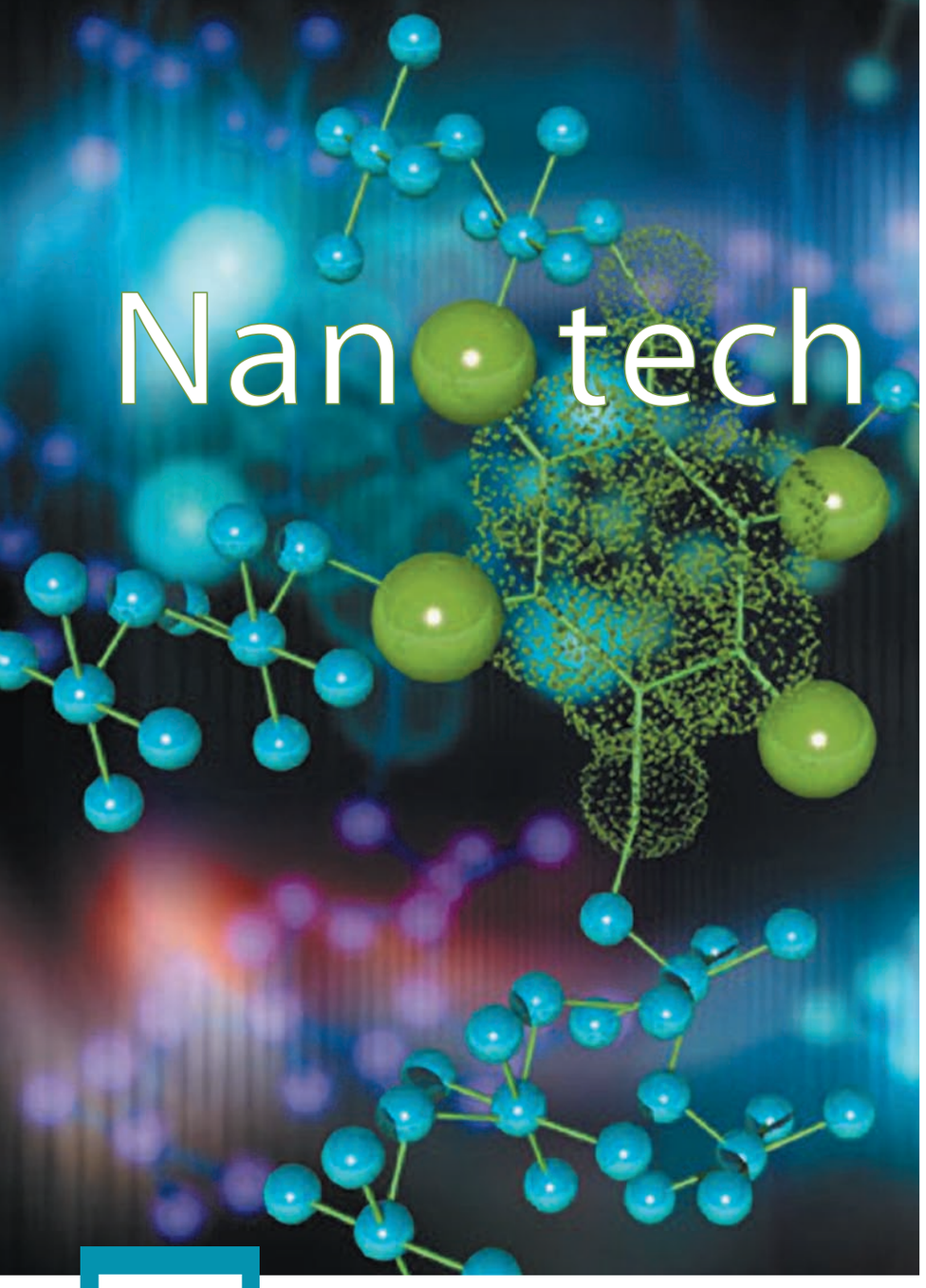


Nanotech COMES OF AGE

BY KIM RIBBINK

The once futuristic science of nanotechnology has come of age and branched into a broad spectrum of applications. Among these is nanomedicine: medicinal intervention at the molecular level for curing disease, repairing damaged tissue, and monitoring biological systems.

The National Institutes of Health defines nanotechnology as the creation and use of materials and devices at the level of molecules and atoms. A nanometer is one-billionth of a meter, too small to be seen with a conventional lab microscope. It is at this scale — about 100 nanometers or less — that biological molecules and structures inside living cells operate.

A number of initiatives have been established to advance nanotechnology, including the National Nanotechnology Initiative, which is a federal R&D program established in 2001 to coordinate the multiagency efforts in nanoscale science, engineering, and technology. Recent information shows 26 federal agencies participate in the initiative, including the Food and Drug Administration and the National Institutes of Health, and 13 of these agencies have an R&D budget for nanotechnology.

In an effort to fully grasp the potential for nanomedicine, the NIH has established a national network of eight Nanomedicine Development Centers to better understand the intricate operations, processes, and networks inside living cells.

Already, nanomedicine can boast a number of successes in areas ranging from cancer to immunosuppressants, from hormone therapy to cholesterol reduction, from bone replacement to imaging and diagnostic tests. (For more information, see box on page 24.)

Nanotech **POTENTIAL**

"There is reporting in the broader media and lay press that nanotechnology applied to therapeutics might be coming in the future, but it's really happening now," says David Nance, president and CEO of Introgen Therapeutics.

Nanotechnology-based products are even starting to become market leaders in some areas.

For example, there is a wound dressing product from Smith & Nephew called Acticoat that uses an antimicrobial nanocrystalline silver.

"Acticoat's sales grew at a rate of about 40% last year, whereas the category grew at about 12%," says Mark Bunger, research director at Lux Research. "Clearly, Smith & Nephew is taking share away from other competitors in this field."

As new nanomedicines, nanodiagnostics, and nanotech-based medical supplies and devices enter the U.S. marketplace, demand for such products is expected to grow significantly. Industry research firm Freedonia Group predicts that the demand for nanotech-based medical products will increase more than 17% per year to $53 billion in 2011 and to more than $110 billion in 2016.

Analysts and industry experts believe that therapies for cancer and hyperproliferative disorders, such as rheumatoid arthritis, as well as diagnostics and devices, are where nanotechnology has the greatest short-term potential in healthcare.

There are varying reasons for this, particularly with regard to cancer therapies.

"There's a good match between the pharmacokinetics of nanoparticles and the cell-level interaction needed to fight small metastases and such," Mr. Bunger says.

Nanomedicine also is expected to play a key role in areas such as regenerative medicine, gene therapy, and neuroprosthetic devices, industry watchers say.

Additionally, the ability of nanotechnology to improve imaging techniques and the advances made with the lab on a chip has huge implications, says David Rejeski, director of the Project on Emerging Nanotechnologies.

"Being able to conduct pre-emptive and preventive medicine could have large impacts on healthcare costs, and advances in these areas will be built on the ability to do better imaging and better laboratory diagnostics," he says.

Nanotechnology provides the opportunity to develop very

With products already in the marketplace and a huge amount of research going into nano-based drugs and devices, **NANOTECHNOLOGY IS BOTH EXCITING SCIENCE AND A GROWTH MARKET.**

specific imaging agents with extremely high contrast, says William Moffitt, president and CEO of Nanosphere.

"In diagnostics, the opportunity is there for nucleic acids and protein biomarker detection at a limit of detection and sensitivity that the world has never seen before," he says. "This will create new diagnostic tests for diseases where no tests exist today."

The emergence of sensitive and specific biomarker detection tailored to the individual patient is creating a shift in the healthcare system, says David Browning, CEO of Oxonica Healthcare.

Nanotechnology also is bringing about structural changes in the way companies operate and blurring the lines between diagnostics and therapeutics and between devices and therapeutics, experts say.

"All of the traditional boundaries in the industry of research tools and equipment, device makers, drug makers, and diagnostics tools are getting weaker because of nanotechnology," Mr. Bunger says. "When the wall comes down, this will lead to innovation, to mergers and acquisitions, and to new categories of therapies and diagnostic tools."

State of **PLAY**

First-generation nanomedicines, which include products on the market today, are nanotechnology reformulations of existing drugs to improve their toxicity profiles. For example, Abraxane is a new formulation of Taxol (paclitaxel) for treating advanced (metastatic) breast cancer with the benefit of reduced side effects.

Abraxane is marketed in the United States under a copromotion agreement between Abraxis BioScience and AstraZeneca. In 2006, the product had revenue of $174.9 million versus $133.7 million in 2005.

Abraxane is the first albumin-bound taxane particle of about 130 nanometers that takes advantage of albumin, a natural carrier of water-insoluble molecules (e.g., various nutrients, vitamins, and hormones) found in humans.

Abraxis's technology creates protein nanoparticles that are suitable for *in vivo* delivery of a potentially broad range of drugs. Called Protosphere, this technology offers the ability to convert insoluble or poorly soluble drugs into nanoparticles allowing them to become soluble and easier to deliver.

Investments in nanomedicine research are beginning to pay off. Mr. Rejeski says the number of nano-based drugs and biomedical devices in the FDA pipeline went up about 70% between 2004 and 2005.

As the science has become better understood, there has been movement into more flexible delivery systems.

"By combining nanoscale delivery systems with biologics, it becomes possible to treat some diseases, such as cancer, earlier in the disease stage and develop products that can harness the body's normal cancer-fighting or cancer-repair mechanisms," Mr. Nance says.

Introgen Therapeutics is focusing on targeted molecular therapies to treat cancer and other diseases. Last November, the company obtained an exclusive, worldwide license to a portfolio of patents from The University of Texas M.D. Anderson Cancer Center focused on the delivery of biologically active proteins, polypeptides, and peptides using novel nanoparticle delivery complexes.

Introgen's nanoparticle vector technology combines DNA with the lipids DOTAP and cholesterol to create a synthetic gene-delivery vehicle. The nanoparticle vectors have broad utility in the development of systemic cancer therapies. The nanoparticle lipid-DNA complex is formulated as particles of lipid surrounding DNA that encodes a gene with therapeutic potential.

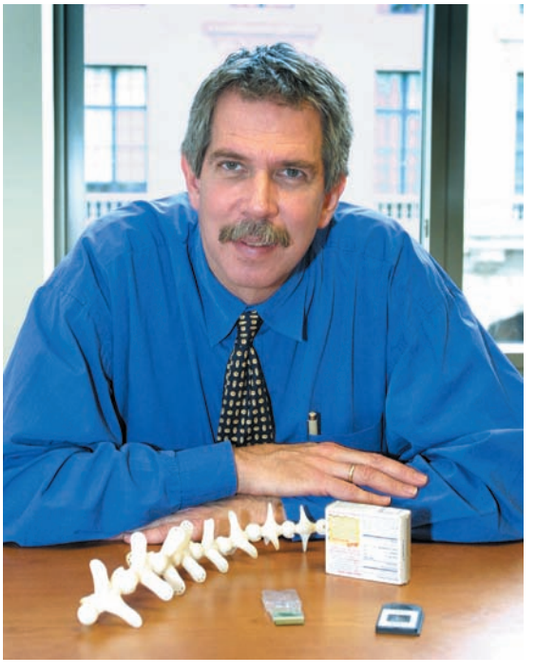
The lipid in the delivery system fuses with the cell membrane, leading to uptake of the particle into the cell. Normal cellular processes degrade the lipid, and the DNA is taken into the nucleus and expressed, producing a therapeutic protein that induces anticancer effects.

"We have a program with the center that's now in Phase I clinical testing using a synthetic nanoparticle that delivers the FUS1 tumor suppressor; FUS1 has been discovered to be associated with the early onset of cancers, and we're testing the compound now in patients with metastatic lung cancer," Mr.

U.S. Nanotechnology
MEDICAL PRODUCT DEMAND

Item	2006	2011	2016
Nanotech Medical Product Demand	$23.6	$52.8	$110.5
Pharmaceuticals	$17.6	$39.2	$82.0
Diagnostics	$5.5	$8.4	$12.3
Medical Supplies and Devices	$0.4	$5.2	$16.2

Note: Dollars are in billions
Source: The Freedonia Group Inc., Cleveland.
For more information, visit freedoniagroup.com.



DAVID REJESKI
Project on Emerging Nanotechnologies

PEOPLE GENERALLY VIEW NANOTECHNOLOGY AS SCIENCE FICTION, but there are hundreds of nanotech products in the marketplace.

MARK BUNGER
Lux Research

NANOTECHNOLOGY BRIDGES THE GAP between the diagnostic and therapeutic areas and the drug and device areas.

Commercialized **NANOMEDICINES**

CATEGORY	PRODUCT	MARKETER(S)	INDICATION
Appetite Control	Megace ES (megestrol)	Par Pharmaceutical Companies Inc.	Treatment of anorexia, cachexia, and unexplained, significant weight loss in patients with AIDS
Cancer	Abraxane (paclitaxel protein-bound particles)	Abraxis BioScience/ AstraZeneca	Treatment of advanced breast cancer
Cancer	Doxil (doxorubicin)	Alza Corp.	Treatment of refractory ovarian cancer and AIDS-related Kaposi's sarcoma
Cancer	Emend (aprepitant)	Merck & Co.	Prevention of chemotherapy-related nausea and vomiting
Cholesterol	TriCor (fenofibrate)	Abbott	Treatment of high cholesterol with or without elevated triglycerides
Hormone Therapy	Estrasorb (estradiol)	Esprit Pharma Inc./ Novavax Inc.	Treatment of moderate-to-severe vasomotor symptoms (hot flushes) associated with menopause
Immunosuppressant	Rapamune (sirolimus)	Wyeth	Prevention of organ rejection in patients age 13 years old or older receiving renal transplant

Source: Project on Emerging Technologies, Washington, D.C. For more information, visit nanotechproject.org/86.

Nance says. "The therapeutic protein is incorporated into a nanoparticle delivery system, which can then pass through the vasculature because it's so small."

Mr. Nance says results to date from studies with INGN 401 show that the therapy has no significant toxicities and is well tolerated.

The company also is researching nanoparticle systems that deliver other therapeutic proteins such as the p53 tumor suppressor and mda-7 gene, another tumor suppressor gene, in the form of dermal and orally delivered products to prevent oral cancers and treat leukoplakia, which is a disorder leading to oral cancer.

"We are finding that these small-scale, tiny delivery nanoparticles allow us to administer products via IV but also topically because the particles are small enough to penetrate several layers deep into the cells," Mr. Nance says

Mr. Bunger says there are a number of "disruptive" innovations that potentially could shake up approaches to treatment.

Among these is Nanospectra Biosciences Inc.'s AuroLase Cancer Therapy, which combines the unique physical and optical properties of AuroShell microparticles (also known as nanoshells) with a near infrared laser source to thermally destroy cancer cells without significant damage to surrounding tissue.

AuroShell particles are injected into the blood stream and accumulate in solid tumors, after which the cancerous area is illuminated with a near-infrared laser. The particles absorb this light, and convert the energy into heat to thermally destroy the tumor. AuroLase therapy has been demonstrated to be highly effective in animal models of cancer with no evidence of toxicity.

Another is MagForce Nanotechnologies, a German company, whose patented therapy allows the targeted destruction of tumors using magnetic nanoparticles.

The company is conducting a Phase II trial of LDR brachytherapy (seed implantation) in prostate cancer with intermediate risk. The primary aim of the study is to improve local tumor control (PSA control) and thus to increase the progression-free survival time.

In the field of diagnostics, Nanosphere uses gold nanoparticle probe technology for nucleic acid and protein detection for application in genetics, infectious diseases, cancer, pharmacogenomics, blood screening, and neurodegenerative and cardiovascular diseases.

"Gold nanoparticle probes are easily detectable using white light, so it's a very sensitive and very specific probe for nucleic acids, and it doesn't take any sample manipulation so it's simple, easy to operate and to use, and it's a low-cost option," Mr. Moffitt says.

The low cost and simplicity of use mean genetic testing won't need to go to commercial labs but can be conducted at hospitals and even physicians' offices, he says.

Oxonica Healthcare, the health division of nanomaterials group Oxonica Plc., has developed high-performance biomarker detection tags, Nanoplex Biotags, for immunodiagnostic assays and/or for use with DNA for ultrasensitive molecular diagnostics applications.

Mr. Browning says because Nanoplex particles contain reporter molecules providing ultraspecific signals, highly sensitive multiplex analyses can be achieved directly in complex biological matrices.

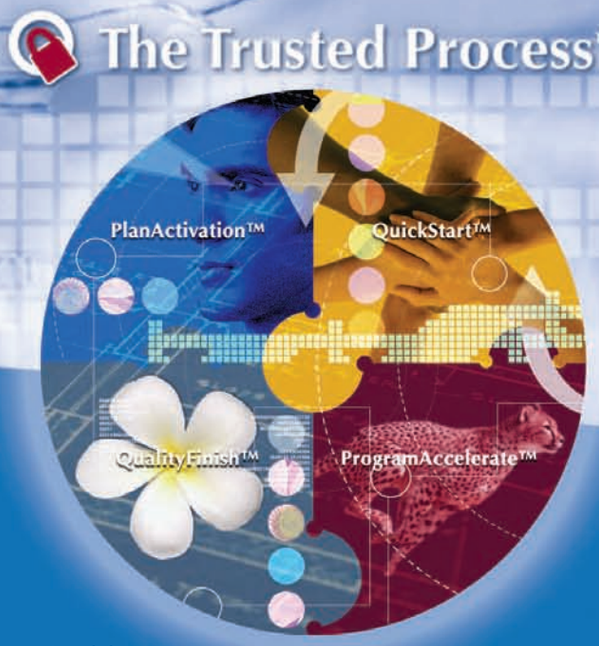
"Furthermore, because the signal comes from the inside of the particle and is shielded by a 20-nanometer thick glass coating, the optical signal is insensitive to changes in pH, ionic strength, and solution composition, an enormous benefit to assay development," he says. "In addition, the silica outer surface is easily chemically functionalized, making covalent attachment of proteins, DNA, and so on, as labels in immunodiagnostic and molecular assays exceedingly simple."

Obstacles and **RISKS**

Some concern has been raised over whether the FDA has the tools it needs — legal, resource, and scientific — to oversee the introduction of nanotechnology in a way that meets public expectations. In a report published last October, Regulating the Products of Nanotechnology: Does the FDA Have the Tools It Needs?, Former FDA Deputy Commissioner

We've Expanded Our Focus

Announcing New Infectious Disease Capabilities from INC Research



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From the very first customer interaction to final data delivery, INC Research promises to bring our renowned therapeutic foresight to the table and to support customers using our tried and true Trusted Process.™ And now, we will apply this proven methodology in the worldwide fight against infectious disease.

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WILLIAM MOFFITT
Nanosphere

NANOTECHNOLOGY OFFERS THE OPPORTUNITY to break the analytical system down to conform to the level of biology.

for Policy Michael R. Taylor found the agency has gaps in legal authority and fundamental inadequacies in resources as it attempts to better understand and manage the potential risks from new products using nanotechnology.

The FDA faces several impediments, Mr. Rejeski says. First, the FDA has been struggling with a lack of funds. Second, there are questions whether the agency will be able to bring together the scientific expertise needed to evaluate nanotech products, given the competition with the private sector for talent. And third, there are questions about whether the existing set of *in vitro* models, animal bioassays, and clinical-trials methods will work for nanotechnology.

"These are products that never existed, and to understand and regulate the safety and the efficacy of them requires new standards that don't yet exist and new ways to measure their effectiveness," Mr. Nance says. "So while we're working to solve problems on the atom level we also need to develop metrics and standards at that same level to be able to understand where the products go in the body, how they are assimilated, excreted, and measured. These activities are challenging and demand substantial time and resources to move at the cautious pace required by regulatory agencies."

According to Mr. Rejeski, the FDA's capacity to handle nanotechnology has large implications for commercialization, including how long it will take to get products through the pipeline.

DAVID BROWNING
Oxonica Healthcare

THE CHALLENGES ASSOCIATED WITH THE DEVELOPMENT AND COMMERCIALIZATION OF NANOTECHNOLOGIES IN CLINICAL DIAGNOSTICS ARE SIMILAR to those associated with any new biomarker or biomarker detection system — namely gaining regulatory approval.

"The timeline has significant ramifications in terms of a company's ability to attract venture capital and arrange licensing agreements, because time is money in the drug-development area," he says.

Mr. Moffitt says the FDA, however, has been working hard to develop the experience and expertise needed to deal with the questions nanotechnology poses.

The agency last August formed an internal Nanotechnology Task Force, which is charged with determining regulatory approaches that encourage the continued development of innovative, safe, and effective FDA-regulated products that use nanotechnology materials.

Another obstacle facing nanomedicine is demonstrating improvement over a more conventional medicine, given all the variables that need to be adjusted.

"Nanomedicines are very experimental, not just in their modes of action but also in how they are administered," Mr. Bunger says. "With a nanomedicine it is possible to fine tune the pharmacokinetics of a particle and adjust its shape. But in a large study, tweaking all these variables means that the results will invariably be off with some patients."

The fact that the field is so new means the knowledge base is thin and there are relatively few scientists, manufacturers, and regulators who are experts.

"The challenge then is how to scale up production from a conceptual, small-scale batch at the laboratory to large-scale, commercial production," Mr. Nance says.

Much of the innovation in nanomedicines and nanodevices is coming from small businesses that may lack the resources and expertise to take products through clinical trials to the market, Mr. Rejeski says.

"Many of those firms will have to find partners and how successful they are in terms of finding partners, constructing licensing agreements, and handling intellectual property with nanoengineered devices or drugs will be important over the next few years," he says. ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

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DAVID REJESKI. Director, Project on Emerging Nanotechnologies, Washington, D.C.; The Project is dedicated to helping ensure that as nanotechnologies advance, possible risks are minimized, public and consumer engagement remains strong, and the potential benefits of these new technologies are realized. For more information, visit nanotechproject.org.