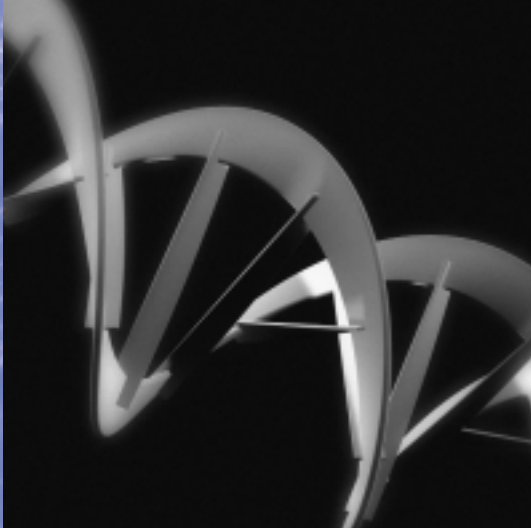
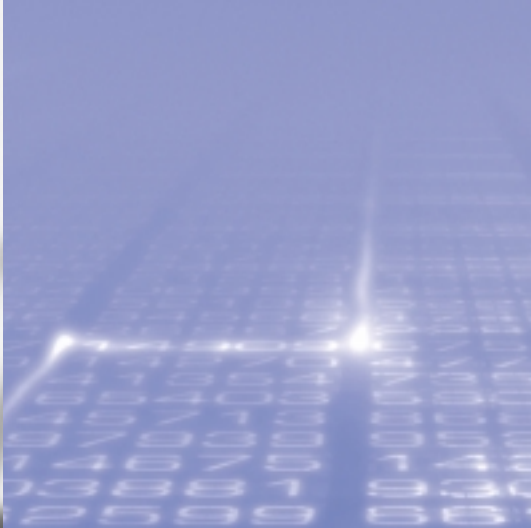
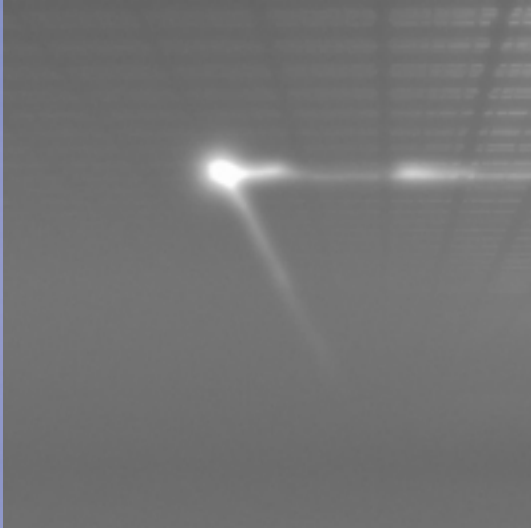
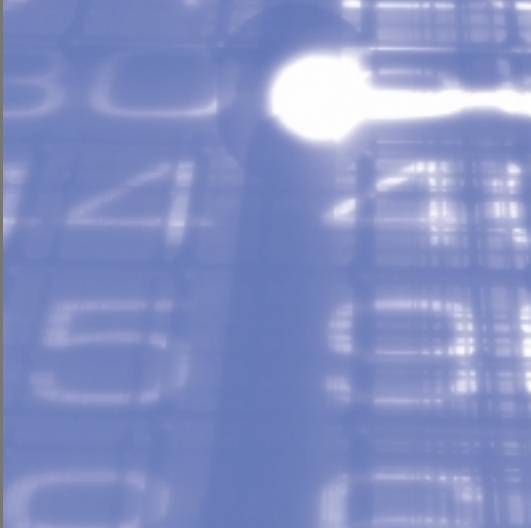


*The Role
of the
Private
Sector in
Training
the Next
Generation
of Biomedical
Scientists*



Proceedings of a
conference sponsored by
the American Cancer Society,
the Burroughs Wellcome Fund,
and the Howard Hughes
Medical Institute

February 2000



Letter from the Co-Sponsors

Biology in the postgenomic era will require individuals with new sets of skills who can establish themselves successfully in rapidly moving fields of research. Philanthropy has played and will continue to play an important part in jump-starting the careers of new investigators, particularly during the transition from postdoctoral fellow to faculty member, and in building bridges between traditional and emerging fields of research. The receipt of funding from a prestigious foundation, health agency, or medical research organization can be the push that launches a research career. In addition, because the mission of philanthropy is often problem based, private funds can support inherently interdisciplinary research and training that breaks new ground.

Although the magnitude of private contributions to biomedical research training cannot match that of the federal government, philanthropy plays a special role. Foundations can complement public programs to realize a substantial impact. In addition, they can support alliances that typically would not be supported through public mechanisms. Private philanthropies, particularly voluntary health agencies with a disease focus, can provide critical help to fill the gap between the rate of advance in research and the translation of new knowledge into therapies for human disease. Private funders can use their resources to encourage beginning investigators to enter a research area critical to the agency's mission or to encourage midcareer investigators to change course in their area of research focus.

We sponsored and convened this conference to explore in depth the unique contribution private funders can make to ensure that appropriate and adequate training programs are available for basic and clinical research. Two years ago, in February 1998, we convened a successful first meeting on this topic and subsequently determined that an ongoing dialogue in the private funding community was a most useful step toward achieving an objective important to all those invited—ensuring that future biomedical research questions can be answered by a well-prepared cadre of basic and clinical scientists.

We believe this gathering met our goals. Participants formed new relationships with other private funders and considered new directions in which they might take their own organizations. The conference reinforced our belief that private funds can change the culture and structures of research and education, not merely supplement the substantial investment made by the public sector. Because some of the most exciting work of the postgenomic era will occur at the interface of disciplines, private funders can provide the “glue” needed to compel faculty to work together toward research and educational goals. Importantly, the private sector can search for the right niche and experiment with innovative approaches.

This report summarizes the meeting and is intended to provide similar stimuli for those who were unable to attend. It is our hope that the philanthropic community will continue the many conversations that were initiated at this conference.

Thomas R. Cech, Ph.D.
President
Howard Hughes Medical Institute

Enriqueta C. Bond, Ph.D.
President
Burroughs Wellcome Fund

John Stevens, M.D.
Vice President for Extramural Grants
American Cancer Society

Executive Summary

On February 14-16, 2000, the American Cancer Society, the Burroughs Wellcome Fund, and the Howard Hughes Medical Institute convened a meeting on private sector support for biomedical research training. The goal of the meeting was to address the unique contribution that private funders can make in ensuring that appropriate and adequate training programs are available for basic and clinical research. Representatives from government, academia, and nongovernmental funding agencies had the opportunity to hear presentations and discuss current programs and plans of public and private funders and to consider goals for the future.

The meeting focused on training two groups of future investigators: basic biomedical and clinical scientists. In addition, cross-cutting topics were addressed, such as the move toward electronic grantsmaking and ethical issues facing future biomedical research.

Conclusions and Recommendations for Training of Basic Biomedical Scientists

Out of the sessions on training basic biomedical scientists emerged the following conclusions and recommendations:

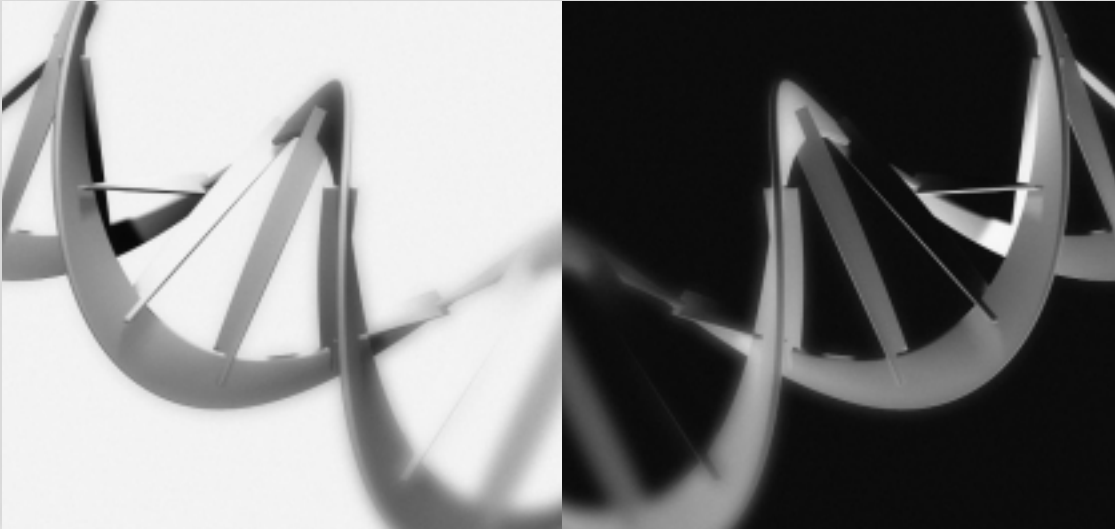
1. In the postgenomic era of research, multidisciplinary and interdisciplinary research will command center stage, requiring team approaches and the collaboration of many individuals from vastly different fields, ranging from computational mathematics to clinical science.

2. The need for team approaches to scientific research suggests that private funders can make a significant difference in building expertise and collaborations by providing support to clusters of faculty.
3. Support of postdoctoral students and new faculty is important, but insufficient. Philanthropy must also invest in the development of scientists from underrepresented groups, provide appropriate support for foreign students, and recognize that with the globalization of the research enterprise, it will be vital to provide experiences for U.S. students abroad.
4. The changing paradigm of research calls for innovations and changes in the education of scientists along the spectrum of K-12, undergraduate, and graduate education. The increasing need to value teaching in all settings could be improved by making grants that help free the time of scholar/researchers for teaching.
5. The private sector can facilitate some areas or types of research more easily than can public agencies. This would include, for example, research with embryonic stem cells or prehypothesis-driven work to assemble and organize information that can provide a platform for hypothesis-driven work and infrastructure support.
6. Partnerships among private funders and between the public and private sector will be valuable in moving the postgenomic research and training agenda forward and in leveraging the investments of both private sector and public sector groups.

Conclusions and Recommendations for Training of Clinical Researchers

The genetic revolution and other scientific advances are providing vast new and exciting opportunities in clinical research. Investments to advance the training of clinical researchers were proposed in two major areas—human capital and training programs.

1. The development of clinical scientists is a good target for private support. As with training basic scientists, it is critically important to support young clinical scientists, although other steps in the ladder also require attention. Research experiences during medical school, modeled after programs such as the Howard Hughes Medical Institute-National Institutes of Health (NIH) Cloister Program and the NIH-Pfizer Clinical Research Training Program, are excellent examples of support of clinical investigators early in their careers.
2. The M.D.-Ph.D. is the most successful model for the development of clinical scientists. This paradigm should be supported by the private sector in order to expand the numbers of trainees at currently funded sites or to develop new programs at institutions that could then become eligible for NIH support.
3. Despite the predominance of the M.D.-Ph.D. scientist, there are other essential types of physician-scientists, and these scientists require different types of support.
 - Numerous new master's-level programs are in development for clinical research training. The private sector can make a contribution by assisting with tuition support.



- Ph.D.s, if trained in pathobiology or other human disease constructs, can provide an invaluable resource to the clinical research team.
4. Transition support to assist individuals at key points in their training and career development, such as between thesis work and the first independent faculty position, can be essential to prevent young scientists from leaving research. In this respect, debt relief is crucial.
 5. The development of multidisciplinary and generic training programs in clinical research is urgently needed, and the collaboration of disease-oriented groups could make a critical difference. Such a consortium could provide funds for junior faculty and graduate students as they make key education and career transitions.
 6. The private sector could support innovative mechanisms by which to develop and support mentorship skills in new and existing faculty.
- At the meeting's end, several private funders agreed to pursue a joint project or collaboration in some specific area where organizations share a need and desired outcome. Possible collaborations include 1) pilot programs to enhance the supply of clinical investigators (Ph.D. or M.D.); 2) institutional training programs that break down departmental barriers and promote new models for training; 3) loan repayment programs to entice M.D.s to continue in research; and 4) career development programs.

Training Basic Scientists for the Postgenomic Era

In a field moving as rapidly as biomedical science, it is difficult to predict which skills are required of today's scientists, let alone those that will be necessary for the next generation. A survey of the existing landscape, however, provides a sense of the directions in which science is headed.

In his keynote speech, David Botstein, Professor and Chairman in the Department of Genetics at Stanford University, provided a perspective that is both invigorating and demanding. In the new world of genomics, scientists are at the beginning of a journey that will lead to the eventual understanding of every human protein and its role both in health and disease. As the Human Genome Project reaches completion—resulting in a complete map of the human genetic code—the next challenge will be to identify the functions of the genes that have been mapped, the proteins for which they code, and the functions of those proteins in the body.

Such information will move the practice of medicine in the direction of prevention and treatment based on molecular makeups. Initially, discovering how health depends on single mutations (genotypic features) and single proteins (phenotypic features) will be relatively straightforward. For example, it may involve understanding how single nucleotide polymorphisms (SNPs) are related to how cancers develop and ways in which we can diagnose disease and tailor medications. With time, however, more intricate relationships likely will be discovered through population-based studies, entailing the generation, storage, and analysis of enormous quantities of epidemiologic, genotypic, and phenotypic data.

The immense amount of information generated by the Human Genome Project is stimulating new collaborations between the traditional sciences of biology and chemistry and the fields of bioinformatics, computer science, and mathematics.

“Computers allow us to make discoveries on which we can base beautiful hypotheses that can then be tested.”

David Botstein
Stanford University

In the words of Botstein, “When you are working with 750 megabytes of biological information, computational power is not optional, it is necessary. Without a computer we cannot do anything with the human genome.”

Botstein predicts that scientists will spend the next 20 years figuring out the significance and relationships of the human genome map. To understand the similarities and differences among organisms and between species, sophisticated comparisons must be conducted, and these comparisons cannot be done by hand or by eye. Advanced bioinformatics, combined with well-designed databases and powerful computers, is providing a view of the relationships among organisms that are sometimes separated in evolution by billions of years, and computers can display patterns and periodicity that would never be found if searched for manually. Said Botstein, “Computers allow us to make discoveries on which we can base beautiful hypotheses that can then be tested.”

Molecular biologists and biochemists have developed a variety of laboratory-based assays that are powerful and readily adaptable to large-scale efforts. Engineers have developed innovative robotic and automation technologies that are capable of skyrocketing the number and variety of laboratory experiments. Computer scientists have developed programming languages and database management systems that have provided the basic building blocks for improved environments for scientific collaboration. And physicists (driven by the need to share the large amounts of data generated in high-energy particle physics) have catalyzed the development

of the Internet, which is literally transforming the ways in which scientific and technical collaborations take place.

Never before have biologists been faced with so much data, and never has the need to organize the data been greater. Bioinformatics provides a common language for many disciplines, an essential element for applying the wisdom of biology, chemistry, physics, and mathematics to a problem. The beauty of the integration of biology and information science, claims Botstein, is the ability to make discoveries *ex post facto* from the computer. “We cannot get to where we need to go using a frontal assault based on biology alone,” said Botstein. “We are in the genomic revolution, in

Changing Paradigms in Basic Biology

- High-throughput technologies may be regarded as an enabling technology for modern biology.
- Databases and biological repositories are essential facilities.
- Sequence databases are revolutionizing the way we study the structure and function of biomolecules and cells.
- Sequence data provide powerful insights into evolutionary relationships and biodiversity.
- Genomic information will be essential for understanding biocomplexity in the environment.

Mary Clutter, National Science Foundation

which we must figure out a system that makes sense, use bioinformatics to support the system, develop a clear language about the data and the outcomes, produce a suitable display system, and apply all this to clinical samples that were saved in a useful and informative way.”

On the “digital” side, researchers have growing access to supercomputers that perform millions of operations per second, Internet backbones that transmit 10^9 bits of information per second, and databases that contain 10^{15} bits of information. Thus, more than ever, new tools and technologies from engineering, computer science, mathematics, chemistry, and physics hold great promise for tackling scientific challenges in medicine and biology.

So, How Do We Get There from Here?

In the postgenomic era of research, multidisciplinary and interdisciplinary research will command center stage, and some of the most interesting research will take place at the boundaries of disciplines and from combining knowledge from various fields. This requires team approaches and the collaboration of multiple individuals from vastly different fields, such as computational mathematics and clinical research.

This is not to say that there is no longer room for the specialist. In many cases, concentrated work in a single discipline will remain the best way to advance the development of knowledge. However, basic scientists working together from more than one disciplinary vantage point can advance fundamental knowledge in important ways that cannot be attained without such collaboration. This means that providing opportunities for students to work collaboratively will be an increasingly important part of an education in science.

Good Teaching, Rich Classroom and Laboratory Experiences, Mentoring, and Hard Work

What is the best way to educate an individual so that he or she develops the skills needed to conduct science in the postgenomic era? There is no simple or single solution, agreed participants, but there are many good models. David Botstein talked about the importance of good teaching and the necessity of today's seasoned scientists to return to the classroom. He believes that many leading scientists are actively involved in interdisciplinary research and thus serve as the best examples for aspiring young scientists.

Freeman Hrabowski, President, University of Maryland, Baltimore County, credits one person in particular for sparking the excitement of countless minority students who have gone on to careers in science. “Mike Summers, a Professor of Chemistry and Biochemistry and Adjunct Professor of Biological Chemistry, brings joy to his teaching,” said Hrabowski. “He is a true mentor and is singularly responsible for my campus sending more minority students on to graduate school in the sciences than any other institution.”

Hrabowski emphasized the need for patience and said that many students, especially those from minority populations, come to college unprepared. “This doesn't mean it's over for them,” he commented. “It just means we need to work with them, even if it means taking a course twice to get it right.” And, he added, educational institutions have to get beyond what he calls the “deficit model” of teaching. Not all minority students fall into the category of remediation, and some students who are superbly talented are not recognized because of the narrowness of our view. “How do you promote minority students in science education?” Hrabowski challenged. “You find the best students, insist on a culture

“How do you promote minority students in science education?” Hrabowski challenged. “You find the best students, insist on a culture that encourages the best faculty to be involved, get the students connected to research, provide environments for group work across disciplines, and make them repeat their courses until they are ready to move on.”

Freeman Hrabowski
University of Maryland, Baltimore County

that encourages the best faculty to be involved, get the students connected to research, provide environments for group work across disciplines, and make them repeat their courses until they are ready to move on.” Botstein noted that the entire educational system would be more effective if Hrabowski’s approach were adopted for all students.

In terms of formal training, students must have adequate breadth in both instruction and laboratory experiences, said Nicholas Cozzarelli, Professor in the Division of Biochemistry and Molecular Biology, University of California-Berkeley. Cozzarelli routinely asks his students to be open-minded, to take

chances, and to be prepared for facing multiple options. There is nothing wrong with specialization, added Botstein. Our academic structures are quite good at producing specialists, he noted, but these specialists must have “sockets” so they can communicate with others with different training and focus. Nonetheless, these specialists need sufficient exposure to a broad range of other specialties, or cross exposure, so that they are able to

The David and Lucile Packard Foundation: Changing the Culture by Example

Historically Black Colleges and Universities Science Program

To improve the teaching of science at historically black colleges and universities (HBCUs), the Packard Foundation invites proposals annually from a selected set of HBCUs and awards grants totaling approximately \$2 million. The goal of this program is to increase the number of young black graduates qualified in science who can become leaders in their fields and role models for the next generation of students. An advisory panel of eminent black educators assists Foundation staff members in setting guidelines and evaluating proposals.

Tribal Colleges Science Program

Often overlooked by the general population, tribal colleges are now being recognized as an important part of the educational landscape in America. These are mostly community colleges founded by American Indians and located on or near reservations in mid-western and western states. The goal of the Tribal Colleges Science Program is to help tribal colleges better serve the needs of students studying science. Grants totaling approximately \$2 million are awarded annually. An advisory panel of experts who are actively involved in tribal colleges assists Foundation staff members in evaluating proposals and monitoring grants in this area.

realize when they have reached their limitations and should seek help. To illustrate the need for cross exposure, Thomas Cech, President, Howard Hughes Medical Institute, quoted biologist Lewis Thomas, who wrote

If you want a bee to make honey, you do not issue protocols on solar navigation or carbohydrate chemistry, you put him together with other bees....And you do what you can to arrange the general environment around the hive. If the air is right, the science will come in its own season, like pure honey.

Stephen Burley, Rockefeller University, described the Burroughs Wellcome Fund Interfaces Training Program, which aims to create an environment in which “cross-pollination” can occur. The Program has a unique structure. It has no formal departments and 75 faculty in chemistry, physics, and biology who report to the president. Two centers—one in physics and biology and one in chemistry and biology—comprise collections of faculty with common interests, who conduct collaborative research and training. The long-term goal of this approach is to bring quantitative tools to bear on problems in biology. Burley admits that this strategy is likely to increase the training time of new scientists.

Cech suggested that to understand training and career models that work, we should look to the common denominators in the training of individuals who have successful careers as interdisciplinary scientists working with teams of diverse individuals. He cited Howard Hughes Medical Institute Investigators Sharon Long, Stanford University, Stephen L. Mayo, California Institute of Technology, and Roderick MacKinnon, Rockefeller University, as exemplars of individuals trained in multiple disciplines who conduct interdisciplinary research.

Overcoming Barriers to Interdisciplinary Research and Training in the Basic Sciences

Many panelists cited the traditional and persistent barriers to interdisciplinary research and training that must be addressed if post-genomic biomedical research is to reach its full potential. These include attitudinal resistance; differing research methodologies and communication barriers among disciplines; the length and depth of training in a single field that is needed to develop scientists who will be successful in competing for funds; the difficulty in forging a successful career path outside of the single-discipline structure; impediments to obtaining research funding for interdisciplinary research early in one’s career; the scarcity of interdisciplinary departments in academe; and the perceived lack of outlets for the publication and dissemination of interdisciplinary research results.

Cozzarelli noted that it takes certain interpersonal skills to conduct interdisciplinary research and that laboratory training alone might not be sufficient to develop those skills. Moreover, interdisciplinary research teams must be led by individuals who understand the challenges of group dynamics and who can provide appropriate leadership.

Academic departments create the environment within which education and research occur and often perpetuate disciplinary identity through training and mentoring practices, said Howard Hughes Medical Institute’s Cech. This can inhibit interdisciplinary research, because investigators intrigued by the same multifaceted problem are likely to work in different departments. Moreover, promotion and tenure policies and practices, which serve as tremendous motivators and controlling devices for academic scientists, also are driven by departmental cultures. In addition, the priority given to contributions in

The Face of Modern Biomedical Research: Interdisciplinary Investigation Conducted with Public and Private Support

Sharon R. Long, Ph.D.

Dr. Long, a Howard Hughes Medical Institute Investigator, is also Professor of Biological Sciences at Stanford University and Adjunct Professor of Biochemistry at Stanford University School of Medicine. She received her B.S. degree from the California Institute of Technology, in the Independent Studies Program, and her Ph.D. degree in cell and developmental biology from Yale University. Dr. Long has been awarded a MacArthur Prize fellowship and is a member of the National Academy of Sciences. She is a fellow of the American Academy of Arts and Sciences and the American Academy of Microbiology. Her laboratory combines a number of approaches—including genetics, biochemistry, and cell biology—in the study of a symbiotic bacterium-plant association to ask how new cell division, growth, and gene expression arise in each partner due to stimulation from the other. Dr. Long's team has identified and cloned the genes in the bacterium that cause it to stimulate nodule formation in its host and has found that these genes are only expressed in the bacterium when in the presence of a signal from the plant host root. This signal is a small molecule in the chemical category known as flavonoids. Flavonoids and related compounds have been proposed to have health benefits as components of human diets, but no specific mechanisms have been established.

Stephen L. Mayo, Ph.D.

Dr. Mayo is Assistant Professor of Biology at the California Institute of Technology and Adjunct Assistant Professor of Biochemistry and Molecular Biology at the University of Southern California School of Medicine, Los Angeles. He is a Howard Hughes Medical Institute Assistant Investigator. Dr. Mayo received a B.S. degree in chemistry from Pennsylvania State University and a Ph.D. degree in chemistry from the California Institute of Technology, where he studied biological electron transfer. Dr. Mayo developed a rule-based molecular mechanics force field as

a Miller Fellow at the University of California, Berkeley, and studied hydrogen/deuterium exchange reactions in proteins as a postdoctoral fellow with Robert Baldwin at Stanford University School of Medicine. Dr. Mayo is also a Rita Allen Foundation Scholar, a Searle Scholar, and a Packard Fellow. His laboratory focuses on the coupling of theoretical, computational, and experimental approaches for the study of structural biology. In particular, he has developed quantitative methods for protein design, with the goal of developing a systematic design strategy that is called protein design automation.

Roderick MacKinnon, M.D.

Dr. MacKinnon, a Howard Hughes Medical Institute Investigator, is also Professor of Molecular Neurobiology and Biophysics at Rockefeller University. He received a B.A. degree in biochemistry from Brandeis University and an M.D. degree from Tufts University School of Medicine. He completed a medical residency at Beth Israel Hospital, Harvard Medical School, and postdoctoral work at Brandeis. Dr. MacKinnon has received the Young Investigator Award from the Biophysical Society and the prestigious 1999 Albert Lasker Medical Research Award. His work focuses on ion channels, membrane-spanning proteins that form a pathway for the flow of inorganic ions across cell membranes. Ion channels are extraordinarily simple physical systems, and yet they are responsible for all electrical signaling in biology. Among their many functions, ion channels control the pace of the heart, regulate the secretion of hormones into the bloodstream, and generate the electrical impulses underlying information transfer in the nervous system. Dr. MacKinnon's laboratory relied on molecular biological and electrophysiological techniques, but when the lack of molecular structure limited their progress, they embraced the distant field of x-ray crystallography. The result was a much-heralded atomic-level photo of the potassium ion channel.

areas recognized by departmental structures may fail to nurture interdisciplinary approaches.

Departmental chairs are generally recruited or appointed because they are outstanding examples of the discipline that is represented by the department. It may be difficult, therefore, for junior faculty whose interests range beyond the formal subject matter of a given department to be viewed as either making substantial contributions to the field or as meriting advancement in a given department.

The issues surrounding disciplinary identity can spill over into training. Current departmental structures, particularly the lack of mechanisms for mentoring in specific training programs, may restrain the development of interdisciplinary researchers. With the increased competition for research funds, many departments have developed models for mentoring junior faculty, both in the grant-writing process and in obtaining hands-on research experience early in projects. But all too often, junior investigators in a department are limited to mentoring or training opportunities provided by the faculty of that department.

Finally, a scientist's research reputation is essential to obtaining research support, gaining employment, getting promotions, and winning grants. Authorship on papers is perhaps the single most important predictor of one's success in these areas. In the past, the size of collaborative groups has posed problems for interdisciplinary researchers, particularly when it came to listing authors on publications. Fortunately, this trend is reversing. However, the important contributions of those who historically have been considered the "handmaidens" or technical support in large interdisciplinary efforts (computer scientists, statisticians) are still often under-recognized.

Until more academic departments are willing to acknowledge individual contributions to an interdisciplinary research effort, rather than author position on a journal article, young investigators will be dissuaded from engaging in interdisciplinary research with multiple

collaborators. That "luxury" will be reserved for the tenured professor who has already established a research career.

Private Funders Making a Difference

With the strong economy of the past decade, new philanthropic efforts have emerged. Total annual giving by over 44,000 foundations is estimated to be more than \$20 billion. The scientific share of philanthropy, however, is not increasing, reported Jaleh Daie, Director of Science Programs at the David and Lucile Packard Foundation, who noted that only about 300 foundations regularly support science.

Even though the private contribution cannot match that of the federal government, said Daie, philanthropy plays a special role. Foundations can leverage off of public programs to realize a substantial impact. Private givers can catalyze innovation by jump-starting emerging fields, she added. In addition, they can support alliances that typically would not be supported through public mechanisms. Perhaps one of the most rewarding roles of philanthropy, said Daie, is to "prime the pump" by supporting young investigators at the beginning of their careers.

Investing in the Future

Philanthropic organizations have long made critical contributions to support the early careers of basic scientists. The importance of private support of young investigators was emphasized by Donella Wilson, National Scientific Program Director for the American Cancer Society, which spends \$100 million annually on research award programs that are peer reviewed by external committees. In recent years, an oversight group has recommended that the Society refocus its research awards on beginning investigators to help them become securely established.

Similarly, the American Heart Association has carved an important niche in supporting the development of beginning investigators and offering innovative funding mechanisms to stimulate research in promising science areas, reported Susan Barnett, Vice President of Research Administration. Although the federal government provides more money for research through the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), the Association makes a substantial contribution in a more focused way. In 1999, it spent \$130 million on research, received more than 3,000 applications, and funded 1,000 awards. Of this, \$64 million was dedicated to beginning investigators (not more than four years from first faculty appointment).

The Association also supports the career development of highly promising clinician-scientists and Ph.D.s who have recently acquired independent status. This is done by encouraging and adequately funding high-quality, innovative research projects for which financial support has not been previously obtained from any other agency.

The same is true for the W.M. Keck Foundation, through its Distinguished Young Scholars in Medical Research Program. This Program is designed to promote the early career development of a select group of the country's brightest young biomedical scientists. It supports groundbreaking research addressing the fundamental mechanisms of human disease by young investigators who exhibit extraordinary promise for independent basic biological and medical research and who demonstrate a capacity for future academic leadership.

According to Maria Pellegrini, Keck Program Director for Science Engineering and the Liberal Arts, the Foundation invites 30 outstanding research universities and independent research institutes annually each to nominate one faculty member who is in the second to

The Keck Graduate Institute of Applied Life Sciences: Supporting “Good Human Protoplasm”

Launched in 1997 with a \$50 million founding grant from the W.M. Keck Foundation, the Keck Graduate Institute of Applied Life Sciences is the first graduate school in the country solely dedicated to the marriage of the life sciences and the subdisciplines of engineering. Reflecting the significance—and potential—of this endeavor, this is the second largest grant ever made by the Foundation for a single project.

The Keck Graduate Institute of Applied Life Sciences seeks to build on the profound insights into the understanding of biological processes now emanating from corporate and government research laboratories and to play a central role in translating the vast potential of these discoveries into practical applications by preparing a uniquely qualified class of professionals for responsible and productive careers in life science-based organizations. In the words of Maria Pellegrini, Program Director, the goal is to support “good human protoplasm.”

Specifically, the Graduate Institute will focus initially on three or four “niches” where it can build distinctive competencies. These areas of concentration, which will be chosen from among such fields as biochemical process engineering, bio-instrumentation, biomaterials, medical devices, bioinformatics, and biomechanics, will be complementary to one another and will have strong cross-linkages with regard to research opportunities, industrial interests, and curricular requirements.

A particular feature of the Graduate Institute will be its emphasis on giving students a full understanding of the climate and culture in which scientists and technologists in industry must function. Accordingly, instruction in management, ethics, economics, systems, and policy issues, as well as substantial team-based project work, will be central to the curriculum.

“There are times when the interests and goals of voluntary health groups and federal funders overlap and collaboration is in order.”

Robert Goldstein
Juvenile Diabetes Foundation

fourth year of his or her first tenure track position. Up to five recipient institutions receive a maximum of \$1 million each. These grants support the research activities of the selected candidates for a period of up to five years and enable the institution to purchase necessary equipment and resources to facilitate the investigative process.

The Keck Foundation's goal is to provide these institutions and their young scientists with the opportunity to investigate promising and unproven new ideas for which funding can be difficult to obtain, even for established researchers with steady funding streams. Pellegrini emphasized that these awards are not intended to remove these scientists from the academic environment or to relieve them of their teaching responsibilities and the grant-writing and administrative burdens of running a laboratory, all of which the Foundation believes are important parts of every young scientist's training.

Targeting Research

In addition to supporting new investigators while they establish their research careers, philanthropy can target areas of research that are not supported or that are underfunded. This is particularly true for voluntary health agencies, which have targeted missions and tangible goals.

For example, the Juvenile Diabetes Foundation makes a crucial contribution by focusing on research that has the promise of producing a cure for Type I diabetes. A secondary outcome of research support is the training of new investigators in research that is important to the Foundation's mission. To

illustrate, since September 1998, the Foundation has funded nine new research centers—large-scale, multidisciplinary, high-priority initiatives that are focusing on solving specific problems within the three priority goal areas: 1) restoration of normal blood sugar levels; 2) avoidance of and improved treatment for complications; and 3) prevention of diabetes and its recurrence. Through the initiation of human clinical trials, the centers will use the expanded diabetes knowledge base to move research out of the laboratory and into the lives of those with diabetes.

Robert Goldstein, the Foundation's Chief Scientific Officer, emphasized that the goal of the Foundation, and of organizations like it, is to commission scientists to solve a problem, such as islet cell transplantation. “We recognize that training is a component of that goal, if not the primary goal,” he added.

The American Heart Association's Barnett also commented on the targeted approach to research funding. For example, this year the Association set specific content goals for its research program, including patient care and outcomes research, brain blood vessel biology, functional genomics, and stem cell organogenesis.

Many voluntary health agencies rely on lay reviewers of research to help them meet their goals. The Juvenile Diabetes Foundation's Goldstein noted that the lay review conducted after scientific review adds a valuable component to research evaluation. He added that the Foundation adopts a proactive approach to the scientific research community by introducing early in the process the priority problems it wants to address using a flexible, fast-track

review of applications for research projects. Not all voluntary health agencies have the resources to conduct rigorous peer review of protocols. The Life Sciences Research Foundation supports an annual postdoctoral fellowship program, which provides built-in peer review for funders, at no additional cost. Juried by a panel of Nobel laureates and other distinguished scientists, these fellowships are highly competitive and have been offered since 1983. Dr. Donald Brown, Life Sciences Research Foundation President, said the

Foundation provides a cost-effective way for funders to support research training.

Collaborating with Public Funders

Although it is rare, some private funders have entered into productive collaborations with federal funders. For example, from 1986 to 1998, the Alfred P. Sloan Foundation provided support for research in molecular evolution. Beginning in 1994, the Foundation operated a jointly sponsored program with the National Science Foundation in this area, consisting of

Progress in Electronic Grantsmaking

Dr. Joseph Perpich, Vice President for Grants and Special Programs, Howard Hughes Medical Institute, invited participants to share their ideas and views regarding the “new world of electronic grantsmaking” and introduced a panel of representatives of several funders of biomedical research training that have undertaken the development of Web-based systems for electronic grantsmaking. (See also Appendix A.)

Ellis Rubinstein of the American Association for the Advancement of Science discussed new enhancements that have been made to the Association’s successful online database and career development sites, GrantsNet and NextWave, and T. J. Koerner, Director of Research Information Management at the American Cancer Society, Carolyn Miller, Director of the FastLane Project, the National Science Foundation, and George Stone, Chief of the Commons, Extramural Inventions and Technology Resources Branch, NIH, demonstrated their online grant application systems and talked about current and future challenges and opportunities in the area of electronic grantsmaking. Participants agreed that the four systems created by these funders clearly demonstrate the value of Web-based systems for handling applications and grants online and the benefits of sharing data.

Dr. Perpich provided an overview of the Howard Hughes Medical Institute online physician-postdoctoral competition program and called participants’ attention to the Institute’s exciting new virtual discussion forum (www.hhmi.org/grants/forums.htm). With a section devoted to topics in electronic grantsmaking, as well as one on general grantsmaking issues, the virtual forum will provide both public and private funders of biomedical research training with an opportunity to explore a variety of issues, including the use of current and developing technologies in data sharing among multiple systems that have not been built around common data fields.

In opening remarks, Enriqueta Bond, President of the Burroughs Wellcome Fund, also focused on the importance of sharing information, commenting that it is clear that private funders can be more strategic about their investments if they know what others are doing and have an understanding of current trends, challenges, and opportunities, including those for partnerships. John Stevens, interim Strategic Business Manager for the American Cancer Society’s Research and Health Professional Training Program and Vice President for Extramural Grants, added that the meeting is a critical component in spreading the word about what grants are available and ways in which individuals can apply for those awards.

two parts: a Postdoctoral Research Fellowship, which provided 18 awards per year for two-year postdoctoral fellowships, and a Young Investigators Program, which provided awards of \$100,000 to five applicants in the first few years of their independent research careers.

The Alfred P. Sloan Foundation also has collaborated with the U.S. Department of Energy (DOE), reported Program Director Michael Teitelbaum. In 1995, the Foundation approved a Postdoctoral Fellowship Program in Computational Molecular Biology, jointly sponsored with the Office of Health and Environmental Research of DOE, to support up to 10 postdoctoral fellowships each year. The Program is aimed at catalyzing career transitions into computational molecular biology from physics, mathematics, computer science, chemistry, and related fields. Teitelbaum said the programs have worked well, as long as the funds contributed by each donor are kept separate.

Programs of Federal Funders

Several federal funders provide critical training support for basic biological and biomedical scientists. Federal support tends to be broad based rather than categorical, although some training grants can target specific areas of research in which trainees can be supported. For example, the National Institute of General Medical Science (NIGMS), NIH, provides predoctoral training grants in bioinformatics and computational biology; biotechnology; cellular, biochemical, and molecular sciences; chemistry-biology interface; genetics; molecular biophysics; pharmacological sciences;

and systems and integrative biology, reported Marvin Cassman, NIGMS Director.

The primary mechanism through which NIH supports predoctoral and postdoctoral trainees and fellows is the National Research Service Award. NIGMS and other NIH Institutes also make awards to institutions for the training of predoctoral students and postdoctoral researchers. In addition, the NIH Medical Scientist Training Program (MSTP), leading to the combined M.D.-Ph.D. degree, supports the integrated medical and graduate research training that is required for the investigation of human diseases.

NIGMS's goal in its predoctoral programs is to provide trainees with broad access to research opportunities across disciplinary and departmental lines while maintaining high standards of depth and creativity. Cooperative involvement of faculty members from several departments or doctoral degree programs is one essential aspect of this multidisciplinary emphasis. Another is breadth in research training instruction, with regard to both the curriculum and laboratory rotations. Students are typically supported by the NIGMS predoctoral training grant for one to three years of graduate studies in Ph.D. programs or for two to six years in the M.D.-Ph.D. programs, and by other mechanisms in subsequent years. The rationale for this approach is that students supported by the training grant have greater flexibility early in their studies in making crucial choices about courses and research fields. However, the current stipend level for FY 2000 for predoctoral trainees of \$15,060 per year is far too low, said Cassman.

The public sector historically has been an important source of funds for training minority scientists. For example, NIGMS participates in

The primary mechanism through which NIH supports predoctoral and postdoctoral trainees and fellows is the National Research Service Award.

an NIH-wide program of individual predoctoral fellowship awards for minority students. These awards provide up to five years of support for research training leading to a Ph.D. or equivalent research degree, a combined M.D.-Ph.D. degree, or another combined professional doctorate-research Ph.D. degree in the biomedical or behavioral sciences. Eligible for this award are highly qualified students who are members of minority groups that are under-represented in the biomedical or behavioral sciences in the United States. The intent of this fellowship program is to encourage these students to seek graduate degrees, thus furthering the goal of increasing the number of minority scientists who are prepared to pursue careers in biomedical and behavioral research.

John Ruffin, Associate Director for Research on Minority Health, Office of the Director, NIH, noted that many programs aimed at minority students are efforts to retain students who are already interested in the sciences and that it is an important federal role to capture the interest of students who currently are not thinking about science. In response to these concerns, NIH offers its investigators supplements to attract under-represented minorities into biomedical and behavioral research throughout the continuum from high school to the faculty level. In addition, the Initiative for Minority Students: Bridges to the Baccalaureate Degree provides training that leads to the baccalaureate degree for selected students from under-represented minority groups. The objective is to encourage the development of new and innovative programs and the expansion of existing programs to improve the academic competitiveness of under-represented minority students and to facilitate the transition from two-year junior or community colleges to four-year institutions.

Other NIH Institutes support training programs of importance to their research portfolio. The National Human Genome Research Institute (NHGRI) has a small but targeted

program to support predoctoral and postdoctoral training in areas of importance to the NHGRI mission, such as the interfaces between biology and physics, reported Elke Jordan, NHGRI Deputy Director. NHGRI also supports numerous career development awards, such as the Genome Scholar Development and Faculty Transition Award, made to promising new genome researchers to establish an independent research program in genomic research and analysis and to secure a tenure-track appointment in an academic institution in the United States.

Jordan also described NHGRI's Curriculum Development Award in Genomic Research and Analysis, which supports the development of courses and curricula designed to train interdisciplinary scientists who combine knowledge of genomics and genetics research with expertise in computer sciences, mathematics, chemistry, physics, engineering, or closely related sciences. Jordan anticipates that these courses or curricula will be useful to students and scientists who wish to develop new conceptual approaches to genome research and analysis or to organize, analyze, or interpret large data sets resulting from genomic and genetics research.

“The best place to educate people is in the discovery-rich environment of research.”

Mary Clutter
National Science Foundation

The National Science Foundation is another important supporter of training in the basic biological sciences, but it also provides essential backing for education in mathematics, physics, and chemistry. Moreover, the Foundation historically has emphasized the integration of research and education, because, according to Assistant Director Mary Clutter, “the best place to educate people is in the discovery-rich environment of research.”

National Science Foundation programs include Research Experiences for Undergraduates, Collaborative Research at Undergraduate Institutions, Graduate Teaching Fellows in K-12 Education, Faculty Early Career Development, and Postdoctoral Fellowships. An important new program, the Integrative Graduate Education and Research Traineeship (IGERT) Program, was initiated in 1997 to meet the challenges of educating Ph.D. scientists and engineers with the multidisciplinary backgrounds and the technical, professional, and personal skills needed for the career demands of the future.

The IGERT Program is intended to catalyze a cultural change in graduate education for students, faculty, and universities by establishing new and innovative models for graduate education in a fertile environment for collaborative research that transcends traditional disciplinary boundaries. It is also intended to facilitate greater diversity in student participation and preparation and to contribute to the development of a diverse, globally aware science and engineering workforce.

Goals for Private Funders

Biology in the postgenomic era will require new sets of skills and individuals who can establish themselves successfully in rapidly moving fields of research. Clearly, philanthropy has played and will continue to play an important part in jump-starting the careers of new investigators, particularly during the transition from postdoctoral fellow to faculty member. The receipt of funding from an organization such as the American Cancer Society or the American Heart Association, for example, can be the push that launches a research career. In addition, philanthropy, because its mission is often problem based, can support inherently interdisciplinary research and training that breaks new ground.

Several meeting participants emphasized the value of private funds in trying to change the culture and structures of research and education. Because some of the most exciting work of the postgenomic era will occur at the interface of disciplines, private funders can provide the “glue” needed to force faculty to work together toward research and educational goals. Private foundations can provide financial incentives to institutions to change behavior and to encourage scientists to teach.

Two currently funded American Cancer Society trainees, Anne Blackwood, M.D., and Michelle Tallquist, Ph.D., emphasized the need for transitional training mechanisms to teach scientists how to move from being a student to becoming a successful faculty member; manage a laboratory; ensure continued education; and receive departmental credit good toward professional promotion while engaging in interdisciplinary research projects. Also mentioned was a need for more grant funding for junior faculty past the five-year faculty career mark, which should also provide possible internship experiences for alternative career choices.

Unlike the public sector, because of its mission and more limited resources, private funders can be elitist, choosing the best students and developing them faster. Finally, the private sector frequently has the freedom to take chances and change directions quickly.

The following conclusions and recommendations emerged from the sessions on training basic biomedical scientists:

1. In the postgenomic era of research, multidisciplinary and interdisciplinary research will command center stage. Some of the most interesting research will take place at the boundaries of disciplines and from combining knowledge from different disciplines, requiring team approaches and the collaboration of many individuals from vastly different fields, ranging from computational mathematics to clinical science.

2. The need for team approaches to scientific research raises questions about how to invest private dollars to support such work beyond the center or program grant approaches. Several examples of possible approaches to meeting this goal were cited, including providing grants to support clusters of faculty in order to build expertise and collaborations and establishing programs that force collaborative research.
3. The development of human capital with a set of new skills is essential. Support of postdoctoral students and new faculty is important, but more is needed. Philanthropy must also invest in the development of scientists from underrepresented groups, provide appropriate support for foreign students, and recognize that with the globalization of the research enterprise, it will be vital to provide experiences for U.S. students abroad.
4. The changing paradigm of research calls for innovations and changes in education of scientists along the spectrum of K-12, undergraduate education, and graduate education. Some examples identified ranged from such simple innovations as requiring biology courses for all engineering students, to the development of a valued terminal master's degree in bioinformatics, to wholesale changes in undergraduate education. The increasing need to value teaching in all settings could be improved by making grants that free the time of scholar/researchers for teaching.
5. The private sector can facilitate some areas or types of research more easily than can public agencies, such as research with embryonic stem cells or prehypothesis-driven work to assemble and organize information that can provide a platform for hypothesis-driven work and infrastructure support.
6. The unfolding of the postgenomic era raises many ethical issues that deserve consideration and study as well as the establishment of guidelines if private sector support is considered for areas in which controversy exists.
7. Partnerships among private funders and between the public and private sector will be valuable in moving the postgenomic research and training agenda forward and in leveraging the investments of both private sector and public sector groups.

Supporting Beginning Cancer Research Investigators

The American Cancer Society, a community-based volunteer health organization, is the largest source of private, not-for-profit cancer research funds in the United States. A major focus of its research program is the support of cancer investigators early in their careers.

Research Scholar Grants for Beginning Investigators are awarded to support basic, preclinical, clinical, or epidemiologic research projects initiated by investigators in the first eight years of their independent research careers. Initial awards are made for up to four years and up to \$250,000 per year, including 25 percent indirect costs.

Postdoctoral Fellowships support the training of researchers who have just received their doctorate. Awards are made for one to three years, with progressive stipends of \$28,000, \$30,000, and \$32,000 per year, plus a \$2,000 per year institutional allowance.

Clinical Research Training Grants for Junior Faculty support the training of junior faculty within the first four years of independent faculty appointment to conduct mentored clinical, epidemiological, or health policy and outcomes research. Awards are made for up to three years for up to \$150,000 per year, including 25 percent indirect costs.

The Future of Clinical Research Training

In his keynote speech, Richard Lifton, Howard Hughes Medical Institute Investigator and Director of the Program in Cardiovascular Genetics at the Boyer Center for Molecular Medicine at Yale University, commented that we have moved beyond relying on the “handshake test” to define clinical research. “No longer does clinical research require that an investigator and patient be in the same room,” he added. With the advent of molecular biology, extensive research now can be done on the pathogenesis and pathophysiology of human disease by working at the DNA level on stored samples.

This advance gives researchers the ability to identify the underlying causes of disease based entirely on the genetic nature of the disorder, without prior knowledge of its pathophysiology. Thus, the paradigm that has emerged of positional cloning of disease genes has revolutionized our understanding of human disease, affecting every medical discipline, stressed Lifton. He added that as of February 15 of this year, 990 diseases with an inherited component had been characterized at the molecular level, most within the past five years.

Although the majority of these are single-gene disorders, the genetic understanding of these disorders is central to discerning the fundamental physiologic pathways that may be relevant to more common forms of disease. In addition, gene targets in rare diseases may provide opportunities for therapeutic intervention for common disorders. Lifton cited the example of the groundbreaking research on familial hypercholesterolemia, conducted by Michael Brown and Joe Goldstein. Although hypercholesterolemia is a rare disease, the work of Brown and Goldstein led to the eventual development of HMG CoA reductase inhibitors, which have had a profound effect on reducing risk of coronary artery disease in the general population.

The challenge for clinical research is that most common diseases are complex, multi-etiological disorders in which a multiplicity of genes interact with each other and with environmental factors, revealing subtle variations in DNA. Common genetic variations are attracting enormous interest because it is suspected that they may contain clues to inborn susceptibility to common diseases. Clinical research must find the resources and intellectual capital to locate large enough cohorts of patients with good enough phenotypes to relate common variants in the population. The goal is to determine how many genes are imparting an effect in any given disease and to evaluate the magnitude of the effect.

To illustrate, Lifton described recent research on Alzheimer's disease, which was once thought to be multifactorial and complex, but which is now emerging as a nearly monogenetic disease. The inheritance at a single locus of a particular allele of an apolipoprotein contributes about 50 percent of the risk of development of Alzheimer's disease. Thus, a single gene has a relatively large effect.

In addition to genomics, other companion technologies will advance the goals of clinical research, such as the use of chips to monitor expression of genes. This tool has the potential to identify pathways that are altered in disease physiology, and they can be used as diagnostic tests (molecular diagnostics). Eventually, this technology will allow clinical scientists to tailor treatment to underlying abnormalities. In addition, functional MRI and NMR spectroscopy provide new tools to investigate fundamental physiology in living patients, such as the study of glucose transport in patients with diabetes. The study of *in vivo* biochemistry in humans can only be conducted with the participation of clinical scientists, particularly the physician-scientist, emphasized Lifton.

"With the advent of the Human Genome Project we are going from an open-ended

The challenge for clinical research is that most common diseases are complex, multi-etiological disorders in which a multiplicity of genes interact with each other and with environmental factors, revealing subtle variations in DNA.

Richard Lifton
Yale University

problem to a closed biological problem," said Lifton. "This will have profound effects on the understanding of clinical medicine. In a short period of time we will know all of the common genetic variants. It will take the clinical scientist to figure out how to tie all the variants to particular diseases."

Lifton argued that after the genome is mapped, science will have to rely on clinical investigation to conduct gene-based studies, to redefine the biology and the phenotypes of disease, and to refine diagnostic classifications. He added that clinical research is by definition interdisciplinary and that clinical investigators are comfortable with that paradigm and noted that unlike the basic scientist, the clinical scientist routinely seeks consultation from other specialists to understand a clinical problem.

Yet, the funding trend has been away from the physician-scientist, a phenomenon that has been repeatedly noted with dismay over the past decade. Lifton's view is optimistic, however, because he believes clinical

Ethical Issues Facing Biomedical Research

R. Alta Charo, Professor of Law and Medical Ethics at the University of Wisconsin, provided a broad view of emerging ethical issues in biomedical research. In addition to highlighting substantive topics that are the focus of debate—such as stem cell research, reproductive technology, gene patenting, and international research—Charo noted the special concerns that arise when research is conducted with human subjects.

In the area of protecting human subjects in research, clinical science must contend with

- The great divide between research that is regulated and research that is not, because of source of funding.
- The challenge of distinguishing between experimental therapy and research.
- The determination of what defines a human subject in research and the assurance of privacy protection.
- The technological imperative and the drive to produce versus the assurance of patient safety.
- The changing paradigm of research participation, with patients now demanding access to clinical trials.

The private sector can play an important role in

- Extending protections to all human subjects in research, regardless of funding source.
- Developing and enforcing a code of ethics for supported investigators.
- Ensuring the protection of vulnerable populations.
- Not supporting research that masquerades as care.
- Supporting responsible multicultural initiatives in research.

advances cannot come from the human genome without the participation of the trained clinician. The opportunities will draw the intellect, as long as the environment is conducive to the physician trained in basic biology. He referred to a number of model programs, such as the NIH MSTP, that have been essential mechanisms for training physician-scientists. Still, Lifton said, economic forces, such as medical school indebtedness and pressures from academic health centers to increase patient revenues, continue to dissuade physicians from a research career.

Who Should Conduct Clinical Research?

Edward Holmes, Dean of the School of Medicine at Duke University, posed a schema for categorizing those who conduct clinical research. He believes that the training and research pathways of each type of investigator are unique and that the various categories reflect the need for diverse mechanisms of support.

- *Professional clinical investigator*—spends 80 percent of his or her time conducting clinical research (conducts Phase III clinical trials, outcomes research, epidemiology); often has advanced training obtained beyond the M.D. (for example, M.S., M.P.H.).
- *Clinician investigator*—primary effort is in patient care, but may work with a professional clinical investigator; has no special training in research; is the hands-on team member in terms of patient contact and therefore is a critical player.
- *Physician-scientist*—spends 80 percent of his or her time conducting research, typically laboratory investigation exploring the pathogenesis of human disease; works at the interface between the laboratory and the clinic (may conduct

Phase I and II clinical trials); has advanced research training.

- *Ph.D. translational scientist*—conducts clinically oriented research, such as outcomes research, health services research, biostatistics, epidemiology, animal models of human disease, and molecular analysis; nearly always works as a member of a team.

It is the physician-scientist group that is most threatened in major medical centers, said Holmes, because of the time, effort, and expense of training. The most effective point of entry for these individuals is the medical

student level, and students must be enticed early so they can make their career choice at an appropriate time. Holmes would like to be able to offer 40 percent of his students the opportunity to take advanced training in science during the time they are receiving their medical education.

Holmes believes that the issue is not so much whether Ph.D.s go to medical school or whether medical students should get Ph.D.s, but rather that both groups must work together to be successful. “A medical school cannot be successful if it only has a single category of researcher,” he added, and “awards that encourage people from basic and clinical

Burroughs Wellcome Fund: Targeting Clinical and Interdisciplinary Research

The Burroughs Wellcome Fund supports several programs designed to foster clinical and interdisciplinary research. Clinical Scientist Awards in Translational Research are intended to foster the development, productivity, and mentoring capabilities of established physician-scientists who will strengthen translational research—the two-way transfer of information from the laboratory bench to clinical medicine.

Career Awards in the Biomedical Sciences are available to both Ph.D.s and M.D.s and provide support during the critical transition from training to gaining research independence. Approximately 24 awards are made annually. Each award provides research and salary support for two to three years of postdoctoral training and three years at the faculty level. The awards are transportable, and preliminary evaluation data indicate awardees have been highly successful in securing faculty positions.

Through its Interfaces in Science Program, the Fund supports the interdisciplinary training of promising graduate and postdoctoral students from the physical, chemical, and computational sciences so they can better apply their unique knowledge and talents to biological problems. Awards are made to institutions that promote interdisciplinary training. Degree-granting institutions in the United States and Canada are invited to propose graduate or postdoctoral training programs, or a combination of both.

science to work together are the most efficient means to meet that goal.” Holmes believes this approach should be especially attractive to private philanthropy, because of its interest in translational research, which cannot be done by a single individual or through a single approach.

Models of Training: Building Bridges Between the Basic and Clinical Sciences

Irwin Arias, Chairman and Professor in the Department of Physiology and Professor of Medicine at the Tufts University School of Medicine, provided another view of filling the gap between basic and clinical research. “Any gap you want to cross necessitates a bridge,” he said. “There are many components to a bridge, and we should look at all of them to see how they come together to facilitate the overall structure.” Quoting German pathologist Werner Kollath, Arias said, “Much is known, but unfortunately in different heads.”

Arias described the Pathobiology Program at Tufts University, of which he is the director. For the past 13 years, the Program has been conducted for Ph.D. students, fellows, and faculty, based on the following principles:

- Because they are interested in a career that bridges basic science with human health, virtually all graduate students select a basic science department in a medical school rather than in a university.
- The progressive depletion in physician-scientists has created an increasing number of excellent academic opportunities for Ph.D. scientists to be “first-class citizens” in outstanding clinical departments where they work “with” rather than “for” physicians.
- Bridging the gap between advances in biology and disease is the greatest challenge facing academic medicine today. Training basic scientists in pathophysi-

ology is only one mechanism for bridging this gap and does not replace efforts to increase the number of well-trained physician-scientists and M.D.-Ph.D. graduates.

The Program involves a one-semester course for 15 students that meets twice weekly for 90 minutes. The clinical-pathologic and basic mechanisms of the 20 major diseases of man are considered. During the course, students see patients, handle pathology specimens, and become informed about every major diagnostic and therapeutic facility in a modern hospital.

*“Much is known, but
unfortunately in
different heads.”*

Werner Kollath

From the results of an outcome survey completed by 182 students and fellows who have taken the pathobiology course, 78 have completed postdoctoral fellowships. Of these, all but 2 have a position in industry or academia, and 33 have positions in biotechnical and pharmaceutical companies, where they are engaged in research that affects human health. Twenty-seven have tenure track positions in basic science departments in excellent institutions, and most have obtained grant support. It is of considerable interest that the remaining 22 individuals hold tenure track positions in six clinical departments in different medical schools throughout the country.

In addition to student and fellow outcome results, various other evidence reveals the Program’s success. For example, substantial interest has been expressed by more than 50 institutions to replicate the Program. The Lucille P. Markey Charitable Trust supported nine such centers in 1997. A number of foundations, NIH, and the National Academy of

Arias believes that it is important to “demystify medicine,” saying that “it is far easier to teach basic pathophysiology to bright Ph.D. students than to take last year’s chief medical residents and turn them into bench scientists.”

Sciences have developed an interest in further evaluating the theory that Ph.D. students and fellows have an important role in bridging advancements in basic sciences with medicine.

Arias believes that it is important to “demystify medicine,” saying that “it is far easier to teach basic pathophysiology to bright Ph.D. students than to take last year’s chief medical residents and turn them into bench scientists.”

Graduate Training in Clinical Investigation

N. Franklin Adkinson, Jr., Physician-in-Charge at the Johns Hopkins University Asthma and Allergy Clinics, described a graduate training program in clinical investigation, which serves as one model of clinical research training. The first of its kind in the United States, the program was created in 1992 to address the growing national concern over the shortage of academic clinical investigators by training clinical fellows to be more effective clinical scientists.

Participants in the program acquire the necessary skills to design and conduct clinical investigations into emerging medical treatments and technologies, new diagnostic techniques, and new approaches to the study of pathophysiology.

The usual career track is a four-year program, which leads to both clinical board eligibility in a medical discipline and a Ph.D. in clinical investigation. One full year of didactic

instruction is ordinarily taken after an initial clinical year in a medical or surgical specialty, providing the scientific grounding for subsequent original research. Faculty from the program and a preceptor from the fellow’s home division or department jointly mentor this research effort.

Fellows already enrolled in a clinical fellowship program at Johns Hopkins may apply to enter the program during their last year of clinical training. Program fellows normally receive tuition and stipend support consistent with the usual level of postdoctoral support for their clinical specialties.

Funding for students usually comes from a variety of sources. Stipends and tuition can be provided from some NIH training grants or from other external training funds. Some departments have used internal funds to support students or have obtained special fellowships from pharmaceutical companies, said Adkinson. Many career development awards are suitable sources of support, but they may be difficult to obtain before completing the first year of the program. Adkinson reported that one of the program’s greatest challenges has been gathering sufficient financial support for what is essentially an interdisciplinary program. In addition, many students cannot continue with the program because of the pressures of indebtedness. Adkinson believes that there is a vital role for public-private partnerships in addressing this very real concern.

American Heart Association: A Track Record of Supporting Promising New Scientists

Without sufficient funding during their early training, many talented young people may be unable to pursue careers in academic medicine or the biological sciences. Helping to develop promising young scientists is a priority of the American Heart Association, which offers, through many of its affiliates, postdoctoral fellowships to provide beginning researchers with essential research experience under the guidance of a mentor. Other affiliate and national programs targeted at scientists in their first faculty positions facilitate the move from a mentor's research program to a fully independent research effort.

Association Affiliate Research Programs are critical to new investigators. Most affiliates offer programs aimed at investigators who need postdoctoral training or initial project support before they can successfully compete for national awards, and affiliate research committees—because of their familiarity with local universities, medical schools and hospitals—have a unique opportunity to cultivate the research potential of less experienced scientists.

National research programs focus on bridging the time between the postdoctoral fellowship and the time when a beginning investigator is prepared to independently compete for federal research funds. Scientist development awards and assistance for newly established investigators provide assistance to individuals beginning with their first faculty position and continuing through the next 9 to 13 years, while also supporting important research projects.

Wanted: Team Builders

In addition to the knowledge base required of future clinical investigators, J. Claude Bennett, President and Chief Operating Officer of BioCryst Pharmaceuticals, said that post-genomic medicine will need team builders. Because molecular biology and clinical medicine are converging, said Bennett, drug developers are desperately seeking highly trained individuals who are conversant in bench and bedside science. This is a big challenge, he acknowledged, because the requirements in basic science and clinical training are greater than ever before.

"Being in the pharmaceutical industry, I see the real need for clinical scientists,"

said Bennett. "But we can't just wait for it to happen. We have to be proactive. Formal programs are a necessity."

Bennett mentioned that the pharmaceutical industry spends \$20 billion to \$25 billion annually on research, of which 10 to 12 percent is for basic discovery. Yet, all the drugs currently on the market are probably related to 500 molecular targets. With the Human Genome Project, there may be 10,000 good targets for drug development. "We need to efficiently and quickly explore the therapeutic opportunities provided by those data," he added.

Clinical scientists must have the necessary knowledge base to use modern-day tools, such as understanding molecular concepts, how to use databases, and pharmacokinetics.

“Medical students are not being taught these skills,” said Bennett. “There have to be mechanisms to provide these proficiencies to individuals who have a knowledge of human biology.”

Efforts of Private Funders to Support the Development of Clinical Investigators

Private philanthropies, particularly voluntary health agencies with a disease focus, historically have played a significant role in filling the gap between the rate of advance in research and the translation of new knowledge into therapies for human disease. Importantly, the private sector can search for the right niche and experiment with innovative approaches. Private funders can use their funds to encourage beginning investigators to enter a research area critical to the agency’s mission or encourage midcareer investigators to change course in their direction.

For example, the Leukemia & Lymphoma Society provides support for individuals pursuing careers in basic, clinical, or translational research in leukemia, lymphoma, Hodgkin’s disease, and myeloma. Likewise, the Cancer Research Fund of the Damon Runyon-Walter Winchell Foundation is a nonprofit organization dedicated to advancing cancer research. Sometimes the bequest of a foundation’s founder requires that the organization spend its money in a particular area of research. The Doris Duke Charitable Foundation is one such organization.

Foundations can target areas that are traditionally underfunded. The Robert Wood Johnson Foundation, for example, has supported development of clinical investigators for 28 years, but has “built the fields that we feel have been neglected that could improve the health of the population,” said Lewis Sandy, the Foundation’s Executive Vice President.

Organizations have used a variety of approaches to support training and have developed new models in recent years as needs have changed, including postdoctoral support, early career awards, and midcareer awards. Most are focused on the physician seeking a career in clinical research.

Postdoctoral support is a common mechanism employed by many organizations. It is typically seen as a traditional approach to providing stable support for beginning investigators to establish their laboratories.

This type of support has been a focus of the Damon Runyon-Walter Winchell Foundation since 1946, reported Sarah Caddick, Director of Award Programs for the Foundation’s Cancer Research Fund. It encourages the nation’s most promising young investigators to pursue careers in cancer research by funding initial postdoctoral fellowships and Damon Runyon Scholar Awards. The Damon Runyon Scholar Award was established to support the development of outstanding biomedical and biochemical scientists as independent investigators in the cancer field by ensuring the continuity of their research productivity at the critical transition from research training to first faculty position.

Importantly, the private sector can search for the right niche and experiment with innovative approaches.

Similarly, the Leukemia & Lymphoma Society awards fellowships to promising investigators with less than two years of postdoctoral research training at the time of review. Fellows are encouraged to embark on an academic career involving clinical or fundamental research in or related to leukemia, lymphoma, Hodgkin’s disease, and myeloma. Fellowships are \$33,250 per year for three years.

Doris Duke Charitable Foundation: Targeting Clinical Training in Specific Disease Areas

The Clinical Scientist Award Program of the Doris Duke Charitable Foundation supports new investigators at the Assistant Professor level as they begin their careers as independent clinical researchers. The program is limited to the development of researchers in the areas of heart disease, AIDS, cancer, and sickle-cell anemia and other blood disorders.

The Foundation, which was formed in 1996, is specifically interested in

- Studies on the etiology and pathogenesis of these diseases in man.
- Therapeutic interventions.
- Clinical trials.
- Disease control research that investigates how scientifically obtained information on prevention, early detection, and early diagnosis can be efficiently applied.
- Epidemiological studies.
- Health outcomes research that either attempts to systematically determine the risk/benefits and costs of various medical practices or attempts to utilize these results in defining more effective medical practice guidelines.

Candidates must have received an M.D. or equivalent degree from an accredited institution within the past 10 years, must have completed 2 or more years of clinical training and 2 years of postdoctoral experience, and must hold a full-time university faculty appointment.

Each three- to five-year award is for \$100,000 per year. Should the applicant require additional training in order to meet the Foundation's educational demands, an additional \$25,000 will be awarded for six months of formal course work in the areas of bioethics, protection of human subjects, informed consent, study design, clinical trial record-keeping, quality assurance and control, and biostatistics.

Private philanthropy also provides support for physicians who want to be trained in research. Since 1972, the Robert Wood Johnson Foundation's Clinical Scholars Program has provided a two-year fellowship for physicians interested in broad nonbiological aspects of health and health care, such as epidemiology, health economics, ethics, and health services research. Fellowships are available at seven sites around the country

that also receive support for institutional infrastructure and administration.

Elaine Gallin, Program Director for Medical Research at the Doris Duke Charitable Foundation, provided an example of midcareer awards for clinical investigators. The Doris Duke Distinguished Scientist Award targets physician-scientists who are midcareer level (associate level or full professor for no more than five years). The Award provides

stable research funding for investigators conducting translational research—five years at \$600,000 per year.

Relieving Medical School Debt

“One in four medical school graduates has over \$100,000 in debt after completing his or her degree,” said Caddick of the Damon Runyon-Walter Winchell Foundation. “In this age of endless opportunity,” she remarked, “the Cancer Research Fund is delighted to announce a new program to help rescue an endangered species—physicians willing to devote their careers to the development and application of new diagnostic approaches and therapeutic strategies for cancer and cancer prevention through clinical investigation.” The Fund’s Clinical Investigator Award is earmarked for young physicians willing to commit themselves to substantive and innovative clinical research; the Award bridges the gap between the research laboratory and patient care.

The Cancer Research Fund created the program because of its belief that although there has never been a more promising time for clinical cancer research, fewer young physicians are entering this area of investigation every year. Often, a major deterrent to physicians making a commitment to clinical investigation is their need to address major debts that they acquired during medical training.

The Fund’s new Award offers solutions to this reality. The awardee and his or her senior mentor receive financial support for up to five years, as well as assistance for certain research costs, such as the purchase of equipment. Upon successful completion of the Clinical Investigator Award program, the Fund will also retire up to \$100,000 of any medical school debt still owed by the awardee.

Applicants may apply during the final year of their subspecialty training or within the first

two years of their junior faculty appointment. Each applicant must be nominated by his or her mentor and institution, and the institution is expected to guarantee the allocation of sufficient research and office space to ensure the proper start-up of the awardee. In addition, the institution must provide the difference in salary between the amount allocated by the Award and the level appropriate for the position the applicant holds at that institution.

The applicant is required to apply in conjunction with a mentor who is established in the field of clinical translational cancer research or cancer prevention and epidemiology and who can provide the critical guidance needed during the Award period. The mentor will receive partial salary support to be used specifically to foster the education of the awardee. A letter of commitment from the institution is required defining the position that the applicant will occupy and outlining how the institution will enable the mentor to commit a sufficient amount of time to the applicant’s training and development.

Caddick estimates that the cost to the Fund of a single award package is \$1,125,000. She reported that her phone has “been ringing off the hook since the program was announced in November 1999.”

An Alternative to the Career Ladder Approach

Ray Vento, Assistant Vice President for Scientific Program Administration, American Lung Association, noted that his association, which is the oldest voluntary health agency in the country, must constantly compete with other similar groups for support. The American Lung Association is a fundraising organization rather than an endowed organization, and as such it must balance national goals with local programs. In addition, it spends most of its funds every year. Supporting the academic enterprise is not a primary goal.

The Association has supported investigator-initiated research since 1915. In 1980, it switched to the “career ladder approach,” said Vento, a strategy that was aimed at bringing young people into pulmonary medicine and allowing them to establish their independence. Other modifications were made in the program in the ensuing years, changing some of the “steps” of the ladder and placing it in “different places,” added Vento. For example, doctoral awards were granted, and efforts were made to reach out to minority communities.

In the 1990s, it became clear that to raise funds as well as to support research, the Association would have to change its strategy. In 1991, the Association Council voted to focus on asthma, an approach that was important for advancing research but also for raising revenue. Since then, the Association has supported Asthma Research Centers that combine research and training.

Public Sector Programs

How to revitalize the nation’s clinical research enterprise has been a popular topic in recent years. Since 1996, NIH has focused efforts on how to stem the precipitous decline in the numbers of physician-scientists. NIH became alarmed when between 1994 and 1997 the number of first-time M.D. applicants plummeted 31 percent, from 838 to 575 applicants. With only a 22 percent success rate in 1997 among M.D. applicants, only 126 M.D.s served as first-time principal investigators on NIH research project grants. NIH statistics showed a similar situation among M.D. postdoctoral trainees supported by NIH through individual fellowships and training grants. The total number of M.D. postdoctoral trainees plateaued at around 2,300 in the 1980s. But between 1992 and 1997, that pool shrank to 1,261 such trainees.

In recent years, NIH has followed up on recommendations of the “Nathan Report” through such efforts as establishing the K23

and K24 training awards for young and midlevel career faculty and expanding the number of medical students invited to take a year off from school to do research at NIH, reported Wendy Baldwin, NIH’s Deputy Director for Extramural Research.

The purpose of the Mentored Patient-Oriented Research Career Development Award (K23) is to support the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research, said Baldwin. This mechanism provides support for three to five years of supervised study and research for clinically trained professionals who have the potential to develop into productive clinical investigators focusing on patient-oriented research. In 1999, 139 awards were made. With a view towards stabilizing clinical research settings and preventing an interruption in trainee mentoring, NIH has chosen to establish the Midcareer Investigator Award in Patient-Oriented Research (K24). This award is intended to relieve clinical investigators from patient care duties and administrative responsibilities in order to increase the opportunities for midcareer clinicians to become well grounded in patient-oriented research. In 1999, 81 such awards were made, reported Baldwin.

Baldwin said that NIH supports loan repayment programs in its intramural and extramural programs and would like to increase the amount of repayment awarded, a change that would require new congressional legislation.

Development and Support of Clinical Training on the NIH Campus

NIH also has undertaken new clinical training programs in its own clinical setting, reported John Gallin, Director of the NIH Warren Grant Magnuson Clinical Center. “Adequate training and the infrastructure to support principal

investigators conducting clinical research are essential to patient safety, protocol implementation, and quality assurance,” said Gallin, “especially in interventional clinical trials.” Indeed, even in natural history studies, such infrastructure can only enhance the quality of and access to the research by ensuring that data are collected as required by the protocol and are stored in a way that allows access to the information without depending on any individual clinical researcher.

Training and education are first-order requirements to ensure that clinical trial investigators have a consistent and complete understanding of their responsibilities, added Gallin. Clinical protocol design requires a working knowledge of clinical trials methodology, biostatistics, and regulatory medicine. Similarly, monitoring the trial during its execution involves many distinct responsibilities, including reviewing each study subject’s record to confirm his or her protocol eligibility, reviewing each study subject’s record to determine compliance with the protocol, reporting adverse events to the Institutional Review Board (IRB), determining necessary changes in the protocol and the informed consent documents and submitting them as protocol amendments to the IRB, monitoring accrual to the study, and stopping the study when the requirements of the study design have been fulfilled or when it is clear that the rate of accrual fails to meet expectations.

Under Gallin’s direction, all clinical principal investigators on the NIH campus are required to take an overview training course, or the equivalent, on the roles and responsibilities of clinical investigators.

In recent years, this approach has been extended beyond the NIH campus and beyond the M.D. The NIH-Duke Training Program in Clinical Research leads to a Master of Health Sciences in Clinical Research, a professional degree awarded by the Duke University School of Medicine. There is also a nondegree option for qualified students who want to pursue specific areas of interest. The

Warren Grant Magnuson Clinical Center, National Institutes of Health: Introduction to the Principles and Practice of Clinical Research

Introduction to the Principles and Practice of Clinical Research is a study curriculum on how to effectively conduct clinical research that was established at the Warren G. Magnuson Clinical Center—the clinical research hospital of NIH. This curriculum is designed to teach researchers how to design a clinical trial. It covers epidemiologic methods and focuses on study design and development, protocol preparation, patient monitoring, quality assurance, and regulatory issues and also includes data management and legal and ethical issues, including protection of human subjects.

Course objectives are to become familiar with the basic epidemiologic methods involved in clinical research; to be able to discuss the principles involved in the ethics of clinical research, the legal issues involved in clinical research, and the regulations involved in human subjects research, including the role of IRBs in clinical research; to become familiar with the principles and issues involved in monitoring patient-oriented research; and to be able to discuss the infrastructure required in performing clinical research and to understand the steps involved in developing and funding research studies.

Duke program, established in 1986, is one of the nation's first training programs in clinical research. This collaboration between the NIH Warren G. Magnuson Clinical Center and the Duke University School of Medicine marks the first time that the program has been made available for long-distance learners, said Gallin. In addition, students at NIH can attend classes at Duke by way of video conferencing. The curriculum covers the principles of clinical research, including research design, statistical analysis, health economics, research ethics, and research management. The availability of teleconferencing and telemedicine provides unprecedented opportunities for reaching out to clinical centers that have been "islands," said Gallin.

Finally, Gallin mentioned a program offered to medical students between their third and fourth year of training. Like the Howard Hughes Medical Institute-NIH Cloister Program, students spend a year working with a research mentor on campus to gain exposure to laboratory investigation. The program is funded by Pfizer, Inc., which committed \$1.6 million over two years to the National Foundation for Biomedical Research to sponsor 16 clinical research training fellows at NIH.

The program focuses on third-year medical and dental students and brings them to the NIH campus for a year of didactic and practical hands-on experience. The students are selected in a competitive process by an advisory committee of experts in clinical research. Students work in NIH laboratories and clinics and are mentored by senior clinical investigators. They also take a core course in clinical research and receive a stipend for living expenses and other support.

The Medical Scientist Training Program

The NIH MSTP, administered by Bert Shapiro, supports the integrated medical and graduate research training that is required for the

investigation of human diseases. It is widely believed to be a model that works, as 85 percent of the individuals who participate in the Program remain actively involved in academic medicine.

The MSTP assures highly selected trainees a choice of a wide range of pertinent graduate programs in the biological, chemical, and physical sciences, which, when combined with training in medicine, lead to the M.D.-Ph.D. degree. Programs are encouraged to provide a breadth of doctoral research training opportunities consistent with individual institutional strengths. In addition to the above disciplines, support of trainees in other disciplines, such as computer sciences, social and behavioral sciences, economics, epidemiology, public health, bioengineering, biostatistics, and bioethics, is appropriate. According to Shapiro, MSTP programs should be flexible and adaptable in providing each trainee with the appropriate background in the sciences relevant to medicine, yet they should be sufficiently rigorous to enable graduates to function independently in both basic research and clinical investigation. In 1999, the Program awarded \$26 million to 40 participating institutions. This type of program provides "the perfect model" for collaboration between the public sector and the private sector, commented Shapiro, who added that despite the success of the Program, the participating institutions are chronically underfunded. Clinical research training is expensive, he concluded, and public-private sector partnerships are essential in bridging the gap.

Goals for Private Funders

There are many new and exciting opportunities in clinical research that have been provided by the genetic revolution and other scientific advances. "We are seeing increasing demand for clinical research as we enter into this much-heralded postgenomic era," concluded Richard Lifton. "But we have to overcome enormous institutional challenges as the

traditional streams of revenue are redirected or dry up.” Two major investment areas have emerged to advance clinical research—human capital and training programs. Both require innovative approaches as we enter the realm of molecular medicine.

Human Capital

1. The development of clinical scientists is a good target for private support. However, as with training basic scientists, it is critically important to support young clinical scientists, although other steps in the ladder also require attention. Research experiences during medical school, such as the Howard Hughes Medical Institute-NIH Cloister Program and the NIH-Pfizer Clinical Research Training Program, are excellent examples of programs that support clinical investigators early in their careers, before receiving the doctorate.
2. The M.D.-Ph.D. is the most successful model for the development of clinical scientists. This model should be supported by the private sector in order to expand the current numbers of trainees at currently funded sites or to develop new programs at institutions that could then become eligible for NIH support. The NIH program currently supports only six years of training, leaving institutions to fill the gap for what is an eight-year program.
3. Despite the predominance of the M.D.-Ph.D. scientist, there are other essential types of physician-scientists, and these scientists require different types of support.
 - Numerous new master's-level programs are in development for clinical research training. The private sector can make a contribution by assisting with tuition support.
 - Ph.D.s, if trained in pathobiology or other human disease constructs, can provide an invaluable resource to the clinical research team.
4. Transition support to assist individuals at key points in their training and career development, such as between thesis work and the first independent faculty position, can be essential to prevent young scientists from leaving research. In this respect, debt relief is crucial. Because it is difficult for government agencies to provide adequate funds in this area, private philanthropy can make a valuable contribution.

Training Programs

1. The development of multidisciplinary and generic training programs in clinical research is urgently needed, and the collaboration of disease-oriented groups to provide such support could make a critical difference. Such a consortium could provide funds for junior faculty and graduate students as they make important education and career transitions.
2. There are a number of possible models for Ph.D. training for clinical research that could be targets of private support.
3. The private sector could support innovative mechanisms by which to develop and support mentorship skills in new and existing faculty.
4. Although a number of master's-level programs for clinical research have been funded, innovation in training approaches is needed to meet emerging needs in academic and industrial science.

Appendix A: The New World of Electronic Grantsmaking

American Association for the Advancement of Science GrantsNet and NextWave

Ellis Rubinstein, Editor of *Science* magazine, traced the progress of the American Association for the Advancement of Science Websites, GrantsNet (www.grantsnet.org) and NextWave (www.nextwave.org) (developed through collaborations with the Howard Hughes Medical Institute and the Burroughs Wellcome Fund), both of which represent unusual partnerships for a science magazine that has been produced as a sole venture for most of its 120 years. GrantsNet, part of the Association's NextWave Website, is a free, searchable online database of funding options for biomedical scientists in the training phases of their careers. The site was funded by a three-year, \$900,000 grant from the Howard Hughes Medical Institute and has been in operation for two years. Currently, it has 250 participating organizations, 52,000 registered users, and 604 programs in its database.

NextWave, established through support from the Burroughs Wellcome Fund, is the parent of GrantsNet. In operation since 1995, NextWave targets graduate and postdoctoral students and provides career advice and the opportunity for online exchanges among young scientists and between young scientists and experts. The site currently features a career development center that was initiated through a grant from the Burroughs Wellcome Fund and the Howard Hughes Medical Institute, and, in addition to support through a number of professional societies and government agencies, NextWave has a number of international collaborators.

Current plans include the redesign of the GrantsNet homepage, the development of a database for undergraduates in search of research opportunities, and expanded international scientific collaborations. Both GrantsNet and NextWave, said Mr. Rubinstein, demonstrate what can be accomplished by combining Web-based technologies for electronic grants-making with effective partnerships with organizations that have been at the forefront of the use of these technologies.

Howard Hughes Medical Institute Graduate Competition System

Joseph Perpich, Vice President for Grants and Special Programs, focused on the online application system the Institute has developed for its graduate fellowship programs—the Graduate Competition System. Prospective applicants access the system by going to the graduate program's home page, where they are linked to program announcements, eligibility criteria, application forms, and instructions and tips. An applicant registers and is given a personal identification number (PIN) and password for the application, as well as PINs and passwords for third parties, such as mentors and references, who also use the Web system to submit information.

Several features of the system are particularly useful. An application checklist, for example, tells applicants which third-party materials—transcripts, references, mentor materials—have been received by the Institute. This relieves staff from having to field many telephone calls and e-mails from applicants. Data entry is handled in two ways: Some fields use free-form entry (for example, current position), while others are selected from

standardized lists (for example, institutional affiliation, research field). Essay material on the application is handled by uploading a Rich Text Format file.

Applicants and mentors must complete the forms online and submit them to the Institute via the Web. After the application is submitted, the data are transferred to the non-Web component of the Graduate Competition System for management during the review and award process. For most Institute grants programs, the review process is handled almost entirely online. The Graduate Competition System is viewed by the Institute as "shareware" that can be made available to other funders at no cost (although funders would have to assume costs associated with any adaptations).

In addition, the Institute has undertaken significant standardization efforts. As a result, staff can analyze programs in terms of an array of variables and can also conduct a variety of cross-program analyses (for example, educational origins of graduate fellows, number of under-represented minorities participating in Institute-supported programs).

American Cancer Society Foundation Commons

The American Cancer Society has established the Foundation Commons Consortium, which provides a shared online application system for voluntary health agencies (www.foundationcommons.org). The Society coordinates this system, explained Dr. T.J. Koerner, Director of Research Information Management, with a number of other voluntary health agencies, including the Alzheimer's Association, the Cystic Fibrosis Foundation, and the Juvenile Diabetes Foundation. ScienceWise, the vendor that developed the system, is experienced with e-commerce applications and grant processes and serves as the point of contact for the member organizations, each of which has different needs for data and services.

At this time, Foundation Commons is not sharing grant results and is instead focusing on the application process. The system does not attempt to alter internal institutional review processes, but rather frees applicants from the burden of updating multiple profiles by creating one common profile for each applicant. After selecting the consortium member to which they wish to apply, users register by filling out and submitting a personal profile information form. They then download the application in Portable Document Format (PDF), complete the application offline, and submit the application in electronic and paper format per the consortium

member's instructions. The information goes to the Foundation Commons' central database and is transferred electronically to the consortium member's own system. Because the technology allows the use of both specialized and standardized fields, data standardization is used where it makes sense. For example, through this system, an application can be submitted to any organization that uses the federal government 194 Data Set standard.

To save completed forms in PDF, applicants are required to have access to Adobe Acrobat Exchange 4.0, which, unlike Adobe Acrobat Reader, is not free, although this is the system's only limiting technological requirement. In discussion, participants noted the lack of inexpensive, nonproprietary software as a common obstacle to use and standardization of online application systems and emphasized the need to think carefully about how the proliferation and use of these systems may affect those who are submitting research applications, where overhead and indirect costs are involved.

National Science Foundation FastLane Project

The National Science Foundation developed this Web-based system for the submission and review of grant proposals (www.fastlane.nsf.gov) and currently receives approximately 22,000 applications a year through the site. In addition, approximately 80,000 reviews and 99 percent of project reports have been received through FastLane. Carolyn Miller, Branch Chief, External Systems, stressed the importance of having appropriate external and internal functions in place in order for this kind of system to work. External functions that need to be in place at agencies include proposal preparation and submission; reference preparation and submission; proposal review; panel travel; and organizational management. The Foundation provides a number of internal functions to its staff through FastLane, such as an electronic jacket that includes all available information; a review management utility that allows staff to manage reviewers and panels; functions that provide the ability to generate reports and track progress; and the ability to transfer information to and from internal processing systems.

From the perspective of proposal processing, an important advantage to this system is that parts of the review process can be initiated before the actual review begins. Overall, Ms. Miller noted, processes that involve mainly straightforward data transactions

have worked well; in the area of awards management, for example, the system has significantly reduced the time it takes to apply and receive approval for a no-cost extension. The most complicated process to implement electronically has been proposal preparation.

FastLane's vision for the future, one that will help meet the challenges of Internet accessibility and server performance (especially when deadlines are involved), is one of a connection-free process for all FastLane functions. Through a connection-free process, for example, reviewers can download a function and work off-line and then submit their work either through e-mail or the Web. Another important challenge is the need for software that can be used with any word processor and that can support scientific images. Currently, FastLane uses PDF files for documents that include scientific illustrations; however, a promising competitor, called GoScript 6.0, is now available and is supported on Unix, PC, and Mac platforms.

National Institutes of Health NIH Electronic Research Administration Commons Project (NIH Commons)

George Stone, Chief, Commons, Extramural Inventions, and Technology Resources Branch at the National Institutes of Health (NIH), noted that the federal government's mandate to reduce the amount of paperwork within the next 18 months will significantly affect how the government processes applications and awards. Through its NIH Electronic Research Administration Commons (www-commons.cit.nih.gov), NIH is working to accomplish this transition from paper to electronic processes throughout the grants lifecycle and to make its systems more applicable and less proprietary in a thoughtful way, despite the speed with which the new technology is advancing and the challenges that are presented in replacing the 30- to 50-year-old legacy systems. The NIH Commons is implementing Internet processes for information exchange through two main strategies: The first is to disseminate unrestricted information, which does not require a user log-in. The second is to provide for the exchange of confidential information, which requires registration and log-in.

NIH Commons uses a system of controlled deployment in which the system is first offered to a small number of organizations that have expressed interest in it, and then, after the system is refined based on feedback from these organizations, it is offered more

widely. Currently about 125 schools are using the system, which is now considered to be in expanded deployment. "To be successful, we must take into account the diversity of the grantee population and accommodate the differences through a combination of structure and flexibility," remarked Dr. Stone, who added that NIH Commons employs a common standard, the 194 Data Set, which serves as a common data dictionary that is used by both the government and the private sector.

NIH Commons supports an online electronic profiling system and provides a secure and confidential environment within which users can conduct their business. Because the goal is to be flexible in the use of technological approaches, NIH Commons tries to avoid the use of proprietary software, such as PDF; however, no nonproprietary method currently is available that can be used for the scientific illustrations that are often included in applications. NIH Commons will support Extensible Markup Language technology, which, once a tool is available to support it, could render PDF obsolete. At this time, the system adheres to standard syntax formats, such as Interactive Web, Electronic Data Interchange, HyperText Markup Language, and Adobe forms filling.

Recent developments at NIH Commons include the use of e-Snap for the submission of noncompeting application data into a streamlined awards process and the use of e-Fellowships for the preparation and submission of fellowship applications via Interactive Web. X-train, for electronic trainee activities, is a secure interactive Website for statement of appointments and termination notices of extramural trainees. NIH Commons also supports a profiling system and a system for checking the status of pending applications. In addition, an application viewer is available that allows an applicant to see how the application will look before submitting it.

Discussion focused on whether the Web could make it easier for those who are not serious applicants to apply for awards and in the process disrupt grants-making sites. Dr. Stone noted that because NIH Commons uses a strong authorization protocol, such use would be unlikely. Registration includes a faxed authorizing signature, and all information that is provided by the applicant is validated. In addition, affiliation is required in order to submit an application, except for fellowship applications, which must be submitted by a sponsor in order to be accepted.

Appendix B:

Meeting

Agenda

Monday, February 14, 2000

Welcome and Opening Remarks

- Thomas R. Cech, Ph.D., President, Howard Hughes Medical Institute
- Enriqueta Bond, Ph.D., Burroughs Wellcome Fund
- John Stevens, M.D., American Cancer Society

Forum on the New World of Electronic Grantsmaking

Moderator: Joseph G. Perpich, M.D., J.D., Howard Hughes Medical Institute

- Ellis Rubinstein, "GrantsNet," "NextWave," *Science* magazine
- T. J. Koerner, Ph.D., "Foundation Commons," American Cancer Society
- Carolyn Miller, "FastLane," National Science Foundation
- George Stone, Ph.D., "NIH Commons," National Institutes of Health

Tuesday, February 15, 2000

Basic Biomedical Research Training

Welcome

Thomas R. Cech, Ph.D., President, Howard Hughes Medical Institute

Perspectives on the Future of Basic Biomedical Research

David Botstein, Ph.D., Stanford University

Competencies Required of the Next Generation of Basic Scientists

Thomas R. Cech, Ph.D., Howard Hughes Medical Institute

Challenges and Opportunities in Training Basic Biomedical Scientists

Moderator: Thomas R. Cech, Ph.D., Howard Hughes Medical Institute

- Stephen Burley, M.D., D.Phil., Howard Hughes Medical Institute, Rockefeller University
- Nicholas R. Cozzarelli, Ph.D., University of California-Berkeley
- Freeman A. Hrabowski, Ph.D., University of Maryland, Baltimore County
- David Botstein, Ph.D., Stanford University

Current Programs and Plans of Private Funders

Moderator: Donella Wilson, Ph.D., American Cancer Society

- Jaleh Daie, Ph.D., The David and Lucile Packard Foundation
- Susan Barnett, M.A., American Heart Association
- Robert Goldstein, M.D., Ph.D., Juvenile Diabetes Foundation
- Maria Pellegrini, Ph.D., W.M. Keck Foundation

Current Programs and Plans of Federal Funders

Moderator: Michael Teitelbaum, Ph.D., Alfred P. Sloan Foundation

- Marvin Cassman, Ph.D., National Institute of General Medical Sciences
- Mary Clutter, Ph.D., National Science Foundation
- Elke Jordan, Ph.D., National Human Genome Research Institute
- John Ruffin, Ph.D., National Institutes of Health

Summary of the Day

David Botstein, Ph.D., Stanford University

Evening Speaker

Ethical Issues Associated with Future Biomedical Research
R. Alta Charo, J.D., University of Wisconsin-Madison

Wednesday, February 16, 2000

Clinical Research Training

Welcome

Enriqueta Bond, Ph.D., President, Burroughs Wellcome Fund

The Future of Clinical Research

*Richard P. Lifton, M.D., Ph.D., Howard Hughes Medical Institute,
Yale University School of Medicine*

Challenges and Opportunities in Training Clinical Researchers

Moderator: John Stevens, M.D., American Cancer Society

- Edward Holmes, M.D., Duke University Medical Center
- Irwin M. Arias, M.D., Tufts University
- N. Franklin Adkinson, Jr., M.D., Johns Hopkins University
- J. Claude Bennett, M.D., BioCryst Pharmaceuticals

Current Programs and Plans of Private Funders

Moderator: Lewis G. Sandy, M.D., Robert Wood Johnson Foundation

- Elaine Gallin, Ph.D., Doris Duke Charitable Foundation
- Sarah Caddick, Ph.D., Damon Runyon-Walter Winchell Foundation
- Marshall Lichtman, M.D., The Leukemia & Lymphoma Society
- Ray Vento, American Lung Association

Current Programs and Plans of Federal Funders of Research

Moderator: Myrl Weinberg, CAE, National Health Council

- John I. Gallin, M.D., Warren G. Magnuson Clinical Center
- Bert Shapiro, Ph.D., National Institute of General Medical Sciences
- Wendy Baldwin, Ph.D., National Institutes of Health

Summary of the Day

*Richard P. Lifton, M.D., Ph.D., Howard Hughes Medical Institute,
Yale University School of Medicine*

Closing Remarks and Adjournment

John Stevens, M.D., American Cancer Society

Enriqueta Bond, Ph.D., Burroughs Wellcome Fund

Thomas R. Cech, Ph.D., Howard Hughes Medical Institute

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American Cancer Society

1599 Clifton Road, N.E. • Atlanta, GA 30329
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The American Cancer Society is a nationwide, community-based health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives from cancer, and diminishing suffering from cancer through research, education, advocacy, and service. It is one of the oldest and largest voluntary health agencies in the United States, with over two million volunteers working to conquer cancer through balanced programs of research, education, patient service, and rehabilitation. The American Cancer Society, Inc., consists of a National Society with chartered Divisions throughout the country and over 3,400 local Units.

Burroughs Wellcome Fund

P.O. Box 13901 • 21 T.W. Alexander Drive • Research Triangle Park, NC 27709
Phone: (919) 991-5100 • Fax: (919) 991-5160
www.bwfund.org

The Burroughs Wellcome Fund is an independent private foundation dedicated to advancing the medical sciences by supporting research and other scientific and educational activities. The Fund's general strategy is to help outstanding scientists early in their careers develop as independent investigators and to support investigators who are working in or entering undervalued or underfunded fields in the basic medical sciences. With its endowment of approximately \$670 million, the Burroughs Wellcome Fund makes some \$35 million in grants annually in the United States and Canada. Based in Research Triangle Park, North Carolina, the Fund was founded in 1955 as the corporate foundation of the pharmaceutical firm Burroughs Wellcome Co. In 1993, the Burroughs Wellcome Fund became independent from the company, which was acquired by Glaxo in 1995. The Burroughs Wellcome Fund has no affiliation with the firm now known as Glaxo Wellcome or with any other corporation.

Howard Hughes Medical Institute

4000 Jones Bridge Road • Chevy Chase, Maryland 20815-6789
(301) 215-8500 • www.hhmi.org

The Howard Hughes Medical Institute, the nation's largest private philanthropy, is a medical research organization whose scientists include many of the world's leaders in the fields of cell biology, genetics, immunology, neuroscience, and structural biology. Howard Hughes Medical Institute Investigators carry out research at universities and academic medical centers across the United States. In addition, the Institute has a grants program that is the largest private initiative in U.S. history to enhance science education at all levels from preschool through postgraduate training. Through its grants program, the Institute also supports the research of outstanding biomedical scientists outside the United States and provides funding to help medical schools sustain their commitment to research. The endowment of the Institute by late 1999 was approximately \$13 billion. The Institute's headquarters is located in Chevy Chase, Maryland, just outside Washington, D.C.

