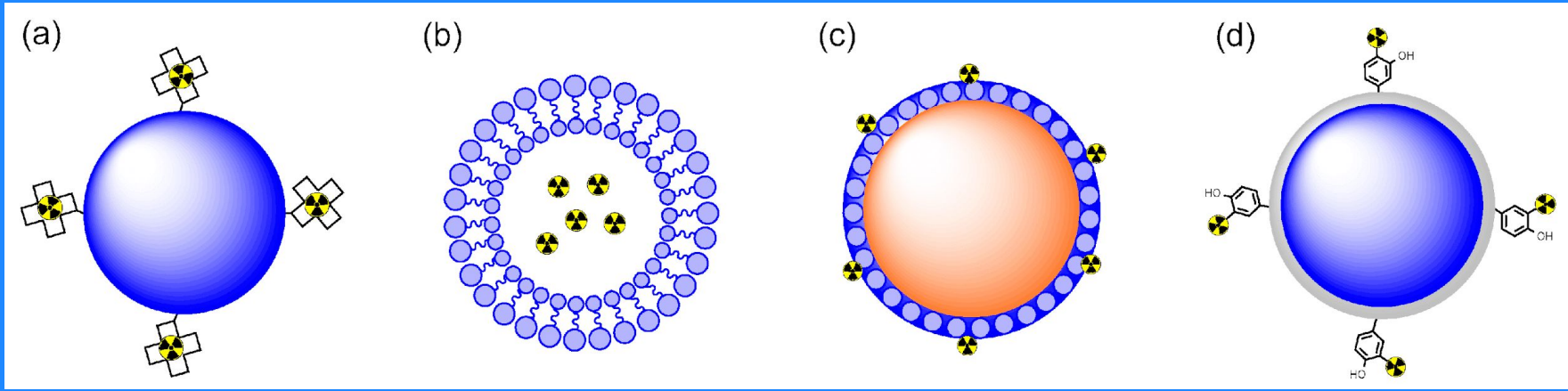


***Figure 2.** Incorporation of therapeutic radionuclides into the nanocarrier by (**a**) chelation, (**b**) entrapment, (**c**) sorption, and (**d**) covalent bonding.

*From: Jeon, J. Review of therapeutic applications of radiolabeled functional nanomaterials. *Int. J. Mol. Sci* **20**, 2323 (2019).

Many Possible Radioisotopes

Beta emitters (e.g.)

- I-131
- Cu-67
- Y-90
- Ho-166
- Lu-177
- Re-186
- Re-188
- Au-198

Alpha emitters (e.g.)

- At-211
- Bi-212
- Bi-213
- Ra-223
- Ac-225

The following publication alone lists 51 different nanoconstruct/radionuclide combinations: Jeon, J. Review of therapeutic applications of radiolabeled functional nanomaterials. *Int. J. Mol. Sci* **20**, 2323 (2019).

Microspheres

- Radiolabeled glass or resin spheres (~20-60 micron diameter)
- Differentiation from nanoconstructs is primarily a matter of size

Microsphere examples

- ^{90}Y-SIR-Spheres. Resin spheres, 20-60 micron diameter, for hepatic tumors. FDA approved.
- ^{90}Y-TheraSpheres. Glass spheres, 20-30 micron diameter, for hepatic tumors. FDA approved.
- ^{32}P-labelled glass microspheres.[1] For radioembolization (under study).
- ^{166}Ho-labeled biodegradable poly(L-lactic acid) microspheres.[1,6] In clinical trials

Uncertain categorization

- Radiolabeled iodized oils[1] delivered trans-arterially for hepatocellular malignancies. [Clinical trials.]
  - ^{131}I-labelled iodized oil (“Lipiodol”)
  - ^{188}Re-labelled iodized oil

So what can be said about the future?

- Many new RPT agents in clinical trials or pre-clinical development will be seen (or are already being seen) at many healthcare and biomedical research facilities. [*Reference #1 provides a table listing examples of 31 agents already commercially available or in various stages of development*.]
- Many of these agents will ultimately gain FDA approval and become commercially available, so utilization will spread beyond those facilities where clinical research and human trials are performed.
- Some already commercially available agents may find new uses (i.e. different malignancies to treat) so numbers of procedures will go up).
- Some already commercially available agents may become paired with other non-radioactive treatments (improving efficacy), again with the potential for higher workloads.

Recent news story…..

- https://www.nbcnews.com/health/mens-health/new-radiation-therapy-prostate-cancer-reduces-deaths-study-shows-n1269566

So the likely scenarios are that….

- Historically “familiar” isotopes will continue to be used in familiar forms (RPT agents), for familiar therapy targets (conditions treated)
- Familiar isotopes, in familiar forms, may find new uses (or increased uses)
- Familiar isotopes, in new RPT agents, will be used for new and/or familiar targets
- Unfamiliar (rarely used to-date) isotopes will be used with both familiar and new agents, for new and/or familiar targets

For the Medical Health Physicist (and Regulator)….

- Each new use or RPT agent will have to be evaluated, and related issues addressed, based on;
  - Radiological characteristics of the radionuclide
  - Physical characteristics of the radiolabeled agent
  - Chemical characteristics of the radiolabeled agent
  - Biological/physiological characteristics of the radiolabeled agent
  - Biological/physiological characteristics of the specific patient population (e.g., incontinence?)
  - Caregiver needs post-therapy
- Considerations:
  - Radiation levels
  - Shielding
  - Contamination control (including patient skin)
  - Patient and caregiver instructions

BUT REALIZE THAT…..

- Even though there will be use of radionuclides that have not been commonly used, the medical community already has decades of experience with energetic beta and/or gamma emitters (and now years of experience alpha-emitting radiopharmaceuticals).
- The “unfamiliar” radioisotopes do NOT pose any unique or unusual radiological hazards or related challenges (e.g., detection) compared to those that we already deal with.
- There will be nothing new about the modes of administration (i.e., “parenteral”) used to deliver these RPT agents to patients.
- With the exception of “microspheres”, all of the categories of RPT agents discussed in this presentation meet the criteria as is 10 CFR35.300 (i.e., no new regulations are needed – only the awareness of how to apply appropriate, standard radiation protection procedures are necessary).

Some of those “Unfamiliar” Radioisotopes

Copper -67 (Cu-67)

- Primary emission: beta (0.58 MeV_{max})
- Significant other emissions: Zn x-rays including 0.184 MeV, 40%
- Half-life: 2.60 days
- Progeny: Zn-67

Holmium-166 (Ho-166)

- Primary emission: beta (1.85 MeV_{max})
- Significant other emissions: γ's (0.08 MeV, 5.4%; some others up to 1.66 MeV but low yield)
- Half-life: 1.12 days
- Progeny: Er-166

Rhenium-186 (Re-186)

- Primary emission: beta (1.07 MeV_{max})
- Significant other emissions: γ's (11%, highest 0.137 MeV)
- Half-life: 3.72 days
- Progeny: Os-186

Rhenium-188 (Re-188)

- Primary emission: beta (2.12 MeV_{max})
- Significant other emissions: γ's (8.3%, mostly 0.155 MeV)
- Half-life: 17 hours
- Progeny: Os-188

Gold-198 (Au-198)

- Primary emission: beta (0.96 MeV_{max})
- Significant other emissions: γ's (primarily 0.412 MeV, 95%)
- Half-life: 2.70 days
- Progeny: Hg-198

Astatine-211 (At-211)

- Primary emission: alpha (to Bi-207); beta (to Po-211)
- Significant other emissions: none
- Half-life: 7.2 hours
- Progeny: Bi-207 or Po-211 (Po-211 decays by alpha to Pb-207 with a 0.516 sec half-life)

Lead 212 (Pb-212)

- Primary emission: beta (0.58 MeV_{max})
- Significant other emission: γ (0.24 MeV, 47%)
- Half-life: 10.6 hours
- Progeny: Bi-212 (alphas [35%], $T_{1/2}$ 1.0 hour; associated beta and multiple gammas up to 1.62 MeV, <14% total)

Actinium-225 (Ac-225)

- Primary emissions: alphas
- Significant other emissions: Fr x-rays; various daughter radiations
- Half-life: 10.0 days
- Progeny: Decay chain from Fr-221 ending at Pb-209 (includes 4 alpha emissions after Ac-225)

Thorium-227 (Th-227)

- Primary emission: alphas
- Significant other emissions: γ's – 0.05 MeV (8%). 0.237 MeV (15%), 0.31 MeV (8%)
- Half-life: 18.2 days
- Progeny: Ra-223

References

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Questions/Comments?

“Stop! Who would cross the Bridge of Death must answer me these questions three, ere the other side he see.”

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