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

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Director, National Heart, Lung, and Blood Institute

November 2007

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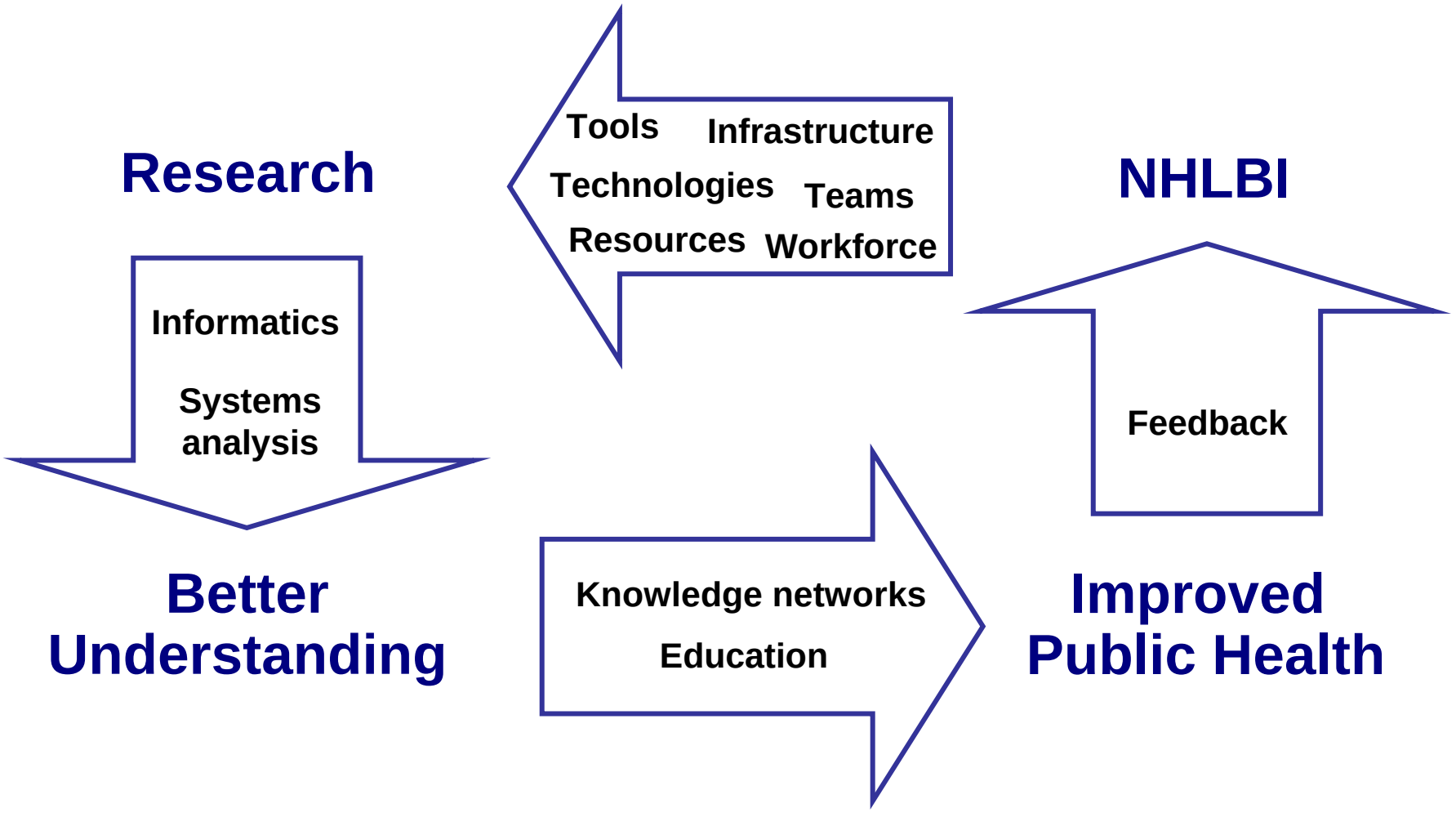
NHLBI's Strategic Plan Promotes Advances in Research Approaches



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Planning Principals

Our Approach

Work in partnership in an ever evolving environment.

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NHLBI Strategic Plan Objectives

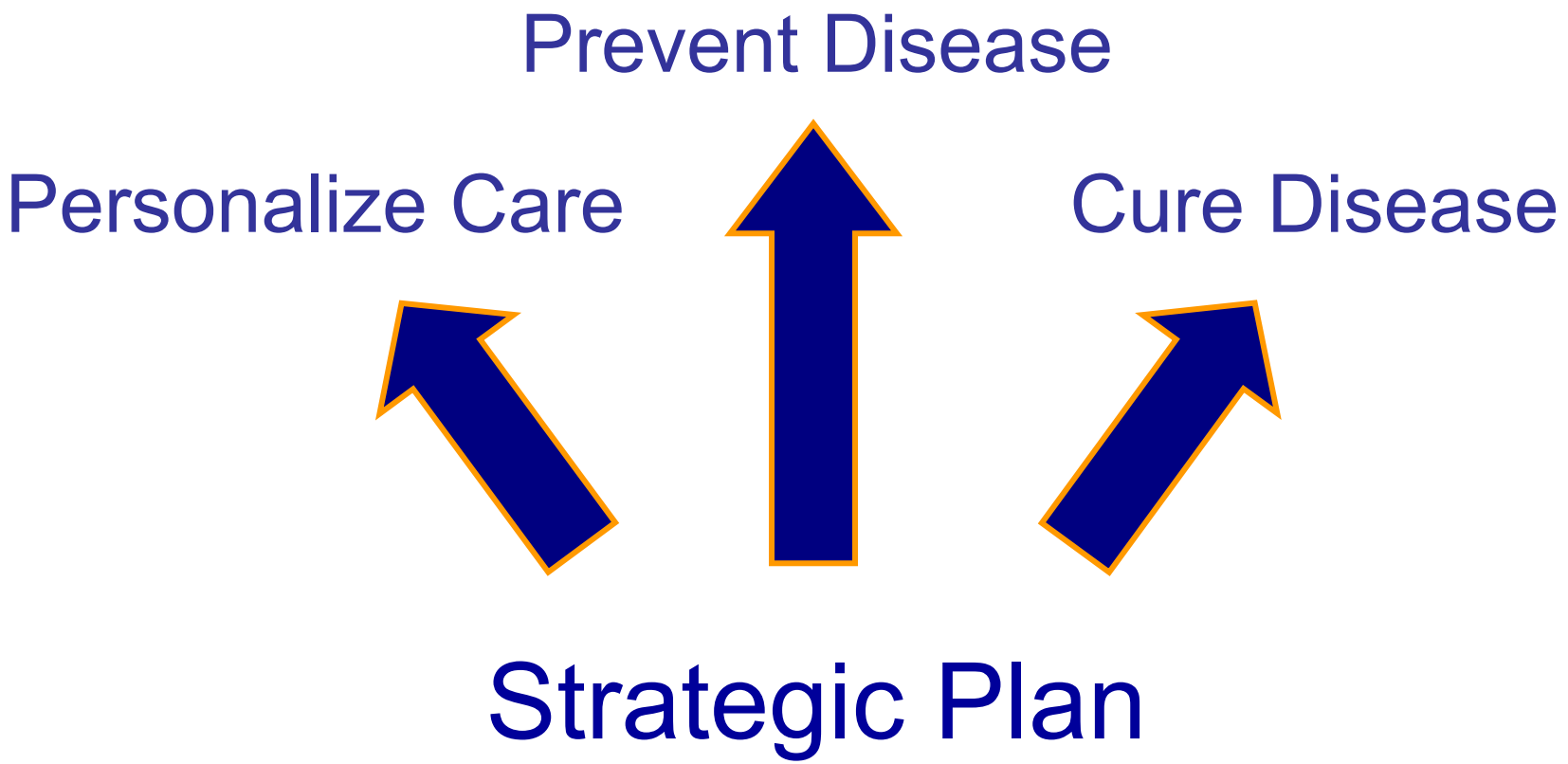
Develop a scientific blueprint for the next decade.

- 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

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



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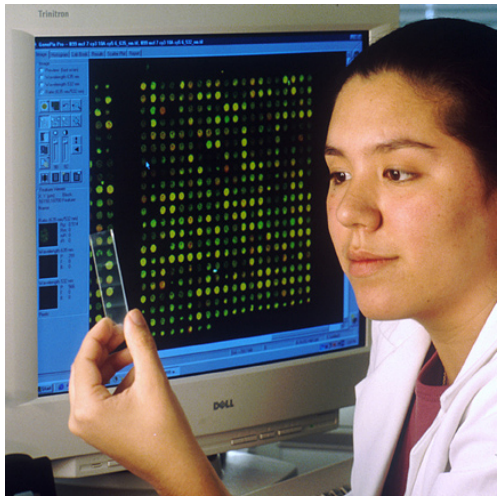
Need to Transform Medical Research in the 21st Century

20th Century	21st Century
Treat disease when symptoms appear and normal function is lost	Intervene before symptoms appear and preserve normal function for as long as possible
Did not understand the molecular and cellular events that lead to disease	Understanding preclinical molecular events and ability to detect patients at risk
Expensive in financial and disability costs	Orders of magnitude more effective

The Future Paradigm: Transform Medicine from Curative to Preemptive



Predictive ⟷ Personalized ⟷ Preemptive

Participatory

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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

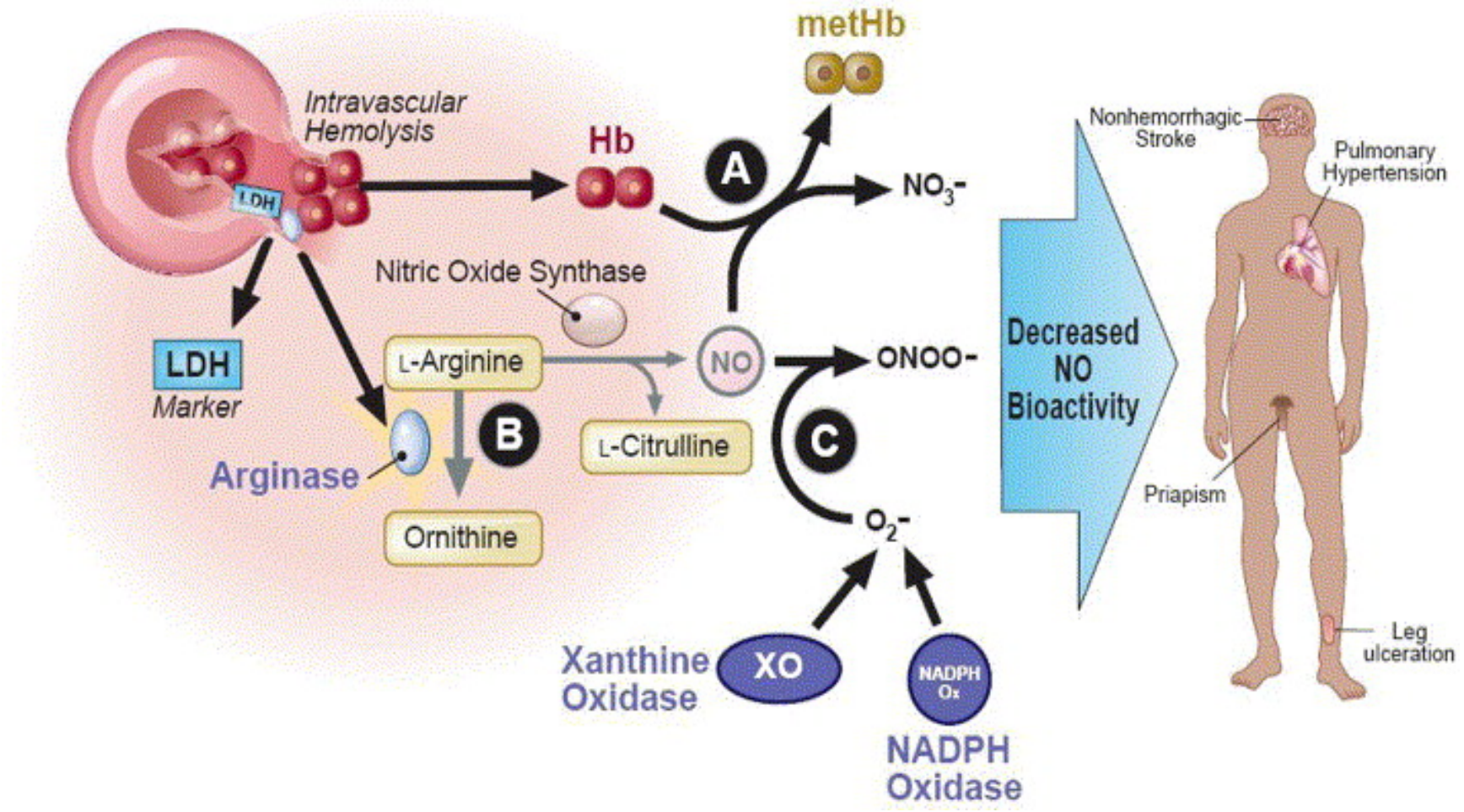
Thrombosis

Bleeding Disorders

Stroke

Stem Cells

Deconstructing Sickle Cell Disease Pathophysiology- The Role of Hemolysis in Clinical Subphenotypes



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

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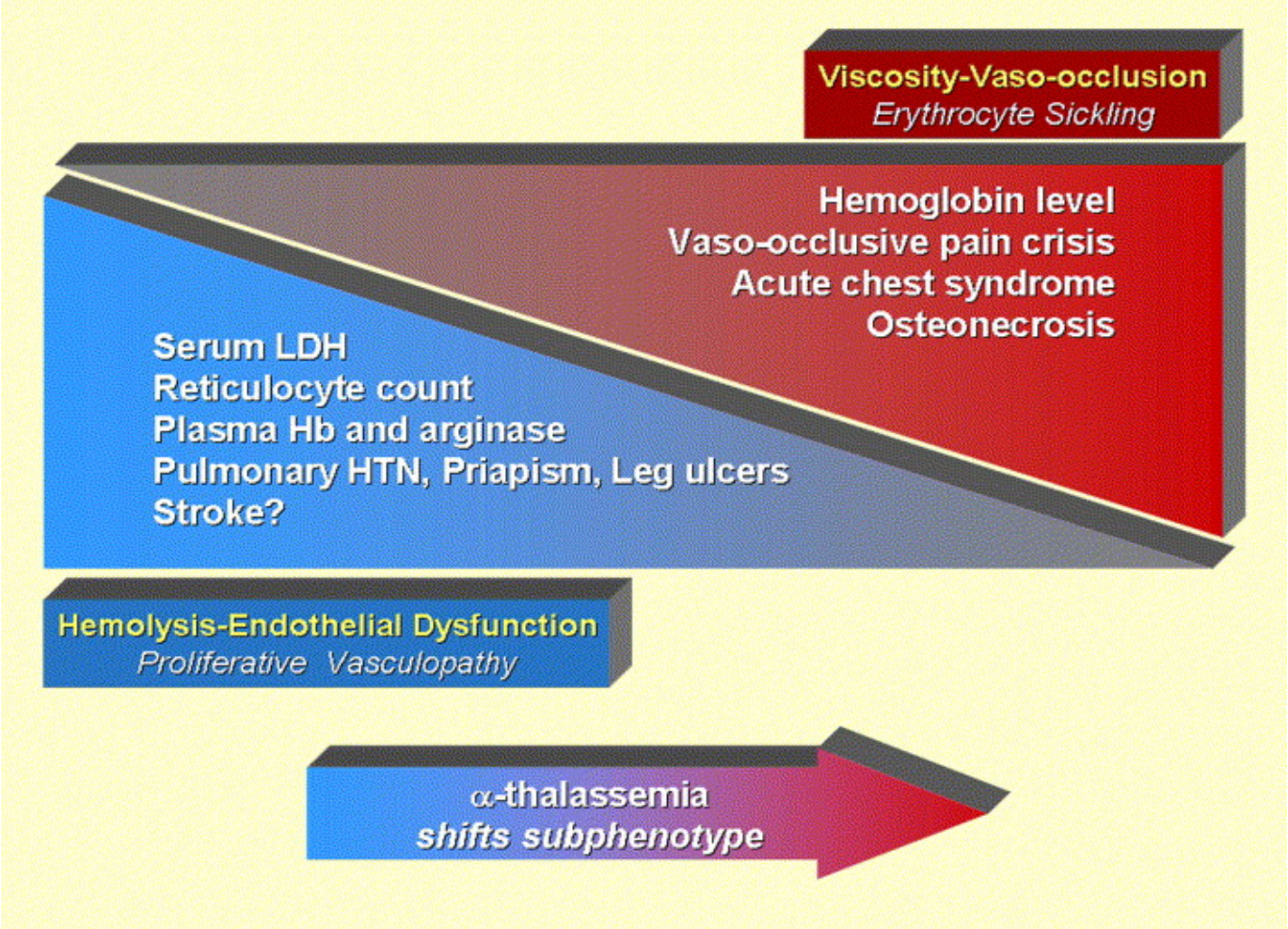
Need for Therapeutic Strategies to Prevent Complications Caused by Two Different Mechanisms



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

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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

Ribosomal Protein S24 Gene Is Mutated in Diamond-Blackfan Anemia

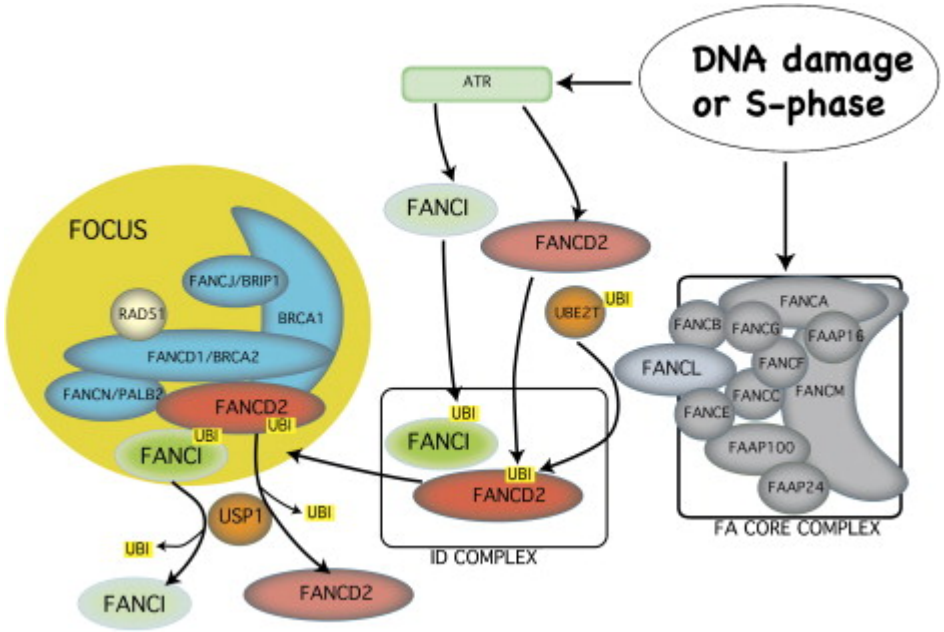
Hanna T. Gazda, et al.

Blood, May 2007

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

Karthik A. Ganapathi, et al.

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

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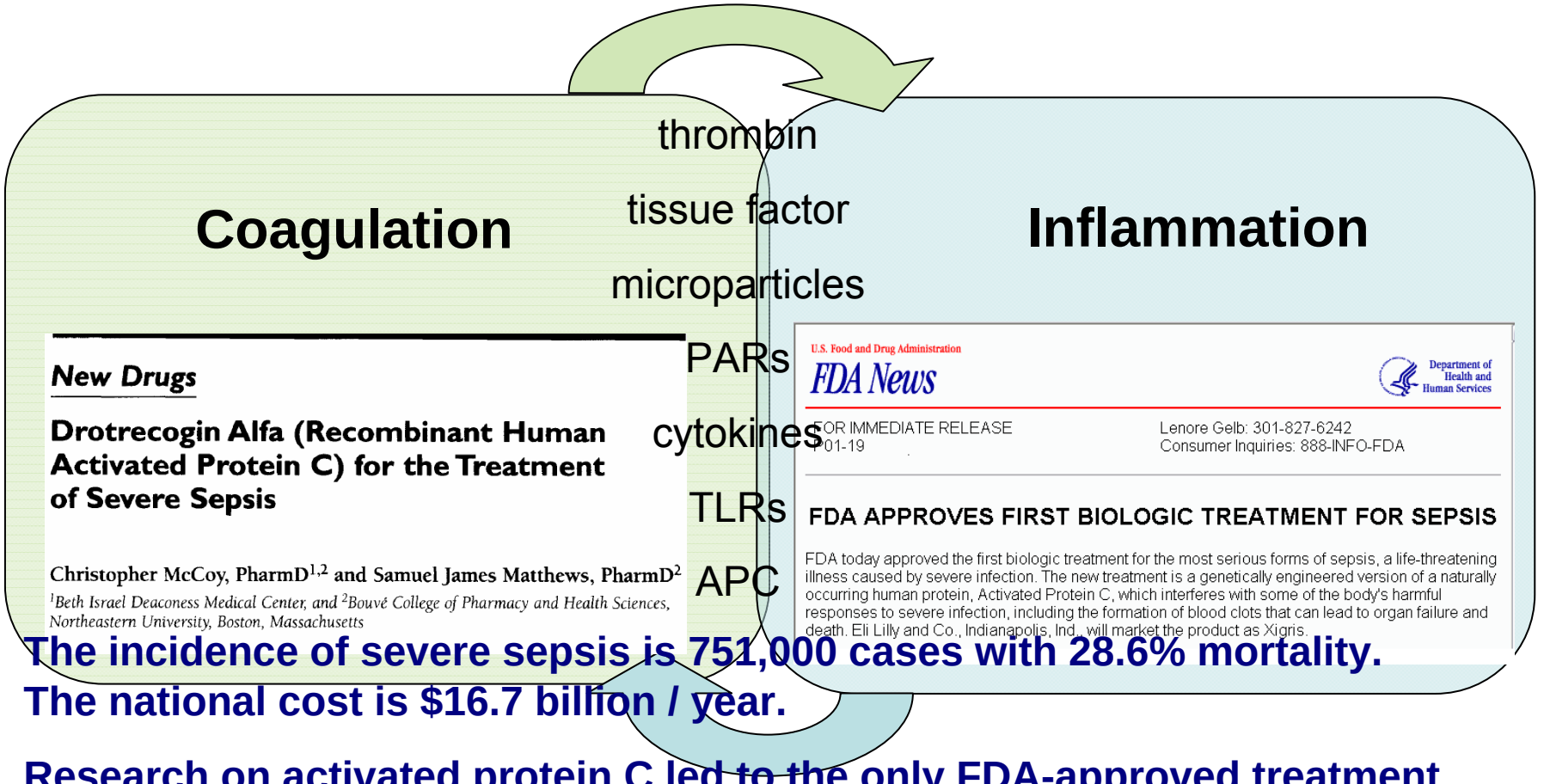
The Interface Between Thrombosis and Inflammation



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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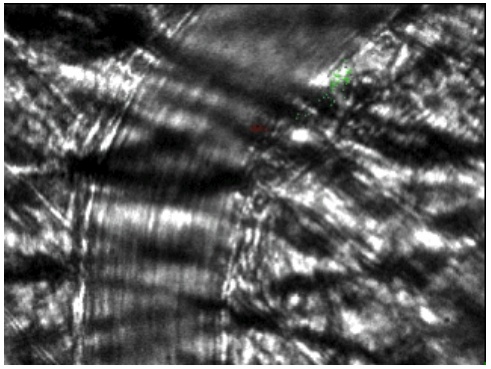
Novel Technologies in Thrombosis and Hemostasis

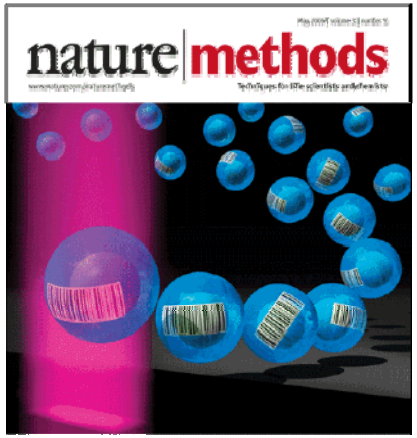


In-vivo visualization provides tool to study pathophysiology of thrombosis and to validate new therapeutic interventions.

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

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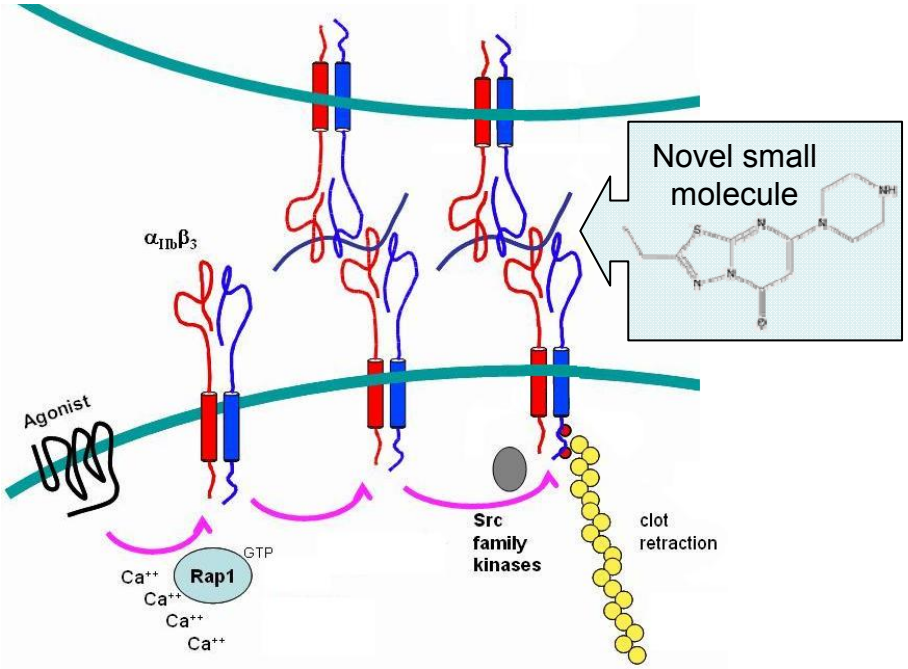
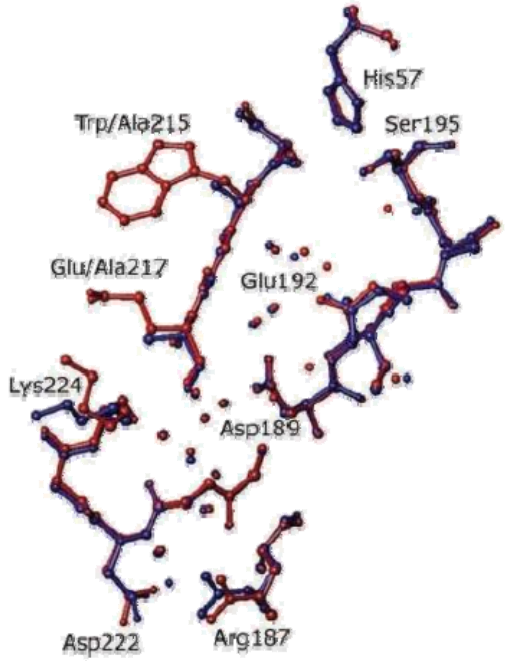
Novel Antithrombotic Drug Development

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

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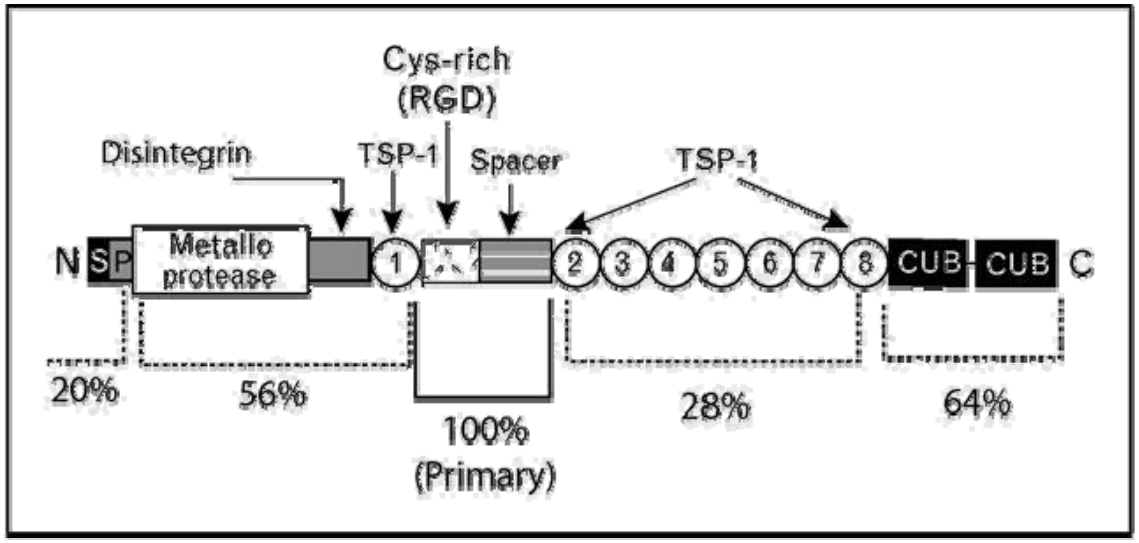
Rare Autoimmune Disorder Leads to Critical Discovery in Thrombosis

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.

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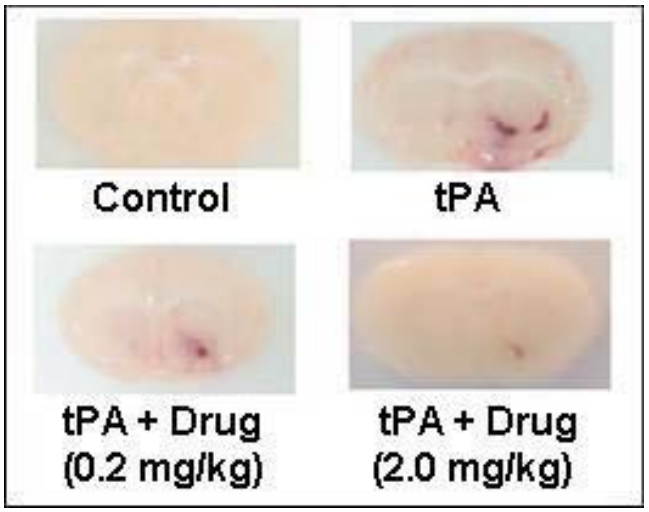
Two Strategies for Improving the Therapy of Stroke

- 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

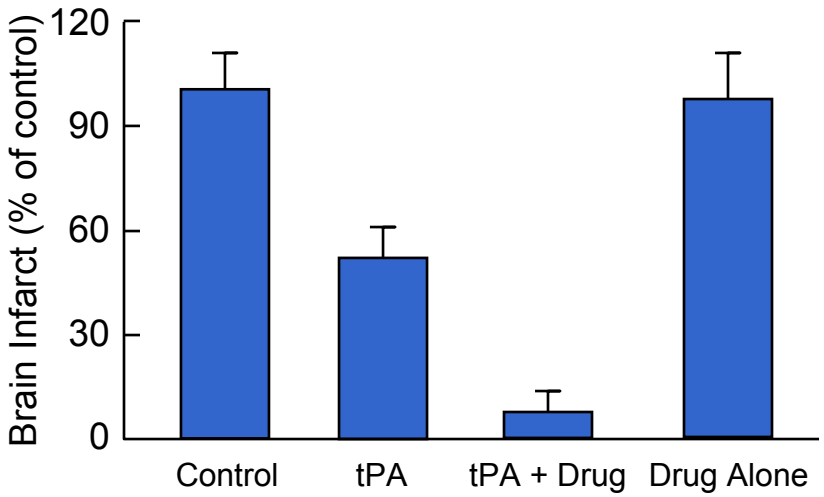
a



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

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

b



Fragment 350-355 neutralized the neurotoxic effects of exogenous and endogenous tPA.

Armstead et al, Nat Neurosci. 2006 Sep;9(9):1150-5

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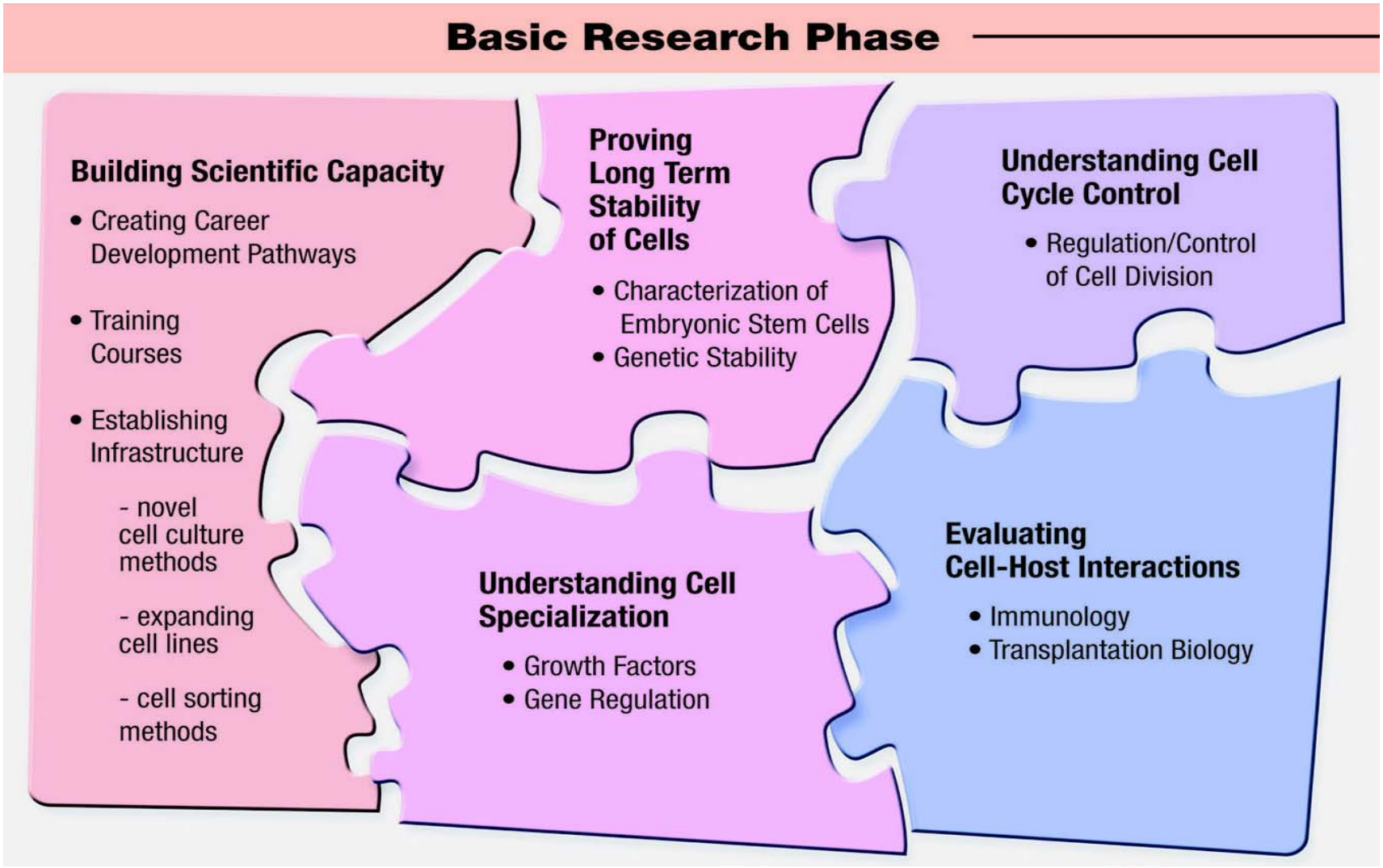
The Scientific Challenges of Human Stem Cells



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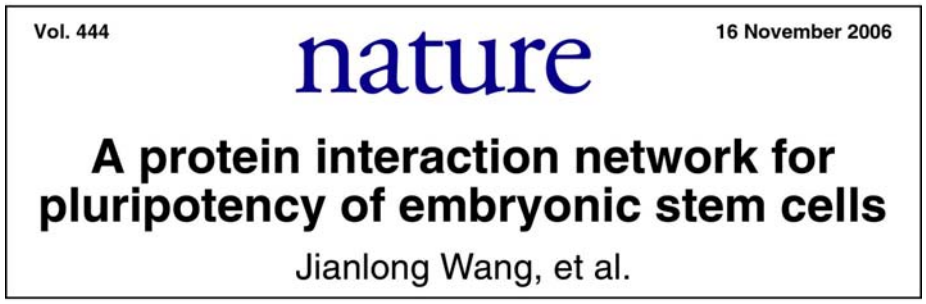
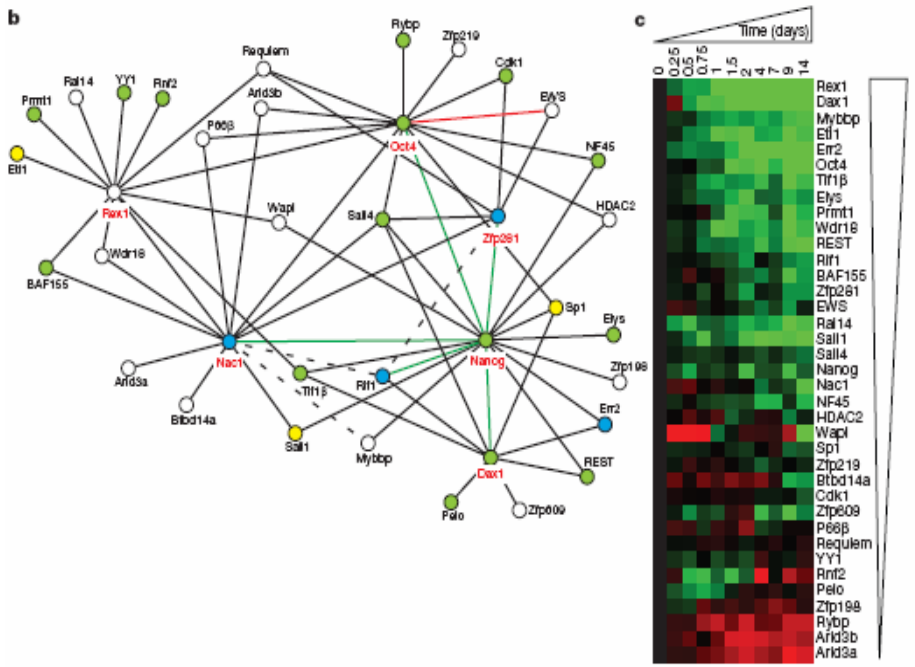
Provided by James Battey, NIDCD, NIH

Stem Cell Biology

Defining a Protein Interaction Network in Embryonic Stem Cells





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.

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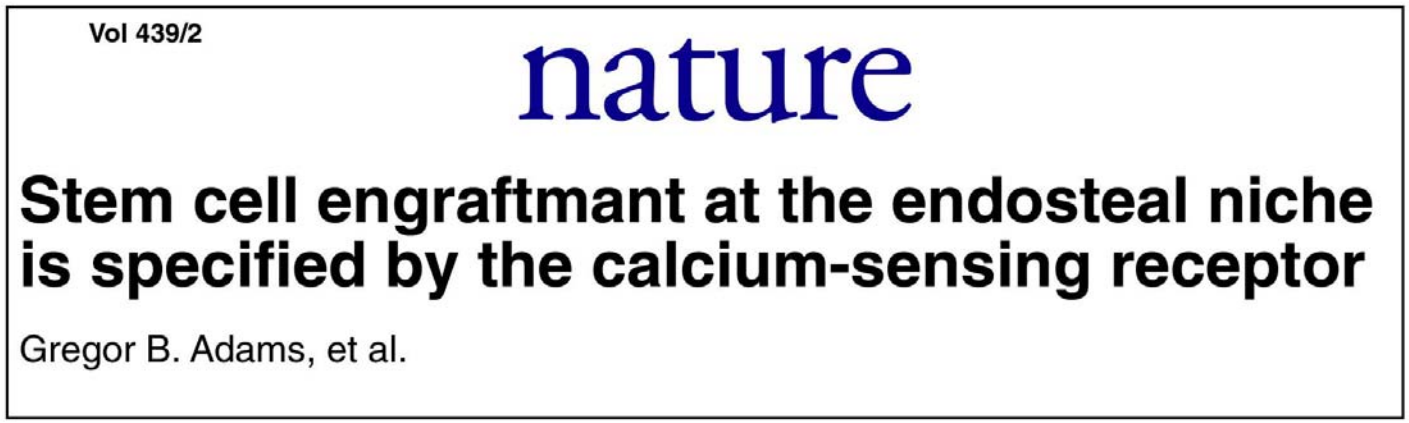
Characterizing the Stem Cell Microenvironment



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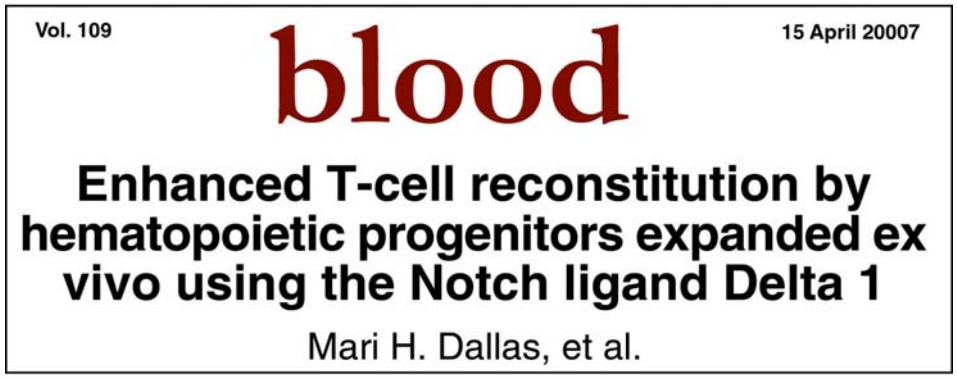
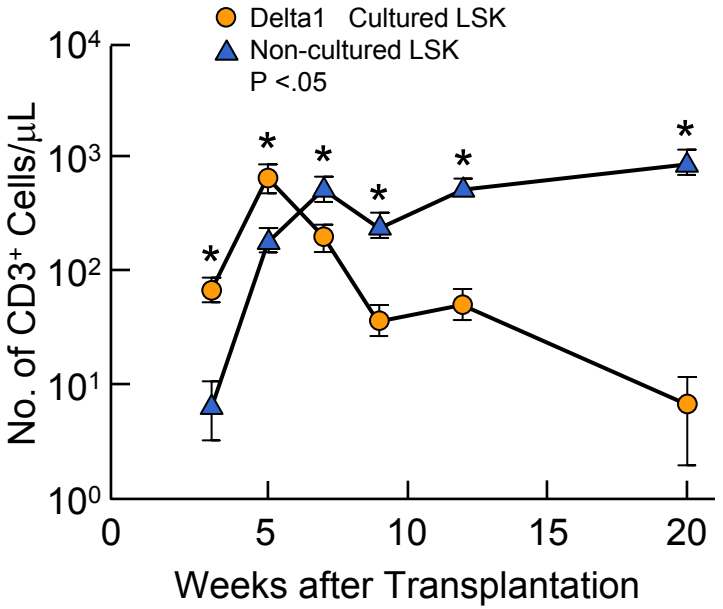
Post-transplant T-cell Immune Reconstitution



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

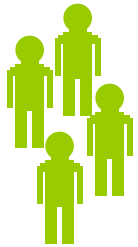
Bench to Bedside to Community + Infrastructure + Research Training

CSCC
Comprehensive Sickle Cell Centers Clinical Trials Consortium

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

Research training from high-school through post-doctorate

Translation to Practice (Goal 3)
- Psychosocial and behavioral research
- Health services research
- Patient reported outcomes

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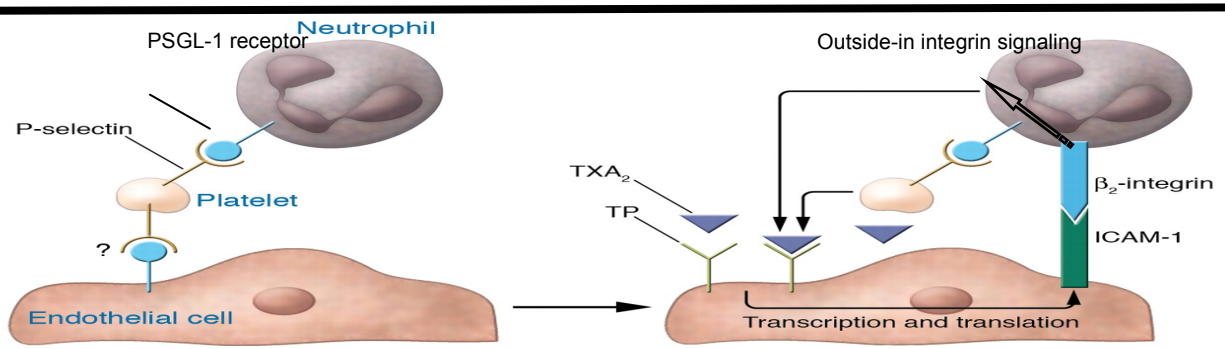
SCCOR in Transfusion Biology and Medicine: Transfusion Related Acute Lung Injury (TRALI)

Bench



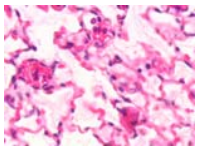
Vol. 116 December 2006

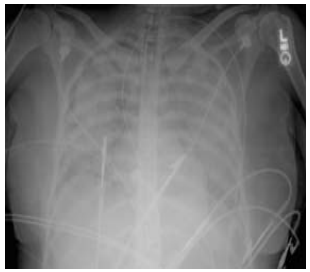
JCI
The Journal Clinical Investigation

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

Bedside

Provided by Mark Looney, UCSF

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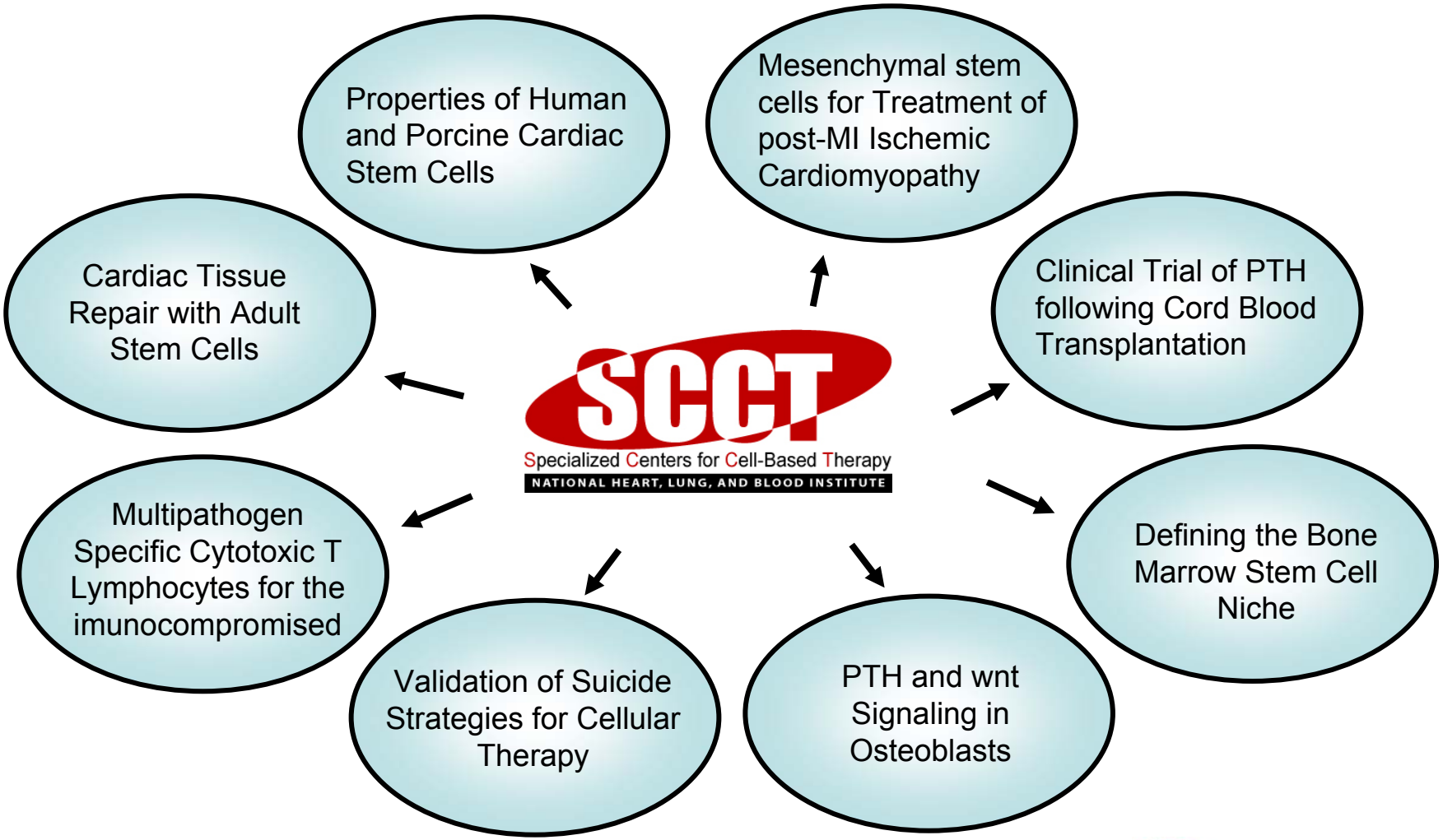
Cellular Therapies

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



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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

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

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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

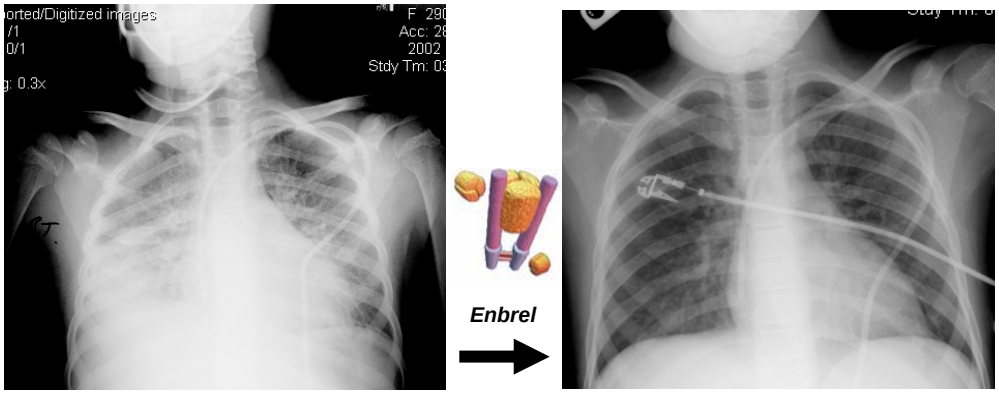
Advancing Cellular Therapies

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% FiO2

Day 3: Enbrel therapy Room air

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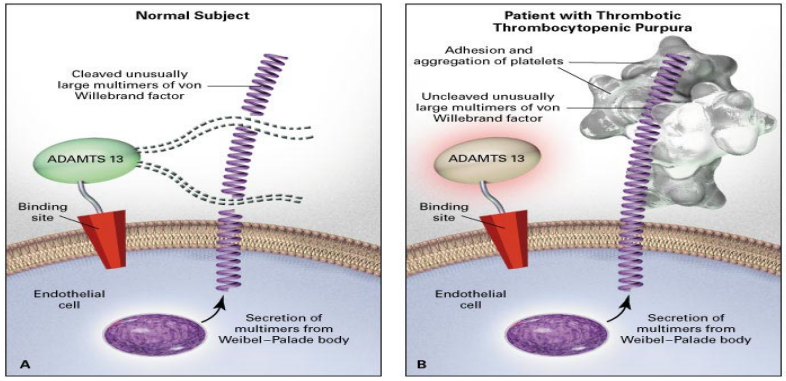
The Transfusion Medicine / Hemostasis Clinical Trials Network

Clinical trials to evaluate:

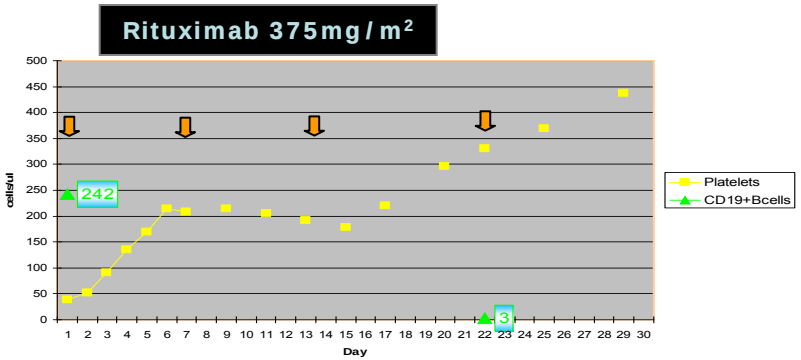
- Novel management strategies of potential benefit for children and adults with hemostatic disorders
- Blood products for the treatment of hematologic disorders

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

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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

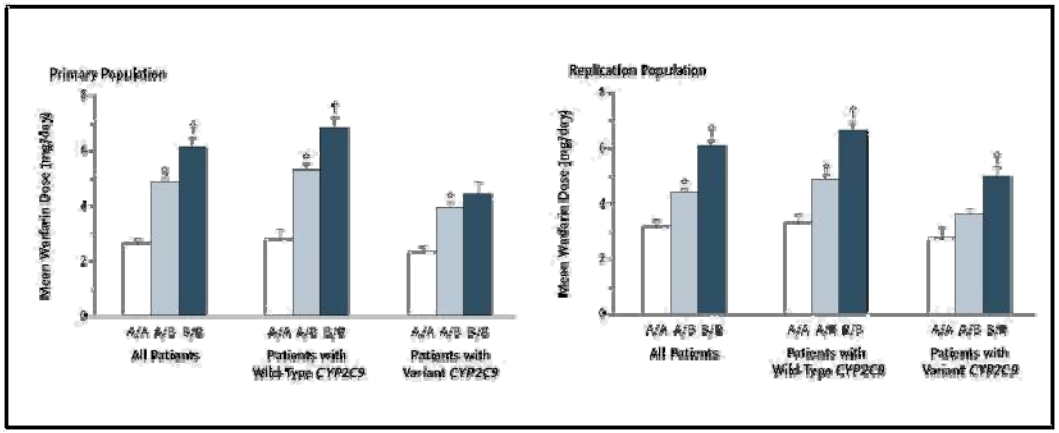
- Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) Trial - to compare standard therapy (transfusions with chelation) to alternative therapy (hydroxyurea with phlebotomy) for the prevention of recurrent stroke in children with sickle cell anemia.

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

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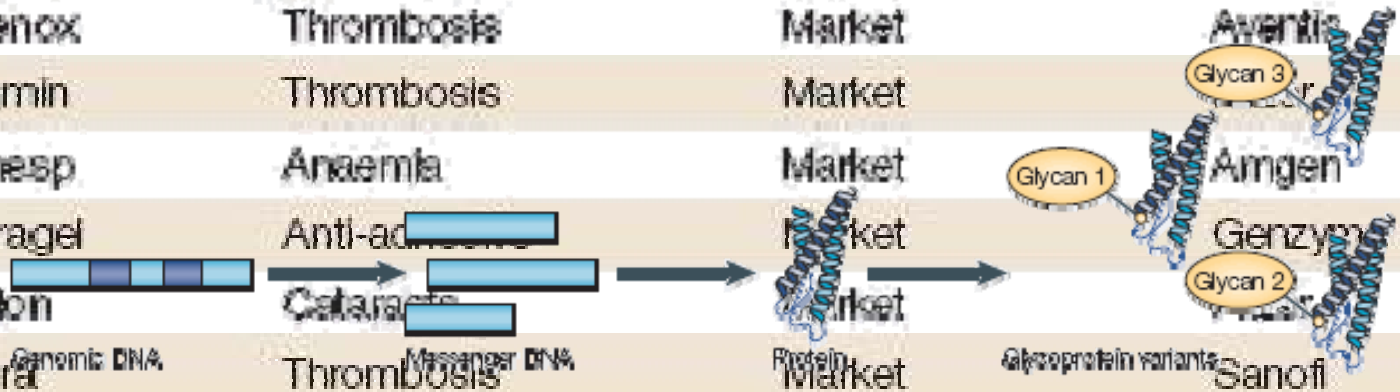
Glycomics: A Novel Pathway to Improved Therapeutics

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	
Aranesp	Anaemia	Market	Amgen
Sepragel	Anti-ad	Market	Genzyme
Healon	Cataract	Market	
Arixtra	Thrombosis	Market	Sanofi
Cerezyme			Genzyme
Aldurazyme	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

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

[1]Department of Haematology, University College London and [2]National Blood Service, United Kingdom; [3]Division of Experimental Hematology and [4]Department of Surgery, St Jude Children's Research Hospital, Memphis, TN; [5]Department of Haematology, National Institute for Biological Standards and Control, Potters Bar, United Kingdom; and [6]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,[1,2,3] David A. Wilcox,[1,2,3] Scot A. Fahs,[1] Hartmut Weiler,[1,2] Clive W. Wells,[2] Brian C. Cooley,[2] Drashti Desai,[1,2,3] Patricia A. Morateck,[1] Jack Gorski,[1,2] and Robert R. Montgomery[1,2,3]

[1]Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, Wisconsin, USA. [2]Departments of Pediatrics, Physiology, Microbiology, and Orthopedics, Medical College of Wisconsin, Milwaukee, Wisconsin, USA. [3]Children's Research Institute, Children's Hospital of Wisconsin, Milwaukee, Wisconsin, USA.

LETTERS

nature medicine

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

Catherine S Manno[1,2,15], Glenn F Pierce[3,15], Valder R Arruda[1,2,15], Bertil Glader[4,15], Margaret Ragni[5], John J E Rasko[6], Margareth C Ozelo[7], Keith Hoots[8], Philip Blatt[9], Barbara Konkle[10], Michael Dake[4], Robin Kaye[1,2], Mahmood Razavi[4], Albert Zajko[10], James Zehnder[4], Pradip K Rustagi[11], Hiroyuki Nakai[4], Amy Chew[1,3], Debra Leonard[2,12], J Fraser Wright[3], Ruth R Lessard[3], Jürg M Sommer[3], Michael Tigges[3], Denise Sabatino[1], Alvin Luk[3], Haiyan Jiang[3], Federico Mingozzi[1], Linda Couto[3], Hildegund C Ertl[1,13], Katherine A High[1,2,14] & Mark A Kay[4]

National Heart Lung and Blood Institute

NHLBI Strategic Plan Goals

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*

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

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*

Cause to Cures

Improving Blood Safety and Availability

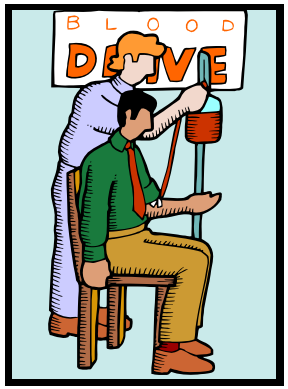
A global perspective

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.

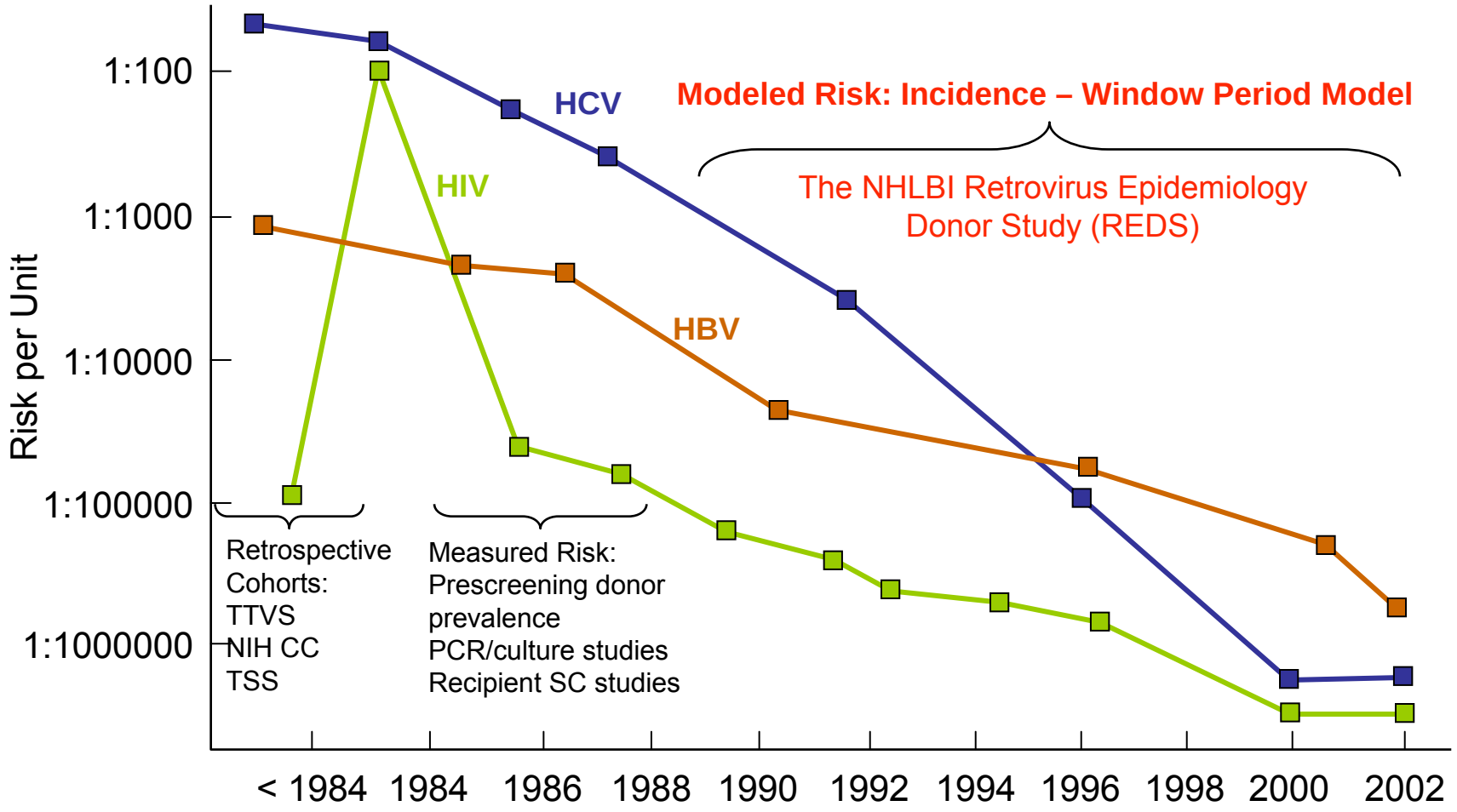


Quality Donor System™ (QDS)
Audio Visual Touch Screen Computer Assisted Self Interviewing (AVT-CASI)

Paul D. Cumming, PhD - Talisman Limited - SBIR

National Heart Lung and Blood Institute

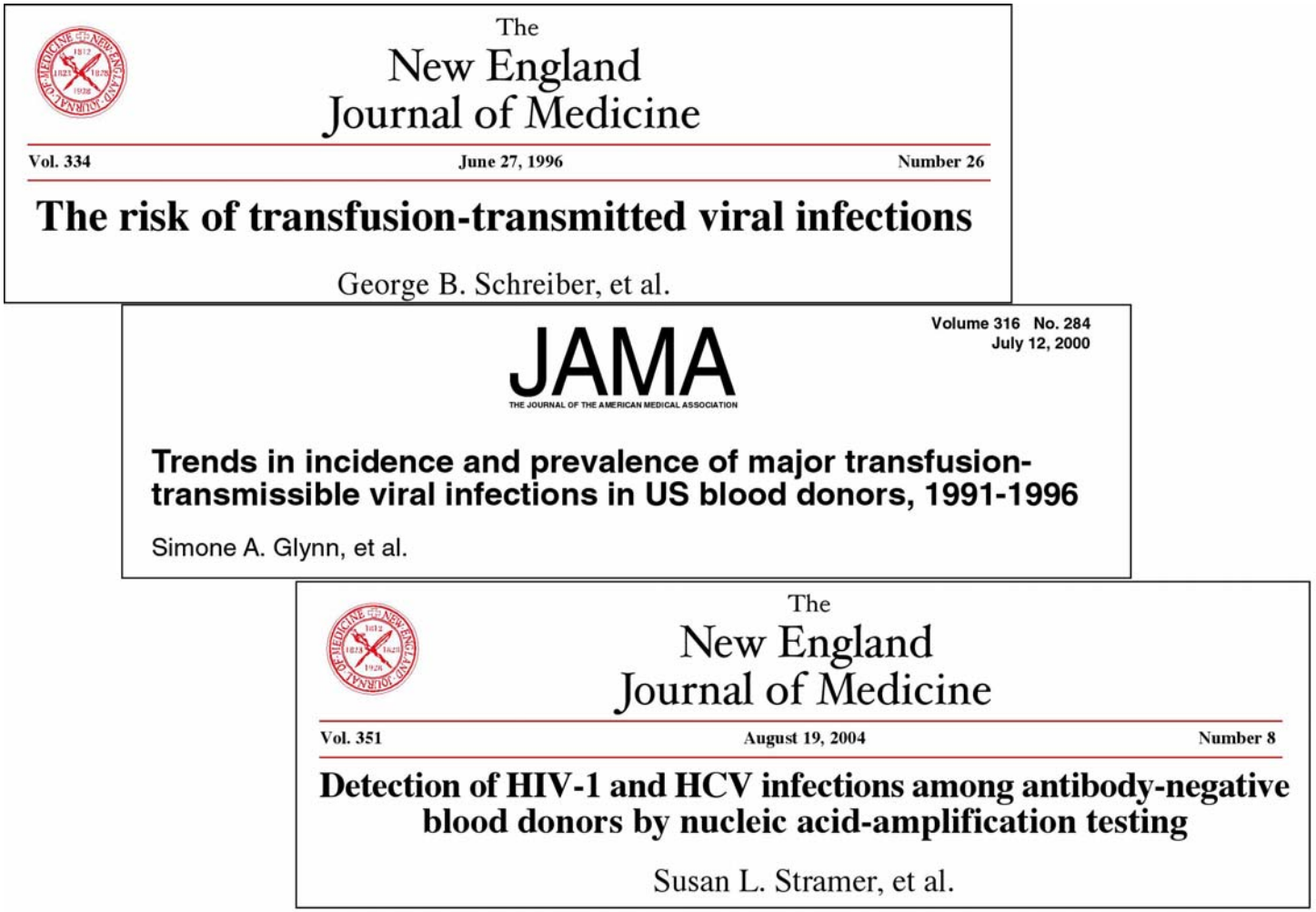
Increasing the Safety of the Blood Supply



Provided by Michael Busch, Blood Systems Research Institute, SF

National Heart Lung and Blood Institute

Increasing the Safety of the Blood Supply



The
New England
Journal of Medicine

Vol. 334 June 27, 1996 Number 26

The risk of transfusion-transmitted viral infections

George B. Schreiber, et al.

JAMA
THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Volume 316 No. 284
July 12, 2000

Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991-1996

Simone A. Glynn, et al.

The
New England
Journal of Medicine

Vol. 351 August 19, 2004 Number 8

Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid-amplification testing

Susan L. Stramer, et al.

National Heart Lung and Blood Institute

Blood Safety
Emerging Infectious Risks

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-

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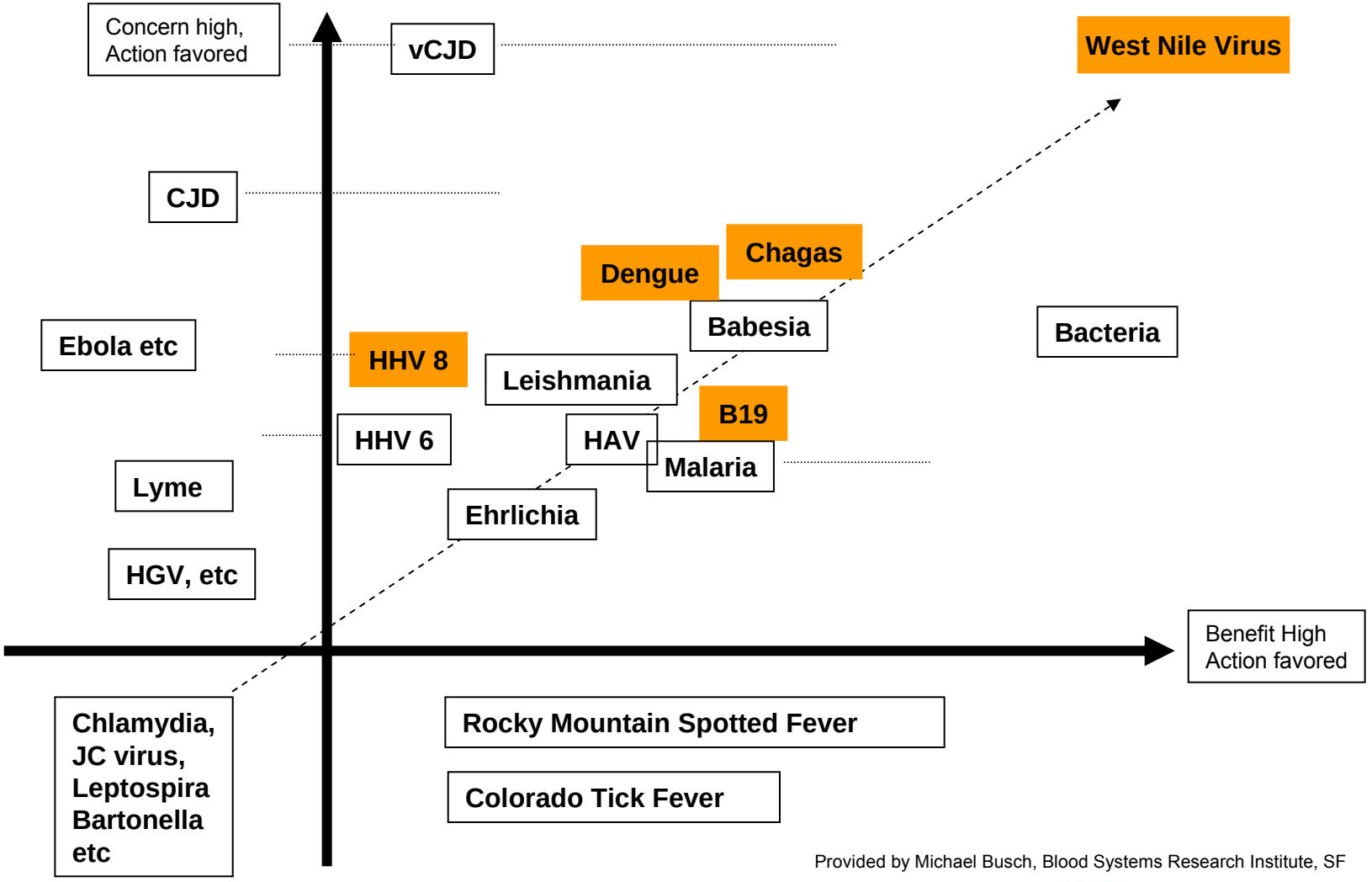
Blood Safety

Emerging Infectious Risks: REDS and REDS-International



idprio2001

Provided by Michael Busch, Blood Systems Research Institute, SF

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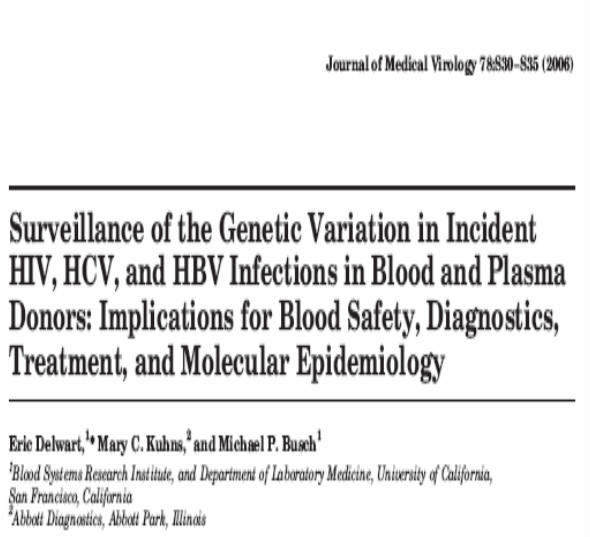
The REDS-II Molecular Surveillance Study

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)

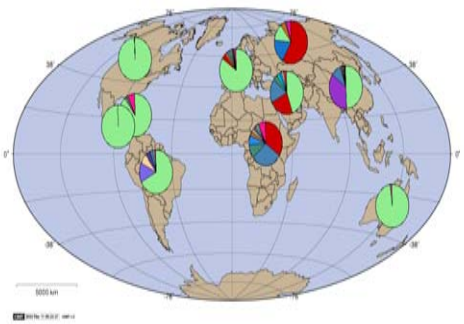


Journal of Medical Virology 78:830–835 (2006)

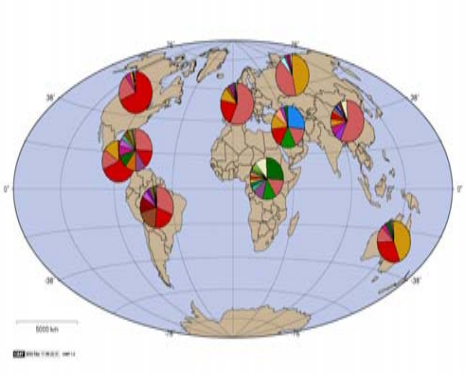
Surveillance of the Genetic Variation in Incident HIV, HCV, and HBV Infections in Blood and Plasma Donors: Implications for Blood Safety, Diagnostics, Treatment, and Molecular Epidemiology

Eric Delwart,[1]* Mary C. Kuhns,[2] and Michael P. Busch[1]

[1]Blood Systems Research Institute, and Department of Laboratory Medicine, University of California, San Francisco, California
[2]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

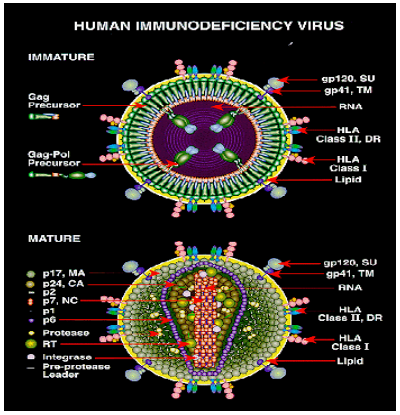
National Heart Lung and Blood Institute

Safety of the Global Blood Supply

REDS- II International

Laboratory, epidemiologic and survey research to:

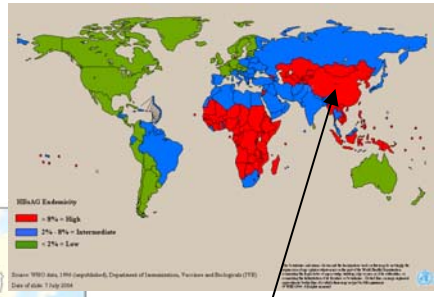
- assess and monitor the prevalence, incidence, and transfusion-transmitted risk of HIV 1, HIV-2, and other existing as well as newly discovered infectious agents that pose a threat to blood safety in selected developing countries seriously affected by the HIV/AIDS epidemic
- assess the impact of existing 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

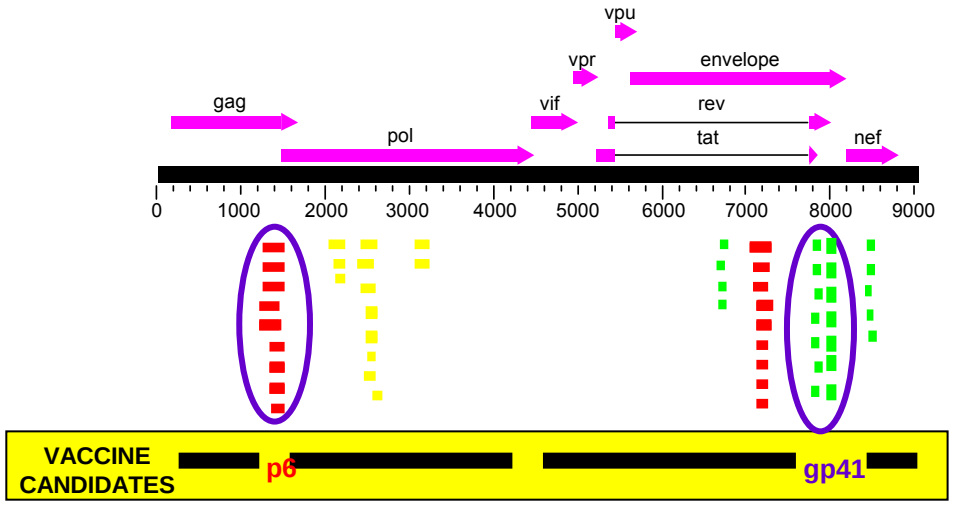


CHINA

National Heart Lung and Blood Institute

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.

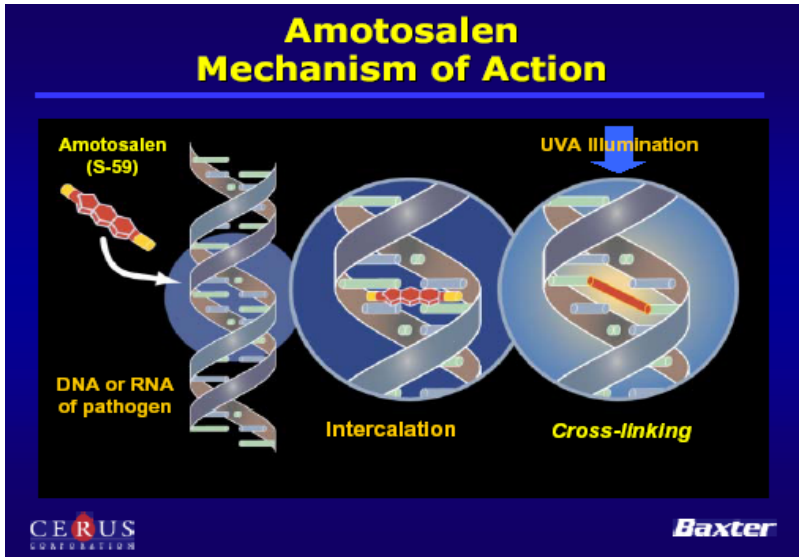
Khurana, S, Needham, J., Mathieson, B., et al. Human Immunodeficiency Virus (HIV) Vaccine Trials: a Novel Assay for Differential Diagnosis of HIV Infections in the Face of Vaccine-Generated Antibodies. Journal of Virology, 2006, Vol. 8, No. 5, 2092/2099, March 2006.

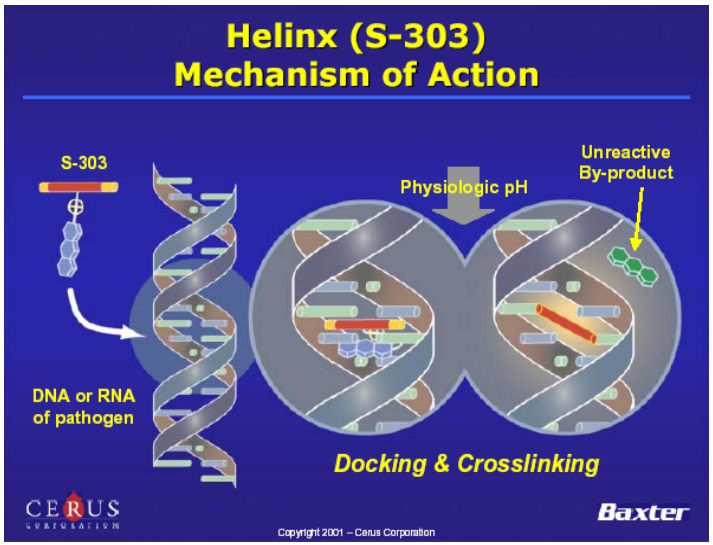
National Heart Lung and Blood Institute

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.



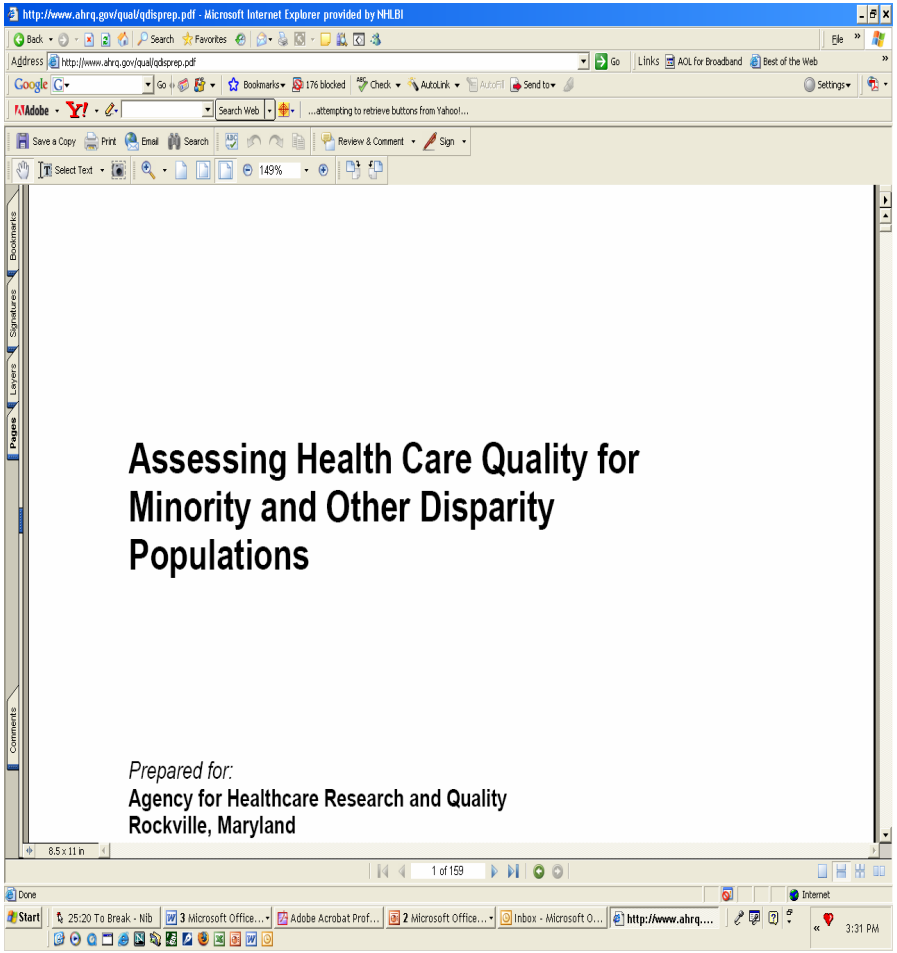


National Heart Lung and Blood Institute

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

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

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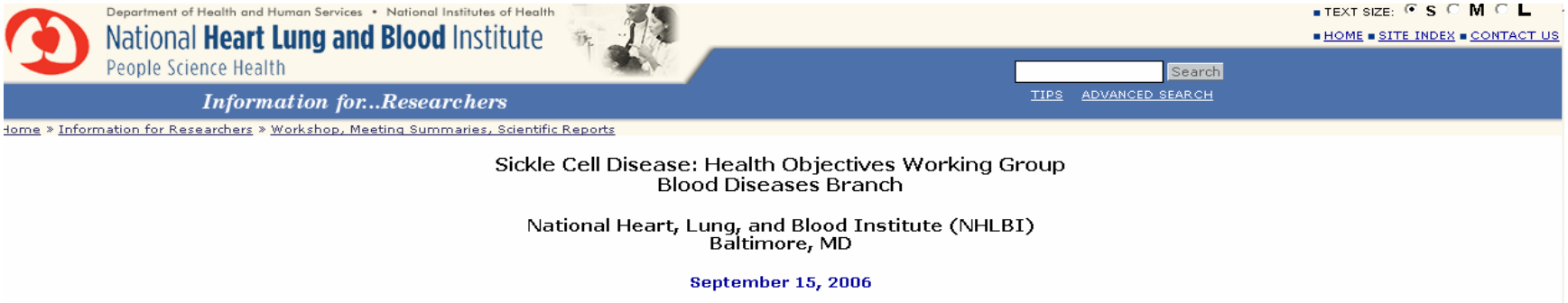
Enhancing the Evidence Available to Guide the Practice of Medicine and Improve Public Health: SCD Objectives



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

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

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

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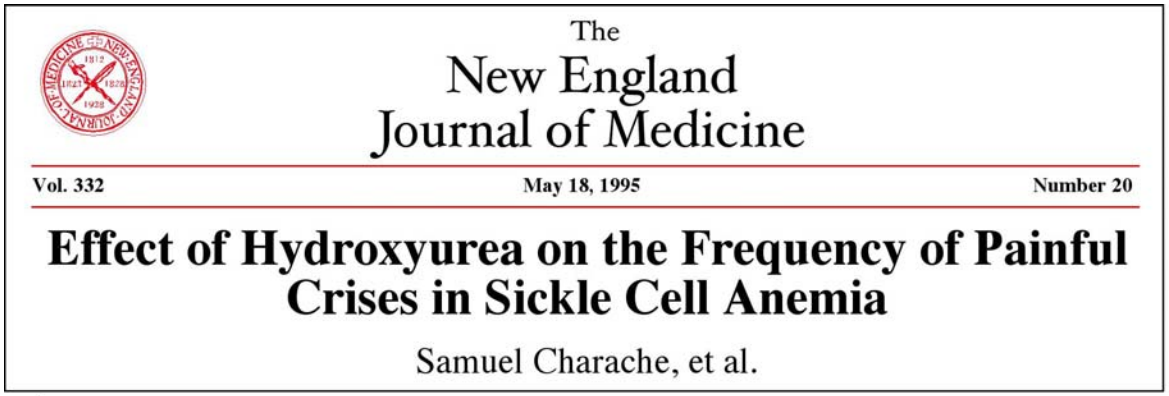
Generating an Improved Understanding of the Process Involved in Translating Research into Practice

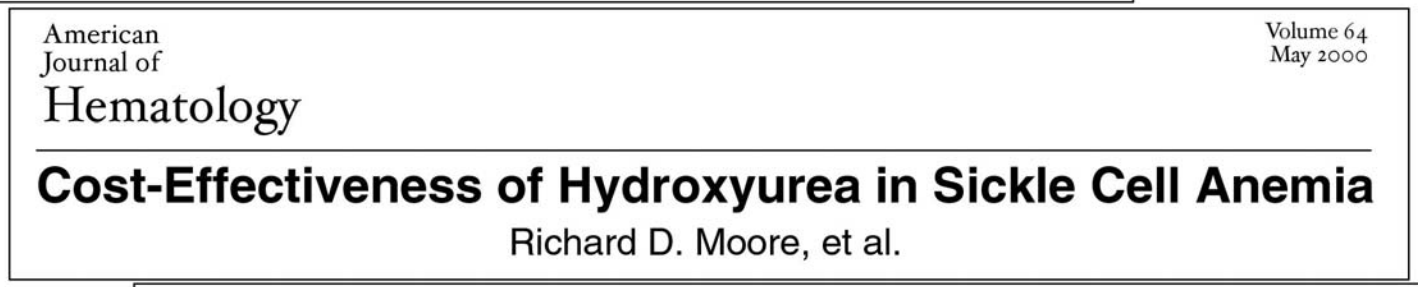


The
New England
Journal of Medicine

Vol. 332 May 18, 1995 Number 20

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

Samuel Charache, et al.

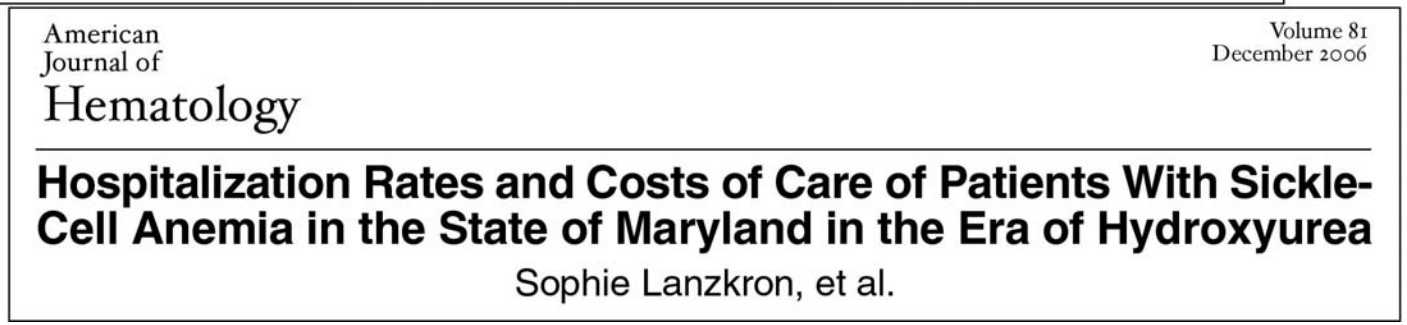


American
Journal of
Hematology

Volume 64
May 2000

Cost-Effectiveness of Hydroxyurea in Sickle Cell Anemia

Richard D. Moore, et al.



American
Journal of
Hematology

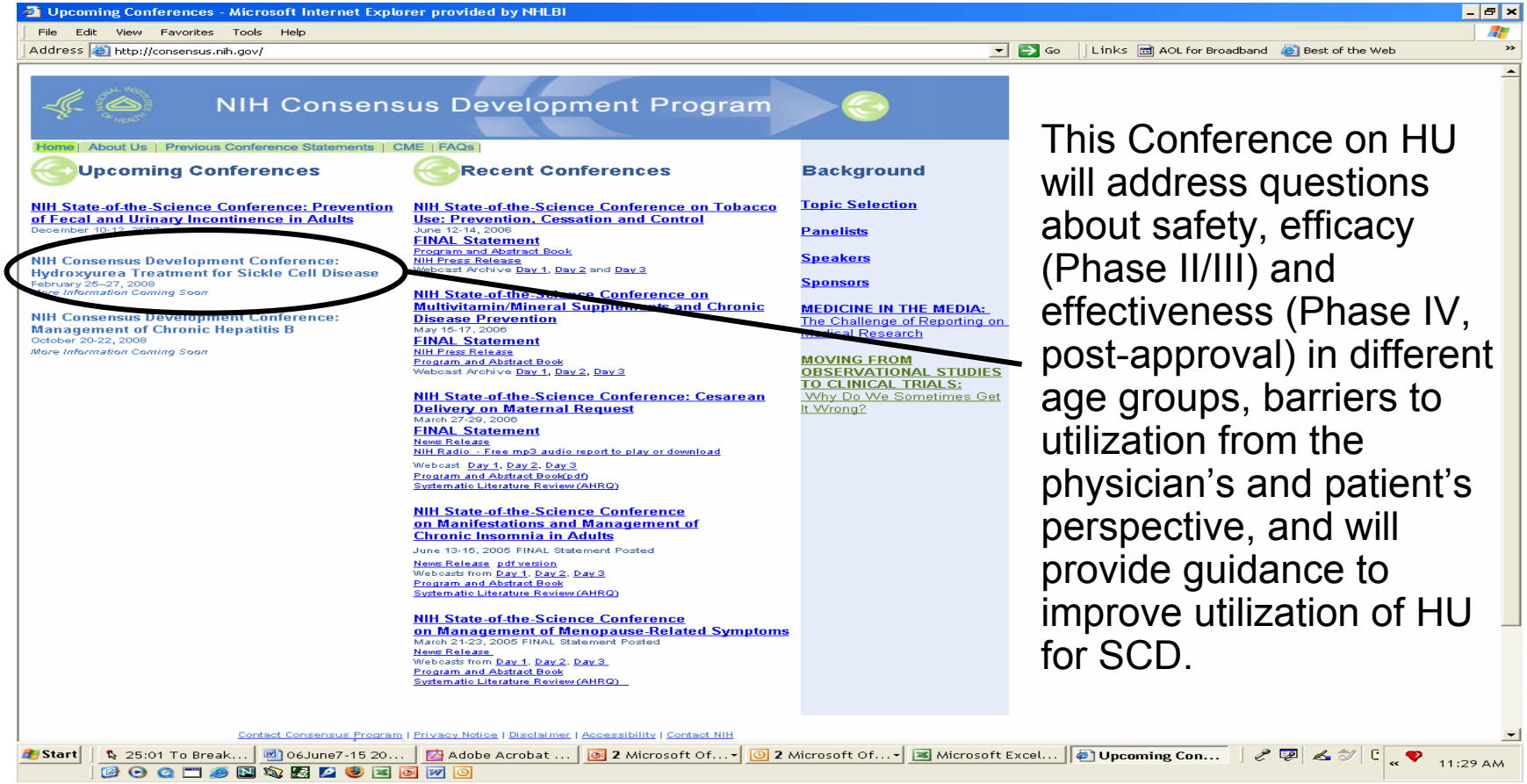
Volume 81
December 2006

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.

National Heart Lung and Blood Institute

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

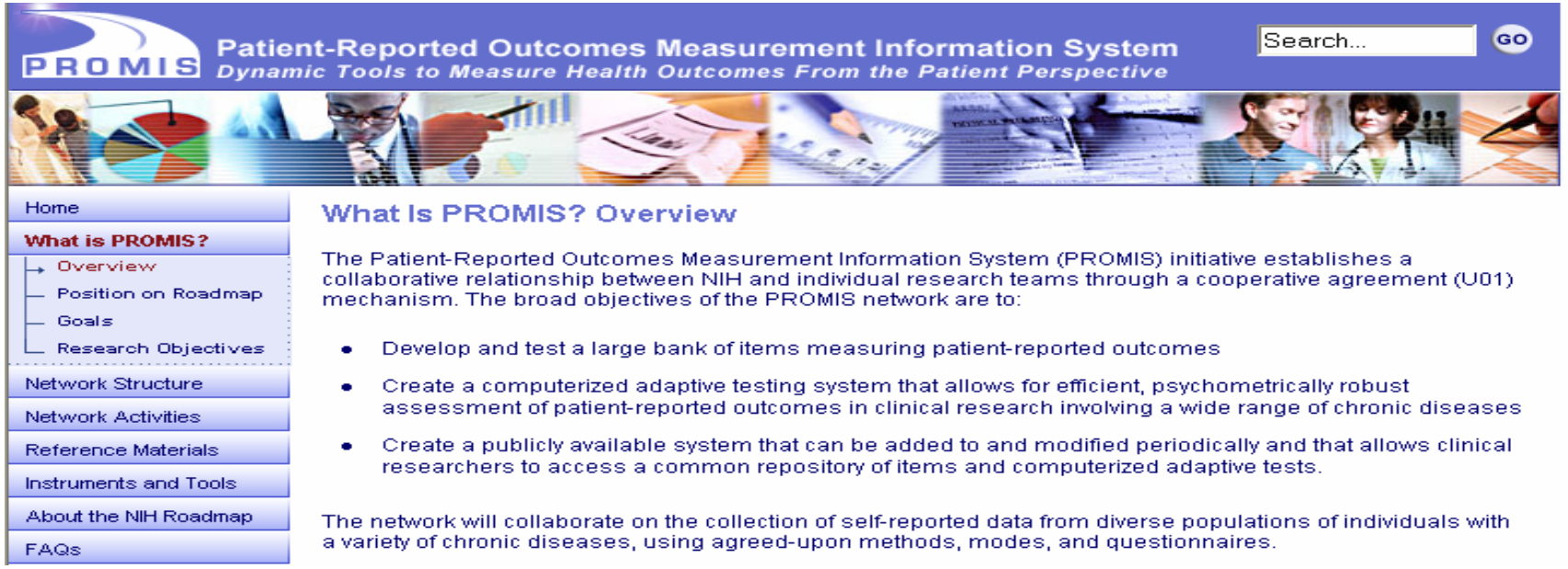


This Conference on HU will address questions about safety, efficacy (Phase II/III) and effectiveness (Phase IV, post-approval) in different age groups, barriers to utilization from the physician's and patient's perspective, and will provide guidance to improve utilization of HU for SCD.

http://consensus.nih.gov/

National Heart Lung and Blood Institute

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/

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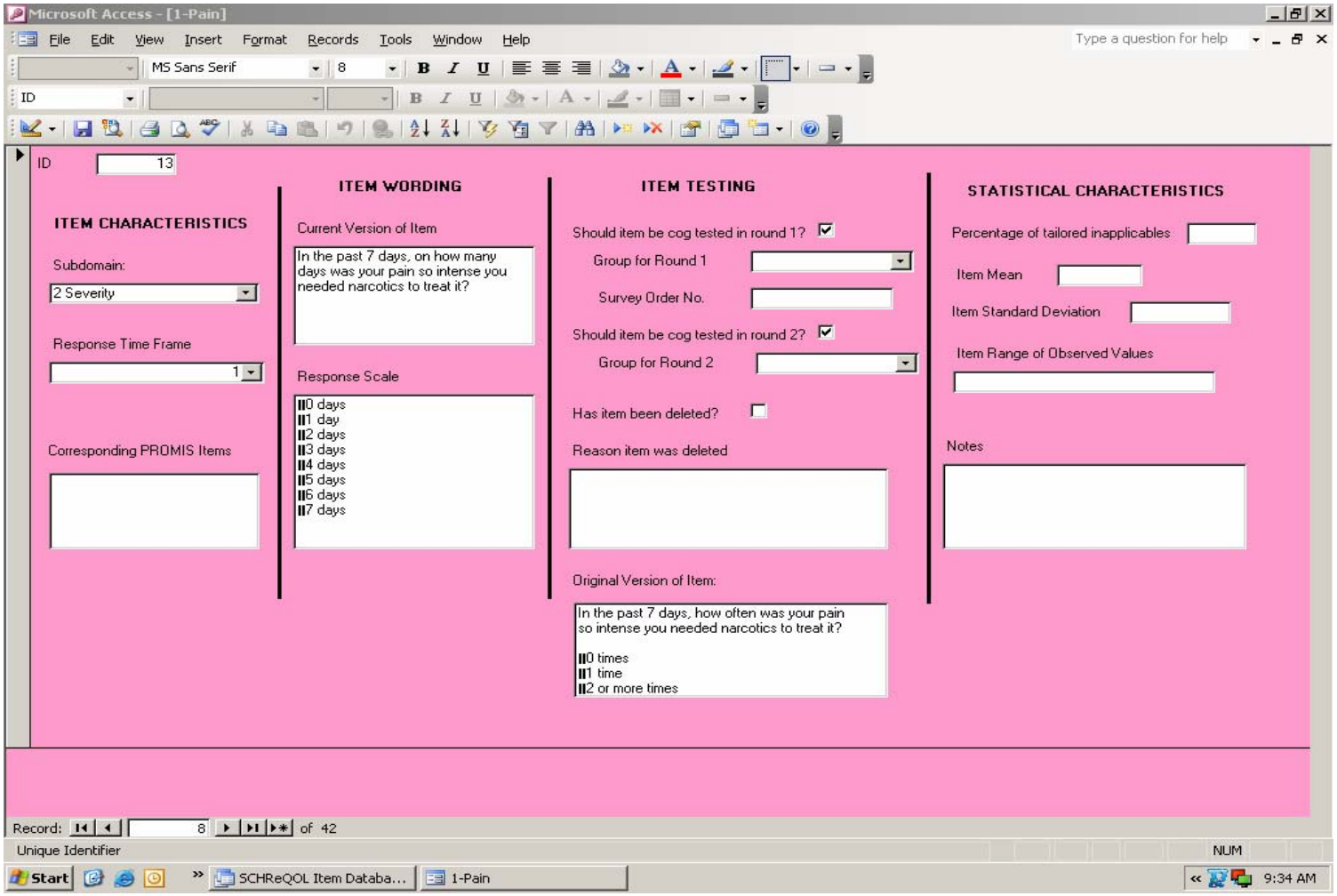
Sickle Cell Health-Related Quality of Life (SCHRe-QoL) Measurement Information System

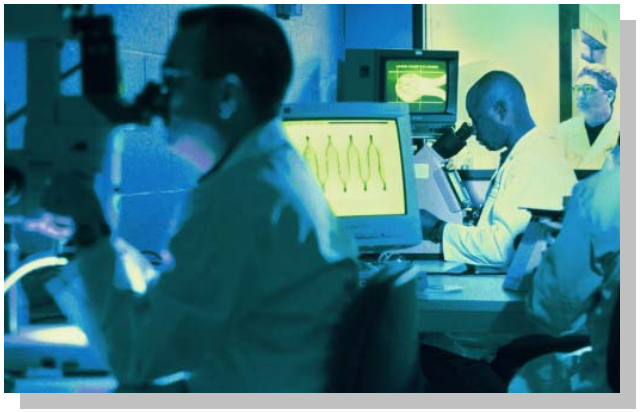


National Heart Lung and Blood Institute

Strategies

Training and Mentoring of Emerging Scientists and Physicians

Training of New Clinical Investigators



National Heart Lung and Blood Institute

Pipeline of Opportunities to Assure Diverse Research Teams

K-12

Faculty

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

National Heart Lung and Blood Institute

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

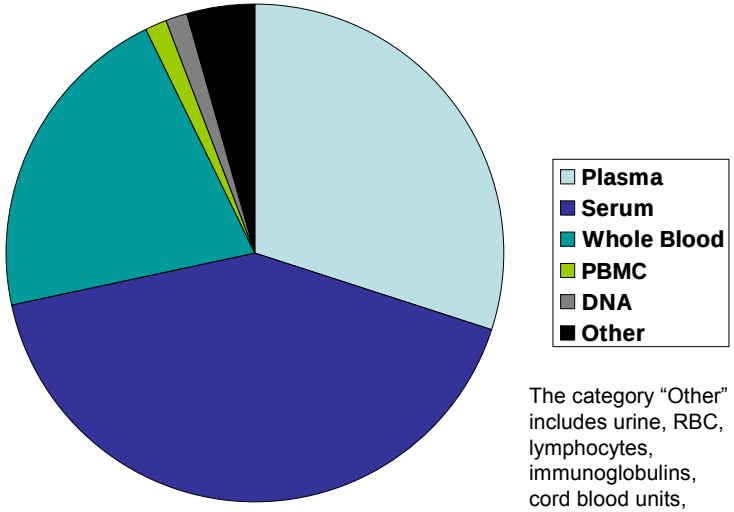
The Repository currently includes about 4 million plasma, serum, cellular or tissue specimens

- 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.
- 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.

National Heart Lung and Blood Institute

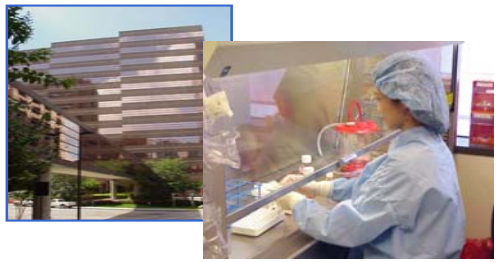
Production Assistance for Cellular Therapies (PACT)

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.

PACT

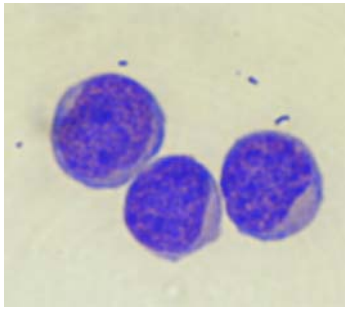
Production Assistance for Cellular Therapies

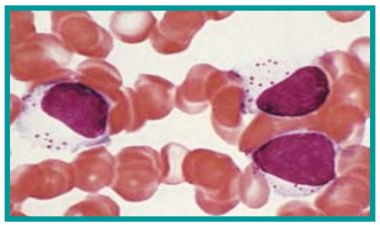


Center for Cell and Gene Therapy (CAGT), Baylor College of Medicine

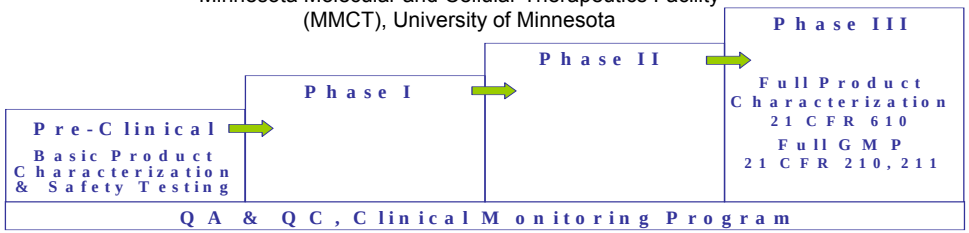
Minnesota Molecular and Cellular Therapeutics Facility (MMCT), University of Minnesota

University of Pittsburgh Cancer Institute (UPCI)





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



National Heart Lung and Blood Institute

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.

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

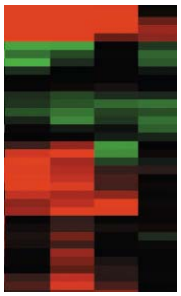
National Heart Lung and Blood Institute

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**



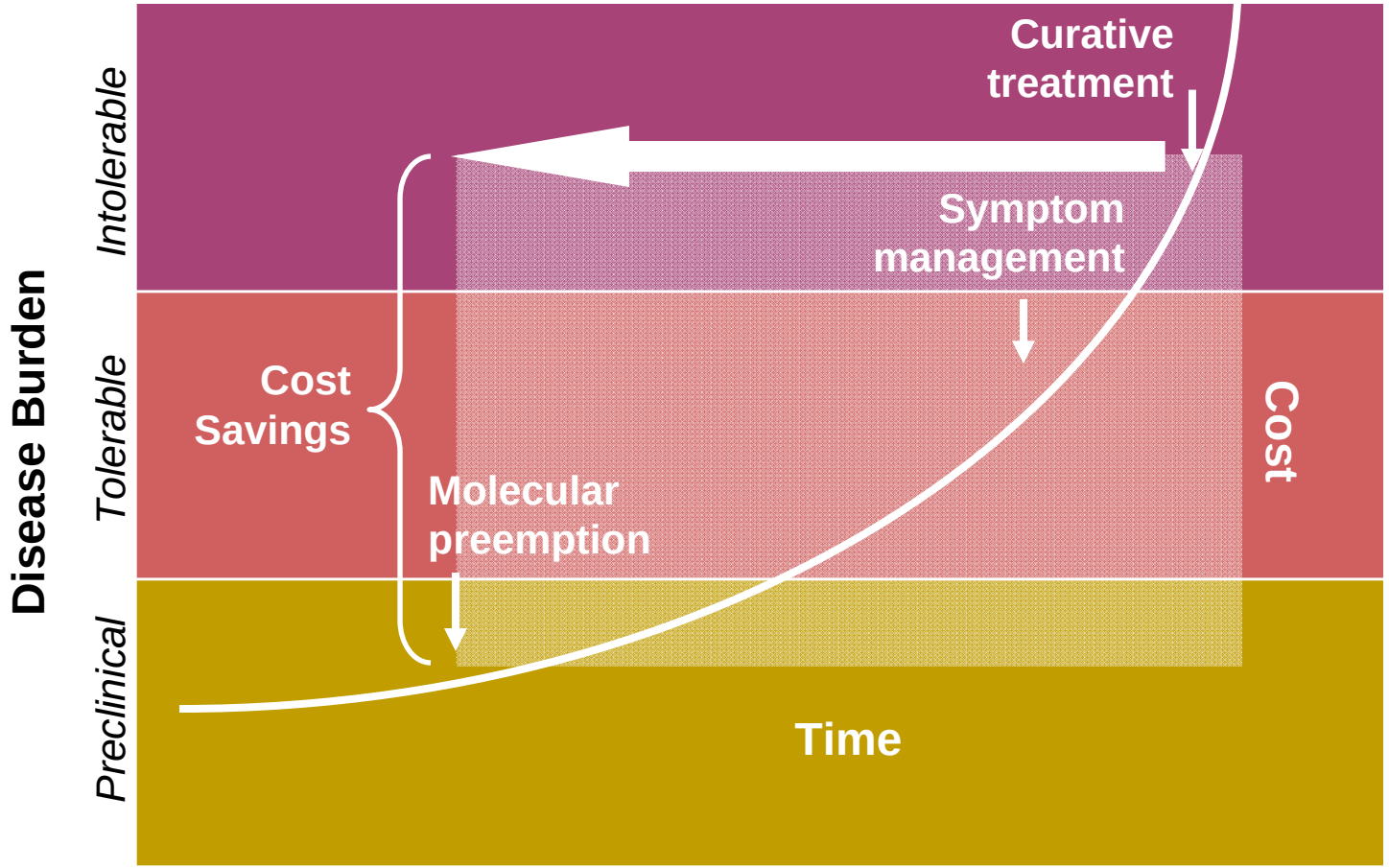
Genomics Proteomics

Stem Cell Research
Tissuegenesis

Cell Imaging
Translational

National Heart Lung and Blood Institute

The Future Paradigm: Preempt Disease



National Heart Lung and Blood Institute

Goal One: Form to Function

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.

Challenge 1.1

To delineate mechanisms that relate to 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 life-span.
- **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 inflammation in the development and evolution of disease.

Goal One: Form to Function

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: 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 promote translation of clinical research findings back into the laboratory.

- **2.1.a** Integrate advances in regenerative biology (cell, tissue, and gene therapies) to develop clinically feasible applications.
- **2.1.b** Apply discoveries in nanotechnology to 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

Challenge 2.3

To develop personalized preventive and therapeutic regimens for cardiovascular, lung, and blood diseases.

2.3.a Improve 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

Enhance the evidence available to guide the practice of medicine and improve public health.

Goal Three: Causes to Cures

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.

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 life-style interventions.

3.1.b Develop and evaluate policy, environmental, and other approaches for use in community settings to encourage and support life-style 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

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 the life-span.

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 system-oriented approaches to the increase use of evidence-based guidelines in the practices of individuals, communities, health-care providers, and public institutions, and increase the use of evidence-based guidelines in populations experiencing a disproportionate disease burden.
- **3.3.c** Communicate research advances effectively to the public.