Novita' dell'EHA: Globuli Rossi

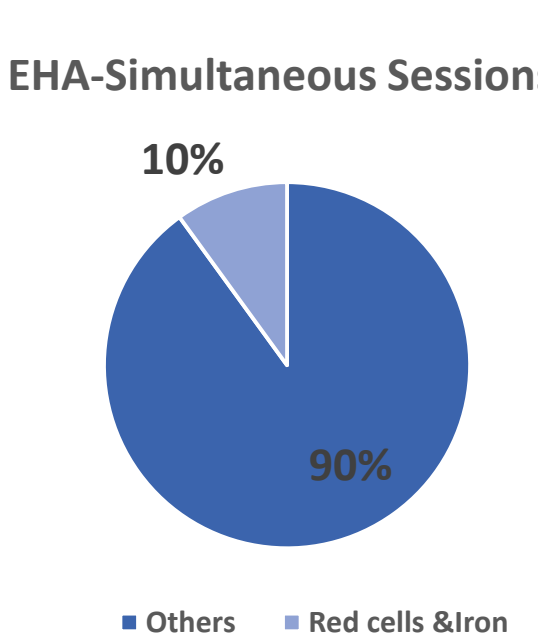
Lucia De Franceschi

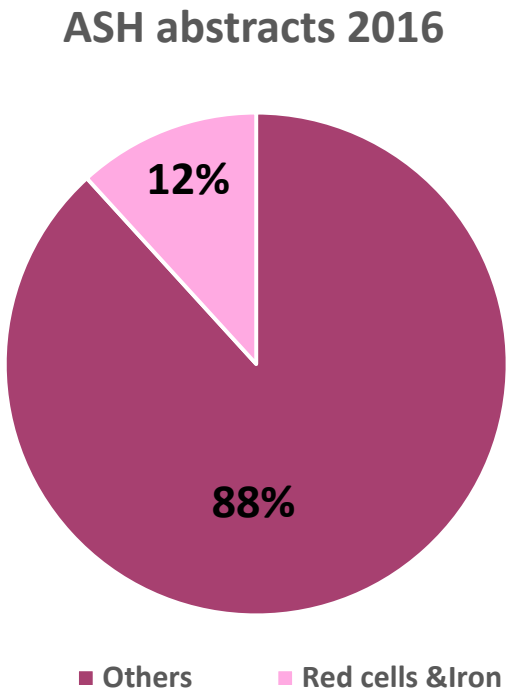
Dept of Medicine, University of Verona-AOUI Verona; Verona

Firenze, 22-23 Settembre 2017

10th EHA Highlights from EHA

EHA 2017: Red cells & Iron metabolism





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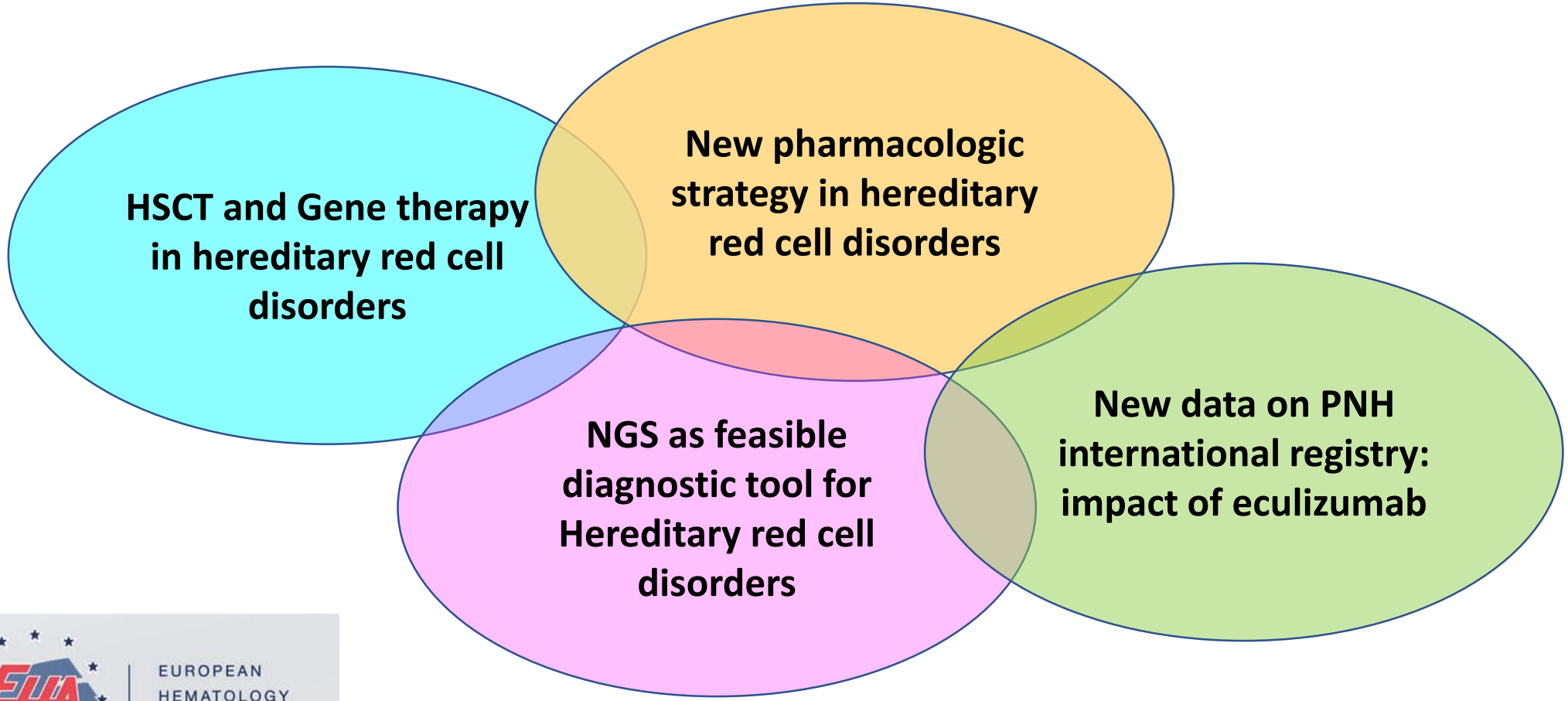
American Society of Hematology

Helping hematologists conquer blood diseases worldwide

Highlights on Red cells and Erythropoiesis



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NGS as Feasible Diagnostic tool for Hereditary Red Cell disorders

- Next Generation Sequencing (NGS) is a new powerful tool that allows the simultaneous analysis of large panel of genes involved in hereditary red cell disorders

- Hereditary red cell disorders with atypical clinical presentation are easily misdiagnosed.

- NGS requires a careful patient history collection and pedigree analysis.

Identification of new mutations in patients with red cell membrane disorders using NGS

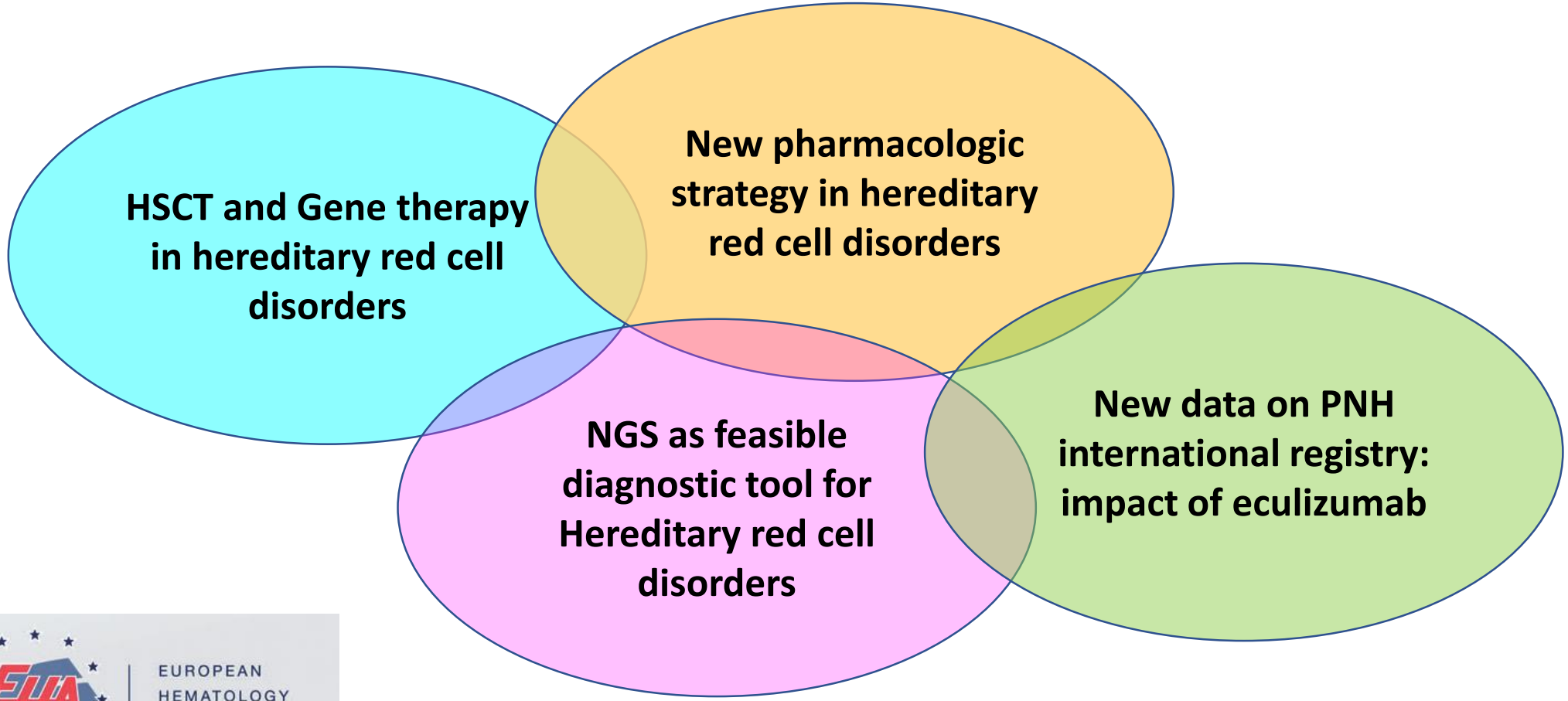
- 116 pts from 74 unrelated families were analyzed using NGS

- 42 new variants were identified:
  - Beta spectrin (23)
  - Ankyrin (21)
  - Alpha spectrin (16)

- Manu Pereira et al. NGS panel resulted in 89% of molecular diagnosis of previously unknown membranopathy (11% still undetermined molecular defect).

Manu Pereira MD et al Haematologica 102: P615, 2017

Highlights on Red cells and Erythropoiesis



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HSCT and Gene Therapy in Hereditary Red Cell Disorders

1. HSCT in hereditary red cell disorders:

- **β-Thalassemia: Long-term study (1985-2012) in French cohort of TM patients (134 transplanted pts, median age 5.9 yrs):**
  - Source BM (85%), with matching sibling donors
  - Hb median levels 12.5 g/dL
  - Long-term complications:
    - 2 pts died of chronic GVHD
    - 12% of the pts showed: hypothyroidism (7); Heart failure (2); Diabetes (5); Chronic respiratory failure (5)
- **PK deficient patients (16 pts, median age 6.5 yrs)**
  - Source: BM (36%), Peripheral blood (45%), Cordon blood (19%)
  - GVDH grade 4 (38%)
  - Risk of death: age (>10 yrs) and splenectomy

Rahal I et al. Haematologica 102: S131, 2017; Van Straaten S et al Haematologica 102: S452, 2017; Kim et al Bone marrow Transplantation 2016

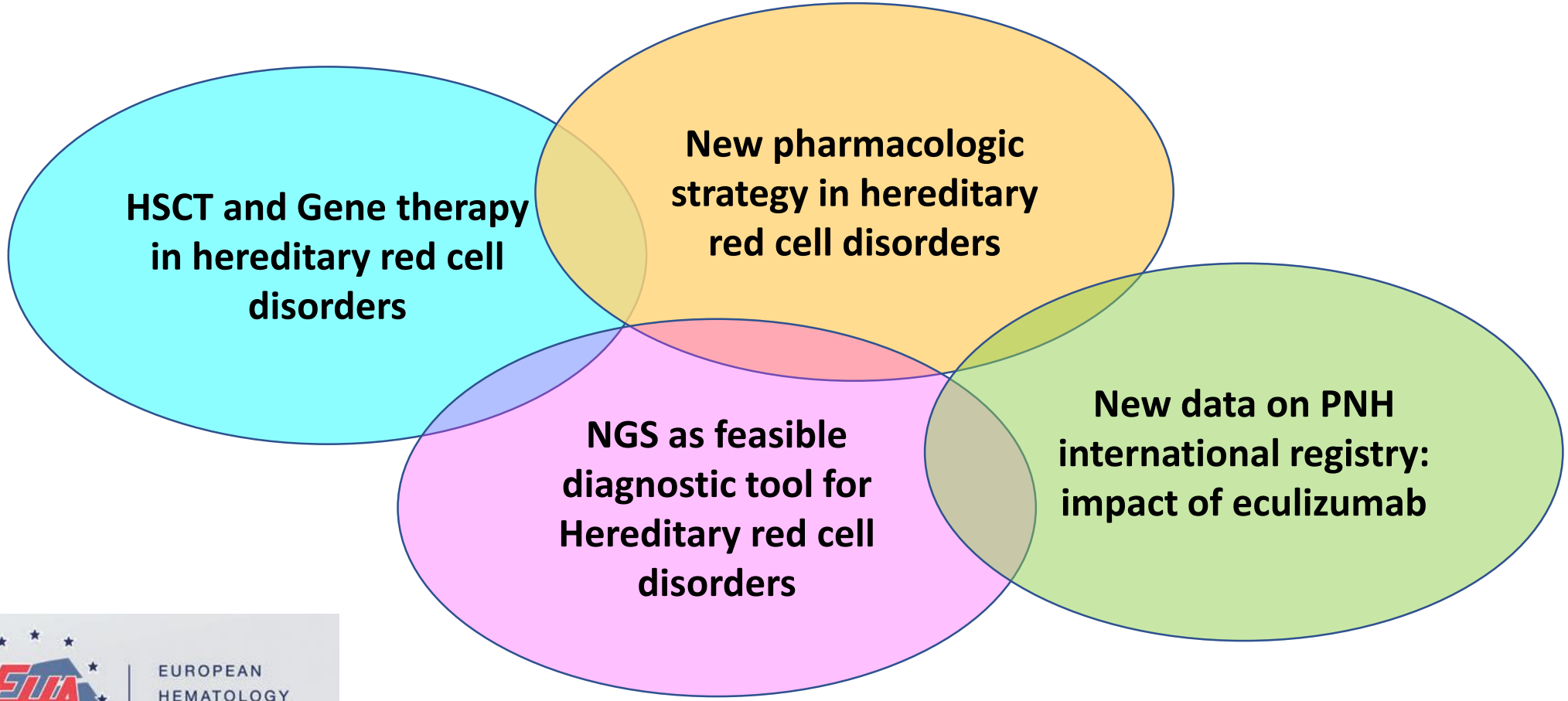
2. Gene therapy in hereditary red cell disorders:

- **β-Thalassemia- phase I-II clinical trial (3 adults and 4 children)**
  - Autologous transplantation of hematopoietic stem cells engineered by lentivirus vector expressing a transcriptionally regulated human β-globin gene
  - Genotype: β^0/β^0; β^+/β^+; β^0/β^+
  - Reduction of transfusion requirement in both adult and children

- **Fanconi Anemia (FA)- clinical trial (6 pts aged 6-8 and 2 pts aged 15-16 yrs)**
  - HSC mobilization by plerixofar and G-CSF as mobilization regimen
  - CD34+ collection, then engeenired with lentivral vector (PGK-FANCA-Wpre* vector) in the absence of pre-conditioning regimen
  - Engraftment and proliferation advantage of gene corrected HSPC (5-17 months follow-up).

Marktel S et al. et al. Haematologica 102: S128, 2017; Sevilla J et al Haematologica 102: S144, 2017

Highlights on Red cells and Erythropoiesis



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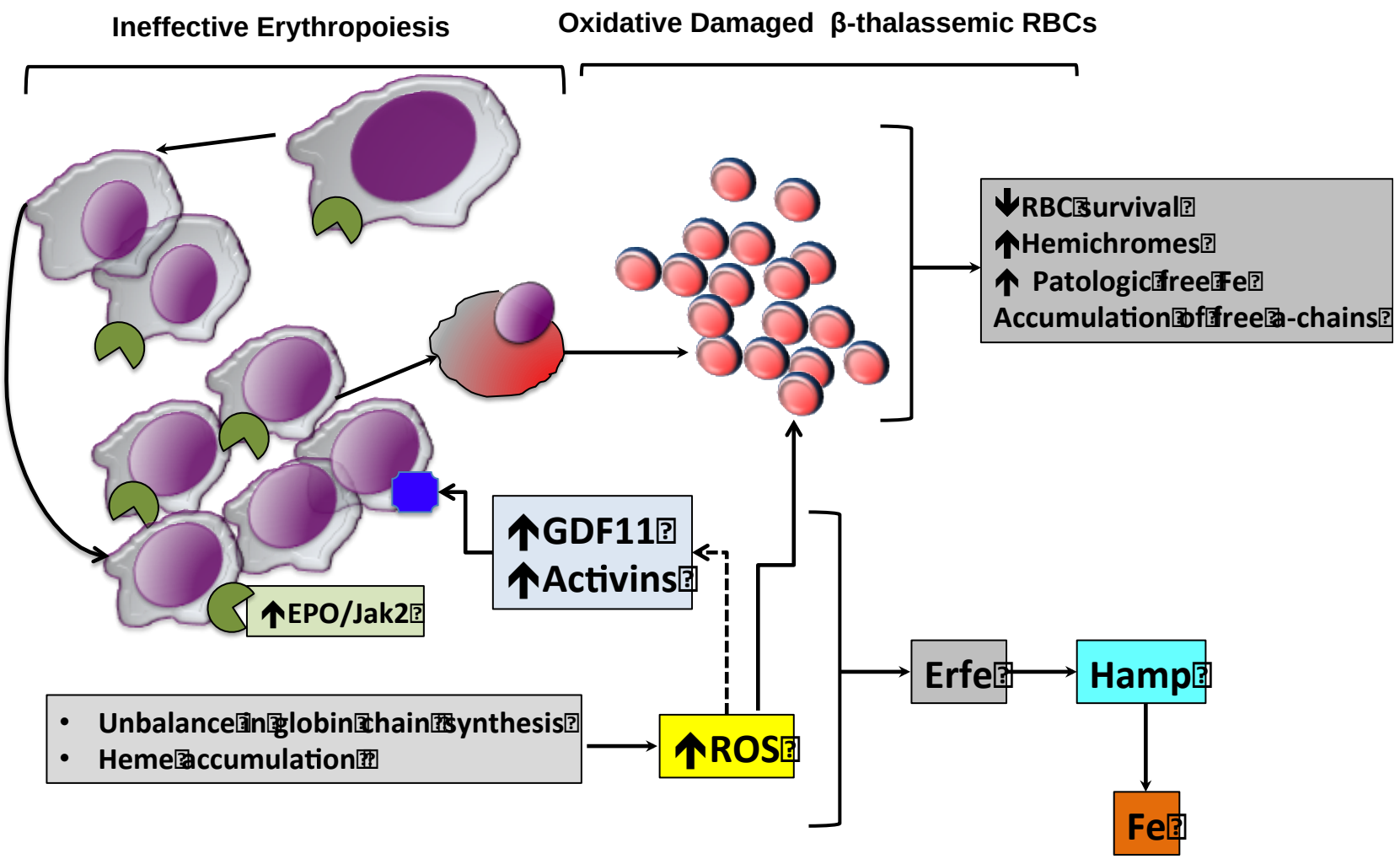
New Pharmacologic Strategy in Hereditary Red Cell Disorders

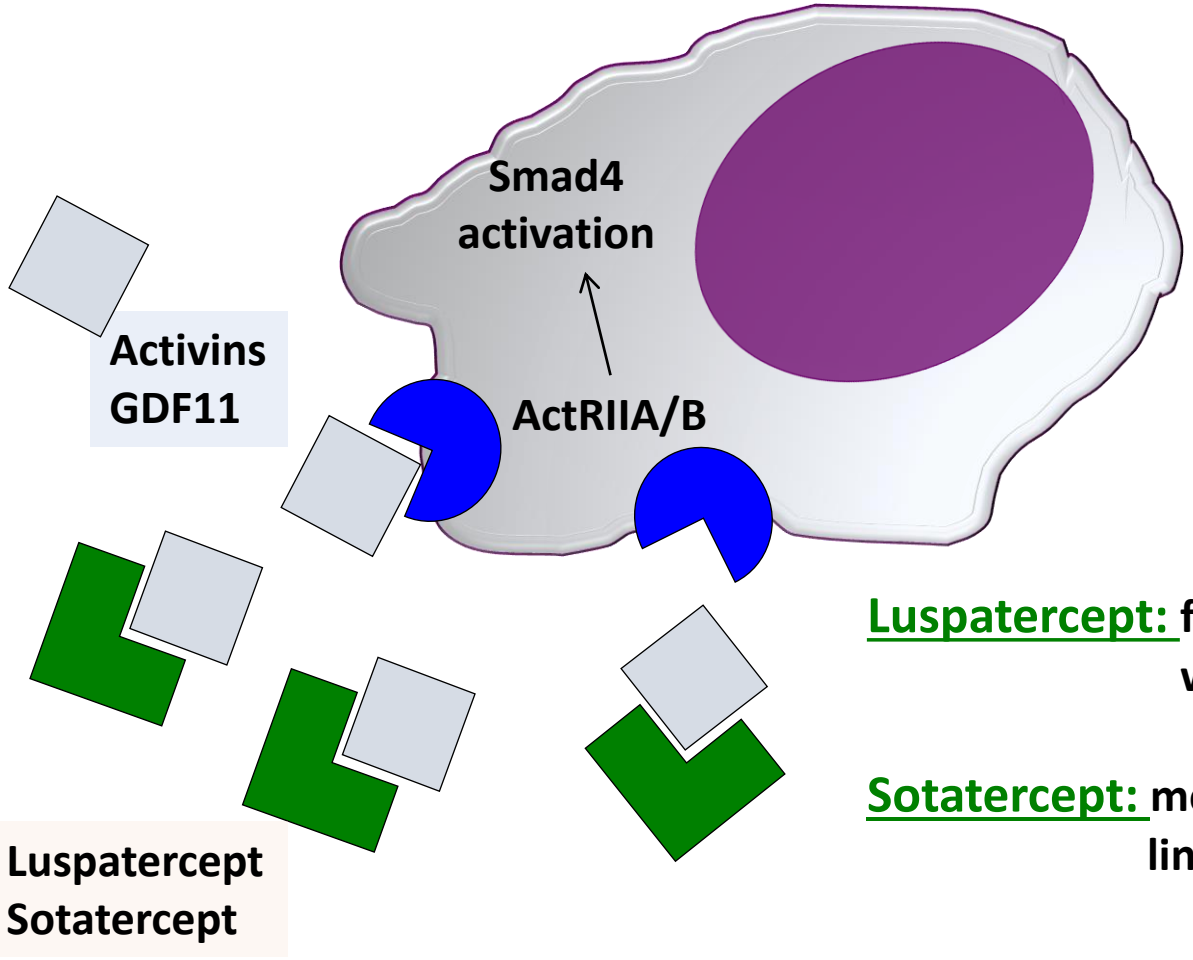
- **Agents targeting ineffective erythropoiesis:**
  - **β-Thalassemia**
  - **CDA II**
- **Agents modulating endogenous red cell enzymes:**
  - PK deficiency
- **Agents targeting vascular dysfunction and RBC-neutrophil adhesive mechanisms:**
  - **acute clinical manifestation in sickle cell disease (SCD)**

Anemia in β-Thalassemia



Rund D et al NEJM 353: 1135, 2005; De Franceschi L et al. Oxi Med Cell Longev 2013: 985210, 2013; Makis A et al AJH 91: 1135-45, 2016; Gardenghi S et al Blood 109: 5027, 2007

TGF-β Superfamily Ligant Traps



Luspatercept: fusion of extracellular domain of ActRIIA/B with Fc part of human IgG

Sotatercept: modified extracellular domain of ActRIIA/B linked to the Fc region of human IgG1

Makis A et al AJH 91: 1135-42, 2016

Sotatercept and Luspatercept in β-Thalassemic Syndromes

- **In TI and TM, Sotatercept and Luspatercept improve anemia with a dose-dependent effect**

- **Satisfactory profile for safety and tolerability**

- **Main AEs of Sotatercept and Luspatercept:**
  - Headache
  - Bone pain
  - Myalgia
  - Asthenia

- **The maximum tolerated dose was not reached.**

Makis A et al AJH doi 10.1002/ajh 24530, 2016; Piga A et al. #758, EHA 2016; Cappellini MD et al EHA abstract #S137, 2015; Porter J EHA 103616, 2014; Piga A et al ASH abstract # 851, 2016; Chen N et al ASH # abstract 2063, 2016; Piga A et al. Haematologica S129, 2017

Impact of Sotatercept on Anemia in β-Thalassemic syndromes

- **Sotatercept in Transfusion-dependent thalassemia:**

  ⬇ ≥20% transfusion requirement: 33% patients (0.3 mg/Kg), 67% of patients (0.75 mg/Kg).

- **Sotatercept in Thalassemia intermedia:**

  ⬆ Hb: 1 g/dL in 0.75 mg/Kg group (100% of patients; 67% of patients with 0.3 mg/kg).

Makis A et al AJH 9:1135-45, 2016; Cappellini MD et al EHA abstract # S137, 2015

Impact of Luspatercept on β Thalassemic syndromes: phase II multicentric open label study followed by long-term extention in TM and TI patients

Outcome measure	TD patients in base study (n=31)	TD patients in extension study (n=24)
≥33% reduction transfusion burden	71% (22)	83% (20)
≥50% reduction transfusion burden	55% (17)	71% (17)
	NTD patients in base study (n=21)	**NTD patients in extension study (n=27)**
≥1.0 g/dL increases in mean Hgb	62% (13)	78% (21)
≥1.5 g/dL increases in mean Hgb	33% (7)	52% (14)

Piga A et al. Haematologica S129, 2017

- ↓ transfusion requirements
- ↓ in LIC in TD patients under iron chelation therapy (16 weeks of treatment)
- Leg ulcer healing
- Improvement of QoL
- On going phase 3 study in β-thalassemia (BELIEVE, NCT02604433)

PK studies:

- luspatercept serum levels correlate with ↑ Hb levels (TI)
- Starting dose 1.0 mg/kg

Makis A et al AJH 91: 1135-45 2016; Piga A et al. Abstract #758, EHA 2016;; Piga A et al ASH abstract # 851, 2016; Chen N et al ASH abstract # 2063, 2016; Piga A et al. Haematologica S129, 2017

Evidences of Involvement of GDF-11-ActRIIA/B Pathway in CDA-II Pathologic Erythropoiesis

- **Congenital dyserythropoietic anemia type II (CDA-II):**
  - AR disorder mainly related to SEC23B mutations
  - It is characterized by ineffective erythropoiesis with dyserythropoiesis
  - Standard treatment: transfusion support and iron chelation

- **CDA-II patients show increased serum levels of GDF11, similarly to β-thalassemic patients.**

Russo R et al. Am J Hematol 89: E169, 2014; Iolascon A et al. Blood 122: 2162, 2013;
De Rosa G et al Haematologica S811, 2017

- **In vitro study on engineered K562 cells, mimicking CDA-II erythropoiesis:**
  - K562 cells stably silenced for SEC23B by lentivirus
  - K562 cells carrying SEC23B variants

- **K562 erythroid differentiation was associated with increased p-SMAD levels**

- **RAP011** (Sotatercept) **reduces p-SMAD activation, which in turn may increase GATA1 function, improving CDA-II erythropoiesis.**

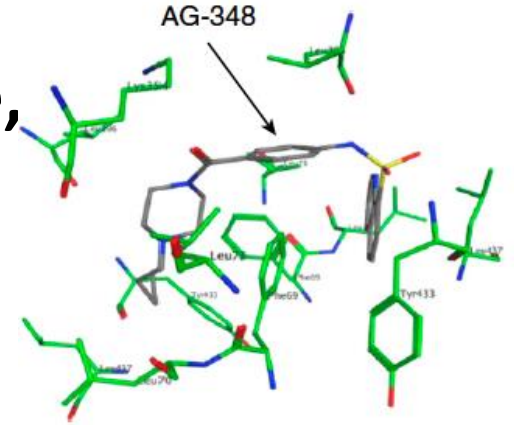
De Rosa G et al Haematologica S811, 2017

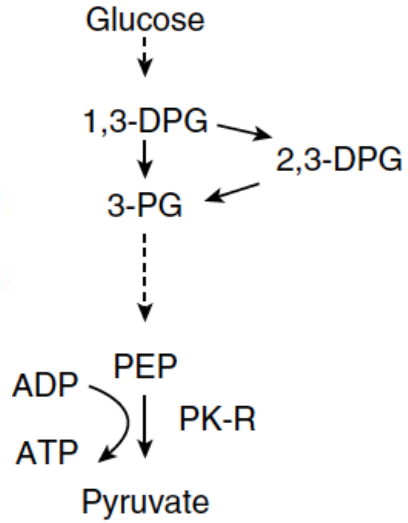
AG348, a PK-R activator, beneficially impact anemia in PK deficient patients

- **PK is a key enzyme in glycolytic pathway**

- **PK deficiency is the most common inherited enzymatic red cell disorder (51/1.000.000), causing non spherocytic hemolytic anemia**
  Beutler E Blood 95: 3585, 2000

- **AG348 is an orally available small molecule, acting as allosteric activator of PK-R**
  Kung C et al. Blood 130: 1347, 2017





Grace RF et al Haematologica S451, 2017

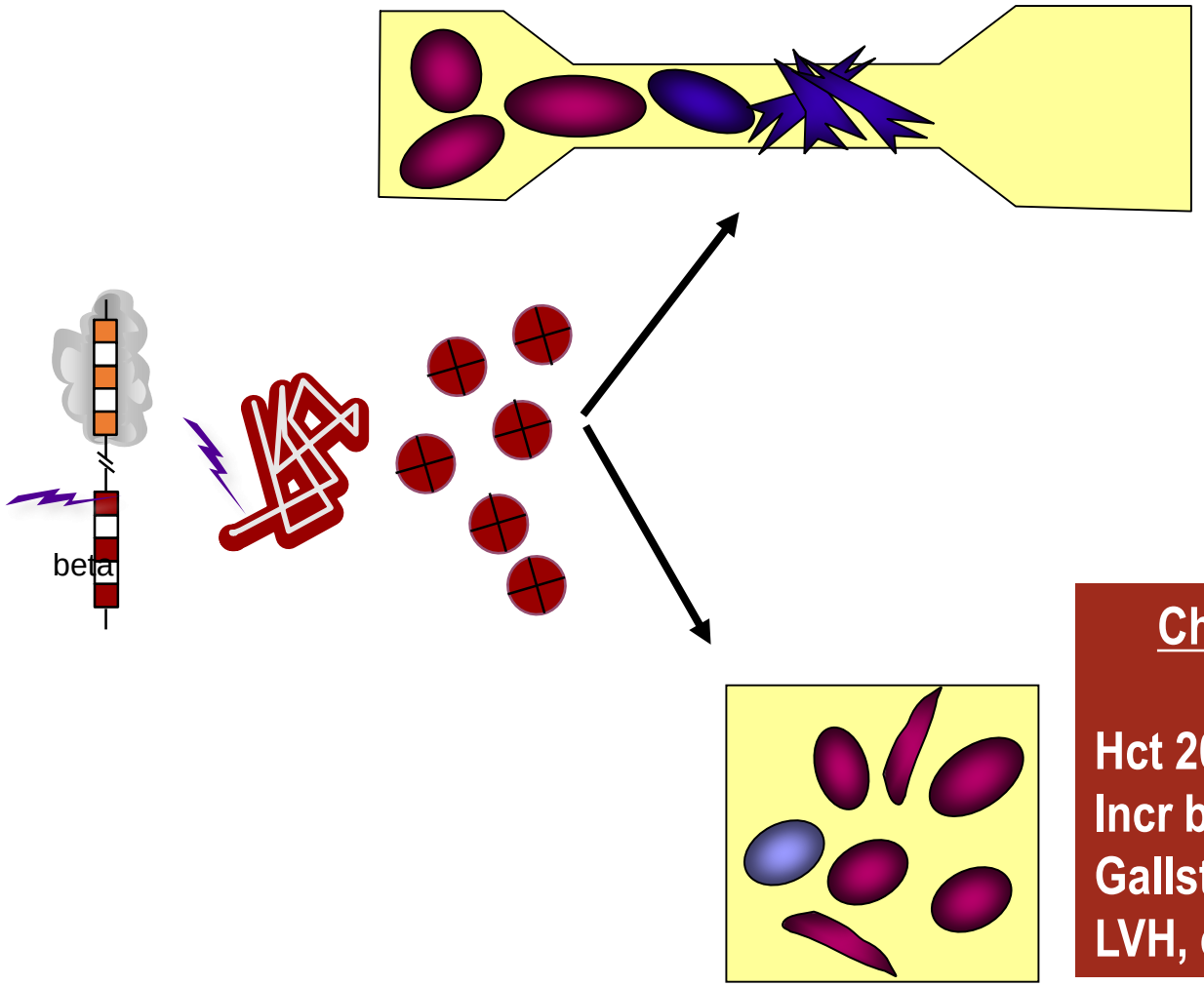
- **Open label dose ranging trial of AG348 in transfusion-independent adult patients with PK-deficiency** (52 patients were enrolled; NCT 02476916)

- AG-348 was administrated at the dosage of 50-300 mg BID for 6 months

- Hb increased > 1 gr/dL was stably observed in **47% of PK-D patients**

Grace RF et al Haematologica S451, 2017

SCD: Unmet Therapeutic Needs: Acute Events and Prevention of SCD Related Vasculopathy



Vasoocclusion:
pain crisis,
organ /endoth
damage

Chr. hemolytic anemia:
Hct 20's; retic 20's
Incr bili, LDH, etc
Gallstones
LVH, easy CHF

Molecules Interfering with Sickle-RBCs-Endothelial Adhesive Mechanisms:

Selectin and SCD

- **Endothelial cell P-selectins are cell adhesion molecules**
- **P-selectins play a key role in leukocyte recruitment and sickle red cell adhesion to endothelium**
- **P-selectin values are increased in plasma of SCD patients**

Pan J JBC 273: 10058, 1998; Matsui NM Blood 98: 1955, 2001; Turhan A PNAS 99: 3047, 2002; Kato GJ Br J Haematol 130: 943, 2005; Blann AD J Thromb Thrombolysis 25: 185, 2008.

Therapeutic Strategies to Block Selectin-mediated processes in SCD

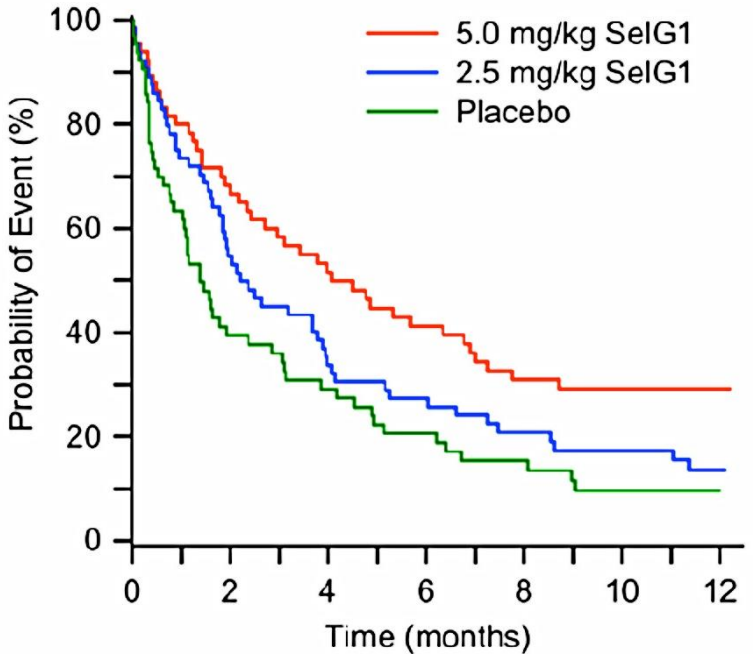
- **To block all selectins**:
  - Pan-Selectin antagonist (GMI-1070, Rivipansel) **(Chang J et al. Blood 116: 1779-86, 2010; Telen MJ et al. Blood 125: 2656-64, 2015; Wu T et al. PlosOne 2014: 9: e101301, 2014)**

- **To target only P-selectin:**
  - Humanized anti-P-Selectin antibody (Crizanlizumab) **(Mandarino D et al Blood 122: abstract #970, 2013; Ataga KI et al Blood abstract 1, 2016; Ataga K et al NEJM 376: 1796, 2017; Slomski A et al JAMA 317: 798, 2017)**
  - Sevuparin **(Telen MJ BJH doi 10.111/ BJH 14303, 2016)**
  - P-selectin aptamer **(Gustaeva DR et al. Blood 117: 727-35, 2011)**

Humanized Monoclonal Ab against P-selectin (Crinalizumab) and Acute events in SCD

In a double blind placebo-controlled mutinational trial:

- **was safe and well tollerated**
- **Induced a 1 month P-selectin block**
- **Reduced pain crisis**
- **Increased the time between pain crisis**



Mandarino D et al Blood 122: abstract 970, 2013; Telen MJ Blood 127: 810-19, 2016; Ataga KI et al Blood-ASH 1, 2016; Kutlar A et al Haematologica S454, 2017

- **SUSTAIN: double blind placebo controlled phase II study (NCT0185361) with P-selectin inhibitor-Crizanlizumab**

- **Genopyte: SS, SC, S/β0, S/β$^+$**

- **66 pts on 2.5 mg/Kg every 4 weeks and 67 pts on 5 mg/Kg every 4 weeks**

- **Crizanlizumab (5 mg/Kg every 4):**
  - **increases the likelihood of SCD adult patients being sickle cell pain crisis free**
  - **is effective also in patients under HU**

Kutlar A et al Haematologica S454, 2017

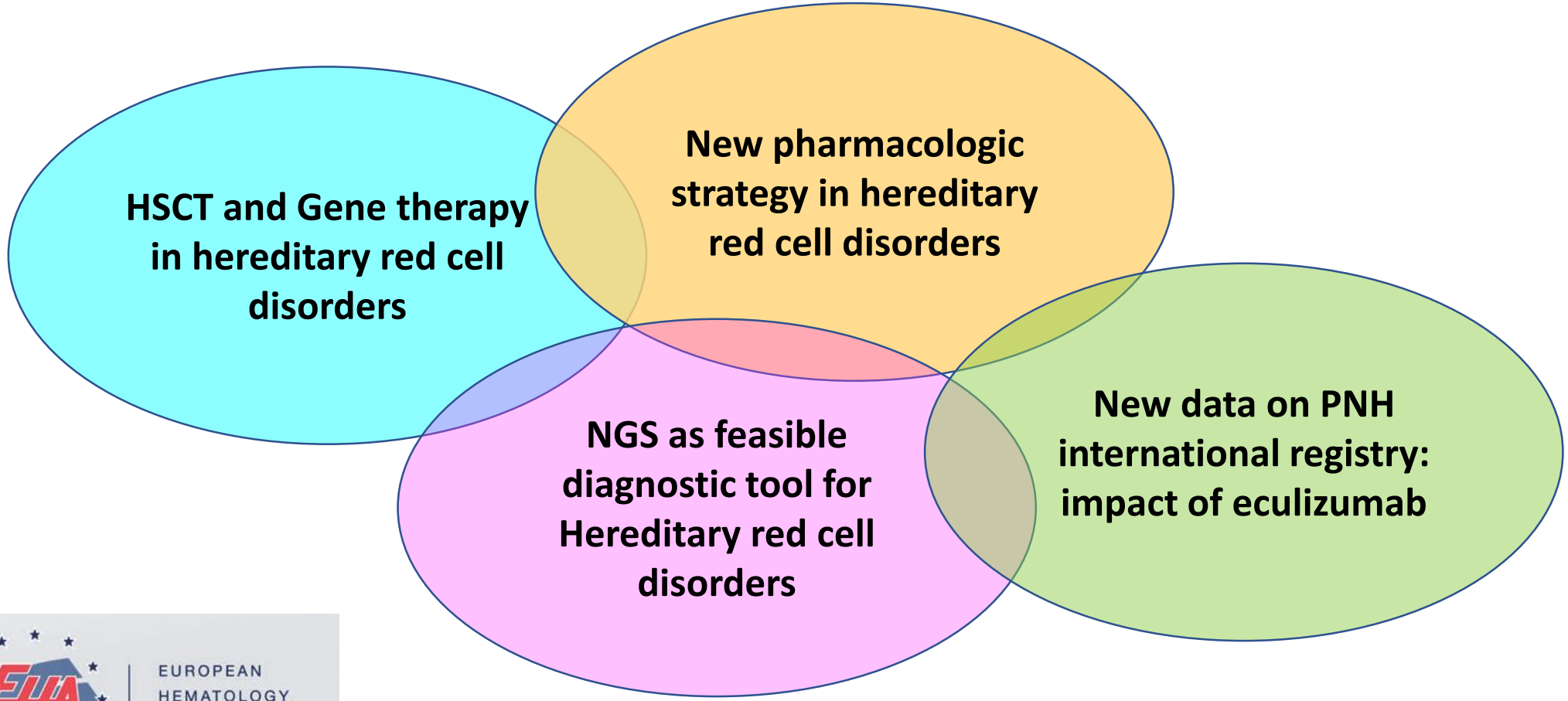
New Data on PNH International Registry: Impact of Eculizumab

- **International paroxysmal nocturnal haemoglobinuria (PNH) Registry collected data on Eculizumab in patients with PNH and high disease activity (HDA) (NCT01374360)**

- **HDA is defined as LDH ratio ≥1.5x upper limit of normal within 6 months of baseline and history of any of the following:**
  - fatigue, haemoglobinuria,
  - abdominal pain,
  - dyspnea,
  - anaemia (Hb<100 g/L),
  - major adverse vascular events (including thromboembolisms),
  - dysphagia.

Höchsmann B et al. Haematologica S498, 2017

Highlights on Red cells and Erythropoiesis



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- **4,717 patients that were enrolled, were stratified into 4 groups:**
  - HDA/ eculizumab-treated;
  - HDA/never eculizumab-treated;
  - no-HDA/ eculizumab-treated;
  - no-HDA/never eculizumab-treated.

- **In PNH patients with HDA, Eculizumab promotes:**
  - Stable reduction of LDH
  - Reduction of transfusion requirement
  - Amelioration of patient QoL, mainly related to the reduction in chronic fatigue

Höchsmann B et al. Haematologica S498, 2017

Conclusions

- **Pathologic red cell and erythropoiesis counted for 10% of the simultaneous session and in 6% of poster abstracts**
- **In red cell and erythropoiesis field, EHA 2017 meeting highlights the following topics:**
  - **HSCT and Gene therapy in hereditary red cell disorders**
  - **NGS as feasible diagnostic tool for Hereditary red cell disorders**
  - **New pharmacologic strategy in hereditary red cell disorders**
  - **New data on PNH international registry: impact of eculizumab**
- **Promising data on phase- II clinical trial were reported in invalidating chronic disorders**
- **Pathologic red cell and erythropoiesis might require more space and attention in EHA future meetings since disorders of red cells and erythropoiesis are endemic in Europe, South Asia, India and in low-developed countries.**

Brain-storming e Discussion

- **HSCT trapianto e gene therapy nelle malattie ereditarie del glubulo rosso/eritropoiesi ???**
- **NGS e' uno strumento attuabile nella diagnosi di malattie ereditarie del glubulo rosso/eritropoiesi ??**
- **Quali strategia terapeutica in malattie ereditarie del glubulo rosso/eritropoiesi…???? Come scegliere???**

The experience of extended blood group genotyping by next-generation sequencing (NGS): investigation of patients with sickle-cell disease

Y. Fichou,[1,2] M. Mariez,[1,2] C. Le Maréchal[1,2,3,4] et C. Férec[1,2,3,4]

[1] Etablissement Français du Sang (EFS) – Région Bretagne, Brest, France
[2] Institut National de la Santé et de la Recherche Médicale (Inserm), UMR1078, Brest, France
[3] Laboratoire de Génétique Moléculaire et d'Histocompatibilité, Centre Hospitalier Régional Universitaire (CHRU), Hôpital Morvan, Brest, France
[4] Faculté de Médecine et des Sciences de la Santé, Université de Bretagne Occidentale (UBO), Brest, France

Vox Sanguinis

Background Patients suffering from haemoglobinopathies may be treated by red blood cell (RBC) transfusion on a regular basis and then exposed to multiple antigens with a recurrent, potential risk of alloimmunization routinely prevented by extended RBC antigen cross-matching. While time-consuming and labour-intensive serological analyses are the gold standard for RBC typing, genotyping by current high-throughput molecular tools, including next-generation sequencing (NGS), appears to offer a potent alternative.

Study design and Methods The potential of extended blood group genotyping (EBGG) by NGS of 17 genes involved in 14 blood group systems was evaluated in a cohort of 48 patients with sickle-cell disease. Sample preparation and sequencing were simplified and automated for future routine implementation.

Results Sequencing data were obtained for all DNA samples with two different sequencing machines. Prediction of phenotypes could be made in 12 blood group systems and partially in two other blood group systems (Rh and MNS). Importantly, predicted phenotypes in the MNS (S/s), Duffy, Kidd and Kell systems matched well with serological data (98·9%), when available. Unreferenced alleles in the *ACHE* and *ART4* genes, respectively, involved in the Yt and Dombrock blood groups, were identified, then contributing to extend the current knowledge of blood group molecular genetics.

Conclusions Overall, we consider that our strategy for NGS-based EBGG, assisted by a simple method for genotyping exons 1 and 2 of the pairs of homologous genes (i.e. *RHD*/*RHCE* and *GYPA*/*GYPB*), as well as the future support of potent bioinformatics tools, may be implemented for routine diagnosis in specific populations.

Received: 23 March 2016, revised 4 June 2016, accepted 6 June 2016, published online 21 July 2016

Key words: blood group genes, genotyping, next-generation sequencing, variants.

Introduction

In line with numerous fields of clinical biology, next-generation sequencing (NGS) of blood group genes has emerged for the past few years. Stabentheiner and colleagues identified variants within the *RHD* gene in 21 donors with weak D phenotype [1]; Rieneck *et al.* [2] provided the proof of principle that the fetal *KEL1/KEL2* (*K*/*k*) polymorphism in circulating cell-free DNA in the maternal plasma may be resolved by this approach; and very recently, Lane *et al.* [3] carried out whole-genome sequencing-based prediction of red blood cell (RBC) and platelet antigens. Before this latter report, we designed an

Correspondence: Yann Fichou, Etablissement Français du Sang (EFS) Bretagne, Inserm UMR1078, 46 rue Félix Le Dantec, CS 51819, 29218 Brest Cedex 2, France
E-mail: yann.fichou@efs.sante.fr

NGS in blood group matching strategy:

SCD in chronic transfusion regimen

PK D patient and HSCT

	Survivor	Non-survivor	P value
Age	7,5 *3,0* (0,8-41)	17,4 *15,2* (6-39)	0,036*
Asian origin	8/11 (72,7%)	0/5	0,026*
Splenectomy performed	3/11 (27,3%)	4/5 (80%)	0,106
mean Hb (mmol/L) (N=13)	3,7 *3,4* (2,8-4,9)	4,4 *4,3* (3,7-5)	0,112
Pre-transplant ferritin level (ng/ml) (n=12)	804 *771* (2066-1650)	2167 *675* (596-7026)	0,432
myeloablation	6/11 (54,5%)	4/5 (80%)	0,588
Conditioning techniques			
ATG	10/11 (90,9%)	4/5 (80%)	1
Cyclophosphamide	8/11 (72,7%)	2/5 (40%)	0,299
Fludarabine	9/11 (81,8%)	4/5 (80%)	1
Busulfan	6/11 (54,5%)	3/5 (60%)	1
Busilvex	0/11	1/5 (20%)	0,313
Thiothepa	3/11 (27,3%)	1/5 (20%)	1
Treosulfan	3/11 (27,3%)	1/5 (20%)	1
Thymoglobulin	0/11	1/5 (20%)	0,313
Graft type			0,507
MSD	2/11 (18,2%)	0/5	
MUD	6/11 (54,5%)	3/5 (60%)	
CORD	2/11 (18,2%)	0/5	
MFD	1/11 (9,1%)	2/5 (40%)	
Transplant source			0,333
Bone marrow	4/11 (36,4%)	4/5 (80%)	
Peripheral blood	5/11 (45,5%)	1/5 (20%)	
Cord blood	2/11 (18,2%)	0/5	
Transfusion free after transplant	10/11 (90,9%)	4/5 (80%)	
GvHD			0,015*
None	7/11 (63,6%)	0/5	
Grade 1	1/11 (9,1%)	0/5	
Grade 2	1/11 (9,1%)	0/5	
Grade 3	0/9	1/5 (20%)	
Grade 4	2/11 (18,2%)	4/5(80%)	
(descriptive statistics: mean-median (range) (N), frequencies number/total (percentage) *P=<0.05			

Van Straaten Set al Haematologica 102: S452, 2017;

Pediatr Transplantation 2014: 18: E130–E133

Pediatric Transplantation
DOI: 10.1111/petr.12254

Successful hematopoietic stem cell transplantation in a patient with congenital dyserythropoietic anemia type II

Unal S, Russo R, Gumruk F, Kuskonmaz B, Cetin M, Sayli T, Tavil B, Langella C, Iolascon A, Cetinkaya DU. Successful hematopoietic stem cell transplantation in a patient with congenital dyserythropoietic anemia type II.

Abstract: CDA are a group of inherited, rare diseases that are characterized by dyserythropoiesis and ineffective erythropoiesis associated with transfusion dependency in approximately 10% of cases. For these latter patients, the only curative treatment is HSCT. There are very limited data on HSCT experience in this rare disease. Herein, we report a five-yr six-month-old girl with compound heterozygous mutations in *SEC23B* gene, who was diagnosed to have CDA type II and underwent successful HSCT from her matched sibling donor.

Sule Unal[1], Roberta Russo[2,3], Fatma Gumruk[1], Baris Kuskonmaz[1], Muslla Cetin[1], Tulin Sayli[4], Betul Tavil[1], Concetta Langella[2,3], Achille Iolascon[2,3] and Duygu Uckan Cetinkaya[1]

[1]Division of Pediatric Hematology, Hacettepe University, Ankara, Turkey, [2]Department of Molecular Medicine and Medical Biotechnologies, University Federico II, Naples, Italy, [3]CEINGE Advanced Biotechnologies, Naples, Italy, [4]Ankara Pediatric Hematology and Oncology Research Hospital, Ankara, Turkey

Key words: transplantation – congenital dyserythropoietic anemias – iron – *SEC23B*

Sule Unal, Division of Pediatric Hematology, Hacettepe University, Ankara 06100, Turkey
Tel.: +90 312 305 1170
Fax: +90 312 311 2398
E-mail: suleunal@hacettepe.edu.tr

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Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study

Uwe Platzbecker, Ulrich Germing*, Katharina S Götze*, Philipp Kiewe*, Karin Mayer*, Jörg Chromik*, Markus Radsak*, Thomas Wolff*, Xiaosha Zhang, Abderrahmane Laadem, Matthew L Sherman, Kenneth M Attie, Aristoteles Giagounidis**

Summary

Background Myelodysplastic syndromes are characterised by ineffective erythropoiesis. Luspatercept (ACE-536) is a novel fusion protein that blocks transforming growth factor beta (TGF β) superfamily inhibitors of erythropoiesis, giving rise to a promising new investigative therapy. We aimed to assess the safety and efficacy of luspatercept in patients with anaemia due to lower-risk myelodysplastic syndromes.

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AG-348 enhances pyruvate kinase activity in red blood cells from patients with pyruvate kinase deficiency

Charles Kung,[1] Jeff Hixon,[1] Penelope A. Kosinski,[1] Giovanni Cianchetta,[1] Gavin Histen,[1] Yue Chen,[1] Collin Hill,[1] Stefan Gross,[1] Yaguang Si,[1] Kendall Johnson,[1] Byron DeLaBarre,[1] Zhiyong Luo,[2] Zhiwei Gu,[2] Gui Yao,[2] Huachun Tang,[2] Cheng Fang,[2] Yingxia Xu,[2] Xiaobing Lv,[2] Scott Biller,[1] Shin-San Michael Su,[1] Hua Yang,[1] Janeta Popovici-Muller,[1] Francesco Salituro,[1] Lee Silverman,[1] and Lenny Dang[1]

[1]Agios Pharmaceuticals, Inc., Cambridge, MA; and [2]Shanghai ChemPartner Co., Ltd., Shanghai, China

Key Points

- AG-348 is a small-molecule allosteric activator of WT red

Pyruvate kinase (PK) deficiency is a rare genetic disease that causes chronic hemolytic anemia. There are currently no targeted therapies for PK deficiency. Here, we describe the identification and characterization of AG-348, an allosteric activator of PK that is currently in clinical trials for the treatment of PK deficiency. We demonstrate that AG-348 can

Table 1. Kinetic parameters from recombinant PK-R enzymes measured with or without treatment with AG-348

	No compound				5 μM AG-348				
Enzyme	V_{max}, μmol/s/mg	PEP K_M, mM	k_{cat}, 1/s	k_{cat}/K_M	V_{max}, μmol/s/mg	PEP K_M, mM	k_{cat}, 1/s	k_{cat}/K_M	% of WT PK-R k_{cat}/K_M
WT	0.69	1.13	42.5	37.6	0.74	0.32	45.7	142.0	378
R532W	0.22	1.73	13.6	7.9	0.21	0.42	12.9	30.4	81
R510Q	1.60	1.45	98.8	68.1	1.64	0.32	101.5	317.3	844
R479H	0.50	1.65	30.9	18.7	0.53	0.55	32.4	58.5	156
R486W	0.34	1.45	21.2	14.6	0.39	0.25	24.2	98.4	262
G332S	0.14	2.73	8.3	3.0	0.15	1.11	9.4	8.5	23
R490W	0.37	1.52	22.8	15.0	0.39	0.51	24.2	47.6	127
G364D	0.16	2.14	10.1	4.7	0.22	0.55	13.5	24.7	65
T384M	0.11	1.42	6.9	4.8	0.12	0.37	7.2	19.3	51

k_{cat}, first-order rate constant; k_{cat}/K_M, measure of enzymatic efficiency[39]; K_M, substrate concentration to achieve half maximal velocity; V_{max}, maximum velocity.

PNH patient under Eculizumab Treatment

Outcome Measure*	HDA/Ecu-treated (n=786)	HDA/Never Ecu-treated (n=636)	No-HDA/Ecu-treated (n=111)	No-HDA/Never Ecu-treated (n=1138)
	n=787	n=636	n=108	n=1135
Years from baseline to last follow-up, median (min, max)	3.1 (0.0, 11.0)	1.5 (0.0, 10.0)	2.1 (0.1, 11.0)	1.5 (0.0, 9.5)
	n=583	n=356	n=67	n=582
Change from baseline in LDH ratio, mean (SD)	−5.0 (3.7)	−0.4 (2.3)	−0.4 (2.0)	0.2 (0.9)
	n=210	n=107	n=25	n=248
Change from baseline in % GPI-deficient granulocytes, mean (SD)	3.5 (23.9)	−0.5 (20.2)	6.3 (21.8)	1.3 (17.6)
Change from baseline in number of patients requiring blood transfusions, n (%)	n=599	n=425	n=74	n=747
Yes to no	225 (37.6)	67 (15.8)	21 (28.4)	161 (21.6)
No change	332 (55.4)	317 (74.6)	47 (63.5)	549 (73.5)
No to yes	42 (7.0)	41 (9.6)	6 (8.1)	37 (5.0)
Change from baseline in number of patients with MAVE, n (%)	n=699	n=460	n=94	n=766
Previous history of MAVE and occurrence of MAVE after baseline	17 (2.4)	3 (0.7)	3 (3.2)	4 (0.5)
Previous history of MAVE and no occurrence of MAVE after baseline	216 (30.9)	60 (13.0)	28 (29.8)	80 (10.4)
No previous history of MAVE and occurrence of MAVE after baseline	10 (1.4)	12 (2.6)	2 (2.1)	12 (1.6)
No previous history of MAVE and no occurrence of MAVE after baseline	456 (65.2)	385 (83.7)	61 (64.9)	670 (87.5)
Change from baseline in FACIT-Fatigue score, mean (SD)	4.1 (10.3)	0.5 (6.8)	−3.8 (14.5)	0.3 (7.7)

*All analyses of change from baseline to last follow-up were restricted to patients with at least 6 months of follow-up and who had data at both baseline and last follow-up time points. Abbreviations: Ecu, eculizumab; FACIT, Functional Assessment of Chronic Illness Therapy; GPI, glycosylphosphatidylinositol; HDA, high disease activity; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; SD, standard deviation.

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