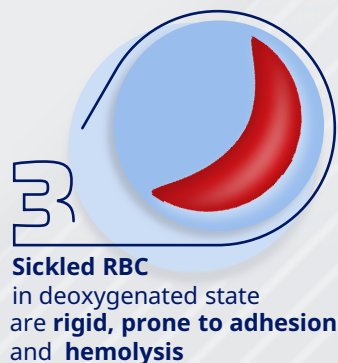
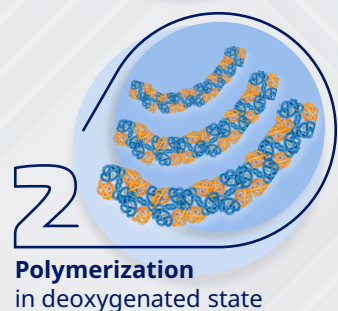
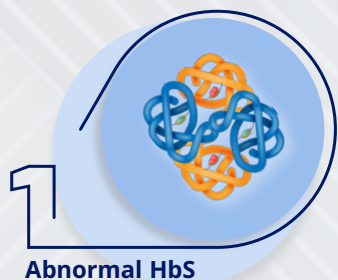


Sickle Cell Disease (SCD)

Multimodal treatment approach

Understanding the pathophysiology of SCD

Polymerization of HbS following deoxygenation is key to the pathology of SCD.^{1,4-6}



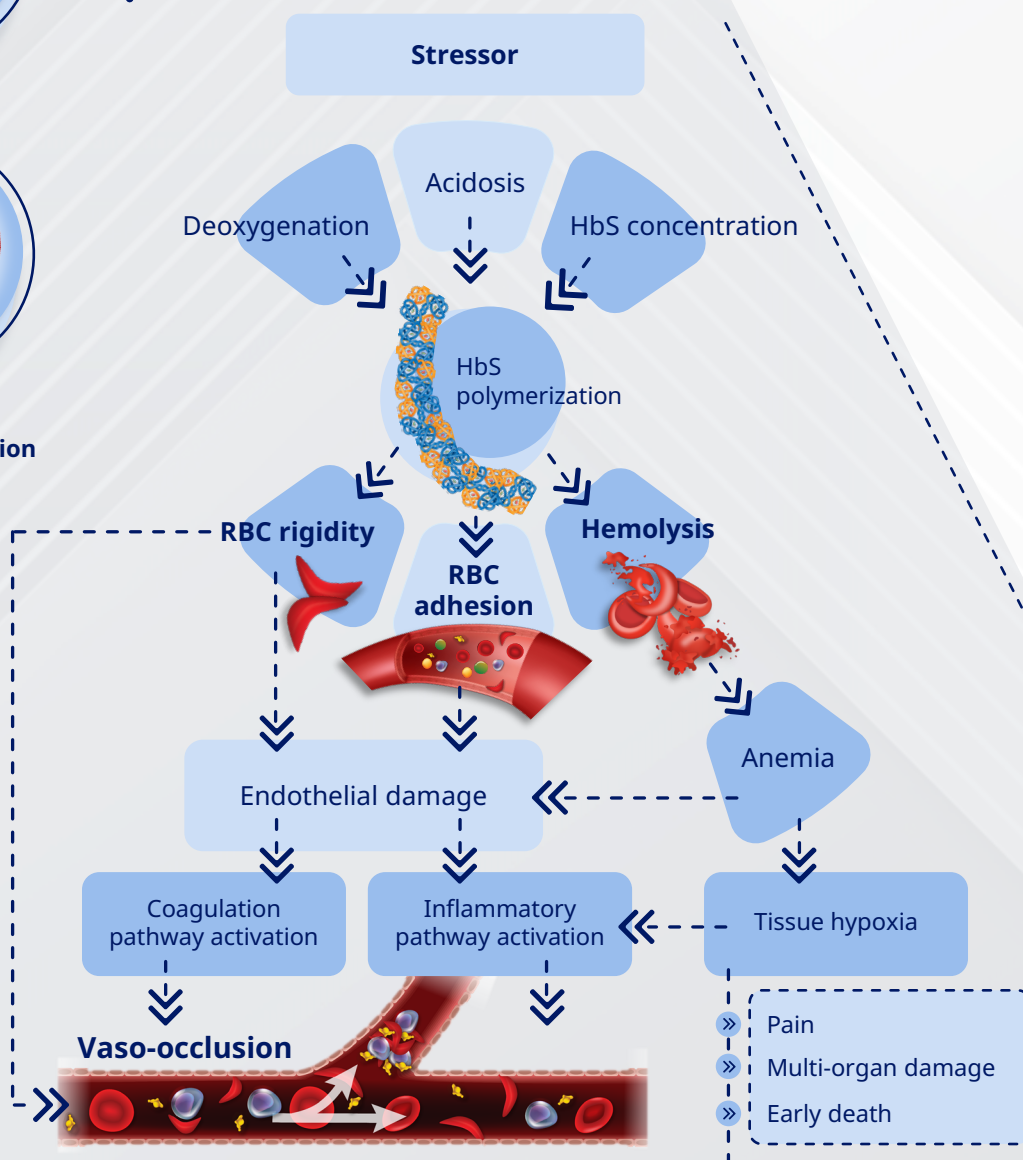
Click on 'RBC rigidity', 'RBC adhesion', 'Hemolysis' in the diagram to identify the therapeutic targets.

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}

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}



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>

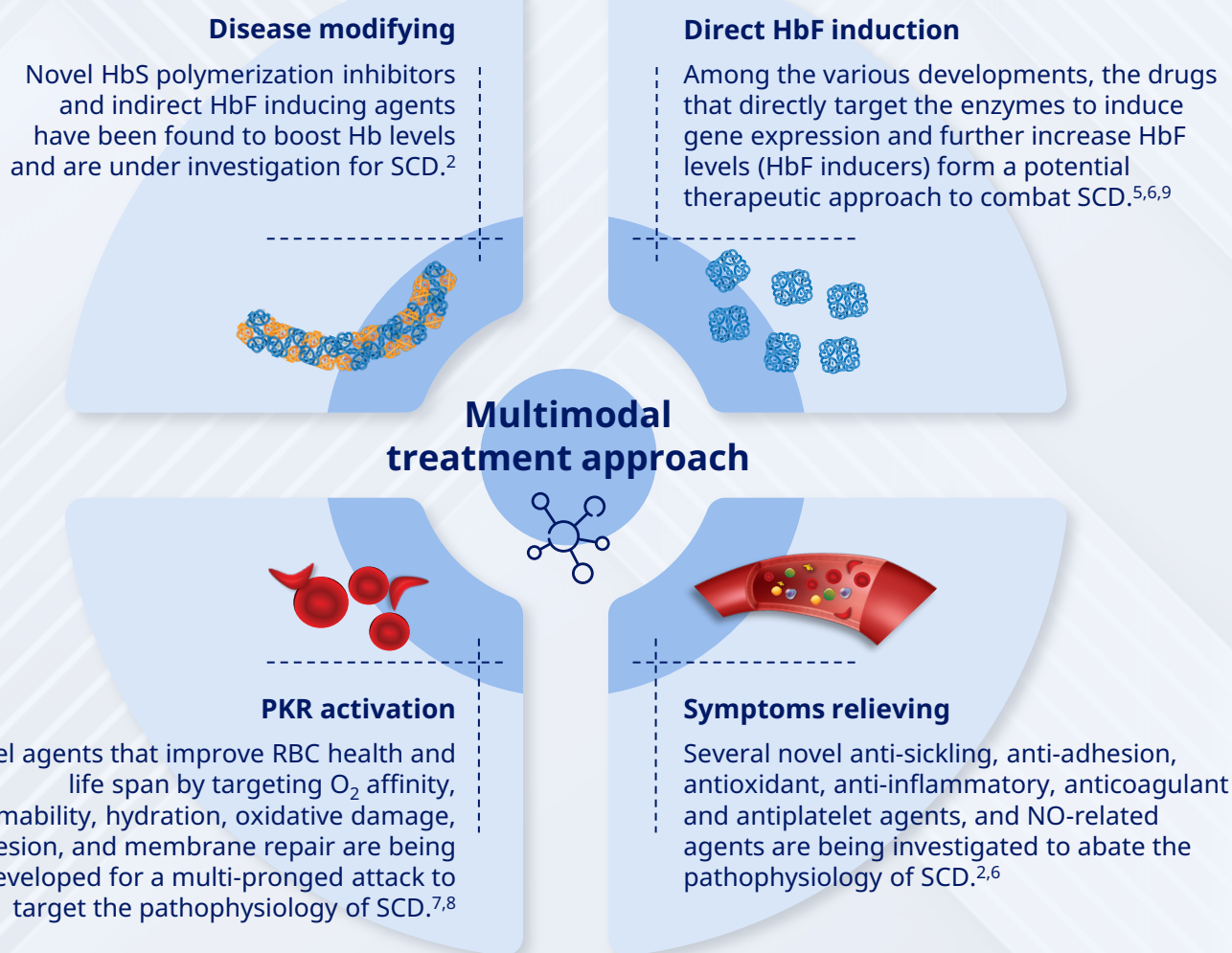
Sickle Cell Disease (SCD)

Multimodal treatment approach

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}



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.