

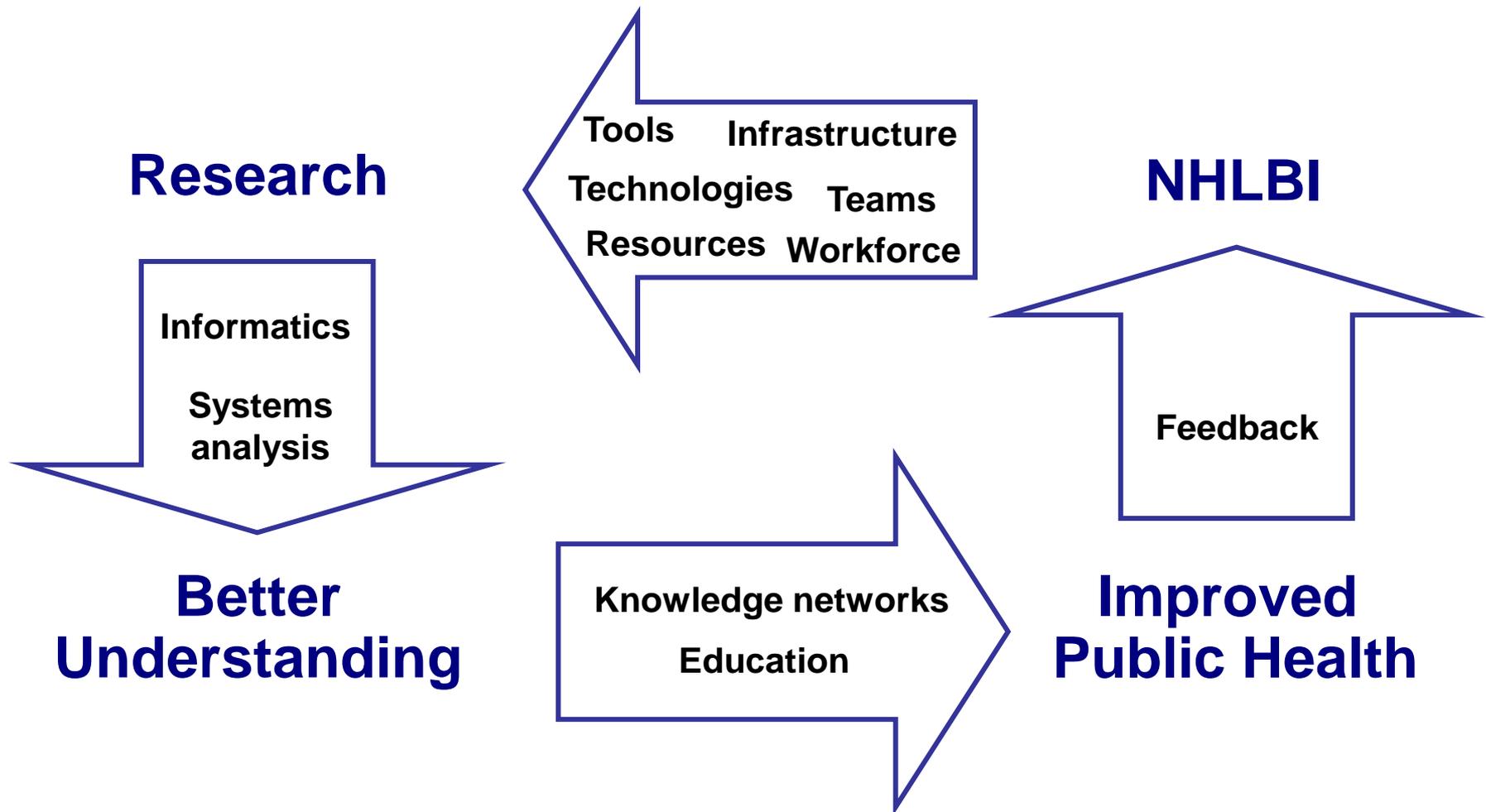
# NHLBI Strategic Plan: Current and Future Opportunities for Blood Diseases and Resources Research



**National Heart, Lung, and  
Blood Institute**



# NHLBI's Strategic Plan Promotes Advances in Research Approaches



# Planning Principals



# NHLBI Strategic Plan Objectives

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



# Need to Transform Medical Research in the 21st Century

## 20<sup>th</sup> Century

**Treat disease  
when symptoms appear and  
normal function is lost**

**Did not understand the  
molecular and cellular  
events that lead to disease**

**Expensive in financial and  
disability costs**

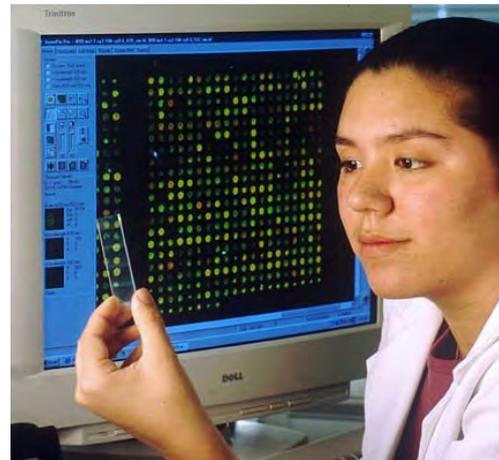
## 21<sup>st</sup> Century

**Intervene before symptoms  
appear and preserve normal  
function for as long as possible**

**Understanding preclinical  
molecular events and ability to  
detect patients at risk**

**Orders of magnitude more  
effective**

# The Future Paradigm: Transform Medicine from Curative to Preemptive



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# Division of Blood Diseases and Resources

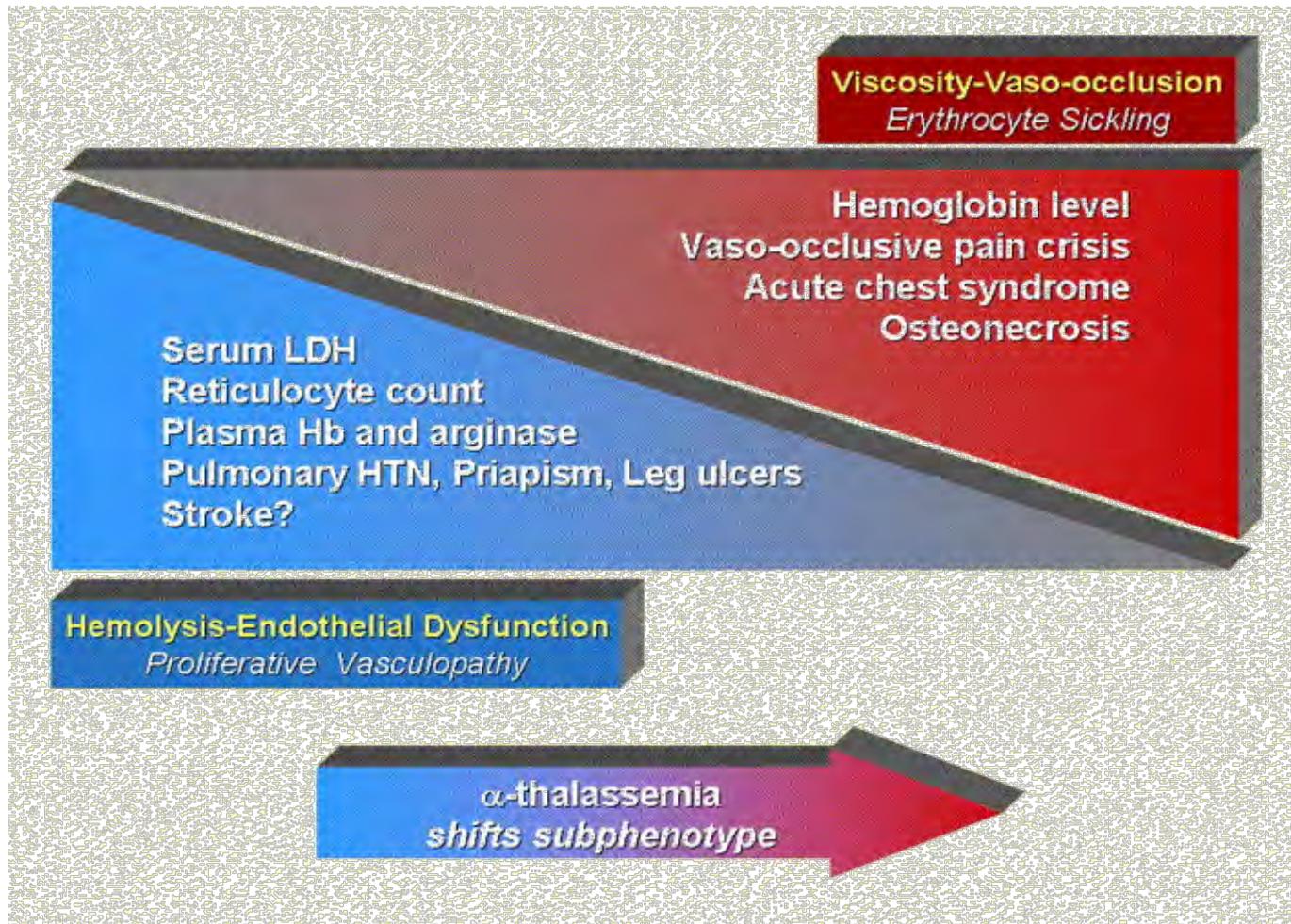
## *Form to Function*

### Basic Discoveries about the Causes of Disease

- Sickle Cell Disease
- Hemolytic Anemias
- Thrombosis
- Bleeding Disorders
- Stroke
- Stem Cells



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



Source: *Blood Rev.* 2007 Jan;21(1):37-47.

# Bone Marrow Failure Disease: Model for Ribosomal Regulation

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.

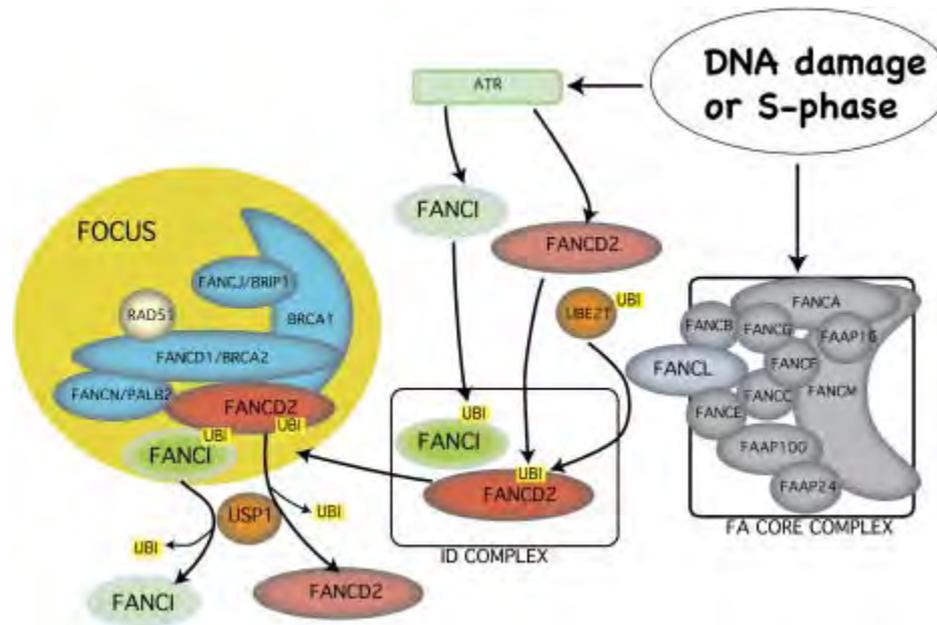
Blood, May 2007

## **The Human Shwachman-Diamond Syndrome Protein, SBDS, Associates with Ribosomal RNA**

Karthik A. Ganapathi, et al.

Nat. Genet. 1999 Feb;21(2):169-75

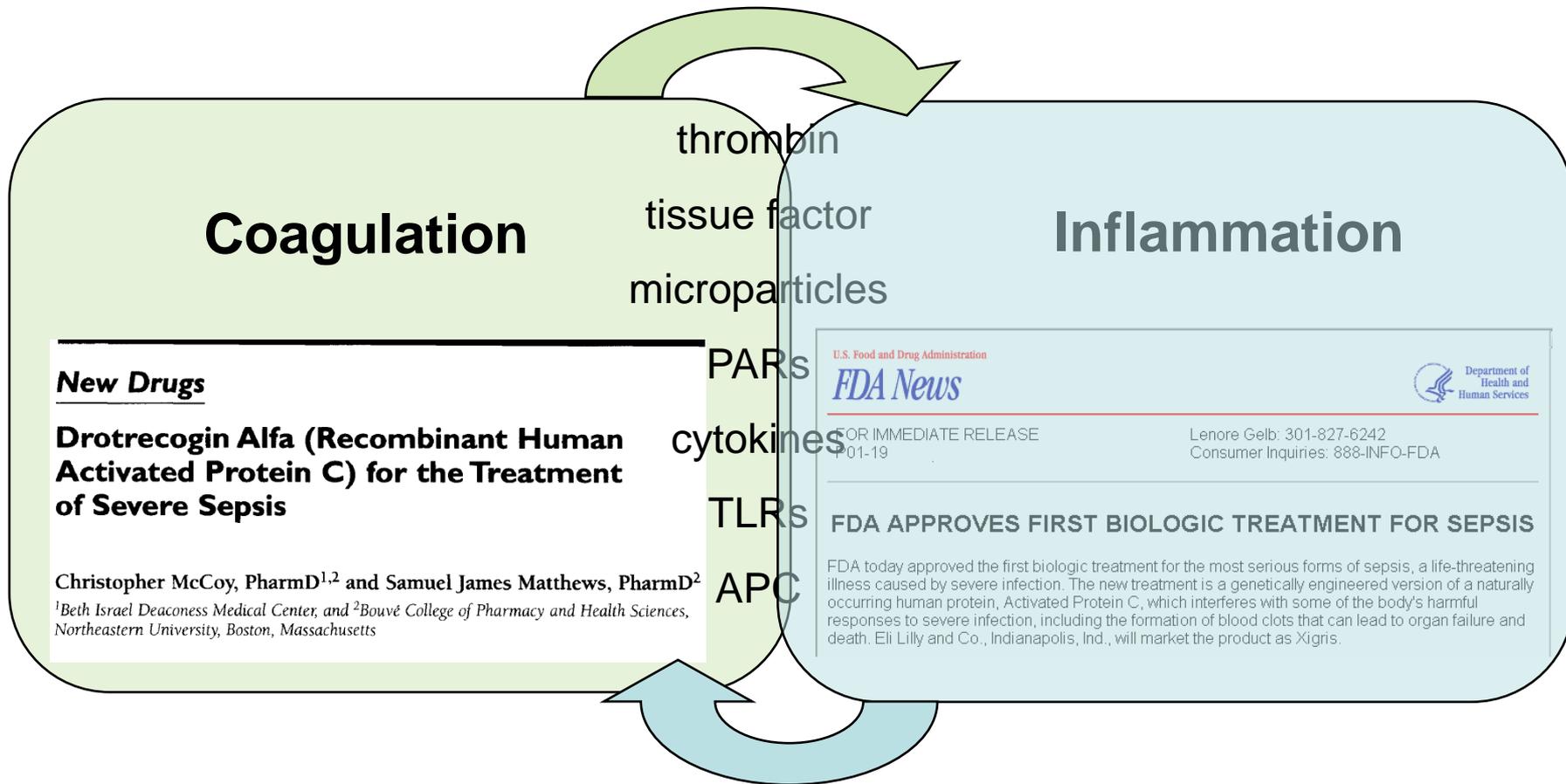
# Rare Genetic Disorders Can Illuminate Important Biological Pathways



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

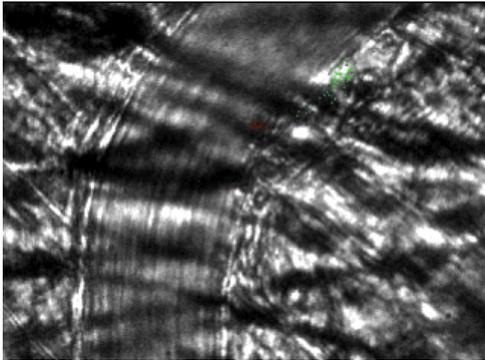
# The Interface Between Thrombosis and Inflammation



**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.**

# Novel Technologies in Thrombosis and Hemostasis



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

Furie et al, *J. Clin. Invest.* 115:3355-3362, 2005

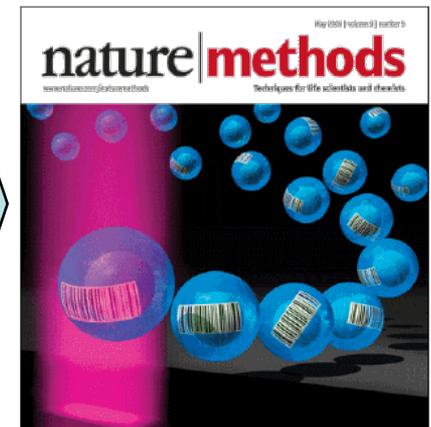
Fluorescent cell barcoding allows multi-sample, high throughput flow cytometry for drug screening and profiling disease states.

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



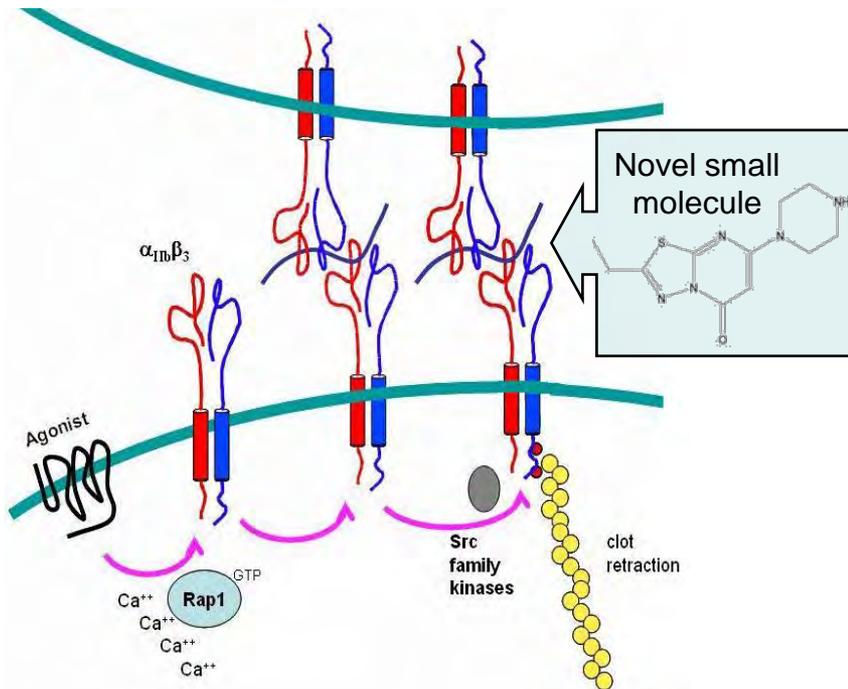
Transgenic pigs could provide an efficient system for production of hemophilia proteins.

Bioengineering Research Partnership Grant R01 HL078944



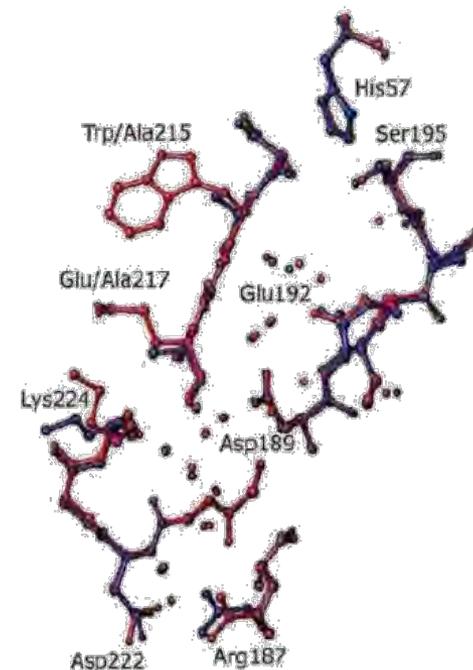
# Novel Antithrombotic Drug Development

## Small molecule platelet integrin inhibitors



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

## Mutant thrombin as anticoagulant



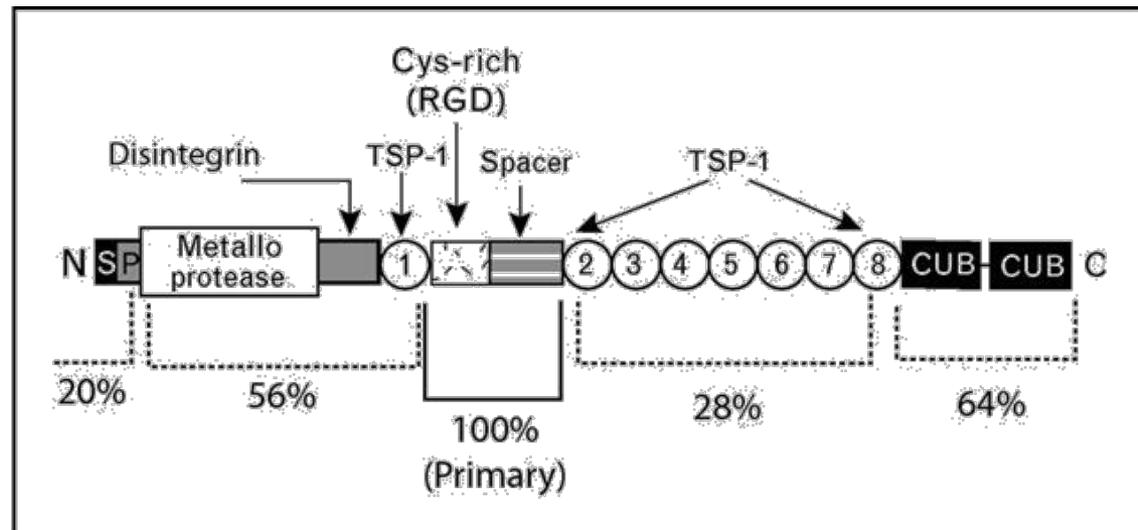
Pineda et al, J. Biol. Chem., Vol. 279, issue 38, 39824-8, 2004  
Gruber et al, Blood, Vol. 109, 3733, May, 2007

# 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



Dong, JF, Curr Opin in Hemat. 14 (May 2007) 270.

Gao W. et al, Proc Natl Acad Sc (USA) 103 (Dec 2006) 19099.

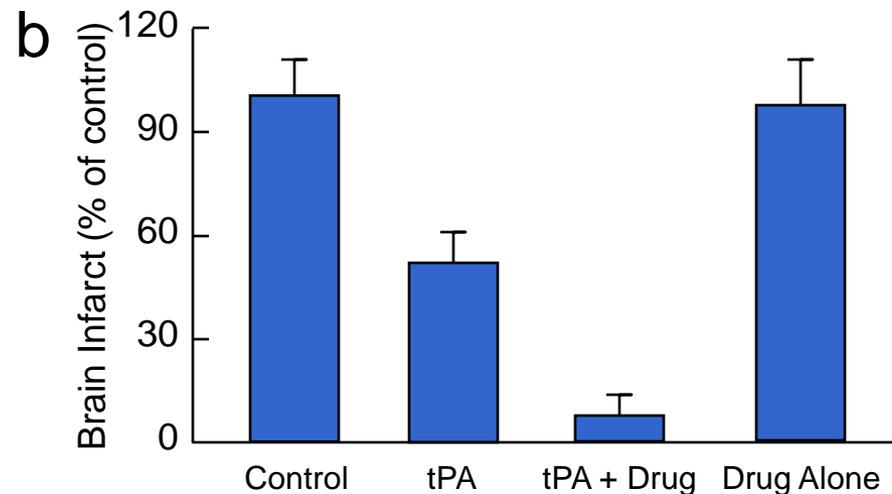
# Two Strategies for Improving the Therapy of Stroke

- 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.

Cheng et al, Nat Med. 2006 Nov;12(11):1278-85



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

# Stem Cell Biology

## Defining a Protein Interaction Network in Embryonic Stem Cells

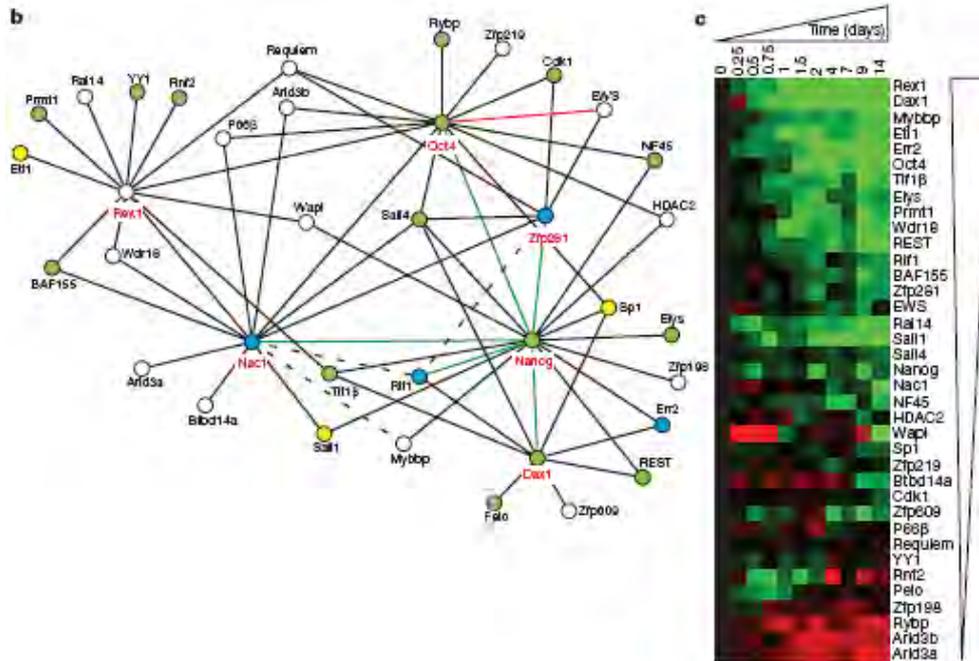
Vol. 444

nature

16 November 2006

### A protein interaction network for pluripotency of embryonic stem cells

Jianlong Wang, et al.



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-repressor pathways critical to maintaining pluripotency and to inhibiting differentiation.

# Characterizing the Stem Cell Microenvironment

Vol 439/2

**nature**

**Stem cell engraftment at the endosteal niche is specified by the calcium-sensing receptor**

Gregor B. Adams, et al.

Vol. 316

**nature**  
Biotechnology

January 21, 2007  
Epub ahead of print]

**Therapeutic targeting of a stem cell niche**

Gregor B. Adams, et al.

# Post-transplant T-cell Immune Reconstitution

Vol. 109

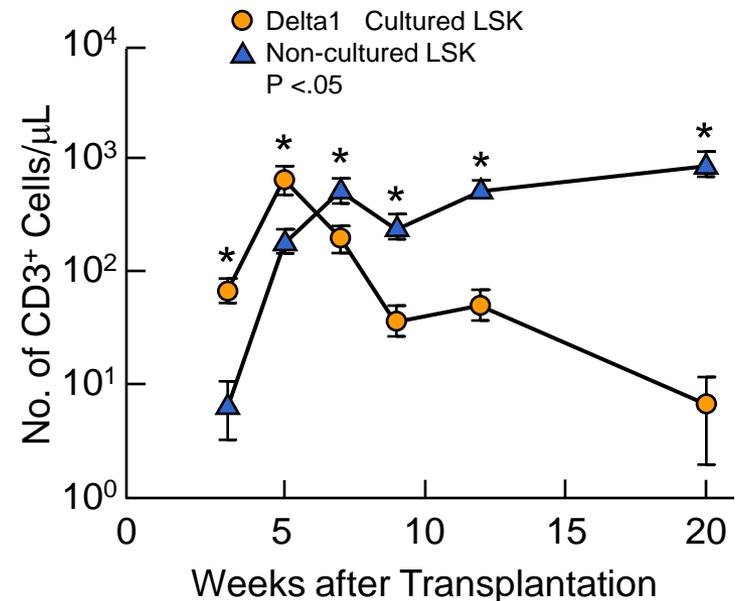
## blood

15 April 2007

**Enhanced T-cell reconstitution by hematopoietic progenitors expanded ex vivo using the Notch ligand Delta 1**

Mari H. Dallas, 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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## ***Function to Cause***

## **Translating Basic Discoveries into Clinical Practice**

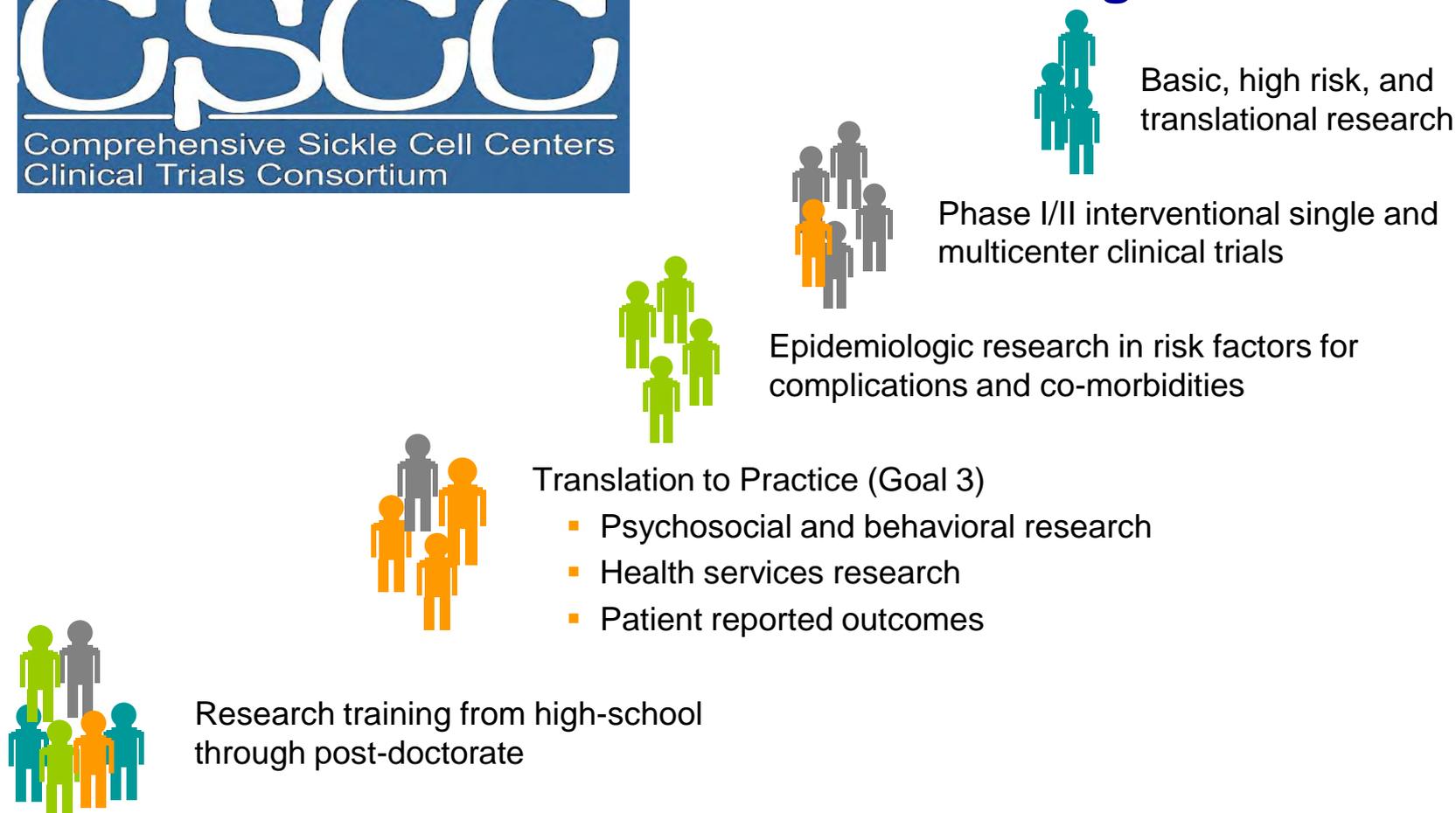
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- Comprehensive Sickle Cell Centers
- Specialized Centers of Clinically Oriented Research
- Specialized Centers of Research
- Clinical Research Networks
- Clinical Trials
- Pharmacogenetics in Practice
- Glycomics
- Hemophilia Therapy

# Bench to Bedside to Community + Infrastructure + Research Training

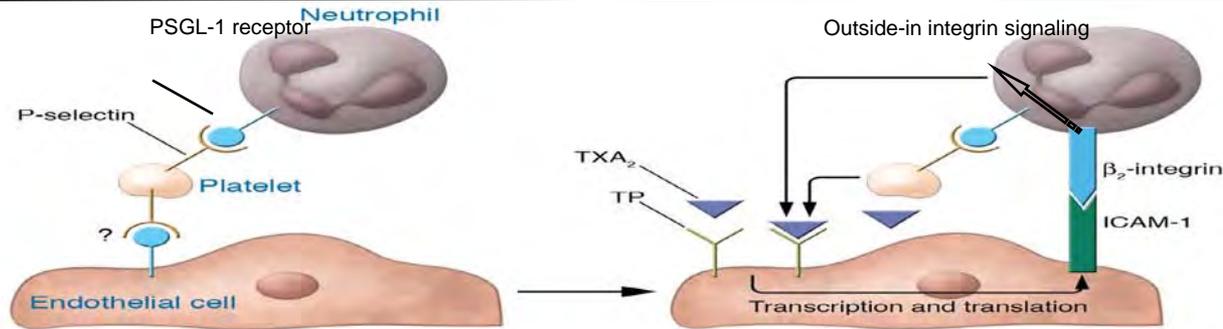


## Program Structure



# SCCOR in Transfusion Biology and Medicine: Transfusion Related Acute Lung Injury (TRALI)

Bench

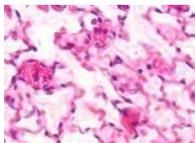


Vol. 116  
**JCI**  
 The Journal Clinical Investigation  
 December 2006  
**Complete reversal of acid-induced acute lung injury by blocking of platelet-neutrophil aggregation**  
 Alexander Zarbock, et al.

Does platelet-depletion prevent TRALI in a mouse model?

Are patients with thrombocytopenia less likely to develop TRALI ?

Evaluation of therapies aimed at blocking platelet-neutrophil interactions

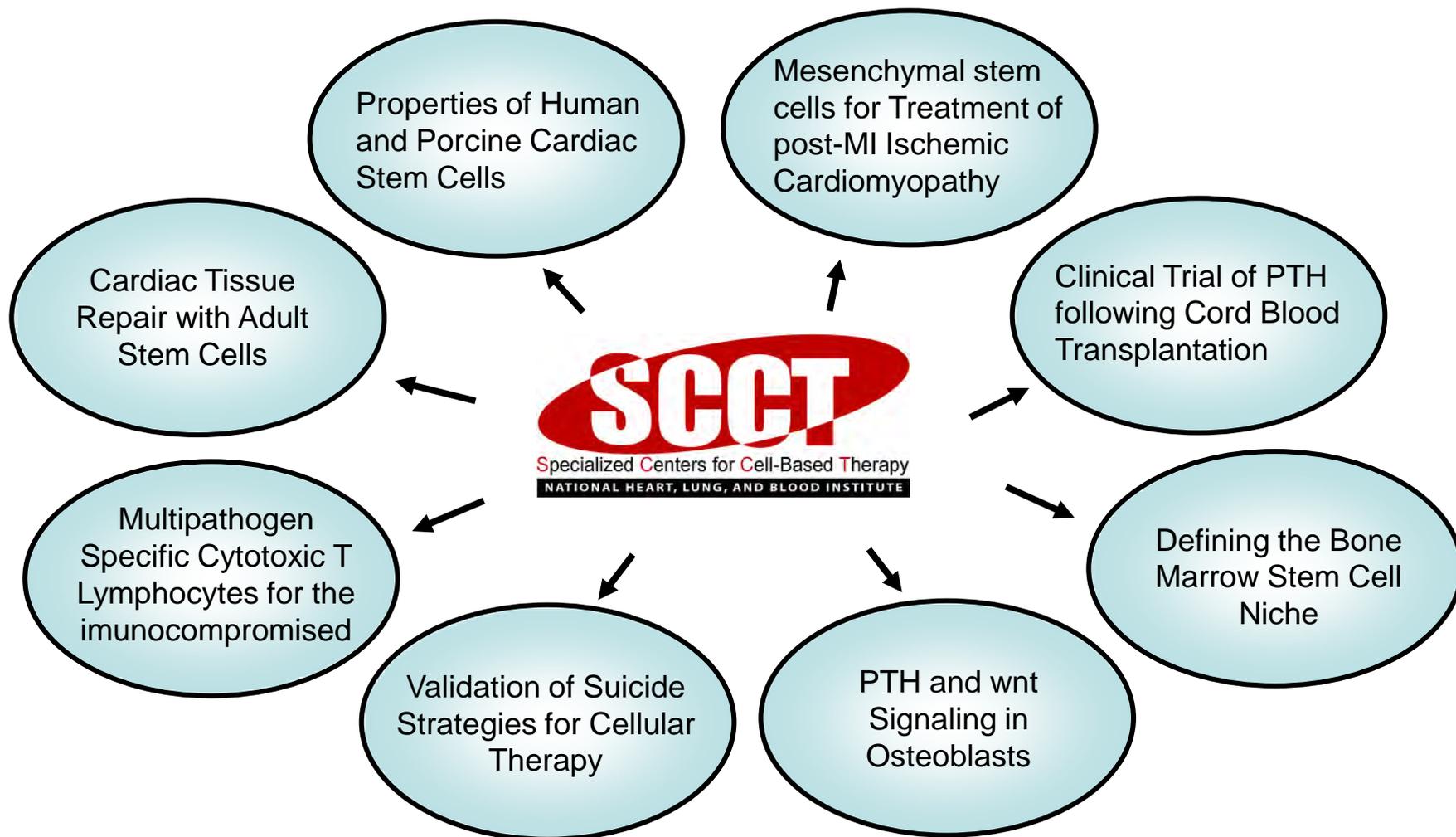


Provided by Mark Looney, UCSF

Bedside

# Cellular Therapies

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



# Clinical Research Networks Excel in Bench to Bedside Research

## Thalassemia Clinical Research Network



**Transfusion  
Medicine/Hemostasis  
Clinical Trials Network**



**Sickle Cell Disease Clinical  
Research Network**



**BLOOD AND MARROW  
TRANSPLANT  
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



BLOOD AND MARROW  
**TRANSPLANT**  
CLINICAL TRIALS NETWORK

***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

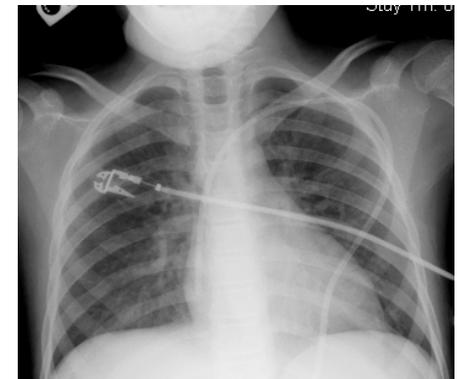
***BMT CTN #0403, currently enrolling:*** Phase III Randomized Double Blind, Placebo Controlled Trial of Soluble Tumor Necrosis Factor Receptor: Enbrel (etanercept) for the Treatment of Idiopathic Pneumonia Syndrome



***Day 0: Pre-Therapy  
100% FiO<sub>2</sub>***



***Enbrel***



***Day 3: Enbrel therapy  
Room air***

# The Transfusion Medicine / Hemostasis Clinical Trials Network

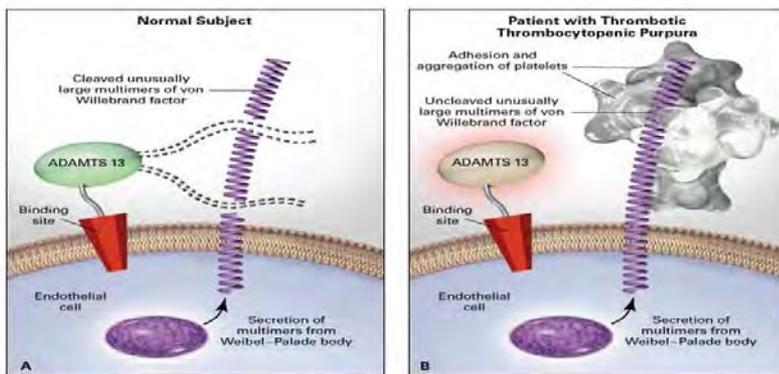


## Clinical trials to evaluate:

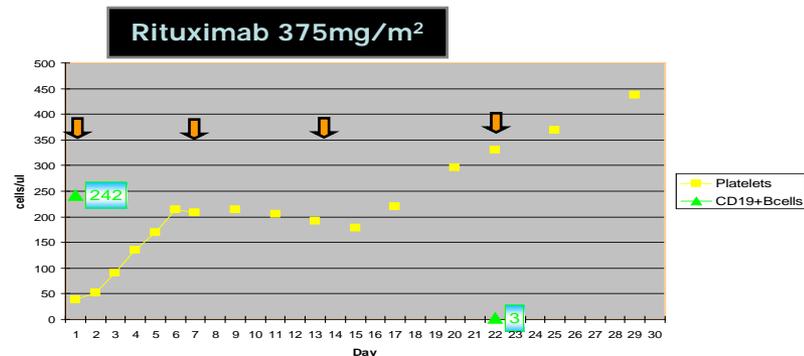
- Novel management strategies of potential benefit for children and adults with hemostatic disorders.
- Blood products for the treatment of hematologic disorders.

## 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 **A**nd **M**etalloproteinase with **T**hrombo**S**pondin Motifs



Provided by Joseph E. Kiss, University of Pittsburgh

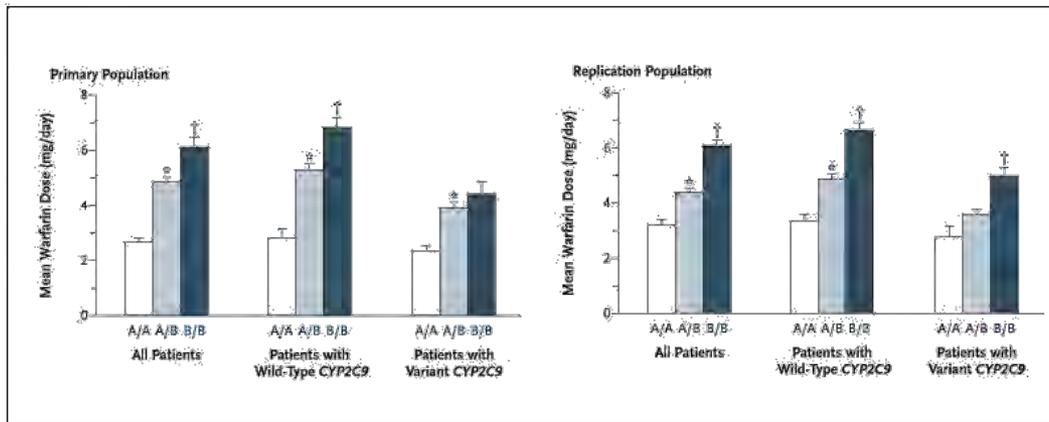
# Clinical Trials - Targeted Drug Strategies to Prevent Disease Progression in Sickle Cell Disease

- 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.

The screenshot shows the 'WARFARINDOSING' website interface. At the top, it says 'www.WarfarinDosing.org'. Below the header, there is a navigation menu with links: Warfarin Dosing, Hemorrhage Risk, Patient Education, Contact Us, References, and Glossary. A 'Admin' section is also visible. The main content area is titled 'Initial Information' and asks the user to provide their information, including whether they are a new or existing patient, their patient ID, and the version of the software (Version 5.0, build 1.08 June 2007). A 'CONTINUE' button is at the bottom. The footer contains copyright information for 2004 Barnes-Jewish Hospital at Washington University Medical Center and a disclaimer regarding the use of the website for research purposes.

Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose.

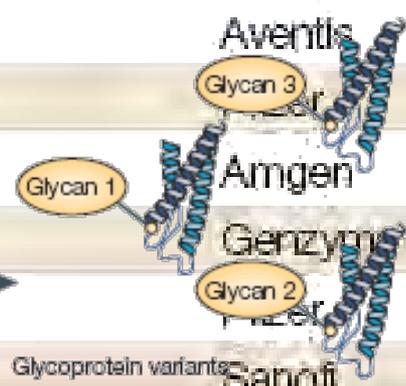
Rieder et al, N Engl J Med. 2005 Jun 2;352(22):2285-93.

# 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.

Drug	Disease	Clinical status	Manufacturer
Lovenox	Thrombosis	Market	Aventis
Fragmin	Thrombosis	Market	Genzyme
Aranesp	Anaemia	Market	Amgen
Seprigel	Anti-acid	Market	Genzyme
Healon	Cataracts	Market	Genzyme
Arixtra	Thrombosis	Market	Sanofi
Cerezyme	MPS I	Market	Genzyme
Aklurazyme	MPS I	Market	Genzyme
PI-88	Cancer	Phase II	Progen



MPS I, mucopolysaccharidosis type I.

Varki, Nature. 2007 Apr 26;446(7139):1023-9

Crocker et al, Nat Rev Immunol. 2007 Apr;7(4):255-66

# Promising Future of Hemophilia Therapy

*Journal of Thrombosis and Haemostasis*, 4: 2223–2229

## ORIGINAL ARTICLE

### Neutralization of antifactor VIII inhibitors by recombinant porcine factor VIII

R. T. BARROW and P. LOLLAR

Aflac 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.

## Plenary paper

### Immunomodulation of transgene responses following naked DNA transfer of human factor VIII into hemophilia A mice

Carol H. Miao, Peiqing 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

Tie 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

Amit C. Nathwani,<sup>1,2</sup> John T. Gray,<sup>3</sup> Jenny McIntosh,<sup>1</sup> Catherine Y. C. Ng,<sup>4</sup> Junfang Zhou,<sup>4</sup> Yunyu Spence,<sup>4</sup> Melanie Cochrane,<sup>1</sup> Elaine Gray,<sup>5</sup> Edward G. D. Tuddenham,<sup>1,6</sup> and Andrew M. Davidoff<sup>3,4</sup>

<sup>1</sup>Department of Haematology, University College London and <sup>2</sup>National Blood Service, United Kingdom; <sup>3</sup>Division of Experimental Hematology and <sup>4</sup>Department of Surgery, St Jude Children's Research Hospital, Memphis, TN; <sup>5</sup>Department of Haematology, National Institute for Biological Standards and Control, Pottery Bar, United Kingdom; and <sup>6</sup>Katharine Dormandy Haemophilia Centre, London, United Kingdom

*Haemophilia* (2006), 12, (Suppl. 3), 42–51

### Strategies towards a longer acting factor VIII

E. L. SAENKO\* and S. W. PIPE†

\*Center for Vascular and Inflammatory Diseases, University of Maryland School of Medicine, Baltimore, MD, USA; and

†Department of Pediatrics, University of Michigan, Ann Arbor, MI, USA

Research article  Related Commentary, page 1840

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

Qizhen Shi,<sup>1,2,3</sup> David A. Wilcox,<sup>1,2,3</sup> Scot A. Fahs,<sup>1</sup> Hartmut Weiler,<sup>1,2</sup> Clive W. Wells,<sup>2</sup> Brian C. Cooley,<sup>2</sup> Drashti Desai,<sup>1,2,3</sup> Patricia A. Morawiec,<sup>1</sup> Jack Gorski,<sup>1,2</sup> and Robert R. Montgomery<sup>1,2,3</sup>

<sup>1</sup>Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, Wisconsin, USA, <sup>2</sup>Departments of Pediatrics, Physiology, Microbiology, and Orthopedics, Medical College of Wisconsin, Milwaukee, Wisconsin, USA, <sup>3</sup>Children'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 Manno<sup>1,2,15</sup>, Glenn F Pierce<sup>3,15</sup>, Valder R Arruda<sup>1,2,15</sup>, Bertil Glader<sup>4,15</sup>, Margaret Ragni<sup>5</sup>, John J E Rasko<sup>6</sup>, Margaret C Ozelo<sup>7</sup>, Keith Hoots<sup>8</sup>, Philip Blatt<sup>9</sup>, Barbara Konkle<sup>10</sup>, Michael Dake<sup>4</sup>, Robin Kaye<sup>1,2</sup>, Mahmood Razavi<sup>3</sup>, Albert Zajko<sup>10</sup>, James Zehnder<sup>5</sup>, Pradip K Rustagi<sup>11</sup>, Hiroyuki Nakai<sup>4</sup>, Amy Chew<sup>1,3</sup>, Debra Leonard<sup>2,12</sup>, J Fraser Wright<sup>3</sup>, Ruth R Lessard<sup>3</sup>, Jürg M Sommer<sup>3</sup>, Michael Tigges<sup>3</sup>, Denise Sabatino<sup>1</sup>, Alvin Luk<sup>3</sup>, Haiyan Jiang<sup>3</sup>, Federico Mingozzi<sup>1</sup>, Linda Couto<sup>3</sup>, Hildegund C Ertl<sup>1,13</sup>, Katherine A High<sup>1,2,14</sup> & Mark A Kay<sup>4</sup>

nature  
medicine

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## *Cause to Cures*

## Improving Blood Safety and Availability

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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.*

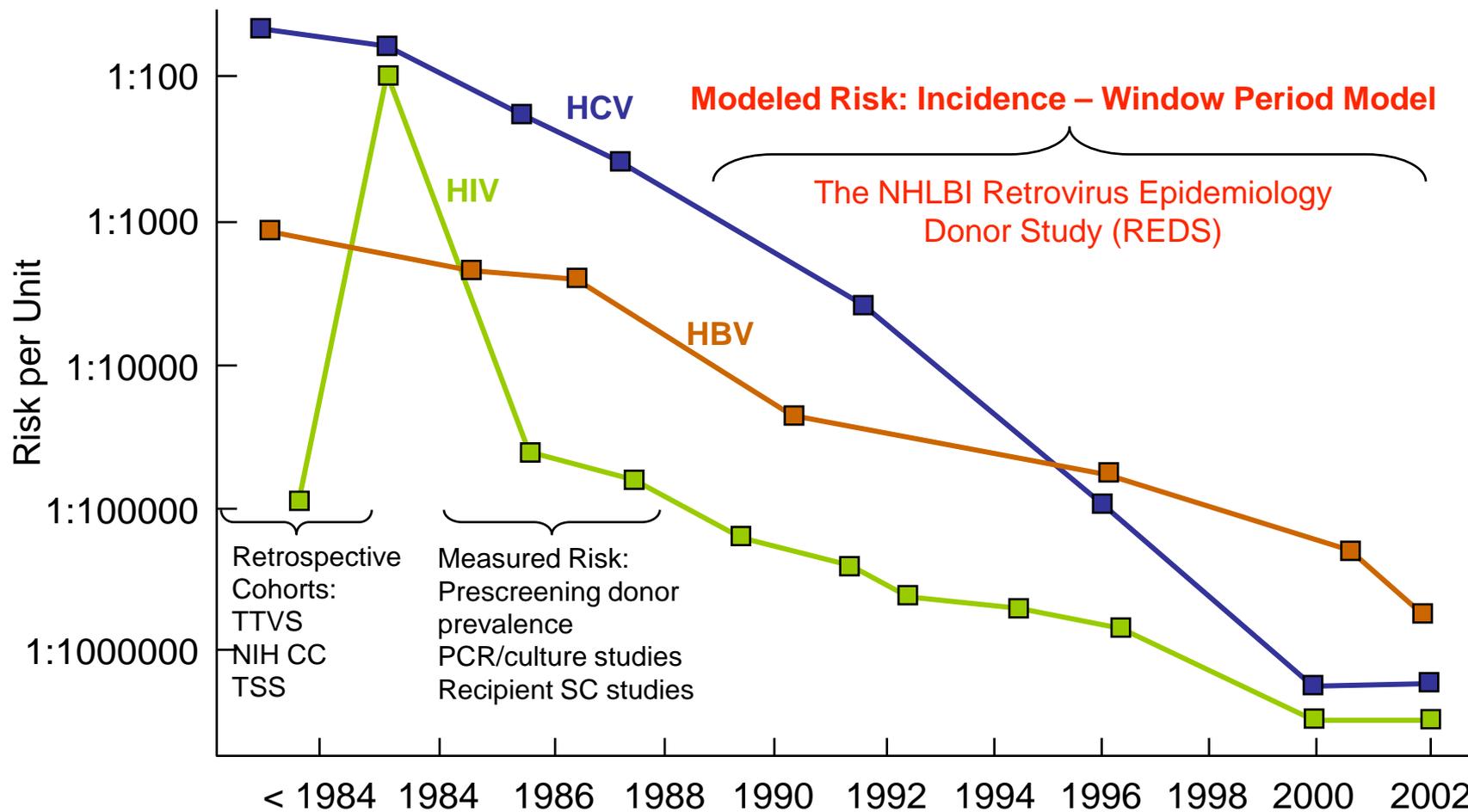


### **Quality Donor System™ (QDS)**

### **Audio Visual Touch Screen Computer Assisted Self Interviewing (AVT-CASI)**

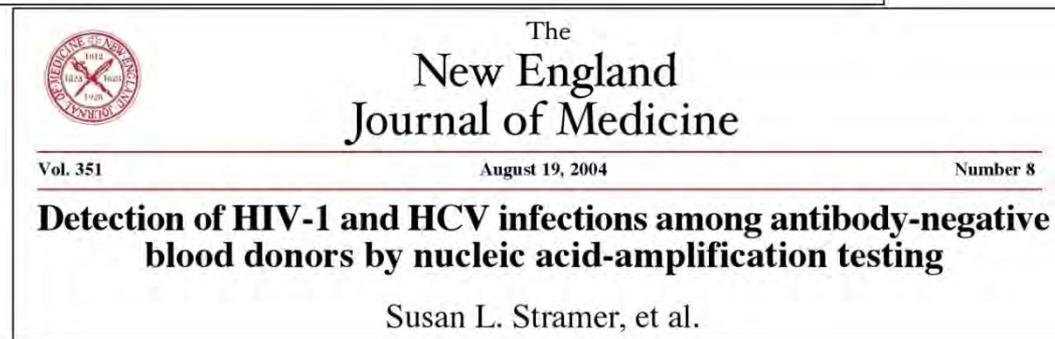
Paul D. Cumming, PhD - Talisman Limited - SBIR

# Increasing the Safety of the Blood Supply



Provided by Michael Busch, Blood Systems Research Institute, SF

# Increasing the Safety of the Blood Supply



JAMA 2003. 289;8

**CONTEMPO UPDATES**  
LINKING EVIDENCE AND EXPERIENCE

## Current and Emerging Infectious Risks of Blood Transfusions

Michael P. Busch, MD, PhD

Steven H. Kleinman, MD

George J. Nemo, PhD

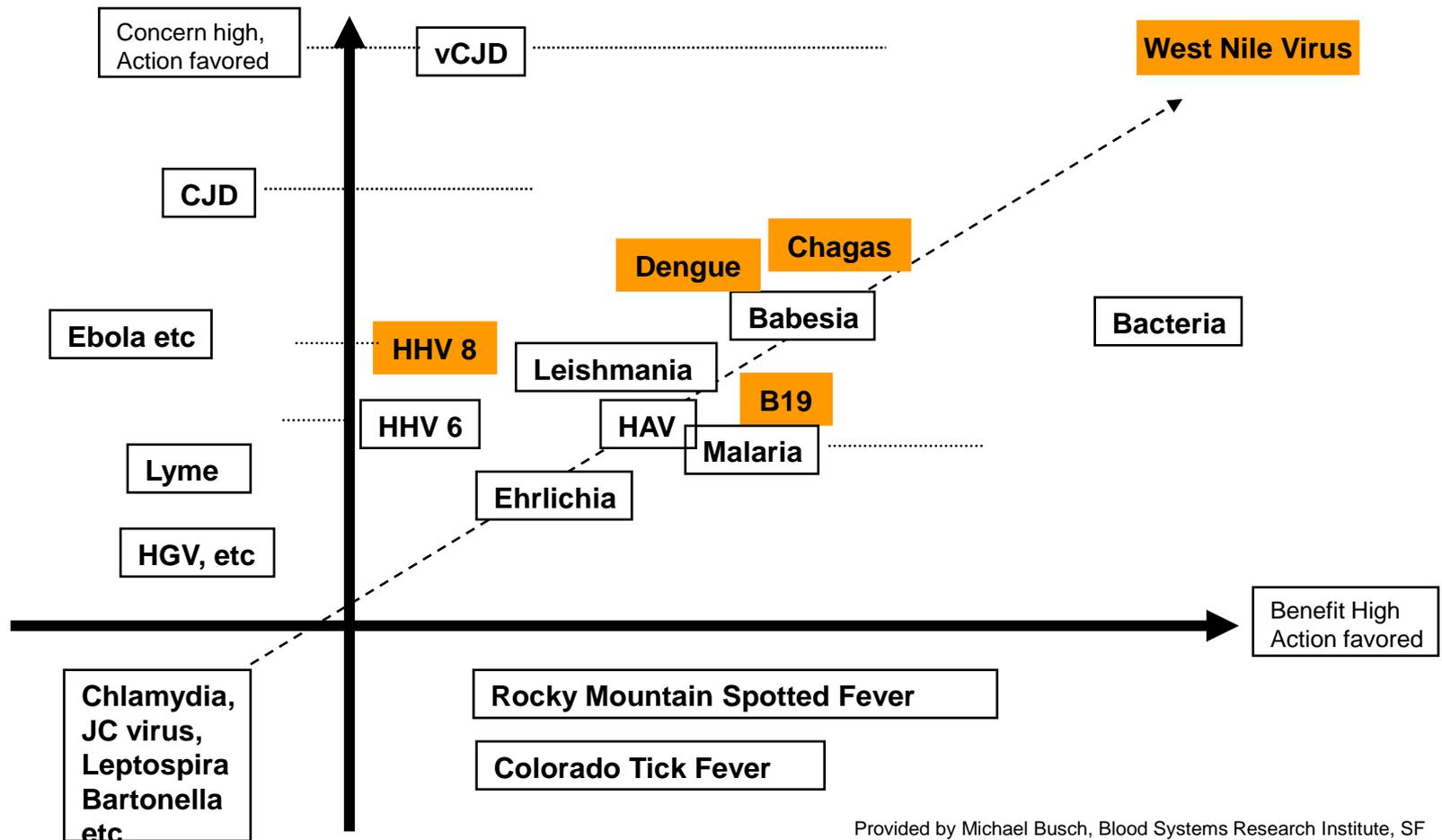
countries where resources are insufficient to enable basic infectious disease donor screening.

**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



idprio2001

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)

Journal of Medical Virology 78:S30-S35 (2006)

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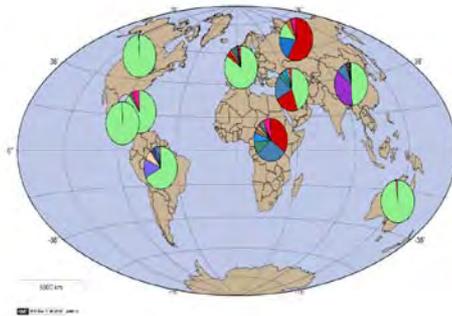
### Surveillance of the Genetic Variation in Incident HIV, HCV, and HBV Infections in Blood and Plasma Donors: Implications for Blood Safety, Diagnostics, Treatment, and Molecular Epidemiology

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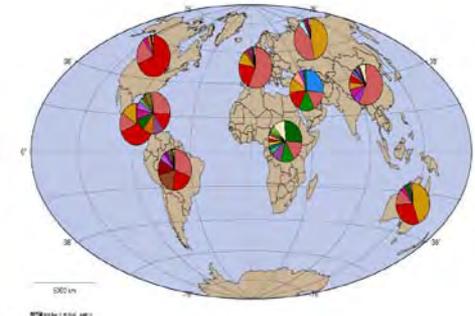
Eric Delwart,<sup>1\*</sup> Mary C. Kuhns,<sup>2</sup> and Michael P. Busch<sup>1</sup>

<sup>1</sup>Blood Systems Research Institute, and Department of Laboratory Medicine, University of California, San Francisco, California

<sup>2</sup>Abbott Diagnostics, Abbott Park, Illinois



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



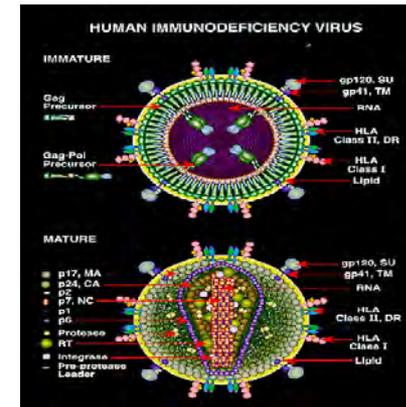
Global distribution of HCV genotypes  
At <http://hcv.lanl.gov/content/hcv-db/index>

# 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).

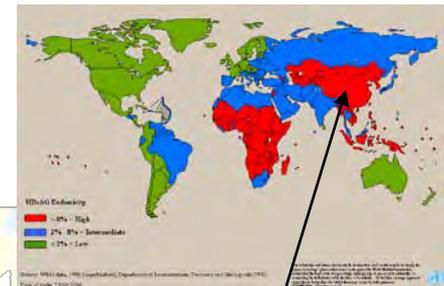


<http://www.niaid.nih.gov/daids/dtpdb/VIRTARG.asp>

Hepatitis B



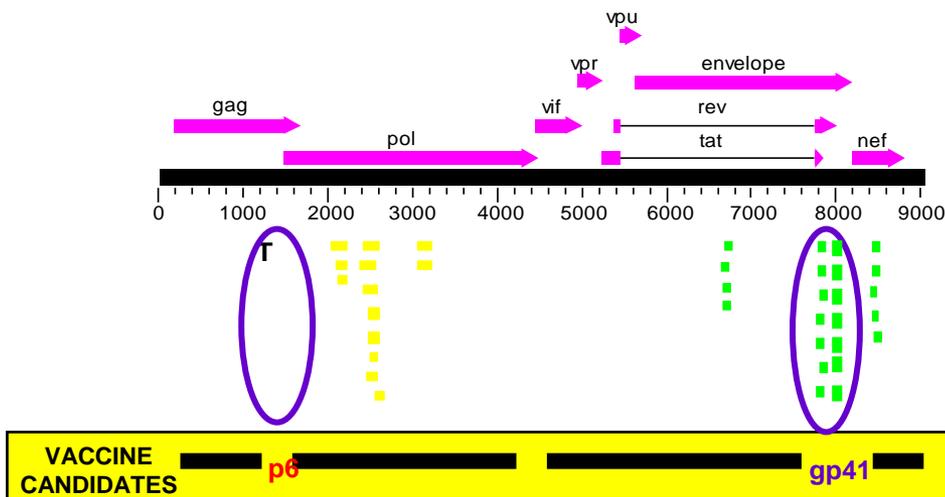
BRAZIL



CHINA

# A Novel Assay for Differential Diagnosis of HIV Infections in the Face of Vaccine Induced Antibodies

*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

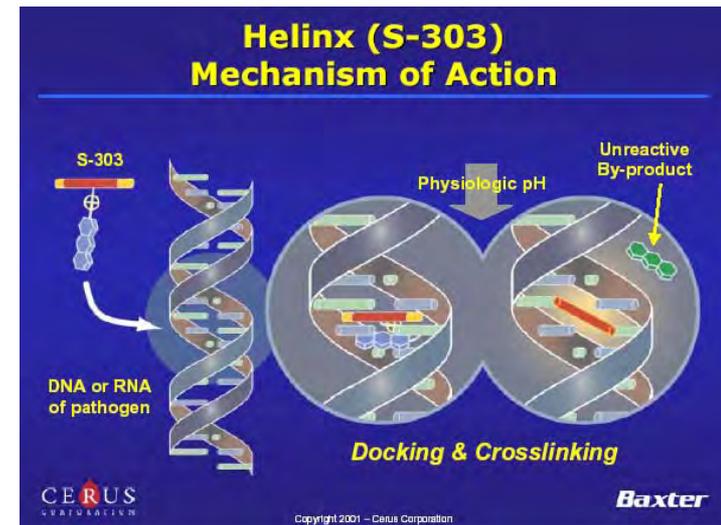
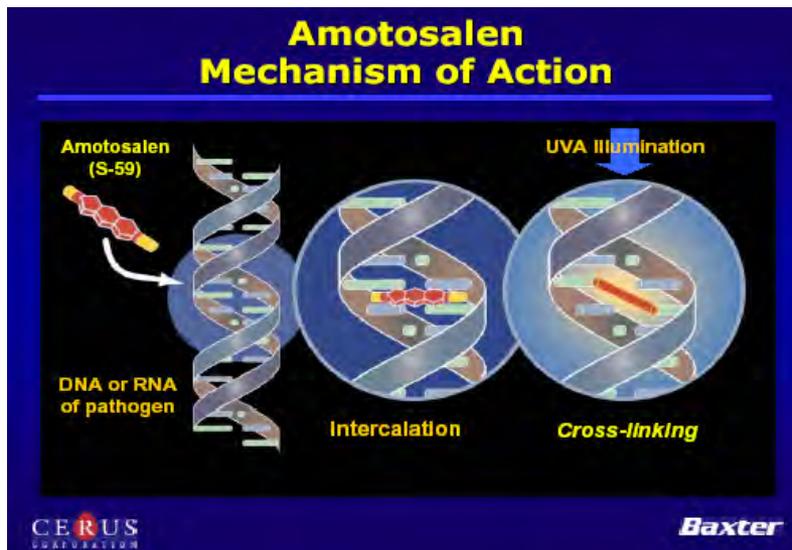
- based on the Gag-p6 and Env-gp41 peptides which are recognized soon after infection, are not protective epitopes and are therefore, not part of putative HIV vaccines being developed.
- is 99% specific and sensitive for detecting true HIV infection
- does not detect HIV vaccine-generated antibodies.

Khurana, S, Needham, J., Mathieson, et al. B.Human Immunodeficiency Virus (HIV) Vaccine Trials: a Novel Assay for Differential Diagnosis of HIV Infections in the Face of Vaccine-Generated Antibodies. *Journal of Virology*, 2006, Vol. 8, No. 5, 2092/2099, March 2006.

# Blood Safety

## Development of New Technologies

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.

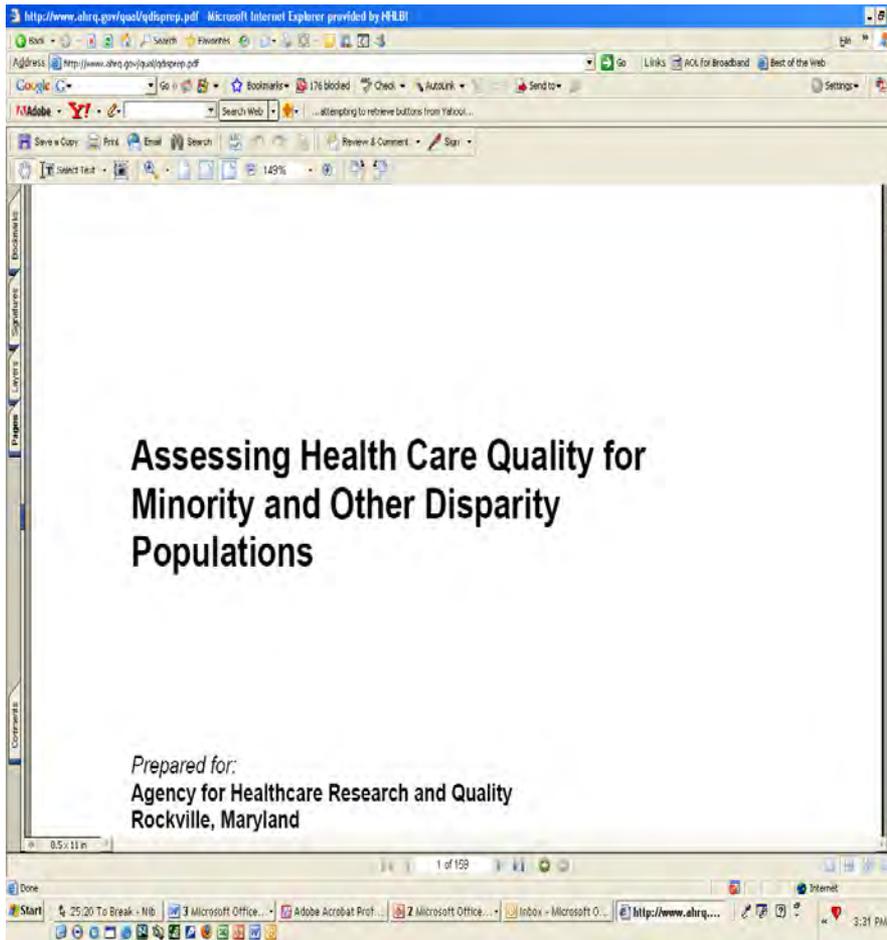


## ***Cause to Cures, con't.*** **Translating Research into Practice**

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Improving public health – sickle cell disease

# Enhancing the Evidence Available to Guide the Practice of Medicine and Improve Public Health



## 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

# Enhancing the Evidence Available to Guide the Practice of Medicine and Improve Public Health: SCD Objectives



The screenshot shows the top portion of a website. On the left is the NHLBI logo and name. In the center, it says "Sickle Cell Disease: Health Objectives Working Group Blood Diseases Branch" and "National Heart, Lung, and Blood Institute (NHLBI) Baltimore, MD" with the date "September 15, 2006". On the right, there are search and navigation options.

Department of Health and Human Services • National Institutes of Health  
National Heart Lung and Blood Institute  
People Science Health

Information for...Researchers

home » Information for Researchers » Workshop, Meeting Summaries, Scientific Reports

Sickle Cell Disease: Health Objectives Working Group  
Blood Diseases Branch

National Heart, Lung, and Blood Institute (NHLBI)  
Baltimore, MD

September 15, 2006

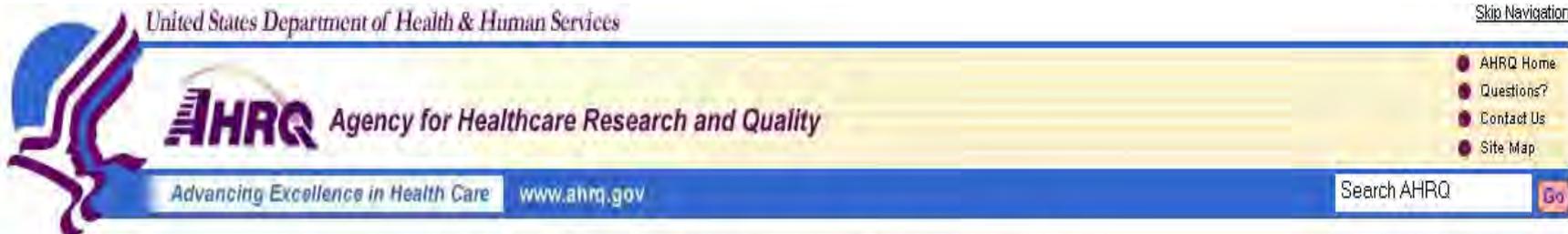
TEXT SIZE: S M L  
HOME SITE INDEX CONTACT US

Search  
TIPS ADVANCED SEARCH

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.

<http://www.nhlbi.nih.gov/meetings/workshops/scd-healthobj.htm>

# Enhancing Evidence Available to Guide the Practice of Medicine and Improve Public Health



[What's New](#)   [Browse](#)   [Información en español](#)

**You Are Here:** [AHRQ Home](#) > [News & Information](#) > [AHRQ News & Numbers](#) > [First Look at Sickle Cell Disease Hospitalizations in 10 Years](#)

## 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, 2,000 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 5 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.
- Medicaid paid for 65 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—699 adults and 47 children.
- In-hospital deaths of children remained low and constant from 1994 to 2004.

<http://www.ahrq.gov/news/nn/nn122006.htm>

# Generating an Improved Understanding of the Process Involved in Translating Research into Practice



The  
**New England  
Journal of Medicine**

Vol. 332

May 18, 1995

Number 20

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**Effect of Hydroxyurea on the Frequency of Painful  
Crises in Sickle Cell Anemia**

Samuel Charache, et al.

American  
Journal of  
**Hematology**

Volume 64  
May 2000

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**Cost-Effectiveness of Hydroxyurea in Sickle Cell Anemia**

Richard D. Moore, et al.

American  
Journal of  
**Hematology**

Volume 81  
December 2006

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**Hospitalization Rates and Costs of Care of Patients With Sickle-  
Cell Anemia in the State of Maryland in the Era of Hydroxyurea**

Sophie Lanzkron, et al.

# Challenge: To Promote the Development and Implementation of Evidence-Based Guidelines

The screenshot shows the NIH Consensus Development Program website. The page is titled "NIH Consensus Development Program" and has a navigation menu with links for "Home", "About Us", "Previous Conference Statements", "CME", and "FAQs". The main content is divided into three columns: "Upcoming Conferences", "Recent Conferences", and "Background".

**Upcoming Conferences:**

- NIH State-of-the-Science Conference: Prevention of Fecal and Urinary Incontinence in Adults**  
December 10-12, 2008
- NIH Consensus Development Conference: Hydroxyurea Treatment for Sickle Cell Disease**  
February 26-27, 2008  
*More Information Coming Soon*
- NIH Consensus Development Conference: Management of Chronic Hepatitis B**  
October 20-22, 2008  
*More Information Coming Soon*

**Recent Conferences:**

- NIH State-of-the-Science Conference on Tobacco Use: Prevention, Cessation and Control**  
June 12-14, 2006  
[FINAL Statement](#)  
[Program and Abstract Book](#)  
[NIH Press Release](#)  
[Webcast Archive](#) [Day 1](#), [Day 2](#) and [Day 3](#)
- NIH State-of-the-Science Conference on Multivitamin/Mineral Supplements and Chronic Disease Prevention**  
May 15-17, 2006  
[FINAL Statement](#)  
[NIH Press Release](#)  
[Program and Abstract Book](#)  
[Webcast Archive](#) [Day 1](#), [Day 2](#), [Day 3](#)
- NIH State-of-the-Science Conference: Cesarean Delivery on Maternal Request**  
March 27-29, 2006  
[FINAL Statement](#)  
[News Release](#)  
[NIH Radio](#) - Free mp3 audio report to play or download  
[Webcast](#) [Day 1](#), [Day 2](#), [Day 3](#)  
[Program and Abstract Book](#)  
[Systematic Literature Review \(AHRQ\)](#)
- NIH State-of-the-Science Conference on Manifestations and Management of Chronic Insomnia in Adults**  
June 13-15, 2005 FINAL Statement Posted  
[News Release](#) [pdf version](#)  
[Webcasts from Day 1](#), [Day 2](#), [Day 3](#)  
[Program and Abstract Book](#)  
[Systematic Literature Review \(AHRQ\)](#)
- NIH State-of-the-Science Conference on Management of Menopause-Related Symptoms**  
March 21-23, 2005 FINAL Statement Posted  
[News Release](#)  
[Webcasts from Day 1](#), [Day 2](#), [Day 3](#)  
[Program and Abstract Book](#)  
[Systematic Literature Review \(AHRQ\)](#)

**Background:**

- [Topic Selection](#)
- [Panelists](#)
- [Speakers](#)
- [Sponsors](#)
- MEDICINE IN THE MEDIA:**  
[The Challenge of Reporting on Medical Research](#)
- MOVING FROM OBSERVATIONAL STUDIES TO CLINICAL TRIALS:**  
[Why Do We Sometimes Get It Wrong?](#)

The browser window title is "Upcoming Conferences - Microsoft Internet Explorer provided by NHLBI". The address bar shows "http://consensus.nih.gov/". The taskbar at the bottom shows the Start button, system clock (11:29 AM), and several open applications including "Upcoming Con...".

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



**PROMIS** Patient-Reported Outcomes Measurement Information System  
*Dynamic Tools to Measure Health Outcomes From the Patient Perspective*

Search... GO

Home

**What is PROMIS?**

- Overview
- Position on Roadmap
- Goals
- Research Objectives

Network Structure

Network Activities

Reference Materials

Instruments and Tools

About the NIH Roadmap

FAQs

## What Is PROMIS? Overview

The Patient-Reported Outcomes Measurement Information System (PROMIS) initiative establishes a collaborative relationship between NIH and individual research teams through a cooperative agreement (U01) mechanism. The broad objectives of the PROMIS network are to:

- Develop and test a large bank of items measuring patient-reported outcomes
- Create a computerized adaptive testing system that allows for efficient, psychometrically robust assessment of patient-reported outcomes in clinical research involving a wide range of chronic diseases
- Create a publicly available system that can be added to and modified periodically and that allows clinical researchers to access a common repository of items and computerized adaptive tests.

The network will collaborate on the collection of self-reported data from diverse populations of individuals with a variety of chronic diseases, using agreed-upon methods, modes, and questionnaires.

“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/>

# Sickle Cell Health-Related Quality of Life (SCHRe-QoL) Measurement Information System



Microsoft Access - [1-Pain]

File Edit View Insert Format Records Tools Window Help

MS Sans Serif 8

ID: 13

ITEM CHARACTERISTICS	ITEM WORDING	ITEM TESTING	STATISTICAL CHARACTERISTICS
<p>Subdomain: 2 Severity</p> <p>Response Time Frame 1</p> <p>Corresponding PROMIS Items</p>	<p>Current Version of Item</p> <p>In the past 7 days, on how many days was your pain so intense you needed narcotics to treat it?</p> <p>Response Scale</p> <ul style="list-style-type: none"><li>  0 days</li><li>  1 day</li><li>  2 days</li><li>  3 days</li><li>  4 days</li><li>  5 days</li><li>  6 days</li><li>  7 days</li></ul>	<p>Should item be cog tested in round 1? <input checked="" type="checkbox"/></p> <p>Group for Round 1: [Dropdown]</p> <p>Survey Order No. [Text]</p> <p>Should item be cog tested in round 2? <input checked="" type="checkbox"/></p> <p>Group for Round 2: [Dropdown]</p> <p>Has item been deleted? <input type="checkbox"/></p> <p>Reason item was deleted [Text]</p> <p>Original Version of Item:</p> <p>In the past 7 days, how often was your pain so intense you needed narcotics to treat it?</p> <ul style="list-style-type: none"><li>  0 times</li><li>  1 time</li><li>  2 or more times</li></ul>	<p>Percentage of tailored inapplicables [Text]</p> <p>Item Mean [Text]</p> <p>Item Standard Deviation [Text]</p> <p>Item Range of Observed Values [Text]</p> <p>Notes [Text]</p>

Record: 8 of 42

Unique Identifier

NUM

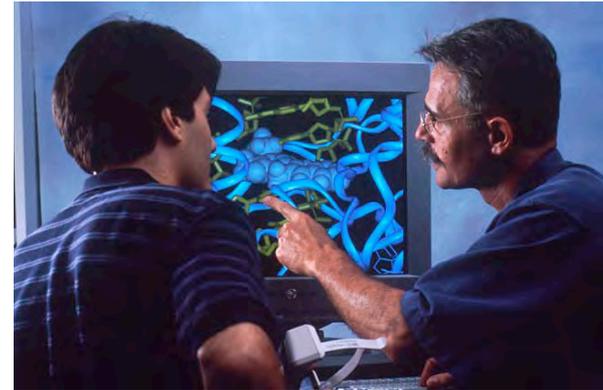
Start SCHReQoL Item Databa... 1-Pain 9:34 AM

## *Strategies*

Training and Mentoring of Emerging Scientists and Physicians

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# 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

Faculty

# 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

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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**

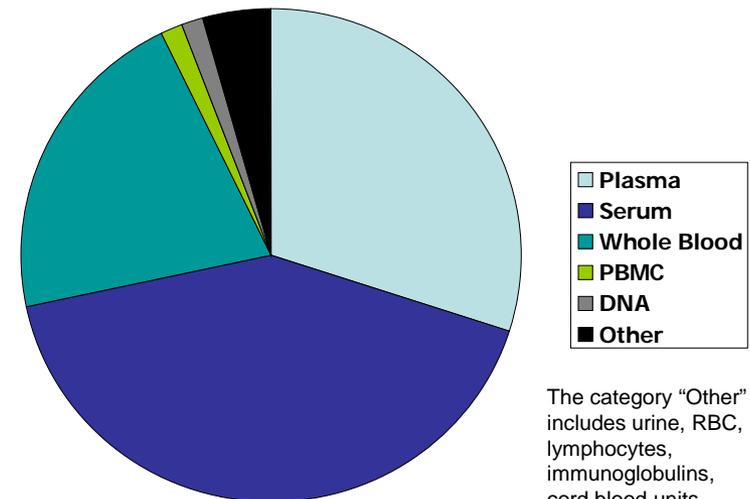
- Managed since the mid-1970s by the Division of Blood Diseases and Resources, Transfusion Medicine and Cellular Therapeutics Branch, NHLBI.
- Currently resides at SeraCare Bioservices in Gaithersburg, MD.
- Information on the NHLBI Repository can be viewed at <http://www.nhlbi.nih.gov/resources/medres/reposit/reposit.htm>.



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**



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.



Production Assistance for Cellular Therapies



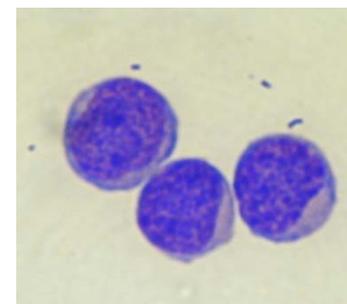
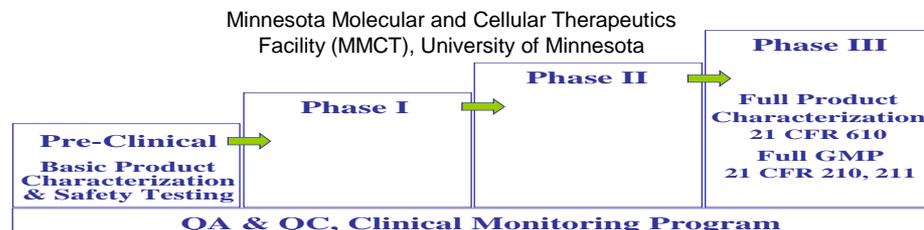
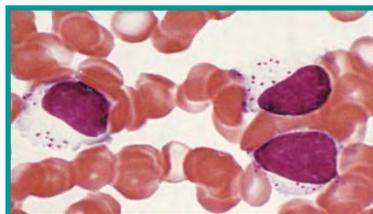
Center for Cell and Gene Therapy (CAGT), Baylor College of Medicine



Minnesota Molecular and Cellular Therapeutics Facility (MMCT), University of Minnesota



University of Pittsburgh Cancer Institute (UPCI)



# 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

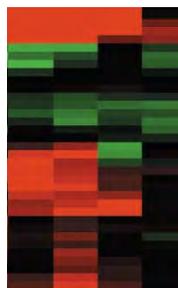
- Transform medicine and health from a Curative to a Preemptive paradigm
- Support basic research to identify the earliest molecular stages of disease in complex biological systems
- Accelerate translation of findings from the bench to the bedside to the community
- Provide the evidence and knowledge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

# Future Directions

**Basic Discovery**

**Clinical**

**Communication**



Genomics



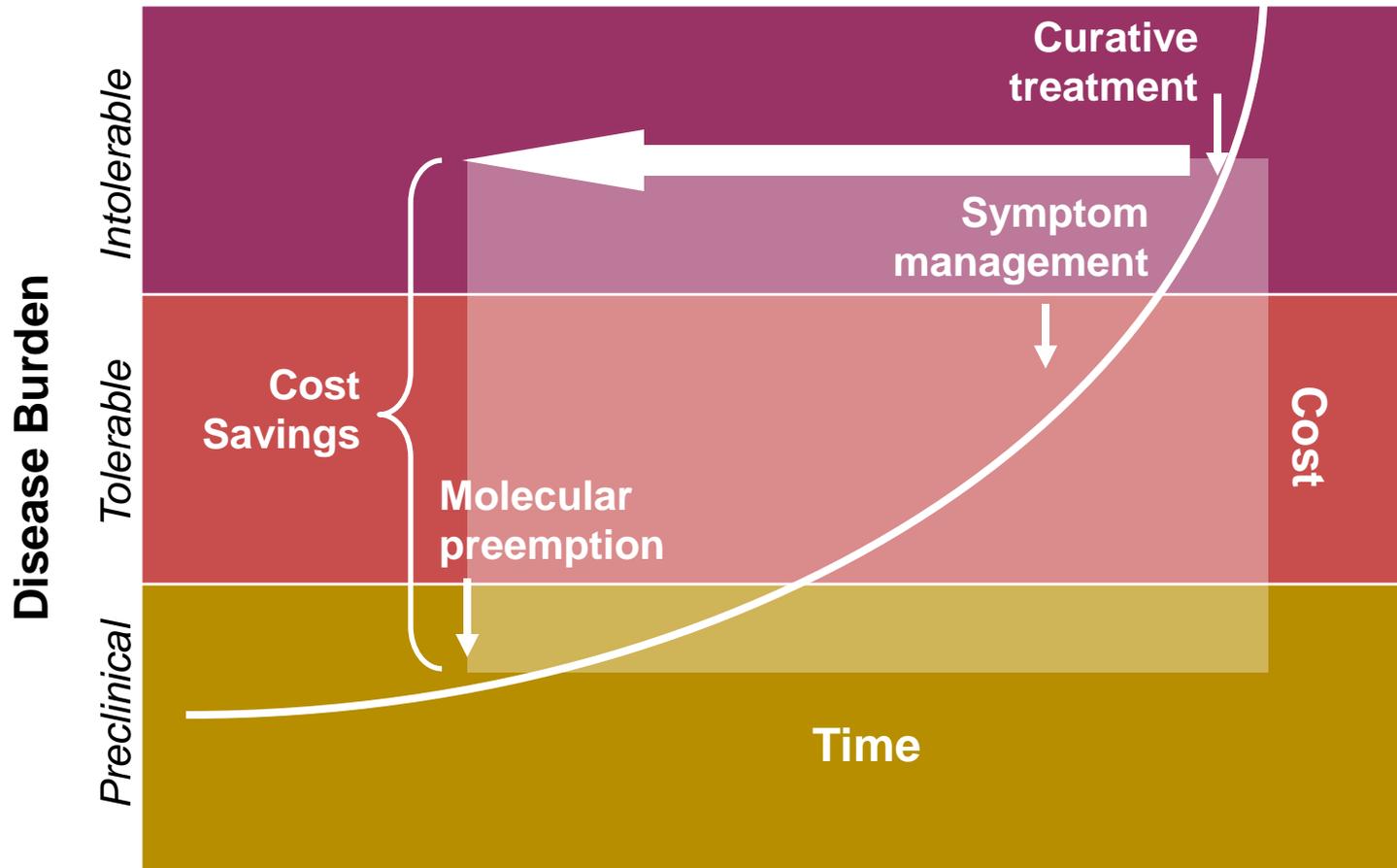
Proteomics



Stem Cell Research  
Tissueogenesis

Cell Imaging  
Translational

# The Future Paradigm: Preempt Disease



# 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.

# Goal One: Form to Function (continued)

## **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.

# Goal Two: Function to Causes (continued)

## **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.

# Goal Three: Causes to Cures (continued)

## **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.