Universität Bern | Universität Zürich
vetsuisse-fakultät
Santoro Lab
Chromatin & Epigenetic Dynamics
https://www.santorolab.org

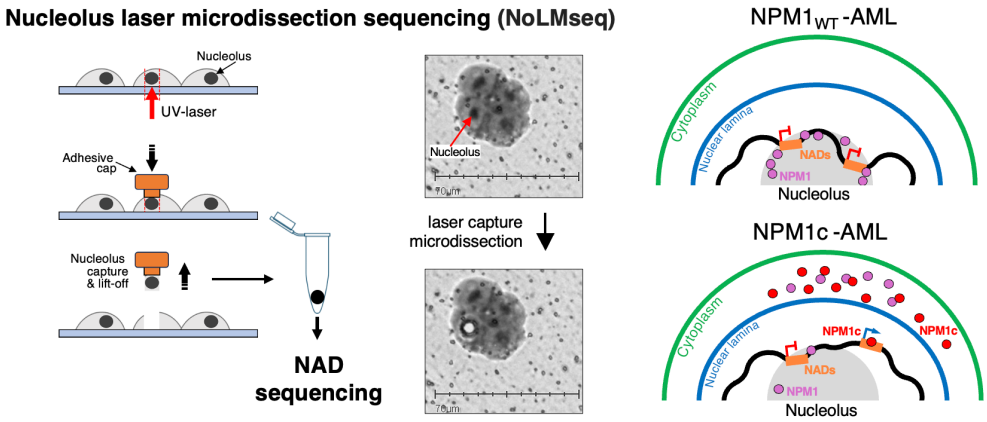
University of Zurich
Mathematisch-naturwissenschaftliche Fakultät
department of molecular mechanisms of disease

Genomic and functional analysis of nucleolar disruption and 3D genome dysregulation in NPM1c-driven leukemia

The 3D organization of the genome plays a fundamental role in regulating gene expression, with profound implications for both normal physiology and disease. A striking example of this is the nucleolus, a large nuclear compartment responsible for ribosome biogenesis and surrounded by repressive chromatin regions called nucleolar associated domains (NADs). Structural alterations of the nucleolus are frequently observed in cancer and may result in aberrant chromatin organization and gene expression.

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy affecting blood and bone marrow. Approximately 30% of AML cases harbour mutations in NPM1 (NPM1c), a nucleolar protein with essential roles in ribosome production, nucleolar structure, and positioning of repressive chromatin at nucleoli. NPM1c mutations disrupt the nucleolar localization signal of NPM1, leading to its mislocalization to the cytoplasm. Despite its prevalence, the molecular consequences of NPM1c remain incompletely understood, hindering therapeutic advances. Most research has focused on its gain-of-function effects, such as cytoplasmic sequestration. However, the corresponding loss-of-function effects, particularly on nucleolar structure and genome organization, remain poorly explored. Addressing this critical gap is essential for a comprehensive understanding of how NPM1c mutations drive leukemogenesis.

In this project, we aim to define how the disruption of NPM1 nucleolar functions contributes to malignant transformation, providing novel insights into the pathobiology of NPM1-mutant leukaemia. Key aspect of this proposal is the application of our newly established Nucleolar Laser Microdissection sequencing (NoLMseq) method that uniquely allows the identification of NADs in single cells and under conditions of nucleolar structural alterations, a result that could not be obtained with previous technologies. Specifically, we will apply NoLMseq to identify changes in nucleolus-NAD interactions in AML, focusing on the impact of NPM1c mutations that mislocalizes NPM1 to the cytoplasm. Using transcriptomic and epigenomic analyses, we will characterize these changes at NADs in terms of gene expression and chromatin features and provide mechanistic insights into how NPM1c dysregulates NADs. Using well-established cellular models, this project will provide crucial insights into the role of NPM1c in AML from a novel nucleolar perspective and may uncover new therapeutic vulnerabilities, with broader relevance for diseases involving nucleolar dysregulation.



Interested candidates should send their CV and a brief motivational letter to
Prof. Raffaella Santoro
Dep. Molecular Mechanisms of Disease (DMMD)
University of Zurich
raffaella.santoro@dmmd.uzh.ch
Additional information about our research can be found at https://www.santorolab.org