44° CONVEGNO NAZIONALE
di Studi di Medicina Trasfusionale
Rimini | Palacongressi, 3-5 maggio 2022
SIMTI

Trasfusione, erithroexchange….
Cos'altro?

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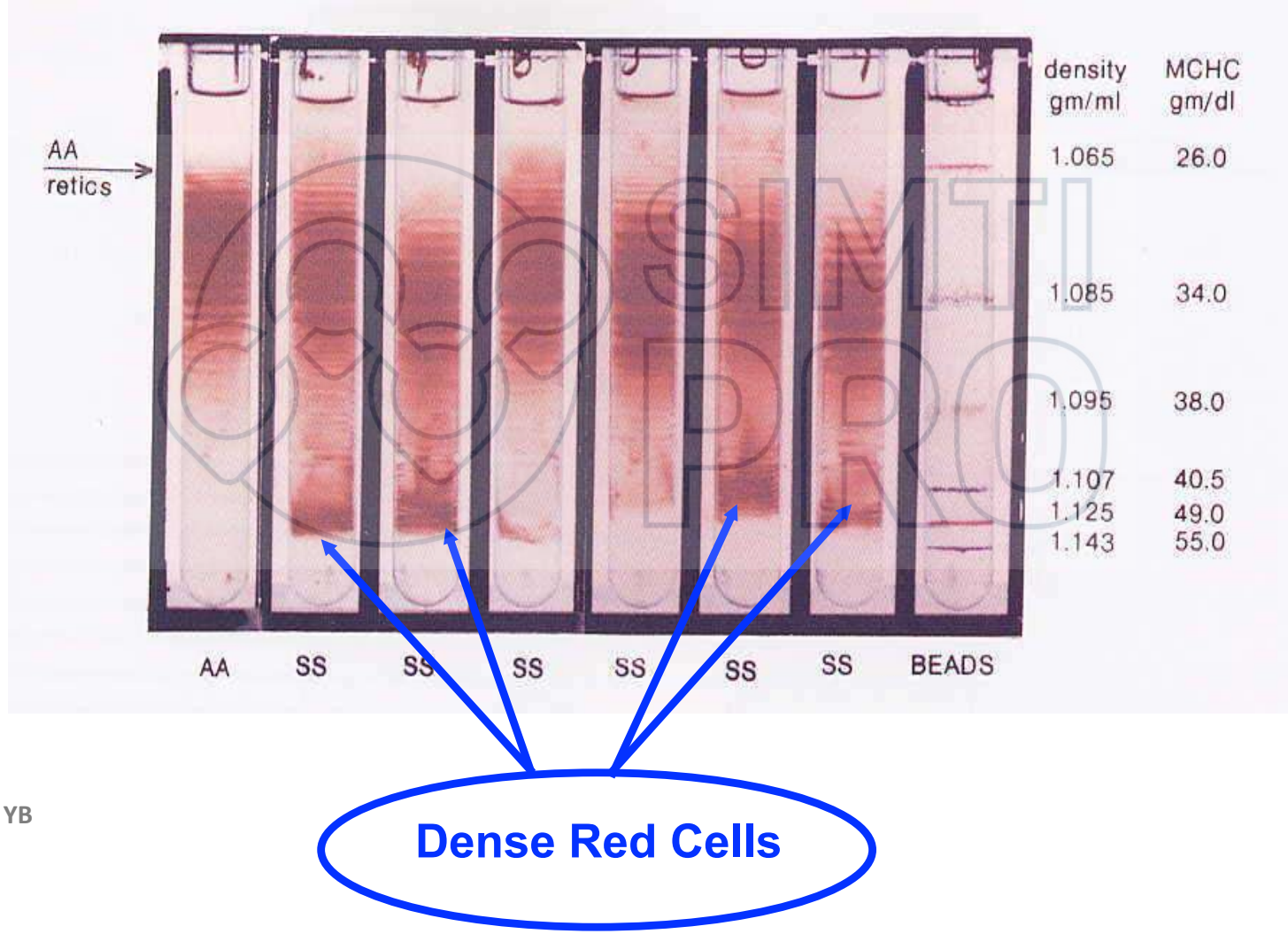
La sottoscritta, in qualità di Relatore
dichiara che

negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario:

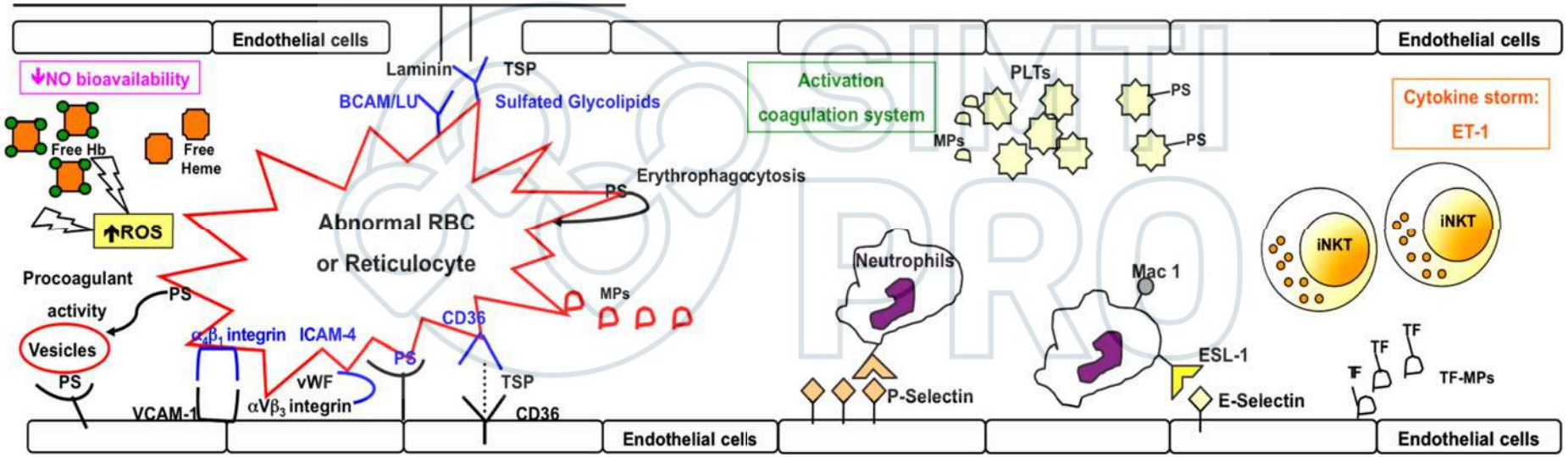
- Novartis: advisory board
- Agios: research grants

Heterogeneity of Cell Hb Concentration in Sickle cell Disease plays a central role in both acute and chronic sickle cell related manifestations



Modified from YB

Behind Sickle Red Cells: Vascular Vulnerability and Amplified Inflammatory Response



Modified from De Franceschi L et al. Seminars in Thrombosis, 37: 266; 2011; De Franceschi L Haematologica 100 (S3): 195-7, 2015; Matte A et al Mediterr J Hematol Infect Disease 11: e2019002, 2019

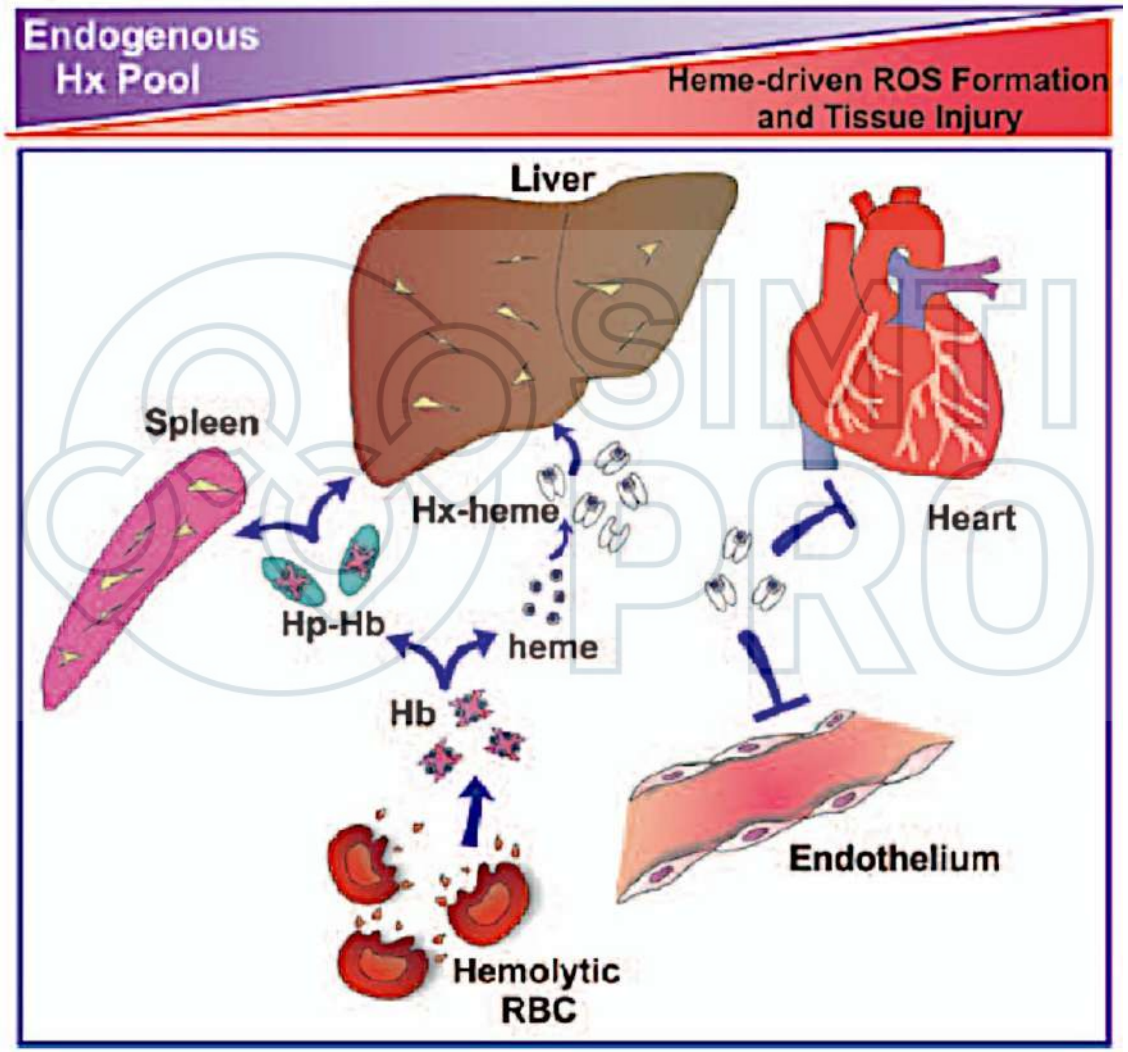
In acute severe VOCs: plasma is a crucial compartment to considered

In SCD patients during acute VOCs contains:

- **Pro-inflammatory and pro-oxidant molecules->** cytokines, free Hb, free heme
- **Components that increase blood viscosity->** ↑↑globulins (IgG), FBG, coagulation factors, relative reduction of ADAST13a activity (↑ large vWF)

Ballas S et al Transfusion 57: 2277, 2017; Matte A et al Exp Opinion Invest Drug 29: 23, 2020; Matte A et al Mediterr J Hematol Infect Dis 11: e22019002, 2019; Schnog JJ et al. Am J Hematol 81: 492, 2006

SCD and the Heme Connection: depletion of Haptoglobin and hemopexin



Vinchi F et al. Circulation 127: 1317-29, 2013; ; Vercellotti GM et al Frontiers in Pharmacology 5: 1; 2014 ; Hebbel RP Am J Hematol 86: 123, 2011

Haptoglobin (Hp) and Hemopexin (Hx) in Fresh Frozen Plasma

- Cases series of SCD patients with severe VOCs and MOFs resistant to RCE and treated with combined TPE with FFP;

- In SCD TPE treated subjects: Hp increases 10-fold time, Hx increases 7-fold time with decreased free heme-> resulting in improvement of clinical picture.

Louie JE et al. Transfusion 58: 470, 2018

Clinical evidence of RCE combined with TPE in SCD patients with severe acute VOCs

- **Siddiqui RS et al.** (cases collection)
  - 2 pts with severe VOCs and MOFs refractory to RCE
  - ↓mortality when RCE was combined with 2-3 TPE

- **Zaidi GZ et al.:** (Retrospective case review, 4 years)
  - 7 pts with SCD severe VOCs and MOFs refractory to RCE
  - ↓mortality (6/7 survivors) when RCE was combined with 2-3 TPE-> ICU 5.6 days, hospital length 14 days.

Siddiqui RS et al J Clin Apheresis 36: 777, 2021; Zaidi GZ et al. J Intensive Care Med 35: 140, 2020

RCE combined with TPE (2-3): setting of severe sickle cell related clinical complications

- ACS resistant to RCE
- Severe VOCs with chest pain
- Priapism
- Sickle cell related acute hepatic crisis
- Fat embolism syndrome with neurologic presentation

Ballas S et al Transfusion 57: 2277, 2017; Tsitsikas DA et al Transfus Apher Sci 25: 103375, 2022; Tsitsikas DA et al. Transfus Apher Sci 60: 103226, 2021

Q: WHY DO WE NEED NEW TREATMENTS FOR SCD?

A: Lack Of Therapeutic Opt
For Acute Events And
Prevention of SCD Re
Vasculopathy

Plasma purified Hemopexin

- **Plasma purified hemopexin** was developed in Japan in 1985

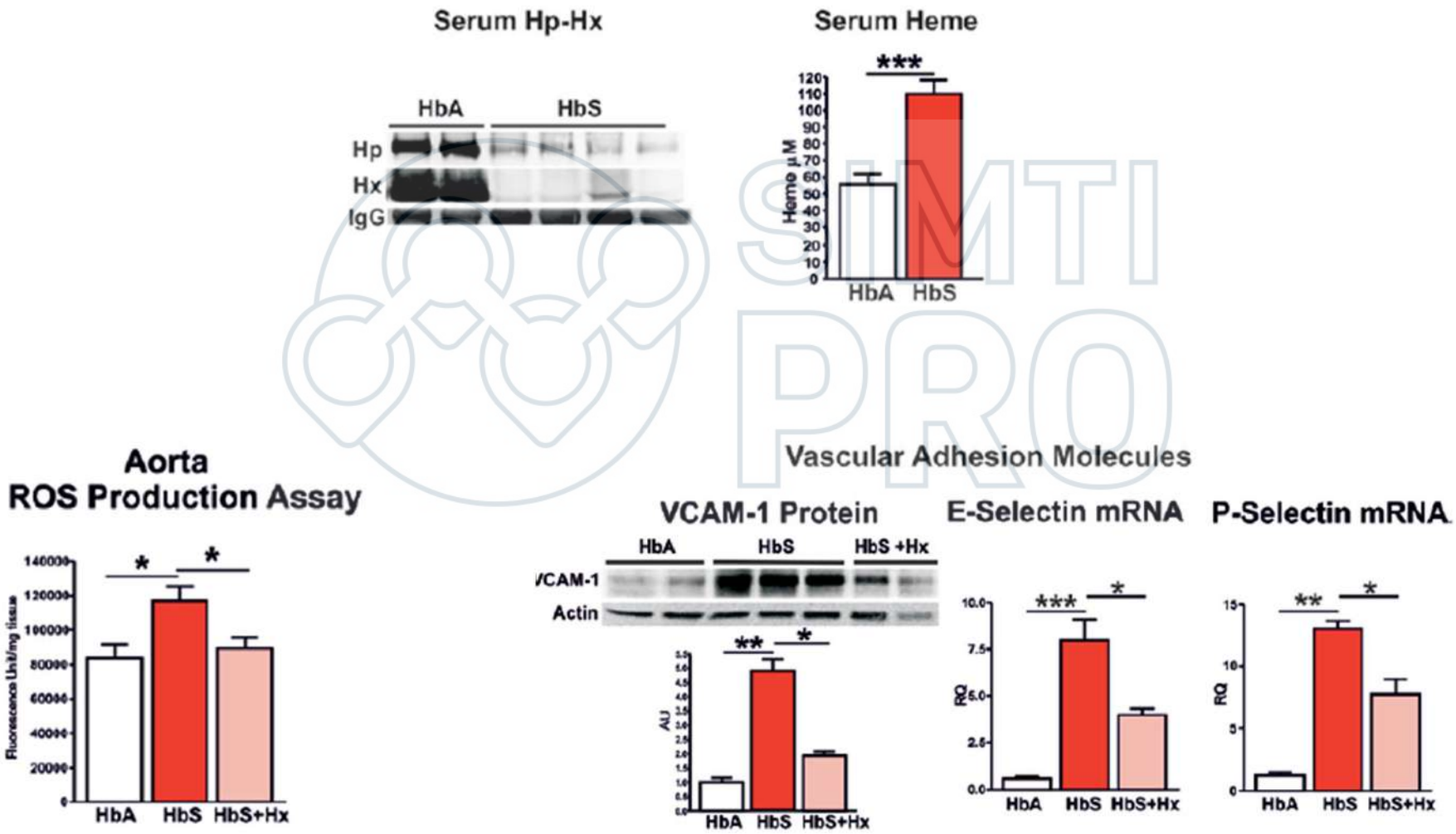
- **Primary indication**:
  - Extracorporeal circulation
  - Massive transfusion
  - Thermal injury

Kidney protection

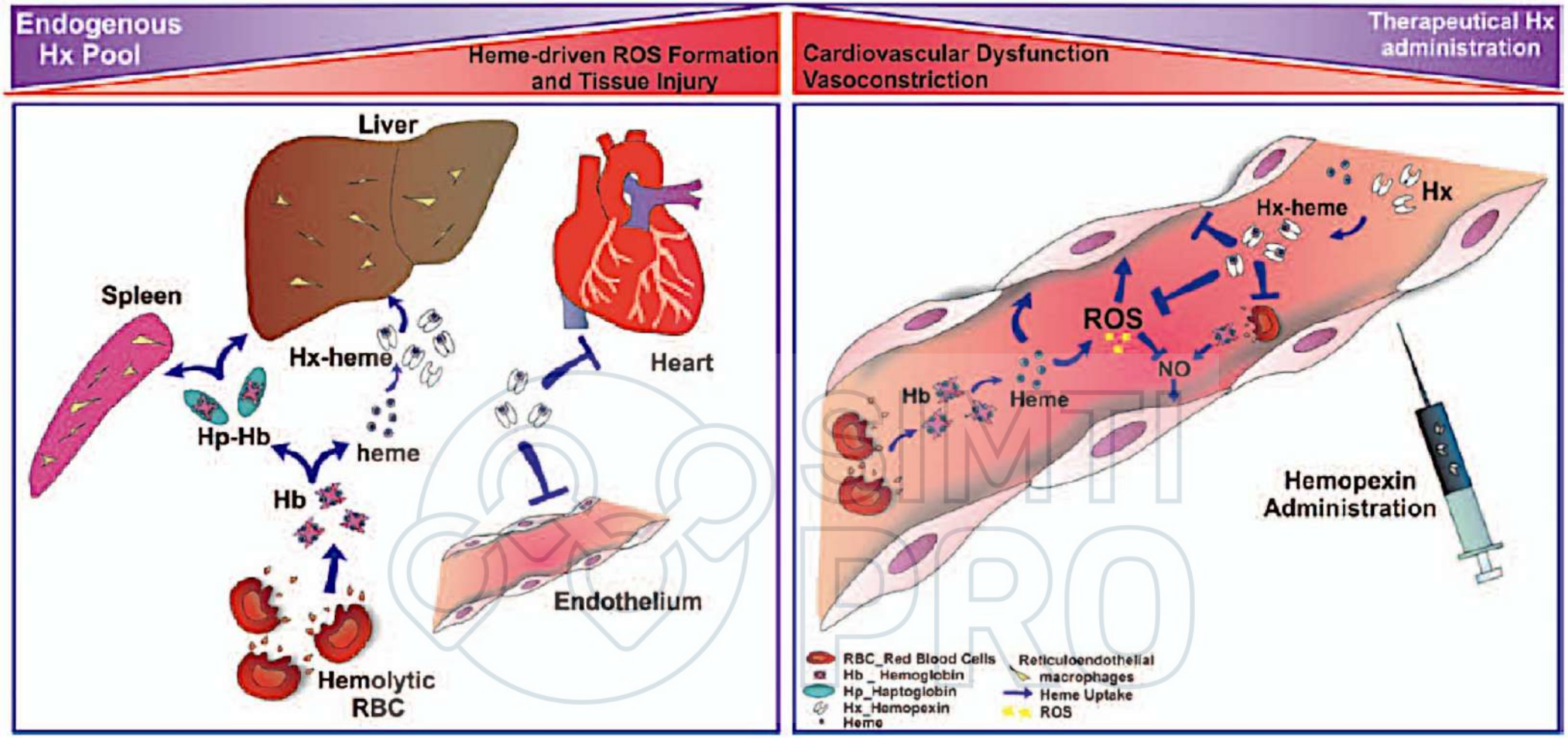
- Protective effects of **recombinant hemopexin** against acute sickle cell related damage in humanized mouse model.

Schaer DJ et al. Front Phsyiol Oct 2014; Gattinette T et al J Clin Med 11: n630, 2022; Menon AV 139: 936, 2022

Treatment with rHemopexin protects against sickle cell related VOCs



Vinchi F et al. Circulation 127: 1317-29, 2013

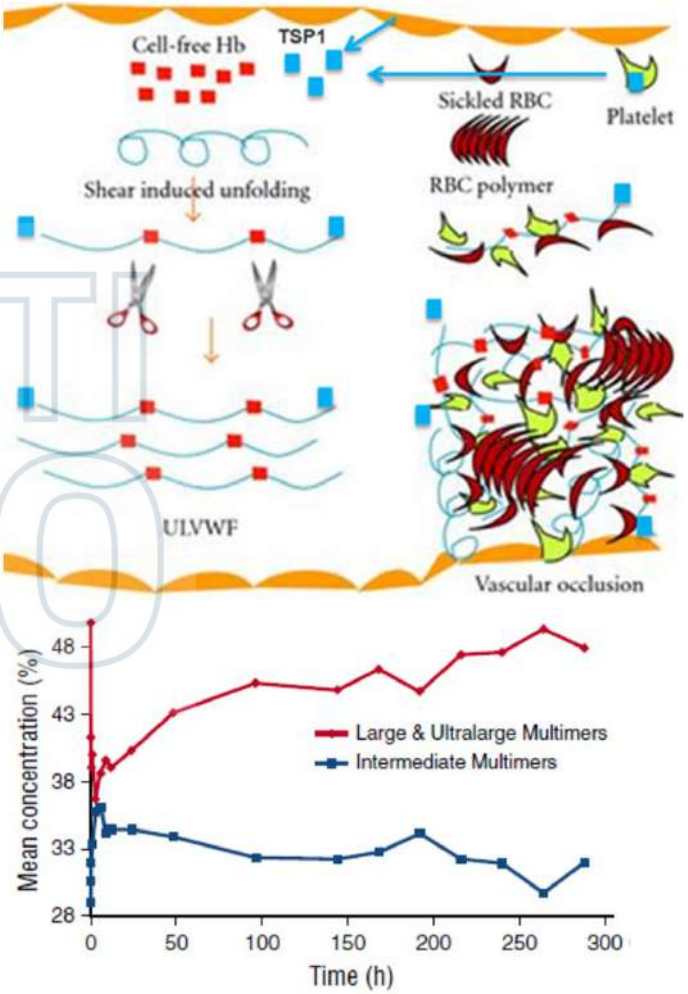


NCT04285827: recombinant hemopexin-> phase 1 multicenter open label single dose study in pts with SCD (safety and PK) (CLS Behring)

Vinchi F et al. Circulation 127: 1317-29, 2013

Sickle Cell Disease and von Willebrand Factor

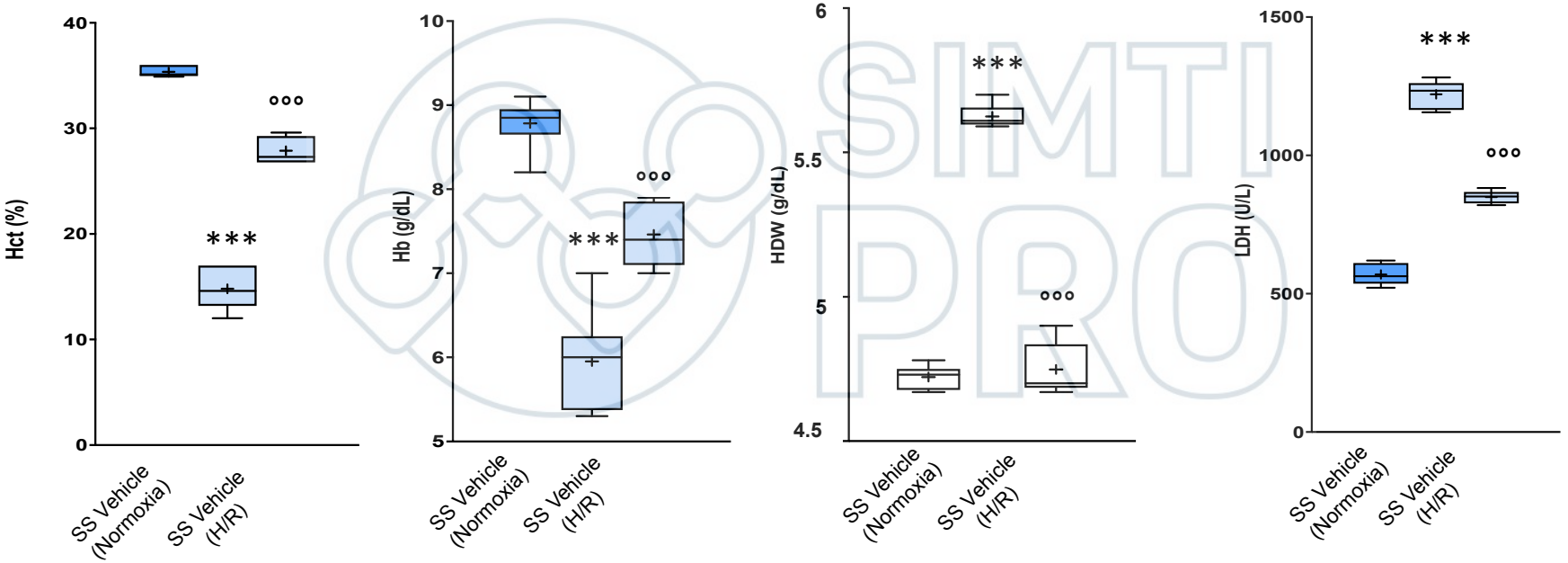
- Increased level of vWF and ultra-large vWF multimers was observed in SCD patients.
- ADAMTS13 activity is inhibited by high plasma concentration of free Hb.
- The reduction of ADAMTS13-to-vWF antigen ratio suggests a possible role of hyper-adhesive ultra-large vWF in SCD vasculopathy.
- In congenital TTP, administration of r ADAMTS13 reduced the concentrations of VWF ultra-large multimers.



Modified from Zhou Z, et al, Anemia 2011; 1-5

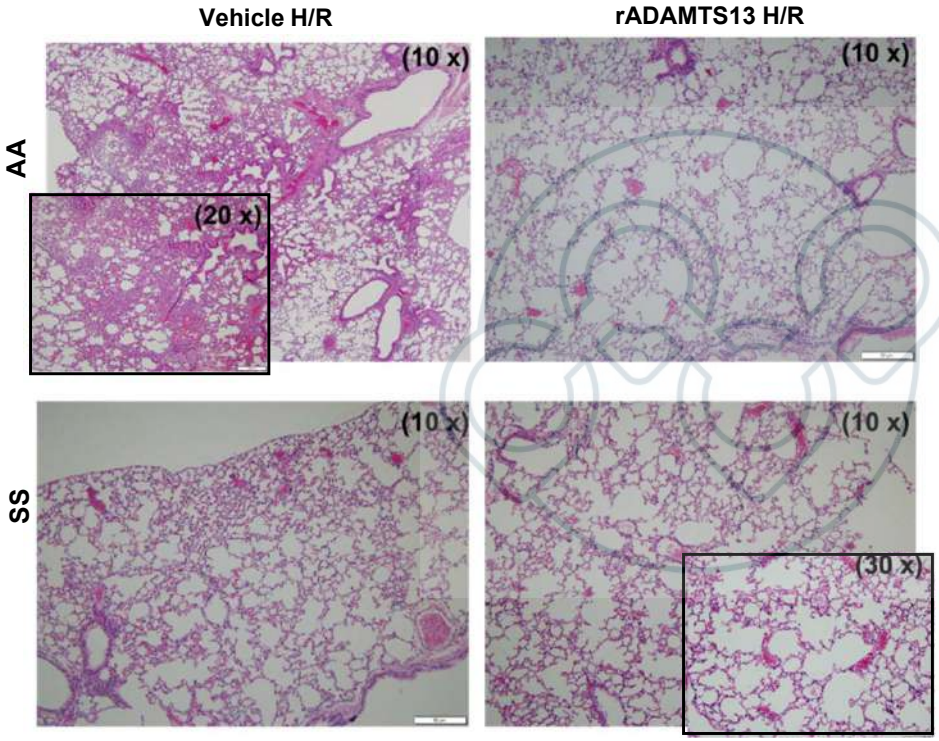
Schnog JJB et al. Am J Hematol 2006; 81: 492-498; Zhou Z, et al. Anemia 2011; 1-5; Scully M et al. Blood 2017; 130: 2055-2063

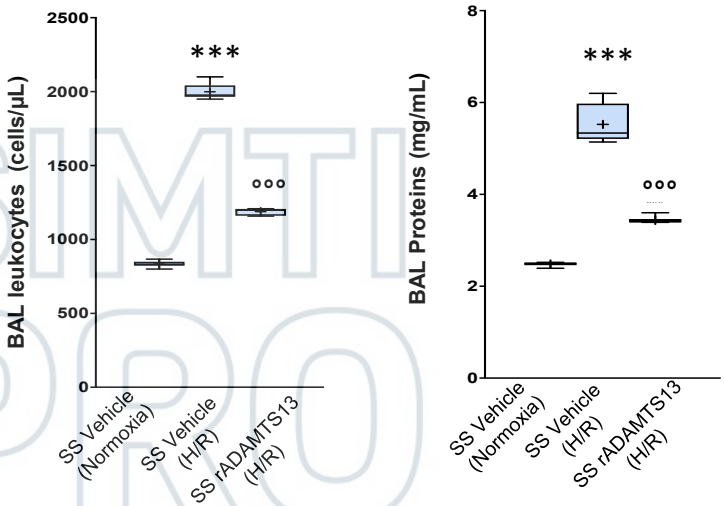
rADAMST13A protects humanized SCD mice against H/R stress Hemolysis

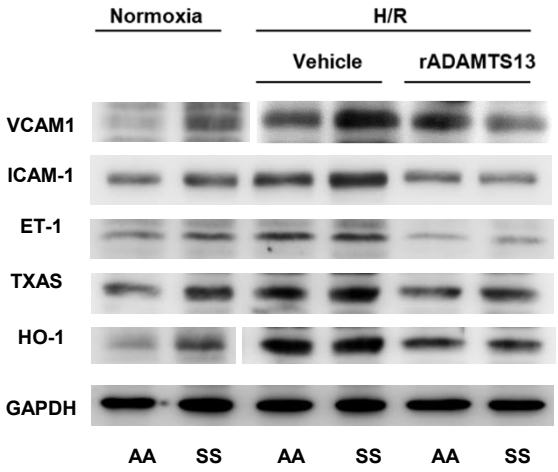


Rossato P et al. Haematologica in press 2022

rADAMST13 reduces the H/R induced acute lung damage and modulates lung inflammatory vasculopathy

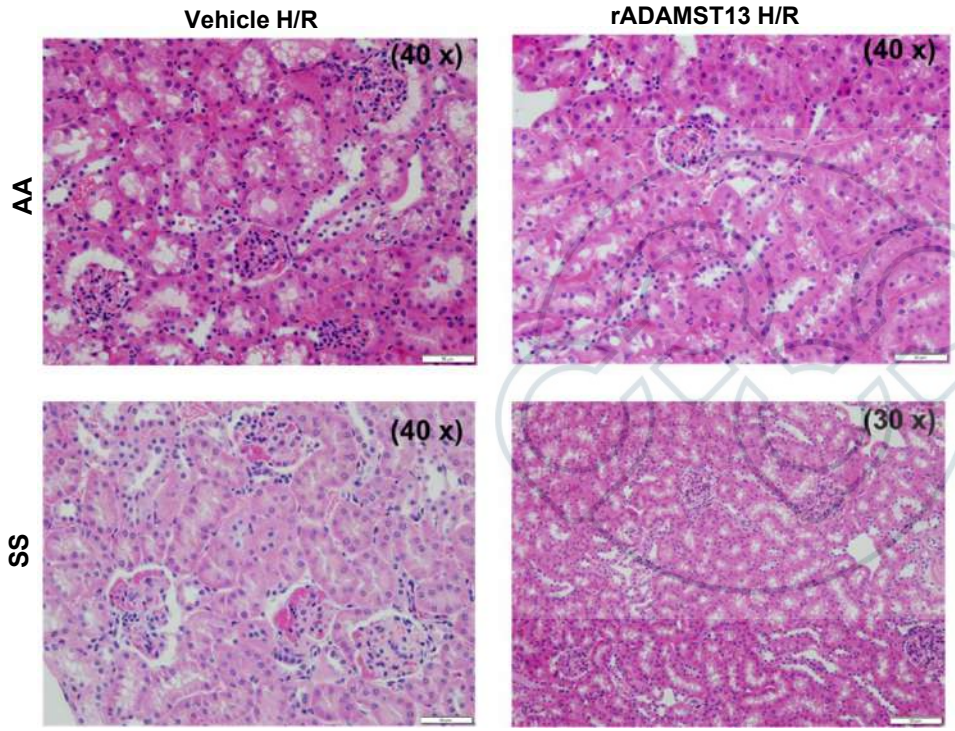


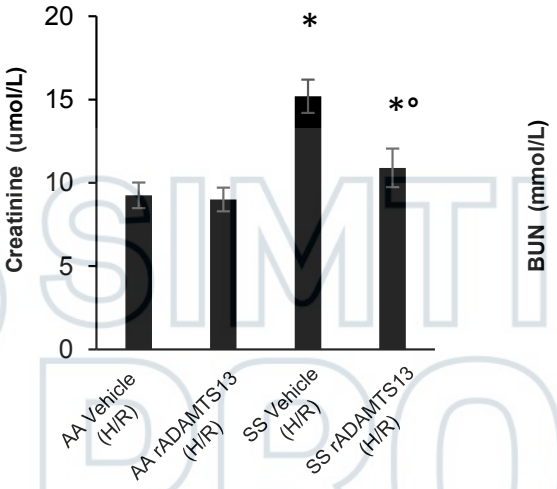


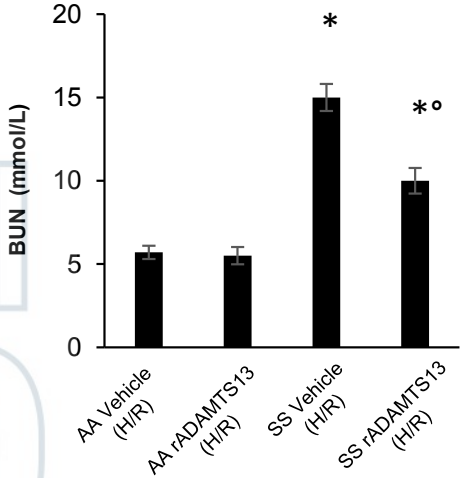


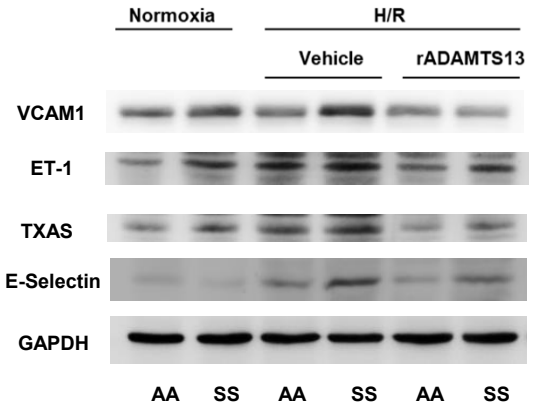
Rossato P et al. Haematologica in press 2022

In SCD mice, rADAMTS13 prevents H/R induced kidney injury and modulates local inflammatory response

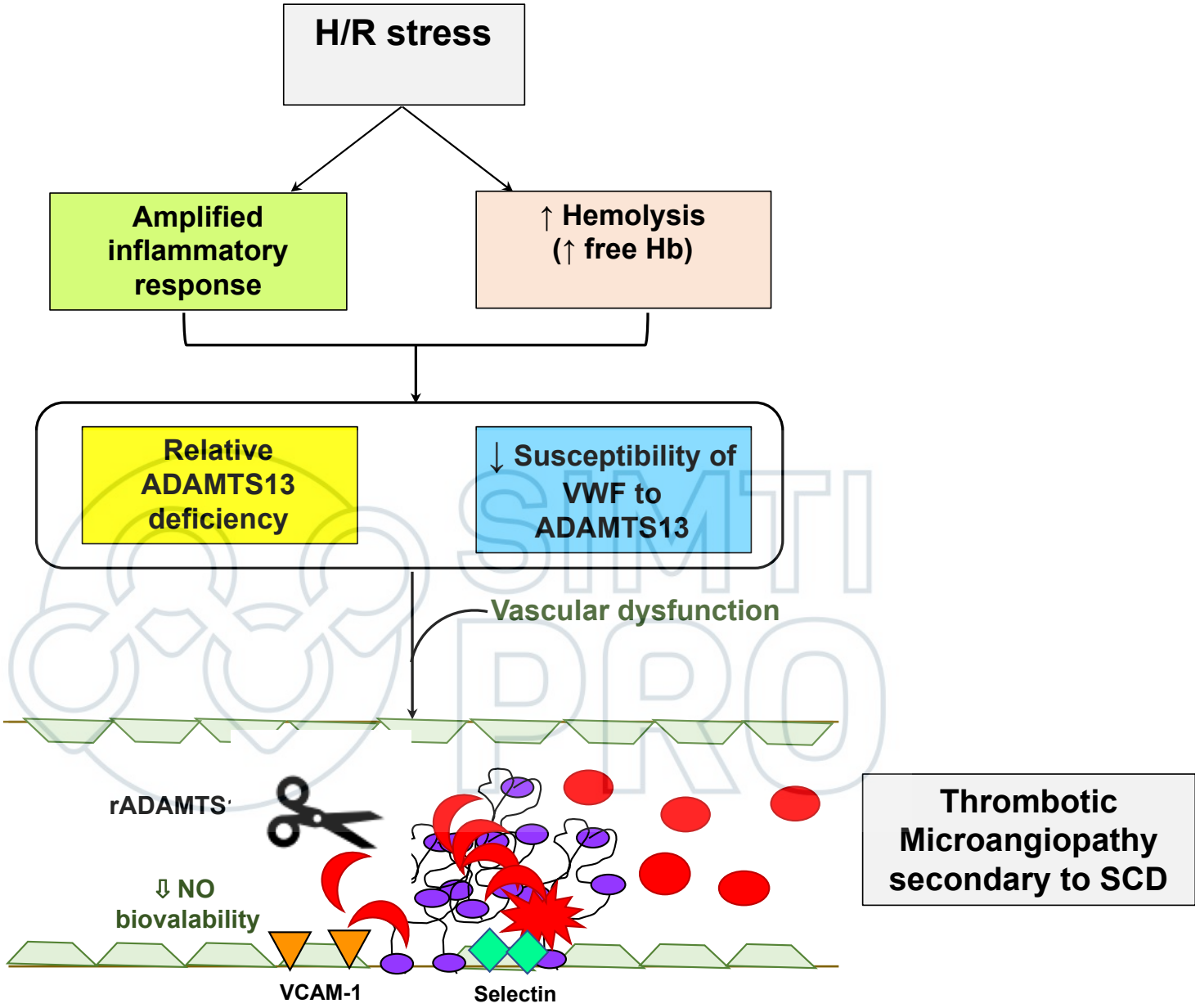








Rossato P et al. Haematologica in press 2022



NCT 03997760, phase 1 randomized double-blind placebo controlled multicenter ascending single dose study rADAMST13 in pts with SCD

Rossato P et al. Haematologica in press 2022; Patwari P et al Blood 3118, 2021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