

# Our Incredible Shrinking World

by Dan Harvey, for *Medical Imaging*

Focused research and preliminary testing show that nanotechnology is the next big thing on medical imaging's horizon.

The thoughtful conclusion of *The Incredible Shrinking Man*, a rather good 1957 science-fiction film that hides its merits behind its lurid title, trumps all of the special effects and sensational plot situations that precede it.

The movie details the ordeal of Scott Carey, a healthy young man who starts shrinking after radiation exposure. In his progressive condition, Carey starts out as a man of average height and build. By the film's end, he's even smaller than the basement spider with whom, in a rousing climax, he engages in battle (armed with a sewing needle). However, there's no happy ending—no miracle cure developed by scientists, no reversal to his appalling fortune. In a tranquil but compelling *anticlimax*, Carey realizes that he'll continue to shrink with no end. And he wonders where this will lead him.

The film is best remembered for its closing soliloquy, when Carey looks up at the moon from his vantage between blades of grass and speculates on his future: "I was continuing to shrink, to become—what? The infinitesimal? What was I? Still a human being? Or was I the man of the future?... Would other beings follow me into this vast new world?... And in that moment, I knew the answer to the riddle of the infinite. I had thought in terms of man's own limited dimension.... As I felt my body dwindling, melting, becoming nothing, my fears melted away."<sup>1</sup>

More so than the house cats that were turned into monsters by Carey's size, these ruminations are what remain with the viewers. Who couldn't help speculate what this new frontier into which Scott Carey was entering would be like?

**Nanoscience and Nanotechnology: Giving Us an Idea**

Because of nanoscience, we know that Scott Carey would eventually shrink down and enter the "nanouniverse." What would this area be like? In the nanouniverse, scale is so small that generally accepted principles of physics seem to no longer apply. Such forces as inertia, friction, and gravity act differently or are meaningless.

"The world that we know is ruled by Newtonian physics, where gravity rules. It follows the standard laws of physics that we know and can see," says Lynn Foster, emerging technologies director with Greenberg Traurig Consulting Inc (Santa Monica, Calif), an international agency that provides consulting services on issues affecting established and emerging businesses. "When you get into nanotechnology, you go below the range of visible light. When you cross the 100-nanometers barrier, the physics actually change because the most dominant force is the quantum effect of individual molecules interacting with each other. That actually becomes the stronger force than Newtonian physics."

In nanoscience, small means microscopic. A nanometer (nm) is 1 billionth of a meter. A comparison puts this into perspective: Five hydrogen atoms side by side span about 1 nm, while a single human cell has an area of thousands of nanometers.

Nanoscience endeavors to make sense of how matter behaves at this level, while nanotechnology involves the manipulation and control of matter at this level.

According to the National Science Foundation (NSF of Arlington, Va), nanotechnology involves:

- research and technology development at the atomic, molecular, or macromolecular levels in the 1–100 nm range;
- creating and using structures, devices, and systems that have novel properties and functions because of their small and/or intermediate size; and
- the ability to control or manipulate on the atomic scale.

Nanophiles say the envisioned nanotechnological devices will have a profound impact on our macro world, touching everything from communications, electronics, and healthcare. The NSF says nanotechnology could create a \$1 trillion global market by 2015. As that target date suggests, nanotechnology has a ways to go.

Nanotechnology is still in its early stages, Foster reports, but he feels its eventual impact will affect the world in much the same way that microelectronics and computing did. "I think there are going to be tremendous advances, but it is not going to be in the near term," he says.

Foster has done some consulting with clients in the healthcare field-primarily on the funding side for organizations seeking venture capital and obtaining research grants-and he thinks it will impact all areas, particularly imaging, diagnostics, therapeutics, and drug delivery. Medical product manufacturers and researchers already have started venturing into nano territory. Within a decade, results of the research should start hitting the market.

## **Nano Contrast Agents**

## What Does the Future Hold?

The GE Global Research Center (Niskayuna, NY) has initiated a nanotechnology program focused on long-term research. The five areas of research include nanotubes and nanowires, nanostructures in metals and ceramics, hybrid materials, hierarchical ceramics platform, and magnetic nanoparticles.

Materials in development would be used in a variety of applications to support GE Co businesses, including GE Healthcare (Waukesha, Wis). In particular, the magnetic nanoparticles could be useful in a variety of applications, such as contrast agents for nuclear resonance imaging. "Nanoparticles as contrast agents are going to be a very big area," reports Nadeem Ishaque, business program manager of the GE Global Research Center.

Nanoparticles have inherent properties that make them very attractive in use for imaging applications, Ishaque says.

"Nanoparticles with ion-oxide-based materials could be very effective as contrast agents used for MRI. One of the biggest problems with MRI is that you need to have a very high concentration of your target in the body before you can

Many folks in the medical field recognize the vast potential of nanotechnology, particularly as it relates to cancer research. This past September, the National Cancer Institute (NCI of Bethesda, Md) announced a \$144.3 million, 5-year initiative to develop and apply nanotechnology to cancer.

As part of the initiative, the NCI has formed the NCI Alliance for Nanotechnology in Cancer, which includes researchers, clinicians, and public and private organizations. The ultimate goal is to take cancer-related nanotechnology research into the realm of clinical practice.

The Alliance consists of four major program activities:

1. Centers of Cancer Nanotechnology Excellence-The Center's goal will be to integrate nanotechnology development into basic and applied cancer research.
2. Multidisciplinary research teams-These teams will involve the training, education, and career development of medical professionals toward nanotechnology.
3. Nanotechnology platforms for cancer research-These platforms will advance new research that supports molecular imaging and early detection, in vivo imaging, reporters of efficacy, multifunctional therapeutics, prevention and control, and

image," he explains. "The nanoparticles we're developing have a lot of ion atoms inside. Once they go to the target, they provide an amplification of the signal coming through the target. So you can visualize the targets better with these nanoparticles."

Ishaque reports that the GE Global Research Center has been testing the nanoparticles in animal models. Research involves using the particles to assess various types of disease states, including arteriosclerosis and inflammation, in mice. He indicates that studies involving humans are quite a ways off, but he believes that nanoparticles as contrast agents could greatly affect imaging. "The overall impact of this technology will be quite significant," Ishaque adds, "but it is still in its infancy in a sense."

Currently, GE Co doesn't expect to see any products come out of its five areas of research for 5–10 years.

## **There's Gold in Them Thar Nanoshells**

The company with a medical nano product closest to market is Nanospectra Biosciences Inc (Houston), which has been developing a new approach to cancer treatment, one that offers a nanotechnological twist to thermal ablation. Specifically, the approach involves nanoshells that kill tumors with heat. Nanoshells are only 100 nm in diameter, which is about 20 times smaller than a red blood cell.

Nanoshells were invented in the late 1990s by Naomi Halas, PhD, and colleagues at Rice University (Houston). Nanoshells are described as optically "tunable" dielectric (or nonconducting) silicon particles coated with metal. The metallic content causes the nanoshells to reflect and absorb light. By reflecting light, they can act as a contrast agent. By absorbing light, they can generate heat.

Halas later began collaboration with Jennifer West, PhD, associate professor of bioengineering at Rice University, to develop medical applications for these new materials. This led to the formation in 2001 of Nanospectra Biosciences.

The noninvasive therapy involves an external laser and nanoshells. It targets various cancers and destroys tumors with heat while leaving surrounding tissue undamaged. During a procedure, a patient would be injected with nanoshells combined with targeting proteins, which would then circulate through the body and accumulate near targeted cancer cells. An external infrared laser would then heat the nanoshells and ablate the tumor tissue.

J. Donald Payne, Nanospectra CEO and president, says the invention is centered on the nanoshell structure's ability to change the wavelength of light absorbed by the metal. For example, gold particles only several nanometers in diameter appear red in solution because they absorb light in a narrow wavelength. On a nanoshell, the gold can absorb infrared light.

For cancer therapy applications, nanoshells coated with gold absorb light and generate heat for tumor destruction. By varying the size of the nanoshell's glass core and its gold shell layer, researchers can "tune" nanoshells to respond to different wavelengths of light. "We can shift the wavelengths of light absorbed out to the near infrared range [NIR]," Payne says. "The NIR range is the region of the spectrum where optical absorption in tissue is minimal while penetration is optimal."

Thus, nanoshell therapy would avoid many of the side effects of chemotherapy and radiation.

So far, the researchers have obtained promising results in studies. In the first of two studies involving mouse models, they injected nanoshells directly into tumors but with no survival. However, in a second study, the nanoshells were injected into the blood stream, allowed to circulate and accumulate near tumors, and then exposed to a laser. The laser heated the nanoshells and generated a high enough temperature to kill the cancer. In two days, the mice were tumor-free and experienced no toxic side effects. Payne says the materials have a very high safety profile and that they don't expect to have a problem with treatment or re-treatment.

In studies, the researchers haven't found any adverse affects associated with the nanoshells. "We've injected a lot of nanoshells into mice and looked for tissue damage as well as for blood chemistry issues, such as liver damage," Payne reveals. "We haven't had any issues, which is what you would expect, because gold has been used inside of the body for a long period of time without any significant toxic effect."

The company expects to begin human clinical trials in about a year. Initial studies will focus on mesotheliomas, a type of lung cancer that results from asbestos exposure, and then expand to other lung tumors and lung metastases. Therapy could be available 18–24 months after the start of the trials.

The company's research recently expanded to involve nanoshells and photoacoustic tomography (PAT). Payne reports that PAT is a fairly new technique, which combines infrared lasers with ultrasound. It can provide structural and functional information by measuring photoacoustic waves that are generated by different light absorptions in soft tissues. Nanospectra Biosciences has been working in collaboration with Lihong Wang, PhD, professor of engineering in the departments of biomedical engineering and electrical engineering of Texas A&M University (College Station, Tex), who has developed very sensitive PAT instrumentation.

In September, the company received a \$2 million award from the Advanced Technology Program of the National Institute of Standards and Technology (Gaithersburg, Md) to develop an integrated approach to the diagnosis and treatment of cancer. Using nanoshells and PAT, the technique would be highly accurate and noninvasive. PAT, which uses light absorption to generate a detectable sound wave, would be able to detect and pinpoint the tumors by finding nanoshell concentrations. "This would allow us to both detect and treat early metastatic disease using nanoshells as a contrast agent," Payne says. Nanoshells as contrast agents, Payne believes, would enable the detection of tumors and metastatic disease at levels currently undetectable by conventional imaging methods.

## Nanotechnology and Optical Imaging

Rebekah A. Drezek, PhD, assistant professor of bioengineering and electrical and computer engineering at Rice University, has been working with Halas and West as part of an interdisciplinary team of researchers from both Rice University and the University of Texas MD Anderson Cancer Center (Houston). She, too, has been working with nanoshells for the diagnosis and treatment of cancer. Drezek's research involves two emerging areas in biomedical engineering: nanobiotechnology and biophotonics. In the lab, Drezek and her researchers design projects toward the development of new technologies to improve women's healthcare. Currently, they are focused on the detection, diagnosis, and monitoring therapy of breast, ovarian, and endometrial cancer. Current areas of emphasis include:

- development of novel optical spectroscopy and imaging instrumentation for tissue diagnosis;
- validating developed optical instrumentation through systematic studies using biological samples of progressively increasing complexity, beginning at the cellular level and culminating in small-scale clinical trials;
- development of molecular-specific optical contrast agents;
- experimental studies to elucidate the biophysical origins of measured optical signals; and
- computational modeling of the interaction of light with biological tissue in order to understand the relationships between measured optical signals and underlying tissue biochemistry, morphology, and architecture.

Drezek's nanotechnology research focuses on medical applications of nanoshells—specifically the design, fabrication, and validation of molecular-specific optical imaging agents based on nanoshell bioconjugates.

"My lab is an optical imaging lab, and we work with a variety of different optical imaging methods that are mostly directed to the infrared portion of the spectrum,

where you can get light through tissue the farthest," she explains. "With the nanoshells, we're designing them in our lab so that they will scatter light very strongly at wavelengths that match some of the different optical systems that we have under development."

Drezek feels that nanotechnology is going to be very important to medicine-and crucial to her areas of research. "If you look at imaging as a field in general, optical technology is the next new technology," she says. "It turns out that a lot of nanomaterials have very interesting optical properties, which let you do things that you simply couldn't do before. For instance, what you need to do with a lot of cancer-type applications is to find a way to light up a very specific signal, which may be either on the surface of the cell or even within the cell. Until nanotechnology, [we had] very few ways to think about doing that in a tunable way. When you can [perform this process] in a way that is general, you can almost look for anything you want. So, for imaging, I think nanotechnology is very important."

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## References

1. IMDB's Memorable Quotes from *The Incredible Shrinking Man* (1957). Available at: <http://uk.imdb.com/title/tt0050539/quotes>. Accessed November 2, 2004.