Pathophysiology and Therapy in Sickle Cell Disease

Miguel R. Abboud, MD
Professor and Chairman
Department of Pediatrics and Adolescent Medicine
American University of Beirut Medical Center
Beirut, Lebanon
Disclosures

- Novartis: Ad Board
- Pfizer: Ad. Board
- Modus Pharmaceuticals: Research Support
- Global Blood Therapeutics: Research Support
- Pfizer: Ad. Board
- Astra Zeneca: Research Support
- Ely Lilly: Research Support
Multiple biological targets in SCD

β6 GTG

GAG → Glu → Valine

DNA

Protein

Cellular

End-organ

HbS solution

HbS polymer

Ischaemia-reperfusion
Hemolysis

Oxygenated

De-oxy

Adhesion
Oxidation
Inflammation
Coagulation

Slide courtesy of C. Hoppe.
# Myelo-ablative HLA-matched sibling transplants in SCD

<table>
<thead>
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</thead>
<tbody>
<tr>
<td><strong>Median F.U. (yrs)</strong></td>
<td>4.8 (3.2-7.9)</td>
<td>5.1 (0.25-14.8)</td>
<td>6 (1.6-17.5)</td>
<td>5.8 (1-12.5)</td>
<td>3 (1.3-9)</td>
<td>7.7 (0.4-21.3)</td>
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<td>160</td>
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<td>42</td>
<td>50</td>
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<td><strong>Age yrs</strong></td>
<td>3.3-15.9</td>
<td>2-27</td>
<td>2-22</td>
<td>1.2-19.3</td>
<td>2-16</td>
<td>0.9-31.8</td>
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<tr>
<td><strong>Primary engraftment %</strong></td>
<td></td>
<td></td>
<td></td>
<td>98</td>
<td>100</td>
<td>97.6</td>
<td>94</td>
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<td><strong>Graft rejection %</strong></td>
<td>10</td>
<td>15</td>
<td>3 [&gt;1992]</td>
<td>0</td>
<td>0</td>
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<td><strong>Acute GVHD %</strong></td>
<td>10</td>
<td>GII: 11.6</td>
<td>GII: 13</td>
<td>GII: 30</td>
<td>GI-II: 12</td>
<td>GI-II: 12</td>
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<tr>
<td></td>
<td></td>
<td>G III-IV: 8.1</td>
<td>G III-IV: 0</td>
<td>GIII-IV: 17.5</td>
<td>G III-IV : 10</td>
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<td><strong>Chronic GVHD %</strong></td>
<td>22</td>
<td>12.6</td>
<td>0</td>
<td>5</td>
<td>20</td>
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<tr>
<td><strong>Death %</strong></td>
<td>6</td>
<td>3</td>
<td>5 &gt; 2000</td>
<td>3</td>
<td>0</td>
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<td><strong>DFS%</strong></td>
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<td>85</td>
<td>95&gt;2000</td>
<td>92</td>
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<td>91</td>
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<td>Krishnamurti</td>
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<td>King</td>
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<tr>
<td></td>
<td>Reduced toxicity</td>
<td>Reduced intensity conditioning</td>
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<tr>
<td>year</td>
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<td>2008</td>
<td>2014</td>
<td>2015</td>
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<td>Median F.U. (yrs)</td>
<td>2.9 (0.4-7.5)</td>
<td>4 (2-8.5)</td>
<td>3.4 (1-8.6)</td>
<td>3.4 (0.7-11.8)</td>
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<tr>
<td>N</td>
<td>18</td>
<td>7</td>
<td>30</td>
<td>43 SCD + 9 thal</td>
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<td>Conditioning</td>
<td>BU, Flu alemtuzumab</td>
<td>BU, Flu, ATG, TLI</td>
<td>Alemtuzumab, TBI(300 cGy), sirolimus</td>
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<td>17-65</td>
<td>0.8-20.3</td>
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<td>Primary engraftment%</td>
<td>100</td>
<td>100</td>
<td>87</td>
<td>96</td>
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<td></td>
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<td>Graft rejection%</td>
<td>0</td>
<td>14 (N=1)</td>
<td>13</td>
<td>2</td>
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<tr>
<td>Acute GVHD%</td>
<td>GII-IV: 17</td>
<td>GII: 14 (N=1)</td>
<td>0</td>
<td>GI-III: 23</td>
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<tr>
<td>Chronic GVHD%</td>
<td>11</td>
<td>14 (N=1)</td>
<td>0</td>
<td>13</td>
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<tr>
<td>Death%</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>7</td>
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<td>TR-infections N=6 Sirolimus-toxicity N=5 Continued immunosuppress. N=3</td>
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<tr>
<td>EFS%</td>
<td>100</td>
<td>86%</td>
<td>87</td>
<td>91</td>
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</table>
Deaths observed in the international survey
*Gluckman et al, Blood 2016*

1000 SCD patients transplanted with HLA-id sibling
- 846 children: median age at HSCT: 9 yrs (0,3-16)
- 154 adults: median age at HSCT: 20 yrs (16-54)

<table>
<thead>
<tr>
<th>OS (%)</th>
<th>EFS (%)</th>
<th>Graft rejection (%)</th>
<th>a GVH (%)</th>
<th>C GVH (%)</th>
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<tbody>
<tr>
<td>92.9</td>
<td>91.4</td>
<td>2.3</td>
<td>14.8</td>
<td>14.3</td>
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</table>

70 deaths:
- infection: 14
- GVHD: 9
- toxicity: 9
- hemorrhage: 3
- secondary malignancy: 2
- no specified cause: 33
Survival among children and adults with sickle cell disease in Belgium: Benefit from hydroxyurea treatment

Kaplan-Meier estimate of Survival 15 years

Strata
- HSCT
- CT
- HU
- No Treatment

Time (years)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Survival Probability
0.7 0.8 0.9 1.0

Numbers at risk:
- HSCT: 90, 90, 89, 89, 89, 88, 83, 81, 76, 71, 69, 68, 65, 62, 59, 49
- CT: 24, 24, 24, 23, 23, 22, 20, 19, 18, 17, 17, 16, 13, 11, 9, 9
- HU: 185, 185, 185, 182, 178, 175, 166, 156, 145, 138, 126, 119, 108, 99, 85, 77
- No Treatment: 170, 168, 156, 147, 131, 112, 102, 88, 79, 77, 64, 57, 51, 41, 37, 35

Current therapy: hydroxyurea (HU)

- Only approved drug therapy for SCD
- Decreases rates of pain and acute chest syndrome
- Besides HbF induction, additional biological effects include
  - decreased WBC count
  - decreased adhesion on reticulocytes
  - in vivo nitric oxide (NO) release
- Data suggest an impact on mortality
- Short- and long-term side-effects are acceptable
  - (male fertility?)

Still, 1/3–1/2 of patients do not respond to HU

Boxplot of total sperm count at inclusion (M0) and after six months of hydroxyurea treatment (M6)
The sickle red blood cell (SS RBC) as source of multiple pathophysiologic pathways.

Marilyn J. Telen Blood 2016;127:810-819
HbF Modulators
Reducing HbS polymerization ameliorates disease severity...

- **Hallmark of disease**
  - HbS polymerization leads to characteristic sickling and oxidative membrane damage

- **Symptoms**
  - vary in frequency and severity in relation to HbF levels

**HbF prevents polymerization**

**When deoxygenated**

- HbS molecules polymerize into long fibres; rigid, dehydrated, adherent sickle cells
Hypomethylating agents

Demethylation

- Open chromatin
- Permits transcription
- Gene expression

Methylation

- Closed chromatin
- Prevents transcription
- Gene silencing

5-azacytidine, decitabine

5-Aza, 5-azacytidine; Dec, decitabine; DNMT, DNA methyltransferase.
DNA methyltransferase inhibitors

5-azacytidine

- Increased HbF in baboons and humans with SCD and β-thal
- No further trials due to carcinogenesis concerns (in rat model)

Decitabine

- Analogue of 5-azacytidine, i.v. or s.c.
- Decreased incidence of tumors in animal models renewed interest in SCD
- Increased γ-globin synthesis, HbF, F cells, total Hb (in all patients)
- DLT: reversible neutropenia, thrombocytosis

Open trials

- Phase 1 RCT – p.o. decitabine + THU (inhibits intestinal metabolism of decitabine; extends absorption time and S-phase depletion of DNMT)¹
- Phase 2 – high-risk patients with SCD²

¹ NCT01685515.
² NCT01375608.

DLT, dose-limiting toxicity; RCT, randomized controlled trial; THU, tetrahydouridine.
Phase 1/2 clinical trial of oral THU + decitabine in SCD

- Cytidine deaminase (CDA) rapidly deaminates the deoxycytidinede analogue decitabine (Dec) and the DNMT1-depleting cytidine analogue 5-azacytidine.

- CDA expression is particularly high in the intestines and liver; a barrier to the oral bioavailability of cytidine analogues.

- Phase 1/2 clinical trial combined oral Dec with a CDA inhibitor oral THU in patients with high-risk, hydroxyurea-refractory SCD.  

1. NCT01685515.
Anti-Sickling Agents
Hemoglobin S Polymerization is the root cause of Sickle Cell Disease

5-hydroxymethyl-2-furfural modifies intracellular sickle Hb and inhibits sickling of RBCs.

Allosteric effect on Hb

O$_2$ saturation (%) vs PO$_2$ (mmHg)

CTRL (DMSO)  Vanillin  FUF  5HMF

5-hydroxymethyl-2-furfural modifies intracellular sickle Hb and inhibits sickling of RBCs: reduced sickle cell mouse deaths when exposed to severely low oxygen level

GBT440: Designed to Bind Hemoglobin with High Selectivity

- Binds to hemoglobin α chain → stabilizes oxygenated conformation
- Properties indicate high selectivity for hemoglobin
  - 1:1 binding of GBT440 to Hb tetramer
  - Preferential partitioning into RBCs (75:1 for SCD; 90:1 for HV)
  - Potent, dose-dependent increase in hemoglobin-oxygen affinity
- Same binding site and mechanism for HbS and HbA
GBT440 increases haemoglobin oxygen affinity, reduces sickling and prolongs RBC half-life in a murine model of sickle cell disease
GBT440 (formerly GTx011)

- Oral, once daily, direct-acting hemoglobin modifier

- Prevents sickling of RBCs: increases hemoglobin’s affinity for oxygen, inhibits polymerization of HbS, restores normal RBC function in preclinical SCD models

- Phase I/II trial of GBT440 in SCD started in December 2014
  Update at ASH 16 patients with SCD

- Increases in Hb decreases in reticulocyte counts and LDH

- No untoward event related to hypoxia

- Headaches

NCT02285088.
Hennaway C ASH 2015 abs 542
Phase 3 HOPE Study Design

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

**Endpoints:**
- **Primary:** Proportion of patients who achieve a > 1 g/dL Hb improvement at week 24
- **Key Secondary's:** Days with a SCD exacerbation (PRO), Total Symptom Score (PRO), VOC requiring a HCP interaction

**Part A**
- Randomize Up to 150 Patients
  - GBT440 1500 mg
  - GBT440 900 mg
  - Placebo

**Part B**
- Randomize 250 SCD Patients
  - GBT440 Selected dose
  - Placebo

- Select dose
- Finalize secondary endpoints

**Part A**
- 3 months treatment

**Part B**
- 6 months treatment

- Announce Top Line Data (1H:2019)
Cell adhesion blockers
Adhesive interactions involving SS RBCs. (A) Multiple interactions between SS RBCs and endothelial cells, extracellular matrix, and plasma proteins.
Selectins mediate WBC adhesion, rolling

Neutrophil entry into tissues

<table>
<thead>
<tr>
<th></th>
<th>P selectin</th>
<th>E selectin</th>
<th>L selectin</th>
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<tr>
<td>Expressed on</td>
<td>Endothelial Cells</td>
<td>Endothelial cells</td>
<td>Leukocytes</td>
</tr>
<tr>
<td>Platelets</td>
<td>CD11a</td>
<td>CD11b</td>
<td>CD15c</td>
</tr>
<tr>
<td>Time to expression</td>
<td>Minutes</td>
<td>Hours</td>
<td>Constitutive</td>
</tr>
<tr>
<td>Role in Adhesion</td>
<td>Initiates</td>
<td>Tighter interactions</td>
<td>Leukocyte interactions</td>
</tr>
<tr>
<td></td>
<td>Slows leukocytes</td>
<td>Signaling</td>
<td></td>
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</tbody>
</table>

- L-selectin
- E-selectin
- P-selectin

CD11a, CD11b, CD15c

Fibronectin, Collagen, Extracellular matrix, Laminin

Attachment (rolling)

Adhesion

Diapedesis

IL-8

Table:

<table>
<thead>
<tr>
<th></th>
<th>P selectin</th>
<th>E selectin</th>
<th>L selectin</th>
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</tr>
<tr>
<td></td>
<td>Slows leukocytes</td>
<td>Signaling</td>
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</tr>
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</table>
• Select expressed on endothelial cells, platelets, and leukocytes, as well as other cell types\(^1\)

• P-selectin and E-selectin mediate rolling and tethering of blood cells to the endothelium\(^2\)
  • may initiate vaso-occlusion in the post-capillary venules\(^2\)

• SCD cellular and animal models: interruption of selectin-mediated cellular adhesion decreases erythrocyte and leukocyte adhesion to the endothelium and improves blood flow\(^3\text{--}^7\)

Selectin inhibitors

- **GMI-1070 (rivipansel, Pfizer):** pan-selectin inhibitor
  - phase 2 trial completed in 76 adults treated for VOC\(^1\)
    - i.v. dosing twice daily in hospital until resolution
    - reduction in duration of VOC, hospitalization, opioids
  - phase 3 multicentre trial planned\(^2\)
- **Sel-G1 (PselhmAb, Selexys Pharmaceuticals):** anti-P-selectin humanized monoclonal antibody
  - T1/2 21 days given q month prevention of VOC
  - phase 1: 100% blockade after single i.v. dose x 28 days
  - phase 2 trial (175 patients, 70 sites) just started\(^3\)
    - i.v. infusion q month x 12 months
    - primary end-point: annual rate of VOC
- **Pentosan polysulfate sodium (TRF Pharma) oral**
  - phase 1 study: single p.o. dose improved microvascular blood flow\(^4\)
    (shortened duration of hyperaemia, as measured by laser Doppler velocimetry)

Randomized phase 2 study of GMI-1070 in SCD: clinical end-points

Randomized phase 2 study of GMI-1070 in SCD: decreased opioid use

Hourly i.v. opioid analgesic use (MEU/kg)

Day 1  Day 2  Day 3  Day 4  Day 5  Day 6  Day 7

Placebo
GMI-1070  p = 0.010

Phase 2 study to assess safety and impact of SelG1 ± HU therapy in SCD patients with pain crises

**Study design**

**Eligibility criteria**
- Adults
- Common SCD genotype
- Stable HU or EPO dose (if prescribed)
- 2–10 acute painful episodes in past 12 months

**Randomization (n = 174)**
- High-dose SelG1
- Low-dose SelG1
- Placebo

**Treatment**: 12 months in form of 14 i.v. injections

**Primary end-point**
- Rate of SCD-related painful episodes (“crises”) within 1 year

**Secondary end-points**
- 1-year rate of SCD-related painful episodes comparing concomitant use or non-use of HU
- Time to 1st SCD-related painful episode
- Time to 2nd SCD-related painful episode
- Number of hospitalization days per year
- Absolute change from baseline in Hb concentration
- Absolute change from baseline in LDH concentration

NCT01895361.
• In this yearlong trial involving patients with sickle cell disease, crizanlizumab, an antibody to P-selectin, was associated with a 45% lower rate of pain crises than placebo and a longer time to their onset.

• Adverse events included arthralgia, diarrhea, and pruritus.
Kaplan–Meier Curves for the Median Times to the First and Second Sickle Cell–Related Pain Crises, According to Trial Group.

Heparins

- Heparin and heparin sulfate bind selectins
- Initial trial of tinzaparin showed efficacy in painful crises\(^1\)
- Lower doses need to bind selectins
- Sulfated non-anticoagulant heparin have been shown to inhibit adhesion of sickle red cells to endothelium;\(^2\) no effect on coagulation
- Sevuparin anticoagulant activity removed through chemical depolymerization removing AT binding domain
- Sevuparin has potential to reach larger target group due to mechanism, study with rivipansel excluded patients with infections, underlying cause of VOC. Phase 2 trial on going (Dilaforette now Modus and Karolinska development)\(^3,4\)

Platelet inhibitors in SCD

- Prasugrel Platelet P2Y12 ADP receptor antagonist
- Phase 2 study completed: 57 SCD patients, oral prasugrel vs placebo x 30 days
  - Primary safety end-point
    - no haemorrhagic events (requiring medical intervention)
  - Secondary end-points
    - decreased pain rate (21% reduction pain days), intensity
    - 33–40% platelet inhibition (VerifyNowP2Y12, VASP)
    - decreased platelet activation (cellular and sP-selectin, sCD40 ligand, TXB2, and prothrombin fragment F1.2)
- Phase 2 study in children completed: no decrease is VOC but trends to improvement
  - largest randomized trial in SCD
- Ongoing trials of ticagrelor in adults and children

## Rates of Vaso-Occlusive Crises According to Demographic Group

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo</th>
<th>Prasugrel</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients</td>
<td>events/person-yr</td>
<td>no. of patients</td>
</tr>
<tr>
<td>Vaso-occlusive crises in all patients</td>
<td>170</td>
<td>2.77</td>
<td>171</td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
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</tr>
<tr>
<td>2 through 5 yr</td>
<td>33</td>
<td>2.31</td>
<td>34</td>
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<tr>
<td>6 through 11 yr</td>
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<td>2.38</td>
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<tr>
<td>12 through 17 yr</td>
<td>71</td>
<td>3.21</td>
<td>71</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Female</td>
<td>86</td>
<td>2.89</td>
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<tr>
<td>Male</td>
<td>84</td>
<td>2.64</td>
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<td><strong>Race</strong></td>
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<td>White</td>
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<tr>
<td>Black</td>
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<td>3.24</td>
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<td><strong>Geographic region</strong></td>
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<tr>
<td>Africa</td>
<td>72</td>
<td>2.97</td>
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<tr>
<td>Americas</td>
<td>29</td>
<td>3.36</td>
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<td>Middle East and Turkey</td>
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<td>≥15.8</td>
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<td>HbSβ⁰</td>
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<tr>
<td>No</td>
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<td>2.68</td>
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Anti-inflammatory Agents
The role of adenosine and adenosine receptors in SCD

Increased 2,3-DPG in erythrocytes

†High HbS polymerization

†Haemolysis, organ damage, priapism

Worsen SCD

Inhibits SCD-activated NKT cells

Cytoprotective and anti-inflammatory

Improve SCD

Specific A\textsubscript{2B} inhibitors

Specific A\textsubscript{2A} activators

SCD therapy

A\textsubscript{2B}

A\textsubscript{2A}

DPG, diphosphoglycerate; PEG-ADA, polyethylene glycol-modified adenosine deaminase; PKA, protein kinase A.

Role of iNKT cells in the treatment of VOC in SCD

- Reduction of inflammation constitutes a strategy to treat VOC
  - studies of corticosteroids provided some of the first evidence that anti-inflammatory medications may improve VOC in patients with SCD\(^1,2\)
- Invariant NKT (iNKT) cells are a lymphocyte subset that can be rapidly activated to produce cytokines
- Inflammatory responses implicated in SCD pathogenesis
- In mouse models of SCD, interrupting the activation of iNKT cells decreases tissue injury\(^3\)
- Adenosine A\(_{2A}\) receptor agonists decrease iNKT cell number and activation
- NKTT120 is a humanized monoclonal antibody directed against a unique epitope on the invariant T-cell receptor of iNKT cells\(^4\)
- Patients need to be monitored for risk of infection

Inhibition of iNKT cells by regadenoson, an A$_{2A}$ receptor agonist

- Invariant NKT cells are central to I/R pathogenesis
  - small subset of T cells that have increased expression of A$_{2A}$ receptors
- In SCD mouse model
  - depleting/blocking iNKT cells inhibits pulmonary inflammation
  - adenosine$_{2A}$ receptor agonist (acting through iNKT cells) decreases pulmonary injury at baseline and following I/R
- iNKT cells elevated and activated in SCD patients with VOC
- Phase 1 study: regadenoson infusion during VOC
  - safe at highest doses evaluated (no change in cardiovascular function)
  - decreased inflammatory markers (NF-kB, IFN-γ)
  - improvement in pain


IFN, interferon; NF-kB, nuclear factor kappa B.
In adults with steady-state SCD, NKTT120 at doses up to 0.3 mg/kg reduces iNKT cells without dose-limiting toxicity


**Time to recovery of iNKT cells correlates with the circulating levels at the beginning, with a longer recovery time for lower cell numbers**

NKTT120 received FDA fast-track designation in October 2014\(^1\)
Role of statins

Statins

HMG-CoA reductase

HMG-CoA

Mevalonic acid

Cholesterol

Prenylated proteins Rac and Rho

Rac

Rac A

Rho

Rho A

PI3-K → Akt

↑eNOS → ↑NO

ROS

ROCK

Role of statins
Simvastatin reduces vaso-occlusive pain in sickle cell anaemia: a pilot efficacy trial
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>HC ($n = 10$)</th>
<th>No HC ($n = 9$)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>NOx ($\mu$mol/l)</td>
<td>21.4</td>
<td>28</td>
</tr>
<tr>
<td>hs-CRP (mg/l)</td>
<td>1.8 (1.2, 2.9, 9)</td>
<td>1.05 (0.58, 1.7)</td>
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<tr>
<td>sE-selectin (ng/ml)</td>
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<td>177.6</td>
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<tr>
<td>sP-selectin (ng/ml)</td>
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<tr>
<td>sVEGF (ng/ml)</td>
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<td>96.0</td>
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<tr>
<td>sICAM-1 (ng/ml)</td>
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<td>sICAM-3 (ng/ml)</td>
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<tr>
<td>sVCAM-1 (ng/ml)</td>
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Hemolysis and vasculopathy (1)

RBC hemolysis

Hb

Hb-dimer

O₂

Met-Hb

Ferric heme

Liver degradation

Haptoglobin

CD 163

Macrophage degradation

Hemopexin

Hemolysis and vasculopathy (2)

RBC hemolysis

Ornithine ⇔ L-Arginine ⇔ NO

Arginase

↓ NO synthesis

Hb

Hb-dimer

2NO

Met-Hb

2NO₃⁻

Ferric heme

NO scavenging

NO depletion

• Endothelial cell dysfunction
• Platelet activation & aggregation
• Impaired regulation of smooth muscles

• Local vasoconstriction
• Smooth muscle dystonias
• Intravascular thrombosis

Arginine for the treatment of VOC in SCD

Arginine i.v. or oral for 5 days or until discharge is safe and inexpensive and may be a beneficial adjunct to standard therapy in VOC

L-glutamine for the treatment of HbSS and Sβ0

In a randomized (2:1), double-blind, placebo-controlled, parallel-group trial of 230 patients, L-glutamine at 0.6 g/kg/day (max 30 g) reduced the incidence of SCD crisis, hospitalizations, ACS, and increased time to first crisis.

Hemopexin (Hx)

Hemopexin (Hx) administration normalizes blood pressure and improves cardiac function in sickle cell disease (SCD) mice

β-Thalassemia Major and SCD
Gene therapy
Hematopoietic stem cells

Gene Therapy Schematic Approach

Vector carrying the therapeutic gene

Reinfusion

Transduction
Engraftment with Transduced Cells and Therapeutic Gene Expression in the Patient.

Strategies for gene therapy for SCD: schematic overview of various approaches for correcting the sickle phenotype via gene therapy.

Reactivation of HbF by targeting BCL11A by genome editing

- BCL11A is involved in the suppression of HbF
- A developmental stage-specific, lineage-restricted enhancer controls expression of BCL11A in erythroid cells

Therefore, it might be possible to delete, by genome editing, BCL11A or this specific enhancer and prevent expression of BCL11A in HSC cells or only in erythroid cells
Conclusions

• Many studies are ongoing or planned to evaluate potential agents
• Studies have been slow to accrue
• Combination therapy may be more effective than single agents
• The future looks bright
"Every great dream begins with a dreamer. Always remember, you have within you the strength, the patience, and the passion to reach for the stars to change the world."

Harriet Tubman
Children with SICKLE CELL DISEASE

THEY HAVE THE RIGHT TO PLAY, LOVE, DREAM & LIVE.

SEVEN SISTERS
Beirut

October 2, 2017. at 8.30PM

A Collaboration between AUBMC
LETTERS

Transfusion independence and HMGA2 activation after gene therapy of human β-thalassaemia

Marine Cavazzano-Calvo1,2,*, Emmanuel Payen1,3,4, Olivier Negre1,4,5,*, Gary Wang6, Kathleen Hehir6, Floriane Fustianni1,4, Julian Down3, Maria Denero1, Troy Brady7, Karen Westerman1,8, Resy Cavallesco1, Beatrix Gillet-Legrand1, Laure Caccavale1, Riccardo Sgarra1, Leila Maouche-Cherif1,2, François Bernaudin1, Robert Giriot7, Ronald Dorazio1, Geert-Jan Malden1, Axel Polack7, Arthur Bank3, Jean Soulier7, Jérôme Larghero8, Nabil Kabbara1, Bruno Dalle9, Bernard Goumelon1, Gérard Socie1, Stany Chéritton1,4, Nathalie Cartier1, Patrick Aubourg1, Alain Fischer1, Kenneth Cornetta1, Frédéric Galacteros1, Yves Beuzard1,2, Eliane Gluckman1, Frederick Buhman1, Salima Hacein-Bey-Abina1,2,8, Philippe Leboulch1,2,8.*

GENE THERAPY

β-Thalassemia Treatment Succeeds, With a Caveat

Downloaded from www.sciencemag.org on March 10, 2010
CRISPR/Cas9 and rAAV6-mediated targeted integration at the *HBB* locus in human CD34+ HSPCs

Correction of the Glu6Val mutation in SCD patient-derived HSPCs