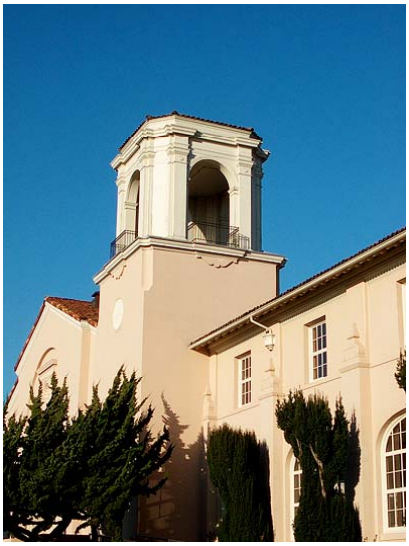


C·H·O·R·I
Children's Hospital Oakland Research Institute

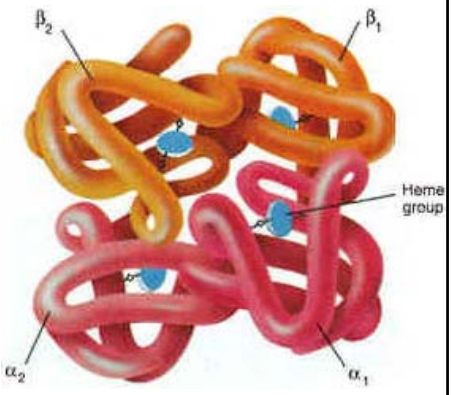
Cell Therapy for Hemoglobinopathies

Mark Walters, MD
Director
Blood and Marrow
Transplantation Program

CHILDREN'S HOSPITAL
& RESEARCH CENTER OAKLAND

What are Hemoglobin disorders?

- Alterations in the hemoglobin molecule that alter its abundance and/or function and stability
- Account for the most common human genetic disorders world-wide
- Associated with anemia, reliance on RBC transfusions, chronic illness



How Many People are Affected?

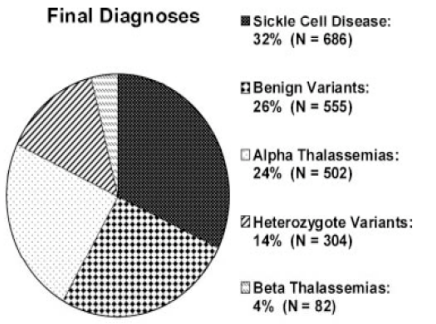


Fig. 1. Final diagnoses of all samples forwarded to the HRL from January 1, 1998 through June 30, 2006.

SCD - United States
80 - 90,000

Sub-Saharan Africa
Millions

World
Many millions

Sub-Saharan Africa: 300,000 babies with sickle cell disease born each year

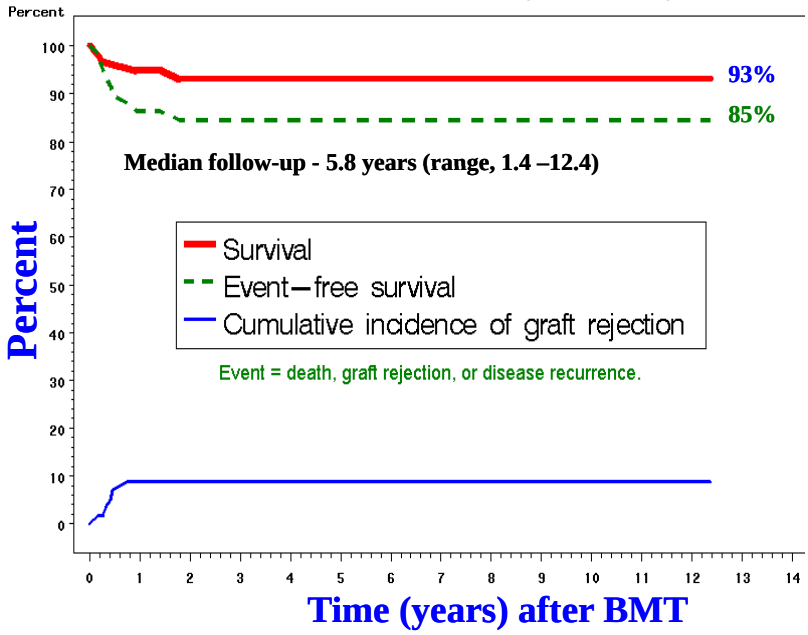
Michlitsch J et al, Pediatr Blood Cancer 2009;52:486–490

Homozygote or Compound Heterozygote Annual Births With Thalassemia: WHO Conservative Estimates

	Births/Year (Homozygous or Compound)		
Area	**Hydrops Alpha**	**Beta**	**Beta E**
Africa	–	4100	–
Americas	–	227	–
Asia	4507	20,508	15,817
Europe	–	1385	–
Oceania	–	100	–
Total (conservative)	4507	26,306	15,817

National Heart, Lung, and Blood Institute. *Cooley's Anemia: Progress in Biology and Medicine – 1995.*

BMT for SCD (N=59)



Current challenges of cellular therapy for hemoglobin disorders

- How to promote participation in therapeutic trials with curative potential by interventions that carry a risk of significant toxicity
- How to ensure access to novel therapeutic therapies – understand socioeconomic and physician referral barriers
- How to establish partnerships between clinicians and cellular therapy investigators

Clinical Endpoints of Cellular Therapy

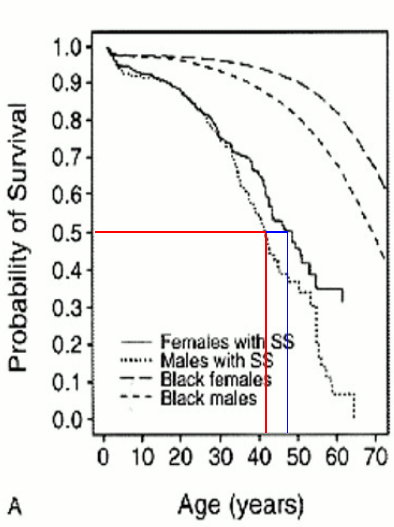
Overall survival

- Adults
- children

Protection from morbidity

- Sickle cell anemia
  - Stroke risk
  - Pain risk
  - Pulmonary hypertension and sudden death
- Thalassemia
  - Fewer transfusions
  - Fe overload

Survival of Patients in the Cooperative Study of Sickle Cell Disease



OS Platt et al. NEJM 330:1639, 1994

Survival of Children with Sickle Cell Anemia

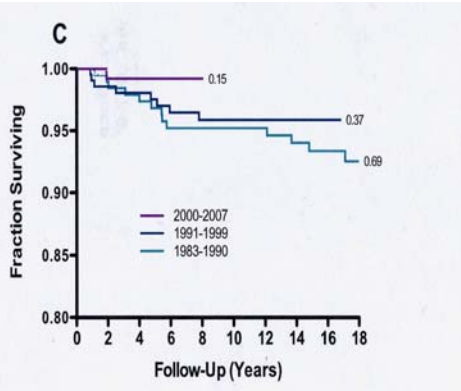
Recent Newborn Cohort Study Data

Cohort	Patients with Hb SS	Survival
Dallas Blood 2004; 103: 4023-27 Blood 2010; 115: 3447-52	511	94% at 18 yrs (CI 90.3 – 96.2)
East London Haematologica 2007; 92: 905-12	180	99% at 16 yrs (CI 93.2 – 99.9)
Western New York State J Pediatr 2009; 151: 121-5	108	97% at 18 yrs*

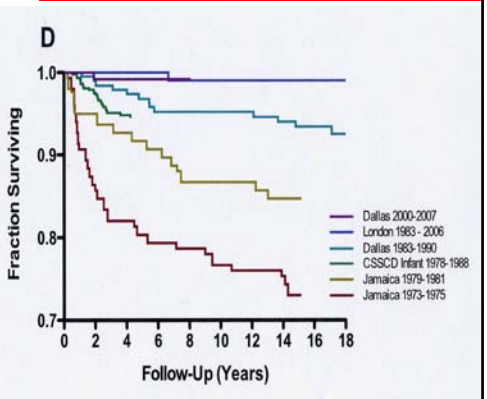
*Includes all genotypes

Survival of Newborn Cohorts - 2010

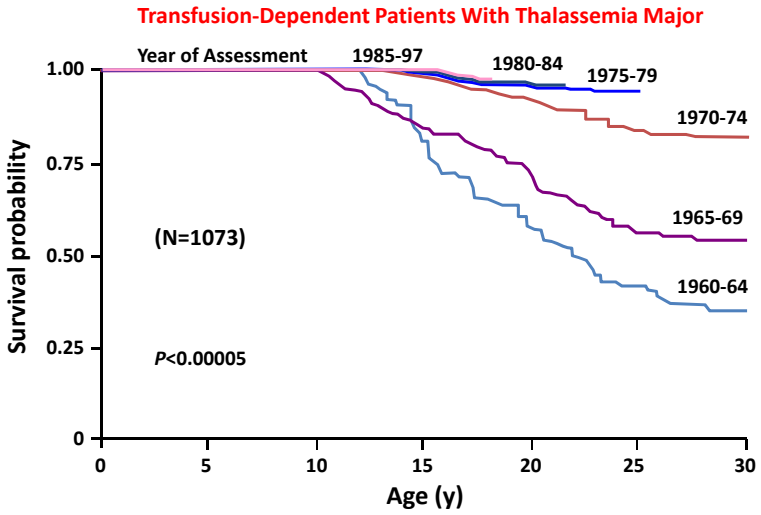
Sickle Cell Anemia-By Birth Year



Comparison of 4 Newborn Cohorts



Survival by Availability of Chelation Therapy



Borgna-Pignatti et al. *Haematologica*. 2004;89:1187.

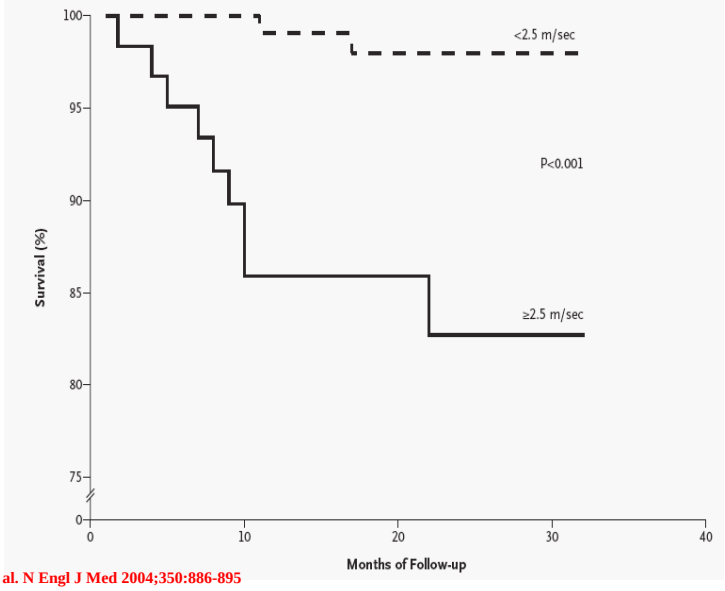
Updated Survival In Adults with Sickle Cell Disease

	1960's	2010
Children	20% mortality by age 5 yr.	**95% survival at age 18 yr**
Adults	Few patients survive to > age 21 yrs.	**Limited data available**

Adult Survival Data

			Median Age of Death (yr) ♂	♀
Platt	1994	CSSCD	42	48
Wierenga	2001	Jamaica	53	58
Haywood	2007	National Database	37	39

Kaplan-Meier Survival Curves According to the Tricuspid Regurgitant Jet Velocity.



Gladwin, M. T. et al. N Engl J Med 2004;350:886-895

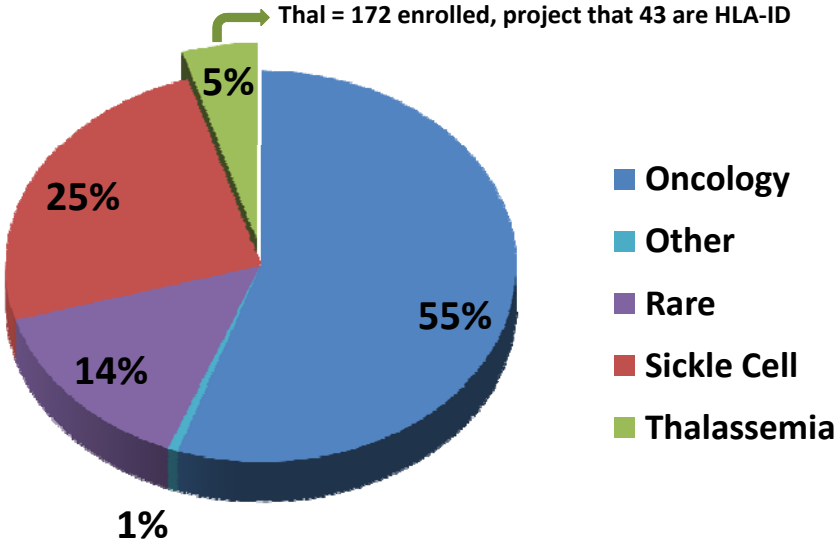
Mortality endpoint - conclusions

- Not a suitable short-term endpoint in a pediatric trial
- Pediatric trials are challenged by how to measure the long-term benefit
- May be a suitable short-term endpoint in a trial with young adults

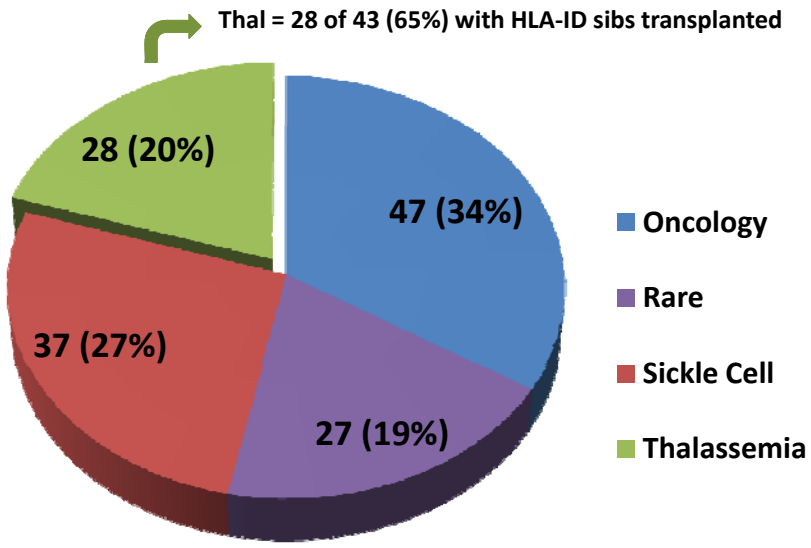
Strategies to Employ

- Select eligibility criteria that target common complications that have a significant clinical impact
- Select criteria that have objective and simple outcome measurements
- In clinical trial planning, develop strategies that will permit a large number of clinical sites to participate
- Target families that are motivated to participate

Total Sibling Collections= 3448



Sibling HPC-C Released for UCBT (n= 139)



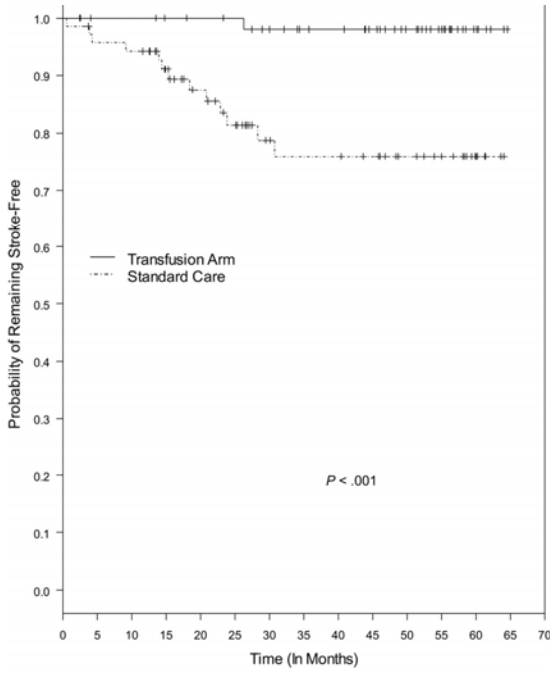
Stroke and SCD

- 8 – 10% of children develop stroke
- Peak age 10 years
- TCD screens children at risk
- RBC transfusions effectively reduce stroke rate in at-risk children screened by TCD
- HU is not as effective as transfusions
- Is this a suitable endpoint of cellular therapy?

Logistics of Stroke Prevention trial

- 2000 screened by TCD children at 14 centers in children ages 2 to 16 without a history of clinical stroke
- mean velocity of 200 cm/sec or higher
- Of 200 eligible children, 130 were enrolled and randomly assigned to transfusions or std care

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



Lee M T et al. Blood 2006;108:847-852

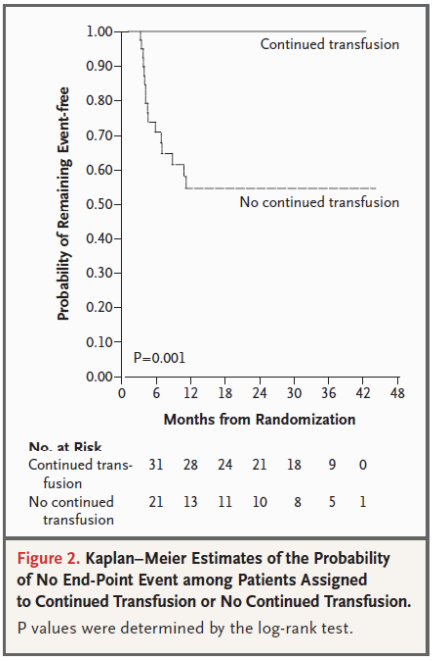


Figure 2. Kaplan–Meier Estimates of the Probability of No End-Point Event among Patients Assigned to Continued Transfusion or No Continued Transfusion.
P values were determined by the log-rank test.

Effect of stopping RBC transfusions on stroke risk

Cellular therapy for Stroke Prevention

- Large scale screening effort – at least 5000 children to identify at-risk 500 children, 14% of whom will have an HLA-ID sib (N=70)
- Assume accrual of 35 children (50%) over 2 years in HLA-ID transplantation arm
- Evaluate protection from stroke compared to supportive care – 25% stroke rate, or from stroke rate with RBC txn (?equivalence)

Cellular therapy for Stroke Prevention - critique

- Requires close collaboration of SCD centers, stroke experts and cellular therapy investigators, > 25 centers with considerable logistical and biostatistical resources
- Relaxing donor matching stringency, or ideally identifying a readily available cellular product would reduce screening effort
- May need to pursue an alternative endpoint to stroke prevention such as protection from iron overload (as in SWitCH trial)

Young adults with SCD – therapeutic endpoints

- **Protection from sudden death**
- **Hyper-hemolysis and pulmonary hypertension**
- **Reduction of pain – pain diary**
- **Improved quality of life – validated QOL tools in sickle cell disease**

Ann Intern Med 2008; 148:94-101

Daily Assessment of Pain in Adults with Sickle Cell Disease

Wally R. Smith, MD; Lynne T. Penberthy, MD, MPH; Viktor E. Bovbjerg, PhD, MPH; Donna K. McClish, PhD; John D. Roberts, MD; Bassam Dahman, MS; Imoigele P. Aisiku, MD, MSCR; James L. Levenson, MD; and Susan D. Roseff, MD

Background: Researchers of sickle cell disease have traditionally used health care utilization as a proxy for pain and underlying vaso-occlusion. However, utilization may not completely reflect the

probability, 56%). Crises without utilization were reported on 12.7% of days and utilization on only 3.5% (unadjusted). In total, 29.3% of patients reported pain in greater than 95% of diary days,

- Daily pain diary maintained for 6 months by 232 patients with SCD ≥ 16 years of age
- Pain reported on 56% of days
- 29% of patients had pain on > 95% of days
- 14% of patients had pain on < 5% of days
- Pain crises occurred on 12.7% of days and a visit to physician or hospital on 3.5% of days
- **Conclusion: "Pain in adults with SCD is the rule rather than the exception….."**

Survey of Adult Providers

- **Suitability of transplant eligibility assuming that disease-free survival after BMT is at least 70%**

Forty-six physicians, who indicated that they care for 3813 patients between the ages of 16-30 years of age participated in the survey

Proposed indication for HCT in SCAPN survey of experts	% respondents who agree
History of ≥3 painful events per year in the 3 years before enrollment despite a trial of Hydroxyurea (HU)	68.5
Acute chest syndrome (ACS) with ≥2 episodes of ACS in the 2 years before enrollment despite a trial of HU	82.5%
Any clinically significant neurologic event (stroke or hemorrhage) or any neurologic defect lasting >24 hours.	82.5%
Pulmonary hypertension defined by a tricuspid regurgitant jet velocity of ≥ 2.7 M/sec	59%
Administration of regular RBC transfusions to prevent vaso-occlusive crisis or other complications.	75%

Summary:

- Three challenges to cellular therapy for hg'opthies were identified – access with resources, defining good endpoints, and cooperation across disciplines
- It is very important to engender trust and enthusiasm among families, patients and their health care providers
- Accrual targets must be realistic and recruitment ideas should be identified and implemented
- Attempt to identify highly motivated sub-groups