Nanomaterials in Medical Devices: A Snapshot of Markets, Technologies and Companies

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ABSTRACT

Nanomaterials are being investigated for use in new medical devices such as diagnostics and implantable devices such as stents and catheters. New nanotech-enabled medical devices aim to provide convenient real-time diagnosis of disease that can be done at a clinic rather than at a laboratory, as well as implantable devices that cause less irritation and have improved functionality. In this article, authors Drew L. Harris and Mark J. Graffagnini provide a snapshot of the market for "point of care" diagnostics and medical implants. They also profile some of the products and companies incorporating nanomaterials in such devices, including Nanosphere's gold nanoparticle diagnostic systems, Nanomix's asthma sensor, Nanotech Catheter Solutions use of carbon nanotubes in catheters and stents, and AcryMed's SilvaGard technology.

I. INTRODUCTION

Engineered nanomaterials will likely make a commercial impact in a variety of industries, ranging from bulk materials to electronics to energy. But perhaps the most profound impact of nanomaterials will be in medicine, where nanoparticles and other nanomaterials will create new classes of drugs and medical devices. For example, nanoparticles are needed for targeted delivery of small molecule cancer drugs and nucleic acids.[1] Additionally, nanoparticles are critical components of a new generation of "multifunctional therapeutics" that can both deliver therapeutics and be imaged to verify effective delivery.[2]

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1 *See* Mark Davis, *Nanoparticles for Systemic Medicines and Imaging Agents*, 3 NANOTECHNOLOGY L. & BUS. 255 (2006) (discussing the use of nanoparticles for treating cancer).

2 *See* Drew Harris et al., *Strategies for Resolving Patent Disputes over Nanoparticle Drug Delivery Systems*, 1 NANOTECHNOLOGY L. & BUS. 372, 374 (2004) (discussing advantages of nanoparticle drug delivery systems).

In addition to their use in new drugs, nanomaterials are also now being investigated for use in new medical devices. Medical diagnostics and implantable devices such as stents and catheters represent a large and critical market in the health care industry. New nanotech-enabled medical devices aim to provide convenient real-time diagnosis of disease that can be done at a clinic rather than at a laboratory, as well as implantable devices that cause less irritation and have improved functionality.

In this article, we provide a snapshot of the market for "point of care" diagnostics and medical implants, and profile some of the companies incorporating nanomaterials in such devices.

II. NANOMATERIALS IN MEDICAL DIAGNOSTICS

A. Market Opportunity for Nanomaterials in Diagnostics

The existing health care system is focused on treating disease rather than preventing disease. Patients are generally not tested until physiological symptoms are present and they meet with their physicians. When samples of body fluid or tissue are taken and sent to laboratories for analysis, the results often take several days and can be inconclusive if the disease is at an early stage. Consequently, many diseases are not diagnosed until long after taking root in the body.

In the coming years, nanotechnology will enable a shift to preventive medicine and the use of "point of care" diagnostics to quickly identify diseases. In contrasts to the laboratory analysis, "point of care" testing is performed closed to the patient, at the time that care is required. Just as kits are available today for women to obtain instant information about pregnancy, portable diagnostic kits will become available to test whether individuals are genetically predisposed to a specific disease, or have the earliest indications of a disease. Long before any physiological symptoms of the disease are present, a doctor (or even a patient in the comfort of her own home) will be able to take a sample of blood or saliva and insert the sample into a small chip. Nanoscale sensors in the chip will detect whether there are particular molecules associated with certain diseases, and the device will quickly provide feedback to the doctor or patient.

"Point of care" diagnostics present a significant market opportunity for companies that can move disease detection out of complex laboratories and into clinics, pharmacies, workplaces, and nursing homes. The global "point of care" testing market is currently estimated to be worth $11.3 billion in 2007, and is growing at 11% a year.[3] Diagnostic testing accounts for only 1-2% of government healthcare expenditures worldwide, yet influences between 60-70% of healthcare decisions.[4] Many companies are now focusing on making diagnostics smaller, simpler, and more widely available in the many places patients receive treatment.

B. Technologies, Products & Companies

A variety of corporate and academic research groups are developing "point of care" diagnostic devices incorporating nanomaterials. Their products are intended to quickly detect whether particular genetic variations, proteins, gas molecules or viruses are present in a sample. In this section, we provide a snapshot of the diagnostic technologies and products being developed at several companies.

1. Nanosphere

Nanosphere is commercializing a molecular diagnostics platform using an optical detection system. The technology platform is based on functionalized gold nanoparticles. The particles are attached to

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[3] Espicom Healthcare Intelligence, *Global Market for Point of Care Diagnostics* (Dec. 7, 2007), *at* http://www.marketresearch.com/product/display.asp?productid=1635947&xs=r&SID=90374973-403569516-493811793&curr=USD&kw=& (available for purchase).

[4] *Id.*

oligonucleotides (DNA or RNA) or antibodies that bind to nucleic acid or protein targets. When there are binding events, the optical properties of the gold nanoparticles change and can be detected.

Nanosphere markets its Verigene System—illustrated in Figure 1—which is comprised of two laboratory instruments (the Verigene Reader and the Verigene Processor) and test cartridges.[5] The primary benefit of the system over existing testing platforms is that the system is simple and accessible. Hospital laboratories can rapidly perform sensitive and accurate tests without substantial technical and operational expertise.

FIGURE 1: NANOSPHERE VERIGENE SYSTEM BASED ON GOLD NANOPARTICLES

Courtesy of Nanosphere

Nanosphere has focused its initial products on genetic and pharmacogenetic tests. Genetic tests identify DNA sequence variations that shed light on whether an individual is at risk for having an inherited genetic disorder or is at risk for passing on a disorder to offspring. Pharmacogenetic tests identify genetic variations within individuals that increase the likelihood that an individual will respond in a certain way to a particular medication.

The company already has Food & Drug Administration approval for three tests for the detection and genotyping of single point mutations in patients with suspected thrombophilia. Nanosphere also has clearance for a test to determine whether patients are genetically predisposed to experience undesirable side effects of Warfarin, the most commonly prescribed treatment for thromboembolic therapy. Nanosphere recently completed an initial public offering and is developing a variety of additional genetic and pharmacogenetic tests to be used in conjunction with its instruments.

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5 Nanosphere, Products, http://www.nanosphere.us/Products_4389.aspx (last visited Dec. 26, 2007).

2. Nanomix

While Nanosphere relies on the optical properties of the nanoparticles to detect targets present in samples provided by patients, Nanomix relies on the electrical properties of nanomaterials to detect target molecules in gas or fluid. The Nanomix technology platform is based on a random network of carbon nanotubes. The nanotubes are functionalized; when genes, proteins, or gas molecules bind to the functional groups, the electrical properties of the nanotubes are altered and detected.[6]

Nanomix currently offers for sale a hydrogen sensor and has a carbon dioxide sensor in the final stages of development. The company also has a biosensor program aimed at detecting genetic variations, proteins and glucose. Similar to the Nanosphere system, the Nanomix platform is intended to offer a cheaper, quicker and less complex approach to early detection of disease.

The company is primarily focused on low-cost asthma sensors.[7] Nitric oxide tests are generally used to diagnose and gauge the severity of asthma, but existing techniques require large, expensive machines that are only available in medical offices. The Nanomix product would be a hand-held device that patients breathe into and obtain an electronic readout of nitric oxide levels. High levels of nitric oxide may signal the likelihood of an asthma attack in two to three weeks; enabling patients to seek preventive treatment.

3. Alpha Szensor

Alpha Szensor was recently formed to commercialize medical sensors using carbon nanotube networks. The company, located in Woburn, Massachusetts, has licensed Nantero Inc.'s intellectual property for solution coating of random networks of carbon nanotubes. While little is known about the company at this point in time, the company has expressed an aggressive timeline for introducing its first products. Alpha Szensor expects to have its first product for convenient low-cost detection of disease on the market in a very short time frame, and aims for eventually detecting biomarkers for everything from HIV and cancer to heart disease.[8]

4. Other Technologies Under Development

A variety of university research groups are developing different types of nanosensors that can be used in medical diagnostics. For example, some researchers are exploring nanoscale mechanical sensors.[9] Lithography tools are used to etch silicon cantilevers that oscillate, and the cantilevers are functionalized with the appropriate capture molecules. Binding events are measured by a change in the resonant frequency of the cantilevers. Unlike optical and electrical detection systems, nanomechanical sensors may even be able to determine the binding force or mass of the substance being analyzed. Researchers at Northwestern University have developed silver "nanoprisms" that exhibit usual optical properties and could be used to construct multicolor diagnostic labels.[10]

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6 Nanomix, Products, http://www.nano.com/Nanomix_Products.html (last visited Dec. 26, 2007).

7 Press Release, Univ. of Pittsburg, People with Asthma Could Breathe Easier Anywhere with Nano Sensor that Could Indicate Oncoming Attacks and Help Minor Symptoms (Aug. 22, 2007), *at* http://mac10.umc.pitt.edu/m/FMPro?-db=ma&-lay=a&-format=d.html&id=2995&-Find (last visited Dec. 26, 2007); *see also New Gadget Could Prevent Asthma Attack*, RT MAGAZINE (2007), *at* http://www.rtmagazine.com/news/2007-09-05_02.asp (last visited Dec. 27, 2007).

8 Paula Doe, *Early Electronics Applications of Carbon Nanotubes*, SEMICONDUCTOR INT'L (Sept. 1, 2007), *at* http://www.semiconductor.net/article/CA6471333.html (last visited Dec. 37, 2007).

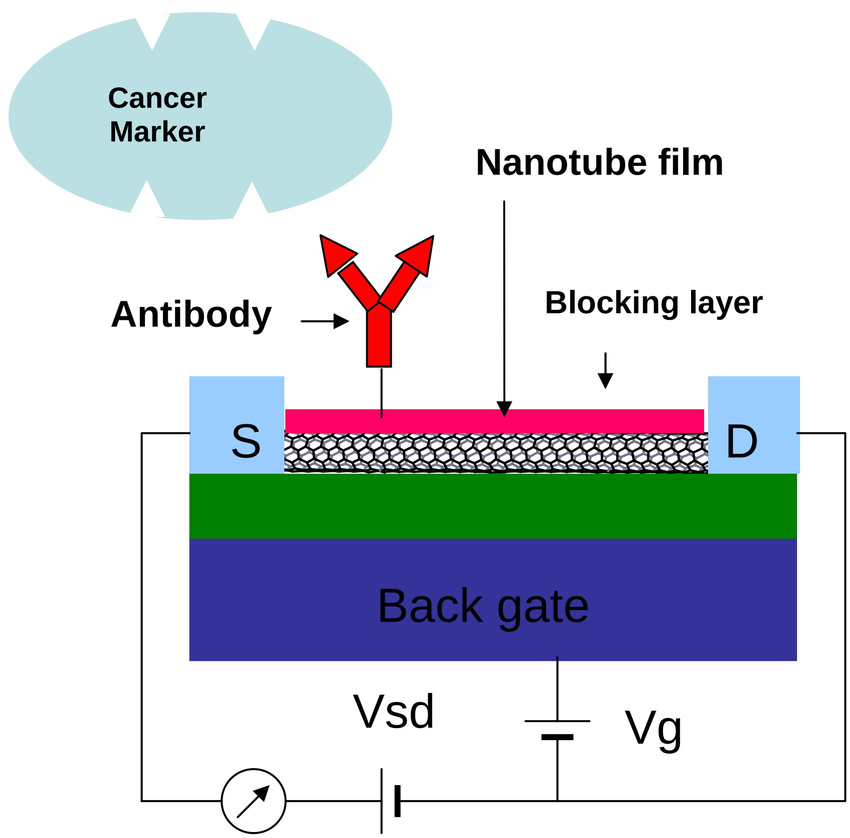
9 *See, e.g.,* Amit K. Gupta et al., *Anomalous Resonance for Nanomechanical Biosensors*, 103 PROCS. OF NAT'L ACAD. OF SCIENCES., U.S.A. 13362 (Sept. 5, 2006), *available at* http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1569169 (last visited Dec. 27, 2006).

10 Rongchao Jin, *Photoinduced Conversion of Silver Nanospheres to Nanoprisms*, 294 SCIENCE 1901 (2001).

Other research groups are exploring the use of silicon nanowires or thin films of silicon on insulator ("SOI") for electrical detection systems.[11] Researchers at UCLA are developing carbon nanotube transistors for electrical detection of biomolecules, such as cancer markers.[12] Figure 2 provides an illustration of how a carbon nanotube biosensor works. Antigens that are known cancer markers bond with antibodies to create a change of the current between the Source and Drain between the carbon nanotubes. Transistors, resistors, and capacitors are used in the circuit for detection mechanisms. A blocking lawyer is used to prevent non-specific bindings from interfering.

Electrical detection systems such as the one illustrated below, although still in early development stages, are gradually emerging as effective alternatives to optical detection methods.

FIGURE 2: ILLUSTRATION OF A CARBON NANOTUBE BIOSENSOR



Courtesy of George Grüner, UCLA

[11] Petra A. Neff, et al., *Label-Free Electrical Detection of Trypsin Activity by a Silicon-on-Insulator Based Thin Film Resistor*, 8 CHEMPHYSCHEM 14:2133-2137 (2007), *available at http://www.e22.physik.tu-*muenchen.de/bausch/pdf/ChemPhysChem_Neff_Label-Free%20Eletrical.pdf (last visited Dec. 26, 2007).

[12] *See* George Grüner, *Carbon Nanotube Transistors for Biosensing Applications*, ANAL. BIOANAL. CHEM. 384: 322-335 (2006)

III. NANOMATERIALS IN IMPLANTABLE MEDICAL DEVICES

A. Market Opportunity

The market for medical implant devices in the U.S. alone is approximately $27 billion annually, and it is expected to increase by about 9% annually for the next several years.[13] There are a variety of unmet needs in the medical device industry that can potentially be addressed by engineered nanomaterials. Medical devices such as catheters, stents, and orthopedic implants are often infected with opportunistic bacteria and other infectious micro-organisms.[14] Such infections can result in serious illness and require removal of the devices. More than half of all nosocomial infections are caused by implanted medical devices.

Additionally, reconstructive bone surgeries, such as hip replacements, use titanium implants. In many cases, the muscle tissue does not adhere well to titanium's smooth surface, causing the implants to fail after a period of time.[15] Another problem associated with stents is that they can become re-clogged with fat after being implanted.[16] Drug-eluting stents attempt to address this problem by slowly releasing chemicals through a polymer coating. Because the polymers are prone to biodegradation, however, they may not function over long periods of time. Nanostructured materials offer the opportunity to enhance the surface areas of medical devices to address these problems.

B. Technologies, Products & Companies

Medical device manufacturers are increasingly looking to nanomaterials to improve the functionality and reliability of their products. In this section, we provide a snapshot of several technologies and products already being developed and commercialized.

1. AcryMed

AcryMed uses silver nanoparticles to prevent formation of bacteria-protecting biofilms on the surface of medical devices.[17] Silver has unique antimicrobial properties, and silver nanoparticles can be embedded in the surface of an implant without altering the functionality of the implant. The company's business model is to license its SilvaGard technology to customers that manufacture the implants, and the customers must seek regulatory approval for the use of the technology in their products. AcryMed has licensed the technology to several device makers, and the FDA has approved at least one catheter product incorporating SilvaGard.[18] As this article was going to press, AcryMed announced that it had entered a binding letter of intent to be acquired by I-Flow, a medical device manufacturer seeking to integrate SilvaGard into its products.[19]

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13 Freedonia Group, *Implantable Medical Devices to 2011* (Oct. 2007), http://www.freedoniagroup.com/DocumentDetails.aspx?ReferrerId=FG-01&studyid=2255 (available for purchase).

14 Nanosys, Inc., *Medical Device Applications of Nanostructured Surfaces* (WO/2005/084582), *at* http://www.wipo.int/pctdb/en/wo.jsp?WO=2005/084582 (last visited Dec. 27, 2007)

15 Press Release, Univ. of Arkansas, Nanowire Coating for Bone Implants, Stents (Aug. 20, 2007), *at* http://dailyheadlines.uark.edu/11205.htm (last visited Dec. 26, 2007).

16 *Id*.

17 *See* Acrymed, http://www.acrymed.com (last visited Dec. 26, 2007).

18 *Getting FDA's OK To Go Inside The Body*, SMALL TIMES, Feb. 13, 2006, *at* http://www.smalltimes.com/Articles/Article_Display.cfm?ARTICLE_ID=270481&p=109 (last visited Dec. 26, 2007).

19 Press Release, I-Flow, I-Flow Announces Agreement to Acquire AcryMed, Inc. (Dec. 13, 2007), *at* http://biz.yahoo.com/bw/071213/20071213006186.html?.v=1 (last visited Dec. 26, 2007).

2. Altair Nanotechnologies

Altair Nanotechnologies is working with the National Research Council of Canada to develop a new coating for orthopedic implants using Altair's nanoscale titanium dioxide materials. In a recently published study,[20] the coating exhibited mechanical properties such as hardness and bond strength superior to those of existing implant coatings such as hydroxyapatite. Additionally, the coating demonstrated high biocompatibility with bone cells that could result in longer lifetime of the implant. Altair is also seeking to sell nanoscale zirconium oxide particles for dental applications, including fillings and prosthetic devices.

3. Nanotech Catheter Solutions

In 2007, Nanotech Catheter Solutions ("NCS") licensed intellectual property from Unidym to develop catheters and stents using carbon nanotubes ("CNTs").[21] Although it is unclear what specific products NCS intends to develop, there are several promising ways to leverage the unique properties of nanotubes in medical devices. For example, CNTs can be blended with a matrix resin to generate a composite material with antithrombotic characteristics and biocompatibility.[22] Additionally, the composite material can enhance the mechanical strength of an implant while providing additional flexibility.[23] Networks or arrays of nanotubes might also be used to replace polymer coated stents to provide a non-biodegradable mechanism for gradual release of a drug.[24] Finally, nanotubes might serve as both the passive (electrodes) and active (transistors) components of advanced medical devices.[25]

4. Nanocopeia

Nanocopeia, Inc. is another company incorporating nanomaterials into improve medical devices. Nanocopeia is commercializing its process for creating advanced coatings and drug formulations in what it describes as the converging field of devices, drugs, and delivery.[26] The company has developed an ElectroNanospray technology that transforms drugs and polymers into different nanoscale material states, including coatings, liquids, encapsulated particles, and powders. Nanocopeia uses ElectroNanospray to apply nanoformulated drugs onto the surfaces of medical devices in a single step process that is capable of generating both single-phase and multi-phase coatings with a variety of surface characteristics.[27]

Nanocopeia also aims to improve pharmaceuticals by using its ElectroNanospray technology to produce ultra-pure nanoparticles in the 2-200 nm range. Nanocopeia reports that its process overcomes the inherent limitations of producing nanoparticles using wet milling and supercritical fluid.[28]

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[20] Rogerio S. Lima et al., *Biocompatible Nanostructured High Velocity Oxy-Fuel (HVOF) Sprayed Titania Coating: Deposition, Characterization, and Mechanical Properties*, 15 J. SPRAY TECH. 623 (2006).

[21] *NCS Licenses Unidym's Carbon Nanotubes for Cardiovascular Disease Treatment*, SMALL TIMES (Aug. 8, 2007), *at* http://www.smalltimes.com/articles/article_display.cfm?Section=ARCHI&C=Bio&ARTICLE_ID =302795&p=109 (last visited Dec. 26, 2007).

[22] Morinobu Endo et al., *Medical Instrument,* U.S. Patent Application 11/667,172 (Dec. 20, 2007).

[23] *Id.*

[24] Boston Scientific SciMed, Inc., *Method of Incorporating Carbon Nanotubes in a Medical Appliance, A Carbon Nanotube Medical Appliance, and a Medical Appliance Coated Using a Carbon Nanotube Technology,* PCT (WO/2006/052838), *at* http://www.wipo.int/pctdb/en/wo.jsp?wo=2006052538 (last visited Dec. 26, 2007)

[25] Medtronic, Inc., *Medical Devices Incorporating Carbon Nanotube Material and Methods of Fabricating Same* (WO/2004/052447), *at* http://www.wipo.int/pctdb/en/wo.jsp?WO=2004%2F052447&IA=WO2004%2F052447&DISPLAY=STATUS (last visited Dec. 26, 2007).

[26] Nanocopeia, Inc., http://www.nanocopeia.com (last visited Dec. 26, 2007).

[27] Nanocopiea, Inc. Medical Device Coatings, http://www.nanocopeia.com/med_device_coat.html (last visited Dec. 26, 2007).

[28] Nanocopeia, Inc., Pharmaceutical Applications, http://www.nanocopeia.com/pharm_app.html (last visited Dec. 26, 2007).

5. Other Technologies Under Development

There are a variety of university research groups exploring the use of nanoscale materials for medical implants.[29] For example, University of Arkansas researchers recently reported the use of titanium oxide-based ceramic nanowires to coat the surface of a titanium medical device.[30] After implanting a nanowire-coated joint in small animals for four weeks, the researchers found that the tissue had formed a strong bond to the joint.

With a view toward more long-term applications, University of Texas researchers have demonstrated that networks of nanotubes can transmit electrical signals to neurons, opening up the possibility of using nanotubes as an electrical interface between neural prosthetics and the body.[31] And a group at Brown University has shown that nanotubes combined with adult stem cells can effectively deliver the cells to damaged regions of animal brains and facilitate differentiation of the cells into neurons.[32]

IV. CONCLUSION

A snapshot of companies working with nanomaterials in medical devices reveals a wide range of nanomaterials being considered. Gold and silver nanoparticles, nanotube arrays, nanowires, and even nanoscale mechanical sensors are being incorporated into point of care diagnostics and implantable medical devices. The sizeable market opportunities in medical diagnostics and other devices will likely encourage more companies to experiment with incorporating nanomaterials in novel medical devices.

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29 For a good review article on research involving nanomaterials in medical devices, see Ganesan Balasundaram & Thomas J. Webster, *A Perspective On Nanophase Materials for Orthopedic Implant Applications*, 16 J. MATER. CHEM. 3737 (2006); Huinan Liu & Thomas Jay Webster, *Nanomedicine for Implants: A Review of Studies and Necessary Experimental Tools*, 28 BIOMATERIALS 354 (2007).

30 Wenjun Dong, Tierui Zhang, Lisa Cooney, Hong Wang, Yanbin Li, Andrew Cogbill, Vijay Varadan, and Z. Ryan Tian of the University of Arkansas; Ying-Bing Jiang of the University of New Mexico; and Joshua Epstein of the University of Arkansas for Medical Sciences are reporting their findings regarding nanowires in medical devices in an upcoming issue of the journal *Chemistry of Materials*.

31 Prachi Patel-Predd, *Nanotubes Trigger Neurons: Using Carbon Nanotubes or Small Electrodes Might One Day Lead to Safe and Effective Retinal Implants*, M.I.T. TECH. REV., Aug. 31, 2006, *available at* http://www.technologyreview.com/Nanotech/17389/ (last visited Dec. 26, 2007).

32 Jennifer Chu, *Nanotube Scaffolds for Neural Implants: Tiny Carbon Fibers Are Helping Stem Cells to Grow in Stroke-Damaged Brains*, M.I.T. TECH. REV., Sept. 22, 2006, *at* http://www.technologyreview.com/read_article.aspx?id=17525&ch=biotech (last visited Dec. 26, 2007).