



**Conference Summary**  
**New Directions for Sickle Cell Therapy in the Genome Era**  
**National Institutes of Health**  
**November 19-21, 2003**

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The conference, “New Directions for Sickle Cell Therapy in the Genome Era” was held at the Natcher Conference Center of the National Institutes of Health in Bethesda, MD on November 19-21, 2003. The conference was organized and supported by the National Human Genome Research Institute, the National Heart, Lung, and Blood Institute, 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. Over 120 individuals from the United States and abroad attended this invitation-only meeting.

Sickle cell disease was the first disease whose genetic etiology was defined. That occurred more than half-a-century ago, and since then many excellent researchers have given the disorder much attention. This has produced major gains in both understanding the biology of the disorder, such as the pathophysiological importance of polymerization, and in developing better therapies, such as hydroxyurea. Despite such advances, however, sickle cell disease continues to be a significant cause of mortality, morbidity, and health disparities, both in the United States and globally.

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 great – 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 featured consideration of such issues.

The conference organizing committee is pleased to present this summary of the conference proceedings. The committee wishes to thank all of the conference speakers, workshop leaders, and participants for their active participation and for their thoughtful contributions that form the basis for this summary.

The body of this report summarizes each session and concludes with recommendations from the meeting. Included also are Appendix A (conference agenda), Appendix B (conference participants), and Appendix C (attendees’ votes among options for research on new therapies for sickle cell disease).

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### **Wednesday, November 19**

The conference opened with welcoming remarks from Dr. Elias Zerhouni, Director of the National Institutes of Health (NIH), Dr. Francis Collins, Conference Co-Chair and Director of the National Human Genome Research Institute (NHGRI), Dr. Barbara Alving, Acting Director of the National Heart, Lung, and Blood Institute (NHLBI), and Prof. Sir David Weatherall, Oxford University, Conference Co-Chair.

A series of seven plenary talks was then presented, with highly interactive discussion periods following each talk. Brief summaries of these talks follow:

#### ***The Pathophysiology of Sickle Cell Disease: State of the Art*** - Martin Steinberg, M.D.

Dr. Steinberg presented an overview of current knowledge about the pathophysiology of sickle cell disease (SCD), highlighting polymerization, membrane damage, inflammation, perfusion-reperfusion injury, oxidative damage, and altered nitric oxide biology as important aspects of the disease process. He discussed the clinical features of SCD as falling under the general rubrics of vasoocclusion and hemolysis. He suggested a “new” view of SCD pathophysiology would include that: the hemoglobin S mutation is necessary but insufficient to account for disease pathophysiology; many other modifier genes determine disease phenotype; some of these act “uniformly,” influencing more than one sub-phenotype, while others are phenotype-specific; and these genes and their variants determine disease severity by modulating the effects of the hemoglobin S mutation and interacting with each other and the environment.

#### ***Therapeutics for Sickle Cell Disease: State of the Art*** - Elliott Vichinsky, M.D

Dr. Vichinsky gave an overview of current and promising therapeutic agents in SCD. He noted a trend towards loss of adult-focused clinical research in SCD, leaving an almost sole focus on pediatric aspects of the disease and suggested that this trend needs to be reversed. He also noted that while some recommended interventions, such as penicillin prophylaxis, have proven clinically important and have found wide adoption, some, such as use of hydroxyurea, are not implemented in the care of many patients. Other current impediments that he discussed included lack of autopsy/histology data, pharmaceutical companies viewing SCD as lacking sufficient marketing potential to warrant investment, continuing loss of SCD researchers, and lack of structures to address long-term care needs. Dr. Vichinsky thought that unrelated bone marrow transplant is very promising, especially when extended haplotype matching is utilized, and felt that cord blood transplantation is also promising. He cited a need for prospective studies of various interventions, e.g., steroids, surfactant, pheresis for iron overload, and alloimmunization prevention. He also recommended further consideration of such interventions as chemotherapeutic agents, anti-oxidative therapies, nitric oxide, decitabine, red blood cell rehydration, arginine, and PCA-2 inhibition.

#### ***Therapeutic Implications of Phenotypic Diversity*** - Orah Platt, M.D.

Dr. Platt spoke about the phenotypic diversity seen in SCD and the implications of this diversity for therapeutics and for research. She noted that the degree of phenotypic diversity seen in such

work as the Cooperative Study of Sickle Cell Disease would not have been predicted from knowledge of the underlying molecular lesion alone, but that it was in accord with the diversity seen in the red blood cells themselves (due to varying age and exposure to oxidants, macrophages, viruses, dehydration, etc.). She described SCD as operating in some aspects as a Mendelian disorder, in others as a “sort of Mendelian” disorder, and in still others as a complex disease. Dr. Platt suggested that some therapies (such as bone marrow transplantation or gene transfer) might focus on the Mendelian character of SCD, while others (such as hemoglobin switching or chemical genomics) might aim at the “sort of Mendelian” aspects, and still other therapies (such as those that affect inflammation or adhesion) must approach SCD as a complex disorder. She also discussed the use in research of intermediate phenotypes, unrelated and related subjects with SCD, and related subjects without SCD to understand phenotypic diversity more completely. She stressed both the difficulty inherent in phenotyping those with SCD fully and the importance of doing so. Dr. Platt closed by calling for a “Sickle Cell Phenome Project” that would support the development of experts in clinical medicine, clinical investigation, and cultural aspects of disease, as well as technology-savvy translational researchers with expertise in genomics, expression studies, imaging, etc. Such a project would also support clinical-technology based phenotyping centers that included imaging, physiologic metrics, etc. and centralized phenotyping laboratories that offered biochemistry, hematology, and repository services, as well as informatics and genomics capabilities in a setting that catalyzes cooperative approaches. Through public education and research on overcoming barriers to research participation, this project might also support a national focus on recruitment to participation in research. Finally, the project could help integrate phenomics and genomics into such major clinical trials as the Cooperative Study of Sickle Cell Disease and the Stroke Prevention Trial in Sickle Cell Anemia.

***Hemoglobin Switching*** - George Stamatoyannopoulos, M.D., Dr.Sci.

Dr. Stamatoyannopoulos traced the development of the field of hemoglobin switching in SCD over the past half century, reviewed its current state and outlined promising areas for future research. He noted that, in 2003: efforts to develop pharmacologic induction of fetal hemoglobin demonstrate very slow progress in the discovery of new inducers; follow-up to discovery is absent because it is almost impossible to bring discoveries to the clinic; and a critical mass of SCD investigators no longer exists. Dr. Stamatoyannopoulos felt the paucity of investigators was partly due to the field having become “unfriendly” to young researchers. He characterized SCD clinical trials as having become very conservative, lacking innovation and coordination. He then reviewed in depth what is known about the activation, control and expression of  $\gamma$ -globin genes and current strategies for increasing such knowledge.

***Gene Transfer*** - Michel Sadelain, M.D., Ph.D., Memorial Sloan-Kettering Cancer Center

Dr. Sadelain provided an overview of current and projected gene transfer efforts. He characterized the aim of gene transfer for SCD as to create a long-lasting effect on erythropoiesis. He noted that criteria for effective globin vectors include: being erythroid specific; stage specific differentiation; position independent but copy-number dependent; etc. In terms of “next questions” to tackle in this area, he highlighted stable lentiviral packaging cell lines, large scale vector production, evaluation of lentiviral globin vectors in human stem and

erythroid cells, optimization of conditioning regimens for autologous transplantation with gene transfer, and optimization of conditions for *in vivo* selection (enrichment of gene-modified cells). He also discussed which types of vectors appear particularly promising for further development and use. Dr. Sadelain noted that, because in SCD one needs to affect more than 80% of cells, *in vivo* selection is likely to be necessary.

***Small Molecule/Chemical Genomics Approaches*** - John Haley, Ph.D.

Dr. Haley reviewed pharmacological approaches to SCD and the use of chemical genomics to further understanding of the biology of SCD and to develop new therapeutics for the disorder. He noted that pharmacological agents are usually designed to prevent polymerization through inducing fetal hemoglobin formation, or to combat vasoocclusion through increasing peripheral vasodilatation. Dr. Haley discussed modulators of nitric oxide synthesis in management of SCD. He suggested that combining compounds that induce fetal hemoglobin at sub-optimal, nontoxic plasma concentrations with agents that increase peripheral blood flow (e.g., nitrites) should be investigated. He considered how genomics-based approaches, such as high throughput screening to develop compounds that increase  $\beta$ -globin transcription and microarrays to explore histone deacetylase inhibitor associated gene expression changes, might play a role in SCD. He described lead candidate selection as the major current bottleneck in developing new therapeutics for SCD.

***Historical, Cultural, and Social Context of Clinical Research in Sickle Cell Disease*** - Vanessa Northington Gamble, M.D., Ph.D.

Dr. Gamble depicted SCD as a “racial disease” and explored the relationship between SCD and the construction of race in the U.S. She discussed how historical analysis demonstrates that definitions of race have been fluid, inconsistent, and often influenced by social and political factors. She described 1969-1973 as the period during which SCD emerged from obscurity to visibility and the years afterward as the period during which it went from visibility to controversy. Dr. Gamble discussed SCD’s relationship to ethnic and racial disparities in health, suggesting that social, cultural, and political factors have influenced the history of sickle cell disease and that an understanding of these factors must inform contemporary policy and programs. She closed by detailing a number of opportunities and/or challenges for SCD research, including: analyzing the social and cultural context of SCD within a global context; developing screening and clinical policies and guidelines that take the changing demography of the U.S. into account; overcoming the dilemma of difference and advancing trustworthiness; establishing visibility and support for SCD in the new context of racial and ethnic disparities in health; comprehending the attitudes of members of minority groups toward sickle cell disease and genetics; developing minority investigators in the areas of ethical, legal, and social issues; creating culturally competent educational programs; promoting community partnership and involvement; clarifying the role of social factors in the health outcomes of people with sickle cell anemia; understanding the experience of people with sickle cell disease; and developing strategies to diversify participants in clinical trials.

### **Thursday, November 20**

For the second day of the conference, each attendee participated in two working groups. Each working group discussed one of five topics: the therapeutic implications of phenotypic diversity; hemoglobin switching; gene transfer; small molecule/chemical genomics approaches to SCD; and the historical, cultural, and social context of clinical research in SCD. Reports from these working groups are presented under the Friday session, immediately below.

### **Friday, November 21**

On Friday, each of the five working group reports mentioned directly above were presented to the entire group of attendees, who then discussed them. The reports and points from the subsequent discussions follow:

#### ***Report from the Therapeutic Implications of Phenotypic Diversity Working Groups***

##### I. Where are we now?

- Enormous phenotypic diversity in sickle cell disease
- Inability to predict acute and chronic complications makes management of sickle cell disease very challenging
- Multitude of current and emerging therapies that aim to interrupt sickling process itself and vaso-occlusion at several key pathways
- Not all agents are effective in all patients
- Agents and procedures are not without risk

##### II. What do we mean by phenotypic diversity?

- The parameters for stratification of sickle cell disease patients into severity or organ specific groups need to be defined by a working group, evolving into a consensus statement of specific robust phenotypic criteria
- The creation of these criteria will serve as a basis for consistency in clinical trials as well as for large-scale genotype-phenotype association studies
- Incorporating this into a database of patients eligible for clinical research should be the eventual outcome

##### III. What is the ultimate goal for the field?

- Need risk stratification to facilitate assignment of appropriate treatment
- To be able to stratify risk, the genetic basis of the phenotypic variability needs to be understood
- Design intervention studies to prevent or minimize complications of sickle cell disease

#### IV. What is the science needed?

- Innovative techniques to improve phenotypic definition at all levels:
  - Clinical
  - Laboratory
  - Imaging
  - Newer diagnostic technologies
- Examples of needs:
  - Acute chest syndrome –
    - Defining acute chest syndrome more accurately
    - Improved tests of pulmonary function
    - Use of Micron-CT to evaluate lungs
    - Transcranial Doppler type test for lungs?
  - Stroke –
    - Define more accurately
  - Laboratory tests –
    - Evaluation of vascular biology
    - Thrombosis
    - Acute phase reactants
  - Autopsy Data

#### V. What critical elements can help achieve these goals in the short term?

- Recruit a group to establish criteria for defining phenotypic diversity and create a clinical consortium to share this resource. In tandem regional referral labs for genotyping, novel research tests, and DNA/plasma repositories with patients enrolled with human subjects guidelines in place at the outset.
- A centralized web-based registry with open access
- In order to accomplish the above two elements an educational program for patients, families, communities, and primary care providers is critical
- Establishment of international collaborations is essential to help define the environmental/genetic contribution to sickle cell disease via twin/sib-pair studies and studies of unusually mild phenotypes in long-term survivors

#### VI. What role should the NIH play in helping the community achieve these goals?

- Sickle cell disease should be the prototype disease to apply the consequences of the Human Genome Project and its evolving technologies to accelerate new knowledge and treatment
- The NIH may accomplish this through its funding resources, leadership, and incorporation of the International community
- The NIH should require maximal sharing of data and resources that are developed with public funding.

Discussion following the therapeutic implications of phenotypic diversity working groups' report included these other points:

- The Cooperative Study of Sickle Cell Disease (CSSCD) database available on CD-ROM; the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) clinical data is

owned by investigators, but will work to get access; barriers to access are a significant current problem.

- Need prospective databases of all patients being followed that includes genotypes; many current studies do not include DNA;
- Need long-term thinking about disease – after all, it is a genetic disease that will continue to involve generations to come. Need a smaller, well-defined group to work on this that includes people that are knowledgeable in current technologies.
- Current groups working on SCD are not working together sufficiently and are inefficient;
- Get working groups together to develop standards that investigators can use as guidelines when developing studies;
- A huge investment is needed to cast a wide enough net to gather the data needed - NIH alone cannot fund this, we need to get advocacy community involved;
- Who are the best people to do this kind of work? Clinicians, experts in genomics, experts in high-throughput are not the same people. We need to share knowledge and work together but also to develop a new group of researchers that are comfortable and knowledgeable in all areas;
- Explore the SCD patients who are living longer than expected;
- Shouldn't neglect studying phenotypic diversity in mouse models, as it could provide clues that might parallel humans.

### ***Report from the Hemoglobin Switching Working Groups***

Note: All recommendations in this report are predicated on the infusion of new disciplines, new investigators and increased manpower into the field. There is need for multidisciplinary (biophysics, imaging, informatics, physical chemistry, etc.) teams and for innovative programs to attract and retain these new investigators.

- I. Support for development of a new model to study hemoglobin F reactivation
  - New cell systems are needed, including human adult cell lines (expressing gamma and beta globin) that are responsive to switching agents. Primary cells or cell lines e.g., human embryonic stem cells
  
- II. Resources for drug development for sickle cell disease, to include:
  - Non-human primate testing for comparative activity and pharmacokinetics
  - Resources for preclinical toxicology screens (rodent and non-rodent)
  - Infrastructure for Phase I and II clinical trials
  - Three classes of drugs already screened
  
- III. Genomics tools “service center”
  - High density haplotype map in African Americans and other populations relevant to sickle cell disease
  - Whole genome microarrays
  - Website/database and central facility to send data for analysis

#### IV. Core resource facilities

- Transgenic mice generation and dissemination for performing drug screening
- Depository for critical DNA constructs and cell lines
- Large-scale source of CD34+ cells
- Antibodies for sorting erythroid progenitor cells and methylated/acetylated DNA

#### V. Development of new genomic-based technologies for:

- 3-D imaging of regulatory domains and chromatin structure
- Exploring structure of DNA super molecule
- Step-by-step analysis of activation complex formation in each globin gene
- Identification of all components of regulatory complexes to help target therapies
- Interference of complexes

#### VI. Novel approaches to the reactivation of hemoglobin F

- Signal transduction variables explored in a comprehensive fashion, looking at intra-nuclear and extra-nuclear factors
- Post-transcriptional models
- Program of hemoglobin F expression in adult vs. fetal erythropoiesis

#### VII. Access to clinical trials database and DNA

- From the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), the Cooperative Study of Sickle Cell Disease (CSSCD), the Stroke Prevention Trial in Sickle Cell Anemia (STOP), etc.
- Repository of DNA from patients with high and low hemoglobin F levels, pre and post hydroxyurea
- Support hemoglobin F assays in ongoing unrelated clinical drug trials.

Discussion following the hemoglobin switching working groups' report included these other points:

- Need to distinguish between developmental hemoglobin switching and reactivation of hemoglobin F in adult cells – both of which are important;
- Need to pursue knowledge of mechanisms to develop better drugs based on new and more sophisticated high throughput screening assays; but also need to push to move existing candidate drugs through Phase I and II;
- May want combination treatment for patients; however, an obstacle to this is that FDA will not let two unapproved drugs be in a trial together;
- Need to promote true translational research (current weakness in system);
- Consequences of the sickle cell mutation for overall gene expression have not been explored systematically – use microarrays and proteomics on various tissues to look at gene and protein expression and how that differs between sickle cell disease and normal tissues, and between equilibrium state and crisis.



## *Report from the Gene Transfer Working Groups*

### I. Safety

- Short Term: Need to continue to improve current vector technology and assessment of safety issues related to them
- Long Term: Need to develop new and better vectors and gene transfer systems, includes non-integrating strategies, targeted integration and homologous recombination
- In Parallel With These Studies: Need to develop stem cell purification, expansion and modification while preserving function. Also needed are assays for the number, function and quality control of modified cells.

### II. Stem Cell Biology

- Myeloablation: Need hypothesis-driven research into the relationship between the degree of myeloablation and chimerism
- In Vivo Selection And Amplification: Need to develop human surrogate assays for human stem cell transduction, and large animal models which can be used to develop pharmacological and biological controlled stem cell amplification
- Allogeneic Transplantation: Support the participation of people of African descent in SNP and diversity studies and as well as the BMT registry
- Both gene therapy and allogeneic transplantation would benefit from the development of better immune suppression strategies

### III. Biomarkers

- Need to discover sensitive and reliable biomarkers for disease severity, disease progression and clinical improvement
- Biomarkers are applicable to both the clinical management of sickle cell disease and future clinical trials

### IV. Recommendations

- Strengthen the role of the NIH in the dissemination of biologicals, cytokines, animals and patient materials for sickle cell disease gene therapy
- Use the resources of the NIH to educate and inform the public and investigators with a realistic review of opportunities in gene therapy research and applications. The goal of this is to influence the career choice of young investigators that will translate into therapies for sickle cell disease through funding opportunities.
- Encourage Cord Blood Banks to collect SS and thalassemia cells. These have potential for future treatment and research
- Develop human SS ES cells.

Discussion following the gene transfer working groups' report included these other points:

- Application of lentivirus approaches to hemoglobinopathies – animal studies, of course; however, consensus, if any, was that momentum is building; issues of safety is paramount, but also confident that clinical trials will come soon;

- Perhaps set up some guidelines to be used as yardstick for safety. Maybe FDA should set down guidelines as to what this would require;
- Field cannot tolerate a gene transfer trial that harms;
- Development of young investigators is important; there are training possibilities available, but people are not sufficiently aware of them - need help to identify the young investigators and get them in touch with appropriate NIH staff;
- Red cell biology and gene therapy are not “sexy,” thus young investigators are not interested—need to let them know that one can make a living doing this;
- Nurse practitioners are an untapped resource; nurses are now trained in genetics—there are nurses that are PI’s on projects; need to look into getting nurses involved—this could bridge some of the gaps; enticements might include loan re-payment and mentoring;
- Should NIH specifically support gene therapy trials in thalassemia and SCD; e.g., make clinical grade (GMP) preparations of lentivirus available to investigators, through the National Gene Vector Laboratories?
- As intermediate measures, sensitive biomarkers are important to safety.

### ***Report from the Small Molecule/Chemical Genomics Working Groups***

#### **I. New Targets: Genomics**

- A large cohort
  - Including patients with sickle cell disease, their family members, and related and unrelated controls
  - Well phenotyped
  - Well consented, prospectively followed, with re-contact possible for follow up
  - Includes genomic DNA and lymphoblastoid cell lines at baseline; serial mRNA, proteome studies through mRNA and plasma at least twice (when asymptomatic and symptomatic)
  - Obligatory sharing of materials (NIMH Genetic s Initiative model)
- Proteomics approaches
  - e.g., in depth SS vs. AS vs. AA erythrocytes, “old” vs. “new” SS erythrocytes, etc.
- Transcriptomics
  - Erythroid precursors, reticulocytes, etc.
- Genetic modifier screens
  - Humans
  - Mice
  - Zebrafish

#### **II. Phenotypic Compound Screens**

- Use of NIH Roadmap supported facilities
- Would detect effects on
  - Polymerization
  - Phenotypic sickling
- Would assess compound cell penetrance
- Use SS cells

- With attention to heterogeneity to include SS-specific membrane response
- Use AS cells
  - Minimize cell heterogeneity

### III. Target-Based Compound Screens

- Channels
  - e.g., Gardos channel
- Iron chelators: better than desferoxamine
- Hemoglobin F induction: need improved cell lines that make adult hemoglobin (e.g., cord blood or adult erythroid stem cells, embryonic stem cells?)
- Adhesion assays: need development, better target validation
  - Not yet ready for high throughput screening, but should become so
- Antithrombotics/anticoagulants?
  - Aspirin, low molecular weight heparin possibilities if magnetic resonance angiography first to rule out small vessel disease
- Nitric Oxide
  - Can take advantage of work with NO in other areas, e.g., cardiovascular disease
  - Better target validation needed
  - Screen for compounds that will work in physiologic state of SSD
- Inflammation: less important, needs target validation
- Oxidation: less important, needs target validation

### IV. Development of New Animal Models

- Better utilization of existing animal models
- Is there a need for better animal models?
  - Nonhuman primates
  - Rabbits
  - Rats
  - Mice
  - Zebrafish
- Models need to be shared broadly within community
- Models need to be linked to the human clinical state

### V. Preclinical development

- Need structure for pharmacokinetics, preclinical toxicology, human clinical pharmacology to move sickle cell disease compounds to clinic
- Existing
  - NCI RAID (Rapid Access to Intervention Development)
    - [http://dtp.nci.nih.gov/docs/raid/raid\\_pp.html](http://dtp.nci.nih.gov/docs/raid/raid_pp.html)
  - Translational Research Cores (Roadmap)

### VI. Clinical trials

- Need larger and more integrated research network, including but going beyond current Centers
- DNA collection essential
- Requires involvement of patient advocacy groups in study design and execution
- Need governing board to determine study priorities, appropriate endpoints, statistical power – could be done through a formalized clinical research network
- Studies of psychosocial aspects of disease, incidence, and treatment of co-morbid conditions, e.g., depression
- Lessons from other disease advocacy groups involvement in clinical trials.

Discussion following the small molecule/chemical genomics approaches to SCD working groups' report included these other points:

- Bone marrow cells should be made available to the community;
- There is still a lot we don't know about pathophysiology of the disease.

### ***Report from the Historical, Cultural, and Social Context of Clinical Research Working Groups***

#### **I. Current Realities**

##### **Clinical Care**

- Patients and their families have historically faced barriers to clinical care and social services, which has resulted in distrust of the health care system
- There is a lack of adult medical providers and a resultant lack of continuity of care for adolescents and adults
- Less than 10% of patients in the United States receive care in comprehensive sickle cell centers, which results in a lack of standardization of care across the United States

##### **Research**

- There is a dearth of clinical and social researchers
- There is a dearth of longitudinal studies of sickle cell disease
- Community based education programs for health professionals, patients and their families are limited
- There is a lack of researchers studying sickle cell disease
- There are a limited number of new researchers in the field, as well as a limited number of basic and social science researchers
- Access to research is limited to 10% of the patient population (NIH SCD Centers and SCD Virtual Centers)
- International research and international collaborations between researchers and clinical researchers in the USA and abroad are limited
- More than 95% of patients with sickle cell disease do not live in the United States

#### **II. Where should the field go ultimately?**

Sickle Cell Disease should be the model for the NIH re-engineering of the clinical research enterprise because it lends itself to the fields of: structural, systems and molecular biology; gene

therapy; chemical genomics, human variation, clinical investigation, clinical trials; and education, ethical, social, and cultural factors influencing efficacy of medical intervention.

There should be both a new paradigm and new partnerships for sickle cell disease research. Research on sickle cell disease calls for the establishment of an innovative multidisciplinary sickle cell network and for a new model of research that creates partnerships between communities, clinicians, and researchers.

III. What is the science needed, what are the questions that need to be answered?

- Data are needed!!!!
- Longitudinal studies of social, cultural, genetic, and environmental determinants of the disease
- National and international common data registries that collect genetic, clinical and social environmental information – human genome expertise and collaborative models useful here

IV. Recommendations

1. Establish A Sickle Cell Disease Research Network

A research network of geographically dispersed centers that would conduct clinical trials and genetic studies is needed.

- This network would conduct health services research on such issues as standards of care and conduct translational research, such as longitudinal studies of genetic variation of sickle cell disease
- The network would be a model for clinical, ethical, cultural and social research, as well as for the training of a new cadre of researchers
- The network would also foster the development of international collaborations

2. Build the Research Workforce Capacity

There is a need to develop programs to increase the number of clinical researchers, including nurses and allied health professionals, engaged in the research of sickle cell disease.

- Career development and training mechanisms should be used to increase the number of researchers studying sickle cell disease. This might, for instance, take the form of supplements linked to RO-1, Program Project and Center Grants.
- Loan repayments programs for clinical researchers, genomic and social science researchers conducting sickle cell disease research should be established, as should loan repayment programs for adult hematologists conducting research and providing clinical care to adult patients
- The salary cap on K awards should be increased to make them attractive for clinicians to develop a research career in the study of sickle cell disease

3. Develop Model Community Based Participatory Research

Collaborative partnerships with communities should be developed and communities should be involved in research from its design to its end.

- RFAs should be developed on:
  - Creating model community and researcher collaborative studies concerning genomic issues
  - International-based research on the ethical, legal, social and cultural implications of conducting genetic research on sickle cell disease
  - Trust and genetic research on sickle cell disease
  - Research of social, cultural barriers to participation in clinical trials and genetic studies
- Model programs for education for communities, consumers and health professionals should be evaluated

#### 4. Fund Ethical, Legal, Social, and Cultural Research on Sickle Cell Disease

Ethical, legal, social, and cultural research on sickle cell disease should explore such issues as:

- How do we understand self-identity, ancestry and race in the context of sickle cell disease?
- How do we understand stigma and sickle cell disease?
- Discrimination in employment, insurance, etc.
- Familial implications for sickle cell disease patients
- Trustworthiness
- What are the “best practices” in genetic screening and counseling strategies?
- International aspects of the ethical, social, and cultural issues of genetic research on sickle cell disease.

Discussion following the historical, cultural, and social context of clinical research in SCD working groups’ report included these other points:

- Need for support of clinical researchers; a critical issue is the requirement for translational clinical researchers involved in trials and treating patients are also trying to run community programs - NIH should fund community coordinators (have lost this type of person over the years) - not just tack an expectation for this activity onto existing grants.
- Need community studies that emphasize implementation of validated research results into practice in the community;
- Need ways to acknowledge all collaborators in team-oriented research for their work and for such collaboration to figure in academic promotion;
- Need Health Resources and Services Administration (HRSA) and Centers for Disease Control and Prevention (CDC) involvement, too.

### ***General Discussion:***

Following these discussions of the working groups' reports was a more general discussion of where SCD research and clinical care should go from here. Prior to this discussion, attendees were asked to cast "votes" among approximately 30 priorities that had emerged during the meeting as options for furthering research aimed at developing new, more effective therapies for SCD. All participants were given 100 votes each, which they could then split among any of the possible priorities. Tabulation of those votes is shown in Appendix C, below.

Among points raised in the discussion were:

- Other genetic diseases in which research has made inroads may be instructive. For instance, the Cystic Fibrosis Foundation has advanced research by bringing new researchers into the field through feasibility proposals available only to those new to the field, helping plan the path for research, especially regarding a small molecule approach to therapeutics, coordinating various interests in research through an advisory group, developing joint CF Foundation/NIH funding, establishing a CF patient registry, and helping set standards of care for recognized CF clinical centers.
- The experience of the Human Genome Project may also have something to contribute. It provided a model for integration of different types of expertise and for a consortium approach that included shared data resources for which the project demanded no control or ownership, but maintained an expectation for publication and credit that both funders and academia recognized. It also demonstrated that such consortia require leadership, from both inside and outside the NIH, and that they are particularly well suited to attract and integrate new expertise. Other lessons from the Human Genome Project include that to ensure that a shared database can be utilized effectively requires expertise in its development and that curing patients needs to remain the bottom line of biomedical research.
- The paradox that SCD is a monoallelic disease with such variant phenotypes suggests that it involves a complex system and thus a heavy dose of systems biology will be required to understand it. Thus, information from such sources as the Encyclopedia of DNA Elements (ENCODE) will be important to the identification and understanding of remote modifiers and regulators, etc. It would be interesting to focus part of that study on the  $\beta$ -globin genes.
- The time is right for a whole genome approach to genetic modifiers in SCD.
- Vascular biology is also part of the puzzle, and we will need to use model systems to solve it. Non-invasive means for in vivo studies, such as new imaging techniques, will be important. We need to deal with issues of how to deliver state-of-the-art care and clinical advances from the research arena.

Prof. Sir David Weatherall, Conference Co-Chair, offered observations that included:

- A key issue is to define the disease at the clinical and phenotypic level to make use of new genomic tools. Thus, we need to move quickly in better defining phenotypes.
- It may be that the SCD system starts in a stochastic fashion and then modifier genes play a role.
- We need to think about developing two or three international long-term, sustainable research endeavors.

The other Conference Co-Chair, Francis Collins, noted that:

- The first part of a revolution is admitting you need one – he heard consensus from the meeting participants that one was needed here and that we need new energy and new disciplines.
- Centralized databases with open access are important.
- We need DNA from the parents of those with SCD to look at genetic modifiers.
- An appropriately powered twin study, by definition international, building on the work of Graham Serjeant is needed.
- Need large numbers of patients – this requires a shared sense of mission and a shared database.
- The Haplotype Map (HapMap) will be available soon, which should allow whole genome studies to look for gene modifiers. Nigerian (Yoruba) samples are included. The HapMap will allow taking 300,000-400,000 polymorphisms to do association studies, if pertinent samples are available.
- NIH-supported chemical genomics centers should be utilized to search for new small molecules for SCD, using well-designed assays focused on several aspects of the phenotype. More about this and related NIH Roadmap activities is available at [www.nihroadmap.nih.gov](http://www.nihroadmap.nih.gov).

Among diverse points raised by various participants in the ensuing concluding discussion were:

- What needs to be added?
  - Noninvasive imaging procedures
  - Lessons from other fields
  - A look at outliers in severity, including discordant sib pairs
  - Is this the time to explore regulatory networks and signaling pathways in SCD?
  - A global approach should be applied to issues such as to globin-switching, rather than simply utilizing only currently established researchers
- There are informative models extant for getting information to communities.
- For genetic counseling in general and preimplantation genetic diagnosis (PGD) in particular, we need to know more about perceptions of disease in SCD and the cultural competence of providers.
- Patient advocacy and other community organizations used to see research as competing with community based resources for support; now that seems to be changing. The Sickle Cell Disease Association of America (SCDAA) is a potential advocate for research and research support, but has had a relatively modest impact on research, per se, in the past. The history in this field does raise important issues.
- Innovative trans-agency participation is needed.
- Economic status is an important factor in phenotypic variation in SCD, both in the U.S. and globally. This needs to be recognized in both research and clinical care.
- Pain management in SCD and other quality of care issues are important.
- Historically, SCD Centers have had to compete against each other for funding, which works against cooperative, multi-center projects. Current funding has moved in the direction of encouraging cooperation, but this needs to be further emphasized.



- While there may be lessons to be learned from other organizations, the cystic fibrosis and SCD communities differ and lessons from the experience of one are not always directly applicable to the other.
- There is a real opportunity for an international approach.
- There is a need for leadership, both from NIH and within the SCD research community.

**Summary of Meeting Conclusions (order not intended to convey priority):**

1) The time is propitious to bring to bear the developing tools and approaches of genomics to develop markedly 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. Features of such a network might include:

- Inclusion of environmental, social, cultural, genetic data
- Quality of life data
- Careful attention to human subjects issues, well consented with recontact possible
- Repositories of DNA, cell lines, mRNA, and plasma (the latter two from individuals when both symptomatic and asymptomatic)
- Standardized phenotypes
- Open access to materials and data
- Longitudinal follow-up
- Clinical trials database
- Collaborative community partnerships, both in design and implementation
- A newborn cohort

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 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 2004 of a draft haplotype map, the possibility of haplotyping scores 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) There is need for a wider availability of clinicians able to care expertly for individuals with sickle cell disease. There is also need for therapies that are demonstrated to be effective, such as hydroxyurea, to be made more widely available to those with the disease. 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 optimally, so other agencies, such as the Health Resources and Service Administration (HRSA), the Centers for Disease Control and Prevention (CDC), and the Agency for Healthcare Research and Quality (AHRQ) 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.

## APPENDIX A – CONFERENCE AGENDA

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### WEDNESDAY, NOVEMBER 19, 2003

- 8:30-9:00 am Welcome - Drs. Zerhouni, Collins, Alving, and Weatherall  
Moderator: Greg Evans
- 9:00-9:30 am Plenary I – *The Pathophysiology of Sickle Cell Disease: State of the Art* -  
Martin Steinberg
- 9:30-9:50 am Discussion
- 9:50-10:20 am Break
- 10:20-10:50 am Plenary II – *Therapeutics for Sickle Cell Disease: State of the Art* - Elliott  
Vichinsky
- 10:50-11:10 am Discussion
- 11:10-11:40 am Plenary III – *Therapeutic Implications of Phenotypic Diversity* - Orah Platt
- 11:40-12:00 pm Discussion
- 12:00-1:00 Lunch  
Moderator: Karen Hofman
- 1:00-1:30 pm Plenary IV – *Hemoglobin Switching* - George Stamatoyannopoulos
- 1:30-1:50 pm Discussion
- 1:50-2:20 pm Plenary V – *Gene Transfer* - Michel Sadelain
- 2:20-2:40 pm Discussion
- 2:40-3:00 pm Break
- 3:00-3:30 pm Plenary VI - *Small Molecule/Chemical Genomics Approaches* - John Haley
- 3:30-3:50 pm Discussion
- 3:50-4:20 pm Plenary VII – *Historical, Cultural, and Social Context of Clinical Research in  
Sickle Cell Disease* - Vanessa Northington Gamble
- 4:20-4:40 pm Discussion
- 4:40-5:00 pm Instructions to Working Groups - Alan Guttmacher
- 5:00-6:00 pm Reception

### **THURSDAY, NOVEMBER 20, 2003**

- 8:30-10:00 pm    Concurrent Working Groups- Session A
- ? *Therapeutic Implications of Phenotypic Diversity* - Kwaku Ohene-Frempong
  - ? *Hemoglobin Switching* - Susan Perrine
  - ? *Gene Transfer* - Punam Malik
  - ? *Small Molecule/Chemical Genomics Approaches* - Christopher Austin
  - ? *Historical, Cultural, and Social Context of Clinical Research* - Lennette Benjamin
- 10:00-10:30 pm    Break
- 10:30-12:00 pm    Concurrent Working Groups - Session A (Continued)
- 12:00-1:00 pm     Lunch
- 1:00-2:30 pm     Concurrent Working Groups - Session B
- ? *Therapeutic Implications of Phenotypic Diversity* - Swee-Lay Thein
  - ? *Hemoglobin Switching* - George Dover
  - ? *Gene Transfer* - David Bodine
  - ? *Small Molecule/Chemical Genomics Approaches* - Alan Schechter
  - ? *Historical, Cultural, and Social Context of Clinical Research* - Joseph Telfair
- 2:30-3:00 pm    Break
- 3:00-4:30 pm     Concurrent Working Groups - Session B (Continued)
- 7:00-9:30 pm     Group Dinner - Remarks by Sir David Weatherall

### **FRIDAY, NOVEMBER 21, 2003**

Moderator: Alan Guttmacher

- 8:00-8:30            Presentation/Discussion - Working Groups on Therapeutic Implications of Phenotypic Diversity
- 8:30-9:00            Presentation/Discussion - Working Groups on Hemoglobin Switching
- 9:00-9:30            Presentation/Discussion - Working Groups on Gene Transfer
- 9:30-10:00          Presentation/Discussion - Working Groups on Small Molecule/Chemical Genomics Approaches
- 10:00-10:30         Break
- 10:30-11:00         Presentation/Discussion - Working Groups on Historical, Cultural and Social Context of Clinical Research in Sickle Cell Disease
- 11:00-1:00          Where to go from here - led by Drs. Weatherall and Collins

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## **APPENDIX C – ATTENDEES’ VOTES AMONG OPTIONS FOR RESEARCH ON NEW THERAPIES FOR SICKLE CELL DISEASE**

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Conference attendees were asked to cast “votes” among approximately 30 priorities that had emerged during the meeting as options for furthering research aimed at developing new, more effective therapies for SCD. All participants were given 100 votes each, which they could then split among any of the possible priorities. Tabulation of those votes is shown below:

**22%** of all votes were cast in favor of an innovative multidisciplinary Sickle Cell Disease Research Network with a central prospective registry of several thousand well phenotyped patients.

Features of this might include:

- DNA/plasma repository, cell lines, mRNA (when both symptomatic and asymptomatic)
- Standardized phenotypes
- Inclusion of environmental, social, cultural, genetic data
- Newborn cohort
- Quality of life data
- Careful attention to human subjects issues, well consented with recontact possible
- Collaborative community partnerships
- Open access to materials and data
- Longitudinal follow up
- Clinical trials database

**10%** of all votes were cast in favor of 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. It might also include increasing the number of basic, clinical, and social science researchers, as well as nurses and allied health professionals, doing research on sickle cell disease. Possible mechanisms for accomplishing this might include grant supplements and loan repayment programs.

**8%** of all votes cast were cast in favor of 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.

**5%** of all votes were cast in favor of establishing a working group to define SCD severity by strict standardized criteria. This might include innovative techniques for more precise definition of phenotypes, e.g., for acute chest syndrome and for stroke, as well as the use of laboratory measures.

**4%** of all votes cast were cast for each of the following:

- a) Genomics tools service centers, including such resources as haplotype maps, whole genome arrays, etc.;
- b) Target-based compound screens to explore such possibilities as hemoglobin F induction (for which would need improved cell lines that express beta-globin), nitric oxide,

antithrombotics/anticoagulants and other agents that might affect adhesion, inflammation, or oxidation;

- c) Proteomics and transcriptomics on erythrocytes, reticulocytes, bone marrow, and other tissues;
- d) Clinical trials that included an extensive research network, DNA collection, greater involvement of patient advocacy groups, and attention to the psychosocial aspects of SCD;
- e) Core resources of biological materials, including such materials as transgenic mice for drug screening, a DNA construct repository, antibodies to sort erythroid progenitors, and cord blood banks for SCD and thalassemia cells;
- f) Development of a new model to study hemoglobin F reactivation, especially in adult cells, such as human cell lines that respond to switching agents;
- g) To the extent possible, NIH attempting to catalyze more effective care and broader access to care of SCD patients, perhaps through a standardized care model.

**3%** of all votes cast were cast for each of the following:

- a) Building better relationships with international investigators, including in research regarding ethical, legal, social, and cultural aspects of SCD;
- b) Community and public education programs;
- c) Resources for drug development, e.g., toxicology, non-human primates, and infrastructure for Phase I and II trials, including for drugs that already show promise;
- d) New and better gene transfer vectors that are safe and efficient, including non-integrating systems, targeted integration, and homologous recombination.

**2%** of all votes cast were cast for each of the following:

- a) Phenotypic compound screens, applicable to hemoglobin S polymerization and sickling of red blood cells;
- b) Genetic modifier screens, for humans, mice, and zebrafish;
- c) Biomarkers for disease severity and monitoring of clinical trials;
- d) Timely initiation of gene therapy trials;
- e) Research into such ethical, legal, and social issues as self-identity, ancestry, race, stigma, discrimination, trustworthiness.

**1%** of all votes cast were cast for each of the following:

- a) Education of the public;
- b) Better and more accessible animal models – non-human primates, rabbits, rats, mice, zebrafish;
- c) Human embryonic stem cell methodologies, including derivation of SS embryonic stem cells.

**<1%** of all votes cast were cast for each of the following:

- a) Stem cell purification strategies;
- b) Investigation of barriers to research participation;
- c) New technologies for understanding the molecular switching mechanism, such as three dimensional imaging of regulatory domains and of the anatomy of regulatory complexes;
- d) *In vivo* selection and amplification systems;

- e) Advances in allogeneic transplantation, with improved immune suppression;
- f) Catalyzing preclinical development, e.g., pharmacokinetics, preclinical toxicology;
- g) Myeloablation studies;
- h) Hemoglobin F assays in unrelated clinical drug trials.