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?

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

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

<table>
<thead>
<tr>
<th>Area</th>
<th>Hydrops Alpha</th>
<th>Beta</th>
<th>Beta E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>–</td>
<td>4100</td>
<td>–</td>
</tr>
<tr>
<td>Americas</td>
<td>–</td>
<td>227</td>
<td>–</td>
</tr>
<tr>
<td>Asia</td>
<td>4507</td>
<td>20,508</td>
<td>15,817</td>
</tr>
<tr>
<td>Europe</td>
<td>–</td>
<td>1385</td>
<td>–</td>
</tr>
<tr>
<td>Oceania</td>
<td>–</td>
<td>100</td>
<td>–</td>
</tr>
<tr>
<td>Total (conservative)</td>
<td>4507</td>
<td>26,306</td>
<td>15,817</td>
</tr>
</tbody>
</table>

BMT for SCD (N=59)

Median follow-up - 5.8 years (range, 1.4 –12.4)

- 93% survival
- 85% event-free survival

Time (years) after BMT

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

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patients with Hb SS</th>
<th>Survival at 18 yrs (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallas</td>
<td>511</td>
<td>94% (CI 90.3 – 96.2)</td>
</tr>
<tr>
<td>Blood 2004; 103: 4023-27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood 2010; 115: 3447-52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>East London</td>
<td>180</td>
<td>99% (CI 93.2 – 99.9)</td>
</tr>
<tr>
<td>Haematologica 2007; 92: 905-12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western New York State</td>
<td>108</td>
<td>97% at 18 yrs*</td>
</tr>
</tbody>
</table>

*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

Transfusion-Dependent Patients With Thalassemia Major

Year of Assessment
1985-97
1980-84
1975-79
1970-74
1965-69
1960-64

(N=1073)
P<0.00005

Survival probability
Age (y)
0
0.25
0.50
0.75
1.00


Updated Survival In Adults with Sickle Cell Disease

1960’s
Children: 20% mortality by age 5 yr.
Adults: Few patients survive to > age 21 yrs.

2010
95% survival at age 18 yr
Limited data available

Adult Survival Data

Median Age of Death (yr)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Males</th>
<th>Females</th>
<th>Median Age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platt</td>
<td>1994</td>
<td>CSSCD</td>
<td>42</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Wierenga</td>
<td>2001</td>
<td>Jamaica</td>
<td>53</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Haywood</td>
<td>2007</td>
<td>National Database</td>
<td>37</td>
<td>39</td>
<td></td>
</tr>
</tbody>
</table>
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

- Thal = 172 enrolled, project that 43 are HLA-ID
- 55%
- 25%
- 14%
- 1%
- Oncology
- Other
- Rare
- Sickle Cell
- Thalassemia
Sibling HPC-C Released for UCBT (n= 139)

- Thal = 28 of 43 (65%) with HLA-ID sibs transplanted
- 47 (34%)
- 37 (27%)
- 28 (20%)
- 27 (19%)

**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
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
Daily Assessment of Pain in Adults with Sickle Cell Disease

Wally R. Smith, MD; Lynne T. Penberthy, MD, MPH; Vidit E. Bovbjerg, PhD, MPH; Donna K. McClish, PhD; John D. Roberts, MD; Bassam Dahman, MS; Imaoigle P. Aisiku, MD, MSCR; James L. Leventon, 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.

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

- Three challenges to cellular therapy for h’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