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

Béatrice GULBIS

LHUB-ULB

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.
    - N Engl J Med 2017; 376:83-85January 5, 2017DOI: 10.1056/NEJMe1614384
  - 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

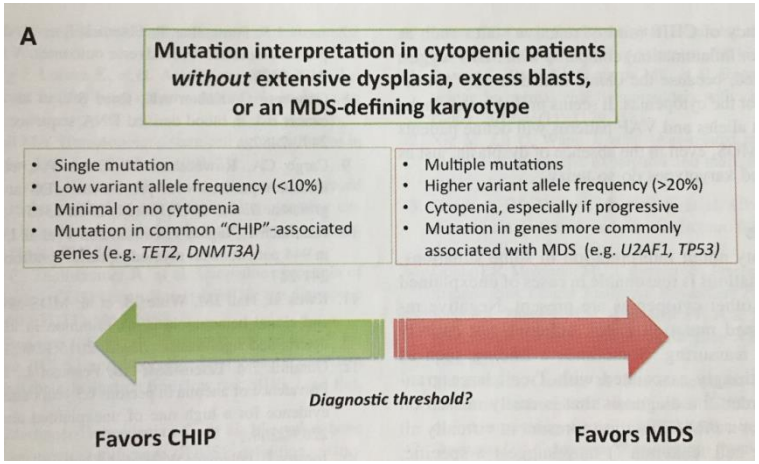
- ***Education program:***

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

Haemoglobinopathies

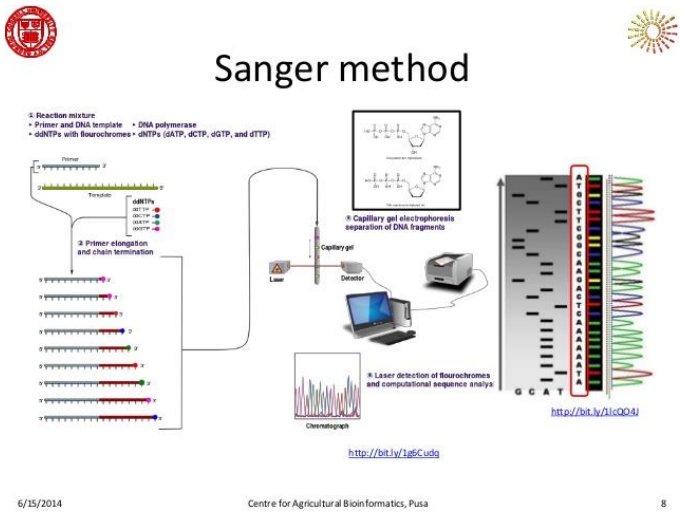
Membrane Cytosqueletal defects

Enzymopathies

- Acetylcholinesterase
- Adenosine deaminase
- Adenylate kinase
- Aldolase
- γ-Glutamylcysteine synthetase
- Glucose phosphate isomerase
- Glucose-6-phosphate dehydrogenase
- Gluthathione reductase
- Glutathione synthetase
- Hexokinase
- Phosphofructokinase
- Phosphoglycerate kinase
- Pyrimidine-5’-nucleotidase
- Pyruvate kinase
- Triosephosphate isomerase

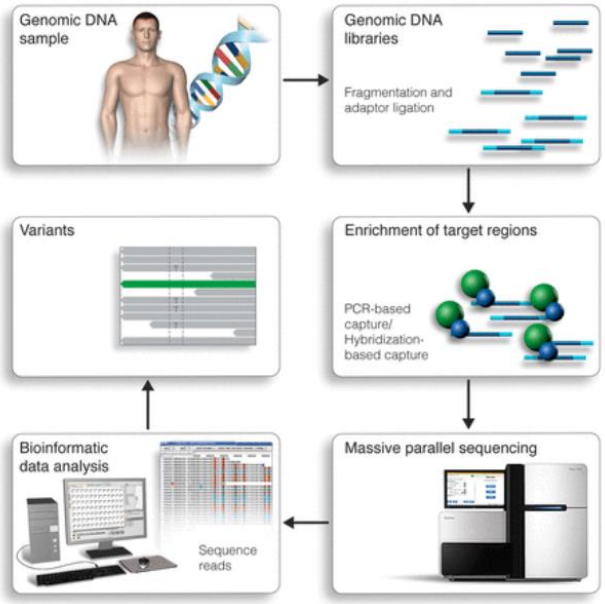
Diagnosis

- Hereditary haemolytic anaemia
  - Phenotype (Clinical, laboratory tests, …)
  - Genotype: focus on one gene or even one exon



Diagnosis

- **Gene panel – « Mendeliome »**
  - **Paper No: 2433 -** « Using a next generation sequencing panel to discover the obscure causes of hereditary hemolytic anemia » *A. M. Agarwal* Br J Haematol. 2016 Sep;174(5):806-14.
  - *Detection of new pathogenic mutations in patients with congenital haemolytic anaemia using next-generation sequencing. Int J Lab Hematol. 2016 Dec;38(6):629-638.*



Diagnosis

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

Table II. Genes included in the panel.

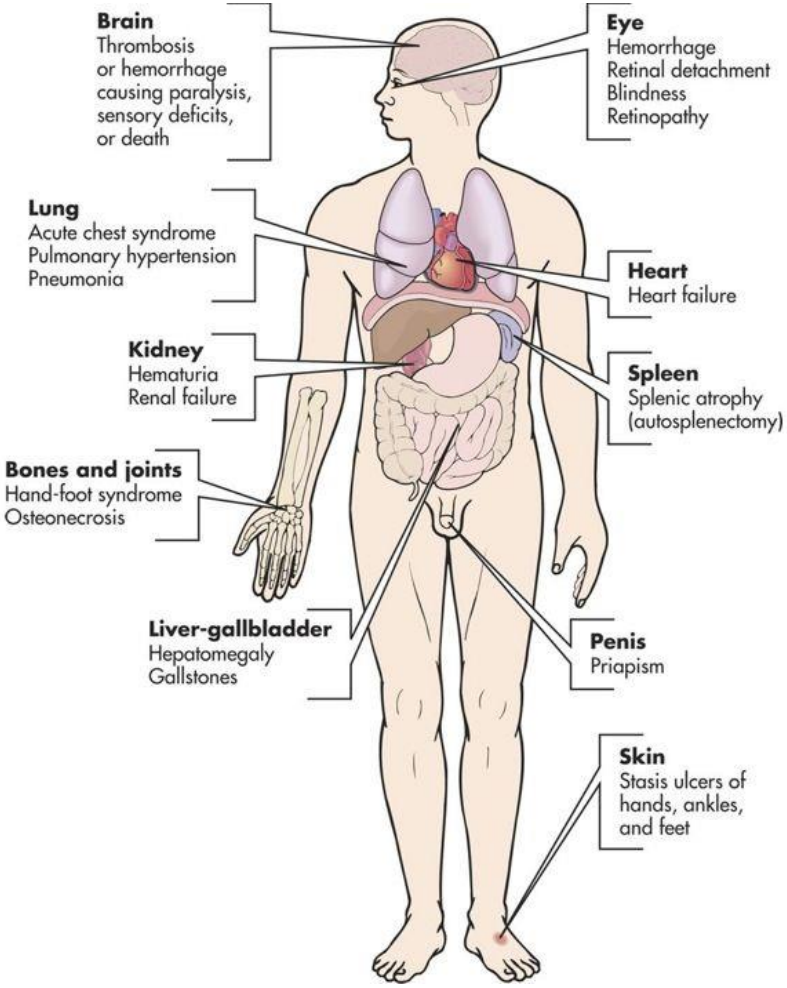
Gene symbol	Gene name	Transcript	OMIM gene	Disorder	Inh
ADA	Adenosine deaminase	NM_000022	608958	ADA deficiency	AR
AK1	Adenylate kinase 1	NM_000476	103000	AK1 deficiency	AR
ALDOA	Aldolase A	NM_000034	103850	ALDOA deficiency	AR
ANK1	Ankyrin 1	NM_000037	607008	Spherocytosis	AD/AR
CYB5R3	Cytochrome b5 reductase 3 (DIA1)	NM_000398	613213	Methaemoglobinaemia type 1 Methaemoglobinaemia type 2	AR
EPB41	Erythrocyte membrane protein band 4.1	NM_004437	130500	Elliptocytosis	AR
EPB42	Erythrocyte membrane protein band 4.2	NM_000119	177070	Spherocytosis	AR
G6PD	Glucose-6-phosphate dehydrogenase	NM_001042351	305900	G6PD deficiency	XL
GCLC	Glutamate-cysteine ligase, catalytic subunit	NM_001498	606857	GCLC deficiency, Hyperbilirubinaemia, Haemolytic Anaemia	AR
GPI	Glucose phosphate isomerase	NM_000175	172400	Acute/chronic haemolytic anaemia	AR
GSR	Glutathione reductase	NM_000637	138300	GSR deficiency	AR
GSS	Glutathione synthetase	NM_000178	601002	GSS deficiency	AR
HK1	Hexokinase 1	NM_000188	142600	Haemolytic anaemia	AR
NT5C3A	5′-nucleotidase, cytosolic IIIA	NM_016489	606224	NT5C3A deficiency, Haemolytic anaemia	AR
PFKL	Phosphofructokinase, liver	NM_002626	171860		AR
PFKM	Phosphofructokinase, muscle	NM_000289	610681	PFKM deficiency, Glycogen storage disease 7	AR
PGK1	Phosphoglycerate kinase 1	NM_000291	311800	PGK1 deficiency	XL
PIEZO1	Piezo-type mechanosensitive ion channel component 1	NM_001142864	611184	Xerocytosis (hereditary)	AR
PKLR	Pyruvate kinase (liver and RBC)	NM_000298	609712	PKLR deficiency, Haemolytic anaemia	AR
SLC4A1	Solute carrier family 4, anion exchanger, member 1, band 3	NM_000342	109270	Spherocytosis, Blood group variation, Anaemia, Stomatocytosis, Acanthocytosis Kernicterus (acute), Ovalocytosis	AD/AR
SLCO1B1	Solute carrier organic anion transporter family, member 1B1	NM_006446	604843	Hyperbilirubinaemia (rotor type), Rotor syndrome	AR
SLCO1B3	Solute carrier organic anion transporter family, member 1B3	NM_019844	605495	Hyperbilirubinaemia (rotor type), Rotor syndrome	AR
SPTA1	Spectrin alpha	NM_003126	182860	Elliptocytosis, Spherocytosis, Pyropoikilocytosis, Elliptopoikilocytosis	AD/AR
SPTB	Spectrin beta	NM_000347	182870	Elliptocytosis, Spherocytosis	AD/AR
TPI1	Triosephosphate isomerase 1	NM_000365	190450	TPI1 deficiency	AR
UGT1A1	UDP glycosyltransferase 1 family, polypeptide A1	NM_000463	191740	Crigler-Najjar syndrome 1 & 2, Hyperbilirubinaemia (unconjugated), Gilbert syndrome	AR
UGT1A6	UDP glycosyltransferase 1 family, polypeptide A6	NM_001072	606431	UGT1A6 deficiency	AR
UGT1A7	UDP glycosyltransferase 1 family, polypeptide A7	NM_019077	606432	UGT1A7 deficiency	AR

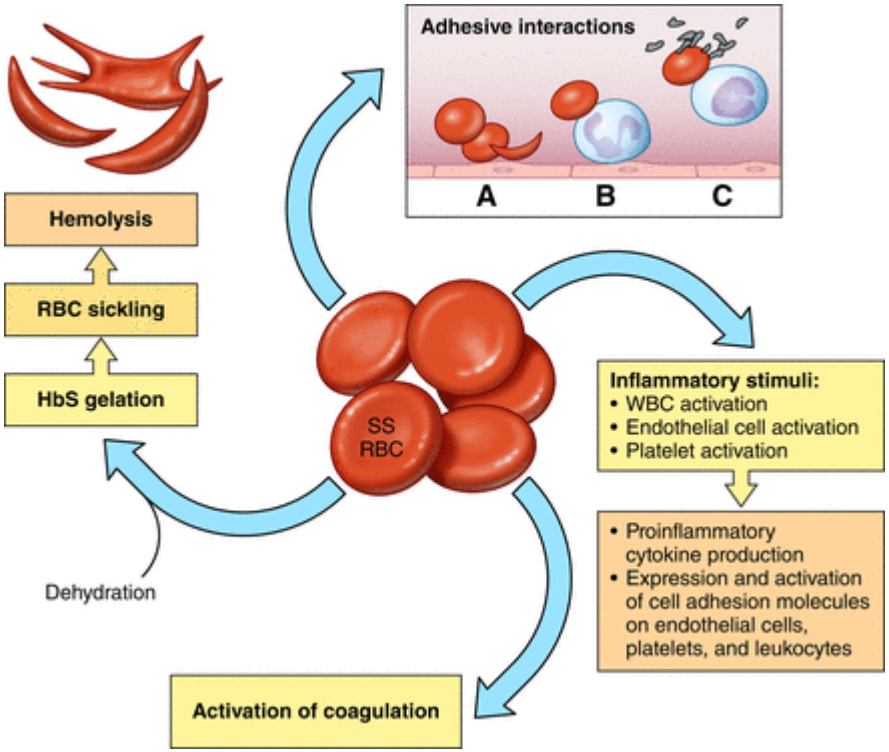
Inh, inheritance; AR, autosomal recessive; AD, autosomal dominant; XL, X-linked.

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

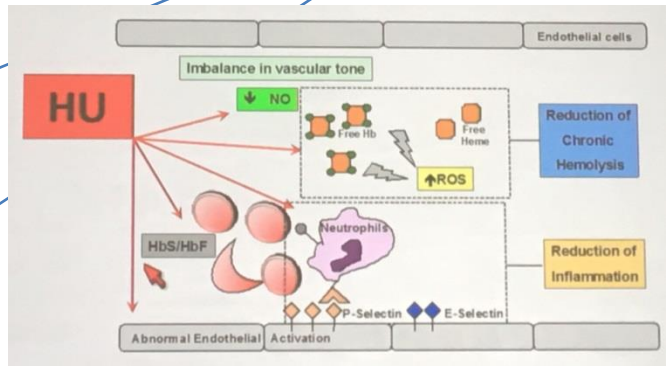
Free Heme
Free Hb

Adhesive interactions

Inflammation

Activation coagulation

Hydroxyurea



From research to new therapeutic options

Sickle cell disease

RBC dehydration

Free Heme
Free Hb

Adhesive interactions

Inflammation

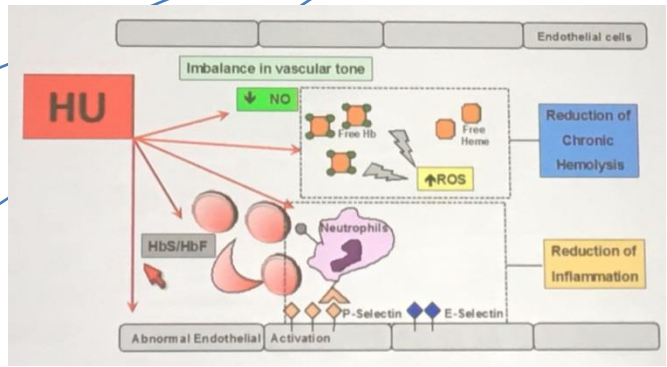
Activation coagulation

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, …

Hydroxyurea



From research to new therapeutic options

Sickle cell disease

RBC dehydration

Free Heme
Free Hb

Adhesive interactions

Inflammation

Activation coagulation

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

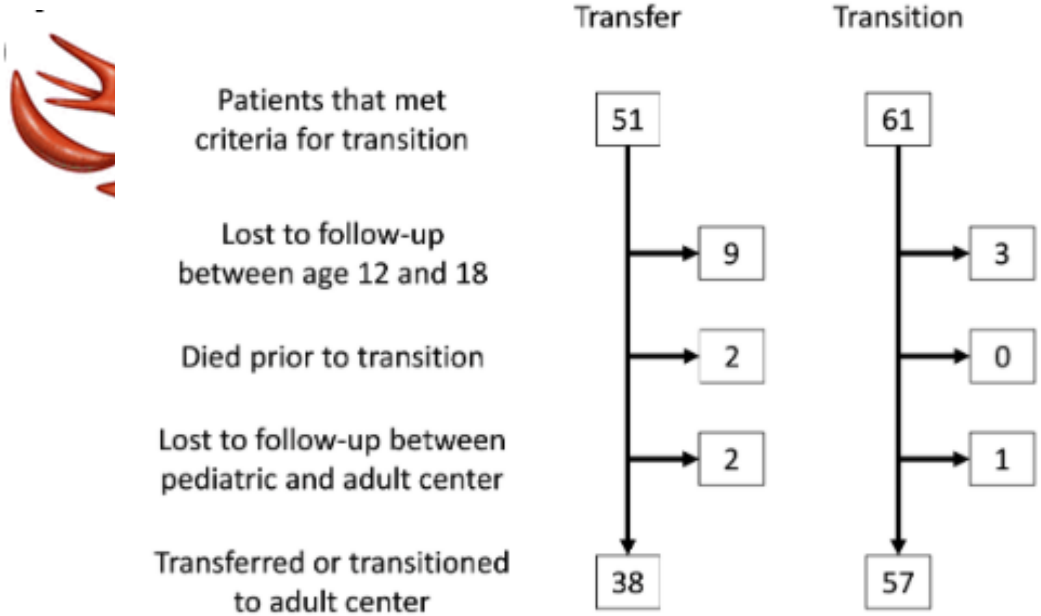


Figure 1: Patient flow diagram through the transfer/transition process

From research to new therapeutic options
Sickle cell disease

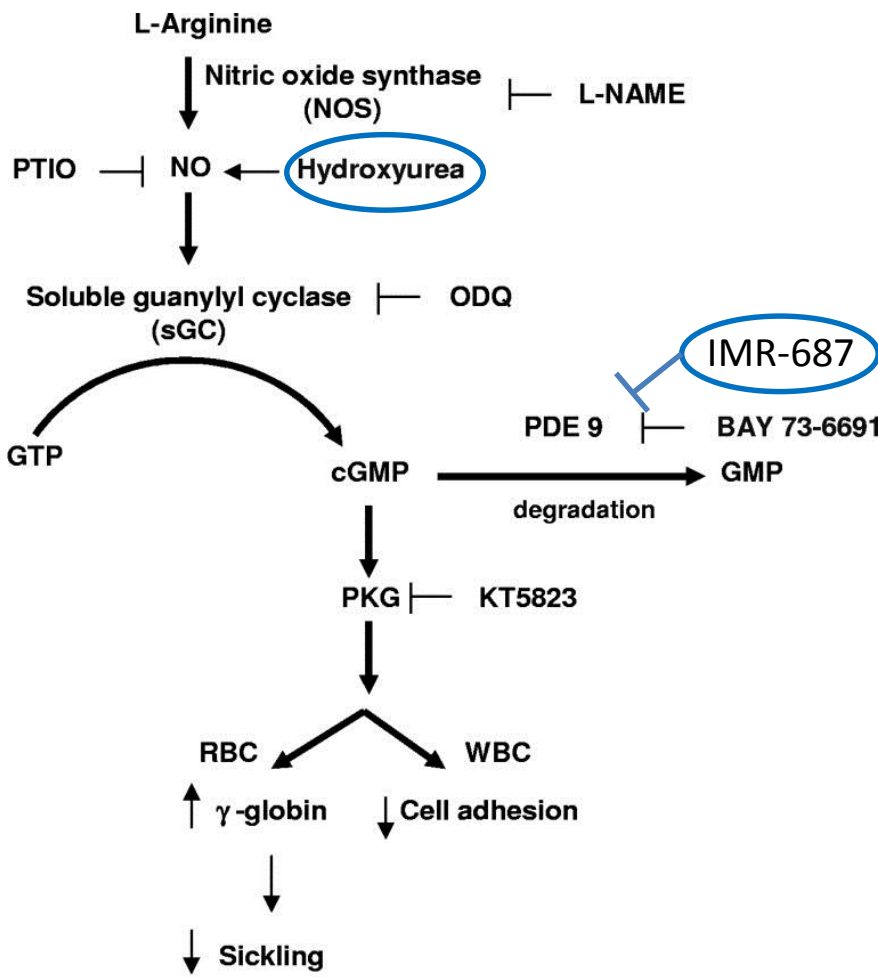
- **Hypothesis:**

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

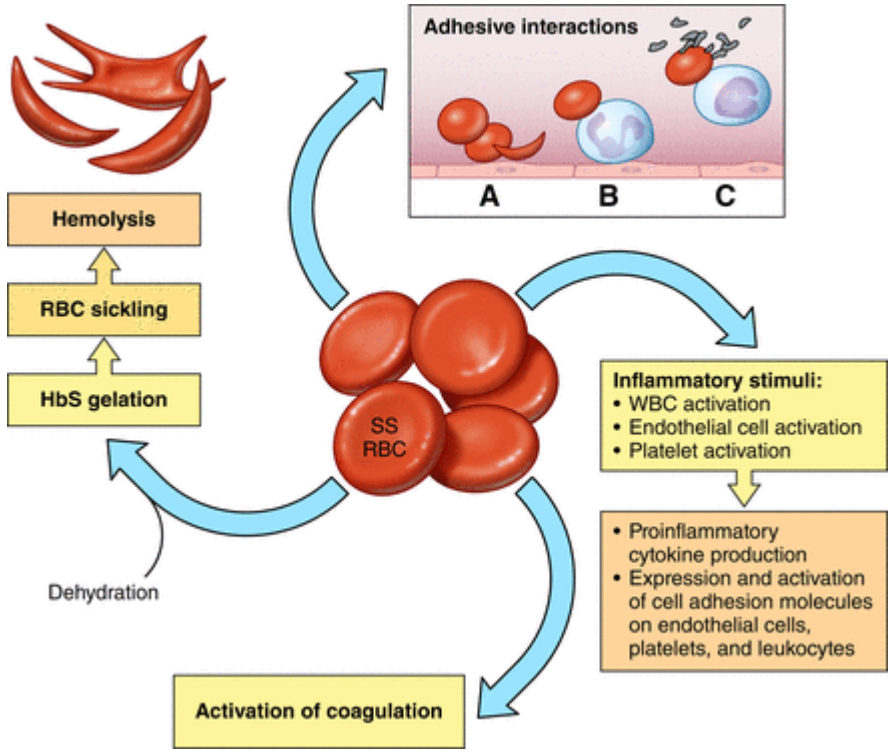
Sickle cell disease

- 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

Hemoglobin-modifying and anti-sickling agents				
Dose-Escalation Study of SCD-101 in Sickle Cell Disease	NCT02380079 Phase 1	SCD-101	Ongoing	Invenux; SUNY-Downstate Med Ctr
Safety Study of MP4CO in Adult Sickle Cell Patients	NCT01356485 Phase 1	MP4CO	Complete	Sangart
Study of SANGUINATE™ Versus Hydroxyurea in Sickle Cell Disease (SCD) Patients	NCT01848925 Phase 1	Sanguinate	Complete	Prolong Pharmaceuticals
Study of SANGUINATE™ In the Treatment of Sickle Cell Disease Patients With Vaso-Occlusive Crisis	NCT02411708 Phase 2	Sanguinate	Ongoing	Prolong Pharmaceuticals
A Study of the Efficacy and Safety of ICA-17043 (With or Without Hydroxyurea) in Patients With Sickle Cell Anemia.	NCT00040677 Phase 2	Senicapoc (ICA-17043)	Complete	Icagen
A Stratified Sickle Event Randomized Trial (ASSERT)	NCT00102791 Phase 3	Senicapoc (ICA-17043)	Terminated (lack of efficacy)	Icagen
A Study Evaluating the Long-Term Safety of ICA-17043 in Sickle Cell Disease Patients With or Without Hydroxyurea Therapy	NCT00294541 Phase 3	Senicapoc (ICA-17043)	Terminated	Icagen
A Single Dose Study of the Safety, Blood Levels and Biological Effects of Aes-103 Compared with Placebo in Subjects With Stable Sickle Cell Disease	NCT01597401 Phase 1	Aes-103	Complete	Baxalta US
Evaluation of Different Dose Regimens of Aes-103 Given for 28 Days to Subjects With Stable Sickle Cell Disease	NCT01987908 Phase 2	Aes-103	Terminated	Baxalta US

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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

Hemoglobin-				
Dose-Escal	9	SCD-101	Ongoing	Invenux; SUNY-Downstate Med Ctr
Safety Stud	5	MP4CO	Complete	Sangart
Study of SA Patients	5	Sanguinate	Complete	Prolong Pharmaceuticals
Study of SA With Vaso-Oc	8	Sanguinate	Ongoing	Prolong Pharmaceuticals
A Study of t Hydroxyurea)	7	Senicapoc (ICA-17043)	Complete	Icagen
A Stratified	1	Senicapoc (ICA-17043)	Terminated (lack of efficacy)	Icagen
A Study Eva Disease Patie	1	Senicapoc (ICA-17043)	Terminated	Icagen
A Single Do Aes-103 Com Disease	1	Aes-103	Complete	Baxalta US
Evaluation Subjects With	8	Aes-103	Terminated	Baxalta US

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

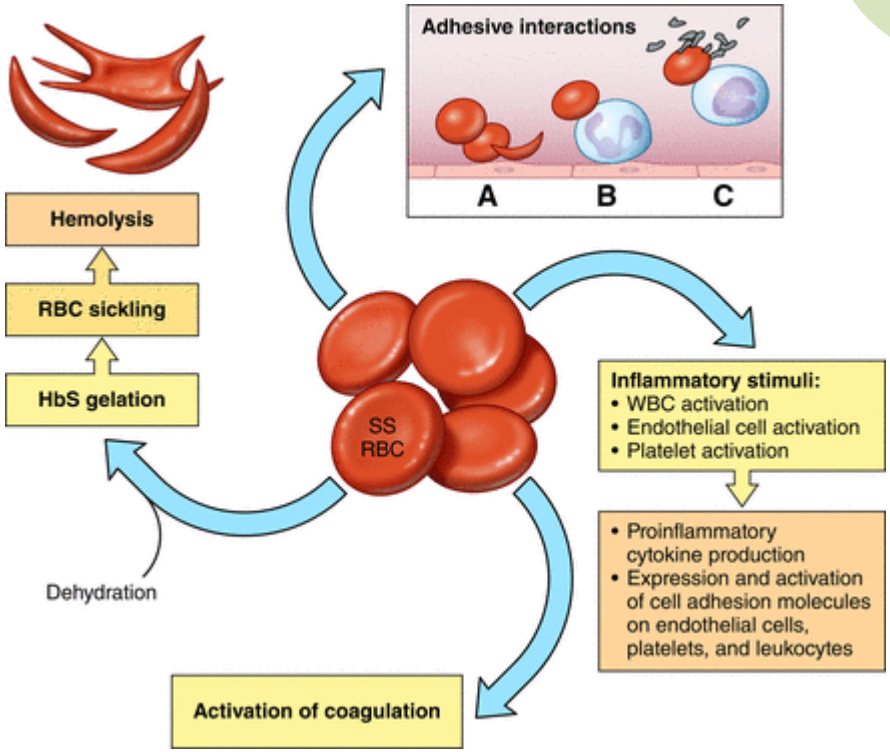
26 patients: stable SCD,
no HU (6 M), no transfusion (90 days)
Results: no significant change in haemolysis
Clinical benefit: pain, fatigue, sleep, ulcer healing
…

From research to new therapeutic options

Sickle cell disease

- New targets

Anti-sickling agent



Agents interfering with RBCs-vascular adhesion events

Reversal of adhesion mediated VO events

Blockade of adhesive mechanisms

Modulation inflammatory pathways

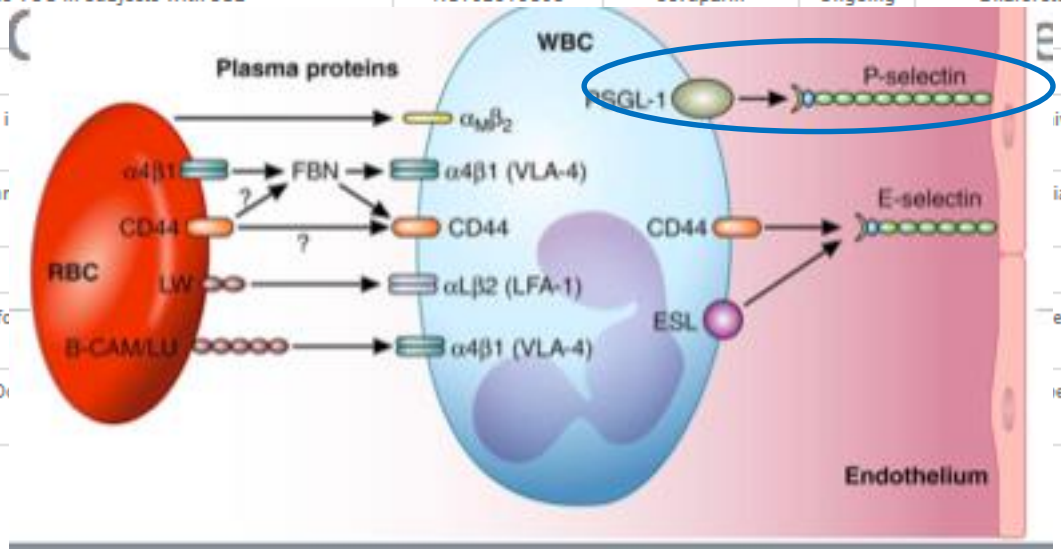
Anti-PLTs
Anti-coagulant

From research to new therapeutic options
Sickle cell disease

- Reversal of adhesion mediated VO events

Recently completed and ongoing studies targeting adhesion

Study title	Clinical trials #/Phase	Intervention	Status	Primary sponsor
Selectin inhibitors				
Study of GMI-1070 for the Treatment of Sickle Cell Pain Crisis	NCT01119833 Phase 2	GMI-1070 (rivipansel)	Complete	GlycoMimetics
Efficacy and Safety of Rivipansel (GMI-1070) in the Treatment of Vaso-Occlusive Crisis in Hospitalized Subjects With Sickle Cell Disease	NCT02187003 Phase 3	GMI-1070 (rivipansel)	Ongoing	Pfizer
Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises	NCT01895361 Phase 2	SelG1	Ongoing	Selexys
Sevuparin Infusion for the Management of Acute VOC in Subjects With SCD	NCT02515838	Sevuparin	Ongoing	Dilaforette
β blockers				
Study of Propranolol as Anti-Adhesive Therapy i				iv.
Propranolol and Red Cell Adhesion in Non-asthr				iami
Other inhibitors of adhesion				
Phase III Randomized Study of Poloxamer 188 fo Disease				eutics.
Evaluation of Purified Poloxamer 188 in Vaso-O (EPIC)				eutics



From research to new therapeutic options
Sickle cell disease

- Reversal of adhesion mediated VO events

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Study of GMI-1070 fo	)1119833 hase 2	GMI-1070 (rivipansel)	Complete	GlycoMimetics
Efficacy and Safety of Hospitalized Subjects W	)2187003 hase 3	GMI-1070 (rivipansel)	Ongoing	Pfizer
Study to Assess Safet Sickle Cell Disease Pati	)1895361 hase 2	SelG1	Ongoing	Selexys
Sevuparin Infusion fo	)2515838 hase 2	Sevuparin	Ongoing	Dilaforette
β blockers				
Study of Propranolol	)1077921 hase 2	Propranolol	Complete	Duke Univ.
Propranolol and Red	)2012777 hase 1	Propranolol	Ongoing	Univ. of Miami
Other inhibitors of adh				
Phase III Randomized Disease	)0004408 hase 3	Poloxamer 188	Complete	Mast Therapeutics. CytRx
Evaluation of Purified (EPIC)	)1737814 hase 3	Poloxamer 188	Ongoing	Mast Therapeutics

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
N Engl J Med. 2016 Dec 3.

)-819

From research to new therapeutic options

Sickle cell disease

- Reversal of adhesion mediated VO events

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Propranolol and Red Cell Adhesion in Non-asthmatic Children with Sickle Cell Disease	NCT02012777 Phase 1	Propranolol	Ongoing	Univ. of Miami
Other inhibitors of adhesion				
Phase III Randomized Study of Poloxamer 188 for Vaso-Occlusive Crisis of Sickle Cell Disease	NCT00004408 Phase 3	Poloxamer 188	Complete	Mast Therapeutics. CytRx
Evaluation of Purified Poloxamer 188 in Vaso-Occlusive Crisis of Sickle Cell Disease (EPIC)	NCT01737814 Phase 3	Poloxamer 188	Ongoing	Mast Therapeutics

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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

haematologica | 2013; 98(6)

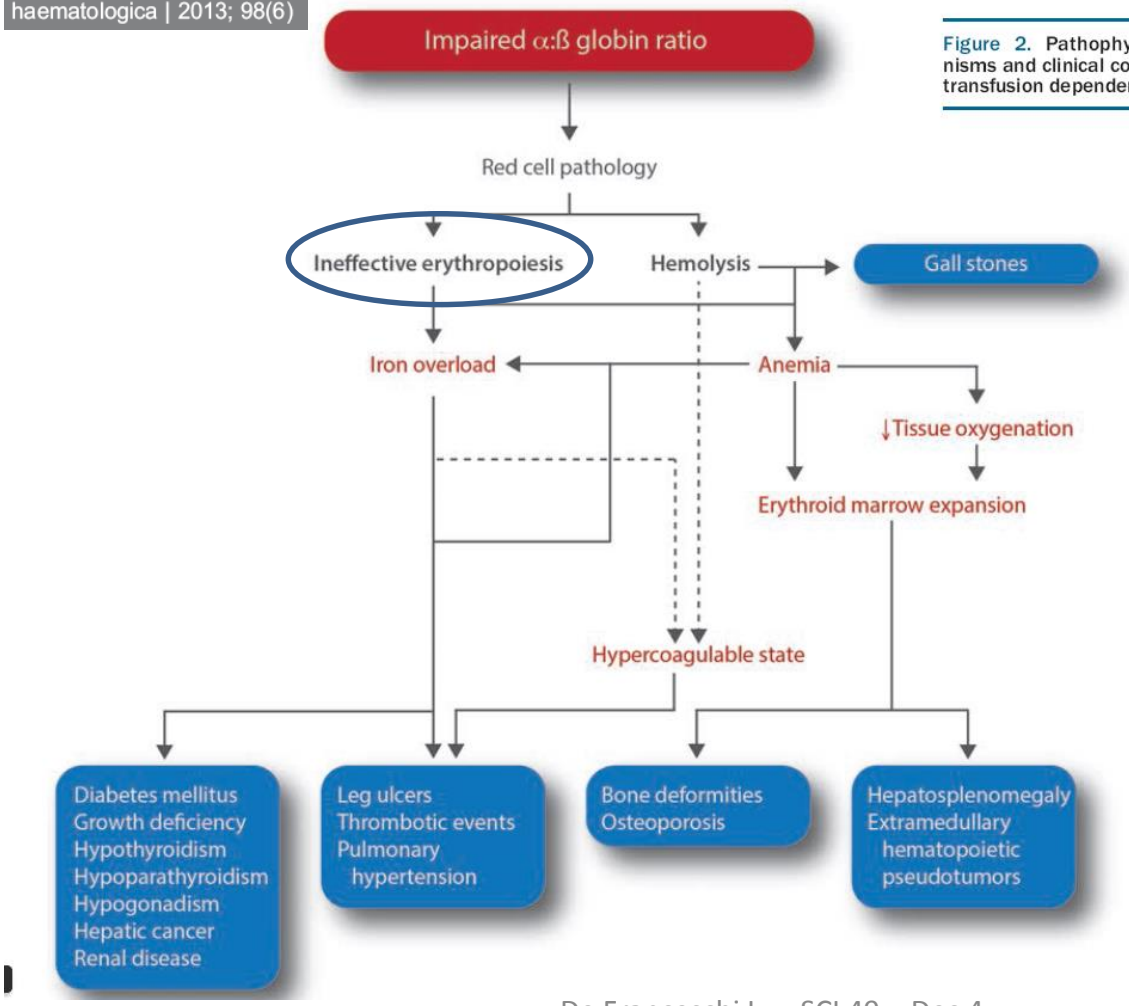


Figure 2. Pathophysiological mechanisms and clinical complications in non-transfusion dependent thalassemias.

2017 Clinical trials update
New treatments of β-thalassemia

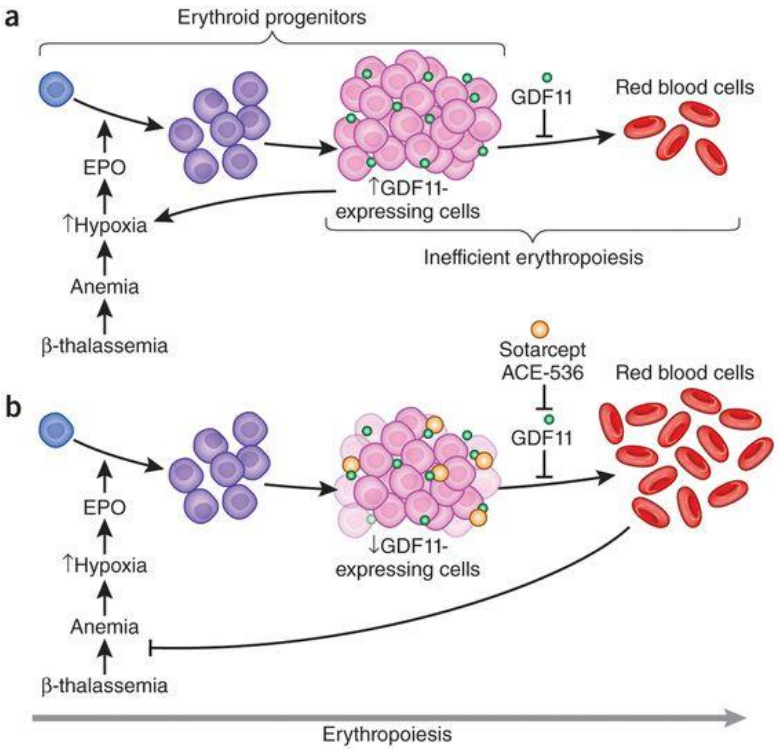
Table 2. Currently Planned, Ongoing, or Recently Completed Clinical Trials of Novel Therapeutics in β-Thalassemia

Drug	Mechanism	Route	Phase	ClinicalTrials.gov	Status	Institution/Develo
Ruxolitinib (INC424)	JAK inhibition	Oral	2	NCT02049450	Open	Novartis Pharmaceutic
Sotatercept (ACE-011)	Ligand trap TGF-β superfamily	Subcutaneous	2	NCT01749540	Active not recruiting participants	Acceleron Pharma, Celgene Corporation
Luspatercept (ACE-536)	Ligand trap TGF-β superfamily	Subcutaneous	2	NCT01749540	Active not recruiting participants	Acceleron Pharma, Celgene Corporation
			2, extension study	NCT02268409	Active not recruiting participants	
			3	NCT02604433	Open	

American Journal of Hematology
Volume 91, Issue 11, pages 1135-1145, 20 OCT 2016 DOI: 10.1002/ajh.24530
http://onlinelibrary.wiley.com/doi/10.1002/ajh.24530/full#ajh24530-fig-0001

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

- Luspatercept (ACE-536)
- Phase 2 clinical trial
- Efficacy endpoints
  - ↑Hb ≥ 1.0; 1.5 g/dL
  - Transfusion reduction: ≥ 20%; ≥ 50%
- Other endpoints
  - Safety
  - Liver iron (MRI)
  - Health-related QoL

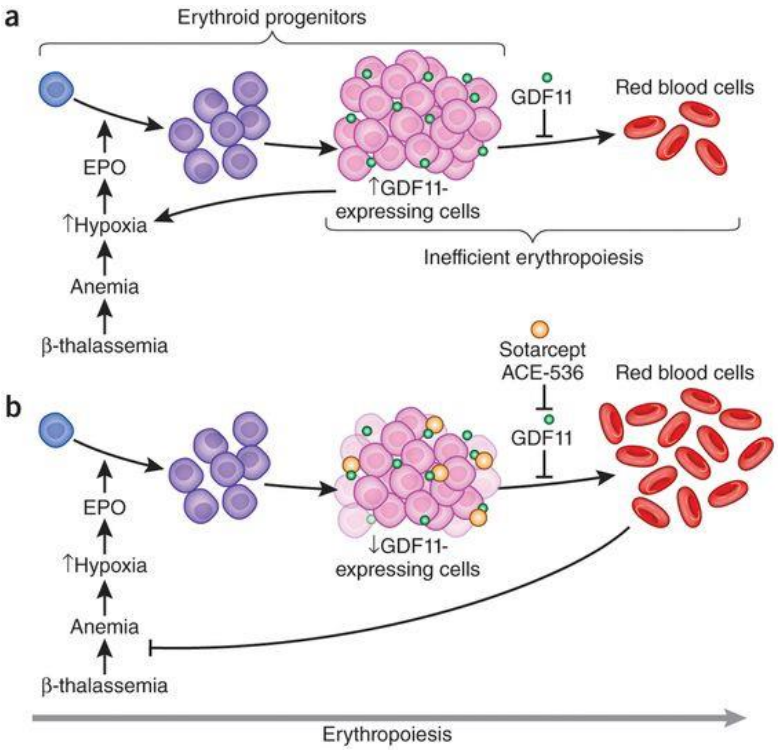


From research to new therapeutic options
β-thalassaemia major/intermedia

- 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

Vectors	Trans-gene	Erythroid enhancer	Key Findings	Key problems and possible solutions
TNS9*	β-globin	HS2-HS3-HS4	Correction of anemia in thalassemia intermedia mice and rescue of lethality in thalassemia major mouse model (Ref 25, 26)	Variable human β-globin expression in thalassemia major mice-indicates need for chromatin insulators
β^{87}**	$\beta^{A\text{-}T87Q}$ globin	HS2-HS3-HS4	Correction of anemia in thalassemia intermedia mice (Ref 27). High level expression of an antisickling β^{87} globin in human erythroid cells derived from cord blood progenitors and integration of vector near potential oncogenes (Ref 48)	Multiple copies are required for correction, gene expression surrounding the integration sites were not analyzed
D432β-^{4}γ	γ-globin	HS2-HS3-HS4	Correction of anemia in thalassemia intermedia mice (Ref 28)	Variable phenotypic improvement in thalassemia intermedia mice due to chromosomal position effects
mLARβΔγ V5*	γ-globin	Extended HS2-HS3-HS4	Correction of anemia in thalassemia intermedia mice (Ref 30)	Improved γ-globin expression and reduced position effects
BG-I	β-globin	HS2-HS3-HS4	Correction of human thalassemia major phenotype in vitro and in immune deficient mice. (Ref 32) Reduced position effects and uniform expression (Ref 34). Identification of minimal regions of cHS4 necessary for optimal insulation (Ref 33)	Low viral titers with full-length cHS4 insulator. Identification of regions of cHS4 that impart optimal insulation and have minimal effect on vector titers.
T10	β-globin	HS1-HS2-HS3-HS4.	Correction of anemia in thalassemia intermedia mice with lower vector copies (Ref 31)	
HS40-11	γ-globin	HS-40	Partial correction of mouse β-thalassemia intermedia with high transduction levels.(Ref 18)	γ-globin expression insufficient for correction of thalassemia major
GLOBE ***	β-globin	HS2-HS3	Correction of β-thalassemia major by gene transfer in murine (Ref 29) and human thalassemia hematopoietic progenitors (Ref 42). LV vector has high titers and β-globin expression comparable to that seen by other groups despite lack of HS4.	High vector copies are required for correction of thalassemia major mouse model.

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

Transgene LV vector	Country	Sponsor	Start time	Results
$\beta^{A\text{-}T870}$-globin BB305	France	Bluebird Bio	Jul 2013	3βE/β°- 1 β^{+}/β^{+} - transfusion independent
$\beta^{A\text{-}T870}$-globin BB305	USA, Thailand, Australia	Bluebird Bio	Aug 2013	18 Pts treated 8 β°/β° non transfusion indep., 60% decreased transf. Vol.
β-globin TNS9.3.55	USA	MSKCC	Jul 2012	4 patients treated Decrease in transf. Requirement = 1
β-globin GLOBE	Italy	Telethon Foundation	May 2015	

β-globin GLOBE gene therapy

2005: Development β-globin LVs

2008:

2010: Correction of Thal. Patients' cells

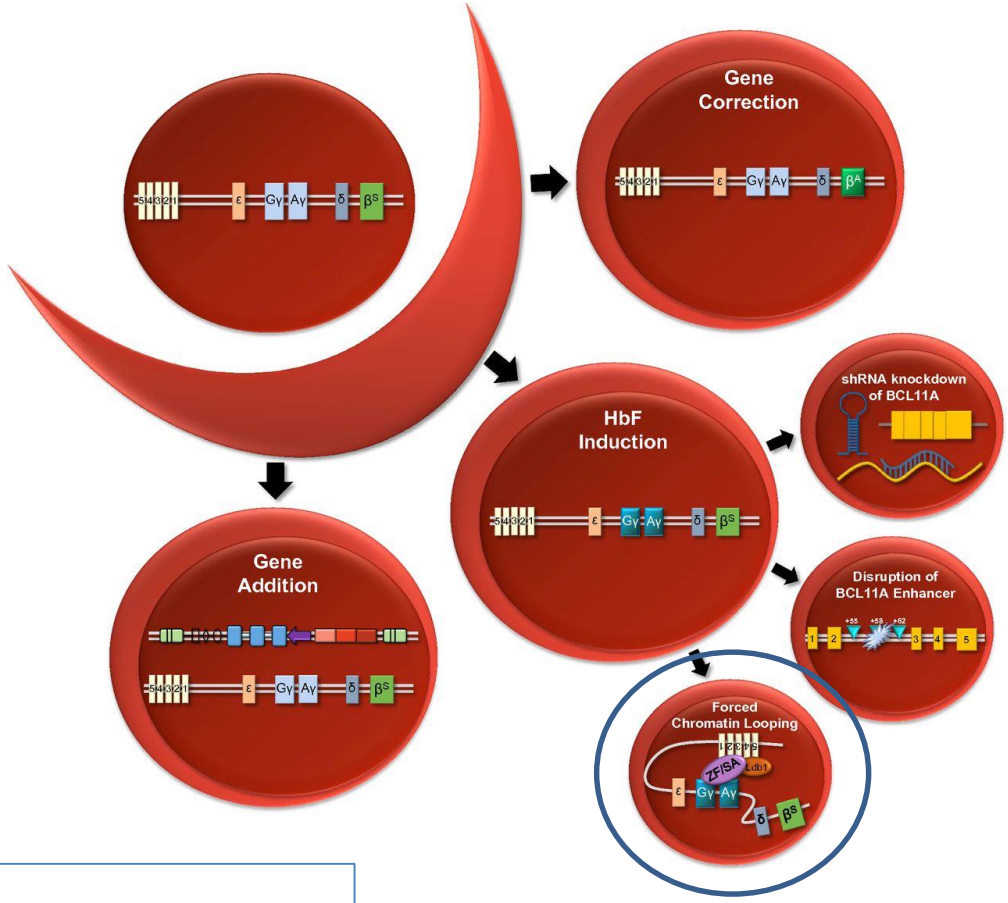
2012: Mapping splice sites; exploring new HSC source in thal. Patients

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 engrafment
  - 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
Blood 2016 128:1139-1143

Megan D. Hoban et al. Blood 2016;127:839-848

Open SCD gene therapy trials

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

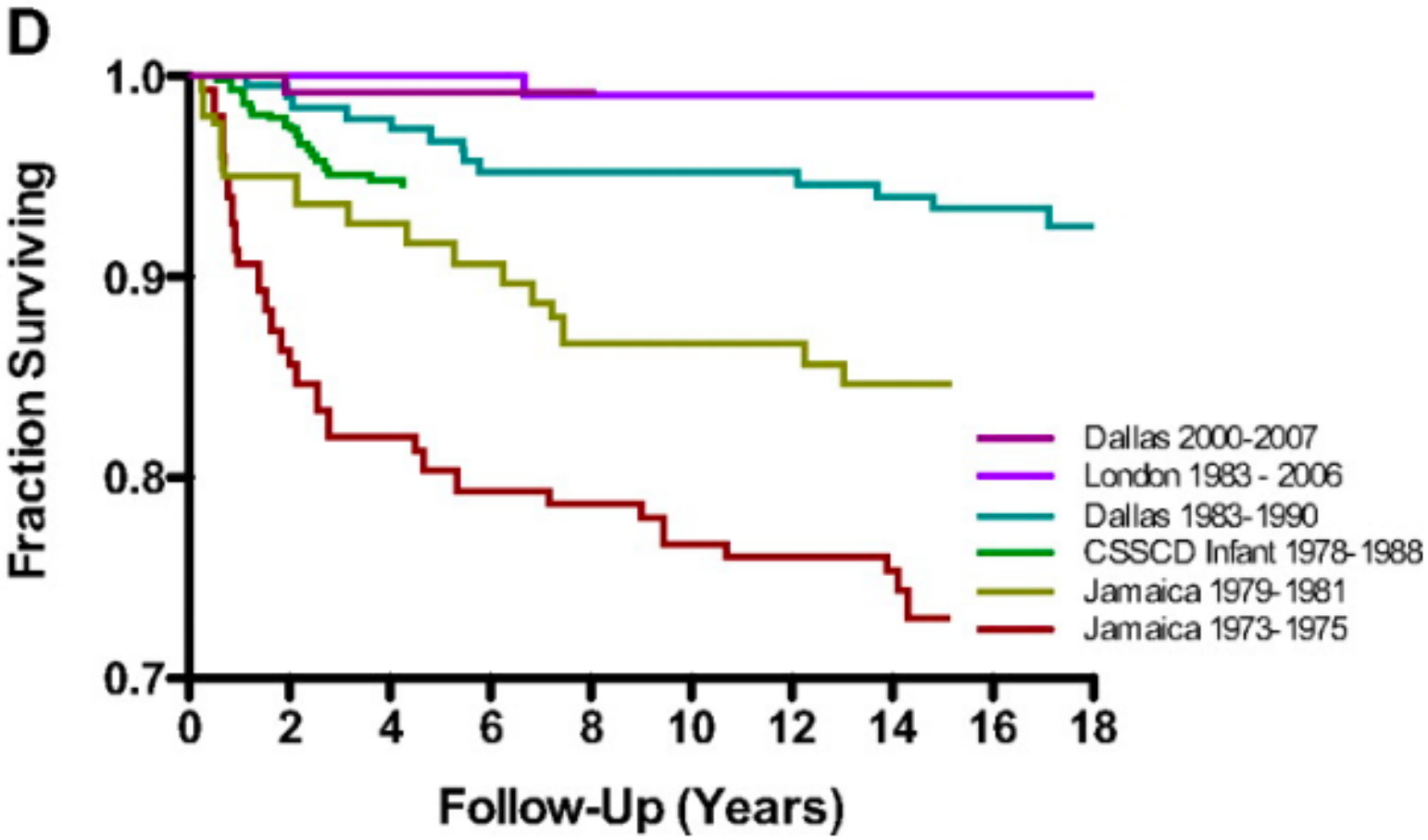
Transgene LV vector	Country	Sponsor	Start time	Results
$\beta^{A\text{-}T870}$-globin BB305	France	Bluebird Bio	Jul 2013	Ongoing: 5-37 years 1 patient treated 47% βT87Q-globin Clinical benefit
$\beta^{A\text{-}T870}$-globin BB305	USA	Bluebird Bio	Aug 2014	7 Pts treated 0.1 – 1.2 $HbA^{TB/Q}$ g/dL
βAS3-globin βAS3-FB	USA	UCLA	Jul 2014	Open (adults): 2 patient treated
Y-globin sG-bG	USA	Children's Hospital Med. Center Cincinnati	Jul 2014	Open (adults): Recruting

Agenda

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

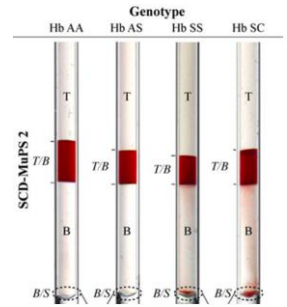
Global perspective of SCD Neonatal screening

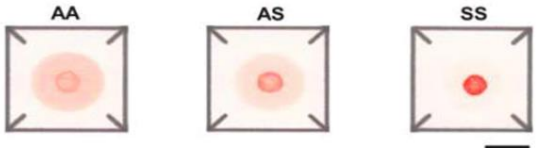
Blood 2010 115:3447-3452

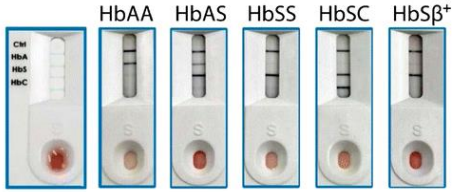


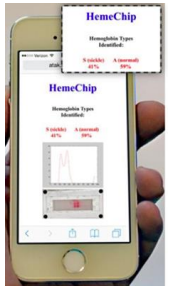
Lower-ressources areas
Access to diagnosis: POCT for SCD

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

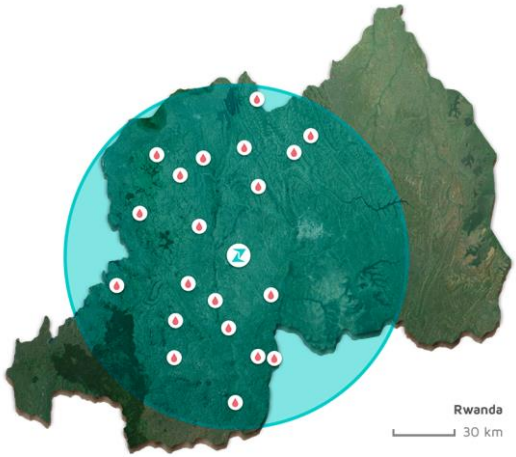


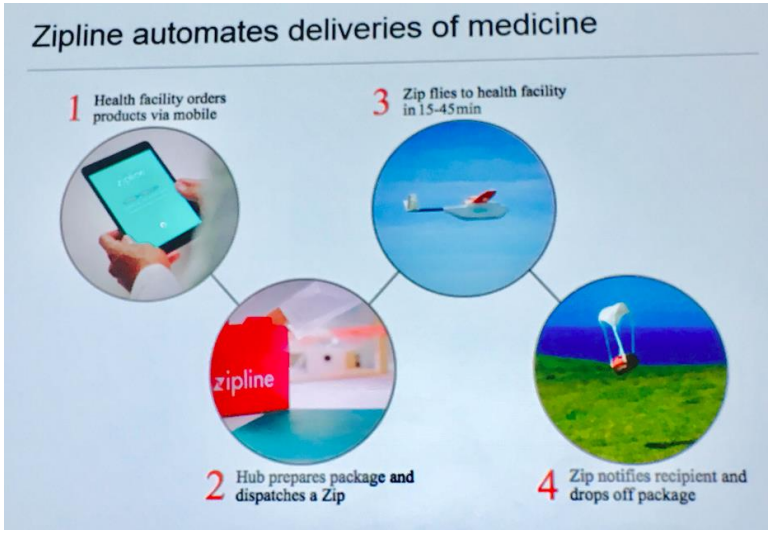






Lower-ressources areas -Access to treatments
Drone delivery systems for blood products





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…