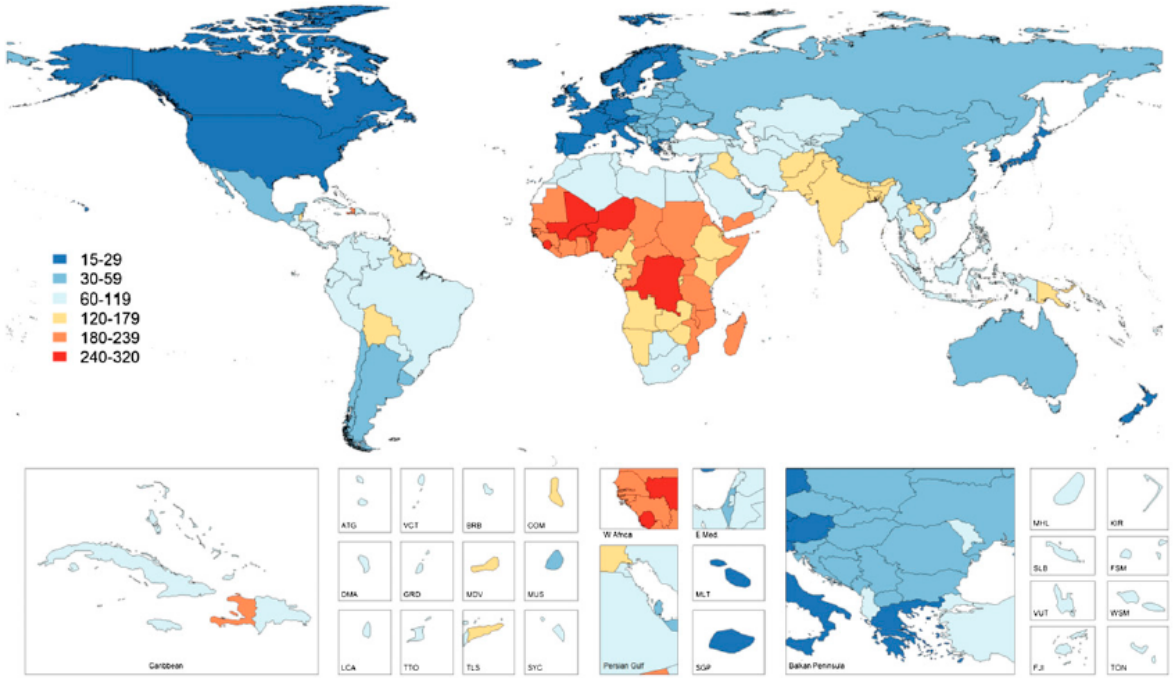
L'ANEMIA FALCIFORME: NUOVI APPROCCI TERAPEUTICI

Lucia De Franceschi

Dept. di Medicina, AOUI Verona e Universita' di Verona- Verona

Treviso 17 Novembre 2017

Hemoglobinopathies are Emerging Problem of Public Health based on YLD and DALYs (1999-2010; 2010-2055)

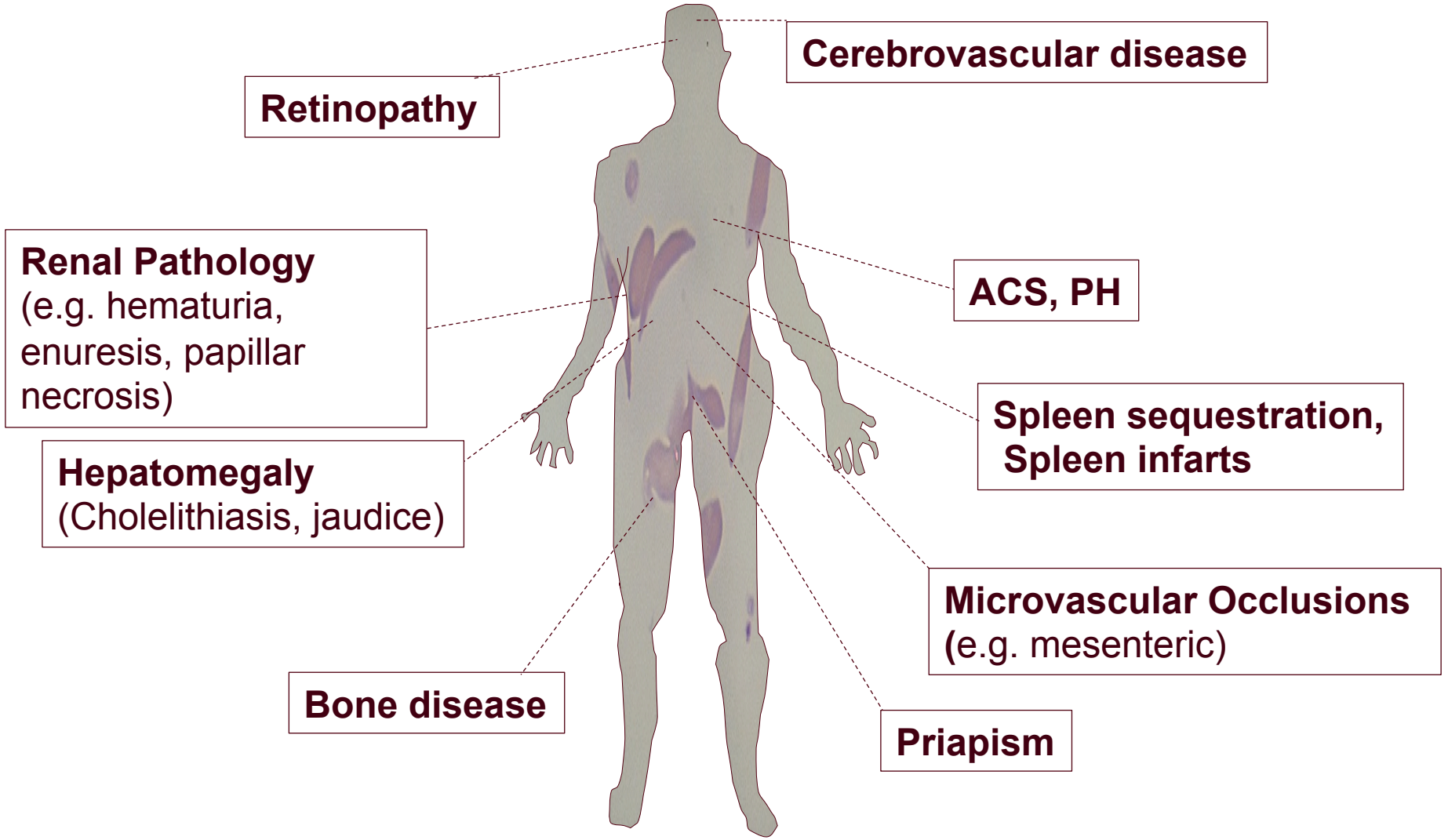


YLDs: years lived with disability for **hemoglobinopathies** (**β-thal and SCD**): **10.197** *vs* 21.342 cardiovascular disorders

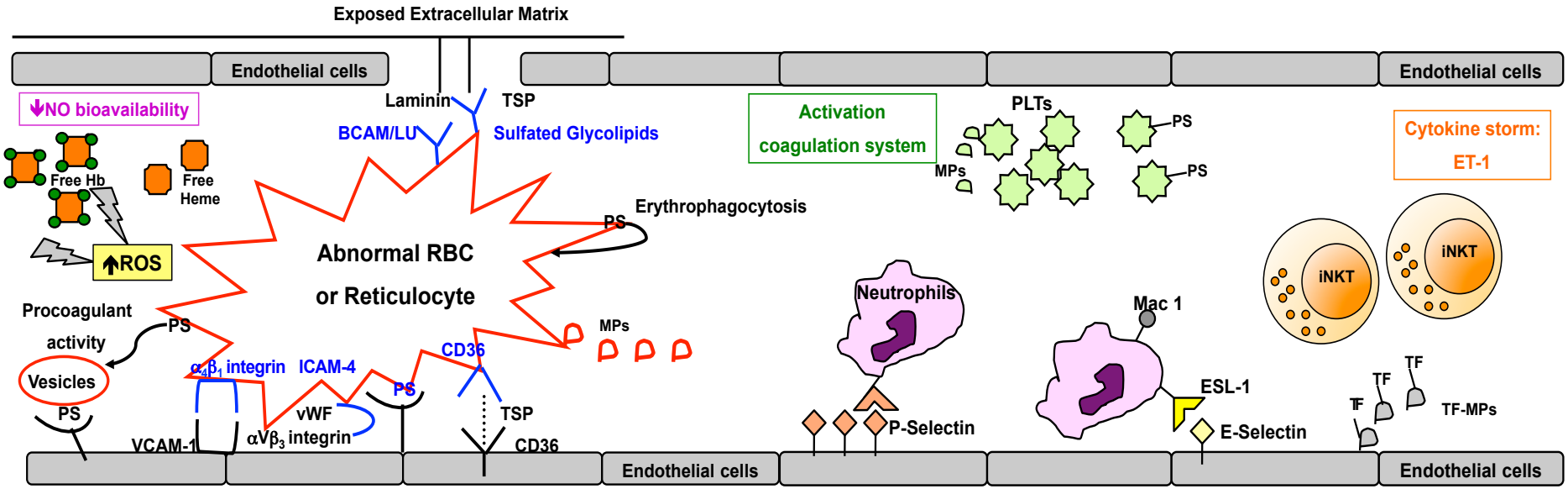
DALYs: disability adjusted life years for **hemoglobinopathies** (**β-thal and SCD**): **15.640** *vs* 75.000 diabetes

Murray CJ et al Lancet 380: 2197, 2012; Kassebaum NJ Blood 123: 615, 2014

SCD is a Monogenic Disorder but a Multiorgan Disease



The high Biocomplexity of SCD Substains Multi-Organ Damage



Modified from De Franceschi L *et al*. Seminars in Thrombosis, 37: 266; 2011

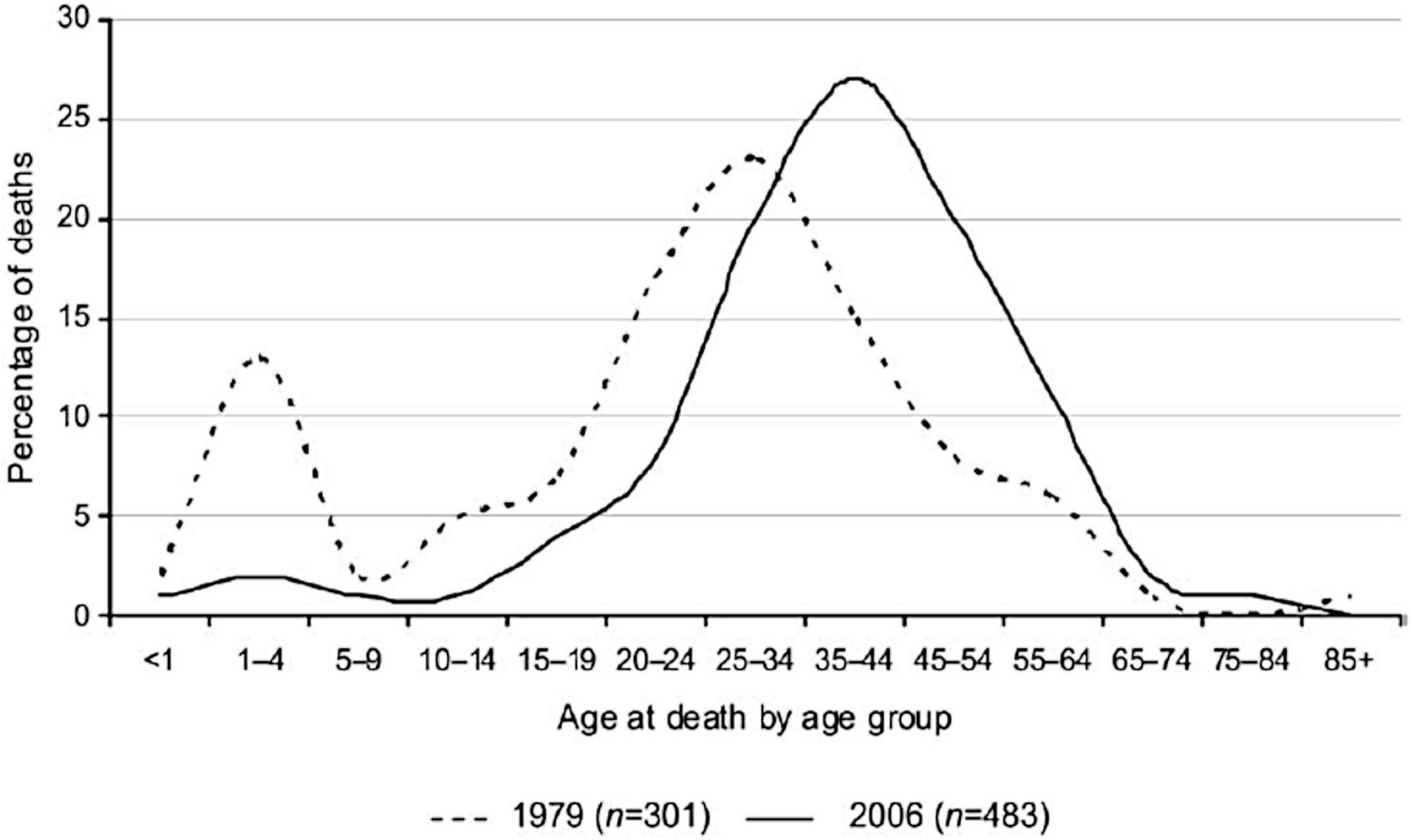
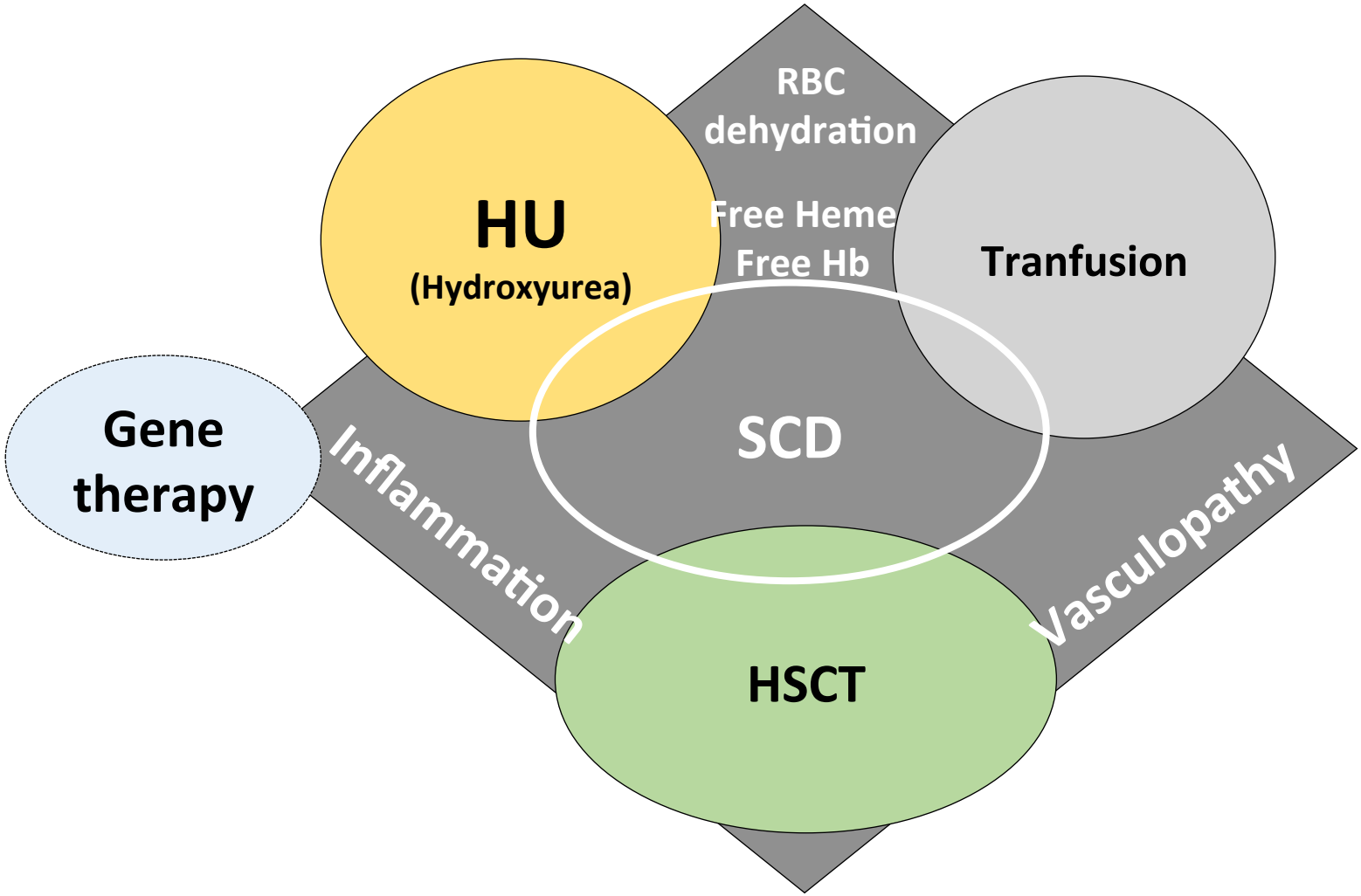


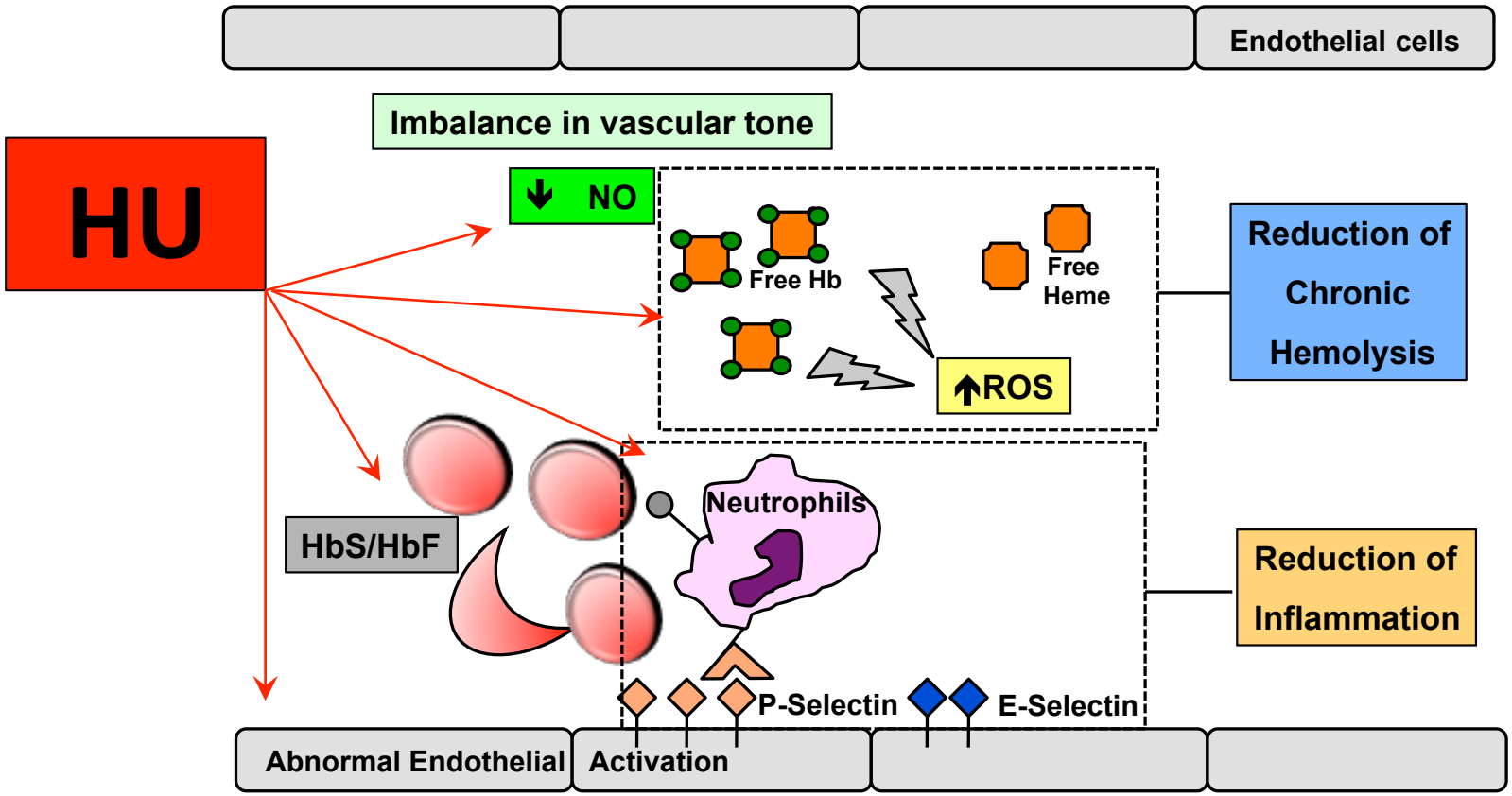
Figure 2. Age at death for individuals with SCD in 1979 and 2006
SCD, sickle cell disease

Hassel K et al. 38: 5512, 2010

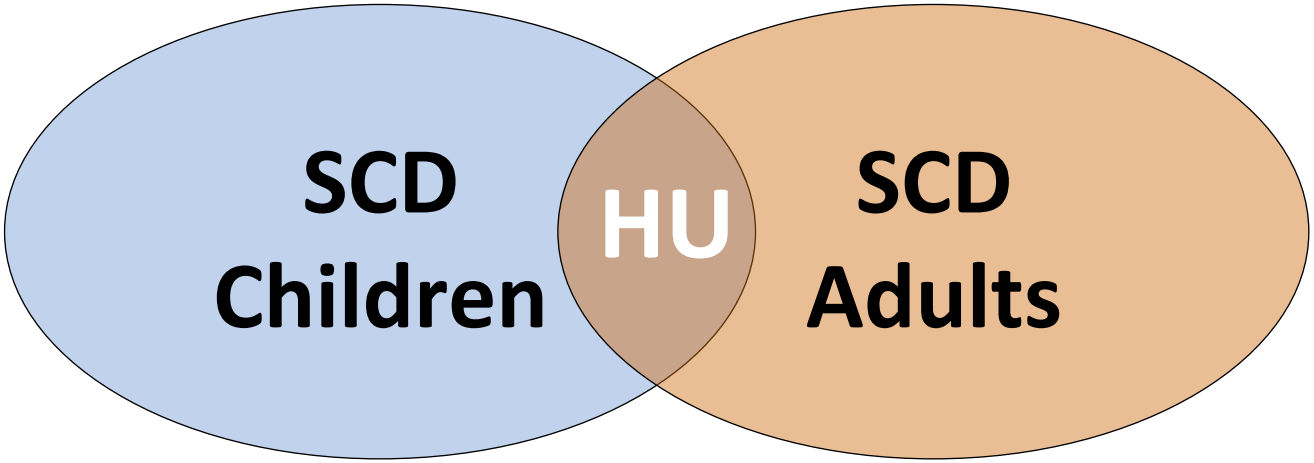
Available Treatments for SCD



HU is a Multimodal Therapy



Platt OS NEJM 358: 1362, 2008; Saleh AW et al. 102: 31, 1999; Charache S et al. 34: 15, 1997; Yarbro JW et al. 19: 1-10, 1992 ; Maier ER et al Pediatric Res doi 10/1038, 2016;



In SCD, HU ameliorates mortality and morbidity and reduces:

- **Frequency of VOC and rate of hospitalization**
- **ACS**
- **Transfusion requirements**
- **Severe dactilitis in SCD pediatric population**

Wong TE et al Blood Epub Oct 2014; Crosby LE et al. Pedriatr Blood Cancer Epub 2014; Voskaridou E et al. Blood 115: 2354, 2010; Wang WC et al. The Lancet 377: 1663, 2011; Yawn BP et al JAMA 312: 1033, 2014.

HU as Acceptable Alternative to Chronic Transfusion in SCD Childre with History of TCD Abnormalities

In SCD children under chronic transfusion regime, a careful transition t HU might be considered with normal TCD, mantaining every 3 month TCD follow-up;

Identified predictive factors for reversion to abnormal TCD velocites:

- **Before HU: High retic count (> 400 x 10^9 cells/uL)**
- **After HU: WBC.**

Bernaudin F et al Blood 127: 1814, 2016; Helton KJ et al Blood 124: 891; 2014 ; Ware RE Blood 119: 3925; 2012; Ware RE et al Lancet 387: 661-70, 2016

Adherence to HU is a Challenge in SCD

- **35-50% SCD patients achieve high adherence to HU therapy;**

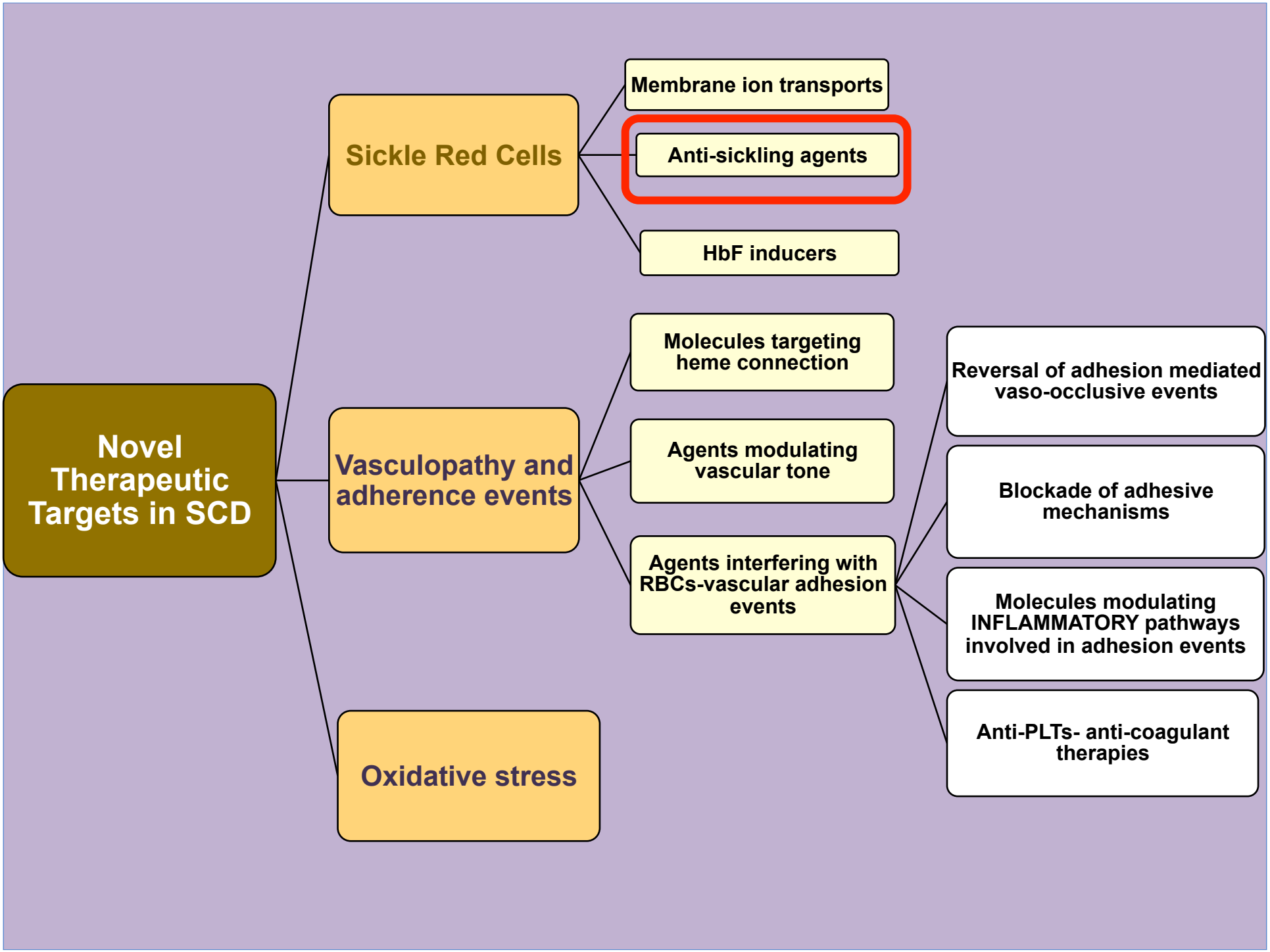
- **Multiple factors:**
  - Chronic medication
  - Socio-economic reasons
  - Adhesion barriers related to adolescence and transition from pediatric care to adult care

- **Ongoing studies on adherence to HU therapy:**
  - **Implementation of pharmacy service**
  - **Glowcap device**
  - **HABIT study: home visits by CHN and text messaging seem to be effective**

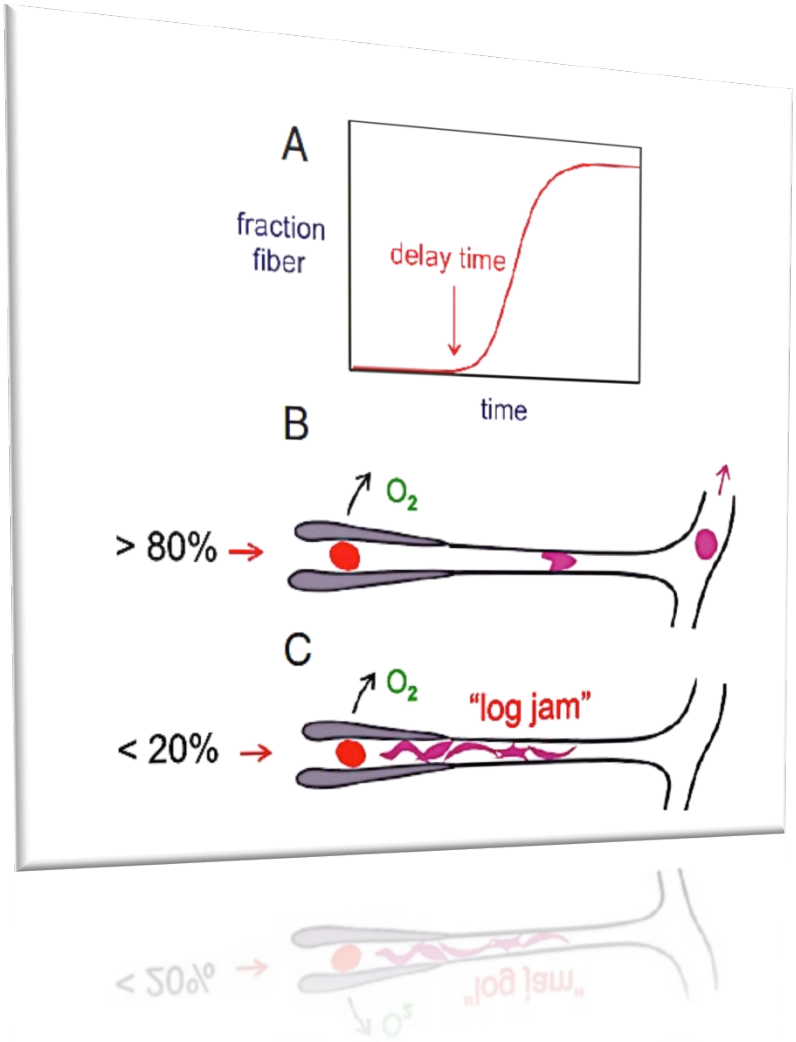
Inoue S et al. Int J Hematol 104: 2000, 2016; Han J et al Pharmacotherapy doi 10.1002/phar.1834, 2016; Cerary S et al. JMIR Res Protoc 5: e193, 2016; Green S et al Pediatr. Blood Cancer 63: 2146, 2146; 2016; Green NS et al ASH poster #1310, 2016

Q: WHY DO WE NEED NEW TREATMENTS FOR SCD?

A: Lack Of Therapeutic Options For Acute Events And Prevention of SCD Related Vasculopathy


Novel Therapeutic Targets in SCD
Sickle Red Cells
Membrane ion transports
Anti-sickling agents
HbF inducers
Vasculopathy and adherence events
Molecules targeting heme connection
Agents modulating vascular tone
Agents interfering with RBCs-vascular adhesion events
Reversal of adhesion mediated vaso-occlusive events
Blockade of adhesive mechanisms
Molecules modulating INFLAMMATORY pathways involved in adhesion events
Anti-PLTs- anti-coagulant therapies
Oxidative stress

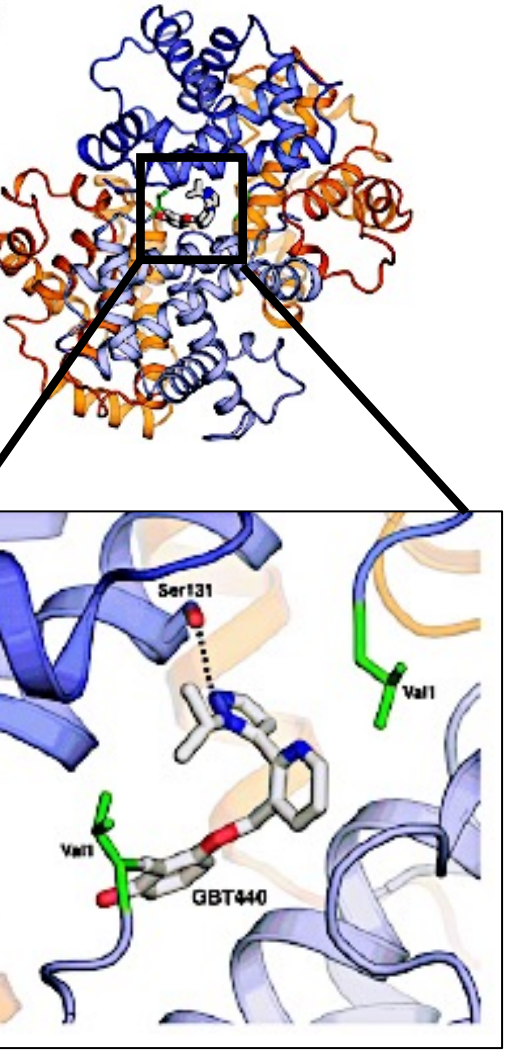
HbS Polymerization and Sickling: Therapeutic Strategies



- **Block intermolecular contacts to prevent HbS fiber generation (GBT440)**
- **Decrease HbS concentration:**
  - **RBC volume increased (CLT, Senicapoc)**
  - **HbF induction (HU)**
- **Increase Hb oxygen affinity**
- **Weaken fiber contacts (intracellular pH or 2-3 DPG)**

Li Q et al PNAS 11: e689, 2017;
De Franceschi L et al Haematologica 89: 348, 2004

GBT440 (Originally named GTx011) and SCD



- **GBT440** is an oral available potent and direct anti-sickling agent
- **GBT440** binds to HbS and promotes a left shift in p50 of HbS, **delaying HbS polymerization and sickling**
- **GBT440** ameliorates *in vitro* red cell deformability and viscosity and **improves sickle mouse red cell survival with reduction in reticulocyte count**

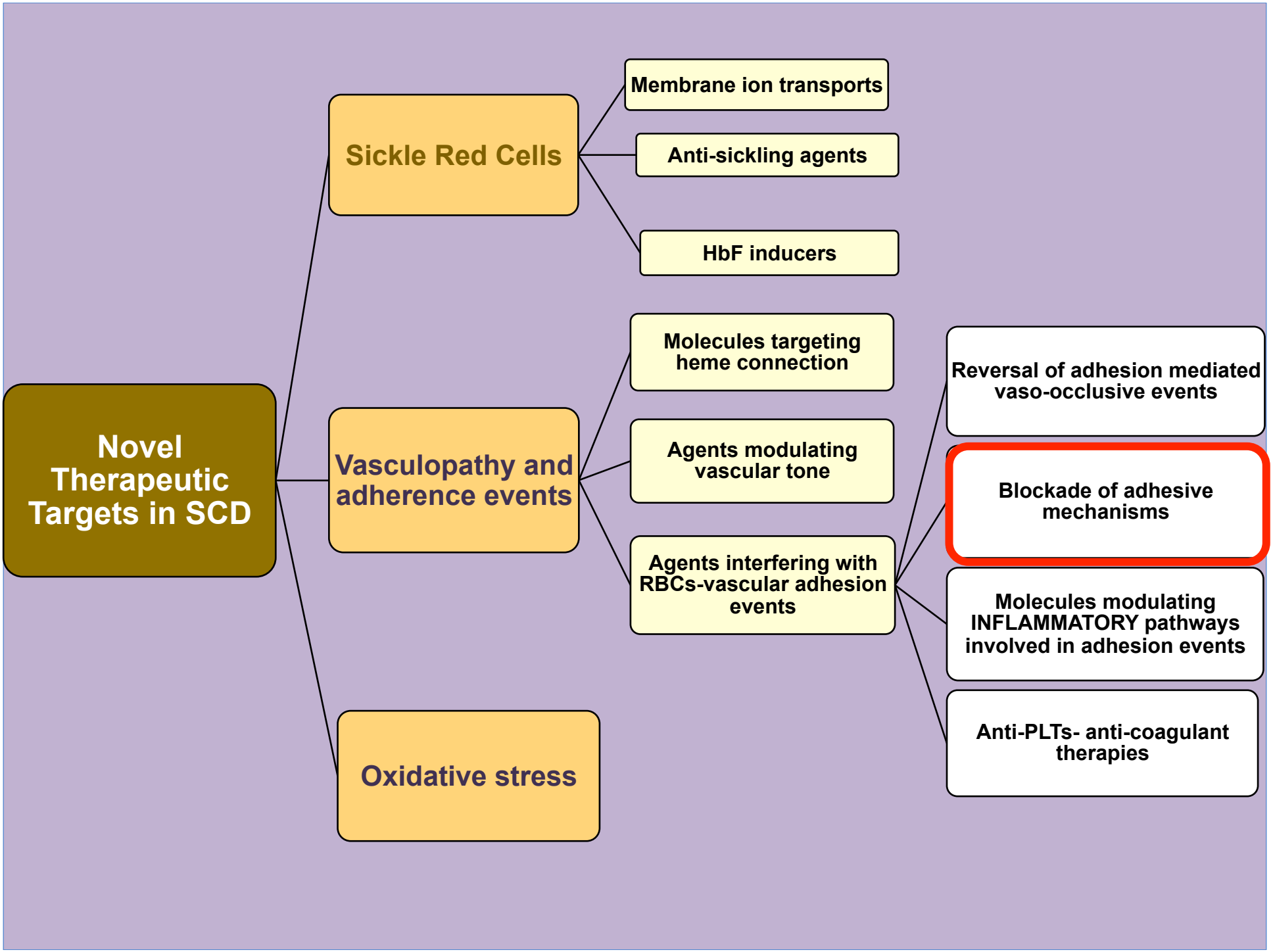
Dufu K et al. . Blood. 2014;124:217; Oder E et al. BJH 175: 24, 2016;
Oksenberg D et al BJH 175: 141, 2016; Li Q et al PNAS 11: e689, 2017;

GBT440 and Clinical Impact in SCD

- **In Phase I/II study double blind placebo controlled trial in healthy volunteers and SCD patients (SS-Sβ° pts), GBT440 showed:**
  - To be well tolerated without major adverse events
  - To modify 10-30 HbS
  - To reduce RBCs hemolysis
  - To decrease reticulocyte counts
  - To decrease EPO levels

- **Phase II open label study in SCD adolescent: GBT440 pharmacokinetic similar to adult SCD patients**

Oder E et al BJH 175: 24, 2016; Oksenberg D et al BJH 175: 141, 2016; Lehrer-Graiwer J et al Blood 126: 542, 2015; Washington C et al. EHA abstract # P620, 2017


Novel Therapeutic Targets in SCD
Sickle Red Cells
Membrane ion transports
Anti-sickling agents
HbF inducers
Vasculopathy and adherence events
Molecules targeting heme connection
Agents modulating vascular tone
Agents interfering with RBCs-vascular adhesion events
Reversal of adhesion mediated vaso-occlusive events
Blockade of adhesive mechanisms
Molecules modulating INFLAMMATORY pathways involved in adhesion events
Anti-PLTs- anti-coagulant therapies
Oxidative stress

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 (SelG1) **(Mandarino D et al Blood 122: abstract #970, 2013; Ataga KI et al abstract # 1, 2016 ASH)**
  - Sevuparin **(Telen MJ BJH doi 10.111/ BJH 14303, 2016)**
  - P-selectin aptamer **(Gustaeva DR et al. Blood 117: 727-35, 2011)**

Pan-Selectin Antagonist (Rivipansel)

- **GMI-1070-Rivipansel is a glycomimetic pan-selectin antagonist**

- **In phase 1/2, GMI-1070 showed:**
  - **a safe profile and tolerability**
  - **reduced E-Selectin levels during acute VOCs**
  - **Study limitation: failure of primary endpoint, enrolment of SC patients**

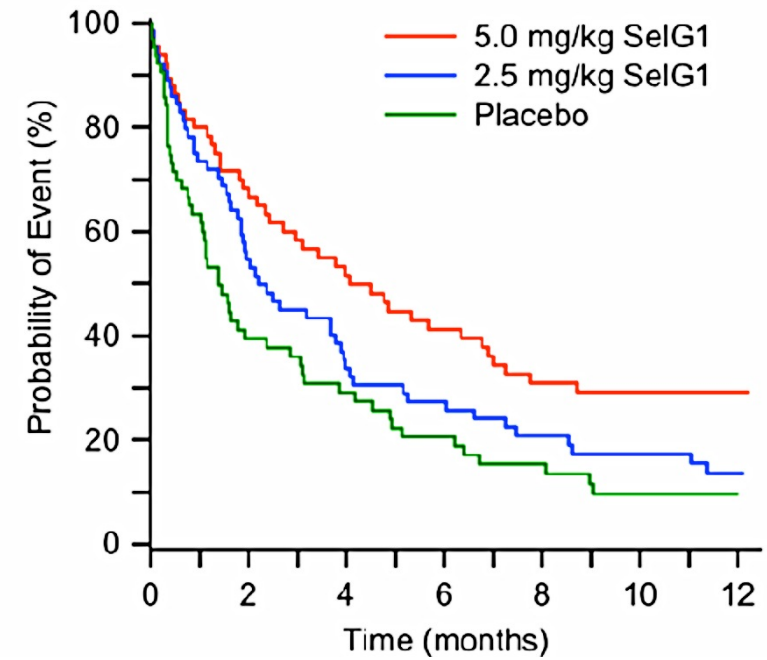
- **On going phase III (NCT 02187003) for acute VOCs.**

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

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

Sevuparin: blocking multiple adhesion targets in SCD

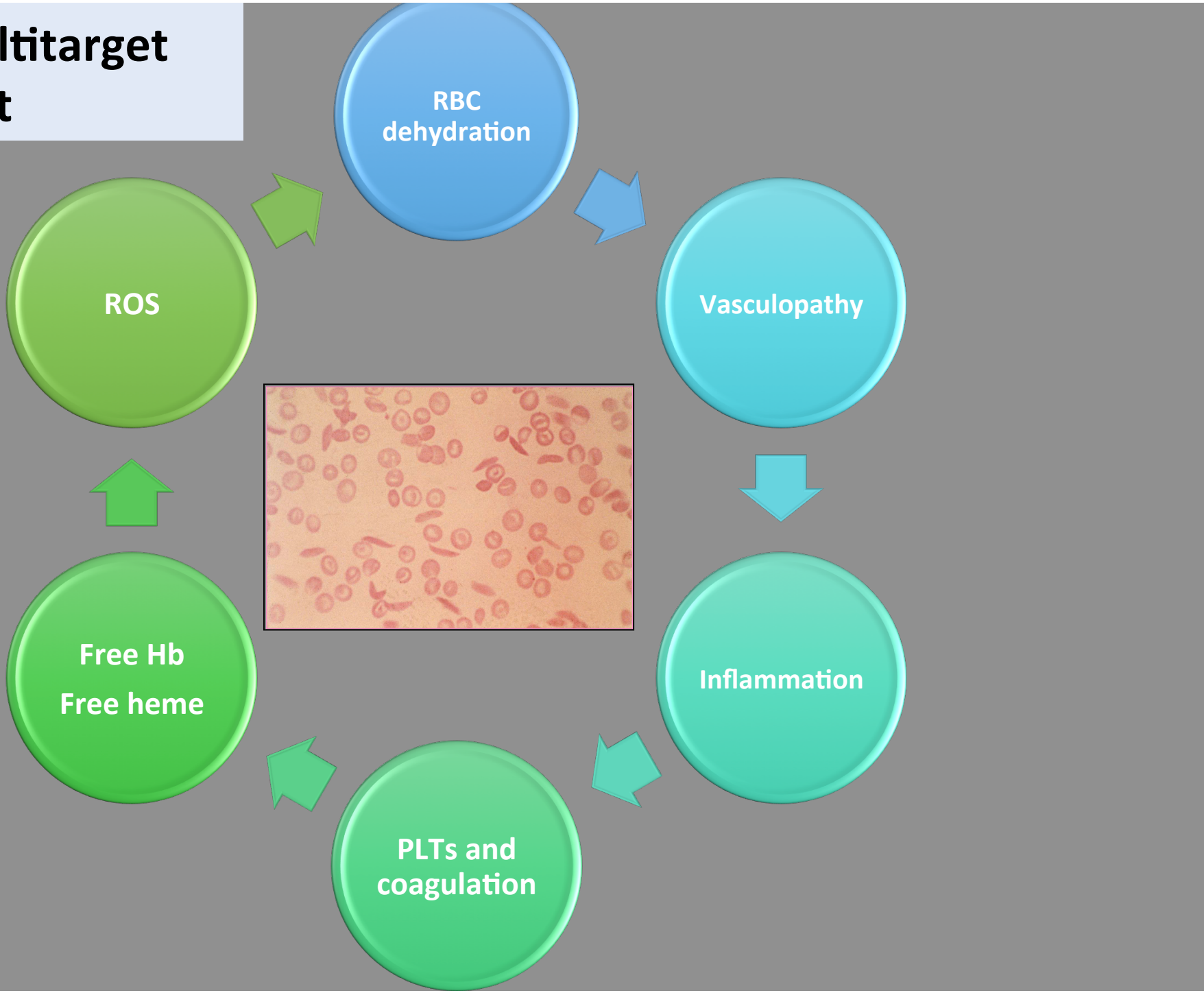
- **Sevuparin is a derivative of low-molecular weight heparin, lacking anticoagulant activity**

- **Sevuparin blocks:**
  - **P and L-selectins**
  - **Thrombospondin- Fibronectin-Von Willebrand factor**

- **On going phase II multicenter international trial on sevuparin in acute VOCs**

Telen MJ Blood 127: 810-19, 2016; Telen MJ BJH doi 10.111/ BJH 14303, 2016

CD Requires Multitarget Treatment



Perspectives: Combination Therapies for SCD

- **HU in combination with:**
  - **Chronic P-selectin blockade** (Ataga KI et al. abstract #1, 2016; Telen MJ et al doi 10.111/BJH14303, 2016)
  - **Nutritional/dietary supplementation (i.e.: ω-3 fatty acid, Mg^{2+} supplementation)** (Kalis B et al Haematologica 100:870-80, 2015; Daak AA et al. AJCN 97: 37, 2013; Hankins JS et al. BJH 140: 80, 2008)
  - **Anti-inflammatory agents (Regadenoson)** (Field JJ Blood 121: 3329, 2013; Field JJ Blood 122 abstract # 977, 2013)
- **Combination treatment without HU:**
  - **Anti-sickling agent(s) combined with P-selectin blockade** (Swift R et al abstract #121, 2016; Lehrer J et al. abstract #2488, 2016; Ataga KI et al. abstract #1, 2016; Telen MJ et al doi 10.111/BJH14303, 2016)
  - **Anti-sickling agent(s) and anti-inflammatory agents such as Regadenoson** (Swift R et al abstract #121, 2016; Lehrer J et al. abstract #2488, Field JJ Blood 121: 3329, 2013; Field JJ Blood 122 abstract # 977, 2013)

CONCLUSIONS

- **New therapeutic strategies for SCD involve pathophysiology-based targets;**
- **Novel treatments are directed to modify natural history of the disease such as acute VOC and related chronic organ complications in SCD**
- **A new field of combinatorial therapy for SCD will require a holistic approach, considering the improvement of patient QoL as an important outcome in designing new clinical studies.**

Studio SITE per la Mappatura dei Pazienti con SCD e in Trattamento Medico Intensivo con HU

Rigano P et al. Blood Mol and Disease Epub 2017