DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL ADVISORY COUNCIL FOR
BIOMEDICAL IMAGING AND BIOENGINEERING
Summary of Meeting[1]
January 27, 2005

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its seventh meeting on January 27, 2005, in Building 31C, 6th Floor Conference Room 6, in Bethesda, Maryland. Dr. Roderic I. Pettigrew, Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), served as Chairperson.

In accordance with Public Law 92-463, the meeting was open on January 27, 2005, from 1:00 P.M. until 5:30 P.M. and on January 28, 2005, from 8:30 A.M. until 12:00 P.M., for the review and discussion of program development, needs and policy. The meeting was closed to the public on January 28, 2005, from 1:00 P.M. until 4:30 P.M. for discussion and consideration of individual grant applications.

Council members present:

Dr. Carlo J. De Luca
Dr. Janie Fouke
Dr. Robert I. Grossman
Dr. Shirley A. Jackson
Dr. Linda C. Lucas
Dr. C. Douglas Maynard
Dr. Barbara J. McNeil
Dr. Norbert J. Pelc
Dr. Stephen A. Williams
Dr. Frank C. Yin
Dr. James A. Zagzebski

Council members not present

Dr. Rebecca R. Richards-Kortum

Ex officio members present:

Dr. Bruce Hamilton
Dr. James G. Smirniotopoulos
Dr. Vincent L. Vilker
Dr. Andrew Watkins
Dr. Michael Weiner

Ex officio members absent:

Dr. Elias A. Zerhouni, Jr.

[1] For the record, it is noted that members absent themselves from the meeting when the Council is discussing applications (a) from their respective institutions or (b) in which a real or apparent conflict of interest might occur.

Executive Secretary:
Dr. Arlene Y. Chiu

Also present:

Dr. Gary H. Glover
Dr. Donald Harrington
Dr. Robert Nerem
Dr. Richard Swaja

NIBIB staff present for portions of the meeting:

Ms. Lillian Ashley
Dr. Prabha Atreya
Ms. Pamela Clatterbuck
Dr. Lawrence Clark
Ms. Nancy Curling
Dr. Anthony Demsey
Dr. Bonnie Dunn
Ms. Angela Eldridge
Ms. Cheryl Fee
Ms. Shirley Finney
Ms. Tinera Fobbs
Mr. Rajal Ganatra
Dr. David George
Ms. Colleen Guay-Broder
Dr. John W. Haller
Dr. William Heetderks
Ms. Christine Hollingsworth
Dr. Christine A. Kelley
Ms. Mary Beth Kester
Dr. Henry Khachaturian
Dr. Brenda Korte
Mr. Maurice Lee
Dr. Alan McLaughlin
Mr. Todd Merchak
Mr. Nicholas Mitrano
Dr. Peter Moy
Dr. Grace Peng
Dr. Belinda P. Seto
Ms. Theresa Smith
Ms. Shana Stepp
Ms. Sandra Talley
Dr. Meredith Temple-O'Connor
Dr. Carol Torgan
Ms. Florence Turska
Ms. Stacy Wallick
Dr. Fei Wang
Mr. Elijah Weisberg
Dr. Anthony Wolbarst
Dr. Yantian Zhang

Members of the public present for portions of the open meeting :

Mr. Robert Atcher, Los Alamos National Laboratory
Mr. Phil Bulman, Equals Three
Ms. Wendy Eichorst, Lewis-Burke Association
Mr. Steven Evangelista, SRI International
Ms. Pat Ford-Roegner, AIMBE
Ms. Kerry Groome, Constella Group
Mr. Michael Hamm, Biomedical Engineering Society
Mr. Robert Harris, MasiMax Resources Inc.
Ms. Molly Laas, Blue Sheet
Dr. John Linehan, Whitaker Foundation
Dr. Troy Nagle, North Carolina State University
Mr. Ed Nagy, Academy of Radiology Research
Ms. Chris Peterson, SRI International

Ms. Michelle Rodrigues, Academy of Radiology Research
Ms. Gloria Romanelli, American College of Radiology
Mr. Peter Schad, Academy of Radiology Research
Dr. Frank Szoka, UCSF
Dr. James Thrall, Massachusetts General Hospital
Mr. Steve Willis, Pfizer
Mr. Jeffrey Young, Blue Sheet

Other Federal Employees Present :

Dr. Sally Amereu, National Institutes of Health/ Center for Scientific Review
Dr. Eileen Bradley, National Institutes of Health/ Center for Scientific Review
Dr. David Brown, Food and Drug Administration
Dr. Mrunal Chapekar, National Institute of Standards and Technology
Dr.Dharam Dhindsa, National Institutes of Health/Center for Scientific Review
Dr. Tom Johnson, National Institutes of Health/ Office of the Director
Dr. Albert Lee, National Institute of Standards and Technology
Dr.Xiang-Ning Li, National Institutes of Health/Center for Scientific Review
Dr.Weihua Luo, National Institutes of Health/Center for Scientific Review
Dr. Kyle Meirs, Food and Drug Administration
Dr. Authur Petrosian, National Institutes of Health/Center for Scientific
Dr. Anthony Wolbarst, Environmental Protection Agency
Dr. Steven Zullo, National Institutes of Health/Center for Scientific Review

I. Call to Order and Opening Remarks: Dr. Roderic Pettigrew

Dr. Roderic Pettigrew welcomed Council members, guests, and staff to the seventh National Advisory Council meeting, and noted some changes in the content and format of the Council meetings. He announced the retirement of Dr. Joan Harmon, the previous Executive Secretary of NACBIB, and acknowledged her contributions and decades of dedicated and distinguished service to the National Institutes of Health (NIH). Dr. Pettigrew then introduced Dr. Harmon's replacement, Dr. Arlene Chiu, and described her academic and professional accomplishments. Dr. Chiu received her B.A. from Stanford and Ph.D. from the California Institute of Technology in the Biological Sciences. She came to NIBIB after serving six years at the National Institute of Neurological Disorders and Stroke where she focused on the spinal cord injury and stem cell research programs.

II. Review of Regulations on Confidentiality and Conflict of Interest: Dr. Arlene Y. Chiu

Dr. Chiu summarized the requirements under the Government in the Sunshine Act and the Federal Advisory Committee Act that govern all Advisory Council meetings. These Acts require the Department of Health and Human Services (DHHS) to open Advisory Committee meetings to the public, except when proprietary and/or personal information

is discussed. To comply with these regulations, she announced that the NACBIB meeting would be open to the public except for the review of individual grant applications scheduled to begin at 1:00 P.M. on January 28, 2005 in closed session. Dr. Chiu briefed the Council members on guidelines for conflicts of interest and confidentiality issues, and emphasized the importance of maintaining confidentiality in all settings, formal and informal. Members were given examples of when these guidelines should be applied and were offered the opportunity to ask questions to clarify any areas of uncertainty.

III. Annual Report on Animal and Human Welfare Concerns:
Dr. Arlene Y. Chiu

Dr. Chiu reported on the involvement of humans and animals in research that is supported by the NIBIB for 2004, in response to a request by Council for an annual update on these topics. Approximately one quarter of the applications received by the NIBIB proposed research using animals; a similar fraction of research applications to all of NIH indicates use of animals. Concerns with animal welfare were found in less than 2 percent of incoming applications to the NIBIB and to the NIH. Applications were awarded only following the resolution of the concerns and approval by the Office of Laboratory Animal Welfare. In summary, the proportion of NIBIB applications using animals is similar to that of the NIH as a whole; only a very small proportion of incoming applications are found to have animal welfare concerns. The NIH and the NIBIB consider animal welfare to be critical to the conduct of research; therefore, no award is made until a concern is resolved. In contrast, the NIBIB received a far smaller proportion of research applications involving human subjects compared with the NIH as a whole. Only 20 percent of applications to the NIBIB involved human subjects compared to 40 percent for all NIH applications. Applications with concerns are also proportionately below those for the whole NIH. The NIH and the NIBIB consider the involvement of humans in a research endeavor to be critical, and all means must be utilized to protect the health and safety of these individuals. Therefore, no award is made until a concern is resolved and approval received from the Office of Human Research Protections.

III. Biennial Report on Compliance with the NIH Policy on Inclusion Guidelines:
Dr. Meredith Temple-O'Connor

Dr. Temple-O'Connor presented the NIBIB biennial report on Compliance with the NIH Policy on Inclusion Guidelines for Council approval. Public law requires that all NIH Institutes and Centers that fund human subject research track the inclusion of women and minorities in projects that are defined as clinical research. The Office of Research on Women's Health (ORWH) requests a biennial report on compliance with these guidelines from each Institute. In comparing fiscal year (FY) 2004 against data from FY 2003, NIBIB-funded research shows an increase in the percent of participation across several race and ethnicity groups including African-Americans, Asians, Hispanics, Caucasians and those classifying themselves as "more than one race." There was also an increase in the percent participation of women and a decrease in the number of individuals where the

race or ethnicity group was classified as "unknown or not reported." The report was approved unanimously by NACBIB for submission to ORWH.

III. Director's Report: **Dr. Roderic I. Pettigrew**

Dr. Pettigrew began his remarks by highlighting key points in the Institute's progress since the September Council meeting. He reviewed the FY 2004 and FY 2005 budgets and summarized the most significant events and activities of NIBIB that took place since the September meeting. Dr. Pettigrew concluded his remarks with a review of four research highlights from NIBIB-funded researchers.

Budget Update

In FY 2005, the NIBIB received an increase of approximately $12 million over the FY 2004 appropriation. The two most notable increases were in the training area to support fellowship and training mechanisms, and in contracts to support the anticipated efforts in Quantum projects.

Blue Ribbon Panel and Intramural Program

Dr. Pettigrew acknowledged the efforts of the Blue Ribbon Panel that was convened to discuss plans for an intramural program. This panel was tasked with reviewing the various challenges and opportunities associated with initiating an NIBIB intramural program. A full report of those findings was presented to the Council for final approval. Effective October 1, 2004, the PET Radiochemistry Laboratory and the Physics and Instrumentation Laboratory, formerly in the Clinical Center, are now officially a part of the NIBIB intramural program. Dr. King Li, Associate Director of the Clinical Center for Radiology, is serving as the acting Principal Investigator of this laboratory.

Workshops and Meetings

The NIBIB continues to participate in and support new initiatives that reach out to NIBIB grantees and the extramural research community. Since the last council meeting, NIBIB has participated in and supported four grantee workshops, meetings and scientific conferences. In addition, NIBIB is engaging in discussions with industry leaders to explore public/private partnerships.

The NIBIB held its first annual meeting for bioengineering grantees who received funding through the Requests for Applications (RFAs) that were issued during the first year of operation. Four of the ten initiatives were featured: biomaterials, tissue engineering, novel drug-delivery systems and biosensors.

In partnership with the National Science Foundation (NSF), NIBIB organized a Congressionally-requested conference on the interface of life sciences and physical sciences. The conference was held on November 9th, 2004, with the participation of ten Federal agencies including the Department of Defense, the Food and Drug Administration , the Environmental Protection Agency, the National Oceanic and Atmospheric Administration, the Department of Energy, the National Aeronautics and Space Administration, the NSF, the National Institute of Standards and Technology, the U.S. Department of Agriculture, and the Defense Advanced Research Projects Agency.

The NIBIB and NSF have also partnered to support a joint initiative in training undergraduates in bioengineering and bioinformatics. All nine institutions currently supported by this initiative participated in the third annual grantee meeting held this past December, where students were given the opportunity to give presentations on their research. These regional meetings are held at specific grantee sites and approximately 50 percent of the students are now pursuing graduate degrees in programs in bioengineering and bioinformatics.

On January 6, 2005, Dr. Belinda Seto, Deputy Director, and Dr. John Haller, Acting Director of the Division of Applied Science and Technology, participated in a workshop on incidental findings in imaging studies. A focus of the meeting was on neuroimaging, specifically circumstances when abnormalities unrelated to the investigation at hand are discovered during the course of a clinical trial. A report and guidelines from this meeting will be posted on the NIH website, and will be made available for public comment.

Scientific Portfolio and Initiatives
A list of all active initiatives supported by the NIBIB was provided to Council members and guests attending the meeting. In an effort to develop working partnerships with industry, the Institute has held meetings with representatives from 25 to 30 companies to explore opportunities for public/private partnerships in Quantum projects.

The NIBIB unveiled the interdisciplinary training initiative in collaboration with the Howard Hughes Medical Institute (HHMI) at a public forum held at the HHMI. The NIBIB will be instrumental in educating a new cadre of scientists for the 21st century who are specifically trained to do interdisciplinary research.

Dr**.** Pettigrew is co-chairing an NIH roadmap initiative on "new pathways to discovery" with Dr. Tom Insell, Director of the National Institute on Mental Health and Dr. Francis Collins, Director of the National Human Genome Research Institute. This initiative focuses on bioinformatics, computational biology and the creation of the National Centers for Biomedical Computing (NCBC). The goal will be to build a computational infrastructure for biomedical computing in the United States. Four sites have already been awarded roadmap funds. The NIBIB is managing two of these sites: the National Alliance for Medical Imaging Computing and the Center for Computing for Computational Biology.

Research Highlights
Dr. Pettigrew concluded his remarks with examples of research currently supported by the NIBIB:

- **Albert Einstein Center for Synchotron Biosciences----Dr. Mark R. Chance, Albert Einstein Center for Synchroton Biosciences:** Dr. Chance is using synchrotron X-ray foot printing, to uncover the "tracks" left by two viral macromolecules as they interact to help the virus replicate. The foot printing technique, coupled with 3-D computer modeling, yielded unprecedented insight

into this molecular interaction. Researchers have already started searching for drugs that might treat infections by blocking that interaction.

- **Nonlinear Dynamic Modeling of Physiological Systems ----Dr. Vasilis Marmarelis, University of Southern California:** As part of a Bioengineering Research Partnership (BRP) grant, Dr. Marmarelis has devised the first practical approach to obtaining nonlinear dynamic models from stimulus-response data.
- **Nonlinear Modeling of the Hippocampus-----Dr. Theodore W. Berger, University of Southern California:** Featured in Newsweek Magazine, Dr. Berger has devised computer programs that replicate the cell's behavior, and has built chips to run them. He hopes to test a chip in live rats within 3 years, then monkeys and ultimately, humans.
- **MRI Vascular Guided Interventions----Dr. John M. Pauly, Stanford University:** Dr. Pauly has developed visualization techniques and control devices for vascular interventions. The device consists of an active guide wire that allows catheter tracking and color flow imaging.
- **Regenerative Scaffold Technologies for CNS and Diabetes----Dr. Sam Strupp, Northwestern University:** Dr. Strupp and his team focus on nerve regeneration and development of self-assemblying bioactive nanofibers. Use of self-assembled nanofiber scaffolding when compared to just extra cellular proteins has shown significant improvement in neural differentiation.

IV. Training and Career Development Subcommittee: Dr. Douglas Maynard

Dr. Maynard provided a brief summary of the Training and Career Development Subcommittee meeting held January 27, 2005. He acknowledged all subcommittee members that were present and thanked Dr. Meredith Temple-O'Connor and Dr. Henry Khachaturian for their hard work in preparing for the meeting.

Current Training Efforts

The number of training opportunities and applicants continues to increase across all of NIH. The NIH-NSF summer program has been highly successful in its first 2 years. With 1 year remaining in the program, NIH and the NSF are exploring ways to continue supporting this program. The new HHMI and NIBIB partnership was well received by the extramural community and continues to grow. The clinical resident program is not developing as fast as the other NIBIB training programs; NIBIB staff are currently exploring options on how to improve the structure and administration of the program.

Needs Assessment

The NIBIB Training Division has secured funding to conduct a needs assessment of the biomedical community and the medical imaging community.

Future Directions

Council members discussed how NIBIB can improve the success rate of first-time applicants with R01 applications. The majority of the subcommittee recommended that NIBIB should not focus on the K02 program.

V. Strategic Plan Development Report: Dr. Frank Yin

Dr. Frank Yin, acting chair for the Strategic Plan Development Subcommittee, provided a brief summary of the subcommittee meeting held on January 27, 2005. Dr. Pettigrew charged the subcommittee to continue service in an advisory capacity to the Institute on the implementation of the strategic plan. Dr. William Heetderks presented an analysis of the Institute's current grant portfolio. Attracting new-investigators and improving their success rate remains a high priority for the NIBIB. Dr. Pettigrew presented an update of the Quantum Grants Program which led to a lively discussion on how NIBIB can facilitate translational research. Dr. Yin ended by reiterating the Council's interest in helping NIBIB move forward with the implementation of the strategic plan.

VI. Review of the NIBIB Program on Drug and Gene Delivery Systems and Devices: Dr. Peter Moy

Dr. Peter Moy, Program Director in the Division of Discovery Science and Technology, presented an overview of the NIBIB research portfolio in drug and gene delivery.

According to a survey conducted by the Centers for Disease Control and Prevention, as of the year 2000, about 85 percent of the U.S. population aged 65 and over reports using at least one prescription drug. With the aging of the population, this trend will continue. When developing drug and gene delivery systems, it is important to consider the desired delivery characteristics depending on the specific clinical application. For example, an anti-hypertensive medication could be maintained at a constant level, without the requirement of multiple dosing throughout the day. In contrast, antibiotic treatment of an acute infection could be achieved with a single dose. It is just as important to be able to direct the therapeutic agent to a specific part of the body to minimize side effects.

The most common drugs are small molecules. These small molecules are generally non-specific in their action leading to several considerations in drug development including pharmacokinetics, bioavailability, side effects and toxicity, clearance from the body, and the ability to target specific organs or tissues. It is important to select carefully the dosage in order to maximize the therapeutic benefit while minimizing the side effects.

The second major category of drugs are macromolecules or large molecular weight compounds such as proteins (e.g., insulin) and RNA or DNA for gene therapy. Macromolecular drugs tend to be less stable and difficult to deliver orally due to their relatively large size. Intracellular delivery of these large molecules is important to further advance gene therapy.

The overarching goals for the NIBIB's Drug and Gene Delivery Program are to improve delivery technologies for more effective targeting of small-molecule drugs, as well as to enable effective and minimally invasive delivery of macromolecular therapeutic drugs,

especially proteins, and, lastly, to improve intercellular therapy where molecular intervention via gene therapy becomes a reality. The Institute supports innovative bioengineering approaches to address these issues by focusing on new or improved technologies for treatment of diverse disease conditions versus disease-specific drug and gene delivery programs that are also supported by other Institutes.

The research portfolio in drug and gene delivery was established in 2003 with the release of an initiative to encourage the development of novel drug and gene delivery systems. Twenty-four projects were funded in response to that announcement. Additionally, investigator-initiated research has been steadily increasing since that time. NIBIB-supported research is focused on drug carrier systems, energy-assisted delivery, viral gene delivery, and non-viral gene delivery.

Dr. Moy presented representative scientific highlights to illustrate the various approaches to address the current problems in drug and gene delivery.

Controlled Release. Controlled-release drug formulations have been in use for a number of years and the most common type is the time-release agent. However, there are still a number of improvements that can be made in this technology. First, the current way of making the microspheres for dosing produces carrier systems that tend to be uneven in size, which can alter delivery of the drug. Dr. Kinam Park, Purdue University, has adopted flow-management technology to create microspheres that are uniform in size. He has extended the technology to produce microspheres using two different materials. Similar research is conducted by Dr. Daniel Pack at the University of Illinois. These investigators have found that by forming the microspheres of polymers with differing rates of degradation, a constant rate of drug delivery can be achieved over time.

Targeted Delivery. Targeted drug delivery to specific cells, tissues, or organs can ensure appropriate therapeutic concentrations while at the same time minimizing toxicity to the rest of the body. In principle, any cell can be targeted by identifying specific cellular receptors and attaching the appropriate "targeting" molecule to the microsphere. The smallest polymer microspheres are about ten microns – approximately the same size as a cell. In order for a targeting microsphere to "grab" the receptor, it should be proportional in size to the cell. To address this size problem, researchers are developing micelles – a block of polymer systems that self-assemble – and dendrimers – highly-branched structures that are covalently formed.

Dr. Vladimir Torchilin, Northeastern University, is using micellar systems to deliver Paclitaxel, an anti-tumor drug, more effectively. Dr. Torchilin has created a micelle which has a hydrophobic (water-hating) core that can easily solublize a hydrophobic drug, like Paclitaxel, while maintaining suspension by having a hydrophilic (water-loving) polymer sheath. Early results show that the micellar systems were able to effectively inhibit the growth of tumor cells, and at levels that are much lower than normal. This technology can be extended to attach imaging agents to show localization of the drug carriers at the site of the tumor.

Oral Drug Delivery. Delivery of drugs orally or by injection is the two most common drug delivery mechanisms used today. One of the biggest problems with oral delivery is that peptide-based drugs cannot be delivered by mouth because of degradation as they pass through the stomach. Dr. Nicholas Peppas, University of Texas, has created copolymer carrier systems consisting of acrylic acid and polyethylene glycol blocks. In an acidic environment, these molecules form strong bonds and are able to shield drugs, such as insulin, from stomach acid. As the material moves through the intestinal tract and reaches a more neutral environment the bonds disassociate thereby releasing the insulin. This method has successfully delivered insulin orally in an animal model of diabetes.

Minimally Invasive Delivery. Like insulin, most protein-based drugs are administered by painful injections. NIBIB-supported investigators are exploring alternative ways to deliver protein-based drugs. One approach, developed by Dr. Mark Prausnitz at Georgia Institute of Technology, uses microneedles as a painless method of drug delivery. These 100 micron diameter microneedles can painlessly penetrate the skin allowing drugs to be administered either topically or through pores in the needles.

In another approach, Dr. Robert Langer, Massachusetts Institute of Technology, has pioneered a process called low-frequency sonophoresis in which the skin is exposed to ultrasound. This generates areas of increased permeability on the skin surface allowing drugs to pass painlessly through the skin into the tissues and blood vessels beneath.

Dr. Sek-Wen Hui, Roswell Park Cancer Institute, has been looking at the process of electroporation for enhanced transdermal delivery of insulin, as well as genes. Electroporation involves application of a high-voltage potential across the skin, causing a breakdown in the cell membranes in the various skin layers. Dr. Hui has demonstrated that through a combination of electroporation and a lipid-enhanced carrier agent, there is a dramatic increase in the amount of insulin that can be delivered through the skin.

Intracellular Delivery of Gene Therapy. Thus far, most clinical studies have used viral-based vectors due to their increased transfection efficiency when compared to non-viral-based vectors. However, there are a number of drawbacks to the use of viral-based vectors that can be improved upon by non-viral-based systems. For example, non-viral-based systems are usually less toxic and less immunogenic. In addition, they can be designed to carry much larger gene products. NIBIB-supported researchers are exploring methods to increase the transfection efficiency of non-viral vectors. Dr. Patrick Stayton at the University of Washington has been studying the use of modified polymers to enhance release of gene therapy treatments into the cytosol of the cell.

Dr. Moy pointed out that advances in drug and gene delivery have been augmented by new developments at the interface of materials technologies, as well as a better understanding of biological systems. The ability to custom design the architecture of these new carrier systems, at all scales, will enable more effective therapy by allowing targeted and controlled release at both the cellular and intracellular level. Alternative delivery modalities, such as transdermal delivery, offer great promise in advancing not

only more effective drug delivery, but also increased patient compliance due to less pain. In the future, we can envision drug-delivery systems whereby we have a closed-loop system in which a smart component can monitor the physiologic need and respond with optimum drug dosage. The NIBIB will continue to support rational design approaches to create new robust platforms based on biometrically inspired delivery systems.

VII. Scientific Presentation: Rational Design of Synthetic Gene Carriers: Dr. Francis Szoka

Dr. Francis Szoka is a professor of biopharmaceutical sciences and pharmaceutical chemistry at the University of California, San Francisco. His research is focused on understanding the physiochemical properties of phospholipid bilayers and the physical factors involved in membrane fusion, with particular focus on how phospholipid bilayer vesicles can be used in pharmaceutical applications. Dr. Szoka is also a founder of SEQUUS Pharmaceuticals, founded in 1981 and later acquired by Alza, and subsequently by Johnson and Johnson in the late 1990s.

Dr. Szoka began his presentation by reiterating the problems with successful gene therapy previously discussed by Dr. Peter Moy. For successful gene therapy, DNA must be delivered intracellularly to be active. Viruses can be effective carriers to get the DNA inside the cell; however, they can also induce strong immune responses leading to adverse clinical events and fatalities. Gene therapy with a small replacement gene requires packaging of a large amount of DNA into a virus carrier. Nature has done this very effectively by compressing large pieces of DNA into virus particles. In the laboratory, this has been replicated to some extent using adenoviruses, adeno-associated viruses, herpes viruses, retroviruses, and lentiviruses. There have been some therapeutic successes using these viral systems. For example, children in France have been cured of an immunodeficiency syndrome using lentivirus-based gene therapy. Unfortunately, a number of these children have developed lymphoma as a result of the treatment.

Dr. Szoka and his colleagues are attempting to use the model of a virus and all of the strategies that have evolved over time to create a synthetic delivery system. To do this, several important barriers, such as assembly of the virus particle, route of administration, and DNA delivery into the cell cytoplasm and nucleus must be considered.

For gene assembly, Dr. Szoka, uses pH-sensitive phospholipids in an organic solution. When the solution is removed, the lipids assemble into a bilayer lipid particle enscapsulating the DNA. Specific targeting molecules can be bound to the surface of the lipid particles to enhance binding to the cellular membrane. Changes in the microenvironment will break apart the lipid membrane and release the DNA into the cell. This sequential assembly process enables modification of size and charge and allows targeting to specific cells in the body.

Dr. Szoka then discussed transport and delivery of the virus particle to cytoplasm. He described the use of a polyamidoamine dendrimer incorporated in the gene therapy

carrier to facilitate entry into the target cell. Fluorescent markers can also be incorporated to monitor delivery of the gene into the cell cytoplasm.

Once the gene has reached the cell cytoplasm, it must move into the cell nucleus to exert an effect. Viruses get DNA into the cell nucleus by using "molecular motors" running along the microtubules in opposite directions. Dr. Szoka demonstrated this with a short video clip. He described efforts to create a fusion protein to mimic the molecular motors found in the cell. When the synthetic protein binds to the microtubules, it can carry the gene therapy agent into the nucleus.

Dr. Szoka described *in vivo* research in animals using the non-viral system described above. He described the use of convection-enhanced delivery to transfect normal or tumor cells in the rat brain.

Dr. Szoka stated that it is important to understand the individual barriers that, when combined, may lead to a single multifunctional gene therapy agent. The goal is to reduce the number of components and then synthesize those in one or a few molecules. He stated that non-viral systems are easy to manufacture and are composed of simple components. These non-viral systems are excellent prospects for continued improvements to increase their efficiency to reach that of a viral system.

VIII. Update on Blue Ribbon Panel: Drs. Jim Thrall and John Linehan

Dr. Jim Thrall and Dr. John Linehan, co-chairs of the Blue Ribbon Panel (the Panel), presented the Panel's recommendations to the advisory Council members. On September 17, 2004, the Panel met with selected members of the NIH leadership to explore key issues in developing the intramural program. Panel members met first with Dr. Michael Gottesman, Deputy Director for Intramural Research at the NIH, to discuss the current status of intramural programs at NIH. Next, Dr. Pettigrew briefed the Panel on pertinent aspects of the Institute's budget and the decreasing payline from 19.3 percent in FY 2003 to approximately 16 percent in FY 2005. Finally, the Panel engaged in a discussion of intramural programs with representatives of the NIBIB, the National Institute of Standards and Technology of the Department of Commerce, and the Food and Drug and Administration.

The Panel discussions centered around NIBIB priorities---whether building an intramural program should supersede maintaining a higher payline for the extramural program with the majority of the panel agreeing that NIBIB should maintain an attractive payline. The Panel recommended specifically that NIBIB should not promote the intramural program at the expense of the extramural program. Recommendations included using intramural funds to expand training opportunities at NIH with an emphasis on the postdoctoral level; and recruiting a full-time Scientific Director. Given the funding limitations, the Panel chose not to make specific recommendations on the subject matter of NIBIB's intramural program.

Council members expressed their concern that the Panel's deliberations were restricted by budget limitations, and expressed a desire for more specific recommendations on the scientific scope of the intramural program and possibilities for growth. Further delineation of these opportunities could, in turn, be used to solicit additional funding support. In response, Dr. Linehan stressed that the Panel discussed every issue that was in the scope of its charge; the recommendations presented to Council reflected the realities of the budget. The recommendation to recruit an intramural Scientific Director is an indication of the Panel's vision to see the program grow. To clarify the budget considerations, Dr. Seto noted that NIBIB is prohibited from using appropriations marked for extramural programs to support an intramural program. Dr. Pettigrew concluded this session by thanking both Dr. Thrall and Dr. Linehan for their efforts in leading the Panel and asked the Panel to draft an addendum to their report to reflect this discussion with Council.

IX. Closing Remarks

The meeting was closed for review of applications at 12:00 P.M.

Closed Session
This portion of the meeting, involving specific grant review, was closed to the public in accordance with the provisions set forth in Section 552b (c) (4) and 552b (c) (6) Title 5, U.S. Code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

We certify that, to the best of our knowledge, the foregoing minutes and attachments are accurate and complete.

/s/

Arlene Y. Chiu, Ph.D.
Executive Secretary
National Advisory Council for Biomedical Imaging and Bioengineering
Director, Office of Research Administration
National Institute of Biomedical Imaging and Bioengineering

/s/

Roderic I. Pettigrew, Ph. D., M.D.
Chairperson,
National Advisory Council for Biomedical Imaging and Bioengineering
Director
National Institute of Biomedical Imaging and Bioengineering

The Council will consider these minutes at its next meeting on May 25-26, 2005. Corrections or notations will be incorporated in the minutes of that meeting.