Sickle Cell Disease: A Look to the Future

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Industrial Relationships

- Scientific Advisory Board: Aileron, Inc
- Consultant: NK Therapeutics, Inc
RESULTS

Clinical data and observations. Earlier hematologic data on the patients used in these studies are shown in Table 1. In no patient did any

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10.2 ± 2.3</td>
<td>9.5 (8.5-10.5)</td>
<td>9.0-11.0</td>
<td>0.05</td>
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<tr>
<td>B</td>
<td>8.8 ± 1.2</td>
<td>8.5 (8.0-9.0)</td>
<td>8.0-9.5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Mean (±SD) of 30 cells.
Figure 2: Distribution of RBC on subconfluent culture plates stained with Giemsa after the fifth plate wash. Sickle RBC distribute themselves in rosette-like clusters around endothelial cells (A), whereas normal RBC are present in fewer numbers and are randomly distributed (B). ×375.
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Hypoxia/Reoxygenation: A Mouse Model of ACS

NY1DD-Vehicle-H/R  NY1DD-ATL146e-H/R

3 h hypoxia (8% O$_2$) 18h reperfusion (air)
A2A agonist started 3 h after reperfusion
Human Blood
Working Model

Antigen Presenting Cell

Tissue injury

lipids

Invariant Natural Killer T Cell

IFN-γ, IL-4, others

Inflammatory mediators (IL-12, IL-18)

A2A R

Regadenoson
Regadenoson Pharmacokinetics

Plasma Concentration (ng/ml) vs. Hours since infusion start

Infusion start: 0
Infusion end: 3
Dose level 0
Dose level 1
Dose level 2
ED50

Hours since infusion start:
1
6
12
18
Subject 9: NFkB during infusion

Mean fluorescence intensity

T cells
Pre-drug
iNKT
1 hr
iNKT
6 hr
iNKT
12 hr
iNKT
18 hr
iNKT
NFκB+ Cells In Activated Gate: Dose Level 2

Fraction of NFκB activated cells

Infusion start

Infusion end

N=5

Hours

1 6 12 18
Proposed Future Studies

- Pilot Study of Regadenoson for the Treatment of Acute Chest Syndrome
  - Primary endpoint: Accrual
- Phase II Trial of Regadenoson for the Treatment of Acute Vaso-occlusive Episodes
  - Primary endpoint: Reduction in inflammatory biomarkers
- Anti-NKT cell monoclonal antibody
Acute and Chronic VOC

• Pain and ACS leading to hospitalization are the tips of the iceberg.

• Thirty percent of adults with SCD report pain on a daily basis.

    Smith et al 2008
iNKT Cell Depletion by NKTT120 (Standard IgG1)
DNA Sequence Polymorphism

- Common SNPs may be biologically trivial or evolutionarily constrained and thereby important in some way.
- Rare variants associated with mendelian disorders are much more apt to be important so full DNA sequencing should be useful (up to a point)
- But “guilt by association” often leads to a dangerous conclusion (SNPs around CRP show big effects in heart disease but obviously have no causal relationship)
Exceptions Prove the Rule

- BCI11A discovered in a common SNP search related to fetal hemoglobin and has a big effect size (ten percent)
- Three other SNPs related to fetal hemoglobin bring the total effect size to near fifty percent
- Alpha thalassemia is also clearly associated with decreased severity
- Yet published and unpublished GWAS that evaluate severity do not reveal HbF associated SNPs or SNPs that might relate to alpha globin synthesis. Faint association with TGF beta suggesting that inflammation might be important
WILL GENOME SEQUENCING REVEAL THERAPEUTIC LEADS IN SCD?

• “Unbiased” research=fishing expedition
• Hypothesis should precede not follow technology application in science
• “Guilt by association” is dangerous in medicine as well as law
• Poorly crafted GWAS are worse than no studies at all
• Best to compare lowest five percent and highest five percent for each severity category
SCD ATTACK POINTS

• Increase delay time with a small molecule without changing O2 affinity (cyanate which does change affinity and is neurotoxic) or a stapled peptide that would compete with Val 6
• Increase or introduce a hemoglobin (HbF or Hb Korle Bu) with hydrophobic binding to val 6 in HbS, prolongs delay time and inhibits stacking of polymers by forming hybrids (hydroxyurea and/or BCL11A inhibition)
• Hematopoietic stem cell transplant
• Gene therapy by excision and replacement by a non S allele
• Suppression of inflammation and ischemia reperfusion injury
• Prenatal diagnosis
• Control asthma