SIS ALMANAC ONLINE:

NANOTECHNOLOGY

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INTRODUCTION:

Nanotechnology involves the ability to engineer, control, and exploit the unique chemical, physical, and electrical properties that emerge from man-made particles having at least one dimension of 100 nanometers or less. By comparison, DNA molecules are 2.5 nm wide; a typical bacterium (i.e. *E. coli*) is 1,000 to 2,000 nm; a virus (i.e. common cold) is 20 nm; and the width of the dot above this letter *i* is approximately 1 million nm. Industries and the scientific community are currently investigating new opportunities in nanotechnology for medical research, diagnosis and therapy. Research into the molecular, atomic and subatomic properties of materials, structures, systems and devices are underway.

Nanotechnology is considered an interdisciplinary science rather than a stand-alone discipline. The potential breakthroughs in this field will demand attention from multiple specialists and research teams working as one, from biomedical and materials scientists, mechanical and electronic engineers, to biologists, physicists and chemists.

Last February 28, 2003, the National Heart, Lung, and Blood Institute (NHBLI) formed a working group comprised of engineers, chemists, biologists, and physicians with an interest in applying nanotechnology and nanoscience to challenges in cardiac, pulmonary, hematologic and sleep medicine.

Existent clinical care for some life-threatening disease is wanting. Further research in nanotechnology will be the key to discovering long sought after remedies. The following disease states that will potentially benefit in the next decade or so are identified.

1. Diagnosis and treatment of vulnerable plaque.

2. In the domain of tissue repair, engineering and remodeling of synthetic biomaterial for replacement and repair of blood vessels and heart and lung tissue.

3. Diagnosis, treatment and prevention of lung inflammatory diseases such as COPD.

4. Thrombotic or hemorrhagic events such as stroke.

5. Sleep apnea with their related cardiovascular consequences such as arrhythmias, myocardial infarction and hypertension.

The NHBLI working group emphasized high-priority recommendations for encouraging nanotechnology research. Among them are:

1. Establish multidisciplinary research centers to focus on developing and applying nanotechnology to heart, lung, blood, and sleep research and medicine; distribute technology, materials, and resources; and mentor a new generation of young investigators.

2. Offer strong support to individual scientists and investigators in conducting groundbreaking nanotechnology research to answer biological and clinical problems.

3. Foster exploratory, pilot programs and developmental research to attract new investigators outside the medical field and stimulate creative, high-impact, innovative research that will yield clinical applications.

4. Encourage small businesses to engage in the development of nanotechnology applications.

Specific research areas were identified as showing tremendous promise with respect to heart, lung, blood and sleep medicine:

<u>Biosensors and Diagnostics:</u>

In the present setting, health care practitioners have relied mostly on *in vitro* diagnostic tests. Because the tests have to be done in an outside clinical laboratory, the reporting of results may take considerable time. In some instances, the time lag may be too late. Consider the boon to medical specialists if tests can be done *in vivo* and detected health problems are reported in real time.

Diagnosis and disease management will be prompt and efficient. Sensors can be miniaturized to nanoscale proportions, injected into the body and once in place, can serve as in vivo diagnostic laboratories. These nanosensors can be programmed to detect even the slightest yet potentially damaging biochemical and physiological changes i.e. cardiac markers for heart attack can be instantly recognized and swift action can be initiated.

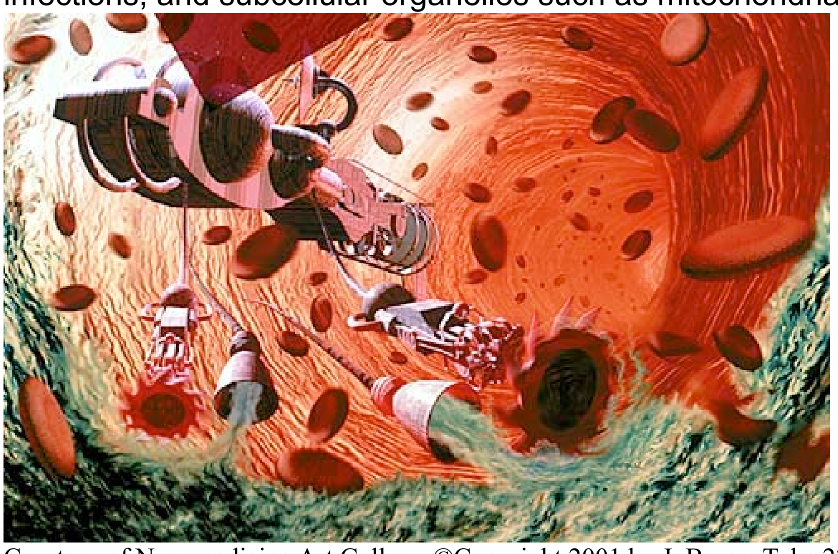
Several nanomaterials are currently being studied for this application. Nanotubes or nanowires are coated with specific capture molecules to detect minute quantities of biological and chemical material. Nanocantilevers can measure the content of DNA segments and can also be used to simultaneously monitor multiple serum protein markers. Nanopores can identify single-base DNA mismatches and defects. They can also be used as parts of sensors for cell signaling molecules. Quantum dots are highly fluorescent semiconductor nanocrystals that are used for highly sensitive screening of specific protein and DNA targets.

Drug Delivery and Therapeutics:

Medications taken systemically can have numerous side effects, some of which can be highly toxic to normal tissues and organs. Factors such as bioavailability, toxicity, drug metabolism and excretion can cause potential problems. What if drugs can be packaged in a vehicle that can be programmed to be organ- or tissue- specific? Drug treatments will be considered more efficient and effective.

Research is currently underway for use of highly branched polymers such as dendrimers and nanospheres for this exact purpose. These drug carriers can improve bioavailability and enable continued release. They can protect the drug from metabolic and excretory processes. Also, the carriers can be programmed to release drugs in response to internal changes such as pH or even external signals e.g., ultrasound, near-infrared light, magnetic fields, or radiofrequency pulses.

Smooth muscle cells, cancer cells, inflammatory mediators, proteins produced in viral infections, and subcellular organelles such as mitochondria can act as potential targets.



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Imaging

Imaging modalities such as computerized tomography, magnetic resonance imaging, and ultrasound provides an accurate picture of anatomical changes. However, the images are limited to the macroscopic level. It may be possible to use the application to visualize microscopic as well as molecular scales. Disease processes undergo various pathologic pathways and molecular imaging can serve as a tool to visualize them. Nanoparticles, nanoprobes and quantum dots can act as homing molecules, when combined with current imaging modalities can assist physicians in early diagnosis, thereby improving clinical outcomes. Cellular components such as smooth muscle cells, cells undergoing molecular destruction and structural complexes can be accurately detected and visualized. The tracking of lymphocyte movement and infectious particles through the circulatory system can be possible. Deep tissue penetration and visualization is made possible. Nanotechnology provides medical imaging with unlimited potential.

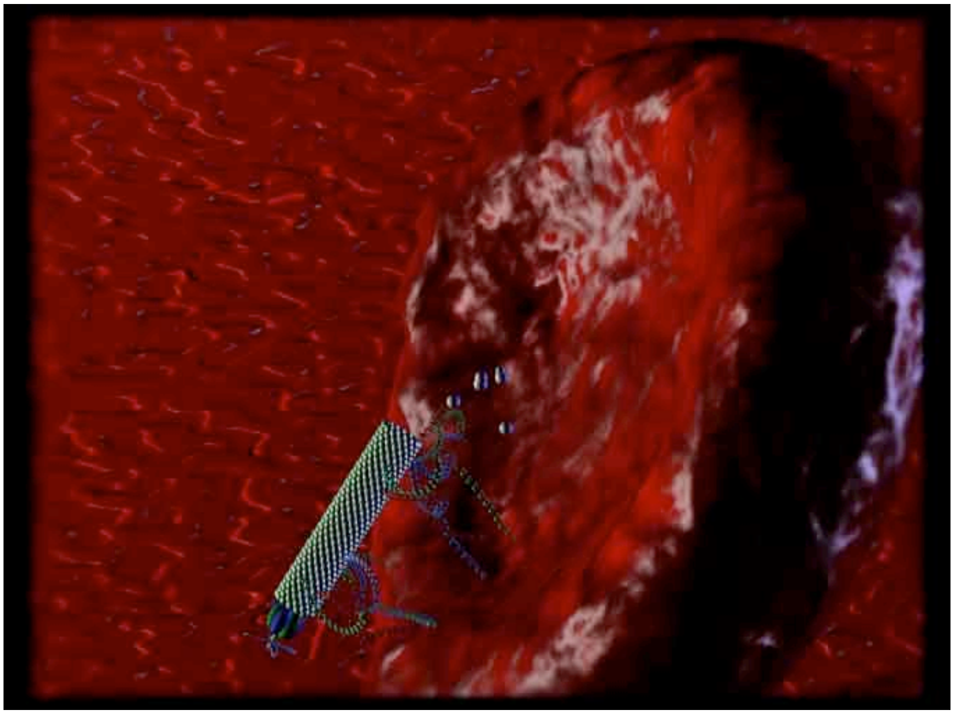
Tissue Engineering and Biomaterials

Synthetic materials are currently being used in the repair of blood vessels, heart valves and other organs. Unfortunately, high potential for rejection, material design failure and device corrosion are prevalent. Nanotechnology is being seen as providing possible alternatives.

Nanostructured biosynthetic materials are being studied for their potential to serve as scaffolds or cellular foundations for the regeneration of injured membranes and tissues. Cells and tissues grow under the influence of biochemical growth factors. Nanospheres can channel these chemicals and enzymes into a specific area to direct cell migration and tissue remodeling.

Researchers are currently looking at nanotechnology applications for use in self-expanding polymer stents and polyurethane heart valve cell delivery systems. The biosynthetic structures and materials may discourage tissue rejection and limit device corrosion. Nanostructures and designs in next generation stents can be combined with miniaturized electromechanical systems that will aid interventional cardiologists. These improved devices can be programmed like guided missiles to reach their targets without manual manipulation. This in effect will improve efficacy and safety of the device.

Studies are also being done to develop new methods in producing functional cardiac tissues and improved vascular grafts, using stem cells and nanobiomaterials. The incidence of graph versus host rejection can be a thing of the past.



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Dr. Constantinos Mavroidis, Bio-Nano Project.

CONCLUSION:

Nanotechnology provides novel ways in detecting, diagnosing and treating a multitude of diseases including cardiovascular disease and cancer at its earliest stages and with minimal side effects. With this in mind, start-up companies, academic research labs and pharmaceutical giants are directing their efforts to maximize nanotechnology's promised potential. Even sectors of the government have joined in. The NIH has pushed for reforms, guidelines and initiatives in establishing nanotechnology "centers of excellence". The FDA is aggressively preparing itself to approve new nanodevices with therapeutic applications.

Predictions abound that in the coming decades, nanotechnology will practically change every sector. In the U.S., an estimate $3 billion a year has been spent on nanotechnology alone, however, nanotechnology products are expected to escalate to $1 trillion in trade by 2015. The U.S. House of Representatives passed a legislative bill last Nov. 20, 2003 called the 21st Century Nanotechnology Research and Development Act (S. 189). S. 189 provides for the creation of a National Nanotechnology Coordinating Office, research centers, education and training efforts, and research into the societal and ethical consequences of nanotechnology. It also supports efforts to encourage technology transfer and includes a series of coordination offices, advisory committees and regular program reviews. The bill allocates $ 3.7 billion to be spread over four fiscal years, from 2005-08.

If these concepts can be translated to practical applications, there will be a brand new world where nagging medical and biological questions are easily answered, chronic diseases and life-threatening conditions finally cured, and people will be experiencing longer and more productive lives than ever before in the history of mankind.

REFERENCES:

1. NIH Guide: "NHBLI Programs of Excellence in Nanotechnology". Available online at http://grants1.nih.gov/grants/guide/rfa-files/RFA-HL-04-020.html.
2. "Leaders in Coronary Stent Technology To Speak About Revolutionary New Designs at CIMIT Forum at MGH." Available online at www.heart1.com/news/newsfeed.cfm/2275/1.
3. **"**House Passes $3.7B Nanotech Bill". Available online at www.nanotech.uiowa.edu/bill.htm
4. **"**May 2004 Nanotechnology Conference to showcase cutting edge products, resources and programs". Available online at http://www.nanotechwire.com/news.asp?nid=869
5. Nanotechnology: looking as we leap. Hood, E. Environ Health Perspect. 2004 Sep; 112 (13): A740-9.
6. Recommendations of the National Heart, Lung, and Blood Institute Nanotechnology Working Group. Buxton DB, Lee SC, Wickline SA, Ferrari M for the Working Group Members. *Circulation.* 2003; 108:2737.
7. Constantinos Mavroidis, Martin L. Yarmush, Atul Dubey, Angela Thornton,Kevin Nikitczuk, Silvina Tomassone, Fotios Papadimitrakopoulos, Bernie Yurke, "Protein based nano-machines for space applications", *Report to the NASA Institute for Advanced Concepts*, December 2002. http://www.bionano.neu.edu/Mavroidis_Final_Report.pdf
8. Illustrations found at Nanomedicine Art Gallery: http://www.foresight.org/Nanomedicine/Gallery/index.html