NHLBI Strategic Plan: Current and Future Opportunities for Blood Diseases and Resources Research

National Heart, Lung, and Blood Institute
NHLBI’s Strategic Plan Promotes Advances in Research Approaches

Research
- Informatics
- Systems analysis

Better Understanding

NHLBI
- Tools
- Infrastructure
- Technologies
- Teams
- Resources
- Workforce

Improved Public Health
- Knowledge networks
- Education

Feedback
Our Approach
Work in partnership in an ever evolving environment.
Develop a scientific blueprint for the next decade.

- A living, working plan from an inclusive and participatory process.
- Identify strategic priorities where NHLBI:
  - Initiates – does not happen unless the Institute takes a lead
  - Catalyzes – Institute facilitates the outcome
  - Supports – investigator-initiated research
NHLBI Strategic Plan Goals

Goal 1
Improve understanding of the molecular and physiologic basis of health and disease. Use that understanding to develop improved approaches to disease prevention, diagnosis and treatment.  *Form → Function*

Goal 2
To develop personalized preventive and therapeutic regimens for cardiovascular, lung, and blood diseases.  *Function → Cause*

Goal 3
Generate an improved understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery.  *Cause → Cures*
NHLBI Strategic Plan Leads Toward Personalized / Pre-emptive Medicine

Prevent Disease

Personalize Care

Cure Disease

Strategic Plan
# Need to Transform Medical Research in the 21st Century

<table>
<thead>
<tr>
<th><strong>20th Century</strong></th>
<th><strong>21st Century</strong></th>
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<tr>
<td>Treat disease when symptoms appear and normal function is lost</td>
<td>Intervene before symptoms appear and preserve normal function for as long as possible</td>
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<td>Did not understand the molecular and cellular events that lead to disease</td>
<td>Understanding preclinical molecular events and ability to detect patients at risk</td>
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<tr>
<td>Expensive in financial and disability costs</td>
<td>Orders of magnitude more effective</td>
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The Future Paradigm: Transform Medicine from Curative to Preemptive

Predictive ↔ Personalized ↔ Preemptive

Participatory

National Heart Lung and Blood Institute
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Form to Function

Basic Discoveries about the Causes of Disease

- Sickle Cell Disease
- Hemolytic Anemias
- Thrombosis
- Bleeding Disorders
- Stroke
- Stem Cells
Deconstructing Sickle Cell Disease Pathophysiology - The Role of Hemolysis in Clinical Subphenotypes

Need for Therapeutic Strategies to Prevent Complications Caused by Two Different Mechanisms

Nature Genetics February 1999

The gene encoding ribosomal protein S19 is mutated in Diamond-Blackfan anaemia
Natalia Draptchinskaia, Peter Gustavsson et al.

Am J Human Genetics December 2006

Fibosomal Protein S24 Gene Is Mutated in Daimond-Blackfan Anemia
Hanna T. Gazda, et al.

Blood, May 2007

The Human Shwachman-Diamond Syndrome Protein, SBDS, Associates with Ribosomal RNA
Karthik A. Ganapathi, et al.

Fanconi anemia (FA) is a prototypical rare genetic disorder that can illuminate important biological pathways. Research into FA has identified several genes important for DNA repair and breast cancer.

Source: Developmental Cell:12(5),2007; Markus Grompe, Henri van de Vrug
The Interface Between Thrombosis and Inflammation

The incidence of severe sepsis is 751,000 cases with 28.6% mortality. The national cost is $16.7 billion / year.

Research on activated protein C led to the only FDA-approved treatment in sepsis.

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**New Drugs**

**Drotrecogin Alfa (Recombinant Human Activated Protein C) for the Treatment of Severe Sepsis**

Christopher McCoy, PharmD¹,² and Samuel James Matthews, PharmD²

¹Beth Israel Deaconess Medical Center, and ²Bouvé College of Pharmacy and Health Sciences, Northeastern University, Boston, Massachusetts

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**Coagulation**
- thrombin
- tissue factor
- microparticles
- PARs
- cytokines
- TLRs
- APC

**Inflammation**

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**FDA News**

FOR IMMEDIATE RELEASE
1/19/19

Lenore Gelb, 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA APPROVES FIRST BIOLOGIC TREATMENT FOR SEPSIS

FDA today approved the first biologic treatment for the most serious forms of sepsis, a life-threatening illness caused by severe infection. The new treatment is a genetically engineered version of a naturally occurring human protein, Activated Protein C, which interferes with some of the body’s harmful responses to severe infection, including the formation of blood clots that can lead to organ failure and death. Eli Lilly and Co., Indianapolis, Ind., will market the product as Xigris.
Novel Technologies in Thrombosis and Hemostasis

In-vivo visualization provides tool to study pathophysiology of thrombosis and to validate new therapeutic interventions.


Fluorescent cell barcoding allows multi-sample, high throughput flow cytometry for drug screening and profiling disease states.

Krutzik et al, Nat Methods. 2006May;3(5):361-8

Transgenic pigs could provide an efficient system for production of hemophilia proteins.

Bioengineering Research Partnership Grant R01 HL078944
**Novel Antithrombotic Drug Development**

**Small molecule platelet integrin inhibitors**

R. Blue et al, ASH Meeting, Nov 2006, Abstract # 144

**Mutant thrombin as anticoagulant**

Pineda et al, J. Biol. Chem., Vol. 279, issue 38, 39824-8, 2004
Rare Autoimmune Disorder Leads to Critical Discovery in Thrombosis

Thrombotic Thrombocytopenic Purpura (TTP)

- Incidence of 1 in a million per year
- Only treatment – plasma infusion that reduces fatality from 80% to 20%
- Genetic studies led to the discovery of new enzyme (ADAMTS 13) and provided insight into the pathophysiology of TTP
- Improved understanding of the molecular processes in thrombosis

Schematic structure of the plasma metalloprotease ADAMTS 13

Two Strategies for Improving the Therapy of Stroke

- 700,000 cases of stroke with 150,000 deaths per year in US
- Leading cause of disability
- tPA is the only FDA approved therapy and has serious complications
- Activated protein C and modified tPA seem promising in animal models

Activated protein C inhibits tissue plasminogen activator-induced brain hemorrhage.

Fragment 350-355 neutralized the neurotoxic effects of exogenous and endogenous tPA.
Armstead et al, Nat Neurosci. 2006 Sep;9(9):1150-5
The Scientific Challenges of Human Stem Cells

Basic Research Phase

Building Scientific Capacity
- Creating Career Development Pathways
- Training Courses
- Establishing Infrastructure
  - novel cell culture methods
  - expanding cell lines
  - cell sorting methods

Proving Long Term Stability of Cells
- Characterization of Embryonic Stem Cells
- Genetic Stability

Understanding Cell Cycle Control
- Regulation/Control of Cell Division

Understanding Cell Specialization
- Growth Factors
- Gene Regulation

Evaluating Cell-Host Interactions
- Immunology
- Transplantation Biology

Provided by James Battey, NIDCD, NIH
Using iterative methods, Nanog-associated proteins including oct-4 were identified and validated to generate a protein interaction network, enriched for nuclear factors critical for maintaining ES cell state. The network is linked to multiple co-represser pathways critical to maintaining pluripotency and to inhibiting differentiation.
Characterizing the Stem Cell Microenvironment

Stem cell engraftment at the endosteal niche is specified by the calcium-sensing receptor
Gregor B. Adams, et al.

Therapeutic targeting of a stem cell niche
Gregor B. Adams, et al.
In a preclinical murine model, progenitors expanded in culture using immobilized Notch ligand were shown to accelerate T cell recovery.
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Division of Blood Diseases and Resources

Function to Cause
Translating Basic Discoveries into Clinical Practice

- Comprehensive Sickle Cell Centers
- Specialized Centers of Clinically Oriented Research
- Specialized Centers of Research
- Clinical Research Networks
- Clinical Trials
- Pharmacogenetics in Practice
- Glycomics
- Hemophilia Therapy
Bench to Bedside to Community + Infrastructure + Research Training

Program Structure

- Basic, high risk, and translational research
- Phase I/II interventional single and multicenter clinical trials
- Epidemiologic research in risk factors for complications and co-morbidities
- Translation to Practice (Goal 3)
  - Psychosocial and behavioral research
  - Health services research
  - Patient reported outcomes
- Research training from high-school through post-doctorate
SCCOR in Transfusion Biology and Medicine: Transfusion Related Acute Lung Injury (TRALI)

Provided by Mark Looney, UCSF

Evaluation of therapies aimed at blocking platelet-neutrophil interactions

Are patients with thrombocytopenia less likely to develop TRALI?

Does platelet-depletion prevent TRALI in a mouse model?

Evaluation of therapies aimed at blocking platelet-neutrophil interactions

Bench

Bedside

Vol. 116
December 2006
The Journal Clinical Investigation
Complete reversal of acid-induced acute lung injury by blocking of platelet-neutrophil aggregation
Alexander Zarbock, et al.
Cellular Therapies

Stem, progenitor, and differentiated cells for repair and regeneration of diseased or injured tissues and biologic systems

- Cardiac Tissue Repair with Adult Stem Cells
- Properties of Human and Porcine Cardiac Stem Cells
- Mesenchymal stem cells for Treatment of post-MI Ischemic Cardiomyopathy
- Clinical Trial of PTH following Cord Blood Transplantation
- Defining the Bone Marrow Stem Cell Niche
- Validation of Suicide Strategies for Cellular Therapy
- PTH and wnt Signaling in Osteoblasts
- Multipathogen Specific Cytotoxic T Lymphocytes for the immunocompromised
- Properties of Human and Porcine Cardiac Stem Cells
- Validation of Suicide Strategies for Cellular Therapy
- PTH and wnt Signaling in Osteoblasts
Clinical Research Networks Excel in Bench to Bedside Research

- Thalassemia Clinical Research Network
- Sickle Cell Disease Clinical Research Network
- Transfusion Medicine/Hemostasis Clinical Trials Network
Targeted Strategies to Prevent Disease Progression in Thalassemia

- Thalassemia Clinical Research Network
  - Perform phase I/II/III clinical trials of new therapies, established international collaboration
  - Create datasets to better characterize patients and their clinical course
  - Apply genomic and proteomic techniques for improved diagnostic and therapeutic approaches

- Deferoxamine/L1 Chelation for Cardiac Iron Overload - to determine if combination chelation therapy is superior to single agent administration for iron overload associated with transfusion therapy

- Decitabine Therapy - to demonstrate the hematological benefits and toxicity of fetal hemoglobin induction using decitabine

- Thalassemia Long Term Cohort - to characterize a stable cohort of thalassemia patients, clinical events, treatment outcomes; collection of samples for genotypic/phenotypic correlation
Advancing Cellular Therapies

A national clinical trials network evaluating critical issues in hematopoietic stem cell transplantation, including:

- Alternative donors/graft sources
- Regimen related toxicity
- GVHD
- Relapse
- Infection/immunity
- Late effects/Quality of Life

BMT CTN #0403, currently enrolling: Phase III Randomized Double Blind, Placebo Controlled Trial of Soluble Tumor Necrosis Factor Receptor: Enbrel (etanercept) for the Treatment of Idiopathic Pneumonia Syndrome

Day 0: Pre-Therapy
100% FiO2

Day 3: Enbrel therapy
Room air
Clinical trials to evaluate:

- Novel management strategies of potential benefit for children and adults with hemostatic disorders.
- Blood products for the treatment of hematologic disorders.

The Study of Thrombotic Thrombocytopenic Purpura (TTP) and Rituximab

vWF Cleaving Protease (ADAMTS13) Activities Absent or Deficient in TTP (Tsai, NEJM 1998; Furlan et al., NEJM 1998)

ADAMTS13 = vWF Cleaving Protease
A Disintegrin-like And Metalloproteinase with ThromboSpondin Motifs

Provided by Joseph E. Kiss, University of Pittsburgh
Clinical Trials - Targeted Drug Strategies to Prevent Disease Progression in Sickle Cell Disease

- Pediatric Hydroxyurea Phase III Clinical Trial (BABYHUG) – to determine if hydroxyurea therapy is effective in the prevention of chronic end organ damage in pediatric patients with SCD. NHLBI-NICHD Collaboration

- Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) Trial - to compare standard therapy (transfusions with chelation) to alternative therapy (hydroxyurea with phlebotomy) for the prevention of recurrent stroke in children with sickle cell anemia.

- Sildenafil Trial for Sickle Cell Disease – Associated Pulmonary Hypertension – to evaluate the safety and efficacy of sildenafil, a nitric oxide potentiator, in adult patients with SCD and pulmonary hypertension. NHLBI Intramural/Extramural Collaboration
Pharmacogenetics-Based Warfarin Therapy

Genetic variants of cytochrome P450 complex (CYP2C9) and vitamin K epoxide reductase (VKORC1) affect the warfarin dose required for a therapeutic level.

**VKORC1 haplotype combinations associated with warfarin dose:** A/A, A/B & B/B.

Website uses clinical and genetic factors to estimate therapeutic dose.

Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose.
Glycomics: A Novel Pathway to Improved Therapeutics

Examples of glycan-based therapeutics

Cell surface glycans amplify the genomic information content of the cell through post-translational modification of proteins.

Varki, Nature. 2007 Apr 26;446(7139):1023-9
Promising Future of Hemophilia Therapy

Neutralization of antifactor VIII inhibitors by recombinant porcine factor VIII

R. T. BARROW and P. LOLLAR

Affl: Cancer Center and Blood Disorders Service, Children’s Healthcare of Atlanta, Atlanta, GA, and Department of Pediatrics, Emory University, Atlanta, GA, USA

To cite this article: Barrow RT, Lollar P. Neutralization of antifactor VIII inhibitors by recombinant porcine factor VIII. J Thromb Haemost 2006; 4: 2223-9.

Immuno modulation of transgene responses following naked DNA transfer of human factor VIII into hemophilia A mice

Carol K. Niazi, Paifang Ye, Arthur R. Thompson, David J. Rawlings, and Hans D. Ochs

Transfusion Medicine

Induction of tolerance to factor VIII inhibitors by gene therapy with immunodominant A2 and C2 domains presented by B cells as Ig fusion proteins

The Chi Lei (and David W. Scott)

Gene Therapy

Safe and efficient transduction of the liver after peripheral vein infusion of self-complementary AAV vector results in stable therapeutic expression of human FIX in nonhuman primates

Amir C. Nathwani,1,2 John T. Gray1,2, Jerry McIntosh,1 Catherine Y. C. Ng1,2, Justang Zhou1, Yunru Spence1,2, Melanie Cochrane1,2, Elaine Gray1,2, Edward G. D. Ruddershaw1,2, and Andrew M. Davidson1,2

1Department of Haematology, University College London and National Blood Service, United Kingdom; 2Division of Experimental Haematology and Department of Surgery, St. Jude Children’s Research Hospital, Memphis, TN; 3Department of Haematology, National Institute for Biological Standards and Control, Potters Bar, United Kingdom; and 4Haematology Department Haemophilia Centre, London, United Kingdom.

Strategies towards a longer acting factor VIII

E. L. SANEK5 and S. W. PIKE6

1Center for Vascular and Inflammatory Diseases, University of Maryland School of Medicine, Baltimore, MD, USA, and
2Department of Pediatrics, University of Michigan, Ann Arbor, MI, USA

Research article

Factor VIII ectopically targeted to platelets is therapeutic in hemophilia A with high-titer inhibitory antibodies

Chihen Shi1,2,3, Arturo A. Wilcox1,2,3, Scott A. Fahs1,4, Hertrud Weiler1,2,4, O’Meara Wells1,5, Brian C. Cooley1,2, Daphna Trulik1,5, Patricia A. Morreale1,1,3, Jack Gorinski1,2,6, and Robert R. Montgomery1,2,3,4,5

1Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, Wisconsin, USA; Departments of Pediatrics, Physiology, Immunology, and Microbiology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA; 2Children’s Research Institute, Children’s Hospital of Wisconsin, Milwaukee, Wisconsin, USA.

LETTERS

Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response

Catherine S Mann1,2,3, Glenn F Pierce1,2,3, Valder R Arruda1,2,4, Bertiil Glader1,2,3, Margaret Ragni1, John E Radko1,2, Margaret C. Oudka5, Keith Hoos1,2, Philip Blain1,2, Barbara Kondak2,3, Michael Dake5,6, Robin Kay5,6, Mahmod Razavi1,6, Albert Zajko5,6, James Zehnder4, Pradip K Rustagi5,6, Hiroaki Nakai1, Amy Chev1,2, Debra Leonard2,4, J Fraser Wright1,2, Ruth R Lesselard1, Juerg M Sommer1,2, Michael Tiggeler1,2, Denise Subarino3, Alvin Lai3, Haiyan Fang1,2, Federico Mingozzi1,2, Linda Couto5,6, Hildegund C Ernst4,5, Katherine A High1,2,3, & Mark A Kay1,2,3
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Cause to Cures
Improving Blood Safety and Availability

A global perspective
Increasing the Safety of the Blood Supply
Screening Blood Donors More Effectively

Donor Computer Assisted Touch Screen Interviewing

Computer-assisted automated interviewing of blood donors increases the elicitation of transfusion-transmitted infection risk behaviors, improves donor and staff satisfaction, and reduces errors and omissions that frequently accompany traditional interview methods.

Quality Donor System™ (QDS)
Audio Visual Touch Screen Computer Assisted Self Interviewing (AVT-CASI)
Paul D. Cumming, PhD - Talisman Limited - SBIR
Increasing the Safety of the Blood Supply

Modeled Risk: Incidence – Window Period Model

The NHLBI Retrovirus Epidemiology Donor Study (REDS)

Provided by Michael Busch, Blood Systems Research Institute, SF
Increasing the Safety of the Blood Supply

The risk of transfusion-transmitted viral infections
George B. Schreiber, et al.

Simone A. Glynn, et al.

Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid-amplification testing
Susan L. Stramer, et al.
Current and Emerging Infectious Risks of Blood Transfusions

Michael P. Busch, MD, PhD
Steven H. Kleinman, MD
George J. Nemo, PhD

countries where resources are insufficient to enable basic infectious disease donor screening,

Major Viral Infections and antibody marker) than currently used HCV antibody, HIV-1 antibody, and antigen assays. The window period for HIV-1, using antibody assays, is ap-
Blood Safety
Emerging Infectious Risks: REDS and REDS-International

Concern high, Action favored

vCJD

CJD

Ebola etc

Lyme

HGV, etc

HHV 8

HHV 6

HAV

Ehrlichia

Leishmania

Babesia

B19

Malaria

Dengue

Chagas

Rocky Mountain Spotted Fever

Colorado Tick Fever

West Nile Virus

Bacteria

Chlamydia, JC virus, Leptospira Bartonella etc

Chlamydia, JC virus, Leptospira Bartonella etc

Benefit High Action favored

Provided by Michael Busch, Blood Systems Research Institute, SF
The REDS-II Molecular Surveillance Study

Evaluation of HIV, HCV, and HBV strains in recently infected blood donors permits

- Early detection of rare variants including vaccine and drug escape mutants
- Characterization by demographics and geographical area
- Longitudinal tracking of changes in genotype frequency of actively transmitted strains
- Comparison with at-risk populations
- Assure screening, diagnostic and supplemental assays are sensitive to circulating transfusion-transmitted viral infection strains
- Monitor for transmission of drug resistant virus into the general population
- Vaccine implications (HIV/HCV vaccines, HBV escape mutants)

Global distribution of HIV genotypes
At http://www.hiv.lanl.gov.

Global distribution of HCV genotypes
At http://hcv.lanl.gov/content/hcv-db/index
Safety of the Global Blood Supply
REDS-II International

Laboratory, epidemiologic and survey research to:
• assess and monitor the prevalence, incidence, and transfusion-transmitted risk of HIV 1, HIV-2, and other existing as well as newly discovered infectious agents that pose a threat to blood safety in selected developing countries seriously affected by the HIV/AIDS epidemic
• assess the impact of existing and new blood donor screening methodologies on blood safety and availability
• evaluate characteristics and behaviors of blood donors including risk factors for acquiring HIV and other blood-borne agents (HBV in China, Chagas and Dengue in Brazil).

A new HIV antibody detection assay, termed HIV-SELECTEST, distinguishes between serological changes induced by HIV vaccines and those induced by HIV infection. This test will allow clinical trial investigators to differentiate between participants recently infected with HIV and HIV-negative vaccinated participants. This test could prove critical for HIV diagnostic and blood screening when vaccination becomes widespread.

HIV-SELECTEST
- based on the Gag-p6 and Env-gp41 peptides which are recognized soon after infection, are not protective epitopes and are therefore, not part of putative HIV vaccines being developed.
- is 99% specific and sensitive for detecting true HIV infection
- does not detect HIV vaccine-generated antibodies.

Encouraging development and risk-safety profile evaluation of technologies for Pathogen Inactivation/Reduction through small Business innovation Research (SBIR) and Small Business Technology Transfer (STTR) mechanisms.
Cause to Cures, con’t.
Translating Research into Practice

Improving public health – sickle cell disease
Sickle cell disease is

- 1 of the 10 leading causes of death for African Americans under the age of 25
- Mortality varies dramatically between regions of the country, suggesting variation in care
- Hospitalization costs are considerable
- Comprehensive care has been shown to reduce hospitalization rates mortality
- “Quality measures…(for) this condition are appropriate for health care plans and/or hospitals who serve a large number of African Americans.” (page 81) AHRQ Pub. No. 03-0047-EF
1. **Health Status**: objectives related to physical and medical status, life expectancy, quality of life, and functioning.

2. **Health Promotion**: objectives related to activities to prevent complications, self-management, health behaviors, health education, and reduction of risk behaviors. [It also includes social support systems, patient knowledge, and coping.]

3. **Health Services**: objectives related primary and specialized health services, medical tests, access to health care, and emergency services.

4. **Health Workforce**: objectives related to the availability of a wide range of health care providers and their skills and knowledge of SCD.

First Look at Sickle Cell Disease Hospitalizations in 10 Years

AHRQ News and Numbers

Release date: December 20, 2006

The first Federal analysis of sickle cell disease hospitalizations in a decade shows that admissions of adults remained stable from 1997 to 2004. In 2004, roughly 83,000 hospital stays were for adults and 30,000 were for children. Of the latter, 2,200 stays were for infants, according to the latest News and Numbers summary issued by the Department of Health and Human Services’ Agency for Healthcare Research and Quality (AHRQ).

Sickle cell disease, an inherited blood disease affecting mostly African Americans, causes red blood cells to lose their shape, block circulation, and causes organ damage. The illness has no common cure and patients with periodic pain are often treated with pain medications.

The study found:
- Patients spent about 6 days in the hospital, which cost facilities an average of $6,223 per stay.
- Total hospital costs for sickle cell disease were nearly $500 million in 2004.
- Medicare paid for 85 percent of the stays involving patients hospitalized primarily for sickle cell disease, while Medicare paid for 13 percent, private insurers were responsible for 15 percent, and 4 percent of the hospitalized patients were uninsured.
- The number of persons with sickle cell disease who died while hospitalized in 2004 was relatively low—693 adults and 47 children.
- In-hospital deaths of children remained low and constant from 1994 to 2004.

Generating an Improved Understanding of the Process Involved in Translating Research into Practice
Challenge: To Promote the Development and Implementation of Evidence-Based Guidelines

This Conference on HU will address questions about safety, efficacy (Phase II/III) and effectiveness (Phase IV, post-approval) in different age groups, barriers to utilization from the physician’s and patient’s perspective, and will provide guidance to improve utilization of HU for SCD.

http://consensus.nih.gov/
Complementing bench and RCTs with focused behavioral and social science research: The NIH Patient-Reported Outcomes Measurement Information System

“There is a pressing need to better quantify clinically important symptoms and outcomes that are now difficult to measure,” says NIH Director Elias A. Zerhouni, MD. “Our clinical research communities would benefit greatly from efficient, consistent, well-validated approaches to measuring these and other subjective outcomes.”

http://nihpromise.org/
Division of Blood Diseases and Resources

**Strategies**
Training and Mentoring of Emerging Scientists and Physicians
Training of New Clinical Investigators
Pipeline of Opportunities to Assure Diverse Research Teams

K-12

Minority K-12 Initiative for Teachers and Students (MKITS)
- Supports research, development, and evaluation of innovative science training programs for minority students in grades K-12

Comprehensive Sickle Cell Centers (CSCC)
- Summer for Sickle Cell Science Program - research training and mentoring for high school through post doctoral levels
- CSCC Scholar’s Program - Research training for junior faculty

Clinical Research Education and Career Development in Minority Institutions
- Curriculum development for training pre- and post doctoral candidates in clinical research

Summer Institute Program to Increase Diversity in Health-Related Research
- Enhancing research skills and knowledge in basic and applied research for faculty and scientists from underrepresented groups
Career Development for New Clinical Investigators

Clinical Hematology Research Career Development Program (K12)
- To develop, implement, and evaluate multidisciplinary career development programs in non-malignant hematology that will equip new investigators with the knowledge and skills to address complex problems in blood diseases

Pediatric Transfusion Academic Career Awards (K07)
- To develop curricula designed to attract new investigators to the field of pediatric transfusion medicine
NHLBI Resources for the Scientific Community

Facilitating the conduct of research in heart, lung, and blood disorders by developing and facilitating access to scientific research resources
The NHLBI Biologic Specimen Repository

The Repository currently includes about 4 million plasma, serum, cellular or tissue specimens

- Managed since the mid-1970s by the Division of Blood Diseases and Resources, Transfusion Medicine and Cellular Therapeutics Branch, NHLBI.
- Currently resides at SeraCare Bioservices in Gaithersburg, MD.

Implementation of a Biorepository and Limited Access Data Information Coordinating Center (BioLINCC) that will:

1. Develop and maintain an interactive web-based platform with inventory search engine, application system, and information kiosk.
2. Store biospecimen data sets and documents.
3. Assist with biospecimen selection.
4. Maintain & coordinate central data warehouse to include the Limited Access Data Sets (LADS).
5. Coordinate acquisition and distribution requests.
6. Coordinate Allocation Committee activities.
7. Provide IRB review, as needed.
8. Track and prepare reports on repository activities.

Types of Stored Biospecimens

- Plasma
- Serum
- Whole Blood
- PBMC
- DNA
- Other

The category "Other" includes urine, RBC, lymphocytes, immunoglobulins, cord blood units, buffy coats, tissue.

67 Collections from 51 Programs
Production Assistance for Cellular Therapies (PACT)

Designed to develop novel somatic cellular therapies that will aid investigators by providing support in areas ranging from basic science through animal studies to proof-of-principle and eventually human clinical trials.

The cell processing facilities provide the cellular product requested by an investigator along with the assurance that it is of clinical grade and is produced in a manner compliant with all regulatory requirements.
A Resource for Blood and Marrow Transplant Clinical Research

The Center for International Blood and Marrow Transplantation Research (CIBMTR) Statistical Center coordinates an international effort to collect and analyze data on outcomes of blood, bone marrow, and umbilical cord blood transplantation.

The CIBMTR database contains clinical data on more than 230,000 recipients of allogeneic and autologous hematopoietic stem cell transplants treated in more than 600 transplant centers in 47 countries.

The database includes information on autologous, related donor, and unrelated donor transplantation.
NIH Core Strategic Vision

- Transform medicine and health from a Curative to a Preemptive paradigm
- Support basic research to identify the earliest molecular stages of disease in complex biological systems
- Accelerate translation of findings from the bench to the bedside to the community
- Provide the evidence and knowledge base to allow for a rational transformation of our healthcare system
Future Directions

Basic Discovery  Clinical  Communication

Genomics  Proteomics

Stem Cell Research  Tissuegenesis  Cell Imaging  Translational
The Future Paradigm: Preempt Disease

- Tolerable
- In tolerable
- Preclinical
- Cost savings
- Molecular preemption
- Symptom management
- Curative treatment

Disease Burden

Cost

Time
Goal One: Form to Function

Goal 1: To improve understanding of the molecular and physiological basis of health and disease and use that understanding to develop improved approaches to disease diagnosis, treatment, and prevention.

Challenge 1.1
To delineate mechanisms that relate molecular events to health and disease.

1.1.a Develop a detailed understanding of the molecular, cellular, and physiological mechanisms that maintain health from embryonic development to the end of the human lifespan.

1.1.b Identify intracellular targets of key signaling and transcriptional pathways in normal and pathologic states.

1.1.c Determine key genetic variants that are associated with specific diseases and delineate the molecular mechanisms that account for susceptibility or resistance to disease.

1.1.d Define molecular, cellular, and organ-specific responses to environmental challenges, and the mechanisms by which heritable and non-genetic factors interact in disease initiation and progression and in therapeutic response.

1.1.e Determine the role of systemic pathological processes, such as inflammation, immunity, and infection, in the development and evolution of disease.
**Challenge 1.2**

To discover biomarkers that differentiate clinically relevant disease subtypes and that identify new molecular targets for application to prevention, diagnosis – including imaging, and therapy.

1.2.a Identify molecular signatures that allow complex disease phenotypes to be stratified into clinically relevant categories.

1.2.b Develop in vivo molecular imaging methods and probes for investigating the biology of disease processes.
Goal Two: Function to Causes

**Goal 2:** To improve understanding of the clinical mechanisms of disease and thereby enable better prevention, diagnosis and treatment.

**Challenge 2.1**
To accelerate translation of basic research findings into clinical studies and trials and to promote the translation of clinical research findings back to the laboratory.

- **2.1.a** Integrate advances in regenerative biology to develop clinically feasible applications.
- **2.1.b** Apply discoveries in nanotechnology to the development of new diagnostic and therapeutic strategies.
- **2.1.c** Integrate, analyze, and share extant and emerging genotypic and phenotypic data.

**Challenge 2.2**
To enable early and accurate risk stratification and diagnosis of cardiovascular, lung, and blood disorders.

- **2.2.a** Exploit noninvasive imaging methods to detect and quantify subclinical disease.
- **2.2.b** Apply new discoveries in biomarkers to improve risk assessment, diagnosis, prognosis, and prediction of response to therapy.
Challenge 2.3
To develop personalized preventive and therapeutic regimens for cardiovascular, lung, and blood diseases.

2.3.a  Improve the understanding of the interactions between genetic and environmental factors that influence disease development and progression and response to therapy.

2.3.b  Identify and evaluate interventions to promote health and treat disease in genetically defined patient subgroups by altering developmental or environmental exposures including drugs, diet and exercise, sleep duration and quality, and infectious agents and allergens.

Challenge 2.4
To enhance the evidence available to guide the practice of medicine, and improve public health.
Goal Three: Causes to Cures

**Goal 3:** To generate an improved understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery.

**Challenge 3.1**
To complement bench discoveries and clinical trial results with focused behavioral and social science research.

- **3.1.a** Develop and evaluate new approaches to implement proven preventive and lifestyle interventions.
- **3.1.b** Develop and evaluate policy, environmental, and other approaches for use in community settings to encourage and support lifestyle changes.
- **3.1.c** Develop and evaluate interventions to improve patient, provider, and health system behavior and performance in order to enhance quality of care and health outcomes.
Challenge 3.2
To identify cost-effective approaches for prevention, diagnosis, and treatment.

3.2.a Evaluate the risks, benefits, and costs of diagnostic tests and treatments in representative populations and settings.

3.2.b Develop research designs, outcome measures, and analytical methods to assess prevention and treatment programs in community and health-care settings across populations and lifespan.

Challenge 3.3
To promote the development and implementation of evidence-based guidelines in partnership with individuals, professional and patient communities, and health care systems and to communicate research advances effectively to the public.

3.3.a Establish evidence-based guidelines for prevention, diagnosis, and treatment and identify gaps in knowledge.

3.3.b Develop personalized and community- and health care system-oriented approaches to increase the use of evidence-based guidelines by individuals, communities, health care providers, public institutions, and, especially, by populations that experience a disproportionate disease burden.

3.3.c Communicate research advances effectively to the public.