Acute Myeloid Leukemias (AML) are clonal hematopoietic malignancies that in the majority of patients remain incurable. This is a type of cancer characterized by differentiation block and uncontrolled proliferation of immature white blood cells in the bone marrow. The therapy of AML has not changed over the past four decades and aside from bone marrow transplantation the disease remains unacceptably fatal in the majority of cases. Despite some advances in AML therapy overall only 50% of patients survive and older patients cannot tolerate toxic chemotherapy. Ironically, incidence of AML increases with age, therefore, the proportion of patients eligible for bone marrow transplantation is small and development of novel therapeutic targets is crucial. As a true malignancy, AML cells invade other tissues, which can complicate therapy.Effective and safe anti-AML therapies remains a major unmet need.

Retinoids such as all-*trans* retinoic acid (ATRA) are natural derivatives of vitamin A that have been shown to possess potent anti-cancer effects in the treatment of AML type called acute promyelocytic leukaemia (APL). It has been shown in 1980s that APL cells are highly sensitive to ATRA the physiologically active metabolite of vitamin A, which as a single agent effectively differentiates the leukemic clone leading to disease remission in over 80% of APL patients. Currently, using ATRA together with other therapeutic agents APL has become a curable disease. Success in APL treatment has brought new hope for the development of new differentiation therapies in other AML subtypes, using ATRA and/or other agents.

However, these compounds have not been clinically effective in non-APL AMLs. This lack of response of AML to ATRA is partly due to the fact that genes normally targeted by ATRA become switched off in a way that makes them non-responsive to this drug, including its mediators the retinoic acid receptors. Little has been known about mechanisms of resistance to
ATRA in non-APL AML. This knowledge gap limits the use of ATRA in a disease that desperately needs novel and successful therapies. Our long term goal is to develop new treatment strategies for acute myeloid leukaemia (AML).

Our focus is to understand the of switching off and variable response of genes that are targeted by ATRA. In particular, we want to focus on epigenetic changes (heritable changes in gene function that are not related to the DNA sequence), and to find drugs that unlock the potential of non-APL AML to respond to retinoids.

We propose that resistance of non-APL AMLs to ATRA therapy is to large extent driven by the balance of RARα and RARγ receptors and miRNA moleculeswhich regulate gene expression. In this proposal we want to focus especially on RARγ receptor and what happens when we switch off RARγ regulating machinery.