PhD project No. 5, Prof. Ehl

Scientific Area	Hematopoiesis and immune cell differentiation
Two project titles	A) STAT3 at the crossroads between cancer and autoimmunity B) Immunopathology in acute versus chronic HLH
Host country	Germany
Supervisor, institution	Prof. Stephan Ehl, Medical Center - University of Freiburg, Germany
Co-Supervisor, institution	A) and B) Prof. Daniel Pinschewer, University of Basel, Switzerland
Mentor, institution	A) and B) to be determined later
Secondment institution	A) and B) University of Basel, Switzerland

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

The Ehl group combines patient observations with mouse models to study immune pathologies associated with disorders in T cell activation, differentiation and effector function.

Topic description, including techniques to be used

Project A) Autoimmunity and cancer frequently share alterations of common signaling pathways, including the JAK/STAT pathway. We detected a STAT3 Y640F mutation - a gain-of-function mutation frequently detected in T cell leukemia - in a patient with a benign clonal T cell proliferative disease associated with autoimmunity. The mutation is linked to a number of functional and metabolic alterations of the T cell clone. However, overexpression of the mutation in healthy T cells is not sufficient to elicit this phenotype. We hypothesize that additional events such as infections are required to drive aberrant T cell differentiation under conditions of increased STAT3 signalling. We aim to analyze mice with a human STAT3 Y640F transgene expressed in hematopoetic cells (generated by Richard Moriggl, Vienna) in acute versus chronic infection models. We will compare T cell differentiation and homeostasis, clonality, cytokine production and organ pathology with our patient observations. We expect to shed light on the role of infections in driving disease associated with uncontrolled cytokine receptor signaling.

Project B) Targeted interventions in T cell-mediated immunopathologies are highly desired for treatment of such diseases. Familial hemophagocytic lymphohistiocytosis (FHL) is an acute inflammatory syndrome characterized by T cell hyperactivation, caused by defects in lymphocyte cytotoxicity. Affected patients are particularly difficult to treat when the disease enters a chronic phase. We hypothesize that immune factors driving acute versus chronic HLH differ and require different therapeutic interventions. *Syntaxin11*-deficient mice (FHL-4 model), develop non-fatal acute HLH, followed by chronic HLH without complete recovery. We aim to analyze the switch from acute to chronic HLH defined by clinical parameters and histopathological changes. The findings will be correlated with the longitudinal differentiation of the disease-inducing T cells by in-depth analysis based on multiplex mass cytometry, RNA sequencing and metabolic flux studies. Data will be compared with those from patients with different stages of familial HLH. We expect that characteristic differentiation patterns of disease-inducing T cells will offer opportunities for more specific and directed therapeutic interventions.

Techniques A) and B): murine infection models, flow cytometry, ELISA, histology, multiplex mass cytometry, RNA sequencing, TCR sequencing, metabolic assays

Recommended applicant's training (technical expertise and knowledge)

Techniques: cell culture, flow cytometry, ELISA; Knowledge: immunology, cell biology

Maximum two relevant publications

Maccari et al., 2021, J Exp Med.:A distinct CD38+CD45RA+ population of CD4+, CD8+, and double-negative T cells is controlled by FAS.

Kögl T et al., 2013, Blood: Hemophagocytic lymphohistiocytosis in syntaxin-11-deficient mice: T-cell exhaustion limits fatal disease.

The EURIdoc programme has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement number 101034170.

Ethics description

1. Humans	
This research involves human participants.	YES ☒ / NO ☐
This research involves physical interventions on the study participants.	YES ☐ / NO ☒
2. Human Cells /Tissues	
This research involves human cells or tissues, such as blood.	YES ☒ / NO ☐
3. Personal Data	
This research involves personal data collection and/or processing.	YES ☐ / NO ☒
This research involves further processing of previously collected personal data (secondary use).	YES ☒ / NO ☐
4. Animals	
This research involves animals, such as mice.	YES ☒ / NO ☐

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