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Perspective

Novel Agents for Molecular Imaging and Possible Therapy of Human Cancers

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Perspective

The clinical utility of radiolabeled monoclonal antibodies and antibody fragments long ago catalyzed research investigations into the usage of other biologically-active, cell- targeting compounds for molecular imaging and therapy of human cancers. For example, the inability of radiolabeled antibodies to penetrate solid tumor, very slow localization of antibody on receptor-specific tumor tissue, and slow clearance rates from blood serum and normal tissues resulting in low-quality, low-contrast molecular images or irradiation of non-target, collateral tissues during therapy can limit their usefulness for molecular imaging of and/or therapy of disease. To overcome the deficiencies associated with radiolabeled antibodies, researchers have continued to investigate peptides and other small molecules to be used for early detection and therapy for human cancer [1].

The ability to selectively target cell-surface receptors or biomarkers that are expressed in very high numbers on most solid tumors via radiolabeled peptides [2-6] has been catalyzed by the early successes of targeting somatostatin receptors for the development of diagnostic and therapeutic radiopharmaceuticals [6]. The successes of Octreoscan® ([^{111}In-DTPA-Octreotide]) have led to the design and development of other monovalent (targeting only a single biomarker) radiolabeled, biomarker-targeting, peptide-based agents including bombesin (BBN), alpha-melanocyte stimulating hormone (α-MSH), Arginine-Glycine-Aspartic Acid (RGD), Vasoactive Intestinal Peptide (VIP), cholecystokinin, and neurotensin (NT) [2,3,7]. Continued investigations into the design and development of these novel agents for molecular imaging and therapy arise from:

1. Their ability to be easily produced (oftentimes via automated synthetic procedures).
2. Rapid clearance from whole blood and other non-target tissues
3. Their ease of penetration into the tumor vascular endothelium.
4. Relatively low immunogenicity.
5. Rapid clearance from the human body via the renal-urinary excretion pathway [8].
6. Their ability to be chemically tuned to target cell-surface biomarkers that tend to be over-expressed on human cancer cells [1].

The pharmacological properties of radiolabeled peptides are defined by many factors including retention in whole blood, receptor/biomarker binding kinetics, and their route of excretion (i.e., hepatobiliary-intestine or renal-urinary). For molecular imaging (PET (Positron Emission Tomography) or SPECT (Single Photon Emission Computed Tomography)), the ideal agent will exhibit very high uptake on target tissue in a relatively short period of time, as to achieve a useful diagnostic signal/noise ratio for high-quality, high-contrast PET or SPECT images. For molecular imaging and therapy, residence time of the agent in blood should be minimal. However, time in blood should be long enough for the agent to reach the binding site and to have an ideal first-pass extraction onto the biomarker. Lastly, radiolabeled, peptide-based agents are oftentimes chemically fine-tuned to exhibit rapid renal-urinary excretion as to minimize accumulation of radioactivity in the gastrointestinal tract. This minimizes irradiation of non-target tissue and, under many circumstances, produces diagnostically useful images of the lower abdomen (especially for visualization of neuroendocrine or prostatic lesions). To modify the pharmacological behavior of tracer peptide-based agents investigators have focused predominantly upon:

1. Chemical modification of the metal-chelate complex.
2. Chemical modification of the biomarker binding region.
3. Introduction of coligands onto the metal center.
4. Insertion of a linking moiety as a pharmacokinetic modifier [9].

The kinetic and thermodynamic stability of the metal-chelate complex (radionuclide delivery mechanism) should be the foremost point considered during development of new peptide-based targeting vectors. Demetallation from the complex or transmetallation reactions of the metal center with *in vivo* serum proteins, for example, could render non- specific uptake of targeting molecule in normal, collateral tissues, resulting in low target to non-target ratios of agent, low-contrast diagnostic images, and non-targeted irradiation of non-diseased tissue.

Chemical modification of the receptor or biomarker-targeting component of the agent should also be considered. Oftentimes, changing the receptor binding component minimally can influence the ability of the agent to remain surface-bound, or to be internalized, which until recently was considered to be ideal for targeted radiotherapy. The ability of peptide-based, agonist ligands to be rapidly internalized coupled with a high incidence of biomarker

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expression on the surfaces of solid tumors has been a driving force for development of novel agents for early detection and therapy of biomarker-positive, neuroendocrine tumors [10,11]. Recent studies by researchers in the European Union, however, have shown that radiopharmaceutical design and development based upon peptide agents that exhibit antagonist-like, binding to cell- surface biomarkers clearly needs to be reconsidered [12]. Antagonists internalize minimally and remain surface-bound to the receptor, and until now were not expected to residualize as effectively in tumor tissue when compared to agonist-based ligand frameworks. Nock and co-workers have recently described ^{99m}Tc-Demobesin1 ([^{99m}Tc-N4$^{0-1}$,bzlg^{0},D-Phe^{6},Leu-NHEt^{13},des-Met^{14}]BBN(6-14)), which demonstrated very high affinity and selectivity for the Gastrin Releasing Peptide Receptor (GRPR) with very high uptake and retention of tracer in human tumor xenografts in rodents [12]. Maecke and co-workers have described the ^{64}Cu-radiolabeled, antagonist-like targeting vector, [CB- TE2A-PEG4-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2](CB-TE2A; 4,11- bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane) [13]. Based upon high tumor uptake and retention, favorable pharmacokinetics, and high *in vivo* stability, they have introduced this new monovalent targeting vector into human clinical trials in Europe [13]. Dumont and co-workers have described the development of [^{177}Lu-DOTA-RM2] (RM2 = [4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu- NH_2]) antagonist which showed high uptake and retention of tracer in a PC-3, tumor- bearing, female athymic nude mouse model [11]. Very high tumor accumulation and retention coupled with a favorable pharmacodynamics profile for [^{177}Lu-DOTA-RM2] when compared to GRPR-targeting agonists of very similar structure could be nothing short of revolutionary in altering the previous mindset of using only cell-internalizing radioligands for targeted radiotherapy [11]. Based upon these studies, investigations into other peptide-based antagonist radioligands has recently begun.

Last of all, insertion of amino acid or aliphatic linkers between the biomarker-targeting region of the small peptide and the metal-chelate complex can greatly influence the *in vivo* pharmacodynamic behavior of the agents. Over time, investigators have concluded that insertion of these "innocent" pharmacokinetic modifiers do little to reduce receptor binding affinity [14,15]. Traditionally, a shorter, highly-polarizable pharmacokinetic modifier will produce radioligand that will exhibit excretion primarily via the renal-urinary pathway. On the other hand, long-chained aliphatic linkers such as 8-aminooctanoic acid tend to produce more hydrophobic radioligands with unfavorable pharmacokinetic and biodistribution properties. In the event that long-chained chemical modifiers are necessary to improve the *in vivo* pharmacokinetics of the agent, a highly-polarizable, metal complexing agent such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) Bifunctional Chelating Agent (BFCA), is oftentimes necessary to stabilize the metal center and to offset the increase in hydrophobicity of the peptide agent rendered by the presence of the aliphatic tethering moiety.

Clinical usage of monovalent probes for molecular imaging can be limited by biomarker density, selectivity, affinity, and pharmacology. High-quality, high-contrast PET or SPECT images and site-directed radiotherapy applications require a high degree of receptor expression on the surfaces of tumor cells with minimal biomarker expression on surrounding, normal, collateral tissue. To overcome many of the inherent factors limiting usage of monovalent tracer molecules, researchers have begun investigating multivalent probes for diagnostic molecular imaging and therapy of tumors expressing either singly- or multi-targetable receptors [7,16,17]. These small molecule/peptide-based molecules have the unique ability of targeting more than one biomarker. In this way, the clinician might be able to capture a larger number of receptor-expressing tumors as compared to using only a monovalent ligand. For example, multivalent agents could overcome inherent limitations of agents targeting only a single biomarker/epitope by not excluding those cells which only express a single receptor. Superiority arises by the inherent ability of these bivalent ligands to target cells that express one or potentially both biomarkers. In other words, usage of bivalent heterodimers allows for the capture of a larger "audience" of biomarker-expressing or heterogeneous tumors that might express only a single biomarker during development. Usage of bivalent heterodimers has been reported for targeting the Prostate Specific Membrane Antigen-(PSMA), integrin-, GRPR- and α-MSH-expressing tumors [16,18-22]. The advantages of using a bivalent multitargetable approach are:

1. Usage of a single agent for targeting of biomarkers that are differentially expressed during tumor development could result in an enhancement of accumulation and retention of targeting vector on tumor.
2. The ability to target the surfaces of non-homogeneous biomarker-expressing tumors.
3. The ability to capture a larger "audience" of biomarker-expressing tumors.
4. A potential increase the sensitivity of detection through an improvement in binding affinity [7].
5. Improved targeting specificity and diagnostic utility.
6. Potential improvement in therapeutic utility [23].

The future of molecular imaging and therapy using peptide-based or small molecule-based agents rests upon cross-disciplinary interactions between nuclear medicine physicians, radiologists, medical oncologists and basic science researchers. For example, as novel agents are being developed and begin to enter translation into the clinic, collaborations and conversations between investigators amongst participating institutions are vital to the successes of moving an agent forward during clinical trials. The future of nuclear medicine remains bright to the extent that interdisciplinary collaborations between inorganic/organic/medicinal chemists, molecular/cell biologists, health physicists, and physicians remain strong.

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