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Agent Optimization: ADME, Dose and Decay

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Targeted radiation therapy (TRT) is undergoing another renaissance attributable to U. S. Food and Drug Administration (FDA) approvals of Xofigo® and Lutathera® in 2013 and 2018, respectively. The former, $^{223}RaCl_2$, though not a TRT agent, exploits Nature's preferences for its biological deposition. Its approval opened an acceptability window to use α-emitting radionuclides in a clinical application. The latter combines ^{177}Lu (β^--emitter) with the somatostatin analogue DOTA-TATE, resulting in a peptide receptor radionuclide therapy (PRRT) TRT agent. This progress since the approval of Zevalin® (^{90}Y) in 2002 is spurring continued optimism within this field. However, many fundamental paradigms and principles exist to reduce the period between renaissances. [1]

A simple principle, often discounted, is balancing physical half-life of radionuclide with targeting agent biological half-life. Why is this important and can it be achieved realistically? It is possible, if one accepts the physical limits imposed by choice of radionuclides. To maximize therapeutic impact, one aims to optimize delivery to and retention at the target to enhance actual radiation decay time on site. Unbound radionuclide is a potential source of toxicity until excreted, hence wasted. Mismatch of a short half-life radionuclide with a slow-targeting, slowly cleared targeting agent; or a long half-life radionuclide to a rapid-targeting, rapidly cleared targeting agent are suboptimal. Promising therapeutic results may occur, however careful optimization is important because significant improvement is almost certainly possible.

What is the best radionuclide? The answer depends on what is being treated, where is it located (accessibility), and the size and extent of disease. The entire list of radionuclides is largely irrelevant. Factoring in realistic half-lives (suitable for TRT), useful emissions (something cytotoxic), reasonably available production potential (can be made in useful quantity and purity), economic considerations (within funding confines), and meaningful chemistry (can be attached to targeting agents) reduces that list to ~20 $\pm$ a few. Choices on emissions tend to be limited to β^-- and α-emitters. Others are possible, e.g., Auger-emitters, but pursued to a lesser degree.[2] Most relevant research questions can be asked and answered with this short list.

O'Donoghue's work in 1995 very neatly provided a correlation between the ranges and energy depositions β^--emitters and activity required for a cure probability of 0.9, at an optimal tumor size.[3] This ideal works well for patients presenting with uniform tumors. It also provides a basis for the combination of distinct β^--emitting radionuclides to cover a range of lesion sizes while balancing therapy with toxicity. And, it also provides the lower limit, *i.e.*, metastatic, single cell and small lesions where α-emitters become effective.

Half-lives of the useful subset of radionuclides range from under an hour (^{213}Bi, $T_{½}$ = 46 min) to weeks (^{227}Th, $T_{½}$ = 18.7 d).[4] Fortunately, most radionuclides on that short list are reasonably available, albeit not at levels adequate to support commercialization. Past history (Zevalin) does teach that FDA approval may significantly impact production (↑) and cost (↓) of

a radionuclide. Both ^{211}At and ^{149}Tb might be described as "anchored" to or limited in distribution from their production sites. The realities of shipping and distribution may limit use beyond a geographical range, despite demonstrations of efficacy, particularly when combined with limits in production technology. This may be preferable given training requirement related the handling and administering of these agents.

The radiolabeling chemistry for using most radionuclides on this short list exists and much is commercially available. Some chemistry clearly would benefit from validated improvements in formation rates (^{225}Ac and ^{227}Th), and perhaps one will simply remain lacking (^{223}Ra). The real challenge here is moving researchers toward validated chemistry, e.g. use of an intact 1,4,7,10-tetraamino-*N,N',N'',N'''*- tetracarboxylate cyclododecane instead of compromised derivatives, not re-inventing wheels, or using obsolete chemistry from dusty literature. This shift obviates continued waste of resources, compromised research, or studies that lack a true comparative nature facilitating clinical translation.

Economic considerations are straightforward. If a radionuclide cannot be made affordably, in suitable quantity and quality, then it is effectively unavailable. Fortunately, the field has access to a range of radionuclides of real potential clinical value.

The remaining challenge for TRT is choosing the targeting agent. Criteria include highly selective and efficient targeting and binding, acceptable pharmacokinetics and dynamics, half-life and residence time (instant targeting, infinite retention on target, all excess instantly excreted), with realistic availability, production, and economics.

Pursuit of better targeting agents has delivered a broad range of options, yet their routine use has been limited. Full IgG antibodies and peptides were followed by F(ab')$_2$ and Fab fragments. These fragments filled gaps in the array of properties required to match radionuclide half-lives. Engineering of immunoproteins has effectively provided an endless possibilities (*5*). Minibodies, flex minibodies, diabodies, and tetrabodies fill molecular size and associated targeting kinetics gaps. Remaining gaps down to the scale of peptides were filled with scFv, nanobody, and affibody formats. This matrix of agents provides serum half-lives from 1-3 weeks to 30-60 min. Striking differences in biodistribution and tumor targeting are evident comparing a ^{177}Lu labeled IgG to a ^{177}Lu labeled nanobody (*6*). Modification of minibody to flex-minibody further altered and increased tumor uptake and clearance kinetics (*7*). The impact by a diabody versus a minibody (and sFv-Fc) on tumor residence time of 105 h vs. 42 h is evident (*8*). The available diversity is well beyond the scope of this article. Yet, that same diversity of possible immunoprotein constructs illustrates the exquisite range of available targeting agents in the immunoprotein realm that should be exploited to optimize targeted radiation therapy.

Peptides, with a long history of modification to optimize target uptake, clearance route and retention therein, clearly play a critical role as targeting agents. Impact of clearance route and retention is critical when developing therapeutics with a peptide targeting agent due to molecular size. Dose incurred via renal excretion and retention from imaging agents may be significantly different when high-LET (Linear Energy Transfer) or longer range β^--emissions are involved. Adjusting functionality and substituents of an agent can clearly enhance renal excretion while

reducing retention to facilitate potential evolution of therapeutics (*9*). Pre-targeting strategies can be viewed as a variant of peptide or small molecule delivery platforms.

Once at the intersection of the matrix of radionuclides with potential targeting agent formats, one has to seriously question if the fundamental paradigm of matching radionuclide half-life to that of the targeting agent is fully addressed. Researchers should carefully choose radionuclide(s) with optimal emissions related to penetration range and energies based upon disease presentation. Next is to rationally match half-life of the radionuclide to potential targeting agent(s). A mix and match, if/then decision tree network could be envisioned. Defining appropriate leading candidates follows from performing the rote *in vivo* therapy experimentation studies with a full complement of controls to arrive at clinical trial candidate(s). Doing *in vitro* studies, cell killing, and similar studies have shown little usefulness as predictors of therapeutic efficacy, particularly when crossing into the macromolecular *in vivo* (*10*). Empirical studies are inescapable. Information on radionuclides and targeting agents, the "tools", has been readily available. Execution of routine, systematic studies needed to generate and extract candidates for clinical translation are not generally being performed. Why might that be?

One could argue that the answer exists at the intersection of funding, concepts and requirements governing academic research. The outlined approach obviously requires funding. These studies are not overwhelmingly novel; can be both large and lengthy; may lack adequate stature to be published high impact journals; and therefore, may be deemed unfundable by the peer-review process. As described, large empirical, rote *in vivo* therapy studies require significant investments in time and resources. Regardless, such studies are ultimately required to deliver optimal therapeutics. For similar reasons, critical subsequent toxicity studies are also largely unfundable and rarely publishable. Incremental peer-reviewed studies often fail to actually support clinical translation, despite appearing novel, while the lack of methodical and systematic studies to optimize matching radionuclide to targeting agent continues. Fundamental change in metrics for funding and publication of studies, such as weighting factors towards *in vivo* efficacy, is required. Shifting towards focused design and execution of comparative empirical studies, and broadening the aperture for funding and publishing beyond select institutions, will aid to keep this renaissance flourishing.

DISCLOSURE

No potential conflict of interest relevant to this article exists.

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