DKMS Stiftung Leben Spenden

Project Summary

John Hansen Research Grant 2026

Stem cell pool size and clonal dynamics as biomarkers for personalizing stem cell therapies in haemoglobinopathies

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Blood diseases such as sickle cell disease and β-thalassemia can now be cured by replacing or repairing a patient's blood-forming stem cells, through allogeneic stem cell transplantation or through gene therapy. Yet outcomes vary: some patients achieve rapid and stable blood recovery, while others experience delayed recovery, graft failure, or—more rarely—an abnormal dominance of a single stem cell clone.

A key factor behind these differences may be stem cell clonality before therapy, and clonal dynamics after therapy. Here, clonality means how many distinct stem cell clones actively contribute to blood production and whether this contribution is balanced or dominated by only a few clones. It goes beyond the concept of clonal hematopoiesis (CHIP), because expanded blood clones without canonical driver mutations are frequent under conditions of hematopoietic stress, potentially including stress encountered in haemoglobinopathies. Today, clonality is difficult to measure in clinical routine and understudied.

In this project, we will use single-cell lineage tracing with epi-mutations (EPI-Clone) to distinguish individual stem cell clones and quantify clonality before and after curative therapies in patients with sickle cell disease and β-thalassemia. We hypothesize that low clonal diversity at baseline may predict who benefits most from allogeneic transplantation versus gene therapy, and that early shifts toward clonal dominance could serve as a safety signal supporting closer monitoring. We will also study patients with failed allogeneic transplants to assess whether their remaining stem cell pool is suitable for subsequent gene therapy. Thereby, we aim to support clinical decision making and improve safety monitoring.