Testimony
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Nanoscience and Nanotechnology Activities at the National Institutes of Health

Statement of

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Executive Summary

Each of the twenty-seven Institutes and Centers (ICs) at the National Institutes of Health (NIH) funds nanotechnology research to improve the health of Americans. Nanotechnology will radically change the study of basic biological mechanisms and significantly improve the prevention, detection, diagnosis and treatment of diseases. One key to this potential is that nanotechnology operates at the same scale as biological processes, offering a unique vantage point from which to view and manipulate fundamental biological pathways and processes.

The most immediate medical benefits of nanotechnology arise because of novel properties of materials. For example, proof of principle has been achieved with nanoparticles that can be targeted to cancer. These nanoparticles can bind exclusively to the cancer cells in a targeted region to deliver both an imaging agent, allowing the physician to observe the cancer, and a therapeutic agent. Further, the nanoparticle may be triggered to disintegrate into harmless chemical subunits that no longer have the characteristics of the intact nanoparticle for clearance from the body.

Support for biomedical nanotechnology research is provided through several initiatives that cut across the missions of the ICs, addressing NIH-wide goals, including the NIH Bioengineering Consortium and the NIH Nanomedicine Roadmap initiative. Additionally, several of the Institutes have established nanotechnology programs focused on their own unique goals, all of which contribute to the development of approaches that eventually will reach all realms of medicine.

Testimony

I am Jeffery Schloss, a program director in the Division of Extramural Research at the National Human Genome Research Institute, a component of the National Institutes of Health (NIH) of the Department of Health and Human Services, with responsibility for DNA sequencing technology development. I have served as an NIH representative to the National Nanotechnology Initiative (NNI) even before it became a formal Federal initiative. And I am co-chair of the NIH Nanomedicine Roadmap Initiative, which I shall discuss below. I appreciate the opportunity to provide an overview of the Nanomedicine initiative and nanoscience and nanotechnology research at the NIH.

Each of the twenty-seven Institutes and Centers (ICs) at NIH funds nanotechnology research to improve the quality of life for countless Americans.

Scientific Opportunities

Nanotechnology has the potential to radically change the study of basic biological mechanisms, as well as to significantly improve the prevention, detection, diagnosis, and treatment of diseases. One key to this potential is that nanotechnology operates at the same scale as biological processes, offering an entirely unique vantage point from which to view and manipulate fundamental biological pathways and processes. Most other technologies require the study of large numbers of molecules purified away from the cells and tissues in which they usually function; nanotechnology offers ways to study how individual molecules work inside of cells.

The most immediate near-term benefits envisioned for the use of nanotechnology in medicine arise because of novel properties of materials, and the ability to prepare and control materials properties with greater precision and complexity than can be achieved by other methods.

For example, early-stage proof-of-principle studies have been accomplished for most of the elements of a system, made of chemical subunits known as dendrimers, in which nanoparticles can be targeted to cancer cells wherever they may be in the body, bind exclusively to the cancer cells in that region, and deliver both an imaging agent to allow the physician to observe the cancer location, and a therapeutic agent to reduce or destroy the cancer. Further, the particle can be triggered to disintegrate upon release of the therapeutic agent, into harmless chemical subunits that no longer have the characteristics of the nanoparticle and are readily cleared from the body. These device concepts can also be applied to other conditions, such as acute vascular injury and inflammation, and can also be achieved by building nanoparticles using materials other than dendrimers. Such particles can also be programmed to sense molecular and physiological signals, and activate the imaging agent, or release the therapeutic agent, only under specified molecular circumstances. These strategies should dramatically reduce side-effects of drugs by delivering them only when and where in the body they are needed. The name “smart” nanoparticle is therefore apt.

Metallic nanoparticles have been used in several ways for experiments on imaging and therapy. Quantum dots (i.e., nanoscale crystalline fluorescent semiconductors) that absorb and emit colors of light that can penetrate body tissues have been used in animal experiments to demonstrate the potential to allow doctors to see, from outside the body, the exact location of certain tumors that occur near the body surface. Even though toxicity was not detected in these studies, the possibility that some of the particles used could be toxic has led to research on the permanence of the coatings and research on particles with the same optical properties but that are composed of non-toxic materials. A second type of metallic nanoparticle can be delivered specifically to tumor locations and heated by the application of colors of light that penetrate the skin, resulting in local heating to destroy tumor cells but not the surrounding healthy cells. Yet other metal particles are already in use to enhance magnetic resonance imaging, providing sharper images than previously possible with other MRI imaging agents.

For tissue repair, several different materials are being tested for their ability to form nanofibers that mimic natural structures that surround cells (extracellular matrix) in the body. Such materials could be injected at sites of injury caused by trauma or syndrome-associated degeneration, to provide both a physical substrate and the molecular signals needed to stimulate and support tissue healing. For example, versions of these materials are being tested to support the growth of bone, muscle, and nervous tissue.

While the examples above describe use of nanomaterials inside the body, nanotechnology is also being used to produce sensors for use in the research or clinical laboratory, or possibly implanted in the body. These sensors have exquisite sensitivity and selectivity. Based on nanomaterials such as carbon nanotubes or silicon nanowires, whose electrical properties change depending on the materials bound to their surface, sensors have been developed that can detect very small amounts of material, such as biosignatures for infection or disease, in complex mixtures such as blood or saliva. These electrically-activated sensors could be deployed in simple, cost-effective devices that could record several different measurements at once from a very small patient sample.

The scientific research is thus proceeding at a good pace. But there is a difference between a successful experiment and a robust device or medical treatment that functions in real-life situations, can pass all regulatory requirements, and be cost-effectively manufactured, commercialized and adopted. The next few years will be very important in establishing the reality of the early vision.

NIH Support for Nanotechnology Research

The opportunities transcend the mission of any single NIH IC. Therefore, trans-NIH grant solicitations were developed by the NIH Bioengineering Consortium (BECON; www.becon.nih.gov), in which all of the ICs participate, and have resulted in funding of dozens of research grants to colleges, universities, research institutions, and small businesses. Since 1999, BECON initiatives have been reaching out to teams of physical scientists, biologists, and clinicians to apply state-of-the-art nanotechnologies that are emerging from research in non-biological disciplines, to solving important problems in biology and medicine, ranging from understanding the mechanisms of disease, to developing novel diagnostic and therapeutic methods. To stimulate those collaborations and explore opportunities, BECON hosted a nanotechnology symposium in 2000 that was attended by over 600 scientists and engineers, and NIH co-hosted with the National Science Foundation (NSF) and other agencies participating in the National Nanotechnology initiative, a workshop on Nanobiotechnology in 2003.

In addition to support through BECON initiatives, much of the support for nanoscience and nanotechnology research is provided by the NIH ICs in response to various other initiatives that are focused on solving specific biomedical problems, and to investigator-initiated grant applications. In many such cases, the programmatic rationale is to develop understanding of biomedical phenomena or the causes of disease or to develop specific diagnostics or therapeutics, and the particular scientific approach chosen by the investigators to achieve the goals incorporates nanotechnology.

Recently, several institutes have developed explicit nanotechnology programs that are central to achieving their missions.

NHLBI Programs of Excellence in Nanotechnology

The National Heart, Lung, and Blood Institute has initiated Programs of Excellence in Nanotechnology (PENs). Its goal is to create multidisciplinary teams capable of developing and applying nanotechnology and nanoscience solutions to the diagnosis and treatment of cardiovascular, pulmonary, hematopoietic, and sleep disorders. To accomplish this goal the centers will conduct research on causes and treatments for these diseases, train investigators to apply nanotechnology to this set of problems, and actively disseminate their results. Four center awards were made beginning in FY 2005, representing a five-year funding commitment of $53 million.

NCI Alliance for Nanotechnology in Cancer

The largest single nanotechnology program at NIH is the National Cancer Institute's (NCI) Alliance for Nanotechnology in Cancer. These activities are integrated with existing NCI programs and resources. The Alliance currently supports eight Centers of Cancer Nanotechnology Excellence (CCNEs) to serve as hubs to develop and apply nanotechnology devices and systems to the diagnosis, prevention, and treatment of cancer. Examples of the goals of the centers include: the development of smart, multifunctional, all-in-one platform capable of targeting tumors and delivering therapeutics; and development and validation of tools for early detection and stratification of cancer through rapid and quantitative measurement of panels of serum- and tissue-based biomarkers.

The Alliance also awarded twelve cancer nanotechnology platform development partnerships. Further, it is supporting the education, training, and career development of graduate, post-doctoral, and mid-career investigators for multi-disciplinary nano-oncology research through fellowship grants and, with NSF, institutionally-based awards. NCI also is engaged in outreach and communication via its publications and website (nano.cancer.gov) about nanotechnology research and development as it relates to cancer and other biomedical applications, including the full spectrum of societal issues attending the development of nanobiotechnology.

Finally, NCI is actively supporting environmental, health, and safety research relevant to the cancer mission, particularly through the Nanotechnology Characterization Laboratory (NCL). The NCL will provide critical infrastructure for studies supporting decision-making about the implications of nanotechnology-based products. It will develop a characterization cascade to characterize nanoparticles' physical attributes, their *in vitro* biological properties, and their *in vivo* compatibility using animal models, from the perspective of intentional exposure (i.e., medical application or delivery). This will enable nanotechnology-based strategies to rapidly and safely transition to clinical applications. The work also will provide a framework for regulatory decisions by the Food and Drug Administration (FDA) concerning the testing and approval of nanoscale cancer diagnostics, imaging agents, and therapeutics. To achieve these goals, the NCL is conducted in collaboration with FDA and the National Institute of Standards and Technology at the Department of Commerce. Overall, the NCI Alliance for Nanotechnology in Cancer represents a five-year funding commitment of $144 million beginning in FY 2005.

NIEHS National Toxicology Program and Collaboration

The National Toxicology Program (NTP) is a partnership of the National Institute of Environmental Health Sciences (NIEHS) with the National Institute for Occupational Safety and Health (NIOSH) at the Centers for Disease Control and Prevention, and the National Center for Toxicological Research (NCTR) of FDA. NTP's research program to address potential human health hazards from unintentional exposure associated with the manufacture and use of nanoscale materials includes investigation of toxicology of nanoscale materials of current or projected commercial importance. The overall goal is to understand critical physical and chemical properties that affect biocompatibility, so in the future nanomaterials can be designed to minimize adverse health and safety issues. Most of the funding for this NTP activity is contributed by NIEHS. The NCTR contributes the use of state-of-the-art capabilities of its NTP Phototoxicology Center. Studies are currently underway examining the absorption, biological fate, and potential toxicity of quantum dots; metal oxides used in sunscreens; and selected carbon-based materials (fullerenes, carbon nanotubes) following application to the skin, or exposure by inhalation or oral ingestion. The NTP and the NCI NCL programs are coordinated to ensure the most efficient development of nanoscale cancer therapeutics that are both safe and effective.

Additionally, NIEHS is participating with the Environmental Protection Agency, NIOSH and NSF in funding a joint solicitation to investigate environmental and human health effects of manufactured nanomaterials. NIEHS will fund research on the routes of human exposure, toxicology, biotransformation, and bioavailability of nanomaterials. These partner agencies are currently designing the next phase of this solicitation and are in dialogue with the Science Directorate of the European Commission to explore the possibility of a joint US-EC research solicitation.

NIH Nanomedicine Roadmap Initiative

The crosscutting nature of this technology is exemplified by its inclusion in the NIH Roadmap for Biomedical Research, a program that began in 2002 to identify major opportunities and gaps in biomedical research that no single IC at NIH could tackle alone, but that the agency as a whole must address to have the greatest impact on the progress of medical research. The Nanomedicine Roadmap Initiative (nihroadmap.nih.gov/nanomedicine/) is a component of the "New Pathways to Discovery Theme" of the Roadmap (the other themes are "Research Teams of the Future" and "Re-Engineering the Clinical Research Enterprise"). All of the NIH ICs collectively support and are responsible for the implementation of all of the Roadmap initiatives.

The Nanomedicine Initiative is envisioned as a ten-year program whose eventual goal is to manipulate precisely cellular processes by repairing or building new structures in cells, to prevent and treat disease and repair damaged tissue. In the near term, interdisciplinary research teams are assembling to devise new methods to study problems in cell biology and biophysics. Those efforts will enable measurement of a host of parameters we cannot measure inside of cells today. This new information will lead to better prediction of the behavior of subcellular assemblies of molecules, and of cells themselves. In combining the knowledge gained from new insights into how biomolecules work and from building the tools that made those measurements possible, research teams can then design new strategies to build molecular-scale tools for disease or injury intervention. Unlike conventional medicine, the approaches taken here should enable interventions to be made with greater precision, much earlier in the course of disease or tissue degeneration, and at a more fundamental level for repair of tissue damage caused by trauma.

In a sense, the goal of the Nanomedicine Roadmap initiative is to use quantitative approaches to understand, from an engineering perspective, the design of biomolecular structural and functional pathways, and to use that information to design and build functional biocompatible molecular tools to “dial” the body’s systems back into “normal” operating ranges after function has been perturbed by disease. One might think of this in context of the way in which we can design and build a functioning electromechanical system, such as the heating and cooling system in your house. We know how to draw it out on paper – which electrical parts and controls, and motors, and valves and structures are needed – and when we build according to those plans, it actually works. We want to be able to understand biology at the molecular and system level, in the way in which we understand the parts and logic of an engineered system. If we can do that, we should be able to precisely repair or replace parts and keep the system operating normally, at the fundamental level at which the system operates, namely, its molecular systems.

The teams that will carry out this initiative consist of people with deep knowledge of biology and physiology, physics, chemistry, math and computation, engineering, and clinical medicine. Even though the first few years require basic biology research, the choice and design of experimental approaches are directed by the need to solve clinical problems. These are extremely challenging problems, and great breakthroughs are needed if we are to be successful in achieving our goals within the projected timeframe. Therefore, NIH is willing to take risks and is working closely with the funded investigators to use the funds and the intellectual resources of the entire network of investigators to meet those challenges.

Nanotechnology is key to the Nanomedicine Roadmap initiative in several aspects. First and most obvious, nanotechnologies critically enable us to measure things that we have been unable to measure in the past, to “fill in the blanks” in the equations we need to understand and to predict how biomolecules work. Those biomolecules are nanostructures, and if we are to be able to touch and measure them with precision, without destroying them and their ability to operate, we will need to employ biocompatible nanotechnologies. Second, successful creation of measurement tools informs the development of manipulation tools for biomolecular repair of cells or subcellular assemblies. And third, in the process of fulfilling goals that are central to the mission of the NIH, we gain knowledge of the design of biological systems that nature has produced over millions of years. That knowledge of system design can be used by scientists and technologists who are working outside of the biomedical realm, to develop novel strategies to solve their own engineering problems, whether in computers, transportation, energy, or national security. In this way, the Nanomedicine Roadmap initiative will give back in full measure to the physical scientists and engineers who developed the earliest ideas from which the National Nanotechnology Initiative was formulated.

To fulfill these goals, the Nanomedicine initiative is establishing a network of highly interactive centers around the Nation. The first four centers were established in FY 2005 with a $6 million investment. The initial centers are:

- *Center for Protein Folding Machinery,* Wah Chiu, Baylor College of Medicine

- *National Center for the Design of Biomimetic Nanoconductors,* Eric Jakobsson, University of Illinois, Urbana-Champaign
- *Engineering Cellular Control: Synthetic Signaling and Motility Systems*, Wendell Lim, University of California, San Francisco
- *Nanomedicine Center for Mechanical Biology,* Michael Sheetz, Columbia University, New York

While this list shows only the names of the team leaders and their home institutions, the teams include distinguished and experienced investigators, and bright new investigators, at institutions across the Nation and internationally. To exemplify the program, the themes of two centers are briefly described.

The first project is the *Center for Protein Folding Machinery*. Proteins are synthesized in cells as linear structures. These proteins must fold in very precise ways to achieve the correct shape required for their function. While a few proteins can fold by themselves, most require the action of other proteins in cells, called molecular chaperonins. The Center will study the mechanisms by which chaperonins select and fold specific proteins, and will use that information to develop chaperonins that can trap misfolded proteins or prevent folding (and therefore activity) of proteins that should not be present in a particular type of cell. This is important because protein misfolding is implicated in several neurodegenerative diseases, such as Huntington's disease and Alzheimer's disease. Some other diseases involve the accumulation of proteins that are normally not present or are present only at very low levels (e.g., cancer), so the Center will develop specific adapters to control the interaction of the proteins with the folding machinery. Additional goals include designing novel chaperonins that can be used to deliver drugs in the body, or to be used during the processing of protein-based pharmaceuticals, to ensure correct folding and activity.

Another project, the *Engineering Cellular Control* center, will endeavor to develop “smart” cells or cell-like devices that have some of the properties of normal immune cells. They would be relatively simple systems (compared to real cells) that are programmed to detect a lesion (e.g., injury) or threat (e.g., infection or cancer cell), then move to that site in the body and respond precisely with a controlled action such as releasing a therapeutic agent or mediating recruitment of the body’s own immune system.

The focus of each center is distinct and complementary to the others, and their discoveries will apply to many tissues and diseases.

NIH Participation in the National Nanotechnology Initiative

NIH activities in the development of nanotechnology for biology and medicine are coordinated with those of other Federal agencies through its active participation in the NNI. A highlight of that activity is the active participation of NIH staff in the planning and development activities conducted through working groups on issues such as environmental and health implications, public engagement, and global issues.

For example, NIH is participating actively in the Public Engagement working group. This group is developing the first stages of an ongoing commitment to engage the public in discourse about societal issues related to emerging nanotechnologies. A broad range of stakeholders, including people from universities, industry, and civic and community-based organizations, will be involved in this process.

Conclusion

The NIH is fully engaged in a wide variety of nanoscience and nanotechnology research and development activities to achieve short- and long-term advances to reduce the burden of disease and disability. Peer-reviewed research support has been growing substantially since the initiation of the NNI, as has participation of NIH staff in the full range of NNI activities. The NIH is fully committed to continuing these activities in ways that capture maximum benefit for improving the health of the American people and individuals around the world.