# Industry corner: perspectives and controversies

## Radio-pharmaceuticals for cancer treatment: are they ready for prime time yet?

Radio-pharmaceuticals (RPs) are one of those decade old 'technologies of the future' that never really made it into the mainstream. The technology is generally robust and intuitive, effective and well tolerated but also viewed as cumbersome and overly complex. The acquisition of Advanced Accelerator Applications by Novartis for $3.9B strongly suggests that it is time to take another look—will RPs see a renaissance or land on the junkyard of failed formerly promising technologies?

## What are RPs?

RPs consist of a targeting agent—monoclonal antibody, peptide, aptamer or a small molecule—with a radioisotope as toxic payload attached to it. Alternatively, if a radioisotope has the propensity to find its target unguided it can be administered alone.

A variation of RPs—pre-targeted RP (PRIT)—includes the administration of a naked bi-specific antibody ahead of the radioactive agent. This approach allows the antibody time to accumulate in the tumor, the low molecular weight radioactive moiety that penetrates quickly, then binds to the antibody thus further reducing off target effects [1, 2].

Radioactive agents are also used as imaging SPECT or PET tracers, alone or in a 'theranostics' combination—neither will be the focus of this article.

A variety of radioisotopes—emitting either beta or alpha particles—can be used as payload to destroy cancer cells. Concomitant gamma and X-ray radiation might require additional precautions or isolation; it can be used for imaging purposes in some cases [3–6].

## A choice of radioisotopes

Radioisotopes as payload differ in their physical properties (see Table 1). The most relevant differentiation is between alpha and beta emitters.

Various beta emitters—in particular I-131, Lu-177 and Yt-90—have been used in clinical practice. Beta emitters emit low energy radiation over a path length of a couple of hundred cell diameters, they therefore produce a bystander effect also killing cells not expressing the target. Depending on the expression level of targets and the therapeutic goal, this can be an advantage or disadvantage. Compared with alpha emitters, more beta particles are needed to kill a cell [6–8].

Alpha emitters (such as Ac-225, Ra-223, Th-227, Pb-212, Bi-212, At-211) decay emitting alpha particles (helium nuclei) that travel a short path length of only a few cell diameters—just enough to kill some adjacent cells—with high energy causing double strand DNA breaks that are irreparable. Given their mechanism of action and the high energy applied, alpha emitters can be expected to be effective even when cancer cells are not radiosensitive; they also work in hypoxic areas of a tumor [9]. The first and thus far only alpha emitter marketed is Ra-223 Cl—Xofigo, a calcium mimetic, that targets osteoblastic bone metastasis leveraging its tissue tropism [10].

Physical half-life of different radioisotopes varies; in addition, the biological half-life of RPs further shortening patient exposure needs to be considered. Generally, RPs that do not bind to target cells are cleared rapidly, typically through the kidneys [2].

## What went wrong?

I-131 has been used for decades to treat thyroid cancer, other radioisotopes (Sm-153, Sr-89) to treat bone metastases (see Table 2). The first antibody-based RPs, Zevalin [11] and Bexxar [12], initially indicated for third line NHL proved effective and safe. Both failed miserably commercially. Their main competitor—Rituximab—was widely used, came with a broad set of clinical data and continued to be studied in dozens of clinical trials. It did also not help that neither product launched with an OS benefit and that a large player, deeply entrenched in oncology, Roche, was marketing Rituximab. But there are other reasons more specific to RPs in general that led to failure.

## The challenges

Complex logistics and manufacturing—Yt-90, the beta emitter used with Zevalin has only a 2.7-day half-life. While manageable, this creates some logistical challenges. RP doses are usually individualized, either based on patient weight or even on dosimetry requiring administration of a test dose followed by imaging. RP doses are manufactured by labeling the 'cold' targeting carrier with the radioisotope at a central manufacturing site or decentrally at radiopharmacies or possibly hospital nuclear labs. Radiation needs to be calibrated individually for each patient and the planned time of administration; transportation of the final product needs to be organized in a timely manner and patients need to show up as planned. Since entire 'hot' batches have generally to be produced whether product is sold or not, there is an interest to administer the drug whenever the batch is being manufactured, not when convenient for patients. One can escape that logic only once larger volumes are reached that allow for continued manufacturing.

Supply of some radioisotopes (e.g. Ac-225) is limited and costly below scale; while improving at scale this still adds a level of

**Table 1. Radioisotopes for therapeutic use [3–6]**

| | Path length (mean) | Energy | Half life | Other rays |
|---|---|---|---|---|
| **Alpha emitter** | **Short** | **High** | | |
| Radium Ra-223 | | 4 particles at 6 MeV | 11.4 days | (Beta and gamma) |
| Lead Pb-212/bismuth Bi-212 | | 1 particle at 6 MeV | 10.6 h | Pb-212 is a beta emitter decaying to Bi-212 and 212 Po that are alpha emitters |
| Actinium As-225 | <100 μm, Few cell diameters | 4 particles at 6 MeV | 10.0 days | (Gamma) |
| Thorium Th-227 | | 5 particles at 6 MeV | 18.7 days | (Beta, Gamma) |
| Astatine At-211 | | 1 particle at 6 MeV | 7.2 h | Minimal decay to Bi-207 |
| **Beta emitter** | **Hundreds of cell diameters** | **Low–medium** | | |
| Iodine I-131 | 0.7 mm | 0.7 MeV, beta- | 8.0 days | 10% gamma |
| Yttrium Yt-90 | 3.9 mm | 2.2 MeV, beta- | 2.7 days | (Photons) |
| Lutetium Lu-177 | 0.25 mm | 0.5 MeV, beta- | 6.7 days | (Gamma) |

complexity and risk for manufacturers. New chelators are needed that allow labeling at room temperature reducing risk of alteration of biological targeting agents as well as increasing yields and specific activity.

RPs must be administered by radiation oncologists or nuclear medicine physicians [13] and the treating oncologist needs to refer the patient. That adds complexity to the process in particular for independent clinics and in a community setting while it is less of an issue in a hospital or within larger integrated provider organizations.

In the USA, oncologists cannot charge for the administration of RPs while administering intravenous cancer drugs is a revenue driver.

Generally well tolerated, most RPs have some hematological side-effects in particular thrombocytopenia making it more difficult to repeat treatments or to combine them with chemotherapy.

With some radioisotopes that either emit X-ray or gamma particles, such as I-131, at therapeutic doses, patients must be isolated for some time before it is safe for their caregivers and family to release them thus requiring patients to be hospitalized with consequences for cost and reimbursement.

While none of these challenges are unsurmountable or involve complexities not known with other oncological therapies, they resulted in Zevalin and Bexxar not being well received by the market and failing commercially given that more convenient, effective alternative therapies were available.

## Why bother with RPs at all?

RPs have some unique properties making them excellent therapies in some cases. However, let there be no illusion—if a conventional therapy has a similar profile as RPs—in terms of safety and efficacy—RPs would not be able to compete successfully because of the added complexities.

The challenge for academia and industry is to identify products and indications that leverage the unique properties of RPs making them clearly superior to any competing technologies.

## How can RPs be successful?

There are different approaches to reach this goal.

Simple linker technology and versatility—think about most RPs as antibody drug conjugates (ADCs)—search and destroy—a targeting agent to find the cell, a toxin in the case of ADCs and a radioisotope in the case of RPs to kill it. Compared with ADCs, RPs are fairly simple and robust: the radioisotope needs to be firmly bound to the carrier but does not have to be released to be effective—this reduces the complexity of linker technologies and improves safety (the side-effect profile of ADCs oftentimes mimics that of the toxin). Some radioisotopes can even bind directly to the carrier without chelate (e.g. I-131, Astatine-211) [2, 14]. Because of the simpler linker technologies RPs can use a variety of targeting agents including small molecules.

Targets—any target that cannot be eliminated by conventional receptor blockers such as a small molecule or naked antibody could be considered. While there is an advantage for RPs to be internalized, it is not required, RPs can kill whether bound to the cell membrane or internalized, this is particularly true for high energy alpha emitters. RPs are therefore also suitable for extracellular targets or targets that do not lead to internalization (e.g. CD45) [2], the chelator will have to be carefully chosen in the case of alpha emitters, however, to avoid off-target effects caused by radioisotope daughters being released outside of the targeted cells (recoil).

Also, targets that are difficult to drug with ADCs for whatever reason could be targeted with RPs for example targeting carriers that are small and cannot be linked easily to a toxin, particularly peptides.

Target expression—ADCs need a significant expression level of a target, the order of magnitude of bindings required to kill a cell is usually in the double digits of thousands [7]. RPs need a significantly lower number of bound carriers to eliminate a target cell—alpha emitters only a handful, beta emitters hundreds or few thousands [7]. RPs can therefore succeed with much lower target expression levels. In theory, this could also lead to a deeper level of response assuming that target expression levels in a heterogeneous cancer vary and that cells with lower expression levels might escape destruction eventually causing the next relapse resistant to the targeted therapy used.

**Table 2. Older therapeutic radiopharmaceuticals (author's selection)**

| Product | Target | Indication | Company |
|---|---|---|---|
| **Radioisotopes** | | | |
| Iodine-131 | | Thyroid cancer | Generic |
| Quadramed (Samarium 153) | | Bone metastasis | Lantheus |
| Metastron (Strontium 89) | | Bone metastasis | GE Healthcare |
| **RP-ADCs** | | | |
| Zevalin (Ibritumomab-Yttrium 90) | CD-20 | Relapsed/refractory NHL, consolidation FL | Spectrum |
| Bexxar (Tositumumab-I-131) | CD-20 | Relapsed/refractory NHL | Withdrawn (GSK) |

**Table 3. Will these RPs prove the point? - The new generation (author's selection)**

| Product | Target | Indication | Company | Status |
|---|---|---|---|---|
| **Beta emitter** | | | | |
| Lutathera (Oxodotreotide-Lu-177) | Somatostatin receptor | NET | Advanced Accelerator Applications/Novartis | Approved |
| Betalutin (Lilotomab-Lu-177) | CD 37 | NHL | Nordic Nanovectors | P3 |
| Azedra (Iobenguane I-131) | Norepinephrine transporter | R/R malignant Phaeochromocytoma | Progenics Pharmaceuticals | Filed |
| Iomab-B (BC8-I-131) | CD 45 | AML conditioning for BMT | Actinium Pharmaceuticals | P3 |
| PSMA-617-Lu-177 | PSMA | PC | Endocyte | P3 planned |
| **Alpha emitter** | | | | |
| Xofigo (Ra-223) | Osteoblasts | CRPC with symptomatic bone metastasis | Bayer | Approved |
| Actimab-A, M, MDS (HuM195-Ac-225) | CD33 | AML, MM, MDS | Actinium Pharmaceuticals | P1/2 |
| FPX-01 (x/Ac-225) | unknown | NSCLC | Fusion Pharmaceuticals | Pre-clin. |
| Pb-212 | various | | Areva/Roche/Morphotec/ Nordic Nanovectors | Pre-clin. |
| CD22-TTC-Th-227 | CD22 | R/R NHL | Bayer | P1 |
| PSMA-617-Ac-225 | PSMA | Prostate cancer | Academic | P1/2 |

Surgical—alpha emitter based RPs can almost surgically remove cells expressing the target without damaging many cells in the vicinity reducing off-target effects. One example is Ra-223 Cl that targets osteoblasts in bone metastases of prostate cancer patients resulting in improved OS and QoL as well as a more favorable side-effect profile than placebo [9]. The unique profile of Xofigo made it the first commercial success story in the space.

Destructive—conversely, if complete destruction is required, beta emitters can kill cells expressing a target and all the cells around them, whether they express the target or not. An example for this approach is Iomab-B a I-131 loaded CD-45 targeting monoclonal used to destroy bone marrow of AML patients in preparation for BMT [15].

Patient population—RPs tend to be well tolerated. One can assume that this is due to the targeted nature of the approach and avoidance of prematurely released toxins. Whenever the balance between effectiveness and tolerability is particularly critical, like in an older or otherwise fragile population, RPs might be particularly suitable. RPs require few administrations, oftentimes only one or two, an advantage for a frail and any potentially less compliant population. When patient isolation is required, targeting a patient population that is typically hospitalized anyhow increases acceptance of the therapy.

## Where does this leave us?

While more technologies are available for oncologists than ever, RPs still provide a valuable tool for certain targets and certain patients. RPs can be successful whenever their unique advantages are leveraged and whenever RPs are clearly superior to any conventional technology at least in some patients. They will fail commercially whenever that is not the case.

Many new developments (see Table 3) leverage the unique advantages of RPs—peptides (Lutathera, Azedra) targeting somatostatin and norepinephrine transporter receptors, respectively [16, 17] might be too small to attach a complex linker and toxin. CD45 targeting Iomab-B might help to improve the delicate balance between efficacy and tolerability thus enabling a very fragile population to receive potentially curative bone marrow transplant. RPs using alpha emitters could 'surgically' take out cancer cells even if their expression level on the cells is low, while limiting off target effects for example with Actimab-A and M [18]. Betalutin [19] whose antibody is internalized could be equally highly targeted despite of being a beta emitter.

Fascinating novel aspects may come into play when combining RPs with immuno-oncology therapy—systemic immune response could be boosted by the so called 'abscopal' effect [20].

Encouragingly, theory appears to translate into clinical results—recently published examples include Lutathera's maturing OS benefit in NET patients or a remarkably high ORR rate and OS signal in very heavily pre-treated mCRPC patients receiving Ac-225-PSMA-617 [21].

Once more clinical success stories are added to that of Xofigo, RPs might become more mainstream. Some of the complexity could be reduced with more frequent use and as stakeholders become more familiar with the technology. While scientifically more fascinating technologies exist, much is to be said in favor of RPs that have one striking advantage: they simply work well.

R. Turck
TurckBio LLC, Montclair, USA
(E-mail: roland.turck@turckbio.com)

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