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The first step

USPTO issues new cross-reference digest for nanotechnology

By Marie Powers

The U.S. Patent and Trade Office (USPTO) has established a new cross-reference digest for nanotechnology designated Class 977/Digest 1. The new digest -- the first step toward establishing a formal nanotechnology classification project -- is designed to facilitate the ability to search and examine nanotechnology-related patents, according to Bruce M. Kisliuk, a director in the agency's biotechnology group who is spearheading the classification effort.

Earlier this year, the USPTO began reviewing existing and proposed technologies as part of the nanotechnology classification project. (See *NanoBiotech News*, May 26, 2004, p. 1.) The agency has been grappling with key definitions of characteristics that distinguish nanotechnology, including size, inherency, and enablement.

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IBN's nano-engineered contact lenses used as drug delivery vehicles

By Steve Lewis

Edwin Chow, PhD, and Yi-Yan Yang, PhD, researchers at the Singapore-based Institute of Bioengineering and Nanotechnology (IBN), have invented a method of making polymeric contact lens materials that can be loaded with eye medication for ophthalmic drug delivery applications, offering the hope of more effective treatment for conditions such as glaucoma.

Their novel one-step process incorporates drugs within a bicontinuous nanostructured polymer matrix via an in situ microemulsion polymerization process. Through this method, transparent and mechanically strong lens materials with a nanostructured polymer network can be easily and cost-effectively fabricated in the form of rods, sheets or ophthalmic molds.

"The real success of forming transparent, solid polymers possessing various nanostructures arises from the polymerization of bicontinuous microemulsions containing a polymerizable surfactant with

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Nanopharma looks to move polymer-based cancer therapeutics to clinic

By Marie Powers

Privately held Nanopharma Corporation, a Boston, MA-based research company that is commercializing technologies developed at Massachusetts General Hospital (MGH), is preparing to file its first investigational new drug (IND) application next year on a cancer compound based on its Fleximer polymer technology.

Nanopharma was launched early in 2002 by PureTech Ventures, a Boston-based life science venture creation company. Its $1.1 million in seed financing was led by a $700,000 stake from New York-based Harris & Harris Group, Inc. (NAS-

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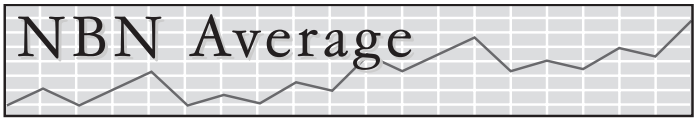

Company	Symbol	Close 10/26	Close 11/02	% Change
Acacia Research Corporation	ACTG	$ 4.34	$ 4.55	4.84%
Accelr8 Technology	AXK	$ 2.08	$ 2.13	2.40%
Aclara Biosciences	ACLA	$ 4.00	$ 3.97	-0.75%
Advanced Magnetics	AVM	$ 13.95	$ 13.55	-2.87%
Advectus Life Sciences	AVXSF.PK	$ 0.03	$ 0.03	0.00%
Affymetrix	AFFX	$ 30.18	$ 29.97	-0.70%
Agilent Technologies	A	$ 24.33	$ 24.92	2.42%
Altair Nanotechnologies	ALTI	$ 2.14	$ 2.04	-4.72%
American Pharmaceutical Partners	APPX	$ 25.94	$ 27.08	4.39%
Biophan Technologies	BIPH.OB	$ 1.12	$ 1.12	0.00%
Biosante Pharmaceuticals	BPA	$ 9.75	$ 8.72	-10.56%
Caliper Life Sciences	CALP	$ 7.03	$ 6.54	-6.97%
Cepheid	CPHD	$ 8.85	$ 8.98	1.47%
Ciphergen Biosystems	CIPH	$ 3.67	$ 3.46	-5.72%
CombiMatrix	CBMX	$ 2.86	$ 2.81	-1.75%
Flamel Technologies	FLML	$ 14.94	$ 16.41	9.84%
Nanobac Pharmaceuticals	NNBP.PK	$ 0.21	$ 0.20	-7.14%
Nanogen	NGEN	$ 3.97	$ 4.00	0.76%
Novavax	NVAX	$ 3.58	$ 3.85	7.54%
SkyePharma	SKYE	$ 9.80	$ 9.79	-0.13%
TOTAL		172.77	174.11	▲ 0.78%

Integrating genes into nanofactories

Ohio researchers developing polymer-based technologies for diagnostics, therapeutics

By Steve Sternberg

For more than a decade, pioneering gene therapists have been trying to tame viruses, one of nature's least compliant life forms.

The logic is irrefutable. Viruses are terrifyingly efficient at injecting their genes into healthy cells, turning them into virus factories. Researchers developing gene therapies had hoped to exploit this capability, using viruses as tiny cellular delivery vehicles that can repair unhealthy cells with a simple genetic injection.

The trouble is viruses can't be tamed, a fact that has derailed clinical gene therapy research, says Ly James Lee, of Ohio State's Center for Affordable Nanoengineering of Polymer Medical Devices.

"We don't know how to control viruses; quite often a mutation will occur after you inject the virus into the body. Gene therapy has been banned in the United States and Europe, because the technology isn't mature," Lee says.

He offers what he regards as a far better solution. "Why not integrate genes into a nanofactory? Design and manufacture a virus?"

The National Science Foundation has gambled $13 million over the next five years under its 2004 Nanoscale Science and Engineering Center Awards program.

Altogether the NSF has announced $69 million in five-year awards to six centers with innovated nanoscale research proposals. The awards are the latest in a series of grants totaling $250 million for nanoscale research in multiple disciplines this year.

Mihail Roco, head of the NSF initiative, notes that vehicles for the delivery of genes into cells are just one task Ohio State scientists and their colleagues from six partner universities have taken on.

The Ohio State-based center, Roco, says "can make a major contribution to the development of polymer-based technologies that will produce new devices that can be used for medical diagnosis and therapeutics."

The electronics industry has pioneered the development of techniques for manufacturing miniature devices in silicon and glass. But these devices break easily, they're not biocompatible, making them poor choices for biomedical use.

Polymers, chains of natural or synthetic molecules, are tougher and can readily be recycled. Some are extremely biocompatible, biodegradable and multipurpose, capable of carrying out different tasks. "The molecules that make up the human body are essentially polymers," Lee says.

The first step: Nanofluidic circuits

Initially, the researchers hope to design and construct polymer-based, 3D nanofluidic circuits for manipulating the shape, orientation and transport behavior individual biomolecules in flow fields of 5 to 100 nm.

The circuits will serve as the basis for medical tests built on enzyme reactions and for moving single molecules to develop therapeutics -- perhaps by wrapping therapeutic DNA in a polymer like polyethylene glycol, rather than a virus, for delivery into cells. Scientists have succeeded in doing something similar with lipids, creating liposomes. But current liposome technology is inefficient.

"Using nanotechnology to manipulate individual molecules would produce much better nanoparticles," Lee says.

The center's long term goal is to perfect nanofactories based on the integration of nanofluidic circuits, synthetic circuits and biological complexes.

It won't be easy, Lee says. To tackle the problem, he has assembled a research team involving 40 faculty members from several different disciplines from seven partner universities, including Ohio State, The University of Akron, Boston University, University of California at Berkeley, Johns Hopkins University, Florida A&M/Florida State University and Purdue University.

Other collaborators include the Battelle Corp., the Cleveland Clinic Foundation, the National Cancer Institute, Oak Ridge National Laboratory and Wright Patterson Air Force Labs. Among other things, the researchers are skilled in gene therapy, polymer fabrication, nanofiber centers, modeling nanofluidics.

The program has an educational component as well. The Ohio State team plans to take the lat-

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est research development and incorporate them into a "practical" student curriculum that imparts multidisciplinary skills to graduate and undergraduate students. Courses will focus on nanoengineering of biomedical devices and other related topics, Lee says, noting that the material used in these courses will also form the basis of web-based science modules for students from kindergarten through 12th grade.

A documentary film crew will track the research for a documentary that can be offered for broadcast on public television nationwide.

Lee says the effort isn't simply designed to advance the science -- researchers have a far more practical goal in mind. "We will, in three to five years, produce a prototype device," he says.

Editor's Note: Contact Ly James Lee at (614) 292-2408. ⊙

Nanogen, Epoch set date for stockholder vote on merger

By Steve Lewis

Nanogen, Inc. (NASDAQ:NGEN), a San Diego, CA-based developer of in vitro diagnostic products, and Epoch Biosciences, Inc. (NASDAQ:EBIO), a Bothell, WA-based provider of products that accelerate genomic analysis, will each hold a special meeting of stockholders on Dec. 8, 2004, to consider and vote on the proposed merger of the two companies.

The two firms had previously announced the signing of a definitive agreement to merge. (See *NanoBiotech News*, Sept. 15, 2004, p. 1.)

The fact that the two firms were able to announce a record date (for the determination of stockholders entitled to notice of the proposed merger) and a special meeting date for the votes "Means the merger has gone through SEC review," explains Robert Saltmarsh, vice president, corporate development, for Nanogen. "If [the SEC] thinks there may be something anti-competitive about the proposed merger, or if they do not like the way we have done the financials, they have the right to come back and review it."

The fact that the SEC has not requested any further review means "We have crossed a fairly significant hurdle, so we are now able to set a date," Saltmarsh continues.

Nanogen and Epoch are each sending a definitive joint proxy statement/prospectus to stockholders of record of both companies. The proxy statement/prospectus will contain important information about the proposed merger, and will urge stockholders to read the statement/prospectus, which will also include the times and locations of the special meetings.

Saltmarsh is confident the merger will be approved by the stockholders. "We've obviously talked to an awful lot of shareholders, and at this point we anticipate the merger will occur," he says. "Obviously, however, the shareholders have the right to vote as they wish, and we won't know for sure until the last minute."

Saltmarsh says the merger makes good business sense for both companies. "Our product lines and customers are very similar," he asserts. "Their product line folds into our customer base and sales force very nicely."

At the time the two companies began discussions, he explains, Epoch had gotten to the point in its corporate development that it was considering the development of a larger sales and marketing force. "That's a pretty expensive thing to do," Saltmarsh notes. "We came along, with 30 people in our sales and marketing forces combined, and seeing that the products were similar, this gave Epoch an instant sales force."

Economics of scale

By the same token, he adds, the merger gives Nanogen's sales force more products to sell. It also offers economies of scale. "We don't need two presidents, two CEO's, two accounting staffs, and so on."

The focal point of Nanogen's technology is the Nano Chip Electronic Microarray, a tiny silicon chip capable of rapid identification and precise analysis of biological molecules. In a lab setting, the company's NanoChip Molecular Biology Workstation allows researchers to load sample DNA onto the chip, then run a protocol which effectively takes and binds the DNA to specific sites on the chip by electrical/chemical combination.

For the lab market, Epoch's core technology is its probe technology. In July 2004, Epoch launched 21 MGB Eclipse Detection Reagents, real-time Analyte Specific Reagents for the molecular diagnosis of infectious and genetic diseases and cancer. It allows researchers to add reagents to the Nanogen chip, which then informs them whether or not there is a match.

Nanogen's stock closed at $4 per share on Nov. 2, 2004; it had been trading at more than $14 per share in February. Epoch's stock closed at $1.98 per share on Nov. 2; its 52-week high was $3.45 per share.

Editor's Note: Contact Robert Saltmarsh at (858) 410-4600. ⊙

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In the meantime, the USPTO decided to begin placing accumulated nanotech patents in a single area to facilitate the searching of prior art related to nanotechnology, Kisliuk explains. The digest will function as a collection of issued U.S. patents and published pre-grant patent applications relating to nanotechnology across the technology centers and assist in the development of an expanded, more comprehensive, nanotechnology cross-reference art collection classification schedule.

"Establishing this nanotechnology cross-reference digest is just the first step in a multi-phase nanotechnology classification project," Kisliuk tells *NanoBiotech News*.

The agency continues to identify and add relevant documents to the new digest, he adds. Eventually, the USPTO plans to replace the digest with a comprehensive nanotechnology cross-reference art collection (Class 977, Nanotechnology) classification schedule, which will include definitions, subclasses, and search notes related to classifications in other U.S. classes.

"Ultimately, we expect to have the nanotechnology class and breakdowns into a variety of subclasses, such as biologics and semiconductors," Kisliuk says. "We're just at the beginning of this process."

In fact, the new nanotechnology digest is not designed to serve as an exhaustive collection of all patent documents pertaining to nanotechnology, Kisliuk cautions, noting that the USPTO has not even finished reviewing all of the documents identified during its search of existing patents in which nanotechnology is defined as part of the claims.

By using a list of 185 relevant terms suggested by patent examiners and industry experts and defining certain exclusions as part of its text search, the agency identified some 6,000 patents related to nanotechnology. Examiners are individually reviewing each patent identified by the text search. To date, 1,000 have been reviewed and 400 have been placed into the new nanotechnology cross-reference digest. Ultimately, Kisliuk expects slightly more than half of all of the patents identified in the search to be placed into the new digest.

Number of patents 'a moving target'

But because new applications continue to stream in to the USPTO and examiners continue to evaluate them, the number of U.S. patents related to nanotechnology is a moving target. "We wanted to get started in this process," Kisliuk says.

Consistent with definitions used by the National Nanotechnology Initiative (NNI) at the National Nanotechnology Coordination Office (NNCO) in Arlington, VA, the USPTO has established several initial definitions for disclosures related to Class 977. A discovery or invention will be considered nanotechnology if it meets both of the following criteria:

- research and technology development at the atomic, molecular, or macromolecular levels in a length scale of approximately 1 nm to 100 nm in at least one dimension; and
- research and technology development that provides a fundamental understanding of phenomena and materials at the nanoscale and creates and uses structures, devices, and systems that have novel properties and functions because of their small and/or intermediate size.

The definitions are designed to be flexible, Kisliuk insists, noting that the size scale "could be a little larger" and that the relevant materials could include technologies such as AFM probes that are not nano-sized but designed to measure nanoscale activity. The key, he says, is to exclude intellectual property (IP) protection simply for reducing something in size without producing a novel outcome or manipulating material such as DNA or proteins that always exist at the nanoscale.

That explanation would allay concerns expressed by some nanotech observers, says Bryan W. Bockhop, a partner in the Atlanta law firm Arnall Golden Gregory LLP, and co-chair of the American Intellectual Property Law Association's nanotechnology subcommittee.

An important distinction

"The USPTO definition of nanotechnology appears arbitrary, because theoretically it would exclude discoveries that might be up to 150 nanometers or technologies such as cantilevers that are important for nanotech discoveries but not, themselves, at the nanoscale," Bockhop says.

The distinction is important, he adds, because many nanotech inventions have one or more elements that might not operate at the nanoscale. Examiners who rely on strict disclosure criteria rather than using them as guidelines may fail to identify valid nanotech discoveries, Bockhop says.

"The establishment of a general class helps to identify nanotech patents but it doesn't involve subclasses, such as silicon nanocrystals, which could help to direct new filings to a particular examiner," agrees Stephen B. Maebius, an IP partner in the Washington, DC, office of Foley & Lardner LLP. "This is a step in the right direction, but it's really just a baby step."

While the USPTO has a fairly well developed system for addressing discoveries in pharmaceuticals, nanomedicine involves technologies that

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"blur the line" between nanotechnology and biotechnology, Maebius adds. Nanobiotech discoveries could be lost in the crossfire between nanotechnology and materials science.

"Nanotechnology crosses all boundaries," he says. "We need examiners who are familiar with all of them."

In fact, the new digest will not even expedite patent searches until and unless the USPTO mandates a non-patent literature search on nanotech discoveries, Maebius adds.

"[The USPTO] couldn't do that up to this point, but now that they have created a class I would like to see them require non-patent literature searches for nanotechnology," he says. "The PTO has access to various commercial databases, and a lot of these findings are reported in journals before patent applications are filed."

One-two years until subclasses announced

Implementing the new classification schedule in a timely matter is another enormous challenge, sources say. Congress is diverting more and more funding from the USPTO, forcing the agency to manage a growing number of filings with limited resources, according to Maebius. At the same time, rapidly evolving technologies such as stem cells require greater amounts of attention from examiners.

Still, "I would hope that in a year or two we will see the first nanotechnology subclasses announced," Maebius says. "There's no reason to take longer than that. The PTO just needs to make this a priority."

Kisliuk is reluctant to predict a timetable for classifying all existing nanotech patents and applications and moving on to the development of the nanotechnology cross-reference art collection. As documents are placed into the digest, the USPTO will begin to consider logical subclasses that could be used in the final classification schedule, he says. The goal is to seek a relatively even distribution across the nanotechnology classification to facilitate searches both for examiners and the public.

In the meantime, the USPTO continues to cross-train examiners, Kisliuk adds. In a process that began this time last year and is likely to continue for another year, the agency is sending 50 examiners per month for outside training and inviting scientists in the field to visit the agency and lecture about specific platforms, such as nanotubes and nanowires. The initiative is directed toward examiners in materials, biotechnology, and semiconductors/electrical components -- where the bulk of nanotechnology discoveries have occurred -- but training is available across all technologies, Kisliuk says.

The cross-training effort is a direct result of customer partnership meetings that USPTO held in September 2003 and April 2004 with IP attorneys, nanoscience researchers, and industry executives. The agency intends to schedule another meeting next year once some of the classification issues have been identified, Kisliuk says.

The USPTO has shown interest in working with inventors and researchers, sources agree, pointing to the customer partnership meetings as evidence of the agency's sincerity. Still, with many inventors now waiting more than two years before they see the first office action on a filing, industry experts worry that a lack of "interference searching" in nanotechnology will lead to overlapping patents and inevitable claims disputes.

"Just because the PTO created a new class, there still are applications going to completely different parts of the office," Maebius says. "This could lead to the unfortunate situation where an inventor creates and files an invention first but an examiner in another area picks up and acts on a later filing. Until the PTO implements interference searching in the nanotechnology area, you can't effectively troubleshoot these problems."

How to avoid claims disputes

Until the details of Class 977 are sorted out, Bockhop advises inventors and researchers to use explicit terms in describing a discovery.

"These inventions cross the boundaries of many technologies," he points out. "If an invention has a mechanical component and a chemical component, my concern is that it may go to a chemical examiner who doesn't understand the mechanical aspects or a mechanical examiner who doesn't understand the chemical aspects.

"There are so many permutations of nanotechnology that an examiner might not even recognize the overlap," Bockhop adds. "Having a few early statements might alert an examiner that he or she will need to do more than simply look at a chemical formula."

Editor's Note: Contact Bruce Kisliuk at (571) 272-0700, Bryan Bockhop at (404) 873-8696, and Stephen Maebius at (202) 672-5569. ⊙

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other monomers," explains Chow. "The evolving polymerizable microemulsion assembly serves a structure-directing role to nanomaterials synthesis."

Microemulsion systems with both hydrophobic- and hydrophilic-structured domains create an opportunity for IBN to use these systems as media for the synthesis of materials with unique properties.

Chow says, "The main theme of this invention is to use bicontinuous microemulsion as a medium to prepare drug-loaded contact lenses material. The choice of monomers/water/surfactants was guided by the need to obtain optically clear materials, whereby the polymerized material possesses a bicontinuous nanostructured network. This means that the material possesses both nanophases of polymer and water domain, and these domains can provide an ideal environment for entrapping the hydrophobic/hydrophilic drug medication."

Depending on the drug nature, notes Chow, the drug can either be located in the nanophase polymer matrix or aqueous domains.

Controlling drug delivery rate

"The size of these aqueous domains (~30 to 100 nm) could further be varied by changing the aqueous content, thereby controlling the drug delivery rate," he says. "A faster release rate is observed for systems with higher aqueous content attributing to the increasing pore sizes.

"We could further prolong the drug delivery by first encapsulating the drugs within the polymeric nanoparticles (diameter: ~10 to 30 nm) before loading them into the bicontinuous microemulsion lens mix to form the lens," Chow continues. "By having this polymeric shield, the drugs must first diffuse out from the polymeric nanoparticle core to the bicontinuous polymer matrix and then out into the post-tear fluid of the eye through the aqueous channels. By controlling the size of these polymeric nanoparticles and the concentration of drugs within these nanoparticles, the drug delivery rate could be further controlled."

Chow and his colleagues have tested the feasibility of loading water-soluble drugs or less water-soluble antibiotic drugs into the system to obtain transparent lens materials. "We could control the release of these drugs for hours or days," he says, adding that the process has been filed for Patent Cooperation Treaty (PCT) application, and that papers pertaining to the research will be submitted soon. The PCT is an international agreement that enables an inventor to file a single international patent application in one language with one patent office in order to simultaneously seek protection for an invention in up to 117 countries

A new twist in microemulsion

The use of microemulsion technology to fabricate nanomaterials is not new, says Chow, "But using bicontinuous microemulsion polymerization to develop new contact lenses materials loaded with drugs for safe, painless, sustained ophthalmic delivery is novel."

The biocompatibility of the lens material has been assessed using human dermal fibroblast cells or human corneal epithelium cells, and the lens' protein adsorption capacity is found to be lower in comparison to some commercial lenses, says Chow. "The mechanical property of the lens materials has also been tested and found to be within the range for most contact lenses to maintain their shape, providing both comfort and visual performance during application."

When a person suffers from eye ailments (e.g. glaucoma) today, nine times out of 10 he will be prescribed eye drops to treat his illness or relieve his discomfort, says Chow. "However, the use of eye drops is less patient-compliant and dosage through eye drops is inconsistent and difficult to regulate, as most of the drugs are released in an initial burst of concentration."

This new approach, he says, could be adapted to deliver glaucoma medication, as it allows safe, painless, sustained release of the drug. "Glaucoma is particularly hard to treat, and existing medications have numerous side effects," says Chow. Glaucoma accounts for 20% of blindness in Singapore, and is rapidly becoming the second major cause of blindness in Asia after cataracts, according to IBN.

Other applications

"Contact lens wearers with dry eyes may also benefit from this invention, as the material can be modified to produce self-lubricating contact lenses," says Chow. "Other examples of novel ophthalmic applications include contact lenses for vision correction, eye color modification, diabetes monitoring, artificial corneas as well as those involved in ophthalmic wound healing applications."

The IBN research team is now looking into in vivo animal studies "To understand the detailed pharmacokinetic release of the drugs in rabbit eyes; this will have important clinical implications," says Chow.

IBN's technology has been identified for Commercialization of Technology funding by A*STAR's Exploit Technologies (IBN is a member of A*STAR's Biomedical Sciences Institutes), and IBN is looking for partners to help with its commercialization.

Editor's Note: Contact Edwin Chow at 65 6824 7135. ⊙

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DAQ:TINY), which continues to hold the company in its nanobiotech portfolio.

Nanopharma's Fleximer polymers, based on glycomimetic technologies, preserve selected characteristics of natural carbohydrates and minimize or eliminate the undesirable biologic effects associated with the use of natural sugars, explains Peter B. Leone, the company's CEO. The platform is designed to improve solubility, targeting, and distribution of prospective drug candidates -- initially for cancer therapies but also in areas such as large molecule and specialty therapeutics.

Nanopharma's technology relies on biodegradable polyacetals developed and patented by Mikhail I. Papisov, MD, PhD, the company's chief scientific officer, who also serves as assistant radiologist in the Department of Nuclear Medicine at MGH and instructor in radiology at Harvard Medical School. The proprietary Fleximer technology is engineered to mimic the activity of sugar molecules found throughout the body, Leone explains.

Fleximer "disguises" proteins and small molecules from the immune system or other biological receptor sites to reduce side effects or toxicity. For small molecule drugs, Fleximer increases the solubility of potent compounds and concentrates therapy in tumors instead of healthy tissue, enabling less frequent administration of injectable drugs such as protein therapeutics.

"Many cancer drug compounds are effective in the lab but fail in the clinic due to toxicity issues or side effects," Leone points out. "Our strategy is to modify these cancer drugs by improving solubility, targeting, and distribution in the body."

Improving drug efficacy

Nanopharma already has demonstrated the ability of its Fleximer polymers to improve drug efficacy in several proof of concept studies. In a paper published earlier this fall in *Molecular Pharmaceutics*, Papisov and colleagues reported that a water soluble macromolecular conjugate of the cancer drug camptothecin (CPT) demonstrated greater effectiveness than unmodified CPT, with lower toxicity.[1]

The researchers assembled a hydrophilic conjugate that releases a lipophilic stabilized CPT prodrug, which, in turn, releases the active drug substance locally (intra- and extracellularly). Results showed that the dual phase drug release system contained a therapeutic level of CPT, was soluble in aqueous media, and showed drug concentration in tumor tissue 50- to 70-fold higher than for unmodified CPT.

"The character of CPT microdistribution in the tumor tissue suggests that, by 24 hours post administration, all tumor-localized drug is distributed relatively homogeneously," the scientists write. "This can be explained by the lipophilic nature of the prodrug, which, being fully released from the carrier, is free to redistribute along cell membranes within the tumor via diffusion."

Nanopharma's dual phase drug release mechanism "can be used to simultaneously improve drug biokinetics and (for unstable substances such as CPT) drug stability in vivo," the researchers add.

Each Fleximer polymer particle measures less than 10 nm, but the tiny technology could reap big benefits. The company's internal pipeline is targeting the current chemotherapy market, with $7 billion in annual revenues and forecast growth of 20% per year, Leone says. In addition to cancer therapeutics, the company is eyeing other injectable platforms, including pain medications and anti-infectives.

The company boasts an impressive intellectual property portfolio. Nanopharma holds an exclusive license from the MGH for the core patents[2] and for a complementary technology that links Fleximer to therapeutics.[3] The company has applied for associated foreign applications and has four additional patent families pending worldwide.

Moving beyond proof of concept

During its seed-funded period, Nanopharma has focused primarily on demonstrating proof of concept for the Fleximer polymers in cancer applications, expanding into protein studies, and arranging deals with corporate partners to validate its commercial prospects, Leone says. With proof of principle data in hand and the creation of four corporate partnerships with major biopharmaceutical companies earlier this year, both of these goals have been achieved, he points out.

The company's next step is to identify pipeline compounds with novel mechanisms and preliminary human data that can be advanced to the clinic only with Fleximer approaches -- an accomplishment Nanopharma expects to complete next year by applying for its first IND. The company expects to take its first Fleximer compound to the clinic in 2006, followed by at least two others the following year.

To that end, Leone is putting together a second financing round to augment the grants the company has received from the National Institutes of Health (NIH). Earlier this year, Nanopharma also formed a collaborative relationship with the

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National Cancer Institute that will provide several million dollars of preclinical development of up to five compounds in the company's pipeline, with a possibility to extend the collaboration through phase II clinical trials.

Editor's Note: Contact Peter Leone at (617) 482-2333.

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Nanobullet may improve non-invasive tumor destruction

By Russell A. Jackson

Virginia Commonwealth University researchers have shown that nano-sized gold-coated silica shells may be used to destroy tumor cells. Once commercialized, the nanobullets could be used to treat cancers earlier than today's larger gold-and-sand clusters are able to -- and in many more parts of the body.

Puru Jena, PhD, lead researchers on the Richmond-based project, says, "Gold-coated silica nanoshells on the order of 100 nm in size have been synthesized experimentally and tests show that they are effective in the treatment of tumors. Our work shows that the same effect can be seen in nanoclusters of 2 to 3 nm in size. The physics involved in the two cases, however, are different."

The application is very similar, though. "The ultimate real-world application is expected to be in the non-invasive treatment of tumor cells," Jena reports. "The ability to tune the optical gap by coating it with gold may also find applications in optical displays and electronics."

Jena and his team examined the electronic structure and bonding properties of gold and silica -- one of the most precious materials on the planet and one of the most common. They observed a "dramatic" change in the physical properties of both elements when their sizes were reduced to 2 or 3 nm. Specifically, a statement from VCU explains, "the scientists identified several defects and dangling bonds on the silicon atoms, which provide potential absorption sites for the gold atoms. The gold atoms readily accept electrons, and the new gold coating on the silicon atoms completely changes the charge distribution and electronic structure of the silica cluster."

Heating up to destroy tumors

That results in "a significant change in the optical gap," the statement adds, "which is a critical factor in determining how light is absorbed." Says Jena: "We have shown that a cluster of only three silicon atoms and six oxygen atoms can bind at least three gold atoms. As a result, the optical gap of the cluster becomes greatly reduced to the point that it can absorb infrared radiation. Therefore, the cluster becomes hot, which in turn can destroy tumor cells."

Previous studies have tested 100- to 200-nm gold-coated silica shells. "The advantage of using smaller particles is they can be inserted into any part of the human body and treat cancer cells in their infancy," Jena points out. "Historically, both gold and silica have been used in biomaterials. The biocompatibility of those materials at the nanoscale will be investigated."

The next step in the research is to synthesize the tiny gold-coated silica clusters and measure their energy gap. That will verify the accuracy of the theoretical prediction and confirm the view that the clusters can absorb infrared radiation. "We still have a lot of research to do," Jena tells *NanoBiotech News*. "First, we have to study how sensitive the optical gap is to the size of the silica nanocluster and the size of the gold island. Second, experiments need to be performed to verify the predicted optical gap. And third and most important, efficient synthesis methods have to be developed for mass production of the clusters before commercialization is possible."

That process has not yet begun. "We have not looked into the commercialization process yet," he says, "as a lot of research work still needs to be done. We will contact the appropriate office in due time," he says. The work was funded by the Department of Energy.

Silica, one of the most abundant elements on Earth, has a wide range of applications in microelectronics, optical communications and thin film technology. Gold, known for its resistance to corrosion, does not oxidize like other metals and it is chemically inert; however, gold particles become very reactive when they are reduced to a very small size.

Jena collaborated with Qiang Sun, PhD, and Qian Wang PhD, both of whom were post-doctoral fellows in VCU's physics department where the research was conducted and both of whom are now research assistant professors.

Editor's Note: Contact Puru Jena at (804) 828-8991.

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Uncovering the biochemical basis for mental illness

Vanderbilt University awarded $1.4M from NIH for nanocrystal studies

By Russell A. Jackson

Researchers at Vanderbilt University, Nashville, TN, are $1.4 million closer to perfecting nanocrystals that track the behavior and movement of proteins -- a chemical process that could dramatically alter the way drugs for a variety of conditions, including depression, are developed and administered.

The National Institutes of Health has just awarded the funds to Sandra Rosenthal PhD, an associate professor of chemistry and of physics at Vanderbilt University (VU) and her team.

The Rosenthal Research Group studies semiconducting nanocrystals. Their optical properties and electronic structure "can be precisely tuned by controlling their size," according to a VU statement.

"We are specifically interested in two applications exploiting the properties of nanocrystals," Rosenthal says, "their use as the light-harvesting element in photovoltaic devices and" -- the project that received the grant -- "the use of fluorescent nanocrystals as biological probes for membrane proteins involved in neuronal signaling."

Mapping proteins related to mental illness

Indeed, she says, "the goals of this proposal are both fundamental and applied. The fundamental real-world application is to dynamically map the distribution of proteins important in regulating neurotransmitters associated with mental illness. That translates to obtaining a better understanding of the biochemical basis for mental illness." Also, she adds, "a specific, ultimate real-world application is the development of fluorescent nanocrystal probes to be used in fluorescence-based assays for drug discovery. Again, those would be drugs to treat mental illness."

The NIH grant is VU's first under the new Nanoscale Science and Nanotechnology in Biology and Medicine program. Rosenthal and her team are in the process of patenting the chemistry of attaching drug molecules to nanocrystals, she notes. For now, she reports, both the NIH and Hayward, CA-based Quantum Dot Corp. have funded the work. "Quantum Dot owns the intellectual property for fluorescent nanocrystals [quantum dots] and would be the commercial outlet," she tells *NanoBiotech News*. "Right now the university owns the research."

Fluorescent nanocrystals have several advantages over organic dye molecules as fluorescent markers in biology. "They are incredibly bright and do not photodegrade," Rosenthal notes. "They have narrow, guaussian emission spectra enabling the co-localization of several proteins simultaneously. Drug-conjugated nanocrystals attach to the protein in an extra-cellular fashion, enabling movies of protein trafficking."

Making quantum dots better

"We have a saying around here: 'We don't make quantum dots, but we help make them better,'" she says. Specifically, "we are synthesizing drug-conjugated nanocrystals that have high affinities and selectivities for serotonin, dopamine and norepinephrine receptor and transporter proteins. They are neurotransmitters that control critical behaviors such as mood, sleep, appetite and aggression. With drug-conjugated nanocrystals, we will be able to map the distribution of those proteins and be able to determine mechanisms that regulate protein expression at the cell surface. The proteins are also drug targets for the serotonin selective re-uptake inhibitors, atypical antipsychotics and drugs of abuse. The drug-conjugated nanocrystals also form the basis of a high-throughput fluorescence assay for drug discovery."

"We still have a long road to go," she says, "We need to develop an assortment of nanoconjugates [a nanocrystal plus its target molecules] that have a high affinity and selectivity for individual proteins. We would ultimately like to be able to light up those proteins with the nanocrystals so we can see what their distribution is in tissue and how that distribution depends on electrical or chemical stimulus and healthy or diseased state. Finally, one of the applied goals is to develop assays for drug discovery."

The NIH grant spans four years. During that time, Rosenthal says, her team should be able to develop a few of the probes and the fluorescence assay for drug discovery. "Consider that the neurotransmitter serotonin has 15 different receptor proteins in the transporter. And if you take into account dopamine and norepinephrine, that's quite a few targets. Developing a probe for every target could take a while. The next step then is we would go for a renewal of the grant."

To market within three years

As the technology gels, she adds, commercialization could occur in the next two or three years. "We could have a probe ready for the market in that time," she says.

Drug maker Eli Lilly and Co., of Indianapolis,

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IN, is reported to be interested in the technology. The newer anti-depressants such as Prozac, Paxil and Zoloft all could use the technology.

Rosenthal's team members include assistant professor of chemistry David W. Wright, professor of pharmacology and psychiatry Elaine Sanders-Bush, Allan D. Bass Professor of Pharmacology Randy Blakely and Stephen Pennycook, a condensed matter sciences division researcher at Oak Ridge National Laboratory. Sanders-Bush and Blakely are also investigators at the Vanderbilt Kennedy Center for Research on Human Development.

Editor's Note" Contact Sandra Rosenthal at (615) 322-2633. ⊙

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