

Project Description (master internship)

TP53 mutations is one of the most recurrent genetic alteration in human cancers. TP53 mutations in acute myeloid leukemia (AML) represent 5-8% of newly diagnosed patients and in 30-40% of those with therapy-related AML. Genetic alterations in TP53 also represents one of the most powerful independent risk factors in AML underscoring the critical tumour suppressive role of p53 in AML. Whereas loss of p53 instantly drives the formation of acute lymphoid leukemia (ALL), development of AML requires additional epigenetic alterations like constitutively activation of the RAS-ERK pathway. Intriguingly, the erythroid progenitor compartment, has been identified to display the cell of origin of AML formation upon p53 inactivation. Loss of p53 activity also has been shown to mark an aggressive subtype of erythroid-defined AML and likewise is also detected in erythroid-defined dysplasia's like myelodysplasia syndrome (MDS). To identify novel genetic aberrations which cooperate with TP53 mutations in erythroid precursor cells that perturb red blood cell formation we recently generated a erythroid precursors cell line harbouring somatic inactivation of TP53 and expression of the RNA-guided Cas9 DNA endonuclease enzyme.

Research Questions

- What genetic alterations prevent erythroid precursors to mature into RBC and accordingly underlie erythroid differentiation?
- Do these mutations also define erythroid-defined dysplasia's and/or leukaemia subtypes?

Approach

During this internship you will employ a genome-wide screening approach, based on Cas9-driven genome editing, to identify novel genetic aberrations which perturb RBC formation. Hence providing novel insights in the underlying mechanisms of RBC formation. The obtained results will be accordingly compared with available MDS and AML patient information in collaboration with our diagnostic department at Sanquin and with the hematopoietic research departments at the Amsterdam UMC.

Your profile

A highly-motivated master student in medical science looking for a master internship in the field of haematology. During this internship you will employ biomolecular skills such as a lentiviral-based state-of-the art genome-wide screening approach to identify novel genes underlying RBC formation.

Additional Information

Head research group: Dr. M.Nethe

Department: Immunohematology Experimental and Haematopoiesis (IHEP) at Sanquin.

Start date: March 2019

Duration: 9 months