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Progress Review

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PROGRESS REVIEW GROUP REPORT

FINAL REPORT

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Introduction

On January 26, 2010 the National Institute of Biomedical Imaging and Bioengineering (NIBIB) convened a Progress Review Group panel of external research scientists expert in nanotechnology to review the NIBIB nanotechnology portfolio progress and to make recommendations for program improvements and future research opportunities. The panel was first informed about the current NIBIB nanotechnology portfolio through a series of presentations. The panel spent the remainder of the meeting discussing critical gaps and opportunities for the future of the nanotechnology portfolio. A summary of the presentations and a synthesis of the panel discussions are presented in this report.

Opening Remarks

Dr. Belinda Seto, Deputy Director, NIBIB

The purpose of this Progress Review Group (PRG) meeting was to gather input from the scientific community on the state of nanotechnology research in the National Institute for Biomedical Imaging and Bioengineering. Suggestions and recommendations extracted from this meeting will be used to provide advice to the nanotechnology portion of the NIBIB strategic plan and funding portfolio.

The mission statement of NIBIB is important when reviewing the nanotechnology program because it is just one of several such programs at the National Institutes of Health (NIH). The central theme of the NIBIB mission statement is to integrate engineering and physical sciences with life sciences, while focusing on translational biomedical research. The focal point of NIBIB is not a specific disease but a commitment to improving health through application of biomedical technologies.

The Progress Review process allows an Institute to look at overall effectiveness of a program. There are three phases to a review: (1) assessment of the state of the portfolio and science, (2) implementation, and (3) reporting. The task of this panel was to examine the assessment phase. Following presentations that described the state of the NIBIB research portfolio, participants engaged in discussion. PRG members were asked to identify research priorities and resources necessary to implement the NIBIB mission. The PRG was also asked to make suggestions on how to develop benchmarks and metrics to assess progress of the program. An important point that was considered is the large scope of nanotechnology. Most programs in NIBIB are easily defined and grouped together. However, nanotechnology grants are spread throughout the Institute's programs. The PRG group discussed whether it would be beneficial to initiate a more centralized nanotechnology program.

The implementation and reporting phases of the review process are performed within NIBIB. The NIBIB working group will use input from this report to develop strategies that will advance research in nanotechnology. The final product will be an implementation plan that will reconcile strengths and gaps identified during this meeting, as well as the Institute's activities and plans for the program. These include identification of both short- and long-term milestones to measure progress. This plan will be shared with the broader scientific community to highlight current status and accomplishments of the NIBIB nanotechnology program.

The strategic plan will be developed by a subset of members from the Institute Advisory Council, and is expected to be finished by May 2010. Program directors will play a key role in drafting the strategic plan, and opinions and viewpoints of the scientific community are being gathered from conferences and workshops sponsored by NIBIB.

NIBIB PROGRAM PORTFOLIO PRESENTATIONS

Overview of NIH Investment in Nanotechnology

Lori Henderson, Ph.D., Program Director
Division of Discovery Science and Technology

Three main areas describe the NIH investment in nanotechnology: (1) areas of funding, (2) major initiatives at NIH, and (3) an overview of NIBIB program areas and investments.

It is important to establish a definition of nanotechnology. Nanotechnology has been defined by the National Nanotechnology Initiative (NNI) as the understanding and control of matter at dimensions that are roughly 1 to 100 nanometers and where unique phenomena enable novel applications. NIH is interested in funding research to look at nanostructures and ways to manipulate them in order to further biomedical research.

Investment in nanotechnology by NIH started four years before the NNI was created. Over the lifetime of nanotechnology projects, funding increased to $311 million by 2009. There was a significant increase in 2005 that correlated with the implementation of several major initiatives. Another apparent increase in funding occurred in 2008, but was actually more a result of changes in coding definitions for grants. The largest funding area is devices and systems, at $164.3 million. Within this category, the device itself may not be nanoscale, but the processes or components to make the device may employ nanotechnology.

NIH has also received an increase in funding from the American Recovery and Reinvestment Act (ARRA). This $73.3 million dollar increase for nanotechnology research has allowed for funding of Challenge Grants, Grand Opportunities (GO) Grants, Summer Research Experiences for students and educators, Competitive Revisions Supplements, administrative supplements, and increased paylines. GO grants fund large-scale research projects, and the National Institute of General Medical Sciences (NIGMS) and the National Institute of Environmental Health Sciences (NIEHS) are currently using these funding sources to investigate nanoparticles to target chemical agents and assess toxicity of nanomaterials, respectively. NIBIB, the National Heart, Lung and Blood Institute (NHLBI), and the National Cancer Institute (NCI) have followed similar strategies to encourage research in multifunctional nanoparticles. These research areas include both therapeutic and imaging studies to aid in diagnosis and treatment of disease through the use of NIH Challenge Grants.

The overall NIH research portfolio in nanotechnology is very diverse. There are projects to develop nanodevices that identify and diagnosis disease; other studies are creating nanoparticles capable of targeting therapeutics within the body and nanoparticle tools that can reveal the biomolecular basis of disease. The portfolio also includes studies to improve control of interfaces between biotic and abiotic structures, development of nanofluidic platforms, and engineering of scaffolds for regeneration of organs and tissues. The research ranges from tools that further basic science to translation of techniques and therapies that improve the lives of patients. The NNI is developing a report describing the breadth of this research across all Federal agencies.

There are four major initiatives for nanotechnology at the NIH, which include: (1) the NIH Nanomedicine Roadmap Initiative, (2) the NCI Alliance for Nanotechnology in Cancer, (3) the NHLBI Program of Excellence in Nanotechnology (PEN), and (4) the NIEHS Nanohealth Enterprise Initiative. These are large investments in centers and partnerships that are designed to discover, develop, and deploy nanotechnology solutions for a wide range of biomedical applications.

The Nanomedicine Roadmap is a 10-year program designed to better understand nanostructures in living cells and to use this information to treat disease by repairing unhealthy tissues and cells.

Currently, $79.8 million has been invested in nanomedicine over five years, and eight centers have been established. However, two of the eight will be phased out in 2010.

The Center for Protein Folding Machinery, directed by Wah Chiu at Baylor College of Medicine, is one example of progress in the Nanomedicine Roadmap. The focus of this Center is to exploit chaperones for therapeutic purposes in diseases such as Alzheimer, Parkinson, and Huntington. Recently, the Center was able to successfully demonstrate that use of type II chaperonins can affect Huntington protein and reduce cell death.

The Nanomedicine Roadmap Initiative also funds the Center for the Optical Control of Biological Function. Ehud Isacoff at the University of California-Berkeley leads this Center, where researchers are developing photoswitches to study protein complexes in living cells and aid in drug delivery. The process involves development of small molecules attached to ligands targeted to specific proteins. These molecules can be activated, when needed, by exposure to light, thereby avoiding side effects that can occur during systemic delivery. Another recent advance at this Center was the incorporation of genes into a photoswitch in both mice and zebrafish to treat blindness.

The second major initiative for nanotechnology at NIH is the NCI Alliance for Nanotechnology in Cancer. The goal of this initiative is to dramatically change the manner in which cancer is diagnosed and treated. It incorporates the Centers for Nanotechnology, the Cancer and Nanotechnology Platforms Initiative, the Nanotechnology Characterization Laboratory (NCL), and support of major training. The Alliance was launched in 2004 and has utilized $143.3 million over five years to promote its objectives. The program encompasses both public and private sectors and emphasizes cross-disciplinary collaborations. Eight Centers of Cancer Nanotechnology Excellence are supported by the Alliance, and 12 Cancer Nanotechnology Platform Partnerships have been formed. The NCL was created to accelerate translation of nanoscale materials into medicine. The Laboratory services both the Alliance and the scientific community at large by performing both *in vitro* and *in vivo* tests for use in preclinical studies.

The third major initiative is the NHLBI Program of Excellence in Nanotechnology, which was designed to establish multidisciplinary centers for diagnosis and treatment of heart, lung, blood, and sleep disorders. The NHLBI funded four centers in 2005 and has currently invested $54 million over five years. Gang Bao, from Emory University and Georgia Tech, is the leader of a PEN-funded project that studies the correlation between shear stress and atherogenesis. This research conjugated quantum dots with antibodies, which allowed for visualization of plaque formation. When these data were combined with micro-CT and ultrasound data, a relationship between shear stress and plaque formation was evident.

The final major initiative is the NIEHS Nanohealth Enterprise Initiative, which is a partnership between NIH Institutes, other Federal agencies, and public and private institutions. The Initiative is designed to look at the physiochemical interactions of nanomaterials with biological systems, and has established a community through NNI workshops focused on the effects of nanomaterials on health and the environment. Several reports have been released, and a new initiative has been launched to create a nanoregistry to better understand the properties of nanomaterials. NIEHS has also been instrumental in developing the strategy for the Environmental Health and Safety Authority.

NIBIB investments in nanotechnology are driven by investigator-initiated projects and fall under six main categories, including: drug and gene delivery systems, molecular imaging, biomaterials, sensors and platform technologies, tissue engineering, and training. The total amount invested Institute-wide in nanotechnology for fiscal year 2009 was $36.9 million.

Examination of spending across NIH Institutes shows that NCI has the highest amount of spending with $91 million, which corresponds to 27 percent of the NIH nanotechnology portfolio. NIBIB is

second with $36.9 million, corresponding to 11 percent of the NIH portfolio. When the percentages of total Institute and Center (IC) budgets are compared, NIBIB spends 12 percent of its budget to fund nanotechnology research, while the other ICs are all below 4 percent. Even though NCI has the largest investment in dollar amounts, NIBIB has allocated more of its resources to the advancement of nanotechnology.

NIBIB Nanotechnology Program Progress Review

Lori Henderson, Ph.D., Program Director
Division of Discovery Science and Technology

There are three main programming areas for the nanotechnology program at NIBIB: (1) drug and gene delivery, (2) biomaterials, and (3) tissue engineering. The drug and gene delivery program was designed to support new or improved technologies for controlled release and targeted delivery of therapeutic agents. The research has focused on new or improved delivery systems and development of new technologies to assess the effectiveness of treatment. This program has three main goals, the first of which is to improve delivery technologies for more effective targeting and dose control of small molecule drugs. The second is to enable effective and minimally invasive delivery of macromolecular therapeutic agents, and the third is to improve effectiveness of intracellular delivery of genetic material to enable molecular interventions.

Drug and Gene Delivery Program

There are a total of 72 grants under the NIBIB Drug and Gene Delivery Technologies Program, and 34 of these grants are focused on incorporation of nanotechnology. Of the $19.7 million that has been spent on this program, $8.6 million has been awarded to nanotechnology projects. Based on these numbers, 44 percent of the investment in the Drug and Gene Delivery Program has been used to fund research in nanotechnology. The highest investment in nanotechnology for drug and gene delivery is at NCI, with 79 grants funded for $21.5 million. NIBIB has the second highest investment, with 34 grants and $8.6 million invested.

Several Institutes within NIH, including NIBIB, NCI, and NHLBI, have a shared interest in the development of nanodelivery systems for detection, diagnosis, and treatment of diseases. One of the main interests for all of the Institutes is developing targeted, multifunctional nanoparticles for imaging and therapy. NIBIB's program is unique from those of the other Institutes because it supports development of new delivery platforms that can be used for treatment of more than a single disease. Currently, the majority of NIBIB nanotechnology grants are focused on cancer as a surrogate model to demonstrate the feasibility of the research approach. However, unlike NCI, which focuses on translation and clinical studies, NIBIB grants focus on early-stage research with limited *in vivo* studies.

Three categories of delivery systems are presently under development: drug carrier systems, nonviral gene delivery systems, and viral gene delivery systems. Examples of drug carrier systems are liposomes, micelles, inorganic nanoparticles, polymeric nanospheres, polymeric nanorods, multifunctional targeted nanoparticles, and stimuli-responsive nanomaterials. The investment in these systems encompasses 21 grants funded at $5.3 million. Nonviral gene delivery research has focused on use of lipoplexes and polymeric nanoparticles, and there are seven grants in this area funded for $1.8 million. Finally, research on viral gene delivery comprises five grants funded at $1.0 million. These grants concentrate on development of viral nanomotors.

Dr. Gayle Woloschak, from the Department of Radiology and Radiation Oncology at Northwestern University, is doing research funded by the Drug and Gene Delivery Program. The goal of her research is to develop therapeutic magnetic resonance probes based on semiconducting properties of

titanium oxide. Specifically, Dr. Woloschak and coworkers have conjugated DNA oligonucleotides to titanium oxide nanoparticles to create an intracellular probe for gene silencing. This is an example of a platform technology that allows attachment of different functional groups to the nanoparticle, enabling cellular and intracellular delivery. It also has the added benefit of being able to image the effects of treatment.

Dr. Raoul Kopelman, from the Department of Biomedical Engineering and Chemical Biology at the University of Michigan, heads another example of ongoing research funded by the Drug and Gene Delivery Program. Dr. Kopelman is developing a nanoparticle technique that allows for both imaging and therapy of brain tumors. This technology affords better contrast of tumors to improve resection and includes an added component of photodynamic therapy treatment of residual cancer cells that improves the survival of brain tumor patients.

Advanced Biomaterials Program

NIBIB's Advanced Biomaterials Program is developing materials that can be used for a broad spectrum of biomedical applications such as implants, tissue engineering, and medical devices. Research and development focuses on new design-driven methods of producing bioactive materials. These materials are designed with physical or chemical cues that enhance biocompatibility or molecular recognition cues capable of controlled memory, movement, and actuation. The goals of the Program are to improve the material's properties for biocompatibility and promote development of new synthetic approaches for production of biomaterials.

There are 37 grants in the NIBIB Advanced Biomaterials Program, 8 of which are focused on nanotechnology. The total portfolio is $10.4 million, and $2.7 million is targeted to nanotechnology, which means that 26 percent of the total investment in advanced biomaterials is in nanotechnology. A comparison with other Institutes indicates that the National Institute of Dental and Craniofacial Research (NIDCR) has the largest investment in biomaterial nanotechnology grants, at 13 with funding of $3.0 million. NIBIB is the second largest investor.

While there is a shared interest in biomaterials development between NIBIB and NIDCR, the latter focuses mainly on dental materials and interventions. The NIBIB program supports the development of new platforms that can be used across different application areas such as tissue engineering, biosensors, and medical devices. Some topics included in the nanotechnology portfolio are surface modification of biomaterials to increase biocompatibility, surface analysis and characterization of biomaterial interfaces, and the mechanistic understanding of cellular uptake of nanomaterials.

Dr. Shuvo Roy from the Biomedical Engineering Department of the University of California, San Francisco and the Cleveland Clinic, heads one example of research funded by the Advanced Biomaterials Program. The goal of his research is to develop a miniature, implantable, bioartificial kidney that would eliminate the majority of dialysis procedures performed in the United States. This research focuses on nanoscale fabrication of materials to control pore size and aid in removal of toxins from the human system.

Tissue Engineering Program

The Tissue Engineering Program emphasizes technologies that develop functional cell, tissue, and organ substitutes to repair, replace, or enhance biological function. Research focuses on scaffold design to control cell growth and differentiation, high-throughput assay development, and advances in imaging. There are 97 grants under this program, with $31.9 million invested; 8 are classified as nanotechnology, funded at $2.5 million. This is equivalent to 8 percent of the total investment in tissue engineering. The National Institute of Arthritis and Musculoskeletal and Skin Diseases

(NIAMS) has the largest investment in this area, with 10 grants totaling $2.4 million. NIBIB and NIDCR have the second largest investments, with eight grants each.

NIH, NIBIB, NIAIMS, and NIDCR have shared interests in developing the research tools and scaffolds necessary to engineer tissue constructs. These interests include scaffolds for bone regeneration, nanostructures that present physical cues for cell signaling and mechanics, nanopatterned surfaces to control cell response and fate, and nanoengineered surfaces to control topography and presentation of ligands.

Andre Levchenko, from the Department of Biomedical Engineering at Johns Hopkins University, leads an example of one of the projects funded by the NIBIB Tissue Engineering portfolio. Dr. Levchenko and coworkers are attempting to use nanofabric with a well-defined architecture to culture myocytes. Depending on characteristics of the nanofabric, the cells grow in an ordered structure aligned with the array that mimics myocardiotissue.

Sensors and Platform Technologies Program

Brenda Korte, Ph.D., Program Director
Division of Discovery Science and Technology

The Sensors and Platform Technologies Program includes *in vitro* diagnostics, with an emphasis on point-of-care technologies, noninvasive monitoring, high-throughput screening, and enabling technologies. NIBIB has 80 grants in this area, which are funded at $27 million; of these, 12 are focused on nanotechnology and are funded at $3.4 million. NCI has the largest nanotechnology portfolio in this area with 19 grants funded at $5.3 million. NIBIB is the second largest source of funding for these types of projects, and NIAID and NIEHS have investments of a similar size.

NIBIB research in sensors and platform technologies follows a trend similar to other areas of research—projects with broad applications are often found in the NIBIB portfolio, while studies that pertain to a specific disease or clinical application are funded by other Institutes. The technological challenges for development of technologies are similar in both cases.

The nanotechnology grants in sensors and platform technologies are divided into two scientific areas. The first is *in vitro* diagnostics, which has 68 percent of the funding, corresponding to $2.3 million. The second is enabling technologies, which is funded at $1.1 million. This allocation reflects a trend in the field towards practical application of technologies. Of the eight grants classified under the heading of *in vitro* diagnostics, there is an emphasis on point-of-care technologies, where the intended end use is clinical diagnostics. Therefore, this research usually focuses on an entire system or device rather than a component, and the analysis is often performed on clinical samples such as blood or urine. The technological advances that are targeted include improving sensitivity, increasing multiplexing capabilities, and enhancing separations. In the area of enabling technologies, there have been similar technological improvements as with *in vitro* diagnostics, but they are not associated with a specific clinical end. Instead, the focus is on components or tools for basic research. One major difference in this area is that testing is rarely performed on clinical samples.

David Erickson from Cornell leads an example of a grant funded through the Sensors and Platform Technologies Program. The project goal is to design an integrated device to detect viral RNA pathogens from Dengue. The device relies on changes in refractive index upon RNA binding. An array of different sized wells improves sensitivity by confining binding to nanostructures.

The second case is an example of an enabling technology grant. Dr. Scott Manalis from MIT is developing a technique called mass-based flow cytometry, a technology that is similar to quartz crystal microbalance measurements. Changes in the frequency of vibration of a cantilever are

measured when a molecule binds as it makes its way through a microfluidic channel. The nanotechnology component of this project is the use of nanoparticles that allow for a distinction in mass between the measured particle and the background. The analysis is linked to the use of conventional nanoparticles.

Training Grants in Nanotechnology

Brenda Korte, Ph.D., Program Director
Division of Discovery Science and Technology
Prepared by Zeynep Erim, Program Director, Division of Interdisciplinary Training

Fifteen grants are devoted to training in nanotechnology and fall into four scientific themes. Three grants are in *in vitro* diagnostics, three grants relate to gene and drug delivery, four grants pertain to imaging agents, and five grants are classified as broad based. The broad-based grants include institutional training programs and faculty positions for future hires at P30 centers.

Just over $2.0 million is committed to investment in the nanotechnology training program. More than half is committed to broad-based opportunities ($1.2 million). Gene and drug delivery is the next largest area, with $360,000, which is followed closely by *in vitro* diagnostics at $310,000. Imaging agents has the smallest training investment at $160,000.

The portfolio in nanotechnology training can also be examined by career level. Most of the investment is at the early career level ($1.3 million), which includes K awards, career awards, and P30 awards. The predoctoral awards consist of F31 fellowships and institutional training grants and have an investment of $600,000. Finally, the postdoctoral awards consist of F32 fellowships and K99 awards and total $360,000.

The entire NIBIB training portfolio is made up of 100 grants totaling $17.3 million. Of these, 15 grants are focused on nanotechnology and are funded at $2.1 million. These numbers correspond to 15 percent of the training grants within NIBIB and 12 percent of the funding. NIBIB has the largest number of funded training grants (15) in nanotechnology at NIH. NCI has the second largest number, at 13 with $1.6 million invested.

Imaging Programs in Nanotechnology

Yantian Zhang, Program Director
Division of Applied Science and Technology

In the imaging area, most NIBIB grants are directed towards technology development and are not at the clinical application level. Most nanotechnology grants within the NIBIB Imaging Program are in the molecular imaging program, which supports development, evaluation, and application of molecular imaging probes and novel imaging methods. Other grants cover nanotechnology in imaging within NIBIB, including ultrasound, MRI, and nuclear medicine.

About one-third of NIBIB nanotechnology grants are in the imaging area, and these are primarily R01 and R21 funding mechanisms; there are two pioneer awards. When the portfolio is compared across NIH, most nanotechnology grants related to imaging are found in the NCI portfolio. One of the major differences between the NCI and NIBIB programs is that the NCI research is more concentrated on application to a specific pathology or biological system. For example, NCI is interested in biological modification of quantum dots for *in vivo* imaging and not in development of quantum dot technology. There is a different programmatic emphasis, but there also are overlaps in the research. In general, NIBIB is more interested in early development of platforms, and NCI is focused on later-stage applications to biology.

There are two broad categories of nanotechnology research for imaging within NIBIB. The first is design of probes and devices, and the second is development of imaging principles and instruments.

An example of research from the first category is led by Dr. Yaunan Xie at Washington University. Dr. Xie and his coworkers are assembling gold nanocages that are able to carry therapeutic or imaging agents and can be targeted by the attachment of ligands to the surface of the nanocage. By manipulating the thickness of the walls, researchers are able to change the optical properties of the constructs. One version of these nanocages incorporates peptides that convert from hydrophilic to hydrophobic as the temperature increases; this change in the properties of the peptides causes the release of the contents of the nanocage.

Dr. Teri Odom from Northwestern University is conducting research that fits into the second category—development of imaging principles and instruments. Dr. Odom is working on structured illumination from plasmonic lenses to increase resolution of optical imaging. This technique uses film with nanoscale holes that create interference as light passes through. The light interacts with the sample through the holes, and the signal can be reconstructed to detect images that are smaller than the diffraction limit. Importantly, this increase is possible without labeling of the sample.

PROGRESS REVIEW GROUP PANEL DISCUSSION

PRG Discussion Highlights

The purpose of this discussion was to gather input from PRG members on the state of nanotechnology research at NIBIB. NIBIB staff will use suggestions and recommendations from this discussion to evaluate NIBIB's strategic plan and funding portfolio. Focus questions included:

- Why is nanotechnology exciting?
- Where is it important?
- Where is it significant?
- What areas are underrepresented?
- What areas are overrepresented?
- Where are opportunities to emphasize new interests or deemphasize projects that are mature?
- What are the characteristics of nanotechnology that might make it different than more advanced areas of research?
- What should the roles of individual investigators be compared with the roles of multidisciplinary teams?
- What is the role of NIBIB versus other NIH Institutes?
- How should the Institute plan for and manage the nanotechnology portfolio?
- What exactly is the nanotechnology portfolio?

Definition of Nanotechnology and Its Use in Classifying Grants and Funding

A concern was raised by Panel members about the method used to define nanotechnology grants and funding. NIBIB staff explained that categorization of grants is performed using the Research, Conditions, and Disease Categorization (RCDC) system. This system uses a computerized search to look for key words and concepts within the abstract of the grant. The system was designed because of controversy over IC differential coding of projects. Even though false positives and negatives can occur, the system allows for a consistent and transparent coding method across NIH. However, it is still a new system and evaluation of its ability to properly classify projects is still under way.

The Panel asked how classification of research and funding impacts the political climate and allocation of funding to Institutes. Does the fact that NIBIB is heavily invested in nanotechnology (at 12 percent) have a negative or positive effect on the amount of funds that are available to the Institute? NIBIB staff explained that most funding in NIH is not earmarked for specific diseases or techniques. So far, there has not been a negative or positive effect from the NIBIB commitment to nanotechnology; instead, it is a signal to the applicant community that NIBIB is interested in advancing this area. Another Institute staff member clarified that use of the RCDC system has made classification consistent within the Institutes and helped to alleviate the problem of over- or underreporting of funding depending on the profile the particular Institute would like to portray.

The Panel asked whether the RCDC system had been tested for accuracy in classifying grants. NIBIB staff responded that many evaluations have taken place. The tests have determined that errors do occur and that there are more errors if the definitions are not well characterized. However, the errors are consistent across NIH and over time, and key words and concepts that are used for classification are constantly updated in order to improve the system.

A PRG Panel member commented that as a member of the Nano Review Panel, there were grant proposals that members felt were misclassified. NIBIB staff clarified that the RCDC system is only used for classifying grants awarded and not for determining appropriate study sections for assignment of applications. A Panel member commented that defining nanotechnology is difficult, and instead of focusing on delineating boundaries of nanotechnology, scientific review panels should instead focus on the importance of the science that is proposed.

Another Panel member mentioned that it is important to have a neutral system of classification so that an Institute cannot increase or decrease the apparent focus of its research based on how they think funding decisions will be made. The RCDC system seems appropriate to look at trends for grants, and that is the key point in compiling this type of data. Definition of categories comes from grants that are assigned. There is a system of negative and positive weighting for specific key words, and changes are based on new terms and grants that are being funded.

The Panel voiced concern that the example of research on nanofabric and myocyte culture should not be characterized as nanotechnology. A Panel member suggested that size may not be the most important factor in defining a project as nanoscale. Instead, the determining factor should be whether the small size would affect outcome of the experiment. In this case, outcome does not seem to depend on special properties that disappear when the components are on a larger scale. NIBIB Program staff explained that a device itself does not have to meet nanoscale criteria. The surface was engineered using nanotechnology, and interaction with the surface affects growth and development of the cells in a specific way. The scientists used surfaces with a range of different sized ridges, and only one produced good cardio-cell growth. NIBIB staff commented that this is an example of a project that has been coded as nanotechnology. They were interested in suggestions for better methods of classification when there is disagreement with the classification of the project.

A Panel member commented that the current definition of nanoscale could be based purely on size where the dimensions of the components are considered, or the definition could be based on the existence of new properties and functions below a certain scale. It is the discovery of new material properties, via size manipulations, that makes nanotechnology exciting. Nanotechnology has facilitated an increase in the number of materials available by expanding their range of properties. By changing a material's shape and size, technology can hone the properties needed. The value of nanotechnology is its ability to harness new properties that were previously nonexistent. Material properties matter more than an arbitrary classification based on size alone.

An example was cited from other research. If the volume manipulated with microfluidics is in the nanoliter range, the process is called nanofluidics; however, the apparatus to control the liquid is in the microscale range. Classification might depend on how the application is focused. The Panel wondered if there is a perceived advantage for having an application labeled nanotechnology. NIBIB staff responded that a researcher's project could fall under the microscale category; however, classification would rely on the RCDC system, and the distinction between nano and micro may not yet be well defined. There has been a perception that being funded by the Nanotechnology Initiative is beneficial; however, the program announcements have been broadened and study sections have been created that are not exclusively correlated with those announcements. Applicants can be penalized in review for overselling a link to nanotechnology.

The Panel suggested that this type of research may be better regarded as advanced materials technology, and that the goal should be to find the best advances to enable the science and applications. The classification of nanoscale or microscale may no longer be important as long as the research advances scientific discovery. Another Panel member discussed that the National Science Foundation (NSF) defined nanoscale in three dimensions to attempt to exclude interfaces as nanotechnology.

Gaps in Nanotechnology Research

Potential for Development of Natural Materials

The Panel noted that most of the NIBIB nanotechnology portfolio focuses on synthetic materials. A Panel member inquired whether NIBIB would support research that utilizes naturally occurring objects. For example, proteins are considered nanoscale, which means that molecular biology could be renamed nanobiology. The current research trends take a systems approach instead of a single molecule approach, which biochemists have used for the last 50 years. The discoveries that scientists are making now are being put back into a cellular context.

Another Panel member agreed that proteins and natural materials could be considered nanotechnology. The important point is the context in which they are used. For example, studying the function of a nuclear pore in its native state would not be considered nanotechnology. However, inserting the pore into a particle and using it to deliver a specific sequence of DNA would constitute nanotechnology. The Panel agreed with that analysis, and mentioned nanomotors as another example. Nanomotors have specific cellular functions; however, a researcher could employ nanotechnology to reengineer the motor to perform a different task. NIBIB staff indicated that there are examples of people using biological materials to make nanostructures. For instance, viruses are genetically modified to function as delivery devices. It doesn't matter if a nanodevice is formed by chemical or biological means. Instead, the important factor is what can be produced and that it has a function. In general, the Panel agreed with this analysis.

The Panel suggested that it is the technology aspect of nanoscale research that makes it appropriate for NIBIB. The current portfolio seems to include both types of research. This might be contributing to the confusion of whether certain research fits into the nanotechnology area. The Panel further clarified the definition by adding that nanotechnology tools can also be used to better understand biology. In this case, conventional molecules are looked at, but with a new set of tools. The Panel suggested that an important part of nanotechnology is the possibility of amplifying effects. Molecules can be manipulated for photodynamic imaging and therapy; a molecule could be engineered to include an imaging portion and a therapeutic portion, with components at a one-to-one ratio. If a nanoparticle is used, the ratio of therapeutic components to imaging components can be adjusted, and a biological component can be added to the surface to facilitate entry into the cell. This type of improvement makes nanotechnology important—it is not just the use of the natural biological molecule.

It is important that the program announcements articulate this view more strongly, which would allow molecular biologists to better understand their nanotechnology peers. The announcements should stimulate the larger community so that the idea of nanotechnology is more broadly accessible. Adding this clarification to the portfolio would be helpful in expanding an understanding of nanotechnology from chemists to molecular biologists.

The Panel commented that there are gaps in research for instrumentation used to assess nanomaterials. The current instruments are not used to their full capacity because researchers lack an understanding of principles involved, and new instruments need to be developed. A Panel member questioned whether NIH funds development of techniques to better characterize nanodevices, and it was indicated that NCL addresses those issues through NCI. The Panel member clarified that the comment refers to new technology, not existing technology. The Panel discussed that a challenge in characterization of nanomaterial is that most batches will have a distribution of properties. Correlating the properties to each subpopulation can be challenging, and it is necessary to have both high-resolution and high-throughput devices.

Potential for Advances in Nanotechnology Research

Basic Science versus Translational Research

The Panel suggested that there are two areas of potential focus for the NIBIB nanotechnology portfolio: basic science and health applications. A Panel member made a case for basic science by describing an example where nanotechnology has benefited catalysis. Development of nanotechnology has almost eliminated UHV surface science over the last 20 years and has changed the field completely. UHV surface science involves use of a platinum cube in a vacuum to look at catalysis. For example, gold is noncatalytic under almost all conditions; however, if the size of the gold particle is changed to 2 nanometers, the metal will catalyze several reactions. At one nanometer or 3 nanometers, it becomes noncatalytic again. The interesting question is why, and whether this property can be used to make better catalysts. This was an unexpected finding that could not have been predicted, while the amplification example previously described could be predicted. Therefore, two fundamentally different types of advances can occur.

The Panel discussed that many advances so far in nanotechnology have been in chemistry. New materials have been developed with new properties, but they are not applicable to biology because they are insoluble. The nanotechnology program should help transition nonbiological components that may have applications in biology. Increasing funding to these areas could facilitate nontraditional translational research. The Panel suggested that nanodots are a good example of a technology that would benefit from this form of attention. They have many properties that would be useful for imaging in cells. Quantum dots are a perfect example of how nanoscience facilitates advances in biomedical sciences. The Panel added that this example also illustrates the need to make materials amenable to biology, or water soluble, to achieve the same results with materials that have lower toxicities. It was suggested that quantum dots highlight how funding can push a field into a medical application. New questions coming from attempts to use quantum dots for imaging would not have been asked if the field had not been nurtured. NIBIB has played a role in developing technologies without a clear translational application.

The Panel commented that single molecule biochemistry and biophysics are important future directions for the field, using optical traps and force measurements through an FMA tip as an example. These techniques could provide a new perspective on the function of multiprotein complexes and provide information that could be difficult to obtain by other methods. Institute staff mentioned that the area of single molecule biology is supported by NIGMS.

NIBIB staff stressed that natural biological molecules are nanomaterials. At NIGMS, researchers are using anthrax toxin to look at transport and its application in medicine. This type of research is not in the NIBIB portfolio.

Three-dimensional cell culture was suggested as an area of expansion within NIBIB. The Panel commented that significant research has been done in developing two-dimensional surfaces. On a two-dimensional level, cells can sense and respond to nanopatterns. The key seems to be control of multiprotein complexes within the cell via confinement on the growth surface. The Panel suggested that three-dimensional cell culture should be an emphasis in tissue engineering. Discovery efforts are necessary to increase their integration into a three-dimensional platform. This is an example of a discovery effort that would fit well with the NIBIB nanotechnology portfolio. One issue is whether to proceed with these efforts using a high-throughput approach.

The Panel commented on how few grants there are in some categories and thought there would be a balance of targeted research and investigator freedom. NIBIB staff indicated that because of relatively small numbers of grants and funding, there isn't much room for targeting of funding.

The Panel suggested that an important use of nanotechnology is detecting low copy number molecules in a clinical setting. This would include cancer stem cells as well as other molecules and could be accomplished by imaging and by *ex vivo* or *in vivo* diagnostics. The Panel mentioned that one strength of nanotechnology in both diagnostics and therapy is that amplification is possible. In the case of therapeutics, this would entail getting large amounts of a specific drug to a target within the body. A Panel member indicated that there has been a large amount of work in controlled release and targeted delivery. What seems to be lacking is targeted removal where a nanomaterial binds a particular molecule within the body and removes it. It would make retrieval of low copy number molecules easier; it would not be necessary to use polymerase chain reaction (PCR) to amplify DNA retrieved from a clinical source. NIBIB staff presented an example where researchers have been able to cluster iron oxide and produce an increased relaxation effect. A Panel member mentioned that there also have been microdevices to enrich certain cell types, while another responded with an example that involved use of nanostructures to obtain fetal DNA to replace the normal amniocentesis procedure. The Panel suggested that the reason these projects are not in the portfolio may be because they are considered too high risk. An Institute staff member mentioned that there are similar projects at the microscale level and there may not be an advantage to moving to nanoscale.

NIBIB staff further suggested that a possible application would be nanoreceptors that target circulating cancer cells and remove them from the body. NIBIB has a grant that is attempting to detect those types of cells, but it does not take the next step to concentrate or remove them. The Panel indicated that perhaps the most important issue is the ability to combine devices that can be targeted and perform both imaging and therapeutics, and suggested that this is an important goal for nanomedicine.

The Role of NIBIB versus Other NIH Institutes

A Panel member suggested that perhaps NIBIB is focused on translational aspects of nanotechnology and not basic science, but another Panel member disagreed and commented that NIBIB is focused on early-stage research, and NCI is focused on translation to human health. To alleviate the confusion, the Panel needs a better understanding of how NIBIB defines translational. Is it defined by transitions from basic science to possible applications or by the more traditional role of translation to medicine? NIBIB staff clarified that NIBIB supports basic science in order to understand materials that are being developed, but not to probe basic biological processes; that type of research is the province of NIGMS. NIBIB staff then inquired whether the NIBIB portfolio should be expanded in this direction. The Panel indicated that NIBIB should consider the context of biological processes; however, emphasis should be on nanotechnology rather than biology, and suggested the underlying goal is to understand and manipulate biological processes, which is the overall mission of NIH. Focusing on this would bring NIBIB into the mainstream of molecular biology, and perception is very important to the scientific community.

The Panel suggested that NIBIB could play a role in development of nanotechnology similar to the role that NIGMS has in basic sciences. For example, most basic methodology projects go to NIGMS and their research is the starting point for more directed applications. Many properties of new materials cannot be predicted, leaving an important discovery phase that is not hypothesis-driven research. NIBIB could develop this type of research. A member of the Institute staff commented that NIBIB has two missions that would cover these areas. The first is bridging physical and the life sciences, which is basic research. The other is to accelerate technology development. When combined, they would address the role the Panel is suggesting. Some Panel members were concerned that if NIBIB focuses on basic research to drive nanotechnology, their mission will be similar to that of NSF. The overall focus of NIBIB should still be related to biology or medicine. This type of research is not currently in the NIBIB portfolio and would be beneficial to the Institute.

The example of nanodots was mentioned again, as the current most visible nanotechnology success story. However, they have a problem with toxicity and current funding is concentrated on coatings that make them less toxic. While it is important to continue that line of research, it would also be helpful to investigate a method to degrade the material into nontoxic components. There is a gap in this line of research that no Institute is funding. While this is a basic research question, it is still a biological question, and NSF would likely not fund this type of research. This research would fit both components of the NIBIB mission. There is a clear application, and it would allow interdisciplinary activity between chemists and biologists.

The Panel suggested that perhaps the term for what was being described is "oriented discovery." When one talks about discovery, it is not general discovery that occurs at the NSF. Instead, it examines specific assays that would likely uncover significant findings and change the application of science to health. For example, the ability to test 300 new materials for inflammatory responses at one time, *in vivo*, would be a significant advance.

A Panel member commented that the original objective of NIBIB was to involve engineers in the process of advanced imaging and other research. Instead of developing and studying the properties of nanoparticles, NIBIB should be developing nanodevices that have a function and will be useful for biological study and disease therapy.

The Panel discussed technology transfer, noting that in the past there were some funding mechanisms that had a component of technology transfer incorporated but were not Small Business Innovation Research (SBIR) funding. They were basic research awards. NIBIB staff explained that NCI had a similar program, but it is no longer funded; these awards now fall under R21 and R33 mechanisms. The R21 is used for the exploratory phase and upon administrative review the grant moves on to a development phase, not commercialization. The concept is good, but NCI was not able to implement the program. This would not have helped with the problems of scaling up production to a commercially available level. The Rapid Access to Intervention Development (RAID) program at NCI helps support development of a potential drug compound and GMP (Good Manufacturing Practice) manufacturing. NIBIB does not have anything resembling the NCI RAID program.

GMP for nanotechnology is not a trivial issue. A Panel member noted that the NCI RAID program does not apply if there is no potential as a drug molecule or if the nanoproduct is classified as a device. Since every nanodevice has very different properties, each device will likely need its own GMP facility.

The Panel pointed out that there are two unique characteristics of high-throughput screening that make it more difficult for biological products. Biological processes are slow, and if attempts are made to speed them up by applying force, there is a possibility of damaging the molecule. Therefore, it is important to develop new techniques that are not just adaptations of the techniques that have been used in the past. Most current methods are similar to techniques developed by the Department of Energy (DOE) and NSF and don't address the problems of size, fragility, and mass transfer. Dr. Mrksich agreed and described systems in which high-throughput screening is not currently possible; for example, *in vivo* experiments are an anti-high-throughput process. Industry is conservative since it has to answer to the Food and Drug Administration. This is an area where basic medical science can introduce new ideas that will result in improved methods.

A Panel member commented that there is nothing special about developing nanotechnology applications with stem cells compared with other cell types. Another member clarified that this is true unless one is attempting to detect or characterize stem cells. For example, detection of cancer stem cells in the bloodstream would require specific improvements. The Panel further commented

that detection of a single type of cell, whether a stem cell or not, would require similar technologies and improvements in the field.

Cutting-Edge Research

The Panel suggested that there may be little nanotechnology research at the cutting edge because budget limitations cause risky projects to go unfunded. There is a large emphasis on having preliminary data. It was indicated that proposals are always written in a conservative way, but the science can still be cutting edge. The Panel then clarified by stating that NIBIB research is at the forefront, but at the forefront of projects that have a high likelihood of success.

The Panel stated that when evaluating recent advances in nanotechnology, NIH-funded projects were innovating and exciting. The Panel agreed that NIBIB would not be a major player in advancing nanotechnology within NIH. The Panel also agreed that most investigators decide which Institute to apply to based on available funds. NCI has the most money available; thus, there is a greater chance of getting funded there.

The importance of determining what part of nanotechnology is associated with NIBIB both now and in the future was discussed. The Panel suggested that NIBIB owns diagnostic imaging, since it started there, but NIBIB staff disagreed and commented that NCI is very involved in this field and that most imaging is still funded through disease-specific Institutes. Another NIBIB staff member indicated that investment in imaging at NIH totals around $700 million, and NIBIB contributes about $150 million to that total. NIBIB is the imaging Institute, but it is not the major funding source. The Panel inquired how the percentage of funding compares with other Institutes, and NIBIB staff responded that NIBIB is at 13 percent while some larger Institutes are in single digits percentage-wise, but the percentage does not accurately represent overall investment. There are huge clinical trials at NCI that cost large amounts of money. The percentage doesn't represent where an applicant will go. Many investigators craft their applications with a cancer component because NCI has made their program very visible and has put out $144 million to fund such programs.

A Panel member commented that nanosensors or biosensors are owned by NIBIB, but other Panel members did not agree because NCI and NIGMS have large programs in nanosensors. The Panel suggested that focusing funded research would allow NIBIB to find an identity; to have an identity, one needs targeted research. However, the scientific community prefers to let investigator initiative guide the research. The Panel suggested that a brand not be created around nanotechnology, but around the problems that nanotechnology can solve. The focus should be distinct medical problems rather than nanotechnology. A Panel member indicated that it is hard to compete with other disease-specific Institutes that are already established, and suggested that NIBIB position itself as an incubator, where a technology can grow until it is ready to be transferred to another Institute that can apply it to a specific disease. The other Institutes do not foster research in the early stages. NIBIB staff responded that Institute staff previously suggested that position and that NIBIB is more comfortable with high-risk projects compared with the other Institutes. This direction would only represent a portion of the overall budget.

The Panel suggested a nontraditional center that would focus on innovation, training, and high-risk projects in one place. It would be a new mode of operation. The Panel further mentioned that there might be an opportunity to link with an existing program like an NSF Nanoscale Science and Engineering Center (NSEC) to create an award that is more focused toward the NIBIB mission. NIBIB as an incubator is an appealing message. Similar to the Defense Advanced Research Projects Agency (DARPA), NIBIB could become the NIH innovator. A Panel member suggested that NIBIB could be the link to the physical sciences, and another member suggested the name High Risk or High Impact Bionanoengineering without mentioning the physical sciences. The Panel also

mentioned that the collaborator-investigator mechanism is another option to approaching an established center.

An Institute staff member suggested that two aspects of NIBIB are unique. The first is the link between physical and biological scientists and the second is technology development. Other NIH Institutes also lay claim to these aspects, but this is the core of what NIBIB represents.

NIBIB staff explained that NIBIB relates to physical scientists differently than other Institutes. One way is through the Bioengineering Partnership. The other mechanism is the P41 grant, which emphasizes the innovative technology aspect of research. NIBIB could implement a new type of mechanism to accommodate recruitment of physical scientists.

A Panel member suggested that programs DARPA is no longer interested in could be moved to NIBIB, while another member commented that NIBIB attempts to promote a DARPA-like culture, in which who is funded is determined, to a certain degree, by the way funding is implemented. One way to determine funding is by organizing panels who give 20-minute talks on what they would like to do. NIBIB staff explained that a similar mechanism is used for the Pioneer Awards and the Director's Innovator Awards.

A Panel member asked whether nanomaterials should be more rigorously characterized, but another member commented that the publication repository already addresses that type of characterization when work is published. A member indicted that if the research is successful, the product can be sent to the NCL, while another member responded that there is a stage where rigorous characterization is important, but there is also a stage where it could retard progress. This is especially true with high-throughput screening. It may be worthwhile to link characterization with publication; if research is not published, there is an assumption that the product is not worth characterizing.

An Institute staff member clarified that the goal is to avoid situations where data are not reproducible and prevent publications where there is inadequate knowledge of the starting material. The Panel agreed that this task should fall to peer review rather the Institute. The Panel commented on the role of NIBIB in translation of applications, noting that clinical translation means there is a disease focus, and another Institute would be more logical in this role. However, NIBIB is the only place where translation from basic chemistry to biology can take place, and there are steps toward clinical translation that would fit into NIBIB, such as toxicity testing. There also is a niche for platforms, which have disease application but still need work to be applied to the clinic. The Panel commented that when a project is at the point of translation, a researcher has already committed to a specific application. Imaging projects that are not yet tied to a specific diagnostic area would fit into NIBIB.

The Panel indicated that everyone seems to agree that NIBIB is a good place to foster early research. It also mentioned that reviewers often ask questions about the biological effects of nanomaterials. There isn't a clear mechanism, except in the Environmental Protection Agency, for characterizing those biological materials. The physical properties of nanomaterials can greatly change how they interact with tissues. For example, a material with a spherical shape is nontoxic, but becomes toxic with a different shape. There is currently no way to determine why the materials have different effects. That could be a role for NIBIB in the early translational phase. NIBIB staff responded that NIEHS has animal models and performs toxicology research, and is the home of the National Toxicology Program; however, their research is not mechanistic.

The Panel suggested there might be political benefit to being involved with clinical translation of nanotechnology. Clinical breakthroughs get more attention. NIBIB currently supports early-stage clinical studies but does not have any clinical trials. The main reason for that is budget. A Panel member indicated that the handoff to clinical translation could be viewed as a success.

The Panel suggested that discussion had defined a breakdown of the funding mechanism. When research is closer to the clinic side, the work is collaborative and interinstitutional. At the early stages of research, it is collaborative through interagency networks with physical scientists. In the middle, the work is investigator initiated.

A Panel member commented that when a project becomes commercially viable, it is transferred to a company that is able to invest large amounts of capital for developing the device. Another member responded that it may go to an SBIR with a small company, and that company may not be able to translate that material without help from NIH. The Panel further indicated that most venture capitalists want to see a Phase I trial before funding a project, and they expect the government or someone else to fund the Phase I part of the research. Other Panel members agreed that taking a point-of-care device to clinical trial is less expensive and easier than a therapeutic, and that device-related clinical trials are within the NIBIB level of funding.

The Panel proposed that there be a way to fund high-risk research that would really change the way things are done, but noted that there may not be an effective plan to accomplish that goal. An example is the electrodeposition of silicon. The only way to approach it at the moment is to experiment in the lab, and there isn't a good way to write an application. An Institute staff member asked about the availability of C grants from universities and a Panel member answered that these are very small, usually only being around $10,000. Institute staff indicated that the first criterion of review is always significance. If there is a reasonable approach to accomplish the goal, there is a reasonable chance for funding.

A Panel member indicated that nanotechnology research at NCI is more cutting edge than research at NIBIB, and commented that if what was presented today is considered the best NIBIB has to offer, then it is probably true that work being funded at other Institutes is of higher quality. Another Panel member responded that it might be a matter of volume, since other Institutes have larger funded programs and, thus, more chances to develop interesting research. The Panel suggested that NIBIB's research should be as diverse as that of other Institutes because funding mechanisms are the same. The other Institutes have a longer history and research takes a long time to come to fruition, and their profiles may look better because their research is further along in the process.

Funding Mechanisms

Roles of Individual Investigators and Multidisciplinary Teams

The Panel suggested that since numbers of awards are small, individual grants or small groups, like a multi-PI format, would be preferable to centers. This would allow for the largest effect in the largest number of places. The Panel expressed a preference for having small teams distributed in many places, which would allow key players to work together. The large nanotechnology centers have really good science, but less interesting projects get pulled along with really good work. With smaller teams, the review process would be able to catch the less important work and keep the focus on the innovators.

However, the Panel indicated that there was only a single P41 grant in the presentations, and asked if there was a reason for this. A P41 mechanism is a research resource that is similar to a center. An Institute staff member responded that there are approximately 20 P41 grants throughout the entire NIH, of which 3 are in the NIBIB nanotechnology portfolio.

Because of the potential for productivity and creativity to decrease as the number of people involved increases, one Panel member recommended that all grants be single-investigator grants or, at most, involve only two researchers. The member discussed that when putting together a center, there are usually a few people who are an exact fit and others are included for political expediency. Inclusion

of these extra people may bring down productivity of the group. As the group gets larger, there are more meetings and relationships may become political. Smaller grants are more productive, and if there is a need to collaborate, scientists know how to reach out and find the help they need.

Another Panel member responded that some large projects, such as the physics accelerators and human genome project, require large centers. While it is easier to define one's own research agenda and funding, it may be necessary to create a mechanism for biology that will allow researchers to work on a much larger scale. It is necessary to get chemists and biologists together to combine their knowledge. There are so many techniques available and so much specialized knowledge that one person cannot know everything. The Panel member indicated that both individual and group funding mechanisms are needed in NIBIB. There should be fewer groups than individuals, but there should be a mechanism to encourage interdisciplinary aspects.

While centers can range in size from 20 principal investigators (PIs) to groups with only 2 or 3 PIs, a Panel member commented that the only advantage in the case of large groups is when the Institute pays for a new facility. In general, groups with three to four principal investigators leave room for collaboration without becoming unwieldy. There is also a need for many individual grants to keep the field moving forward.

Another Panel member highlighted an argument for centers even though the current budget of NIBIB doesn't support implementation of new centers. While centers do not take the place of individual funding, which is necessary to develop ideas and support creativity, in a well-run center many groups can come together and interact, which allows multiple groups the chance to try something based on their own strengths. Centers allow for new combinations that can lead to big advances. The Panel mentioned that there is a gap in funding to pursue the unanticipated, but centers have done a good job of filling that gap. There are also other benefits such as leveraged money from state, university, or corporate sources. This added money can sometimes be as much as the original grant. It also supports a culture of translation and sets up a continuum from basic science to applications, and younger members of the team can benefit from exposure to this sort of environment.

A Panel member suggested that it might be possible for center benefits to happen at a national level. At the NIBIB level, it could benefit a larger number of investigators over a larger geographical range. For example, seed funding for a small investigator at the national level or the R03 mechanism would be helpful to fund high-risk projects for a year or two. The disadvantage of a center is that it puts emphasis on a single geographic area. This is an inefficient use of a small resource with the small amount of money available from NIBIB. Another Panel member agreed that the current budget situation does not allow for large centers, but that it is necessary to separate what is currently possible from what could be done if the budget changes, or if the new direction is important enough to cause a change of the budget. An example is the NSF NSECs. With a larger number of centers, there is likely to be a center in most geographical regions that have a high density of research.

The Panel suggested another possible funding mechanism for research tool development. If a researcher receives an R01 and is successful, there should be a mechanism to apply for an administrative supplement of $100,000 for a year or two. This would allow for a postdoctoral fellow to work with a collaborator and perform preliminary work to determine if the tool has promise in a specific area, but the mechanism would have to be quickly accessible to take advantage of the collaboration. NIBIB staff responded that the Institute is allowed to provide up to $100,000 in an administrative supplement without going through council, as long as the research is within the scope of the original grant.

Currently, there is only a small pool available for administrative supplements ($300,000), and those resources are dedicated to emergencies and special circumstances. The idea the Panel proposed appears to be a more routine application of funds. A Panel member suggested that if a researcher would like to add a collaborator to a project, there should be a link between that collaborator and an existing R01. Another member responded that it would not represent extra money for the original project but, rather, an opportunity to finish the original goal and the process must have a quick turnaround to keep momentum going with the collaborator. NIBIB staff suggested that this sounded like a resurrection of the R21 and R33 funding mechanisms. The downside to those mechanisms was that there wasn't any control over the budget; however, this problem is fixable. A Panel member responded that this is a natural progression of research. Most nanotechnology doesn't begin in the life science community. This type of scenario seems very common and could encourage physical scientists and biologists to collaborate.

The Panel member suggested that this concept is different from the R21 or R33 because those funding mechanisms require the researcher to predict the outcome. In this case, it would be more spontaneous and would be similar to a small grant program that is connected to an existing grant. NIBIB staff clarified that a small grant would have to go through the peer review process, which would slow things down. The Panel member responded that it would also need to accommodate the idea that collaboration would be unanticipated. An Institute staff member explained that anyone could apply for an administrative supplement; the only problem is limited resources to fund a request. There is currently an initiative for administrative supplements to R01 grants, the motivation behind which is to get people involved in standards development. This current initiative could be used as a model.

The Panel asked how a physical scientist who does not have a connection to NIH or life sciences could get involved in such a project, as the culture of NIH is very different from that of NSF or DOE. A NIBIB staff member suggested that if the interested collaborator has an existing NIH grant and the contribution of the physical scientist fits within the specific aims of the existing NIH funding, the collaborator's grant could be supplemented to pay for the physical scientist's research. NIBIB could not supplement an NSF grant.

A question was raised by the Panel about existence of interagency agreements between NSF and NIH to provide funding to allow chemists to work with biologists. NIBIB staff responded that it is possible, but it has not happened to a large degree. An example is multiscale modeling. In this case, NASA and NSF collaborated to create requests for applications and awards were managed by the appropriate agency. The Panel clarified that the role of NIBIB would be to either collaborate at different phases of the project or to initiate the collaboration. NIBIB staff agreed that this type of funding is possible and could be a way to get the physical and life sciences together through multiagency participation. The intent would be stated in the announcement. There are no regulations against it, but NIBIB would need a group to come together with an idea. There has been reluctance to do this in the past, but the culture is changing.

The Panel asked if there is any barrier to having joint principal investigators at different geographical locations. NIBIB staff responded that there is no rule barring geographical separation; however, there is a question of practicality. If physical interactions are necessary to do the science, the issue would come into play in the application review process.

A Panel member suggested that nanodot research exploded because material became commercially available and easily accessible to biological researchers. Research on other materials has not advanced because it has been difficult for non-chemists to acquire them. Another Panel member suggested that the multi-investigator mechanism of the Bioengineering Research Partnerships (BRP) might be helpful in this respect, and yet another member responded that while these mechanisms

might unite one or two researchers, it doesn't allow a thousand people to start working on development of a new technology.

The Panel suggested changing funding to allow an optional sixth year if the researcher is successful and meets milestones. The additional year could be used to make larger amounts of the new material. However, a member questioned whether scaling up of nanomaterials is important enough to add to the NIBIB interests.

Creation of an Integrated Nanotechnology Program

The Panel discussed advantages to creating a specific nanotechnology program. Currently, nanotechnology is spread throughout NIBIB and has no special treatment. This appears advantageous because it enables technology. However, a separate program could encourage early-stage discovery. In the early development stage, a material may not fit into one of the broader categories since its properties are not well determined. An Institute staff member explained that there is a program called novel biomaterials. It is a small program because there is no link to a specific application.

In favor of an integrated nanotechnology program, a Panel member asked whether such a program would increase the amount of funding available to NIBIB. NIBIB staff replied that there might be budgetary implications. Another Institute staff member suggested the issue could be addressed in one of two ways: from a political viewpoint or a scientific viewpoint. The PRG panel is suggesting there is not a scientific reason to create a separate program; however, there may be a political benefit from a funding allocation perspective. The Panel felt that creating a separate program might result in name recognition. There is recognition on a university level and from a student's or postdoctoral fellow's view. It would give the group an identity and might be important for expansion of the NIBIB portfolio. A Panel member inquired if a separate administrative unit would be needed; it might be possible to simply advertise the current research with a specific name. NIBIB staff agreed and mentioned that it would not be necessary to sacrifice what is already in place. However, attachment of a brand or a name would benefit NIBIB in the RCDC coding and make it easier to pinpoint the investments.

A Panel member explained that in similar situations in academics—for example, when a new portfolio program is started—the program has an identity, a Web site, and specific faculty and students associated with it. As an example, while it is not possible to get a degree in nanotechnology, one can receive a specialization certificate. It is not an attempt to replace the administrative program currently in place. Another Panel member commented that the terminology is not consistent, and that there are many ways to describe things on the nanoscale, including nanobiology, nanomedicine, etc. The Panel indicated that it is first necessary to gather compelling success stories about nanotechnology projects that started at NIBIB, and suggested that the current name, NIBIB Nanotechnology Program, is effective and is general enough to cover various projects. Developing another name more uniquely associated with NIBIB might not be as well understood.

An Institute staff member responded that the goal was to have NIBIB bring nanotechnology to NIH. The Panel inquired if there would be an impact on other Institutes with a nanotechnology interest. A NIBIB staff member mentioned that the NNI has made it easy for the different Institutes and even agencies to work well together in regards to nanotechnology. The Panel asked if it is possible to view a program across multiple Institutes in a manner that is similar to graduate programs across departments. Another Panel member explained that growth of nanotechnology at NIH has not happened in a trans-Institute manner. Several Institutes at NIH, such as NCI, identify with nanotechnology. NIBIB would not be able to declare where nanotechnology belongs at NIH. However, nanotechnology does offer something of importance to biomedical science and medicine.

The focus was brought back to the NIBIB mission for nanotechnology, not that of the entire NIH, and the importance of keeping nanotechnology integrated with the other NIBIB research programs. By itself, the nanotechnology program is weak, but it is strong in combination with other programs in the Institute. The question is how NIBIB will position itself in this temporary phase where programs are just beginning to mature. The Panel commented that nanotechnology that has a potential health application is strongly associated with NIH.

Progress Review Group Recommendations for Program Priorities and Future Directions

The PRG Panel meeting concluded with the following recommendations to NIBIB:

1. Differentiate NIBIB's nanotechnology program from those at other NIH ICs by emphasizing tools development.
2. Promote activities that will allow tool builders and users (basic and clinical researchers) to interact and evaluate the tools. Identify the appropriate model for center-based research that allows flexibility in pairing tools with users. Support supplement grants for cross-disciplinary collaborations involving nanobioengineering.
3. Encourage collaborations at the interface between the life and physical sciences by supporting and promoting interdisciplinary, multiple-PI grants. Target collaborations involving new investigators, particularly those in the physical sciences not traditionally funded by the NIH.
4. Utilize appropriate programs and mechanism to support truly high-risk, but plausible, projects.
5. Invigorate the biomedical research community by increasing outreach to new investigators, supporting small grant mechanisms, and supporting additional training grants and undergraduate supplements for nanotechnology education.

Closing Remarks

Dr. Belinda Seto, Deputy Director, NIBIB

Dr. Seto thanked members of the PRG for their valuable input and advice in the process of developing a strategic plan for the Institute. As the plan is drafted into a more complete form, it will be shared with PRG participants for review and comments on further prioritizing areas of nanotechnology for the future.

Attachment 1

NIBIB Nanotechnology Program Review Group Meeting Agenda

Date: January 26, 2010

Location: Marriott Bethesda Suites, Patriot Ballroom

Panel Roster: Milan Mrksich, Ph.D., University of Chicago, Panel Chair
Wah Chiu, Ph.D., Baylor College of Medicine
Richard Crooks, Ph.D., University of Texas at Austin
Raoul Kopelman, Ph.D., University of Michigan
Angelique Louie, Ph.D., University of California at Davis
Jennifer West, Ph.D., Rice University

Agenda

8:45 AM	Coffee and Light Refreshments
9:00 AM	Welcome and Introduction
	Belinda Seto, Ph.D., NIBIB Deputy Director
9:10 AM	NIBIB Program Portfolio Presentations
	NIH Overview and Advanced Biomaterials, Drug and Gene Delivery, and Tissue Engineering—Lori Henderson, Ph.D.
	Biosensors and Training—Brenda Korte, Ph.D.
	Imaging Technologies—Yantian Zhang, Ph.D.
10:00 AM	Panel Discussion
	Panel Chair, Milan Mrksich, Ph.D.
10:30 AM	Break
10:45 AM	Panel Discussion
12:30 PM	Lunch
1:00 PM	Panel Discussion
2:30 PM	Wrap-up
3:30 PM	Adjournment

Attachment 2

Nanotechnology Program Progress Review Group Participants

January 26, 2010

Progress Review Group Members

Milan Mrksich, Ph.D., Panel Chair
Professor, Department of Chemistry
University of Chicago

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Baylor College of Medicine

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University of Michigan

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Associate Professor, Department of Biomedical Engineering
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Jennifer West, Ph.D.
Isabel C. Cameron Professor, Department of Bioengineering
Rice University

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