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

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Summary

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. Published by Elsevier Ltd.

Keywords

Nanomedicine; Cancer; Imaging; Detection; Screening

Recent advances in molecular imaging and nanotechnology are providing new opportunities for biomedical imaging with great promise for the development of agents to address clinical needs for disease staging, stratification, and monitoring of responses to therapy [1].

Materials at the scale of nanometers possess unique optical, magnetic, and chemical properties which allow the creation of imaging probes with increased signal density, signal amplification and quantification, improved contrast, and controlled biodistribution.

In 2011, the NCI Office of Cancer Nanotechnology Research (OCNR) assembled an imaging working group comprised of researchers working in the field of nanoparticle-based cancer imaging with the task of reviewing the current status of the field and identifying challenges associated with developing nanoparticle-based cancer imaging probes and bringing them into the clinic. In this article, we examine the current issues and challenges associated with nanotechnology-based imaging, and suggest opportunities for development of nanoparticle-based cancer imaging modalities.

Limitations of current nanoparticle imaging probes

An ideal nanoparticle imaging probe for clinical use should be biodegradable or rapidly excreted and have a low toxicity while producing a strong imaging signal. Several common issues shared among different nanoparticles compromise their further transition into clinical use.

Barriers for effective tumor delivery

Prior to reaching the tumor target, nanoparticles administered through intravenous injection interact with a complex environment that has evolved to seek out and exclude foreign matter. Primary obstacles to effective delivery of nanoparticles into tumors include clearance by the mono-nuclear phagocyte system (MPS) [2] and the heterogeneity of the tumor microenvironment, particularly in regards to physiological barriers such as antigen expression, and vascular and tumor permeability, which prevent both accumulation of sufficient quantities and uniform delivery of drugs and nanoparticles to all regions of tumors [3]. After entering the blood circulation, nanoparticles often bind plasma proteins (opsonization) and are taken up by phagocytic cells in the blood, liver, spleen and bone marrow. This MPS clearance presents two challenges: first it effectively removes nanoparticles from circulation and thus leaves a small fraction available for uptake at the tumor sites; second, it may lead to long retention times of potentially toxic nanoparticle components or metabolites, which presents significant concerns of off-target and chronic toxicities.

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 nanoplatform 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 biopersistant 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 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 therapeutic 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 epi-genetic 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.

Acknowledgments

Biography

Sandra Chapman is an American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellow working as a projects manager for NCI's Office of Cancer Nanotechnology Research. Sandra recently completed her graduate studies at Pennsylvania State University, College of Medicine, earning her PhD in molecular medicine in July 2010. Her thesis research on the human papillomavirus life cycle was the product of a collaboration between laboratories at Penn sylvania State University and the National Institutes of Health. Her research resulted in publications and is currently under review for patent approval. She received her bachelor's degree in economics from the University of California, Santa Barbara.

At the NCL, **Dr. Dobrovolskaia** directs characterization related to a nanomaterials' interaction with components of the immune system. She monitors acute/adverse effects of nanoparticles as they relate to the immune system, both in vitro and in animal models. Dr. Dobrovolskaia is also responsible for the development, validation and performance qualification of in vitro and ex vivo assays to support preclinical characterization of nanoparticles, and for monitoring nanopar ticle purity from biological contaminants such as bacteria, yeast, mold and endotoxin. Additionally, she leads structure activity relationship studies aimed at identifying the relationship between nanoparticle physicochemical properties and their interaction with macrophages, components of the blood coagulation cascade, and complement systems.


Dr. Farahani is a Program Director in the Image-Guided Interventions (IGI) Branch, Cancer Imaging Program, National Cancer Institute. In this capacity he is responsible for the development of NCI initiatives that address diagnosis and treatment of cancer through integration of advanced imaging and minimally invasive technologies. Since 2002 Dr. Farahani has lead the NCI initiatives in Oncologic IGI focused on small business development, early phase clinical trials, and image-guided drug delivery systems, including nanotechnologies. He has led a series of NCI workshops that promote an open science model to develop, optimize and validate platforms for IGI. These activities have engaged other institutes of the NIH, as well as the FDA, NIST and CMS. Prior to joining NCI in fall of 2001, Dr. Farahani was on faculty of the department of Radiological Sciences in UCLA, where he obtained his PhD ('93) in Biomedical Physics. Dr. Farahani is a member of the American Association of Physicists in Medicine, the Scientific Program Committee of the Radiological Society of North America, and a past president of the Interventional MR Study Group of the International Society of Magnetic Resonance in Medicine.

Andrew Goodwin is an Assistant Professor in the Department of Chemical and Biological Engineering at the University of Colorado Boulder and a recipient of a K99/R00 Pathway to Independence Award through the NCI Alliance for Cancer Nanotechnology. His research focuses on designing "smart" colloids and materials — such as polymeric architectures, organic/inorganic hybrids, and multiphase composites — that can sense their surroundings and change their physical properties accordingly. He obtained his PhD in Chemistry from the University of California, Berkeley and his BA in Chemistry from Columbia University in New York.

Amit Joshi is an Assistant Professor in the Departments of Radiology and Molecular Physiology at Baylor College of Medicine, and an adjunct faculty member in Electrical and Computer Engineering at Rice University, Houston, Texas. Amit's research interests span across the interface of Nanophotonics and Biological Systems. Amit is developing multifunctional nano particle based technologies for simultaneous imaging, and externally triggered therapy of cancer with Near Infrared light and Magnetic resonance based methods.
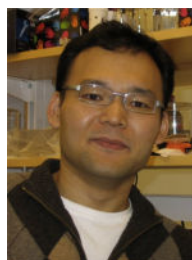
Hakho Lee, PhD is Assistant Professor in Radiology at Harvard Medical School, and Assistant Professor in Bioengineering at the MGH Center for Systems Biology. Prof. Lee studied Physics at Seoul National University, and received his PhD in Physics from Harvard University, and completed his post-doctoral training at Massachusetts general Hospital. His research group focuses on developing highly sensitive, portable biosensors through multidisciplinary integration of nanomaterials, microelectron ics and microfluidics. Over the

past years, Prof. Lee's lab has advanced magnetic sensing technology by synthesizing new types of magnetic nanoparticles and implementing chip-based magnetic sensors.

Thomas Meade, PhD, received a BS in chemistry, MS in biochemistry and PhD in inorganic chemistry. After completing postdoctoral fellowships at Harvard Medical School and the California Institute of Technology, he joined the faculty at Caltech and the Beckman Institute where he pioneered the development of the first bioactivated MR probes and the development of hand-held chips for DNA and protein diagnostics. In 2002, he moved to Northwestern University, where he is the Eileen M. Foell Professor of Cancer Research and Professor of Chemistry, Molecular Biosciences, Neurobiology & Physiology, and Radiology, as well as the Director of the Center for Advanced Molecular Imaging. Professor Meade's research focuses on bioinorganic coordination chemistry and its application in research that include biological molecular imaging, transcription factor inhibitors and the development of electronic biosensors for the detection of DNA and proteins.

Martin Pomper is the William R. Brody Professor of Radiology at Johns Hopkins University. He received undergraduate, graduate (organic chemistry) and medical degrees from the University of Illinois at Urbana-Champaign. Postgraduate medical training was at Johns Hopkins, including internship on the Osler Medical Service, residencies in diagnostic radiology and nuclear medicine and a fellowship in neuroradiology. He is board-certified in diagnostic radiology and nuclear medicine. He has been on the Radiology faculty at Johns Hopkins since 1996. His interests are in the development of new radiopharmaceuticals, optical probes and techniques for molecular imaging of central nervous system disease and cancer.

Dr. Krzysztof Ptak joined the National Cancer Institute Office of Cancer Centers in January 2012 as a Program Director. In this capacity, he contributes to the management of Cancer Center Support Grants. Previously, he served as a Project Manager in the NCI Office of Cancer Nanotechnology Research.

Dr. Ptak holds a PhD in Neuroscience from the University of Paul Cezanne in Marseille and Jagiellonian University in Krakow. He also holds an MBA in Life Science from The Carey Business School at Johns Hopkins University.

Dr. Rao received his BS in Chemistry from Peking University, China, in 1991, a PhD. in Chemistry from Harvard University in 1999 under the guidance of Professor George M. Whitesides, and a Damon Runyon Cancer Research Foundation postdoctoral fellowship at UCSD with Professor Roger Y. Tsien. He began his assistant professorship in the Department of Molecular and Medical Pharmacology at UCLA in 2002, and currently an Associate Professor of Radiology and Chemistry at Stanford University. His research interests include molecular probes, cancer imaging, bionanotechnology, biosensing, and chemical biology.

Ravi Singh, PhD is an Assistant Professor of Cancer Biology, Biomedical Engineering and Physics at Wake Forest School of Medicine. His research interest is the production of nanotechnology-based, multifunctional particles for cancer diagnosis, therapy, and treatment monitoring. He earned a BA in physics from Harvard University then spent eight years

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Srinivas Sridhar is Arts and Sciences Distinguished Professor of Physics at Northeastern University, and Visiting Professor of Radiation Oncology, Harvard Medical School. He is the Director and Principal Investigator of the NSF IGERT Nanomedicine Science and Technology Center. He is the founding Director of the Electronic Materials Research Institute, and formerly served as Vice Provost for Research at Northeastern University, overseeing the University's research portfolio. An elected Fellow of the American Physical Society, Sridhar's current areas of research arenanomedicine and nanophotonics. He has published more than 175 journal articles and has made more than 160 presentations worldwide. For more information visit www.igert.neu.edu and sagar.physics.neu.edu.

Dr. Stern heads the pharmacology and toxicology program at the Frederick National Laboratory's Nanotechnology Characterization Laboratory. Prior to joining the NCL, Dr. Stern was a Post-Doctoral Fellow at the University of North Carolina - Chapel Hill in the Division of Drug Delivery and Disposition, and Curriculum in Toxicology. Dr. Stern's areas of expertise include biochemical toxicology of the liver and kidney, analytical methodology and drug metabolism/pharmacokinetics. He received his BS. degree in biochemistry from the University of Rochester and PhD in toxicology from the University of Connecticut at Storrs. Dr. Stern is a Diplomate of the American Board of Toxicology.
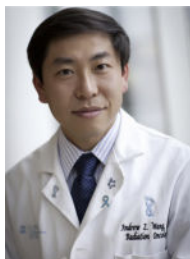
Dr. Wang is a physician-scientist at the Lineberger Comprehensive Cancer Center, University of North Carolina-Chapel Hill. His research is focused on the clinical translation of nanoparticle therapeutics to cancer treatment. Clinically, he specializes in the treatment of gastrointestinal and genitouri-nary cancers.

John B. Weaver is a Professor of Radiology in the Geisel School of Medicine at Dartmouth College with adjunct appointments in the Thayer School of Engineering and the Department of Physics at Dartmouth College. He received his BS from the University of Arizona in 1977, his PhD in Biophysics from the University of Virginia in 1983 and worked for Siemens Medical Systems until 1985 when he joined the Dartmouth faculty. His early research was in fast MR imaging and image processing using wavelet methods. His current research is in sensing and imaging magnetic nanoparticles and in MR elastography.

Gayle Woloschak is Professor of Radiation Oncology, Radiology, and Cell and Molecular Biology, and Associate Director of the Centers of Cancer Nanotechnology Excellence in the Robert H. Lurie Comprehensive Cancer Center, Northwestern University. Prior to 2001 she and her research group were at Argonne National Laboratory. Gayle received her BS. in Biological Sciences from Youngstown State University and a PhD in Medical Sciences from the Medical College of Ohio. She did her post doctoral training at the Mayo Clinic, where she was later became an Assistant Professor there. Her scientific interests are predominantly in the areas of Radiobiology and Nanotechnology studies, and she has authored over 180 scientific papers.

Dr. Lily Yang is Professor and Nancy Panoz Chair of Surgery in Cancer Research at Emory University School of Medicine. Dr. Yang received her medical training in China at West China University of Medical Sciences and then in the Chinese Academy of Preventive Medicine. She received her PhD degree in Molecular and Cellular Biology Program at Brown University. Dr. Yang's research projects focus on the development of novel cancer nanotechnologies and imaging methods to address the major challenges in clinical oncology of early cancer detection, targeted drug delivery, assessment of therapeutic response using non-invasive imaging, and image-guided surgery.

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