



University of
Zurich^{UZH}



USZ Universitäts
Spital Zürich

Translational skin cancer research

The [Levesque laboratory](#) is a translational research group in the Department of Dermatology at the University Hospital of Zurich in the Faculty of Medicine. Thanks to our close collaborations with clinicians, we have built one of the largest live-cell, skin-cancer biobanks world-wide and are applying the latest discovery technologies, such as **spatial transcriptomics**, **CRISPR-a/i screens**, **single-cell transcriptomics**, and **high-throughput small molecule screens** to clinically relevant questions in dermato-oncology. We have a dynamic team of Master's, PhD, and clinical PhD students as well as technicians, post-docs, senior scientists, and clinical researchers developing the next generation of biomarkers, drug targets, and mechanistic models of melanoma and cutaneous lymphoma. Partnerships with spin-offs, biotech, and pharma companies provide exposure to different research questions and paradigms with high clinical relevance.

Master's Project 1: Exploring the impact of Cuproptosis on solid cancers and the immune synapse

Background: We have recently [published](#) a new mechanism of cell death called cuproptosis that targets mesenchymal melanoma cells and other cancers that are in similar metabolic states. Preliminary results in our lab show that these small molecules can also influence the surface expression of MHC molecules and immune check-point proteins, thereby altering the tumor's susceptibility to immunotherapy and CAR T-cell treatments. Understanding the molecular and immunological dynamics driven by copper-ionophores in solid tumors can pave the way for innovative combination treatments to activate immunological cell death.

Research Objectives:

Investigate the effects of copper-ionophores on the signaling pathways of solid tumor cells in **2D and 3D cell cultures** related to changes in immune-related surface markers by **flow-cytometry** and **western blotting**. Elucidate key pathways involved in copper-ionophore sensitivity and resistance using **proteomics**, **transcriptomics**, and **CRISPR-i/a screening**.

Master's Project 2: Characterizing the crosstalk between melanoma cells and tertiary lymphoid structures

Background: The tumor microenvironment (TME) plays a pivotal role in determining the efficacy of immune checkpoint inhibitors (ICIs) in melanoma treatment. Notably, Tertiary lymphoid structures (TLS)—organized aggregates of immune cells within tumors—are increasingly recognized for their association with improved anti-tumor immunity and favorable responses to ICIs. However, how melanoma cells interact with the TME to promote or inhibit TLS formation is underexplored.

Research Objectives:

Perform **spatial mapping** of TLS in human melanoma samples using a large **spatial transcriptomics** dataset to define architectural relationships. Investigate the melanoma-intrinsic signaling mechanisms that initiate or sustain the formation of TLS using **multiplex immunohistochemistry**, **flow cytometry**, and **cell culture**.

Master's Project 3: Developing an mRNA immunocytokine for melanoma therapy

Background: Currently approved first-line therapies for advanced melanoma are immune-checkpoint blockade and Braf/MEK inhibitor treatment, but only at most 50% of patients sustain durable responses to these drugs. A potential new treatment paradigm is the mRNA delivery of immunocytokines to activate anti-tumor immunological responses in patients. We have developed a platform for immunocytokine delivery and need to develop a corresponding antigen targeting approach. The project will involve validating **Chimeric Antigen Receptor (CAR)** targets on melanoma patient-derived cell lines and testing for toxicity in PBMCs. We will correlate antigen expression by immunohistochemistry and in functional in vitro, ex vivo, and potentially in vivo assays.

Research Objectives:

Develop, validate, and functionally test various melanoma-specific **CAR T-cells** in combination with **immunocytokine delivery** in primary immune cell cultures, **high-throughput tumor killing assays, flow cytometry, immunohistochemistry, ELISAs**

Master's Project 4: Mechanisms of Resistance in Cutaneous T-Cell Lymphoma

Background: Cutaneous T-cell lymphomas (CTCL) are rare, incurable skin-homing T-cell cancers marked by strong cellular heterogeneity and therapy resistance. Our recent single-cell analyses revealed two malignant memory T-cell states—a circulating, therapy-sensitive mTCM population and a skin-resident, therapy-persistent mTRM population—highlighting the role of transcriptional plasticity and the skin microenvironment in driving resistant disease. This Master's project integrates experimental and/or computational work to investigate and target therapy-resistant malignant T-cell states in CTCL.

Research objectives:

Model microenvironment-driven resistance using **3D CTCL skin equivalents**. Functionally test key regulators identified through single-cell analyses using **CRISPRa/i perturbations**. Characterize treatment-sensitive and treatment-resistant malignant T-cell states using **single-cell multi-omic analysis**.

Master's Project 5: Dissecting Liver Tropism in Uveal Melanoma Using Single-Cell and Spatial Multi-omics

Uveal melanoma (UM) is the most common primary intraocular cancer and among the most metastatic solid tumors. Nearly 50% of patients develop metastases, over 90% of which occur in the liver, yet the mechanisms underlying this strong organotropism remain unclear. This Master's project uses single-cell multiomics and spatial transcriptomics of paired primary UM tumors and liver metastases, supported by healthy ocular references, to investigate how malignant cell states and their microenvironment evolve during progression. The goal is to identify tumor-intrinsic and niche-derived factors that enable liver-specific colonization.

Research Objectives:

Perform **spatial analysis** to map malignant and microenvironmental cell states across primary and metastatic UM to identify programs linked to liver metastatic potential. **Multi-omics data analysis**, spatial mapping of tumor ecosystems, gene regulatory and **cell-cell communication modeling**, and computational reconstruction of metastatic trajectories. Validate key **cell-cell interactions using IHC and IF staining**.

Master's Project 6: *Validation of Synthetic Lethal Target Inhibitors in GNAQ/11-Mutant (Uveal) Melanoma*

Uveal melanoma is the most aggressive and deadly eye cancer and is associated with a high unmet need for effective systemic therapies. More than 90% of uveal melanoma tumors harbor oncogenic GNAQ or GNA11 mutations. Using functional genomics, our lab has identified novel synthetic lethal protein targets that are selectively required for the survival of GNAQ/11-mutant cancer cells. Importantly, inhibition of this target induces cell death exclusively in GNAQ/11-mutant cancer cells, while healthy cells remain viable. Based on this discovery, we are running a well-funded, drug discovery program to develop first-in-class small-molecule inhibitors against this synthetic lethal target.

Research Objectives: The student will work on an **active drug discovery pipeline**, including **cell-based validation** of synthetic lethal target inhibitors. **in vitro** selectivity testing in GNAQ/11-mutant vs. wild-type models, including biochemical assays with recombinant enzymes; **functional assays** assessing cell viability, apoptosis, signaling, and inhibitor–target engagement. **Disease expansion studies** in additional GNAQ/11-driven tumor models to identify further cancer indications and increase translational and investment potential. The student will gain insight into a **small-molecule drug development program**, including **ADME** and **pharmacokinetic (PK)** studies, and learn how promising compounds are advanced from **hit identification** to **optimized lead candidates**.

If you are interested, please contact Prof. Mitch Levesque mitchellpaul.levesque@uzh.ch for further information.



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