PROJECT 1

**DoS:** Andrea Brendolan, Unit of Lymphoid Organ Development and Function

**Title:** Role of the stromal microenvironment in B-cell malignancies

**Curriculum:** Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page:

**Project description** (*Number of characters, including spaces: 2,000 - 3,000):*
An increasing body of literature indicates that blood cancer maintenance, survival and progression depend on a complex interplay of cell-cell interactions and signalling molecules between neoplastic cells and their surrounding non-hematopoietic stromal microenvironment. However, the different stromal cell subsets involved and the mechanisms by which stromal cells (also known as cancer-associated fibroblasts) contribute to survival and expansion of neoplastic cells are still far to be elucidated. We have started to characterize the lymphoid stromal composition of $\mu$Tcl1 mice - a mouse model of B-cell chronic lymphocytic leukaemia (CLL) - at different stages of disease progression. Our recently published work uncovered the existence of a retinoic acid-dependent stroma-leukaemia crosstalk that promotes tissue remodelling and leukaemia dissemination (Farinello et al., *Nature Communications* 2018). We are now expanding previous findings with the goal of deepening our understanding of the cellular and molecular interactions shaping a tumour-promoting microenvironment and with the focus to identify the different stromal cell subsets involved in disease progression. We have already available bulk- and single-cell RNA-Seq raw data of leukemia and stromal cells isolated from $\mu$Tcl1 mice at different stages of leukemogenesis. We intend to use various computational approaches to deeply characterize the transcriptional and the epigenetic profile, and to uncover the pathways involved in disease initiation and progression. In addition, we will compare the results obtained with the murine model to human CLL datasets with the goal of identifying human B-cell CLL subsets with transcriptional and epigenetic similarities to murine CLL. Finally, we will concentrate on those pathways commonly deregulated in human and mouse CLL leukemias, and use the $\mu$Tcl1 mouse model for targeting deregulated pathways using pharmacologic approaches.

**Skills to be acquired by the student:**
The student will become knowledgeable with the tools of mouse genetics, with in vivo approaches to characterize the tumor microenvironment (e.g. immunofluorescence analysis), and with computational analyses of Next-Generation Sequencing data of murine and human leukemia samples. Finally, the student will learn to organize, discuss and present his/her data through lab meetings, journal clubs and division seminars.

**References** (*max. 3*)
Farinello et al., *Nature Communications* 2018
Heining et al., *Cancer Discovery* 2014.
Caligaris-Cappio et al., *Seminars in Cancer Biology* 2013.