Targeted Drug Discovery in Sickle Cell Disease: From Concept to Clinic

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SCD: DISABLING INHERITED BLOOD DISORDER

+ SCD impacts hemoglobin, a protein found in red blood cells (RBCs) that carries oxygen throughout the body
+ Caused by a genetic mutation in the beta-chain of hemoglobin
  - Results in the formation of abnormal hemoglobin
  - Sickled RBCs stick together and block the flow of blood and oxygen
+ Devastating morbidity and mortality
  - Hemolytic anemia, vaso-occlusion, inflammation/vascular injury
  - Results in multi-organ damage
  - 2 to 3 decade reduction in life expectancy
  - Current treatments are limited
+ Who SCD affects:
  - ~100,000 patients in U.S.; ~60,000 in EU
    - ~90% are African-American
  - Disease is concentrated in populations of African, Middle Eastern and South Asian descent
+ SCD represents a global health problem and new treatment options are desperately needed

No Organ Spared
Common Morbidities

Brain
- Cerebral infarcts, strokes
- Thrombosis or hemorrhage causing paralysis, sensory deficits or death

Lung
- Acute chest syndrome
- Pulmonary hypertension
- Pneumonia

Kidney
- Hematuria
- Renal insufficiency
- Renal failure

Bones and joints
- Bone marrow hyperplasia
- Osteomyelitis
- Avascular necrosis/osteonecrosis

Eye
- Hemorrhage
- Retinal detachment
- Blindness
- Retinopathy

Heart
- Cardiomegaly
- Heart failure

Spleen
- Splenic atrophy (autosplenectomy)

Liver-gallbladder
- Hepatomegaly
- Gallstones

Skin
- Stasis ulcers of hands, ankles and feet

Men/Women
- Priapism
- Adverse pregnancy outcomes
Malaria is the culprit

Plasmodium falciparum evolves from a common precursor in Africa by zoonotic introduction of animal malaria into humans.

Advent of horticulture and stable, stationary human populations in areas where water was abundant and mosquitoes could breed. P. falciparum becomes a major human pathogen.

P. falciparum spreads from Africa to other sub-tropical regions of the Old World.

Malaria drove gene selection for common red cell disorders including SCD

~60,000 to 25,000 BP

~10,000 BP

~6,000 BP
RBC AS A POINT OF MALARIA DEFENSE

*P. falciparum* has an obligate red cell stage.

Red cells are expendable and renewable.

Mechanisms that selectively destroy parasitized red cells reduce the parasite burden.

Reduced parasite burden correlates with improved survival.
HBS rose to high prevalence independently in Africa and India.

Africa - HbS rose to high prevalence independently at least 4 times
Senegal, Benin, Central African Republic, and Cameroon haplotypes

India - A high prevalence HbS haplotype in India spread to the Middle East

Mapping HbS haplotypes in different geographies is used in molecular anthropology.
# RED CELL DEFENSES AGAINST MALARIA

<table>
<thead>
<tr>
<th>Cell Component</th>
<th>Alteration</th>
<th>Global Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane</td>
<td>Duffy antigen null</td>
<td>West Africa</td>
</tr>
<tr>
<td></td>
<td>Melanesian elliptocytosis</td>
<td>Melanesia</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Hemoglobin S</td>
<td>Africa, Middle East, India</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin C</td>
<td>West Africa</td>
</tr>
<tr>
<td>Hemoglobin E</td>
<td>Hemoglobin E</td>
<td>S.E. Asia</td>
</tr>
<tr>
<td>β-thalassemia</td>
<td>Africa, Mediterranean, India, S.E. Asia, Melanesia</td>
<td></td>
</tr>
<tr>
<td>α-thalassemia</td>
<td>Africa, India, S.E. Asia, Melanesia</td>
<td></td>
</tr>
<tr>
<td>Enzymes</td>
<td>G6PD Deficiency</td>
<td>Africa, Mediterranean, India, S.E. Asia</td>
</tr>
</tbody>
</table>
James Herrick and Ernest E. Irons at Cook County Hospital in Chicago first described sickle cell disease in a student from Grenada, Walter Clement Noel. He had an anemia marked by red cells that looked like “crescents or sickles.” Noel returned to Grenada after training in dentistry.

Harvey Itano and Linus Pauling used the newly invented technique of protein electrophoresis to demonstrate that sickle hemoglobin (HbS) differed from normal hemoglobin (HbA).

Vernon Ingram at MRC in London used protein sequencing to demonstrate that HbS derived from a glutamic acid to valine amino acid change at position β-6. The recently elucidated genetic code allowed deduction of the nucleotide change (GAG → GTG).

* First demonstration of disease due to an abnormal protein

* First demonstration of disease due to a specific DNA mutation
MOLECULAR PATHOLOGY OF SCD

HEMOGLOBIN S POLYMERIZATION IS THE TRIGGER IN SICKLE CELL DISEASE

HBS POLYMERIZATION OCCURS DURING TRANSIT TIME THROUGH DEOXYGENATED MICROCIRCULATION

HbS Polymerization Delay Time ($T_d$)

Transit Time through Microcirculation

If Delay Time ($T_d$) > Transit Time, then RBC remains deformable and does not sickle

HEMOGLOBIN F (HBF) DOES NOT PARTICIPATE IN HBS POLYMERIZATION AND PRODUCES AN ASYMPTOMATIC CONDITION AT CONCENTRATIONS OF ~10-30%

Cases of individuals with Co-Inherited HbSS and Hereditary Persistence of Fetal Hemoglobin (HPFH)

<table>
<thead>
<tr>
<th>Cases</th>
<th>HbF (%)</th>
<th>Hb (g/dL)</th>
<th>Reticulocytes (%)</th>
<th>Irreversibly Sickled Cells (%)</th>
<th>Clinical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, 52 yo ¹</td>
<td>24%</td>
<td>12.5</td>
<td>N/A</td>
<td>N/A</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Female, 47 yo ¹</td>
<td>22%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Female, 16 yo ²</td>
<td>35%</td>
<td>14.0</td>
<td>1%</td>
<td>0%</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Female, 22 yo ²</td>
<td>26%</td>
<td>11.6</td>
<td>3%</td>
<td>0%</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Female, 24 yo ²</td>
<td>28%</td>
<td>12.8</td>
<td>2%</td>
<td>0%</td>
<td>Mild retinopathy</td>
</tr>
<tr>
<td>Male, 46 yo ²</td>
<td>30%</td>
<td>16.2</td>
<td>1%</td>
<td>0%</td>
<td>Mild retinopathy</td>
</tr>
<tr>
<td>Male, 39 yo ³</td>
<td>25%</td>
<td>16.4</td>
<td>N/A</td>
<td>N/A</td>
<td>No SCD manifestations except possibly aseptic necrosis of right hip</td>
</tr>
<tr>
<td>Female, 10 yo ⁴</td>
<td>20%</td>
<td>10.3</td>
<td>1%</td>
<td>N/A</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>28 cases ⁵</td>
<td>31% (mean)</td>
<td>13.0 (mean)</td>
<td>N/A</td>
<td>N/A</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Several cases (Hb Kenya-HbS) ⁵</td>
<td>10% (mean)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Mild microcytic anemia</td>
</tr>
</tbody>
</table>

³ Bethelletalvay N, Am J Hum Genet 1975
⁴ Stamatoyannopoulos G, Blood 1975
⁵ Akinsheye I, Blood 2011
FREQUENCY OF PAINFUL CRISES DECREASED BY 80% WITH EXTRACORPOREAL CARBAMYLATION

Frequency and Duration of Painful Crises (n=10)

Frequency of painful crises reduced by 80% comparing 24 months prior vs. 24 months with carbamylation
+ Total hospital crisis days decreased by 85% from 461 to 71 days
+ # of spontaneous crises decreased from 35 to 1

Complete healing of chronic ulcerations in 3/3 patients

D.Diederich, Journal of Clin Inv 1976. Frequency and duration of crises before and during extracorporeal carbamylation. Each crisis depicted by black bar with width of each bar proportionate to the duration of crises. Weekly carbamylation begun at week 0; subsequent carbamylation interruptions shown by the dotted areas in patients 2, 6, 7. Open active malleolar ulcerations in patients 8-10 is depicted by horizontal lines.
GBT104 DESIGNED TO HAVE TIGHTER INTERACTION. FOUND TO BIND MUCH FASTER THAN INN-312. INACTIVE IN WHOLE BLOOD.

GBT104
GBT324 IS ACTIVE IN WHOLE BLOOD, BUT NOT ORALLY AVAILABLE. HBS CO-CRYSTALLIZED WITH GBT324. 1:1 STOICHIOMETRY
VOXELOTOR (GBT440) FIRST ORALLY AVAILABLE COMPOUND. DRAMATIC PARTITIONING INTO BLOOD VS PLASMA

High partitioning believed to reduce risk of systemic toxicity via low plasma concentrations.
VOXELOTOR INHIBITS ABNORMAL HBS POLYMERIZATION, THE FUNDAMENTAL CAUSE OF SCD PATHOPHYSIOLOGY

VOXELOTOR

HbS Polymerization

Red Blood Cell Damage

Hemolytic Anemia

Vaso-occlusion

Organ Damage

Fatigue

Organ Damage

Pain Crisis

+ Stroke
+ Renal failure
+ Pulmonary HTN
+ Priapism
+ Leg ulcers
+ Mortality

001: STUDY DESIGN -- CHRONIC DOSING FOR 90 DAYS AND BEYOND

001: Phase 1/2, Randomized, Double-blind, Placebo-controlled Study in Adult HbSS, HbS/β0thalassemia, HbS/β+thalassemia, or HbSC Patients

Part A – Single Dose
+ Healthy volunteers: 5 cohorts (100, 400, 1000, 2000, 2800 mg)
+ SCD patients: 1 cohort (1000 mg)

Part B – Multiple Doses (15 and 28 days)
+ Healthy volunteers: 3 cohorts (300, 600, 900 mg per day x 15 days)
+ SCD patients: 3 cohorts (500 mg, 700 mg, 1000 mg per day x 28 days)
+ Variant genotype (HbSC): 1 cohort (600 mg per day x 28 days)

Part C – Multiple Doses (90 days)
+ SCD patients: 2 cohorts (700 mg, 900 mg per day x 90 days)

Cohorts = 8 people (6 active, 2 placebo)*

Objectives
+ Pharmacokinetics
+ Pharmacodynamics
+ SCD patients: hematologic parameters
+ Safety

024 (open-label extension study)
Extended dosing of voxelotor (Cohort 17, 900 mg) for a total of 6 months

*Except SCD patients in Part B: 500 mg cohort (10:4); 700 mg cohort (12:4)
001: 46% OF PATIENTS ACHIEVE HEMOGLOBIN RESPONSE >1 G/DL

*Day 15 data presented due to a protocol-specified dose reduction on Day 17 because of a large increase in Hb
**Patient documented non-adherence with study drug regimen
001: ALL PATIENTS DOSED WITH VOXELOTOR SHOWED A REDUCTION IN HEMOLYSIS, RETICULOCYTES AND/OR SICKLE CELLS

Change from baseline to end of treatment

- **Unconjugated bilirubin (%)**
  - Baseline: 2.0
  - Day 90: 2.0

- **% Reticulocytes (%)**
  - Baseline: 9.0
  - Day 90: 15.0

- **Irreversibly sickled cells (%)**
  - Baseline: 9.7
  - Day 90: 79.7

*Data available for n=4
*Data available for n=5

[Bar charts showing changes in levels of unconjugated bilirubin, reticulocytes, and irreversibly sickled cells from baseline to Day 90 for 700 mg voxelotor.]
001: SAFETY AND TOLERABILITY PROFILE

+ Voxelotor was well tolerated
+ No drug-related serious or severe adverse events
+ No evidence of tissue hypoxia
  - No increase in erythropoietin
  - No decrease in $O_2$ consumption with exercise
HOPE-KIDS 1 (007): Phase 2a Open-label, Single- and Multiple-dose Clinical Trial in Pediatric Population

**Part A – Single Dose**
- Cohort 1: SCD patients age 12-17: 600 mg
- Cohort 2: SCD patients age 6-11: 600 mg

**Part B – Multiple Doses**
- Cohort 1: SCD patients age 12-17: 900 mg per day x 24 weeks
- Cohort 2: SCD patients age 12-17: 1500 mg per day x 24 weeks
  - *EHA poster presentation provided results (24 weeks)*

**Objectives**
- Assess efficacy as measured by improvement in anemia
- Effect on clinical measures of hemolysis
- Effects on total symptom score (TSS) from PRO
- Pharmacokinetics
- Safety/tolerability
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>900 mg/d N=25 All Treated Patients to Date (Safety Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>14 (12-17)</td>
</tr>
<tr>
<td>HbSS genotype, n (%)</td>
<td>24 (96)</td>
</tr>
<tr>
<td>Number of VOCs in prior year, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (44)</td>
</tr>
<tr>
<td>1-4</td>
<td>12 (48)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Current HU use, n (%)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Baseline(^b) Hb, median (range), g/dL</td>
<td>8.9 (6.3-11.0(^c))</td>
</tr>
<tr>
<td>Baseline(^b) HbF, median (range), %</td>
<td>10.8 (3.7-29.0)</td>
</tr>
<tr>
<td>Baseline(^b) TAMM for TCD, median (range), cm/s</td>
<td>110 (74-149)</td>
</tr>
</tbody>
</table>

\(^a\)1 patient with HbS\(^b\) thal.
\(^b\)Baseline is the average of the values obtained prior to the first dose.
\(^c\)One patient had a baseline Hb level >10.5 g/dL.

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HbF, fetal hemoglobin; HU, hydroxyurea; TAMM, time-averaged mean of maximum velocity; TCD, transcranial Doppler ultrasound.
007: 43% OF PATIENTS ACHIEVED HEMOGLOBIN RESPONSE ≥1 g/dL AT 24 WEEKS

Not receiving concurrent hydroxyurea.

Documented noncompliance.
007: HEMOLYSIS MEASURES AT 24 WEEKS

Change from baseline median
N=21*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Median Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (%)</td>
<td>9.4</td>
</tr>
<tr>
<td>% Reticulocytes (%)</td>
<td>-22.9</td>
</tr>
<tr>
<td>Unconjugated bilirubin (%)</td>
<td>-38.6</td>
</tr>
</tbody>
</table>

*3 subjects discontinued dosing prior to 24 weeks (withdrew consent, lost to follow-up, noncompliance)
1 subject excluded due to a concurrent acute chest syndrome at week 24.
The STOP-1 study investigated RBC transfusions to reduce HbS concentration to <30 percent total hemoglobin in children with abnormal TCD

Key Findings:

+ In the standard-of-care group, the rate of stroke was 10 percent per year
+ Risk of stroke in the transfusion group was 92 percent lower (p=0.002) than the standard-of-care group over 30 months.
+ Within the transfusion group, 78 percent of patients had at least one hemoglobin S measurement that exceeded the target threshold.
+ Two years after publication of the STOP-1 study results, SCD stroke rates in the state of California dropped by a factor of 5.
The STOP-2 study assessed the discontinuation of transfusions vs. continued transfusions among children with receiving transfusions for abnormal TCD.

**Key Findings:**

+ Increase in stroke risk after discontinuation of transfusions
+ Probability of converting to normal TCD increased by 26.6% per 1g/dL increase in Hb
+ Transfusion group overall associated with +1.7 g/dL Hb and complete protection from stroke/abnormal TCD versus 39% risk

Adams, RJ, Brambilla, D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. NEJM 2005.
007: TRANSCRANIAL DOPPLER (TCD)-Hb RESPONDERS: TCD CHANGE AT WEEK 24 (N=8)

*One Hb responder did not have a TCD assessment performed at 24 weeks.*
Voxelotor 900 mg was well tolerated

Drug-related AEs were Grade 1 or 2 (except one Grade 3 rash*)

No drug-related SAEs

No study drug discontinuations due to AEs

*Did not recur with continued dosing
HOPE STUDY

Hemoglobin Oxygen Affinity Modulation to Inhibit HBS PolymeErization

A randomized, double-blind, placebo-controlled, multi-national, Phase 3 study
**031: ORIGINAL PHASE 3 HOPE STUDY DESIGN AND STATUS**

**SCD Patient Population:**
- 1-10 VOCs in prior year
- Baseline Hb ≤10.5 g/dL
- ≥12 years old
- Concomitant hydroxyurea allowed

**Part A**
- Randomize Up to 150 Patients
  - Voxelotor 1500 mg
  - Voxelotor 900 mg
  - Placebo

**Endpoints:**
- **Primary:** Proportion of patients who achieve a >1 g/dL Hb improvement at week 24
- **Key Secondaries:** PRO exacerbation days and/or Total Symptom Score, VOC requiring a HCP interaction, hospitalizations

**Part B**
- Randomize 250 SCD Patients
  - Voxelotor selected dose
  - Placebo

- 3 months treatment
- 6 months treatment

**In discussions with the FDA on registrational pathway for voxelotor, including potential accelerated approval**
031: 58% OF PATIENTS ON 1500 MG ACHIEVED PRIMARY ENDPOINT OF HB RESPONSE ≥1 g/dL AT 12 WEEKS (p<0.0001)
+ **Improvement in hemolytic anemia:** statistically significant and dose-dependent improvements in hemoglobin, reticulocytes and bilirubin occurred with both voxelotor doses
  - Improvements were similar in patients with or without background use of hydroxyurea. Approximately 64% of patients enrolled in Part A are on background use of hydroxyurea.

+ **Numerically fewer VOC episodes** in both voxelotor groups than in the placebo group.

+ **Voxelotor was generally safe and well tolerated** with similar safety profiles between the two doses. There was no evidence of tissue hypoxia at either dose.
The FDA instituted its Accelerated Approval Program to allow for earlier approval of drugs that treat serious conditions, and that fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. The use of a surrogate endpoint can considerably shorten the time required prior to receiving FDA approval.

- We believe voxelotor meets criteria for accelerated approval under subpart H:
  - SCD is a serious and life-threatening illness
  - Well-established association between chronic hemolytic anemia and SCD-related morbidity and mortality
  - Clinically meaningful increase in hemoglobin and improvement in hemolysis demonstrated in Part A results of the HOPE Study

- In discussions with FDA regarding potential accelerated approval
  - Requires post-marketing clinical studies to confirm clinical benefit and maintain approval
LOWER HEMOGLOBIN LEVELS ARE ASSOCIATED WITH NEGATIVE CLINICAL OUTCOMES IN SCD

<table>
<thead>
<tr>
<th>Clinical Outcome/Event</th>
<th>Δ Hb compared to those without clinical outcome/event*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (95% Confidence Interval), g/dL</td>
<td></td>
</tr>
<tr>
<td>Stroke/SCI History</td>
<td>-0.37 (-0.47, -0.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal TCD Velocity</td>
<td>-0.47 (-0.57, -0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>-0.65 (-0.84, -0.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated PASP</td>
<td>-0.94 (-1.20, -0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>-0.55 (-0.72, -0.39)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SCI – Silent Cerebral Infarct; TCD – Transcranial Doppler Ultrasound; PASP – Pulmonary Artery Systolic Pressure

*Meta-analysis conducted based on data from studies identified from a comprehensive systematic literature review evaluating 139 sickle cell disease peer reviewed publications published over the last 20 years; GBT data on file.
PREDICTED RISK REDUCTION OF STROKE, RENAL DISEASE, AND MORTALITY ASSOCIATED WITH INCREASING HB BY $\geq$ 1 G/DL*

*Based on meta-analysis conducted based on comprehensive systematic literature review evaluating 139 sickle cell disease peer-reviewed publications published over the last 20 years, GBT data on file.
Despite advances in clinical care, SCD shortens median lifespan by at least three decades.

People with SCD survive through adolescence roughly on par with those in the general population.

Lower hemoglobin levels lead to greater complications and mortality.

New therapies are needed to address the fundamental pathogenesis of SCD.

Voxelotor is uniquely suited to address unmet medical need.