The SPARK That Ignited a New Era of Research

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In the spring of 1998, as members of both the House and Senate were signaling their interest in increasing National Institutes of Health (NIH) appropriations substantially over the next several years, the National Heart, Lung, and Blood Institute (NHLBI) convened the “SPARK Working Group,” a panel of prominent scientists, to identify extraordinary opportunities that should be funded with any significant increase in Institute resources.

With that objective in mind, the SPARK group set to work and ultimately identified four broad areas of scientific opportunity, as well as a number of enabling approaches. The areas are (1) Functional Genomics, (2) Gene-Gene and Gene-Environment Interactions, (3) Tissuegenesis/Organogenesis, and (4) Immunobiology. (See http://www.nhlbi.nih.gov/funding/fromdir/sparkweb.htm for a copy of the SPARK report.)

As the research community is well aware, the Congress did its part. The NHLBI has already received four substantial increases in its budget and, if the President’s current budget proposal for fiscal year 2003 is approved by the Congress, the NIH budget will be double what it was in 1998.

The purpose of this editorial is to demonstrate that the Institute, in partnership with the community it serves, did its part, as well. Although the innovative programs developed in response to the SPARK report are too numerous to describe in detail, a few of the major ones are highlighted herein. They are testimony to the extraordinary vision of the SPARK participants—much of the focus of what they recommended and what was, in turn, implemented was on developing resources that would enable the research of individual investigators. Perhaps the most notable examples of this sort of investment are to be found in the combined areas of functional genomics and gene-gene and gene-environment interactions.

**Functional Genomics and Gene-Gene and Gene-Environment Interactions**

In September 2000, the largest basic science program in NHLBI history was launched, the Programs for Genomic Applications (PGAs). Its objectives are to link genes to biological function on a genomic scale, to establish targeted training and education programs to disseminate information and technologies, and to enhance the development of the technologies, biological models, methodologies, reagents, and software that investigators will need to obtain a better understanding of the biology and pathobiology associated with heart, lung, and blood function and disease. One of the main stipulations of the PGA awards is that information and reagents developed as part of the program are to be made immediately and freely available to the research community. Already, mouse embryonic stem cell lines developed by one of the PGAs for identifying genes relevant to cardiovascular and pulmonary disease are being used by investigators at other institutions to develop specific mouse models tailored to their own research interests. (See http://www.nhlbi.nih.gov/resources/pga/index.htm for additional details.)

As recommended in the SPARK report, attention was also focused on areas where the interactions of genes with other genes and of genes with environmental factors are likely to play a role in heart, lung, and blood diseases and sleep disorders. Of particular interest are those diseases which, although known to be caused by defects in a single gene, produce a wide range of clinical manifestations. One example is sickle cell disease, which can be relatively mild in some patients but takes a devastating course in others. To increase understanding of why this occurs, research was initiated to study the modifier genes that interact with disease genes and are responsible for clinical variations. Studies are currently under way focusing on the modifier genes for several additional diseases, including cystic fibrosis, α1-antitrypsin deficiency, and congenital heart disease.

**Tissuegenesis/Organogenesis**

The SPARK group’s interest in research on the fundamental underpinnings of organ development formed the basis for a significant investment in stem cell research. The result is a rigorous research effort to study stem cell plasticity in hematopoietic and nonhematopoietic tissue. NHLBI-supported investigators are also working to develop preparative regimens to advance hematopoietic stem cell transplantation for hemoglobinopathies and, with additional support from other NIH components, to isolate and characterize stem cells in a variety of animal species.

To support the development of functional tissue engineering while allowing investigators free rein to use their imagination and vision, the NHLBI recently announced an initiative to encourage investigators to explore entirely new approaches and test imaginative ideas at the frontiers of tissue engineering and regenerative medicine. It encourages the development of myriad technologies, tools, methods, devices, cells, biomolecules, and biomaterials that can be used for tissue engineering. This initiative has captured the interest of both the academic research community and the small business community.


**Immunobiology**

Building on recent advances in immunobiology, a broad, multidisciplinary research effort is now under way to increase fundamental understanding about the cellular and molecular components and mechanisms and the signaling processes that regulate the immune system in cardiovascular, pulmonary, and blood tissues and that are important in maintaining healthy tissue as well as enabling the development of disease. Collaboration between investigators with interest in cardiovascular, pulmonary, or blood systems and investigators who study inflammation and immunology is an important feature of this new effort.

Other opportunities in this area include investigations of the role of inflammation in the pathogenesis of chronic obstructive pulmonary disease, the immunopathogenesis of chronic graft rejection, and the influence of infectious agents on vascular diseases.

**Enabling Approaches**

As SPARK participants realized, the research envisioned would require dramatically new approaches and access to a vast and expensive assortment of technologies, resources, and tools. Because no one institution could develop everything its investigators would need, collaboration would be essential. Accordingly, many of the new NHLBI initiatives have been structured so that scientific collaboration, including the sharing of information and resources, is a requirement.

For example, the Programs of Excellence in Gene Therapy initiative, a major translational research program launched in September 2000 to facilitate clinical gene therapy studies, was designed to provide investigators with access to the specialized resources needed for the research. It provides for six National Service Cores: two clinical-grade vector production cores, a preclinical-grade vector production core, a cell morphology core, a hematopoietic cell processing core, and a nonhuman primate hematopoietic cell transplantation core. The services are presently available to all NHLBI-supported investigators at no cost. (See http://www.med.cornell.edu/pegf/for additional details.)

New clinical research networks have now been established in pediatric heart disease, pediatric asthma, thalassemia, and blood and marrow transplantation, and a transfusion medicine/hemostasis clinical research network is also being formed. Seen by SPARK participants as critical to facilitating effective clinical studies, the network approach enables expedited evaluation of therapies and management strategies, as well as rapid dissemination of findings to the health care community. The networks typically comprise multiple interactive clinical centers with ready access to patients of interest and a data coordinating center.

In the basic science arena, proposals have been solicited to establish highly interactive, multidisciplinary centers to develop innovative proteomic technologies and apply them to biological questions relevant to heart, lung, blood, and sleep health and disease.

The NHLBI is also participating in NIH efforts in the following areas: development of a public Pharmacogenetics Knowledge Base; development of methods for the phenotypic screening of mice for heart, lung, blood, and sleep disorders; support of innovative research in biomedical information science and technology to promote the progress of biomedical research; and sequencing of the rat genome.

Many of the new programs were designed so that opportunities would be provided for the research community to learn how to use newly developed resources. For example, the PGAs provide workshops and courses to train researchers in the use of the data and related technologies that are developed by the PGAs. Information about this training is available on the PGA Educational Activities website, accessible through the NHLBI home page. Investigators who apply for certain types of clinical research awards are also being offered the opportunity to request additional funds for a Clinical Research Skills-Development Core. (See Circulation. 2002:105:1751–1752.) The Cores will support activities to help new and relatively inexperienced clinical investigators who are participating in the research effort enhance their research skills and thereby progress to more senior and, ultimately, independent investigator status.

Both the Institute and the research community it serves owe a great debt of gratitude to their colleagues on the SPARK Working Group for providing a vision of the future of heart, lung, blood, and sleep research, and to their representatives in Congress and the American public for making available the resources necessary to realize that vision.

In the near future, the NHLBI will reactivate the SPARK Working Group to consider the next phase of research opportunities. Its deliberations, in conjunction with those of the NHLBI Board of Extramural Advisors and the National Heart, Lung, and Blood Advisory Council, will provide invaluable guidance about the best use of Institute resources.

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