NHLBI Activities in Hemoglobinopathies

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NICHD Newborn Screening Translational Research Network Meeting
April 8-9, 2013
Bethesda, Maryland
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- Overview of the hemoglobinopathies
- Milestones in NHLBI Hemoglobinopathy Research
- NHLBI Mission and Current Challenges
- Current NHLBI Activities and Programs to Fulfill Mission
The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives.

The NHLBI stimulates basic discoveries about the causes of disease, enables the translation of basic discoveries into clinical practice, fosters training and mentoring of emerging scientists and physicians, and communicates research advances to the public. It creates and supports a robust, collaborative research infrastructure in partnership with private and public organizations, including academic institutions, industry, and other government agencies. The Institute collaborates with patients, families, health care professionals, scientists, professional societies, patient advocacy groups, community organizations, and the media to promote the application of research results and leverage resources to address public health needs. The NHLBI also collaborates with international organizations to help reduce the burden of heart, lung, and blood diseases worldwide.
What are hemoglobinopathies?
Genetic disorders

Sickle Cell Disease: genetic defect resulting in abnormal structure of 1 of the globin chains of the hemoglobin molecule

Thalassemias: decreased synthesis of hemoglobin often through a mutation in regulatory genes
Sickle cell disease
- Sickle cell anemia (HbSS)
- SC disease (HbSC)
- Sickle beta thal (Hb Sβ thalassemia)

Thalassemias
- Alpha thalassemia } Major (or minor, carrier)
- Beta thalassemia } Major, intermedia (or minor, carrier)
- (Others)
Sickle Cell Disease Population: Estimated Size

- Estimated SCD Total: 88,000 – 98,000
  - Impacted by estimate of early mortality
    - If born after 1972 with HgbSS, life expectancy 50-55 years
    - Age at death shifted over time
      - 85-95% survive to adulthood

### Table 1. Birth cohort-SCD prevalence estimates

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All types of SCD</td>
<td></td>
<td>1:346</td>
<td></td>
<td>1:365</td>
</tr>
<tr>
<td>HbSS</td>
<td></td>
<td>1:700</td>
<td></td>
<td>1:601</td>
</tr>
<tr>
<td>HbSC</td>
<td></td>
<td>1:1,297</td>
<td></td>
<td>1:1,127</td>
</tr>
<tr>
<td>HbSβthalassemia</td>
<td></td>
<td>1:4,056</td>
<td></td>
<td>1:4,198</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All types of SCD</td>
<td>East: 1:1,114</td>
<td>1:1,114</td>
<td></td>
<td>1:16,305</td>
</tr>
<tr>
<td></td>
<td>West: 1:31,847</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbSS</td>
<td></td>
<td>1:45,622</td>
<td></td>
<td>1:18,642</td>
</tr>
<tr>
<td>HbSC</td>
<td></td>
<td>1:364,976</td>
<td></td>
<td>1:57,700</td>
</tr>
<tr>
<td>HbSβthalassemia</td>
<td></td>
<td>1:729,953</td>
<td></td>
<td>1:175,233</td>
</tr>
</tbody>
</table>

AHCPGR, Agency for Health Care Policy and Research; HbSS, sickle cell anemia; HbSC, hemoglobin SC disease; NNSIS, National Newborn Screening Information System; SCD, sickle cell disease

### Sickle Cell Disease versus other Common Newborn Conditions: U.S. Newborn Screening Data Ranked by Incidence

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD-SS + SC</td>
<td>1:2,474</td>
</tr>
<tr>
<td>Primary Congenital Hypothyroidism</td>
<td>1:3,044</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>1:3,924</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>1:10,415</td>
</tr>
<tr>
<td>Clinically Significant Hyperphenylalaninemia</td>
<td>1:13,947</td>
</tr>
<tr>
<td>Classical CAH</td>
<td>1:18,987</td>
</tr>
<tr>
<td>Classical Galactosemia</td>
<td>1:53,261</td>
</tr>
<tr>
<td>Biotinidase</td>
<td>1:61,319</td>
</tr>
<tr>
<td>MSUD</td>
<td>1:230,028</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>1:343,650</td>
</tr>
</tbody>
</table>

Therrell & Adams 2007
Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies

Hemoglobinopathies represent one of the major health problems in the United States and constitute the most common genetic disorders in some populations. Sickle cell diseases (sickle cell anemia, sickle cell–hemoglobin C, and sickle cell–β-thalassemia) alone affect about one of every 400 American black newborns. These and other hemoglobinopathies are common in persons of African, Mediterranean, Asian, Caribbean, and South and Central American origins as well. Although the technology to screen infants for hemoglobinopathies in the newborn period has been available for many years, widespread adoption of screening has not occurred. Reasons have included lack of a demonstrated improvement in outcome with early diagnosis, uncertainty about who to test, technical difficulties caused by the high level of fetal hemoglobin in the neonate, and questions about obligations to those identified as carriers.

For at least 20 years, it has been known that children with significant advantage to infants with other hemoglobinopathies (eg, hemoglobin E–β-thalassemia and homozygous β- and α-thalassemias). Identification by newborn screening may, however, provide natural history data and/or allow testing of potential interventions.

To examine questions surrounding the issue of neonatal screening and to enhance understanding among scientists, health care providers, and the public at large, the National Heart, Lung, and Blood Institute and the National Institute of Child Health and Human Development of the National Institutes of Health (NIH); the Genetic Disease Services Branch, the Division of Maternal and Child Health, the Bureau of Health Care Delivery and Assistance of the Health Resources and Services Administration; and the NIH Office of Medical Applications of Research convened the NIH Consensus Development Conference on Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies April 6 through 8, 1987. For 1½ days, experts in
Milestones in NHLBI Research and Funding and Social-cultural Context: 1970s

- 1972 National Sickle Cell Anemia Control Act
- NHLBI Comprehensive* Sickle Cell Centers
  *Comprehensive = research, not care or services
- NHLBI Cooperative Study of SCD
  - Natural Hx (without treatment!)
  - Planning Phase 1977
  - Phase I 1979-1983
- A best-selling car in USA…
- 1972 Washington Senators move to Texas
Milestones in NHLBI Research and Funding and Social-cultural Context: 1980s

- Penicillin Prophylaxis in Sickle Cell Disease
  - PROPS I 1984-1986
  - PROPS II 1988-1993
  - Conclusion: Use of prophylactic penicillin from birth to 5 yrs of age significantly reduces sepsis and mortality

- NHLBI Comprehensive Sickle Cell Centers

- 1987 NIH Consensus Conference on NBS in SCD

- NHLBI Cooperative Study of SCD
  - Phase I 1979-1983
  - Phase II continued through decade

- My Little Pony popular toy costs $4.99 each
NHLBI grants for diagnostics and treatment of alpha-and beta-thalassemia

Multicenter Bone Marrow Transplant Study demonstrates potential for a cure in children with SCD

Stroke Prevention Trial in Sickle Cell Anemia shows that TCD is an effective screening test

Multicenter Study of Hydroxyurea (MSH)
- 1992 1st of 200+ subjects enrolled
- 1998 FDA Approval of HU

Top TV show *Fresh Prince of Bel-Air*

Pan Am declared bankruptcy
Increases in Life Expectancy of Patients with Sickle Cell Anemia

Life Expectancy (Years)

Year


STOP

National Sickle Cell Act

PROPS I

MSH
Milestones in NHLBI Research and Funding and Social-cultural Context: 2000-2010 (1)

- Baby HUG Trial initiated and implemented
- Thalassemia Clinical Research Network initiated and multiple studies are launched throughout decade
- Stroke Prevention Trial in Sickle Cell Anemia (STOP I and II) shows benefits of chronic transfusion
- 2002 Workshop Adults with SCD: Meeting Unmet Needs
- 2005-2011 Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me)

Key NHLBI decisions
- Increase research on adults
- combine sickle cell and thalassemia
Milestones in NHLBI Research and Funding and Social-cultural Context: 2000-2010

- 2008 NIH Consensus Conference on Hydroxyurea Treatment for SCD
- 2008 NHLBI revamps Sickle Cell Program
- 2009-2012 Basic and Translational Research Program in SCD replaces Comprehensive Centers
- 2010: Healthy People 2020-Blood Disorders and Blood Safety
- 2005 Baseball returns to Washington, DC
BABY Hug
  - 2011 Final Results Paper: HU reduces pain, dactylitis; some evidence of acute chest syndrome, hospitalizations, transfusion
  - Follow-Up Study 2012-2016

Registry and Surveillance in Hemoglobinopathies (RUSH)-Interagency Agreement $ to CDC
  - 2009-2012 Funding for CDC and 7 States
  - Pilot to determine feasibility of using population-based methods to describe sickle cell and thal populations in US

Exploratory Studies in Neurobiology of Pain in SCD (2013)

Sickle Cell Disease Clinical Practice Guidelines
  - [http://www.nhlbi.nih.gov/guidelines/scd/overview.htm](http://www.nhlbi.nih.gov/guidelines/scd/overview.htm)
  - Final due later in 2013

Innovators in Hemoglobinopathies Career Development Award (2015)

SCD Inflammation, Thrombosis and Vascular Dysfunction Awards (2016)
Recent/Current Status of NHLBI Research and Funding 2010-2013 (2)

Trans-DHHS Activities Currently Being Led/Co-Led by NHLBI

- Healthy People 2020 Objectives in Blood Disorders and Blood Safety (HP2020-BDBS)
  [Link](http://healthypeople.gov/2020/topicsobjectives2020/overview.aspx)
- Research Questions for each BDBS Objective
- Data Elements to Answer RQS (HUMLO)
- Data System to Collect Data Elements
What is the Hemoglobinopathies Uniform Medical Language Ontology (HUMLO) Project?

- A collaborative project of the National Heart, Lung, and Blood Institute (NHLBI) and the Health Resources and Services Administration (HRSA) to build a resource of standardized data elements for

  - Investigators to create data dictionaries for their research studies
  - EMRs to include clinically relevant data
  - Federal programs and extramural communities to use in systems which incorporate data elements in hemoglobinopathies
The purpose of the project is

- **Not** to develop data elements when standardized ones accepted by a medical specialty or research group currently exist, or to duplicate others’ efforts, but to

- Build on existing efforts to standardize case definitions and terminology for hemoglobinopathies, and to

- Identify gaps in data elements, and define those data elements
That’s the good news. What’s the bad news? What are we doing about it?

- NIH budget
- Challenges to research
NIH Budget: is it really bad?
Comparison: cost of research vs NIH budget

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>BRDPI $</th>
<th>NIH Budget$³</th>
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<tbody>
<tr>
<td>2003</td>
<td>100.00</td>
<td>$25,868</td>
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<tr>
<td>2010</td>
<td>129.70</td>
<td>$30,200 (116.74)</td>
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<td>2011¹</td>
<td>133.40</td>
<td>$29,944 (115.75)</td>
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<tr>
<td>2012²</td>
<td>136.40</td>
<td>$30,690 (118.64)</td>
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<td>2013²</td>
<td>140.20</td>
<td>$31,000 (119.83)</td>
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<tr>
<td>2014²</td>
<td>144.30</td>
<td>?</td>
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<tr>
<td>2015²</td>
<td>148.7</td>
<td>?</td>
</tr>
<tr>
<td>2016²</td>
<td>153.30-158.10</td>
<td>?</td>
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</table>

1 = preliminary  
2 = projected  
3 = in millions
### NIH RePORT: Estimates of Funding


<table>
<thead>
<tr>
<th>Research/Disease Areas (Dollars in millions and rounded)</th>
<th>FY 2008 Actual</th>
<th>FY 2009 Actual (Non-ARRA)</th>
<th>FY 2009 Actual (ARRA)</th>
<th>FY 2010 Actual (Non-ARRA)</th>
<th>FY 2010 Actual (ARRA)</th>
<th>FY 2011 Actual</th>
<th>FY 2012 Estimated</th>
<th>FY 2013 Estimated</th>
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</thead>
<tbody>
<tr>
<td>Sickle Cell Disease</td>
<td>$80</td>
<td>$63</td>
<td>$14</td>
<td>$73</td>
<td>$12</td>
<td>$65</td>
<td>$65</td>
<td>$65</td>
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### SEARCH RESEARCH/ DISEASE AREAS

| thalassemia | | | | | | | | |

No estimates of funding information found which matched the criteria you specified.
How do we preserve and promote research programs in economic hard times? We...

- Find new ways to use limited resources
- Develop new mechanisms
- Collaborate across NIH Institutes & Centers (ICs)
- Release more Program Announcements (PA, PAR) with no set-aside funds
- Limit awards
Challenges

1. Development of new therapies
2. Fielding new clinical trials
3. Addressing pain research from Basic→Clinical Studies→Dissemination & Implementation
4. Translating clinical research results into practice
Challenge 1: New Therapies will Require Team Science

- Most grant applications are from hematologists

- But SCD involves every organ in the body; expertise required in lung, nervous system, kidney, etc.

- Knowledge gained in genetics, imaging, pain science, inflammation, drug development, vascular biology, stem cells needs to be incorporated into SCD therapeutics i.e., drugs and cellular therapies
Excellence in Hemoglobinopathies Research Awards (U54) (Jan. 2012)

Requires innovative collaborations among investigators in two or more disciplines

Goals

- Development of new therapies, diagnostic studies, and biomarkers
- Attracting scientists from other fields to SCD
- Training a new generation of scientists in team research
# EHRA – Awards not Announced Yet

## Department of Health and Human Services

### Part 1. Overview Information

<table>
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<tr>
<th>Participating Organization(s)</th>
<th>National Institutes of Health (NIH)</th>
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<tbody>
<tr>
<td>Components of Participating Organizations</td>
<td>National Heart, Lung, and Blood Institute (NHLBI)</td>
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<tr>
<td>Funding Opportunity Title</td>
<td>Excellence in Hemoglobinopathies Research Award (EHRA) (U54)</td>
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<tr>
<td>Activity Code</td>
<td>U54 Specialized Center: Cooperative Agreements</td>
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<td>Related Notices</td>
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</tr>
<tr>
<td>Funding Opportunity Announcement (FOA) Number</td>
<td>RFA-HL-13-005</td>
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</table>

This Funding Opportunity Announcement (FOA) solicits five-year Cooperative Agreement (U54) grant applications to the Excellence in Hemoglobinopathies Research Award (EHRA) program. The primary objective of this new program is to support the development of studies that will accelerate high-impact multi-disciplinary basic and translational research in the hemoglobinopathies and facilitate maximal collaborations among basic and translational scientists and clinical hematologists located throughout the US or at international sites. An application must propose a single project that approaches a common scientific theme through innovative collaborations among investigators in two or more relevant disciplines, providing opportunities for research which will translate basic observations to applied clinical research. An EHRA application will also include a Translational Research Skills Development Core (TRC) for new investigators, an optional Summer Research Program for highschool students, and an Administrative Coordinating Center (ACC). One ACC will be selected from the awarded Centers to provide
NHLBI will award 7 to 9 interdisciplinary grants

NHLBI will commit $73.8 million to this program over 5 years (largest SCD program ever)
Challenge 2: Clinical Trials

- Hard to carry out, but worth it!
  - NHLBI funded clinical trials have led to the major breakthroughs in management
- Difficult to plan and implement
- Uncommon diseases in USA
- Wide spectrum of disease severity
- Clinical problem may be an acute event
  - Difficult to recruit or predict achievement of accrual targets
- Geographic distribution/travel/access to centers increases costs, complicates logistics
Investigators w/expertise in disease may not have sufficient experience in conduct of large clinical trials

NIH grant—4 or 5 years

Valuable time lost due to difficulties in planning, coordination

Result: long delays in starting trial—run out of time (in the grant)!
A special planning grant to allow researchers protected time “off the clock” to plan and beta-test complex clinical trials

Planning Grants for Pivotal Trials in Hemoglobinopathies (R34), (April 2010)

R34 grants provide **money** ($450,000) and **time** (3 years)
R34 Program Awardees

- Hydroxyurea to Prevent CNS Complications of Sickle Cell Disease in Children (PI: James Casella, Johns Hopkins)

- Ameliorating Sickle Nephropathy (PI: Punam Malik, Cincinnati Children’s Hospital)

- Adenosine 2A Agonist Lexiscan in Children and Adults With Sickle Cell Disease (PI: David Nathan, Harvard)

- Stem Cell Transplantation for SCD in Adults (PI: Lakshmanan Krishnamurti, Univ. of Pittsburgh)

- Comparative Effectiveness of Strategies to Improve Iron Chelation in Thalassemia (PI: Neufeld, Children’s Hospital of Boston)
Challenge 3: Pain

- No new therapies for pain in decades
- Growing realization of the extent of the problem of chronic pain in adults
- Need for collaboration with neuroscientists, pharmacologists
Pain in Sickle Cell Disease

- Poorly understood
- Pain is variable
- Genotype and biological traits explain only part of these variances
- Little is known about differences in pain responses
NHLBI Responses

- Develop funding opportunities that require hematologists to collaborate with pain scientists on problems specific to SCD pain
- Convene scientific workshops and meetings to bring together SCD specialists and pain scientists at NIH
- Ensure that subjects with SCD are included in clinical trials for new therapies for pain
Challenge 4: Translational Roadblocks on the Way Toward Improved Public Health

Basic Science Research → Translation Into Humans → Translation Into Clinical Practice → Improved Public Health

- Funding Source: National Institutes of Health
- Others

Translation Into Humans:
- Translational Research
- Clinical Trials

Translation Into Clinical Practice:
- Health Services Research
- Effectiveness Research
- Outcomes Research
- Comparative Research

2nd block is integrally tied into Funding of health care delivery
