

The role of extrinsic factors in proliferation of preleukemic cells

Background

As the global population ages, the incidence of acute myeloid leukemia (AML) is expected to rise, highlighting the urgent need for innovative approaches to prevent, detect, and delay disease progression. Additionally, it underscores the importance of a better understanding of the molecular pathways that play a role in disease development and therapy resistance. AML develops through the stepwise acquisition of genetic alterations, many of which can be detected years before diagnosis. This pre-leukemic stage, known as clonal hematopoiesis (CH), is highly prevalent in older individuals and is associated with an increased risk of leukemia. However, while CH is common, only a minority of clones progress to AML. Our research aims to identify the factors that determine clonal progression and malignant transformation. By studying the biological mechanisms that drive clonal expansion, leukemia development, and therapy resistance, we seek to uncover novel opportunities for early detection, prevention, and treatment of AML.

Clonal hematopoiesis is characterized by the expansion of blood cell clones carrying somatic mutations and is highly prevalent in aging individuals. Recent longitudinal analyses from the Lifelines cohort, a large population-based biobank in the Northern Netherlands, demonstrated that CH clones exhibit highly dynamic behavior, including stable growth, rapid expansion, and even spontaneous regression. Remarkably, the substantial interindividual variation in clonal growth could not be explained by conventional factors such as age, sex, smoking status, alcohol consumption, or body weight. These observations suggest that factors beyond the genetic mutation itself contribute to clonal fitness and expansion.

Project goal

In this project, we aim to investigate whether hematopoietic growth factors and cytokines influence the competitive advantage of CH clones. We hypothesize that mutant CH cells respond differently, and potentially more sensitively, to growth-promoting signals than their wild-type counterparts, thereby facilitating clonal expansion. To test this hypothesis, an *in vitro* proliferation model will be established in which hematopoietic cells are exposed to key regulators of blood cell production. Using this system, the effects of individual growth factors on cellular proliferation and clonal expansion will be quantified and compared between mutant and wild-type cells.

During the internship the student will establish and optimize an *in vitro* proliferation model using hematopoietic cells overexpressing either wild-type or CH-associated mutant proteins. Prior to functional analyses, the student will validate the overexpression models by assessing transgene expression at both the RNA and protein level. Following validation of the cellular models, the student will perform cell culture and proliferation assays in the presence of key hematopoietic growth factors. At the end of the culture period, cellular responses to growth factor stimulation will be evaluated using an extensive flow cytometry panel, allowing assessment of proliferation, viability, and differentiation-related phenotypes.

Through these experiments, the student will determine whether mutant cells display an enhanced response to specific growth factors compared with their wild-type counterparts, potentially providing a mechanistic explanation for the heterogeneity in clonal growth observed between individuals.

Research methods

- Cell culture (mainly hematopoietic cell lines)
- Lentiviral work
- Western blot
- qPCR
- Proliferation assays
- Flow cytometry
- Cloning (depending on the progress, in a positive sense)

Place of work

Your internship will take place at the Laboratory of Hematology (Laboratory Medicine) of Radboudumc, within the Experimental Hematology research group of Prof. Joop Jansen and Dr. Maaïke van Bergen, under supervision of Zubi Aimee Govers (PhD candidate). In our research group, we investigate the molecular mechanisms driving hematological malignancies, with a focus on clonal hematopoiesis and acute myeloid leukemia, aiming to improve our understanding of leukemic transformation and identify novel therapeutic targets.

First possible start date is 25/01/2026, with a preferred minimal duration of 6 months (but anything can be discussed 😊).

Interested?

Please contact Zubi Aimee Govers: zubi.govers@radboudumc.nl