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Journal of Molecular Imaging & Dynamics

Commentary

Targeted Therapy and Molecular Imaging using Nanotechnology

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Imaging Applications

Because molecules are too tiny to be photographed directly with noninvasive techniques, epitopes of interest are often depicted using precise and sensitive site-targeted contrast agents. A site-targeted agent, unlike typical blood pool contrast agents, is designed to increase a specific biomarker that would otherwise be difficult to identify from surrounding normal tissue. With the use of targeted radionuclides, molecular imaging has been a clinical reality for some time. Somatostatin-receptor imaging for neuroendocrine tumor identification, as well as Fluoro Deoxy Glucose (FDG) imaging by PET for characterization of various disease states, is just two clinical examples.

The use of technetium-labeled annexing for targeted detection of cellular apoptosis is now in clinical trials based on binding to membrane phosphatide serine epitopes that are exposed during apoptosis. Other nuclear constructions appear to be beneficial for imaging proteins that are produced after reporter gene transcription to monitor transfection events. Herpes virus thymidine kinase genes, for example, can be utilized as a reporter construct in conjunction with a therapeutic gene by phosphorylating exogenously provided radiolabeled probes (or substrates), which are subsequently trapped inside cells and photographed.

However, the rapid development of biocompatible nanotechnologies promises to broaden the scope of molecular imaging and therapy by introducing a slew of new molecules. Long circulating half-life (hours), selective binding to epitopes of interest, low background signal and prominent contrast-to-noise enhancement, acceptable toxicity profile, ease of production and clinical use, applicability with standard commercially available imaging modalities, and promise for adjunctive therapeutic delivery are all desirable properties of such targeted contrast agents. The availability of these agents in the clinic is likely to reshape imaging practice by focusing on cellular and molecular processes of disease, allowing for more accurate and rational design of conjunctive medication and/or gene delivery nano systems.

The contrast mechanism will be determined by the imaging modality chosen, which is in turn determined by the clinical problem and imaging accessibility. Nanoparticles (liposomes or emulsions), dendrimers, viral constructs, bucky balls, or various polymers, for example, can be loaded with large payloads of imaging agents such as paramagnetic or super paramagnetic metals, optically active compounds or radionuclides to enable detection with standard imaging equipment. The intrinsic physical features of the carrier agents themselves (density and compressibility) offer the tools for detection in ultrasonic imaging. When it comes to particular constructions, such as liquid per fluorocarbon nanoparticles, there is a lot of room to use any or all imaging modalities.

Nanotechnology

The contrast agent should have a strong attraction to the target. Monoclonal antibodies or their fragments, peptides, small molecule pepti domimeics, or aptamers are examples of targeting ligands that are directly associated to carriers and confer specificity of binding. It is preferable to have dissociation constants in the Nano molar range or better. Multivalent binding can help increase avidity and reduce "off-rates" so that binding lasts long enough for imaging to be done at a convenient time after the agent is delivered. Polyvalent binding can be achieved by using multiple ligand types per carrier or by combining ligand-carrier complexes directed at distinct targets.

A few examples of MRI and ultrasonic applications in molecular imaging are given to illustrate such Nano systems. Antibody ligands to endovascular integrin's v3 have been utilized in paramagnetic polymerized liposomes to target experimental tumor angiogenesis, and accumulation after 24 hours allows sufficient signal for imaging. Similarly, liquid per fluorocarbon nanoparticle emulsions targeted to allow for strong tumor imaging after only 1 hour in circulation, with in *vivo* competition experiments demonstrating selective uptake. Indeed, by incorporating antibody ligands directed against cross-linked fibrin, liquid per fluorocarbon nanoparticles were the first example of molecular targeting agents widely useful for MRI of thrombi, and they have recently been shown to enable characterization of experimental thrombi in *vivo* and human unstable carotid plaques *ex vivo*.

It is critical for paramagnetic agents to maximize the longitudinal relativity per molecule binding site for the complex, allowing for contrast enhancement with very few paramagnetic

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Received date: September 06, 2021; **Accepted date:** September 20, 2021; **Published date:** September 27, 2021

particles. Particle-based relativities (or "unit signal strength") for paramagnetic per fluorocarbon nanoparticles, for example, are the greatest reported in the literature to date, producing a significant signal to be detected at local concentrations in the Pico molar range. With these chemicals, even single cells can be observed. However, for epitopes in considerably larger concentrations, such as fibrin in thrombi, paramagnetic molecular imaging agents with minor relaxation improvements may be effective for targeting.

Combinations of carriers with iron oxides (e.g., ultra-small particles of iron oxide) or alternative lanthanide species have been used to create "susceptibility" or "cold spot" imaging agents. Recent research has shown that ingestion of ultra-small iron oxide particles in plaque macrophages can be used to delineate early atherosclerosis in animal settings. After therapeutic injection, stem-cell tagging with magneto-dendrites allows for MRI detection and precise localization. Nano scale polymers could also be used to transport magnetic and medicinal compounds. To increase cell uptake, several transport ligands, such as the retroviral "tat" protein, have been attached to these drugs (eg, cross-linked iron oxide nanoparticles).

Other "smart" agents are designed to take up residence in all cells of the body, but to be triggered only by certain enzymes generated in the cell under certain pathologic conditions, or by the protein products (enzymes) of reporter genes following therapeutic transfection. Cleavage of these agents' active sites exposes sequestered gadolinium atoms to free water and allows fast water exchange, resulting in a local proton relaxation action that improves picture contrast.

The first molecular imaging agents for ultrasonic applications, targeted per fluorocarbon nanoparticles, were demonstrated to increase reflectivity from fibrin thrombi in *vivo* by 2 orders of magnitude or more. Furthermore, because these particles can permeate through micro fissures into the circulatory medium, targeting to vascular epitopes such as tissue factor, whose expression is enhanced in smooth muscle cells in *vivo* following angioplasty, is achievable. Reflective liposomes have also been utilized to target endothelial integrin's specifically. Other micro scale systems (stabilized per fluorocarbon gas micro bubbles) have been employed for molecular ultrasound imaging of thrombi, but due to their size (5 m) and sensitivity to destruction with clinical ultrasound imaging intensity, they are mainly limited to the vasculature.