

BACKGROUND ON SICKLE CELL DISEASE INITIATIVE
NHGRI Advisory Council
May 6, 2004

Published one year ago, the NHGRI “Vision for the Future of Genome Research” outlines the grand challenges in this next phase, and includes an increasing emphasis on direct application of the tools of genomics to benefit human health. NHGRI is eager to contribute to the improvement of the treatment of genetic disorders, but cannot hope to tackle all such disorders individually. Instead, it makes sense to focus on a few carefully chosen disorders, using them as “demonstration projects” to develop new genomics-based paradigms that can then be generalized and modified for application to other disorders.

Sickle cell disease was the first disease whose genetic etiology was defined. That occurred more than half-a-century ago. Subsequent research has produced gains in both understanding the biology of the disorder, such as the pathophysiological process of polymerization and the protective effect of fetal hemoglobin, and in developing better therapies, such as hydroxyurea. However, sickle cell disease continues to be a significant cause of mortality, morbidity, and health disparities, both in the United States and globally. For a number of reasons, including sickle cell disease’s history of relative resistance to non-genomic approaches, its significant morbidity and mortality, its contribution to health disparities, and its raising of ELSI issues, sickle cell disease is a logical monogenic disorder with which to explore the new genomics-based paradigm mentioned above. Thus, last summer the NHGRI proposed to other NIH institutes and centers with a history of interest in sickle cell disease that an expert conference be held to discuss the application of genomics to sickle cell disease.

As a result, the conference, “New Directions for Sickle Cell Therapy in the Genome Era” was held at the Natcher Center at NIH on November 19-21, 2003. Organized and supported by the NHGRI, the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases, the Office of Rare Diseases, the Fogarty International Center, and the Foundation for the National Institutes of Health, the conference was co-chaired by Francis Collins, Barbara Alving, Acting Director of the NHLBI, and Sir David Weatherall of Oxford University. Over 120 members of the sickle cell disease research and genomics communities from the United States and abroad attended the invitation-only meeting.

The goal of this conference was to consider how the new tools and techniques of genomics might be applied both to understand more fully the biology of sickle cell disease and to develop more effective therapeutic and preventive strategies for the disease. The ambition of the conference was not merely to refine present approaches to sickle cell disease, but to outline bold new approaches likely to produce significant therapeutic advances. Seeking to move the field of sickle cell disease research and care dramatically forward, and mindful that the history of sickle cell disease research is particularly informative about the social and cultural contexts and consequences of health research and health care delivery, the conference encompassed a broad range of issues.

Among the major conclusions of the conference were:

1) The time is propitious to bring to bear the tools and approaches of genomics to develop more effective therapies for sickle cell disease. The NIH should play a lead - but not exclusive - role in developing and supporting such applications of genomics to sickle cell disease. For this effort to succeed, both the community of existing sickle cell disease researchers and the genomics community must be actively involved and integrated with each other to a degree that they have not been previously. Importantly, the community of individuals, families, and population groups affected by sickle cell disease must also be actively involved. As sickle cell disease is a global health issue, with over 95% of affected individuals living outside the United States, the application of genomics to sickle cell disease requires a global perspective and involvement as well. Within the NIH, a number of institutes and centers should be involved in cooperative design and support of new initiatives in this area.

2) An innovative multidisciplinary Sickle Cell Disease Research Network with a central prospective registry of well phenotyped patients should be established.

3) There are many promising ways to apply genomics tools and approaches to sickle cell disease. Given the phenotypic diversity of sickle cell disease, identification of genetic modifiers is a particularly promising approach. Methods to accomplish this might include case/control studies and/or studies of twins, of sib pairs and of individuals with unusually mild phenotypes. International collaboration might be particularly helpful here. With the anticipated release in 2005 of a haplotype map of the human genome, the possibility of haplotyping a sufficient number of patients with sickle cell disease to look for genetic modifiers and other clues to disease pathophysiology is an exciting avenue of research. A search for genetic modifiers in applicable transgenic animal models might also prove beneficial.

4) Another genomic opportunity is performing proteomic and mRNA microarray-based analyses of bone marrow (if available), leukocytes, erythrocytes and their precursors, endothelial cells, etc. from a variety of patients with differing disease involvement.

5) Genomics could also be brought to bear fruitfully through chemical genomics. Small molecule screens should be utilized to investigate possible new targets for therapeutics for sickle cell disease. Target-based compound screens to explore such possibilities as hemoglobin F induction, nitric oxide, antithrombotics/anticoagulants and other agents that might affect adhesion, inflammation, or oxidation would also be useful.

6) Bringing new people and disciplines into the field is crucial. It is important to increase the number of basic, clinical, and social science researchers doing research on sickle cell disease. There are a number of ways to do this. Perhaps the most important is to renew a sense of excitement and promise in sickle cell disease research, so that it attracts young and/or new researchers to the field. Integrating genomics, proteomics, and high-throughput screening expertise into sickle cell research will help accomplish this. Appropriate support for training and retention of researchers, especially young ones, focused on sickle cell disease will also be important.

7) All new research should be informed by the historical, social, economic, and cultural context of research and health care in sickle cell disease. This becomes increasingly important as research becomes increasingly applicable to health outcomes.

8) Wider availability of clinicians able to care expertly for individuals with sickle cell disease and of therapies that are demonstrated to be effective, such as hydroxyurea, is needed. Further promulgation of a standardized care model should be pursued. Community and public education programs might also prove helpful. While the NIH should be involved in addressing these needs, it is beyond the mandate and the resources of the NIH alone to do so, so other agencies must also be involved.

9) Core resources of biological materials, including such materials as transgenic mice for drug screening, a DNA construct repository, antibodies to sort erythroid progenitors, cord blood banks for SCD and thalassemia cells, and relevant stem cells should be made available to researchers.

10) Core resources for drug development, e.g., toxicology, non-human primates, and infrastructure for Phase I and II trials should also be made available. The new NIH Roadmap goals for translational research should be highly relevant here.

11) There is the need to develop new models to study hemoglobin F reactivation, especially in adult cells, such as human cell lines that respond to switching agents.

12) New and better gene transfer vectors that are safe and efficient, including non-integrating systems, targeted integration, and homologous recombination should be developed.

13) The NIH should take the lead in establishing a working group in 2004 to define SCD severity by strict standardized criteria.

When asked to rank various priorities, the three with the most support among attendees were:

- An innovative multidisciplinary Sickle Cell Disease Research Network with a central prospective registry of several thousand well phenotyped patients.
- Bringing new people and disciplines into the field and training the next generation of researchers. This would include integrating genomics, proteomics, and high-throughput screening expertise into sickle cell disease research.
- Defining the genetic basis of phenotypic variability. Methods to this might include case/control studies and/or studies of monozygotic and dizygotic twins, of sib pairs and of individuals with unusually mild phenotypes. International collaboration would be particularly helpful here.

A Trans-NIH Sickle Cell Disease Therapies Working Group, involving staff from eight NIH institutes and centers, was established to follow up on the recommendations from the conference. It was co-chaired by Alan Guttmacher, Deputy Director of NHGRI and Greg Evans of NHLBI,

and had several other NHGRI staff among its members, including Bettie Graham of the Division of Extramural Research.

The working group has developed brief concept papers about nine proposals. All will be presented briefly to Council at the Monday open session. Included here are descriptions of the two proposals for which concept clearance by Council will be requested on Monday.

**TRAINING PROGRAM: APPLICATION OF GENOMICS AND PROTEOMICS
TECHNOLOGIES TO HEMOGLOBINOPATHIES**

<u>YEARS:</u>	FY2005-FY?
<u>COST:</u>	Total cost per award: ~\$330,000 Total cost for training program (three awards): ~ \$990,000.
<u>LEAD IC:</u>	Shared; NHGRI will contribute up to 50% of funding
<u>MECHANISM:</u>	T90 Institutional Training Grant
<u>PURPOSE:</u>	To train the next generation of hemoglobinopathy researchers who will utilize genomic and proteomic technologies to facilitate the understanding of the biology of hemoglobinopathies in order to prevent disease and/or to develop effective therapeutic interventions.

Target Population: Individuals with research and/or clinical doctorates.

Features of the Program:

- Interdisciplinary, institutional postdoctoral program that would require co-program directors-one who has a research intensive program in hemoglobinopathies and one who has a research intensive program in large-scale genomics and proteomics. The co-directors could be within the same institution or another institution within the United States or a foreign country where a significant part of the population is affected with the disease.
- The training program would have three components:
 - *Didactic training*: Courses relevant to the proposed research might include sufficient courses to prepare the trainee for a research career, such as, understanding the biological basis of the disease; designing protocols; collecting, manipulating and interpreting large data sets; understanding the ethical, social and legal implications of human genetics research; and training in the responsible conduct of research;
 - *Genomics/Proteomics/Bioinformatics Experience*: A laboratory rotation of sufficient length to ensure that the trainee has sufficient skills in and understand how genomics, proteomics, and bioinformatics tools and technologies are utilized in designing large-scale experiments and collecting, manipulating and interpreting large data sets; and
 - *Research in Hemoglobinopathies*. The emphasis would be to pursue a research project that would make maximum use of the didactic training and exposure to genomics/proteomics/bioinformatics tools and technologies to develop a research

program that would focus on understanding the disease, in order to develop better prevention strategies or effective therapeutic interventions.

- The institutional training grant award would be for a maximum of five years. Individual trainees would be appointed to the program for a maximum of three years. The training program of each trainee would have to be designed to ensure that at the end of the three-year period, the trainee has sufficient expertise to pursue an independent research program in the research area and is appropriate to the resources that will be available to her/him upon completion of the program. The training program should be seen as a long-term collaboration between the mentors and the trainees participating in the program.
- An advisory committee would be established consisting of the co-directors, outside scientists who have research-intensive large-scale genomics/proteomics/bioinformatics programs, and NIH staff.
- Annual meetings of all trainees and program directors would be held to discuss the program and the research training progress.
- Clinicians who are U.S. citizens or permanent residents of the U.S would be urged to apply for the Loan Repayment Program in the initial phases of their traineeship.
- Trainees nearing the completion of their program would be encouraged to apply to the “good ideas program” in order to develop preliminary data for a regular R01 application.

Mechanisms: T90, which is a new Road Map mechanism, will be used for this initiative. It allows the training of non-US citizens.

Number of FTEs: Suggest three institutional awards with each award supporting five to ten [?see below] trainees when the program is fully ramped. There should be an equal number of trainees with research and medical doctorates.

BUDGET PROPOSAL: [Is there a problem with the math here? I don't see how you can support 5 – 10 trainees for \$330K per year]

- Stipends for postdocs: Suggest two levels - \$40K for Ph.D. and \$45K for MD or MD/PH.D. (NRSA Range - \$35K for 0 years to \$51K for ≥ 7 years experience)
- Health insurance for fellow and family: \$2,000 per trainee per year
- Tuition: \$5,000 per trainee for entire period
- Travel and meetings: \$2,000 per trainee per year
- Research supplies: \$7,000 per year
- Subtotal for each trainee: \$56K to \$61K
- Time and effort of PI and administrative assistant: Up to \$20,000
- Computers and software licenses: \$15,000
- Indirect cost: 8%

CHEMICAL GENOMICS APPROACHES IN SICKLE CELL DISEASE RESEARCH

<u>YEARS:</u>	FY 2005-2007
<u>COST:</u>	FY 2005: \$300,000 (\$100,000 each x 3 pilot projects) FY 2006: \$800,000 (2 nd year of funding @ \$200,000 each x 3 original pilot projects + \$100,000 each x 2 new pilot projects) FY 2007: \$400,000 (2 nd year of funding @ \$200,000 each x 2 projects)
<u>LEAD IC:</u>	NHGRI will cover up to 80% of costs
<u>MECHANISM:</u>	RFA
<u>PURPOSE:</u>	To improve understanding of the biology of sickle cell disease and to identify promising new agents for sickle cell disease therapy.

In the past several years, a number of scientific and technological advances have combined to make possible, for the first time, the application of “chemical genomics” approaches to sickle cell disease - both to increase our understanding of the biology of the disorder and to facilitate the development of novel therapies for it. The Human Genome Project has provided new targets; advances in combinatorial chemistry and the new availability of commercial compound libraries have created large collections of small molecules; and high-throughput robotic technologies have provided the means for efficient screening of hundreds of thousands of compounds.

To date, academic investigators have had scant recourse to chemical genomics tools that are fairly widely available in industry. To increase the availability of chemical genomics approaches for all researchers, as part of its Roadmap initiatives the NIH is funding a network of Molecular Libraries Screening Centers as a national biomedical research resource. This fall an intramural facility (the NIH Chemical Genomics Center or NCGC) will be established, and subsequently five or six extramural screening centers will be funded (RFI issued 11/21/03; RFA released 4/04, receipt date 8/04, awards Spring 2005), along with a coordinating center. The proposed network will provide access to high throughput screening of a public collection of chemically diverse small molecules (assembled by NIH in a complementary effort) in a variety of assays to identify molecules for use as biological probes and as starting points for the development of therapeutics. The chemical structures of compounds in the small molecule repository and the screening data generated by the centers will be available via a public cheminformatics database (PubChem, being developed by NCBI).

The use of this approach to improve our understanding of the biology of sickle cell disease is promising; however, its potential for developing new targets for sickle cell disease therapy may be even more important. Part of the purpose of the NIH Molecular Libraries Screening program is “to empower multi-disciplinary academic teams to discover small molecules that can be used in basic biological and biomedical studies, and to translate basic research findings into novel therapeutics in disease areas that may not be attractive to the private sector.” Sickle cell disease would appear to be a prime candidate.

The NIH-supported chemical genomics centers could be used to search for promising new small molecules for understanding and treating sickle cell disease, using well-designed assays focused on several aspects of the phenotype. The centers will likely determine which projects to pursue through peer-review of submitted “white papers.” To maximize the likelihood of compelling proposals regarding sickle cell disease, it would be good to stimulate thinking now within the research community regarding how best to conceptualize the problem and develop high throughput assays for critical steps in the pathophysiology of sickle cell disease. The community should also begin to develop the multi-disciplinary teams, including such new elements as medicinal chemists, necessary to convert any promising small molecules that emerge from the screening process into viable new therapies.