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| **Scientific Area** | Immune-related diseases |
| **Two project titles** | A) Identification of novel therapeutic targets in oncogenic JAK/STAT signaling in mastocytosis<br>B) Analysis of immune checkpoint molecules and its therapeutic potential in mastocytosis |
| **Host country** | Switzerland |
| **Supervisor, institution** | Prof. Karin Hartmann, University of Basel, Switzerland |
| **Co-Supervisor, institution** | A and B) Non-determined |
| **Mentor, institution** | Non-determined, potentially BioNTech, Mainz, Germany |
| **Secondment institution** | A and B) Non-determined, potentially University of Freiburg, Germany |

**Short description of the supervisor's lab with introduction to the topic**

Mastocytosis is a neoplastic disease characterized by clonal expansion of mast cells in multiple organs, particularly the bone marrow and skin. Clinical manifestation includes mast cell mediator symptoms such as anaphylaxis as well as dysfunction of various organ systems, such as cytopenia, hepatosplenomegaly, and malabsorption. The most common molecular alteration is an activating mutation in the *KIT* gene, *KIT*D816V, carried by more than 90% of patients. The course of the disease ranges from chronic in non-advanced categories to progressive in advanced categories. Current treatment options include antihistamines, omalizumab, and new KIT-targeting tyrosine kinase inhibitors, like midostaurin and avapritinib, but are often not sufficient to control symptoms. Our group has a long-standing interest in mastocytosis and other mast cell-related diseases. During the past years, we were able to identify novel biomarkers and therapeutic targets, we detected new *KIT* mutations in familial mastocytosis, developed new classifications and conducted clinical trials in mastocytosis. We also generated novel Cre-transgenic mouse models with conditional expression of *Kit*D814V for research on mastocytosis.

**Topic description, including techniques to be used**

To identify novel treatment targets in oncogenic signaling pathways downstream of murine *Kit*D814V and human *KIT*D816V.

**Project A)**

The PhD candidate will explore the JAK/STAT downstream signaling pathway of *Kit*D814V in *ex vivo* generated hematopoietic cells from mastocytosis mouse models by western blot, analyze different cellular functions in these cells (apoptosis, proliferation and cell growth, adhesion, migration and degranulation), compare findings to human mastocytosis cell lines, and study combined treatment approaches of JAK/STAT inhibitors with KIT-targeting tyrosine kinase inhibitors *in vitro* and *in vivo* using our novel mouse models of mastocytosis.

**Techniques**: mouse models, multi-color flow cytometry, histology, primary murine cell culture, culture of human cell lines, western blotting, various assays for apoptosis, proliferation, migration and degranulation

**Project B)**

The PhD candidate will explore the role of immune checkpoint molecules and their potential as therapeutic targets in mastocytosis. We have recently identified several checkpoint molecules in the serum of patients and found them being expressed in the bone marrow niche of mastocytosis patients, either in mast cell aggregates or in cells in close proximity thereof. The aim of the thesis is to learn more about the function of these molecules in mastocytosis. We will use siRNA and CRISPR/Cas9 approaches or recombinant proteins to modify human mastocytosis cell lines or *ex vivo* generated hematopoietic cells from mastocytosis mouse models and analyze cell growth and

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proliferation, apoptosis, adhesion/migration and degranulation. Finally, we will study combined treatment approaches of select checkpoint inhibitors with KIT-targeting tyrosine kinase inhibitors *in vitro* and *in vivo* using our novel mouse models of mastocytosis.
**Techniques**: mouse models, gene modification by CRISPR-/Cas9, siRNA, multi-color flow cytometry, histology, primary murine cell culture, culture of human cell lines, western blotting, various assays for apoptosis, proliferation, migration and degranulation

**Recommended applicant's training (technical expertise and knowledge)**

Techniques: primary cell culture, histology, flow cytometry, mouse handling
Knowledge: immunology, biology of innate immune cells, mouse genetics

**One or two relevant publication(s)**

Gerbaulet A et al., Mast cell hyperplasia, B-cell malignancy, and intestinal inflammation in mice with conditional expression of a constitutively active kit, Blood, 2011.
Rabenhorst A et al., Expression of programmed cell death ligand-1 in mastocytosis correlates with disease severity, J Allergy Clin Immunol, 2016.

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