Sickle Cell Disease (SCD)
Multimodal treatment approach

Medicine, research and the multimodal therapy

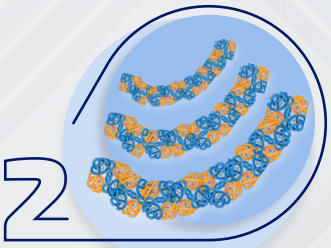
SCD affects millions of individuals worldwide and is a clinical challenge with a profoundly negative impact on patients' health-related quality of life (HRQOL).[1,2]
It is characterized by hemolytic anemia, vaso-occlusive complications, and progressive end-organ damage.[1]

Although pain is the hallmark of SCD, it also affects multiple body organs. Hence, managing SCD requires paying attention to its complex pathophysiology and its nuanced effects on general medical comorbidities, which are becoming increasingly common as individuals survive into adulthood.[1,3]

Understanding the pathophysiology of SCD

Polymerization of HbS following deoxygenation is key to the pathology of SCD.[1,4-6]

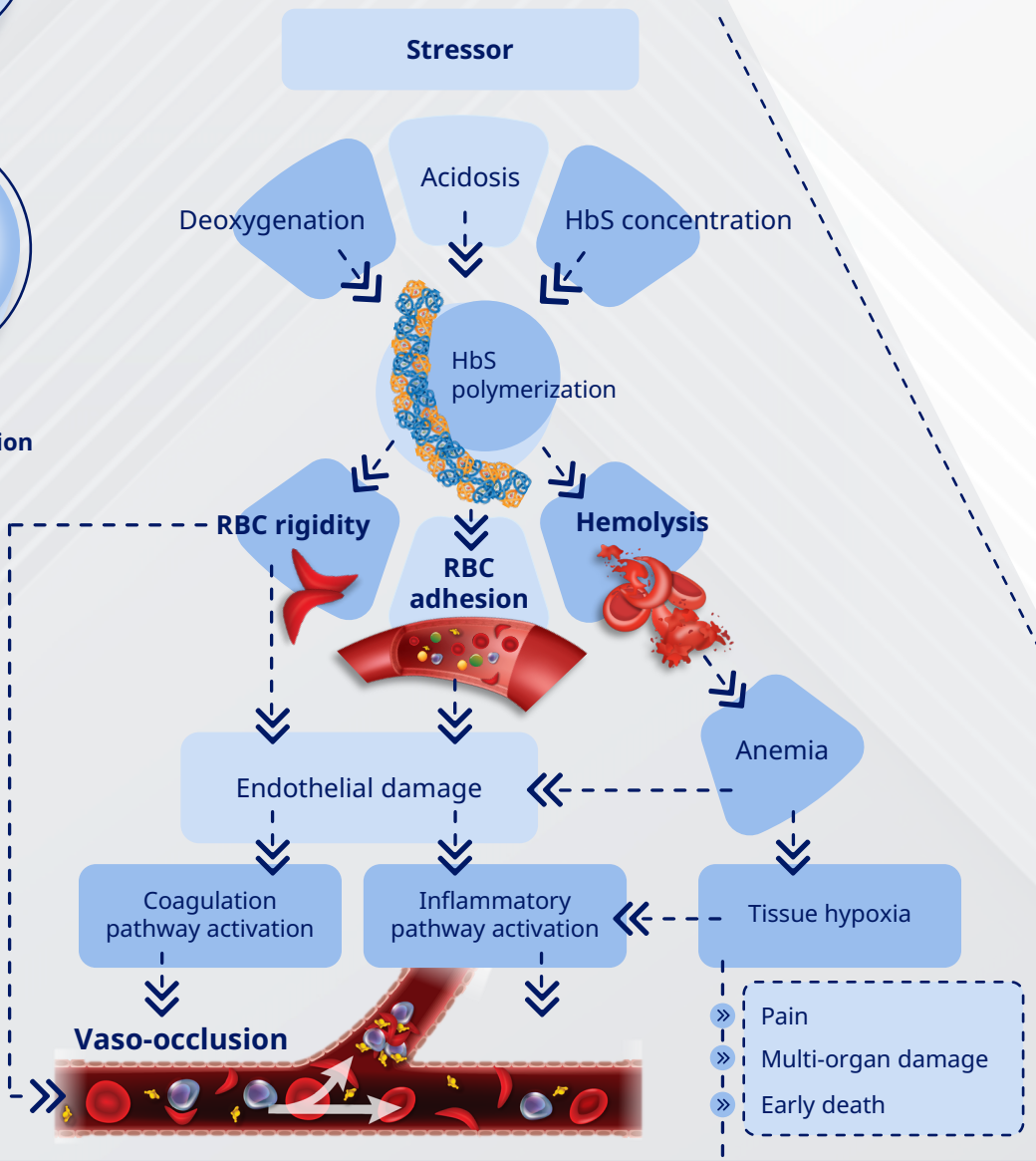
1 **Abnormal HbS**



2 **Polymerization** in deoxygenated state

3 **Sickled RBC** in deoxygenated state are **rigid, prone to adhesion** and **hemolysis**

The formation of HbS polymers trigger a cascade of several other cellular abnormalities, which are part of the overall pathophysiological mechanism that leads to vaso-occlusion.[1,4-7]



Click on '**RBC rigidity**', '**RBC adhesion**', '**Hemolysis**' in the diagram to identify the therapeutic targets.

HbS, sickle hemoglobin; HRQOL, health related quality of life; NO, nitric oxide; RBC, red blood cells; ROS, reactive oxygen species; SCD, sickle cell disease.

References: 1. Rai P, Ataga KI. Hematology Am Soc Hematol Educ Program. 2023;2023(1):519-531; 2. Brandow AM et al. Blood Adv (2020) 4 (12): 2656-2701; 3. National Academies of Sciences, Engineering, and Medicine. 2020. Addressing Sickle Cell Disease: A Strategic Plan and Blueprint for Action. Washington, DC: The National Academies Press. Front Matter | Addressing Sickle Cell Disease: A Strategic Plan and Blueprint for Action | The National Academies Press ; 4. Kato GJ et al. Nat Rev Dis Primers 2018;4:18010; 5. Egesa WI et al. Int J Pediatr. 2022;2022:3885979. doi:10.1155/2022/3885979; 6. Molokie R et al. PLoS Med 2017;14:e1002382. doi: 10.1371/journal.pmed.1002382; 7. Telen MJ. Blood Adv. 2020;4(14):3457-3465; 8. Okpala I, et al. International Scholarly Research Notices, 2013, 236374. https://doi.org/10.1155/2013/236374)

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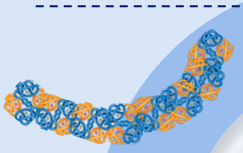
Developing the next generation of multimodal therapies to support a portfolio approach for individualized treatment

Despite recent advances in treatment, majority of potentially disease-modifying drugs have focused on acute pain episodes or VOCs as their primary end point. However, for optimal individualized patient care, combinations of therapeutic agents targeting different SCD complications and surrogate endpoints may be required. [1,2]

A multimodal approach to SCD combines various treatment agents, each targeting different disease mechanisms, and acknowledges the need for tailored therapeutic interventions due to individual patient needs, thereby rejecting a universal or one-size-fits-all approach for effectively managing SCD.[3,4]

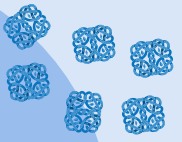
Disease modifying

Novel HbS polymerization inhibitors and indirect HbF inducing agents have been found to boost Hb levels and are under investigation for SCD.[2]

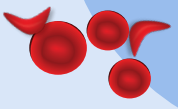


Direct HbF induction

Among the various developments, the drugs that directly target the enzymes to induce gene expression and further increase HbF levels (HbF inducers) form a potential therapeutic approach to combat SCD.[5,6,9]



Multimodal treatment approach



PKR activation

Novel agents that improve RBC health and life span by targeting O_2 affinity, deformability, hydration, oxidative damage, adhesion, and membrane repair are being developed for a multi-pronged attack to target the pathophysiology of SCD.[7,8]

Symptoms relieving

Several novel anti-sickling, anti-adhesion, antioxidant, anti-inflammatory, anticoagulant and antiplatelet agents, and NO-related agents are being investigated to abate the pathophysiology of SCD.[2,6]

Future SCD treatment modalities may combine HbF inducers with other drug classes and multi-agent therapies for enhanced benefits as compared with monotherapy.[6,7]

Thus, developing multi-modal treatments focused on key aspects of SCD will lead to **precision medicines**, **new products**, and **patient-centric research**, improving personalized therapy for each patient's needs.[2,6,7,10]

Hb, hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin; PKR, pyruvate kinase; RBC, red blood cells; SCD, sickle cell disease; VOCs, vaso-occlusive crises.

References: 1. Rai P, Ataga KI. Hematology Am Soc Hematol Educ Program. 2023;2023(1):519-531; 2. National Academies of Sciences, Engineering, and Medicine. 2020. Addressing Sickle Cell Disease: A Strategic Plan and Blueprint for Action. Washington, DC: The National Academies Press. Front Matter | Addressing Sickle Cell Disease: A Strategic Plan and Blueprint for Action | The National Academies Press; 3. Okpala I, et al. International Scholarly Research Notices, 2013, 236374. https://doi.org/10.1155/2013/236374); 4. Brandow AM et al. Blood Adv (2020) 4 (12): 2656-2701; 5. Molokie R et al. PLoS Med 2017;14:e1002382. doi: 10.1371/journal.pmed.1002382; 6. Ala C, et al. Arch Pharm (Weinheim). 2024. doi:10.1002/ardp.202400381; 7. Telen MJ, et al. Nat Rev Drug Discov. 2019;18(2):139-158; 8. Saraf SL, et al. Blood Adv. 2024;8(16):4459-4475; 9. Säll C, Fogt Hjorth C. Xenobiotica. 2022;52(1):1-15; 10. Smith WR et al. Front. Pain Res. 2023;4:1279361.