

Nanotechnology Driving Big Advances in Cancer Imaging

> Throughout the history of modern medicine, and particularly clinical oncology, important advances in treating illness and injury have usually followed the development of new ways to better see within the body. The advent of computed tomography (CT) imaging, for example, provided images of developing tumors in far greater detail than was possible with conventional x-rays, giving oncologists a means of both better localizing tumors before surgically removing them and the first real glimpse of whether a given therapy was causing a tumor to shrink. Similarly, magnetic resonance imaging (MRI) provided greater anatomical detail still, while the development of positron emission tomography (PET) gave both cancer researchers and oncologists the ability to monitor a tumor's metabolic activity, and as a result, an even quicker way of assessing the effectiveness of therapy.

Though undoubtedly a boon for cancer researchers and clinical oncologists, each of these revolutionary imaging technologies could benefit patients even more. Each of these imaging methods suffers from a common shortcoming – they just aren't sensitive enough to accurately find the smallest tumors that are most easily and effectively treated. Also, most imaging methods produce static images, snapshots of a tumor at one particular time that do not reveal much about dynamic events, such as the binding of a drug to a particular tissue. But increasingly, it appears that nanotechnology may be able to provide that leap in sensitivity that would not only impact today's approach to therapy but could lead to entirely new pathways for both detecting and treating cancer.

“The promise of nanotechnology for cancer imaging is such that we have little doubt

that it will lead to far more sensitive and accurate detection of early stage cancer,” says Adrian Lee, Ph.D., an associate professor of medicine who specializes in translational breast cancer research at Baylor College of Medicine. “But I also believe that we are just at the beginning of the process of applying nanotechnology to the problems of imaging cancer. I have confidence that as the oncology and physical sciences communities continue to find common scientific ground that there are going to be some surprising advances that will come of this work. These efforts will blur the boundaries of what we call detection and what we call therapy.”

For example, Lee and his colleagues at Baylor, including chemistry professor Lon Wilson, Ph.D., have begun working on a project funded by the National Cancer Institute to determine how best to use novel

nanoscale MRI contrast agents made of iron or gadolinium, two types of atoms that “resonate” under the influence of magnetic energy, encased within carbon nanotubes. “We have good evidence that these new contrast agents have the potential to give us a big boost in imaging sensitivity, but how exactly we'll use these nanotube-based agents and what role they will play in therapy is still an open question that we're going to work to answer,” explains Lee.

For Jeff Bulte, Ph.D., an associate professor of radiology at Johns Hopkins University in Baltimore, there is little doubt how nanoparticle-enabled imaging can help cancer therapy. Working with Carl Figdor, Ph.D., and his colleagues at the Radboud University Nijmegen Medical Center in The Netherlands, Bulte has been testing the use of iron oxide nanoparticles to track how dendritic cells move through the body (See [Nano.Cancer.Gov News](#)). Dendritic cells are candidates for triggering immune responses that would kill tumors, but for these cells to do their job they must first be injected into a patient's lymph nodes. In fact, by labeling dendritic cells with magnetic nanoparticles and tracking them using MRI, the researchers found that interventional radiologists were successful only half the time at injecting these cells into lymph nodes and not into the surrounding tissues. “Now, with magnetic nanoparticles, we can use a widely available imaging method, MRI, to ensure that we've accurately delivered therapeutic

Courtesy: Jolanda de Vries, Ph.D., Radboud University Nijmegen Medical Center, Nijmegen Center for the Molecular Life Sciences

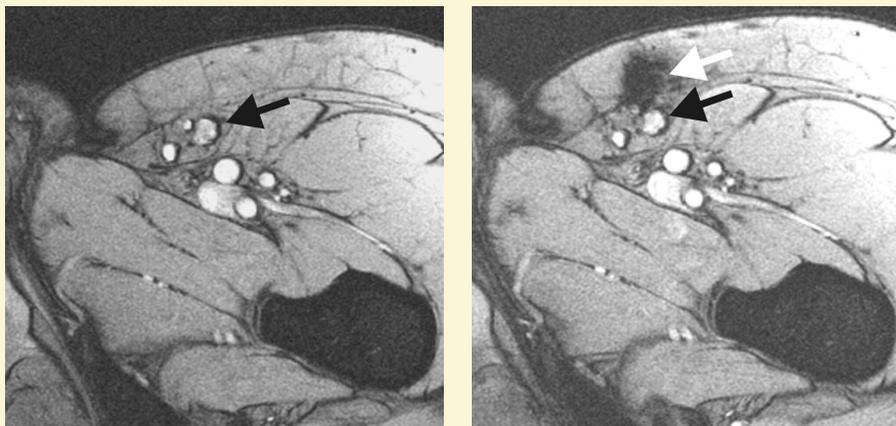


Figure 1. Magnetic nanoparticles can be used to monitor the accuracy of delivering therapeutic agents. In this example, the MR image on the left shows a lymph node (black arrow) into which an interventional radiologist wishes to inject dendritic cells, which have been labeled with magnetic nanoparticles. The MR image on the right shows clearly that in this case, the dendritic cells (white arrow) were not injected into the desired target.

cells to the exact spot where they can do their job,” says Bulte (See Figure 1).

Then, there are the multifunctional nanodevices designed to be both imaging agent and anticancer drug. For example, James Baker Jr., M.D., director of the Michigan Nanotechnology Institute for Medicine and Biological Sciences and director of an NCI-funded Cancer Nanotechnology Platform Partnership team, has been heading a research effort aimed at developing tumor-targeting dendrimers that contain both imaging agent and therapeutic agent. In a recent paper, Baker’s team described its work with a dendrimer linked to a fluorescent imaging agent and paclitaxel, and showed that this agent can identify tumor cells and kill them simultaneously. Several other Platform Partnership teams, such as those headed by Kattesh Katti, Ph.D., of the University of Missouri-Columbia, Panos Fatouros, Ph.D., of the Virginia Commonwealth University, Miqin Zhang, Ph.D., of the University of Washington, Allan Oseroff, M.D., Ph.D., of the Roswell Park Cancer Institute, and Paras Prasad, Ph.D., of the State University of New York in Buffalo, are also developing multifunctional nanoparticles for simultaneous imaging and therapeutic applications.

Boosting a signal, reducing the noise

Virtually all imaging techniques work on the same general principle. Some form of energy is “beamed” into the body, where that energy interacts in some unique way with the body’s molecules and internal structures. An electronic detector specific to the particular type of imaging machine records those interactions, enabling someone with the proper training to “read” the resulting image and make some diagnostic conclusion. A CT scanner, for example, sends focused x-rays into the body, which are either deflected off or pass through the tissues and bones. A detector measures the intensity of the x-rays passing through the body and a computer reconstructs that data to create an image. In optical imaging, the form of energy is usually near-infrared light. In magnetic resonance imaging, a combination of a magnetic field and radio waves are used to gently excite all of the water molecules in the body; the manner in which those water molecules “relax” provides detailed structural information when analyzed by a computer.

In a slight variation, some imaging methods make use of energy that is actually injected into the body and then record how that energy passes out of the body. PET imaging, for example, relies on energy emitted by radioactively labeled molecules that get taken

up by cells. Recently, Sanjiv Gambhir, M.D., director of the NCI-funded Stanford Center for Cancer Nanotechnology Excellence (CCNE), and his colleagues created a novel type of nanoscale quantum dot that uses a chemical reaction to generate its own light in the body, rather than requiring an external light source to trigger the emission of light that signals, “Here I am in the body” (See [Nano.Cancer.Gov News](#)).

A wide variety of physical, anatomical, and chemical properties – too many to list here – affects how useful a given imaging technique will be for detecting a particular type of cancer. There is, however, one concept, known as “signal-to-noise,” that can provide a good idea of what imaging scientists are up against when trying to improve the sensitivity of a particular imaging technique. Signal-to-noise refers to the fact that the data obtained by any imaging technology are a mixture of the diagnostically useful “signal” that says “tumor here” and background “noise” that can hide that signal. The larger the ratio of signal-to-noise, the easier it is to make sense of an image.

To get a handle on this concept, think about having a conversation with a friend. If the two of you are standing in a soundproof booth, the signal-to-noise ratio would be virtually infinite – the signal would be the sound of your two voices, while the noise would be almost nil. In contrast, if you were on opposite sides of a crowded auditorium lobby, the signal-to-noise ratio would be close to one, that is, the sound of your friend’s voice was no louder than the noise from the crowd.

But just as it’s possible to boost the signal-to-noise ratio by using an electronically amplified bullhorn to raise your voice above the crowd noise, it is feasible to create a nanoparticle that can boost the “tumor here” signal over the background noise. The bigger the boost relative to the background noise, the more sensitive the imaging method becomes, which in turn, increases the odds of detecting smaller tumors.

In order to provide the same boost in an imaging setting, the research community has developed a host of molecular bull-

horns. Known collectively as imaging contrast agents, these molecules possess physical characteristics that increase the strength of the signal coming out of the body. MRI contrast agents containing the element gadolinium, for example, do so by altering the magnetic field in the body, which boosts the strength of the MRI signal. In the same manner, optical imaging contrast agents act as light-amplifying devices, sending out light signals strong enough and of the correct frequency to pass through tissues and skin. The key to successful use of these agents, though, is to target them so that they concentrate in tumors and are eliminated rapidly from the rest of the body – in this way, contrast agents boost the desired signal without also increasing the background noise.

In this instance, nanoparticles can play an enabling role. “Nanoparticles are ideal for creating imaging contrast agents because of two properties,” says Lily Yang, M.D., Ph.D., an assistant professor of surgical oncology research and a member of the Emory-Georgia Institute of Technology Nanotechnology Center for Personalized and Predictive Oncology, one of the eight CCNEs funded by the NCI. “First, we can design them so that they are very bright when imaged, and second because we can attach various targeting molecules to their surfaces and achieve a high concentration of the imaging agent at the tumor” (See Figure 2). Because of the promise that nanoparticles have as imaging contrast agents, nearly all of the CCNEs have significant efforts underway involving the development of these agents.

Yang, for example, is working with Shuming Nie, Ph.D., co-director of the Emory-Georgia Tech CCNE, and colleagues Xiaohu

Courtesy: Lily Yang, M.D., Ph.D., Emory-Georgia Institute of Technology, Nanotechnology Center for Personalized and Predictive Oncology

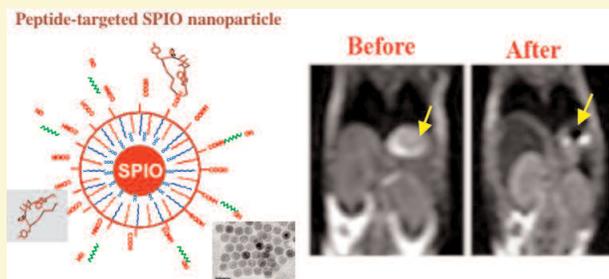


Figure 2. Targeted nanoparticles show tremendous promise for detecting tumors much earlier than is now possible. In the example shown here, a magnetic iron oxide nanoparticle (SPIO) is used to detect a pancreatic tumor in a live mouse. The nanoparticle’s surface contains a molecule that binds to a receptor found on pancreatic tumors. When injected into the mouse, the nanoparticles accumulate in the tumor, leaving a distinct black void on MR image. The yellow arrows show the location of the tumor in images taken before and after nanoparticle injection.

Courtesy: Ralph Weissleder, M.D., Ph.D., MIT-Harvard Center of Cancer Nanotechnology Excellence

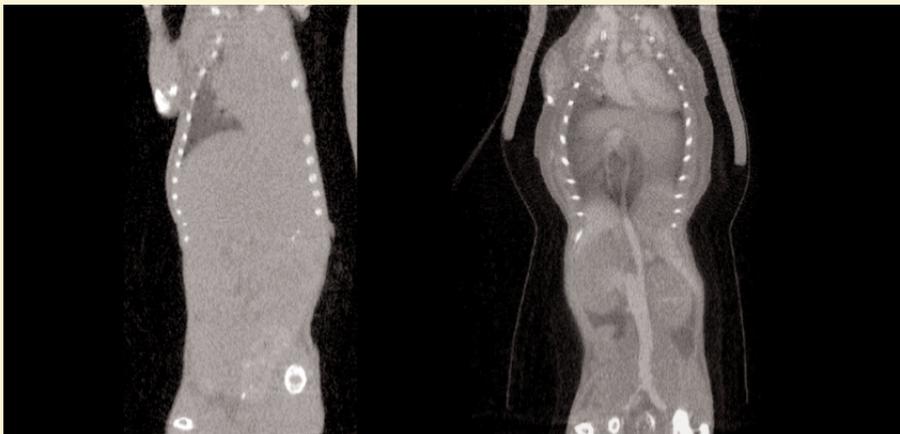


Figure 3. Polymer-coated bismuth nanoparticles are capable of revealing anatomical details that are invisible on a standard CT image. The CT image on the left comes from a live mouse before injection of the bismuth nanoparticles, while the CT image on the right clearly delineates the vasculature, heart and other organs.

Gao, Ph.D., who is now an assistant professor of bioengineering at the University of Washington in Seattle, Hui Mao, Ph.D., in the Department of Radiology at Emory University, and Andrew Wang, Ph.D., from Ocean Nanotech in Fayetteville, AR, on both quantum dots and magnetic iron oxide nanoparticles that are targeted to breast and pancreatic tumors. Using one of two targeting molecules, she and her collaborators have shown that they can detect breast tumors in animal models using optical imaging with quantum dots and MRI with the iron nanoparticles. “What we need to do now is translate this work from the lab into more animal studies and then the clinic. That’s the goal of our CCNE project,” says Yang.

Ralph Weissleder, M.D., Ph.D., co-director of the MIT/Harvard CCNE, and his colleagues have been developing a wide range of nanoparticle-based contrast imaging agents. While most of these are designed to be used in conjunction with MRI, he and his collaborators recently published work showing that bismuth nanoparticles naturally accumulate in lymph nodes containing metastases. More importantly, the bismuth nanoparticles show up as bright white spots in CT images. Weissleder’s team is now working to add tumor-targeting agents to the surfaces of these polymer-coated nanoparticles (See Figure 3).

One factor that will be a key to the success of these and other projects is the multidisciplinary team building that has occurred at the CCNEs. “It is clear that the only way we are going to be able to turn the promising features of nanoparticles into useful imaging contrast agents is by bringing together

experts in the chemistry and materials science aspect of nanotechnology with those who understand the ins and outs of imaging technologies and with clinical oncologists,” explains Gambhir. “Here in our CCNE, for example, we have a team of chemists and biologists working with the imaging experts at General Electric and oncologists at Stanford University and Cedars-Sinai Medical Center in Los Angeles so that we always keep our eye on clinical trials as we’re working out the basic science.”

Certainly, there are technical and scientific challenges ahead on the road from the laboratory to the clinic. But given the talent and resources being applied to these challenges, and the successes to date in developing nanotechnology-enabled imaging agents, the future is indeed bright when it comes to creating new ways of spotting cancer at its earliest stages.

Selected References

- de Vries IJ, Lesterhuis WJ, Barentsz JO, Verdijk P, van Krieken JH, Boerman OC, Oyen WJ, Bonenkamp JJ, Boezeman JB, Adema GJ, Bulte JW, Scheenen TW, Punt CJ, Heerschap A, Figdor CG. Magnetic resonance tracking of dendritic cells in melanoma patients for monitoring of cellular therapy. *Nat Biotechnol.* 2005; 23(11):1407-13.
- Peng XH, Cao ZH, Xia JT, Carlson GW, Lewis MM, Wood WC, Yang L. Real-time detection of gene expression in cancer cells using molecular beacon imaging: new strategies for cancer research. *Cancer Res.* 2005; 65(5):1909-17.
- Rabin O, Manuel Perez J, Grimm J, Wojtkiewicz G, Weissleder R. An X-ray computed tomography imaging agent based on long-circulating bismuth sulphide nanoparticles. *Nat Mater.* 2006; 5(2):118-22.
- So MK, Xu C, Loening AM, Gambhir SS, Rao J. Self-illuminating quantum dot conjugates for in vivo imaging. *Nat Biotechnol.* 2006; 24(3):339-43.
- Wang Y, Iyer M, Annala A, Wu L, Carey M, Gambhir SS. Noninvasive indirect imaging of vascular endothelial growth factor gene expression using bioluminescence imaging in living transgenic mice. *Physiol Genomics.* 2006; 24(2):173-80.

But new nanotechnology-enabled imaging agents stand to do even more to benefit cancer patients. One huge potential contribution could come from using such imaging agents to speed the drug development process by providing new information about how potential anticancer drugs behave in the body, that is, how they reach tumors, gain entry to malignant cells, and kill those cells.

“Any time you can get a better image of what’s going on in the body, and do so in a dynamic manner, you have the opportunity to gain insights that will positively impact our ability to develop new drugs to treat cancer,” says Greg Downing, D.O., Ph.D., director of the NCI’s Office of Technology and Industrial Relations, which oversees the Institute’s nanotechnology initiatives.

In addition, new imaging agents could even speed the clinical trials process in two ways. First, better imaging data could help oncologists better select which therapies to use on a particular patient, and second, increasingly sensitive and specific imaging agents will be able to provide real-time information about whether a therapy is working. Currently, oncologists and their patients must wait months to determine if a given therapy is working. Shorter clinical trials would mean that effective new drugs would reach patients quicker and ineffective drugs would be dropped from clinical trials sooner, allowing drug discoverers to better focus their efforts on more promising therapies. <

—Joe Alper

Author’s note: In writing this story, it became obvious that it would be impossible to discuss all of the innovative cancer imaging projects being done by members of the CCNE network and Cancer Nanotechnology Platform Partnerships. But stay tuned, for those projects will be the subject of future features and news stories that will appear here at nano.cancer.gov.