DKMS Stiftung Leben Spenden

Project Summary

John Hansen Research Grant 2024

Preclinical Development of Lentiviral Vector Gene Therapy for Diamond-Blackfan Anemia

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Diamond-Blackfan anemia (DBA) is a rare inherited bone marrow failure disorder that is caused by mutations in ribosomal protein genes. *RPS19* is one of the commonly mutated genes in DBA. Typically, DBA presents as isolated red blood cell production failure in infants. However, older patients with DBA can develop low white cell and platelet counts suggesting that DBA affects hematopoietic stem and progenitor cells (HSPCs). Currently, DBA is treated with corticosteroids or chronic blood transfusions. Hematopoietic cell transplantation (HCT) is the only curative therapy but this is associated with graft-versus-host disease, prolonged immune suppression and suboptimal outcomes in older patients. Limited availability of DBA patient HSPCs has prevented development of newer therapies for DBA. Gene therapy, which involves autologous HCT of patient HSPCs after gene complementation using a lentiviral vector encoding *RPS19* (RPS19 LV) is a potential curative approach. Using CRISPR/Cas9, I had previously developed an experimental model of DBA in human HSPCs. Leveraging this platform, I have now developed a third-generation, self-inactivating RPS19 LV that is effective in rescuing the hematopoietic defects caused by haploinsufficiency of *RPS19.* In this project, I will perform preclinical evaluation to assess safety and efficacy of RPS19 LV which will allow development of a future first-in-human DBA gene therapy clinical study.