Denise Myshko

# The Nanomedicine REVOLUTION

Nanomedicines have the potential to improve effectiveness and reduce the side effects of therapeutics.

Nanotechnology has the potential to revolutionize healthcare across disciplines and specialties. For medicines specifically, nanotechnology can improve drug targeting and effectiveness and reduce exposure and toxicity.

Nanotechnology allows scientists to create, explore, and manipulate materials on a scale measured in nanometers — particles so small that they cannot be seen with a regular microscope. The technology has a broad range of potential applications, such as improving the packaging of food and altering the look and feel of cosmetics.

## The Nanotech Movement

The market for nanomedicine, which was valued at $78.54 billion in 2012, is expected to be $177.60 billion in 2019, growing at a CAGR of 12.3% from 2013 to 2019, according to Transparency Market Research.

The advent of new applications and technology in the field of nanomedicine will be one of the major growth factors for the global nanomedicine market. North America dominated the market in 2012 and is expected to maintain its market position until 2019, at which point it will be challenged by the Asia-Pacific market, which is estimated to grow at a faster pace (CAGR of 14.6% from 2013 to 2019) and Europe, which is expected to grow at a relatively higher rate compared with North America because of a constantly improving regulatory framework and the presence of an extensive product pipeline portfolio.

The whole field of nanotechnology is growing, says Mike Morgen, Ph.D., director of new technology development at Capsugel.

"There are quite a few different technologies available for different applications," he says. "We found there is an unmet need for approaches that effectively achieve the in vivo profiles of active agents that companies need and want. As companies move into new chemical spaces with different types of molecules that are more difficult to deliver, especially orally, there continues to be a great need for innovative formulation approaches, most of which rely one way or another on nanosized structures."

Nanomedicine, an offshoot of nanotechnology, refers to highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve. A nanometer is one-billionth of a meter.

One of the most successful nanomedicines has been Doxil, Johnson & Johnson's doxorubicin encapsulated in a liposome and indicated for the treatment of ovarian cancer and multiple myeloma. It was the first of such medications, approved in 1995. A liposome, which is made out of the same material as a cell membrane, can be filled with drugs, and used to deliver drugs for cancer and other diseases.

The liposome allows the doxorubicin to stay in the bloodstream longer, so that more of the drug reaches the cancer cells. It has less impact on healthy cells than regular doxorubicin. But the product, now off patent, has limitations in the reproducibility of manufacturing, and there have been drug shortages.

### FAST FACT

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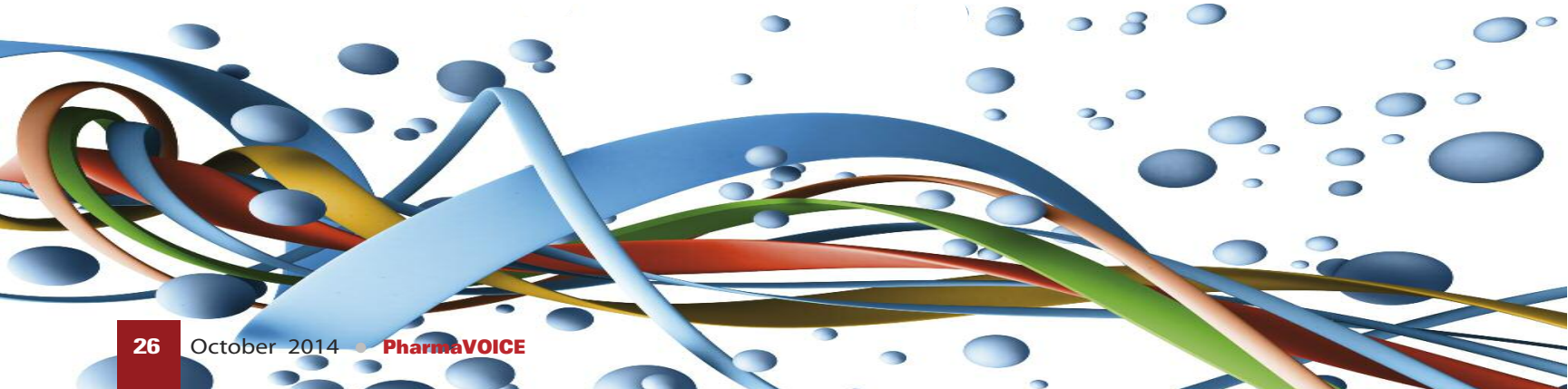
Source: Transparency Market Research

Experts say liposomes are an early nanomedicine technology, and research continues in this area.

"Think of liposomes as version 1.0 of nanotech," says Chris Guiffre, senior VP and chief business officer, Cerulean Pharma. "Nanotech research is now in version 3.0. Nano is a new technology that, like many new technologies, started off with more promise than results. Over the last five to seven years, the state of the art has moved forward significantly. Generally speaking, the promise of nanoparticles is just starting to come to fruition."

He says researchers now understand what nanoparticles can do in terms of creating better products.

"But like many technologies, this didn't happen overnight," he says. "Initially, for ex-



ample, there was a debate about something called the EPR effect, which refers to the leaky vasculature present in solid tumors, and whether nanoparticles could exploit this."

Mr. Guiffre says it is now understood that immature blood vessels in tumors have endothelial linings with much larger pores than those in the mature vasculature in most normal tissue, so tumor blood vessels are indeed leaky, which creates an opportunity for selectively targeting potent chemotherapies to tumor tissue while largely sparing normal tissue.

"We now know that a properly designed nanoparticle will remain more or less stable in the blood stream until it finds a pore in the neovasculature of tumors that is large enough for it to slip through," he says. "This enables the drug to concentrate in the tumor."

Mr. Guiffre says the Holy Grail in cancer research is to be able to concentrate a tumor-killing payload in the tumors while sparing the healthy tissue.

"We've tried a lot of things that have worked modestly or not worked at all, but the one thing we know for sure is that cytotoxic payload, or chemo, kills," he says. "The problem is that this approach kills cells indiscriminately so we need to selectively target the chemo to tumors and then release it slowly from within the tumor cells."

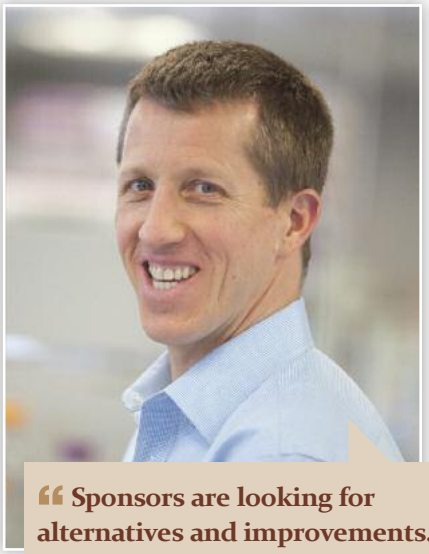
These are early days for nanomedicine as a technology, says Andrew Hirsch, chief operating officer of Bind Therapeutics.

"We've come a long way in the last 10 years in understanding the biology and pathways of diseases, but what we've not changed is how we attack that biology, largely with small molecules," he says. "With the advent of nanotechnology, we've been able to achieve something we couldn't do before: control the biodistribution of small molecules, engineered in, as opposed to relying on the interaction of chemistry and biology."

Continuing the research push in nanotechnology is the National Cancer Institute's Alliance for Nanotechnology in Cancer initiative, which began in 2005, and was recently approved to move to its third phase. The initiative brings together several Centers for Cancer Nanotechnology Excellence, smaller platform grants, training centers, and individual training grants and relies on multi-disciplinary work of cancer biologists and clinicians who define applications in oncology with chemists, materials scientists, and physicists developing new materials and devices at the nanoscale.

Piotr Grodzinski, Ph.D., director of the NCI Office of Cancer Nanotechnology Research at the National Institutes of Health, says the program's third phase will begin in 2015 and extend through 2020. He says the initiative so far has had funding of about $30 million per year.

"We want to continue with the current model where technologies are being developed at the university centers and then they are being handed off for translation and clinical



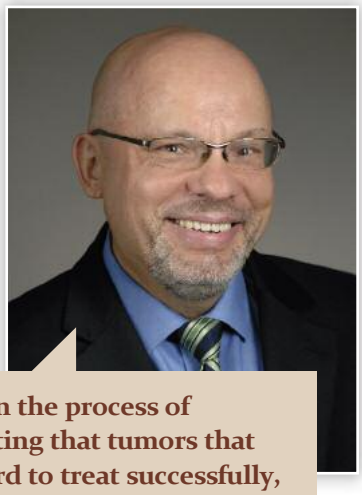
**"Sponsors are looking for alternatives and improvements. There is a greater recognition of the need for nanomedicines."**

**DR. JEFF HRKACH** / Bind Therapeutics

implementation to commercial outlets," he says. "At the same time, we plan to fund several research grants to support development of an even more in-depth understanding of the delivery mechanisms and interactions of nanomaterials with biological systems."

So far over the nine years of the program, Dr. Grodzinski says more than 70 companies have been formed that have grown out of NCI Alliance-funded universities.

"The investigators who are funded through this program have been very prolific when it comes to starting companies to take the technologies that were developed in academia forward to develop practical clinical applications," he says. "We encouraged strong relationships between the academic centers we fund and industry but we didn't really expect that so many companies would be formed."



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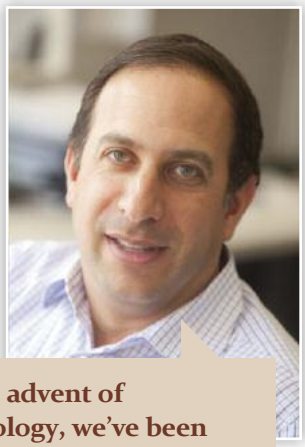
**DR. PIOTR GRODZINSKI**
National Cancer Institute



**"With the advent of nanotechnology, we've been able to control the biodistribution of small molecules, which is something we couldn't do before."**

**ANDREW HIRSCH** / Bind Therapeutics

## Nanotechnology & Research

For pharmaceuticals, research over the last few years has shown that it is possible to deliver toxic chemotherapeutics to tumors effectively and reduce the toxicity and side effects, Dr. Grodzinski says.

"This is important because patients may give up on treatments simply because of the side effects," he says.

Recent advances have seen a number of nanomedicines move from the lab to the clinic, and Dr. Grodzinski says the next step in nanomedicine will be to look at difficult-to-treat cancers as well as the drugs that are so toxic they cannot currently be given to patients.

"Possibly by packaging these medicines within nanoparticles, we can open the therapeutic window and deliver effective treatments more safely," he says. "Maybe some drugs that were too toxic can be rescued by a nanotechnology-based formulation. We are in the process of demonstrating that hard to treat tumors, such as brain or pancreatic cancers, can benefit from nanoparticle-based delivery simply because of increased accumulation of the drug delivered at the tumor site."

Dr. Grodzinski says one such indication that nanomedicines can be used for difficult cancers is the September 2013 U.S. FDA approval of combination therapy involving Celgene's Abraxane as a first-line treatment of patients with metastatic pancreatic cancer, and gemcitabine.

Abraxane is paclitaxel formulated as albumin-bound nanoparticles, and it is the first of the newer nanotechnology-based drugs to treat cancer. Patients treated with Abraxane plus gemcitabine lived, on average, 1.8 months longer than those treated with gemcitabine alone. Abraxane is also approved to treat breast cancer (in 2005) and non-small cell lung cancer (in 2012).

There is a lot of exciting work being done in the nanomedicine space, spanning the spectrum from technologies that are targeted to specific cells and proteins from the systemic circulation to those that incorporate multiple drugs and diagnostic agents all the way to developing novel formulations that are capable of delivering a diverse set of agents orally.

"Being able to deliver nontraditional molecules, whether they are insoluble small molecules, biologics, or middle-sized molecules, such as peptides, will allow us to continue to address difficult-to-treat cancers," Dr. Morgen says.

Jeff Hrkach Ph.D., chief technology officer at Bind Therapeutics, says research of many target drugs require modifications to the molecules, but that this may not be enough to get the therapeutic to the right cell.

### The FDA's Guidances

The Food and Drug Administration regulates nanotechnology products under its existing regulations, and according to FDA officials, the agency doesn't make a judgment about whether nanotechnology is safe. Agency officials will take into consideration the specific characteristics and the effects of nanomaterials in the particular biological context of each product and its intended use.

In June, the FDA issued three final guidances, including one that provides greater regulatory clarity for industry on the use of nanotechnology in FDA-regulated products. This guidance addresses the agency's overall approach for all products that it regulates, while the two additional final guidances and the new draft guidance provide specific guidance for the areas of foods, cosmetics and food for animals, respectively.

Of the three guidances issued, the first one has applicability for the pharma industry. The guidance outlines overarching considerations for all FDA-regulated products, identifying points to consider when determining whether a product involves the use of nanotechnology. It is intended to help industry and others identify when they should consider potential implications for regulatory status, safety, effectiveness, or public health impact that may arise with the application of nanotechnology in FDA-regulated products.

Source: Food and Drug Administration
For more information, visit http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm

> **"Being able to deliver nontraditional molecules, whether they are insoluble small molecules or biologics, will continue to allow us to make progress toward new treatments."**
>
> **DR. MIKE MORGEN** / Capsugel

"Researchers are still realizing that there are severe limitations in getting the appropriate amounts of the therapeutic payload to the tumor to enable it to be as effective as possible," he says. "Pharma and biotech companies are looking for alternatives and improvements. There is a greater recognition of the need for nanomedicines."

Bind has a proprietary technology called Accurins, which are nanoparticles that incorporate a therapeutic payload and are designed to have prolonged circulation within the bloodstream. The Accurins include targeting ligands on the surface, which enables targeting of the diseased tissue or cells. Targeting ligands may include small molecules, peptides, antibodies and antibody fragments.

"We physically entrap or encapsulate the drug molecules, or what we call the therapeutic payload, within biodegradable polymer nanoparticles," Dr. Hrkach says. "Bind has developed strong science and engineering around entrapping a therapeutic within a nanoparticle and the rate at which the therapeutic payload gets released from the particle."

The company's Accurins bind specifically to cell surface receptors that are expressed on the surface of diseased cells. The company's lead candidate is BIND-014, which is in Phase II trials for the treatment of non-small cell lung cancer and metastatic prostate cancer. The company is initiating two additional Phase II trials of BIND-014: one in a subset of non-small cell lung cancers that have a certain genetic mutation in the KRAS gene, and another trial in bladder cancer, cervical cancer, and neuroendocrine cancer. The therapeutic payload is docetaxel, the active ingredient in Taxotere and is widely used for the treatment of breast cancer, non-small cell lung cancer, head and neck cancer, and gastric cancer.

Dr. Hrkach says Bind's technology is able to achieve better targeting because of the physical size, shape, and surface properties of the nanoparticles when they are injected intravenously.

"They are able to circulate through the healthy blood vessels while the parent or naked drug will often quickly distribute throughout the body, escaping the blood vessels, leading to side effects," he says. "But by virtue of the nanoparticle's size, shape, and surface properties, they will circulate in the blood and then when they get to a tumor, the targeting ligands can bind the Accurins to the diseased cells. They can then release the therapeutic payload in a greater amount and with a longer duration to get a much higher concentration at the site of disease."

Dr. Hrkach says Bind has partnerships with Pfizer, AstraZeneca, and Roche to evaluate therapeutic payloads that are still undergoing clinical development but not yet approved.

"These pharma partners came to us to see if we can better target their clinical candidates to enable them to become drugs," he says. "In their parent form, the belief is that there is a low likelihood of being able to get approval on their own."

Bind's most recent partnership with Roche, which was announced in June, involves working together to discover novel nanomedicines using Accurins for the treatment of diseases in therapeutic areas outside of oncology.

"We are taking the platform outside of oncology and this is a different type of collaboration than we've done before," Mr. Hirsch says. "Roche has a library of targeting ligands that are applicable to therapeutic areas outside of oncology and they wanted to apply those ligands to our technology."

Another company developing nanomedicines is Cerulean Pharma. Cerulean has developed a nanoparticle-drug conjugate, or NDC, platform that has roots in both the Massachusetts Institute of Technology and the California Institute of Technology. The company's NDCs target tumors by entering through the abnormally large pores associated with tumor blood vessels and gradually releasing their payload inside the tumor over time.

"Our Dynamic Tumor Targeting platform aims to create a portfolio of products designed to do three things: selectively attack tumor cells; reduce toxicity by sparing the body's normal cells from the effects of the cytotoxic payload; and enable therapeutic combinations so that we can overcome some of the challenges that limit the effectiveness of current cancer treatments," Mr. Guiffre says. "We also believe that, someday, the platform can be applied to additional products beyond cancer."

The company's lead candidate, CRLX101, appears to have overcome the liabilities of its payload, camptothecin, a toxic anti-cancer agent that was discovered in the 1960s, but could not be developed past Phase I clinical trials because of severe toxicities.

Two less potent derivatives of camptothecin — irinotecan and topotecan — were developed, approved, and commercialized. But the original, most-potent member of the class remained undeveloped until it was incorporated into Cerulean's drug candidate. It is in Phase II trials for relapsed renal cell carcinoma and relapsed ovarian cancer and is in a Phase Ib trial for neoadjuvant rectal cancer.

Mr. Guiffre says the product works in a unique way. In vitro experiments of the lead product show that cancer cells view the NDC as food and "eat" it.

"Once the NDCs are in the tumor tissue, they are attractive to the tumor cells and the tumor cells essentially eat them; then, they slowly release the payload from within the tumor cells, which is something liposomes can't do," he says.

Cerulean's NDCs chemically conjugate the anti-cancer drug into the nanoparticle, which allows for a controlled release of the payload over time, Mr. Guiffre says.

Solubility is especially important because anywhere from 40% to 70% of new chemical entities have solubility challenges.

Jim Coward, global head of market development with Capsugel Dosage Form Solutions, says there has been a rise in 505(b)(2) applications, which can be attributed in part to new nanotech formulations. Since some of the information required for approval comes from studies not conducted by the sponsor, the 505(b)(2) pathway provides a relatively fast-track approval process, especially for those that represent a limited change from an existing drug, for example, changes in dosage from, strength, formulation, dosage regimen or route of administration.

"This trend is being driven by sponsors aiming to improve the therapeutic benefit of existing products and expand into new indications, oftentimes through the applications of modified release and/or bioavailability enhancement technologies," he says. PV