ABSTRACT: Fernanda Herrera group UNIL/CHUV

High-grade serous ovarian carcinoma (HGSOC) is one of the deadliest cancers affecting women, characterized by a nearly absent immune cell infiltration, rendering immunotherapy weakly effective. **Radiation and immunotherapy combinatorial treatment (RACIM)** has shown improved responsiveness in murine and human ovarian cancers, due to increased T-cell infiltration elicited by low-dose radiation (Herrera et al., Cancer Discovery 2022), which enabled immunotherapy.

We performed bulk gene expression analysis of murine ovarian tumors treated with 1 Gy, which revealed an upregulation of **CDKN1A and BAX transcripts** and increased expression of **CCL8, CCL5, CXCL12, and TGFβ** cytokines and chemokines, representative characteristics of a **senescent profile**. To further understand the role of low-dose irradiation on senescence, we treated murine ovarian ID8 tumors with increasing doses of irradiation and investigated the senescent state of bulk tumor and individual cell populations of the tumor microenvironment.

Tumors treated with 1 Gy are characterized by an increase in the activity of senescence-associated beta-galactosidase (SA-β-Gal), as well as increased expression of CDKN1A transcript and protein, and a decrease in Laminin B protein expression, indicating a senescent profile. Additionally, we confirmed that 1 Gy treatment induces an increase of **CD8+ infiltrated T-cells**, which are positive for the senescent FDG marker at 1 and 1.5 Gy irradiation treatment. In contrast, infiltration of the CD11b+ myeloid compartment and Ly6G+ neutrophils is prominent and positive for the senescent FDG marker at 2 Gy irradiation treatment.

These data indicate a potential induction of senescence by low-dose irradiation in ovarian tumors, where cell-specific senescent characteristics are dose-dependent.

The work performed by the PhD student will focus on the following questions:

1. Are senescent T cells effector cytotoxic cells?
2. What is the metabolic status of these T cells?
3. Can we reinvigorate them further by combining senolytic drugs with low-dose irradiation?

The PhD candidate will be supported by post-doctoral fellows with strong experience in immunology. The mouse model as well as the techniques are well optimized in our lab. Collaboration for this project is done with the **Vannini lab (UNIL)**, which has strong experience in metabolomics.