The generation of iPSC to model human disease

Introduction: Neutrophils form the first line of defense against invading pathogens, such as bacteria and fungi, as part of the innate immune response. They can kill these invading pathogens using killing mechanisms involving phagocytosis, the production of reactive oxygen species, and the different types of proteins in the granules. A defect in one of these mechanisms, can lead to severe infections. Furthermore, neutrophils have a segmented nucleus and can release their DNA to form neutrophil extracellular traps (NETs) to capture invading pathogens. Lamins are intermediate filaments that compose nuclear lamina, where Lamin B1 is involved in the nucleur morphology and NET formation of neutrophils.
To study neutrophils in more depth, induced pluripotent stem cells (iPSCs) can be used as a source of immune cells to model human diseases. iPSC are an unlimited supplies of hematopoietic stem and progenitor cells, which have the potential to give rise to multiple different cell types. iPSCs were firstly generated from human fibroblasts by the introduction of four transcription factors (Oct3/4, Sox2, Klf4 and c-Myc) by the group of Shinya Yamanka in 2007. Nowadays, iPSCs can be generated from only 5 ml of blood, creating an immortal source of (patient) cells.

Aim: This project will focus on two subjects: i) the generation of iPSC lines from patients with different neutrophil granule defects and differentiating these iPSC towards neutrophils to assess the functionality. The aim of this subject is to find out whether iPSCs are a suitable source to study human diseases. ii) the generation of a Lamin B1 knock-out iPSC line using the CRISPR-Cas system to broaden our understanding of the role of Lamin B1 in the nuclear morphology and NET formation.

Techniques: This project involves cell culture, molecular cloning, CRISPR genome editing, flow cytometry, live cell imaging and neutrophil function assays.

Duration: 7-9 months. Students from the University who are looking for a dynamic and interesting internship and are interested in the above project are encouraged to contact the PhD student of this project, Cathelijn Aarts, by e-mail: c.aarts@sanquin.nl