19th Post-ASH Meeting
58th ASH San Diego, California
Red blood cells disorders

Béatrice GULBIS
LHUB-ULB

January 13, 2017
Take home message?

• **Education program:**
  
  Single-dose intravenous iron for iron deficiency: a new paradigm *Michael Auerbach and Thomas Deloughery*
  
  – Vit B12
    • From IM to oral administration
  
  – Iron
    • From long duration oral to single-dose IV iron administration
Agenda

• Diagnosis
• From research to new therapeutic options
• Gene therapy: where are we?
• Share of experiences, innovation
Diagnosis

• Editorial
  – When One Diagnosis Is Not Enough
    • Kym M. Boycott, M.D., Ph.D., and A. Micheil Innes, M.D.
  – An accurate diagnosis is essential for effective medical management; in the case of rare genetic disease, it also guides genetic counseling. Nevertheless, clinical assessments and conventional genetic testing lead to a diagnosis in less than half of patients.
Diagnosis

- **Education program:**
  New challenges in evaluating anemia in older persons in the era of molecular testing *David P Steensma*

✓ Efforts to explain « unexplained » anemia: possibility of MDS?

*Panel of 98 genes/ exons focused on haematologic malignancies*

- ABL e2-e10
- BCOR e2-e15
- CALR e9
- CSF1R e22
- CUX1 e1-e21
- ...

CHIP – Clonal haematopoiesis of Intermediate Potential
Diagnosis

• Hereditary haemolytic anaemia
Diagnosis

• Hereditary haemolytic anaemia
  – Phenotype (Clinical, laboratory tests, ...)
  – Genotype: focus on one gene or even one exon
Diagnosis

- Gene panel – "Mendeliome"
Diagnosis

- Unexplained or doubtful diagnosis of haemolytic anaemia?
  - A panel of 28 genes or more

Table II. Genes included in the panel.

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>Transcript</th>
<th>OMIM gene</th>
<th>Disorder</th>
<th>Inh</th>
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<tbody>
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<td>NM_000022</td>
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<td>CYP2R1</td>
<td>Cytochrome b5 reductase 3 (DIA1)</td>
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<td>GPB</td>
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<td>HK1</td>
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<td>NTSC3A</td>
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<td>FFKL</td>
<td>Fructose 1,6-bisphosphatase</td>
<td>NM_000262</td>
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<td>PKM</td>
<td>Phosphofructokinase, muscle</td>
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<td>PGK1</td>
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<td>311800</td>
<td>PGK1 deficiency</td>
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<td>FER101</td>
<td>Pero-type mechanosensitive ion channel component 1</td>
<td>NM_001142864</td>
<td>611194</td>
<td>Xerocytosis (hereditary)</td>
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<td>PKLR</td>
<td>Pyruvate kinase (liver and RBC)</td>
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<td>SLC4A1</td>
<td>Solute carrier family 4, anion exchanger, member 1, band 5</td>
<td>NM_000342</td>
<td>108270</td>
<td>Spherocytosis, Blood group variation, Anaemia, Stomatocytosis, Acanthocytosis, Kernicterus (jaundice), Ovalecotosis, Hyperbilirubinemia (reeter type), Retor syndrome</td>
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<td>SLC0A1B1</td>
<td>Solute carrier organic anion transporter family, member 1B1</td>
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<td>Hyperbilirubinemia (reeter type), Retor syndrome</td>
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<td>Solute carrier organic anion transporter family, member 1B3</td>
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<td>SPTA1</td>
<td>Spectrin alpha</td>
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<td>UDP glucuronosyltransferase 1 family, polypeptide A1</td>
<td>NM_000463</td>
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<td>UGT1A6</td>
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<td>UGT1A7</td>
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<td>UGT1A7 deficiency</td>
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</table>
Agenda

• Diagnosis
• From research to new therapeutic options
• Gene therapy: where are we?
• Share of innovation
From research to new therapeutic options
Sickle cell disease

Blood 2016 127:810-819
From research to new therapeutic options
Sickle cell disease

- RBC dehydration
- Free Heme
  - Free Hb
- Adhesive interactions
- Inflammation
- Activation coagulation
- HSCT
- Hydroxyurea
- RBC transfusion
From research to new therapeutic options
Sickle cell disease

- RBC dehydration
- Free Heme
- Free Hb
- Adhesive interactions
- Inflammation
- Activation coagulation

Hydroxyurea
From research to new therapeutic options
Sickle cell disease

- RBC dehydration
- Free Heme
- Free Hb
- Adhesive interactions
- Inflammation
- Activation coagulation

It works for everyone who takes it every day...
Hydroxyurea Adherence for Personal Best in Sickle Cell Treatment (HABIT clinical trial)
Dedicated information, home visit, SMS, ...

Green NS - Poster 1310 – Dec 3
From research to new therapeutic options
Sickle cell disease

Paper N° 317 Kuo KHM Comprehensive structured transition program with dedicated navigator reduced lost follow-up and improved medication adherence ...

Transition navigator

- RBC dehydration
- Free Heme Free Hb
- Adhesive interactions
- Inflammation
- Activation coagulation

Figure 1: Patient flow diagram through the transfer/transition process
From research to new therapeutic options
Sickle cell disease

- **Hypothesis:**
  target the same biochemical pathway as for HU but
  - Not neutropenic, mutagenic, or teratogenic, and no impact on embryogenesis

- **Animal models**
- **Ongoing trial**
  on healthy volunteers
From research to new therapeutic options
Sickle cell disease

• New treatments for SCD, why?
  – Shorten the course of acute vaso-occlusive events
  – Prevention of adverse events related to vasculopathy
  – ...

  – Improvement of quality of life
    • Pain
    • Length of hospital stay
    • ...
From research to new therapeutic options
Sickle cell disease

• New targets

Anti-sickling agent
From research to new therapeutic options
Sickle cell disease

- Anti-sickling drug

<table>
<thead>
<tr>
<th>Hemoglobin-modifying and anti-sickling agents</th>
<th>Study Name</th>
<th>ID Number</th>
<th>Drug/Antagonist</th>
<th>Status</th>
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<td>Dose-Escalation Study of SCD-101 in Sickle Cell Disease</td>
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<td>SCD-101</td>
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<td>Invenux: SUNY-Downstate Med Ctr</td>
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<td>Safety Study of MP4CO in Adult Sickle Cell Patients</td>
<td>NCT01356485 Phase 1</td>
<td>MP4CO</td>
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<td>Sangart</td>
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<td>Study of SANGUINATE™ Versus Hydroxyurea in Sickle Cell Disease (SCD) Patients</td>
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<td>Prolong Pharmaceuticals</td>
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<td>Study of SANGUINATE™ In the Treatment of Sickle Cell Disease Patients With Vaso-Occlusive Crisis</td>
<td>NCT02411708 Phase 2</td>
<td>Sanguinate</td>
<td>Ongoing</td>
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<tr>
<td>A Study of the Efficacy and Safety of ICA-17043 (With or Without Hydroxyurea) in Patients With Sickle Cell Anemia.</td>
<td>NCT00040677 Phase 2</td>
<td>Senicap (ICA-17043)</td>
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<tr>
<td>A Stratified Sickle Event Randomized Trial (ASSERT)</td>
<td>NCT00102791 Phase 3</td>
<td>Senicap (ICA-17043)</td>
<td>Terminated (lack of efficacy)</td>
<td>Icagen</td>
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Telen MJ - Blood 2016 127:810-819
From research to new therapeutic options
Sickle cell disease

- Anti-sickling drug

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From research to new therapeutic options
Sickle cell disease

• Anti-sickling drug

Botanical drug; Mechanism?
Phase 1B dose escalation
Primary Outcome Measures:
Safety, tolerability, and dose limiting toxicities of escalating doses

FU: 6 weeks, frequency and severity of adverse events, laboratory assessments as compared to baseline

26 patients: stable SCD, no HU (6 M), no transfusion (90 days)
Results: no significant change in haemolysis
Clinical benefit: pain, fatigue, sleep, ulcer healing

...
From research to new therapeutic options
Sickle cell disease

• New targets

Agents interfering with RBCs-vascular adhesion events
- Reversal of adhesion mediated VO events
- Blockade of adhesive mechanisms
- Modulation inflammatory pathways
- Anti-PLTs
- Anti-coagulant

Anti-sickling agent

Hemolysis
RBC sickling
HbS gelation
Dehydration
Activation of coagulation

Inflammatory stimuli:
- WBC activation
- Endothelial cell activation
- Platelet activation
- Proinflammatory cytokine production
- Expression and activation of cell adhesion molecules on endothelial cells, platelets, and leukocytes

Adhesive interactions
From research to new therapeutic options
Sickle cell disease

- Reversal of adhesion mediated VO events

Recently completed and ongoing studies targeting adhesion

<table>
<thead>
<tr>
<th>Study title</th>
<th>Clinical trials #/Phase</th>
<th>Intervention</th>
<th>Status</th>
<th>Primary sponsor</th>
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<tbody>
<tr>
<td>Study of GMI-1070 for the Treatment of Sickle Cell Pain Crisis</td>
<td>NCT01119833 Phase 2</td>
<td>GMI-1070 (rivipansel)</td>
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<td>GlycoMimetics</td>
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<td>Efficacy and Safety of Rivipansel (GMI-1070) in the Treatment of Vaso–Occlusive Crisis in Hospitalized Subjects With Sickle Cell Disease</td>
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<td>GMI-1070 (rivipansel)</td>
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<td>Pfizer</td>
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<td>Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises</td>
<td>NCT01895361 Phase 2</td>
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<td>Sevuparin Infusion for the Management of Acute VOC in Subjects With SCD</td>
<td>NCT0215838</td>
<td>Sevuparin</td>
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<td>Dilaforette</td>
</tr>
</tbody>
</table>

**β blockers**

- Study of Propranolol as Anti-Adhesive Therapy in... (Phase 3)
- Propranolol and Red Cell Adhesion in Non-asthmatic... (Phase 3)

**Other inhibitors of adhesion**

- Phase III Randomized Study of Poloxamer 188 for... (Phase 3)
- Evaluation of Purified Poloxamer 188 in Vaso–Occlusive... (EPIC)
From research to new therapeutic options
Sickle cell disease

- Reversal of adhesion mediated VO events

SelG1/SEG101 (Crizanlizumab)
Phase II SUSTAIN Study

**Primary Outcome Measures:**
Safety and effect on frequency of sickle cell-related pain crises

Double-blind, randomized, placebo-controlled, multicenter.

**198 patients**

**Results:** 47% reduction (1 y.; 5 mg/kg)
10% or more adverse events
(arthralgia, diarrhea, pruritus, vomiting, and chest pain)

Ataga KI Plenary session 4 déc
Paper N° 0001
From research to new therapeutic options
Sickle cell disease

- Reversal of adhesion mediated VO events

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<td>Propranolol and Red Cell Adhesion in Non-asthmatic Children with Sickle Cell Disease</td>
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<td>Other inhibitors of adhesion</td>
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<td>Phase III Randomized Study of Poloxamer 188 for Vaso-Occlusive Crisis of Sickle Cell Disease</td>
<td>NCT0004408 Phase 3</td>
<td>Poloxamer 188</td>
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<td>Mast Therapeutics. CytRx</td>
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<td>Evaluation of Purified Poloxamer 188 in Vaso-Occlusive Crisis of Sickle Cell Disease (EPIC)</td>
<td>NCT01737814 Phase 3</td>
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<td>Ongoing</td>
<td>Mast Therapeutics</td>
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From research to new therapeutic options
Sickle cell disease

• Based on the knowledge of mechanisms involved in SCD adverse events
  – New treatments will be available

• Future = probably combination of drugs
  – HU + new drugs
  – Combination of drugs without HU

• One of the major outcome of clinical trials: improvement of patients’ QoL
From research to new therapeutic options 
β-thalassaemia major/intermedia
# 2017 Clinical trials update

## New treatments of β-thalassemia

### Table 2. Currently Planned, Ongoing, or Recently Completed Clinical Trials of Novel Therapeutics in β-Thalassemia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Route</th>
<th>Phase</th>
<th><a href="https://clinicaltrials.gov">ClinicalTrials.gov</a></th>
<th>Status</th>
<th>Institution/Developer</th>
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<tbody>
<tr>
<td>Ruxolitinib (INC424)</td>
<td>JAK inhibition</td>
<td>Oral</td>
<td>2</td>
<td>NCT02049450</td>
<td>Open</td>
<td>Novartis Pharmaceuticals</td>
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<td>Sotatercept (ACE-011)</td>
<td>Ligand trap TGF-β superfamily</td>
<td>Subcutaneous</td>
<td>2</td>
<td>NCT01749540</td>
<td>Active not recruiting participants</td>
<td>Acceleron Pharma, Celgene Corporation</td>
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<tr>
<td>Luspatercept (ACE-536)</td>
<td>Ligand trap TGF-β superfamily</td>
<td>Subcutaneous</td>
<td>2</td>
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<td>Active not recruiting participants</td>
<td>Acceleron Pharma, Celgene Corporation</td>
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<td>NCT02268409.delayed extension study</td>
<td>Active not recruiting participants</td>
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<td>NCT02604433</td>
<td>Open</td>
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</table>

From research to new therapeutic options
β-thalassaemia major/intermedia

- Luspatercept (ACE-536)
- Phase 2 clinical trial
- Efficacy endpoints
  - $\uparrow \text{Hb} \geq 1.0; 1.5 \text{ g/dL}$
  - Transfusion reduction: $\geq 20\%; \geq 50\%$
- Other endpoints
  - Safety
  - Liver iron (MRI)
  - Health-related QoL
From research to new therapeutic options
β-thalassaemia major/intermedia

- Luspatercept (ACE-536)
- Phase 2 clinical trial – adults (TD/NTD)
- Base study 3 M (n= 64)
- Extension study 5 years (n= 51)

- Results (n= 64)
  - Safe, well tolerated (Bone pain 30%; myalgia 17%)
    - NTD patients: sustained Hb ↑, ↓ liver iron, ↑ QoL
    - TD patients: sustained ↓ transfusions, ↓ liver iron

- Phase 3 study ongoing (NCT 02604433)
Agenda

• Diagnosis
• From research to new therapeutic options
• **Gene therapy: where are we?**
• Share of innovation
Gene therapy for β-thalassaemia: from the bench to beside

**Hematology 2010, Education program book Dec 4-7, 2010: 445-**

### Table 1. Comparisons of different β- or γ-globin vectors studied successfully in mouse and human models of β-thalassemia

<table>
<thead>
<tr>
<th>Vectors</th>
<th>Transgene</th>
<th>Erythroid enhance</th>
<th>Key Findings</th>
<th>Key problems and possible solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNS9β2</td>
<td>β-globin</td>
<td>HS2-HS3-HS4</td>
<td>Correlation of anemia in thalassemia intermedia mice and rescue of lethality in thalassemia major mouse model (Ref 25, 26)</td>
<td>Variable human β-globin expression in thalassemia major mice—are the need for chromatin insulators?</td>
</tr>
<tr>
<td>βγ521</td>
<td>β7-γ0.75</td>
<td>HS2-HS3-HS4</td>
<td>Correction of anemia in thalassemia intermedia mice (Ref 27). High level expression of an antisense βγ globin in human erythroid cells derived from cord blood progenitors and integration of vector near potential oncogenes (Ref 48)</td>
<td>Multiple copies are required for correction, gene expression surrounding the integration sites were not analyzed</td>
</tr>
<tr>
<td>D432β-γ</td>
<td>γ-globin</td>
<td>HS2-HS3-HS4</td>
<td>Correction of anemia in thalassemia intermedia mice (Ref 28)</td>
<td>Variable phenotypic improvement in thalassemia intermedia mice due to chromosomal position affects</td>
</tr>
<tr>
<td>mLAR1/2γ</td>
<td>γ-globin</td>
<td>Extended HS2-HS3-HS4</td>
<td>Correction of anemia in thalassemia intermedia mice (Ref 30)</td>
<td>Improved γ-globin expression and reduced position effects</td>
</tr>
<tr>
<td>BG-1</td>
<td>β-globin</td>
<td>HS2-HS3-HS4</td>
<td>Correction of human thalassemia major phenotype in vitro and in lethally deficient mice. (Ref 32) Reduced position effects and uniform expression (Ref 34). Identification of minimal regions of chHS4 necessary for optimal transfection (Ref 33)</td>
<td>Low viral titer with full-length chHS4 insulator. Identification of regions of chHS4 that impart optimal insulation and have minimal effect on vector titers</td>
</tr>
<tr>
<td>T10</td>
<td>β-globin</td>
<td>HS1-HS2-HS3-HS4</td>
<td>Correction of anemia in thalassemia intermedia mice with lower vector copies (Ref 31)</td>
<td></td>
</tr>
<tr>
<td>HS4-11</td>
<td>γ-globin</td>
<td>HS-40</td>
<td>Partial correction of mouse β-thalassemia intermedia with high transduction levels (Ref 18). Correction of β-thalassemia major by gene transfer in mice (Ref 20) and human thalassemia hematopoietic progenitors (Ref 42). LV vector has high titer and β-globin expression comparable to that seen by other groups despite lack of HS4.</td>
<td>γ-globin expression insufficient for correction of thalassemia major</td>
</tr>
<tr>
<td>GLOBE</td>
<td>β-globin</td>
<td>HS2-HS3</td>
<td></td>
<td>High vector copies are required for correction of thalassemia major mouse model.</td>
</tr>
</tbody>
</table>

Status of clinical trials denoted by asterisks: *US trial planned using this vector or with minor modifications; **clinical trial ongoing in France; ***clinical trial planned in Europe
# Open β-thal gene therapy trials

<table>
<thead>
<tr>
<th>Transgene LV vector</th>
<th>Country</th>
<th>Sponsor</th>
<th>Start time</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>β(^{A-T870})-globin BB305</td>
<td>France</td>
<td>Bluebird Bio</td>
<td>Jul 2013</td>
<td>3βE/β(^{-}) - 1 β(^{+}/β^{+}) - transfusion independent</td>
</tr>
<tr>
<td>β(^{A-T870})-globin BB305</td>
<td>USA, Thailand, Australia</td>
<td>Bluebird Bio</td>
<td>Aug 2013</td>
<td>18 Pts treated 8 β(^{0}/β^{0}) non transfusion indep., 60% decreased transf. Vol.</td>
</tr>
<tr>
<td>β-globin TNS9.3.55</td>
<td>USA</td>
<td>MSKCC</td>
<td>Jul 2012</td>
<td>4 patients treated Decrease in transf. Requirement = 1</td>
</tr>
<tr>
<td>β-globin GLOBE</td>
<td>Italy</td>
<td>Telethon Foundation</td>
<td>May 2015</td>
<td></td>
</tr>
</tbody>
</table>
β-globin GLOBE gene therapy

2005: Development β-globin LVs

2008: 

2010: Correction of Thal. Patients’ cells

2012: Mapping splice sites; exploring new HSC source in thal. Patients

2014: Protocol, Ethical Committee
β-globin GLOBE gene therapy

• 7 patients presented
  – 4 < 18 years
  – 26 to 460 days post gene therapy
  – All alive and well
  – Early haematological engraftment
  – Primary endpoits of safety achieved
  – 3 patients evaluable after 6-12 months post GT
    • 3/3 significant transfusion reduction and improved QoL
    • Discontinuation of chelation therapy
  – 4 pediatric patients with preliminary efficacy
Strategies for gene therapy for SCD

Pre-clinical: Humanized SCD mice (9% γ-globin) Rhesus Macaques

Plenary session - Blobel GA
Forced chromatin looping raises fetal hemoglobin in adult sickle cells to higher levels than pharmacologic inducers

## Open SCD gene therapy trials

*Modified from Negre O. et al Hum. Gene Ther 2016*

<table>
<thead>
<tr>
<th>Transgene LV vector</th>
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<th>Sponsor</th>
<th>Start time</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>β&lt;sup&gt;A&lt;/sup&gt;-T870-globin BB305</td>
<td>France</td>
<td>Bluebird Bio</td>
<td>Jul 2013</td>
<td>Ongoing: 5-37 years 1 patient treated 47% βT87Q-globin Clinical benefit</td>
</tr>
<tr>
<td>β&lt;sup&gt;A&lt;/sup&gt;-T870-globin BB305</td>
<td>USA</td>
<td>Bluebird Bio</td>
<td>Aug 2014</td>
<td>7 Pts treated 0.1 – 1.2 HbA&lt;sup&gt;TB/Q&lt;/sup&gt; g/dL</td>
</tr>
<tr>
<td>βAS3-globin βAS3-FB</td>
<td>USA</td>
<td>UCLA</td>
<td>Jul 2014</td>
<td>Open (adults): 2 patient treated</td>
</tr>
</tbody>
</table>
Agenda

• Diagnosis
• From research to new therapeutic options
• Gene therapy: where are we?
• Share of experiences, innovation
Global perspective of SCD
Neonatal screening
*Blood* 2010 115:3447-3452

*[Graph](image)*
## Lower-ressources areas

### Access to diagnosis: POCT for SCD

<table>
<thead>
<tr>
<th>Novel diagnostic testing methods</th>
<th>Density based test to separate Hb in different density fluids</th>
<th>Identifies Hb S and Hb A</th>
<th>Inexpensive, done at the point of care</th>
<th>Interpretation is more difficult. Less reliable results, difficult to distinguish HDSC disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMPS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paper-based Sickle test</strong></td>
<td>Microfluidic assessment</td>
<td>Identifies Hb S and A and C and company has a separate test that can identify Hb F</td>
<td>Inexpensive, done at the point of care, reliable diagnosis of HbSS disease, easily performed by non-skilled personnel</td>
<td>Requires a scanner for final results. Can be difficult to distinguish HbAS (trait) from HbSC, test could be altered in different humidities</td>
</tr>
<tr>
<td><strong>Sickle SCAN</strong></td>
<td>Lateral flow assay</td>
<td>Distinguishes Hb A, Hb S, Hb C</td>
<td>Reliably identifies HbA, HbS, and HbC, easily performed by non-skilled personnel, easily interpreted, rapid test at the point of care</td>
<td>More expensive than the other point of care tests above. Does not identify hemoglobin F. Limit of detection of Hb A is 2%</td>
</tr>
<tr>
<td><strong>HemeChip</strong></td>
<td>Micro-electrophoresis assay</td>
<td>Distinguishes Hb F, S, C, A, and D</td>
<td>Reliable, able to distinguish most types of sickle cell disease including compound heterozygotes</td>
<td>Requires a skilled interpretation, web-based image processing application for automated results</td>
</tr>
</tbody>
</table>
Lower-ressources areas - Access to treatments
Drone delivery systems for blood products

The Future of Healthcare is Out for Delivery

Rinaudo K. Dec 5
ASH – Red blood cells disorders
Take home messages

• Diagnosis and treatments
  – From the bench to the patient’s bed
  – From research to QoL

• Share of knowledge and technological innovations to explore answers to challenges in lower-ressources areas
BEST of ASH...