NEWS AND OPINIONS

Nanoparticles for cancer imaging: The good, the bad, and the promise

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Recent advances in molecular imaging and nanotechnology are providing new opportunities for biomedical imaging with great promise for the development of novel imaging agents. The unique optical, magnetic, and chemical properties of materials at the scale of nanometers allow the creation of imaging probes with better contrast enhancement, increased sensitivity, controlled biodistribution, better spatial and temporal information, multi-functionality and multi-modal imaging across MRI, PET, SPECT, and ultrasound. These features could ultimately translate to clinical advantages such as earlier detection, real-time assessment of disease progression and personalized medicine. However, several years of investigation into the application of these materials to cancer research has revealed challenges that have delayed the successful application of these agents to the field of biomedical imaging. Understanding these challenges is critical to take full advantage of the benefits offered by nano-sized imaging agents. Therefore, this article presents the lessons learned and challenges encountered by a group of leading researchers in this field, and suggests ways forward to develop nanoparticle probes for cancer imaging.

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The tools available to mitigate these effects are limited. A commonly used approach to reducing MPS clearance and increasing circulation times is steric stabilization of particle dispersions by polyethylene glycol (PEG) coating. Long circulation times achieved by PEG-coated “stealth” particles do not necessarily lead to enhanced accumulation deep into tumors, and PEG-coating may inhibit uptake of the nanoparticles by tumor cells. Current understanding of the effect of physicochemical characteristics of most nanoparticle constructs on their blood circulation times and body clearance is limited to basic parameters such as size and zeta-potential, while the role of other properties (shape, hydrophobicity, rigidity, etc.) is less understood. A significant effort is needed to create particles with optimal characteristics associated with both tumor specific accumulation and body clearance.

Imaging very small tumors

A key advantage of using nanoparticle imaging agents as compared to small molecules is the opportunity for preferential localization at the disease site through enhanced permeability and retention (EPR). When a tumor reaches a certain size (typically over 1 mm in diameter), its vasculature becomes leaky and its lymphatic drainage system is dysfunctional, as well. Nanoparticles with long blood circulation times will tend to accumulate in the tumor interstitial space after moving across the leaky tumor blood vessels. The size of the gap openings of tumor vasculature is usually in the range of 400–600 nm, which is much larger than that found in most normal tissues [3,4].

It is generally agreed that targeting ligands facilitate the internalization of nanoparticles by target cells and increase their retention in tumors. However, it is unclear if any nanoparticle-based strategy can enhance detection of the smallest tumors that do not possess a leaky tumor vasculature that favors EPR. Resolving these questions will require parallel developments in the identification of better targeting moieties and nanoparticle design.

Immunology

Immunological reactivity is a common toxicity observed with the clinical use of most contrast agents currently approved for diagnostic imaging. In addition to the immune reactivity of the nanoparticle itself, combination with targeting ligands, repeated administration, and contamination with endotoxins and pyrogens during the manufacturing process, can further increase the likelihood for immunogenicity [5].

Blood compatibility tests are required for nanoparticles distributed within the systemic circulation by the FDA before initiating phase 1 clinical studies. This type of testing is focused on detecting acute toxicities mediated by particle effects on erythrocytes (hemolysis), platelets, leukocytes and coagulation factors (thrombogenicity) and complement system (anaphylaxis). Nanoparticle interference with traditional in vitro tests is a common challenge during this step [5]. Understanding of the correlation between in vitro and in vivo immunotoxicity assays for nanomaterials significantly aids in conducting preclinical studies [16].

Toxicology

The selective tissue distribution of targeted nanoparticles and the accumulation of some nanomaterials within organs of the MPS, both require greater toxicological evaluation. This is especially the case for biopersistent nanomaterials, such as some metallic particles, that may result in chronic toxicities. Due to delayed clearance and increased systemic circulation relative to conventional imaging agents, there is the potential issue for increased systemic exposure to toxic components of nanomaterial-based imaging agents [6,7]. Nanoparticles may form micron-scale aggregates upon injection into the circulation, leading to microcirculation compromise, particularly in the capillary beds of the lungs and can result in inflammation and granuloma formation [8]. It is important to investigate the aggregation tendency of intravenous nanoparticles in plasma, especially when agents are dosed at high particle concentrations, and also to evaluate the lung as a potential target organ.

Hurdles on the road to the clinic

Clinical translation of nanoparticle-based imaging agents has been very challenging and many obstacles have yet to be overcome. In contrast to therapeutic delivery systems, which are administered after confirmed diagnosis of disease, imaging agents are often used for diagnostic purposes prior to confirmed diagnosis. Accordingly, the regulatory burden is much greater for imaging than for therapeutic agents in order to avoid needless toxicity to patients who might turn out to be healthy.

Regulatory considerations

While no new toxicities, specific to nanoparticles, have been reported [5,9], there is always a concern that the nanometer sizes may lead to toxic response even if the nanoparticle constituents are Food and Drug Administration (FDA) approved. At present, in order to receive investigational new drug (IND) or investigational device exemption (IDE) approval, the U.S. FDA requires similar preclinical data for nanoparticle-based therapeutic and imaging agents as for any other new therapeutic or diagnostic [10]. The scope of safety studies is determined by four main criteria: (1) mass dose, (2) route of administration, (3) frequency of use, and (4) biological, physical and effective half-lives [11]. For an imaging probe, it is necessary to demonstrate specificity and sensitivity using a clinically relevant dose, and evaluate in vitro and in vivo stability, systemic toxicity, and pharmacokinetics and pharmacodynamics [12].

Unlike small molecule agents, nanoparticle contrast agents usually have complex formulations and multiple components, which make it challenging for the production of the nanoparticles in a large scale with consistent quality using Good Manufacturing Practice (GMP). Furthermore, systemic biodistribution, toxicity, and clearance of each component of the nanoparticle core, surface coating, and targeting ligand should also be fully examined in appropriate animal models. To facilitate the regulatory review of nanotechnologies intended for cancer therapies and diagnostics, the National Cancer Institute (NCI) established the
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Nanotechnology Characterization Laboratory to perform preclinical efficacy and toxicity testing of nanoparticles developed by the research community and facilitate their progress through the regulatory approval process.

Financial realities

Economic considerations present additional and significant challenges in translating nanoparticle imaging agents to the clinical setting. The cost-effectiveness of these agents will be critical to their commercialization. In clinical medicine, additional imaging information frequently does not translate into changes in patient management decisions. Successful nanoparticle-based imaging agents will possess clear and measurable advantages over existing small molecule agents.

A targeted nanoparticle imaging agent that demonstrates early detection of cancers or detection of micro-metastases could clearly justify its cost by allowing for early intervention. Nanoparticle imaging agents could also provide prognostic indicators of early therapeutic effectiveness, allowing physicians to rapidly alter therapeutic strategies, personalizing care to the individual patient and improving overall response.

Another important consideration is the financial incentive for the commercialization of molecular imaging agents. Although the imaging agent market is projected to expand to approximately $14 billion by 2015, it is not clear whether nanoparticle agents will be financially beneficial for companies developing them [13]. Nanoparticle imaging agents face similar cost concerns as nanoparticle therapeutics agents; R&D costs are inherently high and insurers are becoming more prudent in their re-imbursement policies. Furthermore, due to the existing reimbursement policies for imaging agents, the incentives involved in developing imaging agents are far fewer than those of therapeutic agents. Poor sales of one nanoformulated iron oxide MRI contrast agent, Feridex, and the high barrier for securing regulatory approval for another, Combidex, have prompted their manufacturer to discontinue these products.

Opportunities

One of the most important advantages of nanoparticle imaging agents is their ability to anchor a large number of the same or different molecules. The multi-functional capabilities of nanoparticles can lead to tailor-made imaging agents for personalized medicine. Future nanoparticle imaging agents will include capabilities through appropriate functionalization that will classify tumor subtypes in highly heterogeneous tumors based on identifying genetic or epigenetic markers with in vivo and ex vivo diagnostics leading to personalized therapies.

The ability for multi-functionalization perhaps offers the greatest potential for clinical use by enabling compatibility in multiple imaging modalities (e.g. MR/CT, MR/PET, optical imaging, and others) in a single nanoplatform. Multimodality imaging allows complementary information over different temporal and spatial scales or different resolution or detection ranges for the same marker acquired from probes that localize to the same place at the same time; this provides a far more detailed picture than otherwise would be available. There is a widely acknowledged lack of safe MRI contrast agents especially because of concerns over the safety. It is hoped that use of nanoconstructs using iron oxide nanoparticles (some of which are FDA approved) may overcome some of these safety concerns while increasing contrast enhancement and imaging efficacy.

Theranostic nanoparticles, defined as those that combine the capacity for tumor imaging with therapeutic efficacy and low toxicity, are a novel concept currently at the preclinical stage and may provide the opportunity for real-time imaging of tumors as patients are undergoing therapy. The ability to monitor early indicators of therapeutic response could permit adjustment of treatment regimens and personalization of care. Biotechnology and pharmaceutical companies have expressed a willingness to invest in theranostic agents because of their potential for becoming novel and effective cancer therapeutic agents. However, while there are strong scientific rationales and urgent clinical needs for developing image-guided and targeted drug delivery agents, regulatory approval of these multi-functional agents faces greater challenges due to their complexity.

Nanotechnology is also driving the development of new tools and instruments that may have a broad impact on clinical medicine, even if nanotechnology imaging agents may not make their way into in vivo use. Nanomaterials combined with imaging are being developed for high throughput diagnostic assays and improved tumor biopsies. A significant area of increasing application is in ex vivo diagnostics using imaging agents such as quantum dots, where bio-compatibility is not a requirement. Advances in magnetic nanoparticles have also led to a new imaging modality based on direct detection of particles [14]. Nanomaterials are also being used to develop new X-ray sources [15].

Overall, nanotechnology offers the promise to revolutionize the field of medical imaging. The ability to image and treat simultaneously, the ability to enhance tumor detection, and the ability to have multiple contrast agents on a single platform may drastically change patient management. Despite the challenges associated with clinical translation that must be overcome, nanotechnology is anticipated to play a major role in future medical imaging. Because nanoparticle imaging agents possess many advantages over their small molecule counterparts, we anticipate nanoparticle molecular imaging agents will ultimately be successful in the clinic.

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