NanoBiotech News

The global nanobiotechnology intelligence source

Volume 1 • Number 17 • November 19, 2003

Nanomedicine funding is undetermined

U.S. Senate passes $3.7B compromise version of nanotechnology bill

By Marie Powers

By unanimous consent, the U.S. Senate last night quietly passed a compromise version of the 21st Century Nanotechnology Research and Development Act (S.189). The House is expected to pass the bill by unanimous consent as early as today and send it to President Bush, who, experts say, will sign it without delay.

The bill is the product of negotiations between the House Science Committee and the Senate Committee on Commerce, Science and Transportation to reconcile differences between H.R.766, as passed by the House on May 7 by a vote of 405-19, and S.189, as reported out of the Senate Committee. (See *NanoBiotech News*, Oct. 8, 2003, p. 1.) The original Senate version was cosponsored by Senators Ron Wyden (D-OR) and George Allen (R-VA). House

continued on page 4

Reversing spinal cord injuries with nanobiotech

Magnetic nanoparticles tug severed nerves back together

By Bruce Goldfarb

A Midwest start-up firm is trying to use nanotechnology to achieve the miraculous -- help the paralyzed regain use of their nervous system. Kalamazoo, MI-based Orthopedic Development, Inc., is using magnetic nanoparticles to coax injured nerves into restoring severed connections.

Worldwide, every year more than 1.7 million people sustain spinal cord injuries for which no effective treatments are available. Traditional medical wisdom has held that a nerve, once disrupted by injury, permanently and irreversibly loses its function.

However, recent discoveries suggest that this is not always the case.

Orthopedic Development's approach is based on principles discovered by researchers at the University of Chicago that nerve fibers will grow when

continued on page 5

Affymetrix technology is at the intersection of genomics, nanobiotechnology

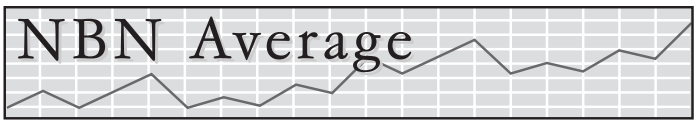
By Marie Powers

The National Human Genome Research Institute (NHGRI) in Bethesda, MD, has awarded the first grants for the next phase of the Human Genome Project. The three-year, $36-million effort known as the ENCODE Project (ENCyclopedia Of DNA Elements) is designed to identify all parts of the human genome crucial to biological function.

Though the sequencing of the human genome was completed in April of this year, the identity of

continued on page 5

Holiday Notice: *NanoBiotech News* will not be published Nov. 26, 2003 in observance of Thanksgiving. We will resume with the Dec. 3, 2003 edition. Happy holidays!



Company	Symbol	Close 11/11	Close 11/18	% Change
Acacia Research Corporation	ACTG	$ 6.10	$ 5.86	-3.93%
Accelr8 Technology	ACLY.OB	$ 2.81	$ 2.80	-0.36%
Aclara Biosciences	ACLA	$ 3.50	$ 3.21	-8.29%
Advanced Magnetics	AVM	$ 12.01	$ 12.05	0.33%
Advectus Life Sciences	AVXSF.PK	$ 0.07	$ 0.07	0.00%
Affymetrix	AFFX	$ 24.58	$ 24.12	-1.87%
Agilent Technologies	A	$ 25.97	$ 27.77	6.93%
Altair Nanotechnologies	ALTI	$ 1.27	$ 1.18	-7.09%
American Pharmaceutical Partners	APPX	$ 26.10	$ 34.85	33.52%
Biophan Technologies	BIPH.OB	$ 0.34	$ 0.35	2.94%
Caliper Technologies	CALP	$ 6.30	$ 6.60	4.76%
Cepheid	CPHD	$ 5.93	$ 6.50	9.61%
Ciphergen Biosystems	CIPH	$ 10.09	$ 10.25	1.59%
CombiMatrix	CBMX	$ 3.82	$ 4.03	5.50%
Emergency Filtration Products	EMFP.OB	$ 0.49	$ 0.51	4.08%
Flamel Technologies	FLML	$ 23.23	$ 24.78	6.67%
i-STAT	STAT	$ 12.86	$ 12.51	-2.72%
Nanobac Pharmaceuticals	NNBP.PK	$ 0.69	$ 0.72	4.73%
Nanogen	NGEN	$ 3.30	$ 3.50	6.06%
Nanophase Technologies	NANX	$ 5.32	$ 5.12	-3.76%
SkyePharma	SKYE	$ 11.90	$ 11.91	0.09%
TOTAL		186.68	198.69	▲ 6.44%

Gene therapy gets boost from nanobiotech

Human trials to gauge effectiveness of nanoparticle spray for asthma

By Marie Powers

A novel nasal spray containing nanoparticles that deliver therapeutic, protein-producing genes effectively reduces allergen-induced airway inflammation and hyper-reactivity in mice, according to a study by University of South Florida (USF) scientists published in the *Journal of Genetics Vaccines and Therapy.*[1] Based on these findings, the National Institutes of Health (NIH) has awarded $1.16 million to the USF researchers to determine if the treatment will be safe and effective for humans with asthma.

"By treating asthmatic mice with this gene therapy, we have allowed their lungs to produce the protein interferon gamma that is needed to reduce asthmatic symptoms," explains Shyam S. Mohapatra, PhD, principal investigator, professor of medicine, and director of basic research for USF's division of allergy and immunology and the Joy McCann Culverhouse Airway Disease Center in Tampa. "Within six hours of intranasal delivery the mice showed reduced airway inflammation" -- a hallmark symptom of asthma.

Asthmatics produce relatively low amounts of interferon gamma, yet efforts to treat asthma directly with the protein have proven unsuccessful because 50% of the protein degrades within one hour of administration, Mohapatra says.

"We want the cells in the lung to make interferon," Mohapatra explains. "This method has the potential to help alter immune response, so that the treatment may only need to be administered once a week rather than several times daily like current asthma treatments.

"Now that scientists and clinicians consider allergy, sinus, and asthma conditions as one disease, this therapy has the potential in the future to modify allergic immunotherapy by reducing injections and increasing effectiveness," he adds.

A new delivery method

Mohapatra and his team selected chitosan nanoparticles as a delivery method for the interferon gamma gene. Previous efforts to deliver the interferon gamma gene to cells in the lungs have used viruses as a vehicle, but eventual immune resistance and side effects of the virus left scientists looking for a new delivery method, according to the USF researchers.

Chitosan, a carbohydrate derived from shellfish, is naturally biodegradable and used in many "fat buster" products. The substance, which is approved by the FDA for treating food allergies, is not a drug but a "glue" that sticks to epithelial cells -- the respiratory system cells that produce mucous -- and delivers the interferon gamma gene precisely where it is needed.

continued on page 3

NanoBiotech 3Q Financial Results

Company	Revenue 3Q 2003	Revenue 3Q 2002	Net earnings/ (loss) 3Q 2003	Net earnings/ (loss) 3Q 2002	R & D expenses	Total operating expenses	Consolidated assets
Acacia Research Corp. (NASDAQ:ACTG)	$367,000	$179,000	($5.8M)	($20.6M)	$1.7M	$6.5M	$94M
Advanced Magnetics, Inc. (AMEX:AVM)	$778,708	$1M	$1.2M	($2.4M)	NA	$1.5M	$29M
Caliper Technologies Corp. (NASDAQ:CALP)	$16.5M	$6.6M	($10.1M)	($9.4M)	$9.1M	$18.8M	$180.9M
Ciphergen Biosystems, Inc. (NASDAQ:CIPH)	$16.1M	$10.2M	($7.9M)	($4.7M)	$6M	$15M	$88M
i-STAT Corp. (NASDAQ:STAT)	$16.1M	$14.8M	($3.7M)	($55.7M)	$1.7M	$6.9M	$72.4M
Nanophase Technologies Corp. (NASDAQ:NANX)	$1.24M	$1.25M	($1.37M)	($1M)	$480,301	$2.6M	$8.2M
Novavax, Inc. (NASDAQ:NVAX)	$4.3M	$2.3M	($3.4M)	($6.8M)	$2.5M	$7.2M	$61.6M

NanoBiotech News™ is published 48 times per year by National Health Information, LLC, 1123 Zonolite Rd., Suite 17, Atlanta, GA 30306-2016.
Telephone: (800) 597-6300 or (404) 607-9500. **E-mail:** info@nanobiotechnews.com **Website:** www.nanobiotechnews.com
POSTMASTER: Send address changes to **NanoBiotech News**, P.O. 15429, Atlanta, GA 30333-0429.
Associate Publisher: **Lynn Yoffee** President: **David Schwartz**
Subscription rates: USA, one year (48 issues): $1295. **Back issues**: $25 each.

Asthma *from Page 2*

"The problem with many drugs, including drugs to treat asthma, is that they accumulate in the body," Mohapatra says. "Chitosan is advantageous as a drug delivery method because it is naturally broken down by the body."

The idea of using chitosan-related nanoparticles isn't new, Mohapatra concedes. For instance, researchers at Johns Hopkins University have used the substance to coat certain foods and offer protection against food allergies.[2]

"We thought other applications for this platform -- not just oral delivery -- could work, so we began looking for an intranasal approach," says Mohapatra, whose basic studies related to the nanoparticle drug delivery also were funded by the NIH. Previous physiological studies have concluded that chitosan does not affect cilia movement, iron transport, and other functions of human nasal epithelial cells, he adds.[3]

Human trials to start next year

With the next round of NIH funding secured, the researchers expect to proceed to phase I human trials early next year, initially at USF but with the potential to expand to multiple centers in six months to a year, Mohapatra says. He hopes to move to phase II trials early the following year and is already looking for partners and potential licensees for the nanoparticle intranasal therapy, which could be ready for commercialization by late 2005. A small biotech start-up company in Tampa, FL, Transgenics Therapeutics, is involved in the nanoparticle production, according to Mohapatra.

The researchers have been issued one patent for the intranasal gene transfer,[4] and USF has filed two provisional and two Patent Cooperation Treaty (PCT) applications related to the technology, which represents "the second and third generation of nanoparticles involving chitosan," Mohapatra says.

"We are possibly the only lab in the United States using nanoparticles to treat asthma," he adds. "When the NIH awarded our grant, experts there said we may be at least 10 years ahead of all others with this method."

Editor's Note: Contact Shyam S. Mohapatra at (813) 974-8568.

References

1. Kumar M, Kong X, Behera A et al. Chitosan IFN-gamma-pDNA nanoparticle (CIN) therapy for allergic asthma. Genetic Vaccines and Therapy 2003; www.gvt-journal.com/content/1/1/3.

2. Roy K, Mao JQ, Huang SK et al. Oral gene delivery with chitosan-DNA nanoparticles generates immunologic protection in a murine model of peanut allergy. *Nat Med* 1999;5(4):387-91.

3. Richardson SC, Kolbe HV, Duncan R. Potential of low molecular mass chitosan as a DNA delivery system: biocompatibility, body distribution and ability to complex and protect DNA. *Int J Pharm* 1999;178:231-43.

4. U.S. Patent 6489306: Method of intranasal gene transfer for protection against respiratory infection. ⊙

Medical diagnostics will come next year

Virus detection device to be used first for bioterror agent detection

By Jane Anderson Cassell

Integrated Nano-Technologies is gearing up to begin marketing a handheld nanobiotech-based device capable of detecting single viruses and bacteria, and the company's president and CEO says the firm's first clients likely will be government agencies intent on finding weapons against bioterrorism.

The Henrietta, NY-based company, which began operations in late 2000, hopes to begin selling the BioDetect device late next year, says president Mike Connolly.

"What we're really doing is looking to get a single, easy-to-use system that's very small," Connolly says, adding that the BioDetect device weighs five pounds and provides data in five to 10 minutes. "Because of the capabilities of our chip, we can get as good or better data than you can get out of a laboratory," he says.

The system is small enough to be carried by hand or installed in an air circulation system, he says.

According to the company, BioDetect technology is a unique combination of molecular biology, chemistry and microelectronics. Integrated Nano-Technologies recently licensed a collection of patents from Technion (the Israel Institute of Technology) which cover the metallization of DNA. The company is combining these technologies with its own expertise in chip fabrication and molecular biology to produce the sensors at the heart of BioDetect.

"The technology behind it is a method for taking a DNA molecule and using that as a substrate for making wires or other electronic components," says Connolly. "We coat the DNA molecule with metal."

The DNA probes then are installed on a microchip to attach and bind to specific sequences in the DNA of the target organism. DNA is extracted from a sample and passed over the

continued on page 7

Nanotech legislation *from Page 1*

Science Committee Chairman Sherwood Boehlert (R-NY) and Rep. Mike Honda (D-CA) introduced the House version.

Passage came without floor debate after the bill had languished since Nov. 3, when the preconference version was dropped on the Senate floor. Senate insiders originally expected action last week, but the bill was held hostage by the GOP's 30-hour executive session, which began last Wednesday evening, and the bottleneck of legislation created in its wake.

The compromise version is long on structure and short on specifics. S.189 puts the President's National Nanotechnology Initiative (NNI) into law, legislates the National Nanotechnology Coordination Office (NNCO), and authorizes $3.7 billion in funding over the next four years for the program.

General nanotech activities directed by the bill include:

• the provision of grants to individual investigators and interdisciplinary research teams;

• establishment of a network of advanced technology user facilities and centers;

• establishment, on a competitive basis, of interdisciplinary nanotech research centers that may include academic institutions and/or federal labs; and

• acceleration of the deployment and application of nanotech R&D in the private sector, including startup companies.

The compromise legislation follows the Senate version calling for the existing National Science and Technology Council to oversee the planning, management, and coordination of the program. The bill also establishes in law the NNCO -- which has existed for the past few years through executive order -- with a director and full-time staff to provide technical and administrative support to the council and to serve as the point of contact on federal nanotech activities.

Panel make-up is critical to nanomedicine

Like the House version of the bill, the legislation requires the "establishment or designation" of a National Nanotechnology Advisory Panel consisting of members from academia and industry to advise the president and council on nanotech research, development, demonstrations, education, technology transfer, commercialization, and societal or ethical concerns.

The composition of this panel could be critical to the allocation of federal funds to nanomedicine initiatives, since the duties of the advisory panel include the assessment of "trends and developments in nanotechnology science and engineering" and "the balance among the components of the program, including funding levels."

In an effort to assuage interests of key sponsors, S.189 calls for the establishment of several new initiatives:

• Under the Department of Commerce, the National Institute of Standards and Technology (NIST) is directed to establish a program to conduct basic research on issues related to the development and manufacture of nanotechnology, including quality assurance, process control, and manufacturing best practice. A clearinghouse related to technology transfer also will be established under NIST.

• An American Nanotechnology Preparedness Center will be created to address the societal, ethical, environmental, educational, and legal implications of nanotechnology.

• A Center for Nanomaterials Manufacturing will "conduct, coordinate, commission, collect, and disseminate" research on nanomanufacturing technologies for materials, devices, and systems.

The $3.7 billion in funding over four years also represents a compromise between H.R.766, which authorizes $2.36 billion over three years for nanotechnology research and development programs at five agencies, and the original Senate version, which authorized $4.74 billion over five years to nine agencies. The lion's share of the funding in S.189 is directed to the National Science Foundation -- $1.7 billion -- and Department of Energy -- $1.5 billion -- with smaller amounts to the National Aeronautics and Space Administration, NIST, and the Environmental Protection Agency.

Senate version excludes $400M to NIH

Gone is the original Senate version's inclusion of more than $400 million in nanotech-related funding for the National Institutes of Health (NIH), though nanotech-related projects may still be funded separately by NIH, sources say.

While the bill "doesn't directly address nanobiotechnology and biomedicine, it does provide a phenomenal foundation for beginning to work in these areas," says Paul Stimers, an associate at Preston Gates Ellis & Rouvelas Meeds LLP in Washington, which has lobbied for the bill on behalf of the NanoBusiness Alliance. Stimers cites specific language in the bill calling for the council to "oversee interagency coordination of the program" with the NIH, among other agencies, as evidence that nanomedicine initiatives will continue to receive federal support and funding.

S.189 does allocate $25 million annually over the next four fiscal years to the DOE for merit-based grants to support consortia that "conduct

continued on page 5

Nanotech legislation *from Page 4*

interdisciplinary nanotechnology research and development designed to integrate newly developed nanotechnology and microfluidic tools with systems biology and molecular imaging."

Whether the funding levels established in the bill will be fully appropriated remains to be seen, but those close to the compromise effort expect the president to offer financial support as well as his signature to the legislation.

"The purpose of the bill is to set strong appropriation levels for the long term so the U.S. can maintain its competitive edge in nanotechnology and to send a signal to the private sector that the federal government will provide a secure funding stream" for nanotechnology, says one Senate staffer.

Ideally, the legislation could improve the coordination of research efforts, stimulate best practice, and encourage technology transfer. The proof will come in articulating the gray areas of the legislation. Stay tuned.

Editor's Note: Contact Paul Stimers at (202)661-3883. ⊙

Orthopedic Development *from Page 1*

subjected to tension, explains Alan Halpern, MD, the company's president.

A cascade of events is triggered when a nerve is damaged by trauma. The delicate tissue is squeezed by swelling that develops after an injury. Over time, scar tissue forms that prevents nerves from regaining connections essential for normal functioning.

Halpern's approach involves injecting the injured nerve with iron oxide particles about 100-250 nm in size, and then exposing the patient to a precise magnetic field that physically tugs the severed nerve back together.

Halpern was issued patent No. 6,132,360 for the approach in 2000.

So far, Halpern says, nerve regrowth has been demonstrated in animal studies with rats and chicks. "We've shown in vitro that we can stretch an axon and actually stimulate it to grow," he says.

Two more years of work with animals

Research by the privately held company has been slow but encouraging. "Absent a monumental infusion of capital, we'll be working with animals for at least the next two years," says Halpern who is also clinical assistant professor at Michigan State University School of Medicine.

In July, Orthopedic Development was awarded a one-year, $100,000 Phase I Small Business Innovation Research (SBIR) grant from the National Institutes of Health. The company is using the funds to optimize the particles and coating for treatment, and is in the planning stages for Phase II of the program.

"We're looking at 5-10 coatings" intended to enhance preferential attachment of the nanoparticles to nerve tissue," says Halpern. Further experiments are planned to determine the volume of particles that must be injected to enable nerve regrowth.

Halpern says his plan for the company is to continue basic research while searching for additional funding or partnership with a larger biotechnology company. He is presently in funding discussions with "a company outside of Boston," but declined to elaborate further.

Editor's Note: Contact Alan A. Halpern at halpern@net-link.net. ⊙

Affymetrix *from Page 1*

functional elements encoded in the DNA sequence -- promoters and other transcriptional regulatory sequences, for instance -- along with determinants of chromosome structure and function remain largely unknown. A comprehensive encyclopedia of these features is needed before researchers can apply the sequence fully to understand human biology, predict potential disease risks, and develop new therapies to prevent and treat disease.

Interrogating single molecules

As the research effort continues, the ability to "interrogate a single molecule rather than an entire group of molecules" -- the convergence between nanobiotechnology and genomics -- is increasingly important, says Thomas Gingeras, PhD, vice president of biological research at Affymetrix and a recipient of first-year funds of $990,000 from ENCODE for mapping sites of transcription and regulation.

In fact, three of the eight initial ENCODE grants for studying large-scale application of existing technologies to determine functional elements were awarded to researchers who will apply the GeneChip brand technology developed by Santa Clara, CA-based Affymetrix, Inc. (NASDAQ:AFFX).

The others are Michael Snyder, PhD, professor and chair of molecular, cellular, and developmental biology at Yale University in New Haven, CT, and director of the Yale Center of Genomics and Proteomics, who will receive first year funds of $1.7

continued on page 6

Affymetrix *from Page 5*

million to study transcription and regulatory elements in ENCODE regions, and Anindya Dutta, MD, PhD, professor of biochemistry and molecular genetics and professor of pathology at the University of Virginia in Charlottesville, who will receive $380,000 for mapping replication elements on human chromosomes.

The objective of the ENCODE project is to identify, locate, and annotate all functional elements in the roughly 98% of the human genome that lies outside the protein-coding regions, Gingeras explains. The cooperative effort will serve as a pilot project to test efficient, high-throughput methods for identifying, locating, and fully analyzing all of the functional elements contained in a representative selection of DNA target regions covering approximately 30 megabases, or about 1%, of the human genome. Information gathered from this initial study will lay the groundwork for future efforts.

Technology developed by Affymetrix is ideally suited to the project, Gingeras maintains.

The next phase

"Now that a complete working draft of the human genome is available, it's important to begin the next phase of our efforts to fully identify its functional content," he says. "The ENCODE Project provides a framework for new technical approaches to discover novel RNA transcription and regulatory regions which play important biological roles.

"The stated aim of the ENCODE Project is to identify the regions of the genome outside the protein-encoding sequences," Gingeras adds. "We know very little about the regulatory and other functional elements that are present in the genome, and the approach to looking for these functions requires looking at them without bias. At Affymetrix, we have the ability to make customized arrays with very small features -- as little as five microns -- and to ask specific questions at each point using oligonucleotides as interrogators."

As an example of what could be discovered in the ENCODE Project, Gingeras and researchers from the National Cancer Institute (NCI) last year published the first empirical data set on chromosomes 21 and 22, revealing greater levels of RNA transcription than previous studies of gene transcription activity through the Human Genome Project have suggested.[1] These findings were made possible through new array and scanner technology developed at Affymetrix that allow the human genome to be probed at a higher resolution than ever before.

Nanobiotech and genomics increasingly are linked as the research community seeks to pinpoint function at the single cell level, Gingeras says. In gene sequencing, researchers look at the predominant response to probes on "millions or billions of cells," he points out. Through the application of nanobiotechnology, they may be able to understand the level of genomic diversity at smaller and smaller sample sizes.

Thus, while the present study of genomics tends to average gene expression results across many molecules in many cells, "uniqueness of function or regulatory response could be found in just a few molecules or a few cells," Gingeras says.

The current dependence on amplification, and its potential to skew results, also could be set aside once principles of nanobiotechnology can be successfully applied to genomics, he adds.

Affymetrix has been moving rapidly in this direction, with sample sizes in its array technology shrinking even within the past six months. In March, the company launched GeneChip brand CustomExpress arrays in 520-, 3,600-, and 8,400-gene formats, enabling researchers to design expression arrays containing 520 to 22,500 genes. Earlier this fall, Affymetrix launched yet another generation of CustomExpress -- an 11-micron array format that can measure up to 61,000 transcripts. By reducing the features from 18 to 11 microns, the company is able to accommodate 1.3 million features -- nearly three times more information than its predecessor.

"The ENCODE Project programs are very complementary to the basic research programs at Affymetrix," Gingeras says. "And the ability to evolve to nano-sized formats is crucial to our technology."

Affymetrix reported net income of nearly $5.8 million for the third quarter ending Sept. 30 compared to net income of $0.6 million for the same period in 2002. Total revenue for the quarter was $76.2 million compared to total revenue of $72.8 million in the same period a year earlier. Third quarter product sales included GeneChip array revenue of $34.5 million and record instrument revenue of $18.1 million, while costs for the quarter were $68.8 million compared to $71.0 million during the third quarter of 2002.

Trading in a 52-week range between $16.25 and $29.93, Affymetrix stock closed at $24.12 on Nov. 18.

Editor's Note: Contact Thomas Gingeras at (888) 362-2447. For more information on the ENCODE Project visit www.genome.gov/ENCODE/.

Reference

1. Kapranov P, Cawley SE, Drenkow J et al. Large-scale transcriptional activity in chromosomes 21 and 22. *Science* 2003;296:916-919. ⊙

Integrated Nano-Technologies *from Page 3*

microchip, where it attaches to the organism-specific probes, which then produce an electrical signal for computer analysis -- sort of like an on-off switch, Connolly says.

PCR is old news

The BioDetect system consists of an electronic analyzer and single-use, disposable test cards. Unlike other detection systems, BioDetect technology does not depend on polymerase chain reaction (PCR), and therefore does not share PCR's problems with speed, stability and sensitivity, according to the company

"The system allows us to detect down to single molecules," Connolly says. "We get a signal for every molecule that binds to the sensor. It [BioDetect] can generate very high levels of confidence in terms of results."

It's possible to place different types of probes in different areas of the chips, he says, adding "the chips we're designing now are doing 200 different tests at once." However, that doesn't mean those chips are detecting 200 different organisms; instead, they might be detecting different parts of the same virus or bacteria, Connolly says. For example, there could be 10 different tests for strep, he says, adding, "redundancy gives better certainty."

Although the first BioDetect units sold most likely will be geared for bioterrorism detection, "by the end of next year, we'll be putting together other tests in the medical diagnostics area," Connolly says. Partnering with companies that want to develop tests for food-borne pathogens also is possible, he tells *NanoBiotech News.*

Integrated Nano-Technologies is talking with a number of companies -- including large defense contractors -- about the possibilities of combining the BioDetect system with air collectors manufactured by other companies, Connolly says.

"We're looking at a system where we would together put out integrated devices – we would provide our device to go with this system," he says.

In addition, the company currently is negotiating development contracts for specific sensor needs with government entities, which Connolly says will use the device to counter bioterrorism.

Angel investors have contributed $10 million since the company's inception, Connolly says. The National Science Foundation has kicked in $100,000 in grant money to fund the development of BioDetect, and Connolly says the firm is seeking additional grant money.

The company holds three U.S. patents related to the technology: number 6,248,529, Method of chemically assembling nano-scale devices; 6,399,303, High resolution DNA detection methods and devices; and 6,593,090, High resolution DNA detection methods & devices.

Editor's Note: Contact Mike Connolly at (585) 334-0170. ⊙

Virus detection in real time

Nano-sensors could be more sensitive that current virus detection methods

By Jane Anderson Cassell

Scientists at Purdue University are using micromechanical sensors that can detect a single virus particle -- with the idea that eventually the micro-machined ultrathin cantilever arrays can be incorporated into a small handheld device that collects air and screens it for airborne viruses, particularly bioterrorism agents and viruses in patient care facilities.

The researchers say the technology could be far more sensitive and easier to use than current virus-detection methods.

The project is starting the second year of a two-year, $440,000 grant from the National Institute of Biomedical Imaging and Bioengineering, says Rashid Bashir, PhD, associate professor in the School of Electrical and Computer Engineering at Purdue.

Although the idea still must clear some major hurdles, Bashir says the scientists involved hope it might be commercialized in the next five to eight years. The ability to detect airborne viruses with a small, easy to use device in real time would be a major advantage in the confinement and management of viral epidemics, he says.

"We're working on developing sensors for the detection of airborne virus particles," says Bashir. The researchers are working with the vaccinia virus, which comes from the same family as severe acute respiratory syndrome (SARS). Bashir says they had chosen the virus before the SARS outbreak last year.

According to Bashir, surface derivatized cantilever structures have been used successfully to detect DNA, proteins and cells, but the detection of viruses hasn't been fully explored using the technology.

"The sensors themselves have the sensitivity to detect a single virus particle," says Bashir. The cantilevers use mass changes on their surfaces to detect the viruses, he says, and are coupled with

continued on page 8

Virus detection from Page 7

specific receptors to which the specific viruses bind.

First of three goals accomplished

As part of the grant, the researchers intend to demonstrate three things: that the sensors have the sensitivity needed to detect a single virus particle; that the sensors can detect the viruses selectively without becoming clogged with other particles; and that it's possible to concentrate enough particles near the sensors to detect airborne viruses.

So far, Bashir says, they have demonstrated the first of these: that the sensors have the sensitivity to detect a single virus particle. "The challenges will be active concentration of the particles, and removal of the non-specifically bound particles -- different viruses we're not looking for that could give a false positive."

If the scientists achieve their goals in the second year of the project, they hope to be awarded funding for three more years, Bashir says, adding that the grant then would total $2.1 million. If they are awarded the three-year extension, they will attempt to construct devices that can look for different virus particles simultaneously, and they also may begin seeking additional funding for their project, he says.

At the end of the five years, Bashir says, the researchers might be in a position to start a company in an effort to commercialize the technology, which has other possible applications as well.

For example, viruses are between 50 and 200 nm in size, Bashir says. Meanwhile, bacteria and spores range between 1 and 2 micrometers. "If we can detect the smaller particles, then the same technology is extendable to spores and bacteria," he says.

The researchers this month filed a patent application on their technology and application, Bashir says.

Editor's Note: Contact Rashid Bashir at (765) 496-6229. ⊙

Pharmacy on a chip

Nanoreservoirs in microchip allow for cyclical delivery of multiple drugs

By Rosemary Clandos

One day when drug treatments call for cyclical delivery, physicians may call for a microchip built in the Langer Lab.

Robert Langer, professor of chemical and biomedical engineering at Massachusetts Institute of Technology, Amy Richards-Grayson, a post doctoral fellow at Cornell University, and their team have designed an implantable and biodegradable microchip that has the potential to deliver periodic doses of vaccines, angina medications, growth hormones and fertility drugs. And it can dispense more than one drug at a time.

"It has the potential to be a pharmacy on a chip," says Langer. The drug delivery system is the first biodegradable device of its kind. Depending on the materials used and the drug requirements, the whole system can degrade in one month to several years. The technology was featured recently in *Nature Materials*.

"It would be revolutionary to provide a whole battery of immunizations and multiple boosters with the chip," says Jennifer West, associate professor of bioengineering at Rice University and a biotech reviewer for *Nature Materials*. In developing countries where children may receive vaccines, but do not always receive boosters to establish real immunity, the microchip could be life saving, she says.

For some tumors, there is less resistance to chemotherapy if drugs are given in the pulsatile fashion that is available through the microchip, West adds.

Built from FDA-approved polymers, the prototype chip is about 1.2 centimeters in diameter and about 500 microns thick. It has 36 nanowells -- the number can go up to 1,000 nanowells -- which can be filled with different drugs. Covering the reservoirs are separate biodegradable polyester membranes. The materials used in the construction of each of the membranes determine how quickly or slowly they will dissolve, or pulse, and deliver the drug payload.

The technology has been tested with growth hormones and heparin, an anti-coagulant. A complex large molecule, heparin was chosen for the test because it has biologic activity, namely clotting time, which can be easily monitored.

Langer says other groups of drugs could be used, but the most effective application of the technology would be for drugs that require frequent or recurrent dosing. In other words, drugs that require a periodic spike. Depending on the potency of the drug, about 500 mg could be loaded on a chip.

"You could have a thousand small doses or other more potent doses," Langer says of the technology, which is still in the animal study stage.

The hands-off drug delivery system will require physicians to make precise calculations about the needs of their patients, because once the device is implanted, it is impossible to adjust the

continued on page 9

Nanoreservoirs *from Page 7*

dosing to accommodate changed medical needs.

"You'd want to know in advance what you want to do with it," Langer says.

The microchip could be implanted under the skin, deep in the brain, or it could be made into a pill or a transdermal patch, Langer says. Similar to other implanted medical devices, it could be anchored into position.

Challenges remain

The challenge for the researchers will be to tightly tune and control the degradation rates of the membranes, says West.

"The degradation of the polymers is very pH-dependent, so if you get different inflammatory reactions in patients then you'd have different pH around the device and different times for the drug release.

"So if you're looking at an application where precise timing is important, you may not be able to get that with this device. For insulin therapy, as an example, timing will be critical. But there are still lots of exciting applications for the device," West says.

For example, when using the chip for vaccinating children in developing countries, the exact timing for the release of the vaccine would be less important -- six months versus six months and one week, for example, would not have a critical impact.

MIT holds numerous patents for the technology. The microchip has been licensed to MicroCHIPS, Inc. a Bedford, MA-based company. Funding for the microchip came from several grants from the National Institutes of Health -- between $250,000 and $l million each year for the last four years.

Editor's Note: Contact Robert Langer at (617) 253-3107 and Jennifer West at (713) 348-5955. ⊙

Advancing the study of protein-protein interactions

Nanostructures may be a template for multiple inventions to aid in drug discovery

By Jane Salodof MacNeil

Today microarrays give scientists unprecedented ability to detect which proteins are turned on by proteins from cancer genes. If Hao Yan, PhD, of Duke University in Durham, NC, has his way, before long they will be able to see single molecules of the proteins interact in a nanoarray.

Yan and his colleagues have built nanostructures in which strands of DNA organize themselves into tiles with empty centers defined by four, four-armed junctions. The tiles, in turn, assemble themselves into lattices, taking one of two geometric forms: a nanoribbon or a two-dimensional nanogrid that looks something like a garden trellis.

And these structures, according to a recent article in *Science*,[1] are "sufficiently rigid to act as a building block in larger superstructures."

If this all sounds a bit like playing with Legos or an interlocking erector set, that's exactly what Yan had in mind. "That's one of the inspirations -- Lego," he tells *NanoBiotech News*.

"The idea comes from a toy -- a kindergarten concept," he says. "When I walk on the street, I always observe patterns, so many different patterns. We can borrow a lot of things from what we observe."

In a way, he says, the nanostructures are like buildings. The same basic architecture can be configured in a variety of ways and put to many different purposes.

One possibility is biosensors. Led by Thomas H. LaBean, PhD, the Duke University team built a nanogrid in which the protein streptavidin bound itself to a biotin group in a periodic protein array on a DNA lattice. Because streptavidin has a diameter of 5 nm, the investigators could see the binding sites as bumps in the center of the 4 x 4 tiles.

Developed further, such an application could advance the study of protein-protein and protein-DNA interactions for drug discovery, according to Yan. "We can see the event in a single molecule," he says. "With the microarray what we see is about the event -- there could be thousand of molecules that would bind to the target. We can use our [nano] system to precisely locate the binding event."

Using magnets to guide delivery system

Yan also described the possibility of a therapeutic delivery system in which a protein -- an antibody, for example -- binds to one "sticky end" of a tile and a magnetic particle to another. Someone could use magnetic attraction to move the protein to specific sites, he says.

The protein arrays and nanowires could be ready for commercialization in five years, according to Yan. Duke University is seeking patents for the work published so far, he says.

Editor's Note: Contact Hao Yan at (919) 660-6525.

Reference

1. DNA-templated self-assembly of protein arrays and highly conductive nanowires. *Science*. 2003 Sep 26;301(5641):1882-4. ⊙

News in Brief

• The **National Institutes of Health** (NIH) is seeking applications focused on new technologies for measuring small metabolites. The NIH Roadmap initiative, Metabolomics Technology Development, (found at http://grants1.nih.gov/grants/guide/rfa-files/RFA-DK-04-001.html) is aimed at stimulating development of innovative technologies to enhance the understanding of metabolic pathways and networks. The range of appropriate technologies includes methods for measuring the biologically active concentrations of metabolites in cells or tissues with high spatial and temporal resolution, for accurately and quickly quantifying multiple metabolites in biological samples, and for significantly extending our knowledge of the entire cell metabolome. Of particular interest are approaches for metabolites with very short lifetimes, those found at low concentrations, and those that exist in several biologically distinguishable forms or locations within the cell. Applications must be received by March 24, 2004. For more information contact Maren R. Laughlin, PhD, Trans-NIH Metabolomics Technology Development Implementation Group, at (301) 480-3503 or maren.laughlin@nih.gov.

• **Southern Research Institute** and **Genome Explorations, Inc**., Memphis, TN, have entered into a collaborative agreement to pursue joint development programs in pharmaceutical target identification using gene expression profiling, and to co-market individual and combined services. Genome Explorations is a microarray genetics testing and analysis provider. Southern Research Institute is a preclinical contract research and development organization for the pharmaceutical and biotechnology industries. Southern Research scientists have discovered or synthesized five FDA-approved cancer drugs on the market, with three other cancer drugs now in clinical trials. Southern Research has facilities in Birmingham, AL, Frederick, MD, and Research Triangle Park, NC and is affiliated with the University of Alabama at Birmingham. ⊙