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Nanogen acquires cardiac diagnostics firm for $7.65M

By Steve Lewis

Nanogen, Inc., (NASDAQ:NGEN) of San Diego, CA, has completed the acquisition of the rapid cardiac immunoassay test business of Spectral Diagnostics (TSX: SDI), of Toronto, Canada.

Nanogen paid CDN$9 million (US$7.65 million) comprised of CDN$5.65 million in cash (US$4.8 million) and CDN$3.35 million (US$2.85 million) in Nanogen common shares.

The company acquired Spectral's rapid cardiac immunoassay test business, including multiple U.S. Food and Drug Administration-approved tests for acute coronary syndrome (ACS) and acute myocardial infarction (AMI). Nanogen has also acquired Spectral Diagnostics' hand-held i-Lynx reader, which is designed to capture and analyze the results of the Cardiac STATus products.

"This acquisition broadens our product line

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Carbon nanotube-derived device detects gene mutations without labeling

By Russell A. Jackson

University of Pittsburgh researcher Alexander Star, PhD, and colleagues at Emeryville, CA-based Nanomix Inc. have developed a carbon nanotube-based device that can detect gene mutations without use of more expensive and time-consuming fluorescent labeling. Once commercialized, the discovery could have a near-term market opportunity value of more than $2.5 billion.

In the research, the detection devices were fabricated using carbon nanotubes "grown by means of a chemical vapor deposition technique on four-inch silicon wafers," Star tells *NanoBiotech News*. "Each device was made of a random network of

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Nanoparticles for asthma, RSV are being tested in dogs in preparation for IND filing

By Steve Lewis

A researcher in Florida is developing a nasal spray containing nanoparticles for the treatment of asthma.

Shyam S. Mohapatra, PhD, principal investigator, professor of medicine, and director of basic research for the University of South Florida's (USF) division of allergy and immunology and the Joy McCann Culverhouse Airway Disease Center in Tampa, FL, has also taken the nanoparticles, combined them with siRNA, and produced positive results in mouse models for respiratory syncytial virus (RSV) infection. The latter research was reported in *Nature Medicine*.[1]

Mohapatra first reported that the nasal spray nanoparticles, which deliver therapeutic, protein-producing genes, effectively reduced allergen-induced airway inflammation and hyper-reactivity in mice. (See *NanoBiotech News*, Nov. 19, 2003, p. 2.)

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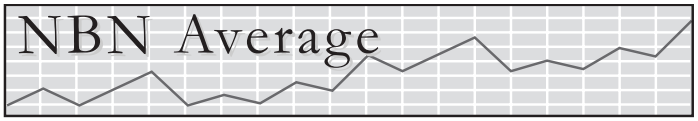

Company	Symbol	Close 01/31	Close 02/07	% Change
Acrongenomics	AGNM	$ 2.90	$ 3.06	5.52%
Advanced Magnetics	AVM	$ 19.98	$ 19.98	0.00%
Altair Nanotechnologies	ALTI	$ 3.45	$ 3.34	-3.19%
American Pharmaceutical Partners	APPX	$ 33.42	$ 33.37	-0.15%
Arrowhead Research	ARWR	$ 5.10	$ 5.02	-1.57%
Biodelivery Sciences	BDSI	$ 2.97	$ 2.97	0.00%
Biophan Technologies	BIPH.OB	$ 1.75	$ 1.57	-10.29%
Biosante Pharmaceuticals	BPA	$ 4.69	$ 4.34	-7.46%
Flamel Technologies	FLML	$ 23.39	$ 22.59	-3.42%
Introgen Therapeutics	INGN	$ 5.34	$ 5.15	-3.56%
Nanobac Pharmaceuticals	NNBP.OB	$ 0.05	$ 0.05	6.38%
Nanogen	NGEN	$ 3.02	$ 2.78	-7.95%
Novavax	NVAX	$ 4.20	$ 4.16	-0.95%
pSivida	PSDV	$ 5.00	$ 4.46	-10.80%
SkyePharma	SKYE	$ 7.82	$ 7.20	-7.93%
Starpharma Holdings Limited	SPHRY.PK	$ 3.95	$ 3.90	-1.27%
TOTAL		127.03	123.94	▼ -2.43%

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in cardiac care; quite honestly, it gives us a larger footprint in that area and adds capabilities and resources into our point-of-care group, which so far has been focused on the cardiovascular field," notes Robert Saltmarsh, Nanogen's chief financial officer.

The assets from Spectral will be integrated with Nanogen's point-of-care businesses, also headquartered in Toronto.

Diversity is important

Nanogen officials say that with the addition of the Spectral cardiac tests the company has the necessary product line to compete in the $1.5 billion worldwide point-of-care testing market. "What customers have told us is that having a variety of tests is important," says Saltmarsh. "For example, having a congestive heart failure [CHF] test is terrific, but doctors want a broader menu. If I were a clinic or an ED, would I really want a device on the shelf I can only run one test on, or a device I can run multiple tests on?"

Nanogen is still awaiting regulatory approval for its CHF test, and filed a report with the U.S. Securities and Exchange Commission about a month ago that slightly changes its contractual relationship with its partner, New Jersey-based Princeton Biomeditech Corp. "Essentially, they have the U.S. rights and we have the international rights," Saltmarsh explains. "We just further clarified the relationship."

Spectral reported nearly CDN$7 million (US$6 million) in product revenues during 2005 from the Cardiac STATus tests and i-Lynx readers. The Cardiac STATus line includes four FDA-cleared tests that can be used at the point-of-care to determine elevations of cardiac markers, providing an aid to physicians to assess and diagnose acute coronary syndrome (ACS) as indicated by chest pain.

The product line includes:

• Cardiac STATus Myoglobin, Troponin I and CK/MB Tandem 3 in 1 Test to rule-in or rule-out ACS;

• Cardiac STATus Troponin I, the single most critical marker to determine acute myocardial infarction (AMI); and

• Cardiac STATus Myoglobin/Troponin I to aid in the diagnosis of AMI

The i-Lynx is a hand-held reader designed to capture and analyze the results of the Cardiac STATus products as well as other rapid tests such as tests for cardiovascular disease, pregnancy and infectious diseases. The portable electronic unit offers connectivity to customers' existing laboratory data management systems to help facilitate patient record keeping and billing functions. The DecisionPoint product line is the same series of cardiac marker assays as the STATus line designed for international markets, with CE marking.

Immediate revenue realized

Nanogen has made several acquisitions and equity investments in the past two years, but this one is a bit different. "One of the nice things about the Spectral acquisition is that it brings immediate revenue -- with no product risk," Saltmarsh observes. "They have had these products for several years."

Why did Spectral want to sell such successful products? "They had also put a fair amount of money into a sepsis product; they had only so many resources, and decided to focus on that," Saltmarsh explains.

In 2003, Nanogen acquired Toronto-based SynX (see *NanoBiotech News*, Feb. 18, 2004, p. 1) and merged with Epoch Biosciences (see *NanoBiotech News*, Dec. 22, 2004, p. 1). More recently, it made a $1.5 million equity investment in Jurilab Ltd., of Kuopio, Finland, a company that focuses on the discovery and identification of new genes and gene markers associated with the root causes of common diseases and drug responses. (See *NanoBiotech News*, August 3, 2005, p. 1.)

"The difference in the SynX transaction is that we bought a company with tremendous promise, but not revenue, that was awaiting FDA approval for products," notes Saltmarsh. Integration of the Spectral operations will also be made easier by its close proximity to SynX. "It's just a couple of miles down from the SynX

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facility," Saltmarsh observes.

Nanogen's point-of-care group will continue to focus on FDA approval of the quantitative CHF diagnostic test, as well as on the development and launch of other complementary tests. "We have pretty good patents in the stroke area, so at some point in time there will be a stroke product -- but it's still in the development stage," says Saltmarsh.

The company also will continue to grow through acquisition. "Acquisition is a key portion of our strategy," says Saltmarsh. "We now have three product lines and we're pretty happy with that; going forward we will look at complementary acquisitions involving more advanced diagnostics."

On another front, Nanogen began shipping its NC (NanoChip)-400 second generation array product in the fourth quarter of 2005. "Market reception at this stage is good," says Saltmarsh.

Nanogen's stock closed at $2.92 per share on Feb. 7, 2006. It had been trading as high as $5 per share in the first quarter of 2005.

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

Nanoparticles *from Page 1*

Mohapatra and his team selected chitosan nanoparticles as a delivery method for the interferon gamma gene, which allowed the lungs to produce the protein interferon gamma that is needed to reduce asthmatic symptoms. Based on those findings, the National Institutes of Health (NIH) awarded $1.16 million to the USF researchers to determine if the treatment would be safe and effective for humans with asthma; it was these funds that have underwritten this latest research.

"Now, with the gene vaccine we reported on before, we have gone to the dog stage," Mohapatra reports, noting that he has added a few wrinkles this time around.

"In the earlier paper we had given it intranasally," he notes. "Some people told us that while this was very important, most people prefer to take their medicines orally."

Still, he had to test for adverse toxicity from intranasal delivery in dogs, as none had been seen in the mice. "In dogs, we tested that as well, and in addition we gave the drugs orally," Mohapatra says. "We fed them food with the particles in it to see if there was a reduction in inflammation, and the answer is yes."

The work is not yet published, says Mohapatra. "We want to submit it to get a phase II grant, which will allow us to go to phase I human trials and file an investigational new drug application [with the U.S. Food and Drug Administration]."

Taking on RSV

In the research reported in *Nature Medicine*, "We have actually taken the nanoparticles and combined them with siRNA and showed that in fact we would be able to treat the infection if it already had taken place, or we could give the nanoparticles intra-nasally before infection and prevent it," Mohapatra reports.

This is an important development, he says, because RSV is a trigger for asthma. "It makes kids prone to developing asthma, so if we can reduce [RSV], that will probably cut down on the number of asthmatics."

RSV, he continues, is usually the very first virus a baby will be infected with; it infects about 120,000 per year and kills 4,500 in the U.S. "If it infects certain babies one, two, or three times it will make them susceptible [to asthma]," he asserts.

The potential applications for this technology are significant, he adds. "Take the flu: If you're going on a plane, you would be able to take the nasal spray and protect yourself from getting a severe infection," he suggests.

The nanoparticles are produced by TransGenex Nanobiotech, Inc., a Florida-based biotechnology company co-founded by Mohapatra in 2002 and incorporated in 2004.

"In terms of licensing with big pharma companies, we are still working on that," he reports.

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

Reference

1. Zhang W, Yang H, Kong X, et al. Inhibition of respiratory syncytial virus infection with intranasal siRNA nanoparticles targeting the viral NS1 gene. *Nat Med* No. 11, Jan. 1, 2005: 56-62. ⊙

Carbon nanotubes *from Page 1*

carbon nanotubes between interdigitated gold electrodes with 10-micron separation."

Specifically, an abstract of Star's published work[1] points out, the devices "were fabricated by using single-walled carbon nanotubes grown at 900 degrees C using dispersed iron nanoparticles as growth promoter and a methane/hydrogen gas mixture on doped Si 100-mm wafers with SiO2 at its surface." Electrical leads, the abstract continues, "were patterned on top of the nanotubes from evaporated Ti-Au films by using standard photolithography techniques."

Each wafer consisted of about 1,000 dies with 2.54 nm x 2.54 mm dimensions. On each die, a random network of SWNTs is patterned into several devices that consist of the interdigitated electrodes. Nanotubes outside the device area were removed with oxygen plasma to electrically isolate each device. Electronic characterization of the nanotube network field-effect transistor devices, such as current flow between source and drain electrodes as a function of applied gate voltage and bias voltage, were conducted by using automated test equipment similar to semiconductor industry set-ups.

Carbon nanotubes, Star says, are basically "rolled-up sheets of graphite only a few nanometers wide -- about the width of a molecule of DNA." The Nanomix team used the nanotubes' electrical properties to find a particular mutation in the gene that causes hereditary hemochromatosis, a disease in which too much iron accumulates in body tissues. "The size compatibility between the detector and the detected species -- DNA molecules in this case -- makes the approach very attractive for further development of label-free electronic methods," he notes.

Fluorescent labeling is eliminated

And that, he points out, "eliminates the necessity of DNA labeling with fluorescent labels -- including the cost of the reagents and of people's time -- and of state-of-the-art fluorescent microscopy." Star adds that the technology "can bring to market hand-held, field-ready devices for genetic screening, as opposed to laboratory methods using labor-intensive labeling and sophisticated optical equipment."

In the research, Star used the fact that carbon nanotubes integrated into a silicon chip "have a characteristic electrical conductance that can be measured by applying a voltage, thus providing a signal for a carbon nanotube-based field-effect transistor device -- our DNA sensor transducer." In particular, he notes, the conductivity of the carbon nanotubes as a function of applied gate voltage was measured.

The hybridization of the DNA molecules -- DNA duplex formation -- on the surfaces of the carbon nanotubes can change their electrical conductance. "In the case of a genetic mutation," he says, "DNA hybridization does not occur under our testing conditions, and the change in the carbon nanotubes' electrical conductance is insignificant compared to normal DNA molecules, which form DNA duplexes."

Because DNA molecules have similar diameter to carbon nanotubes -- about 2 nm -- he continues, "the presence of a DNA molecule and consequent hybridization on the side walls of the carbon nanotubes can readily affect their conductivity."

Star and his colleagues at Nanomix also tested fluorescently labeled DNA molecules to confirm that DNA had attached to the nanotube surfaces and was subsequently hybridized, or matched to its complementary DNA.

"For DNA hybridization experiments -- so-called 'mutation identification' -- we first attached unlabeled DNA molecules to carbon nanotubes and then added complementary DNA molecules that were fluorescently labeled," he explains. "When the hybridization took place, we observed fluorescence in the microscope. In the case of mutated DNA molecules, the hybridization did not take place, which can be observed independently by fluorescent microscopy, a 'conventional technique,' and by measuring carbon nanotube conductivity, which is our new detection method."

"Complementary DNA" is a DNA molecule that has a nucleotide base sequence that is complementary to a probe DNA sequence, which the

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researchers attached to carbon nanotubes first. "Complementary" means that two nucleotide bases form a strong bond with each other. If DNA molecules consist of complementary bases, they can form a duplex; that is, hybridization occurs.

"In the control experiments, we used fluorescently labeled DNA molecules," Star continues. "When you shine a light on them, they emit light of a characteristic color back. The emitted light can be isolated using filters and is easily visible under an optical microscope. Using fluorescence microscopy, we were able to confirm that DNA molecules actually bind to the side walls of carbon nanotubes."

As the abstract puts it: "The development of nucleic acids diagnostics has become the subject of intense research, especially in the post-genome era. Current methods have mainly focused on optical detection using fluorescence-labeled oligonucleotides with dyes, quantum dots or enhanced absorption of light by oligonucleotide-modified gold nanoparticles. On the other hand, label-free electronic methods promise to offer sensitivity, selectivity, and low cost for the detection of DNA hybridization."

Advantages for DNA detection

The abstract points out: "Using smaller nanowires with virtually all atoms on their surface, such as single-walled carbon nanotubes, will provide additional advantages in DNA detection. To date, there are several reports on electrochemical detection of DNA hybridization using multi-walled carbon nanotube electrodes. Whereas electrochemical methods rely on electrochemical behavior of the labels, measurement of direct electron transfer between SWNTs and DNA molecules paves the way for label-free DNA detection. SWNT-based field-effect transistors have excellent operating characteristics and they have already been explored for highly sensitive electronic detection of gases and biomolecules such as antibodies."

That flexibility, of course, is what has Nanomix executives excited about the prospects for the discovery. "We have found that electrical measurement of carbon nanotube devices produces sensor results that are comparable to state-of-the-art optical techniques," Star says. "The applications of our method for detection of other, more serious genetic diseases can be seen."

Commercial applications are already in the works. "Our internal development process is ongoing," reports Bill Perry, vice president, business development, marketing and sales, at Nanomix. "Commercial collaboration efforts will commence in the next nine to 12 months. The first commercial application for non-medical DNA detection is planned to be available within approximately two years."

The pay-off could be huge, he adds. "The total biomolecule detection [market] is approximately $15 billion and growing substantially," he tells *NanoBiotech News*. "The first three areas we have chosen to target -- genetically modified organisms, infectious diseases and pharmacogenomics -- have a current [market] of more than $2.5 billion."

From clinic to bedside

Adds Christian Valcke, vice president of research and development at Nanomix: "Our proprietary platform enables small, automated, handheld devices that allow point-of-care detection of biomolecules. That moves testing from clinical laboratories to the bedside, making it faster, simpler and less expensive. Our expertise with nano-electric devices is backed by an extensive patent pipeline and represents a fundamentally new and advantageous approach to biomolecule detection."

Editor's Note: Contact Bill Perry at (510) 428-5302 and Alexander Star at (412) 624-6493.

Reference

1. Star A, Tu E, Niemann J, et al. Label-free detection of DNA hybridization using carbon nanotube network field-effect transistors. *Proc Natl Acad Sci USA* Jan. 24, 2006 103:4 921-26