PhD project No. 2, Dr. Charvet (Dr. Chan)

Scientific Area	Hematopoiesis and immune cell differentiation
Two project titles	A) Role of Ikaros in Th17 cell development B) Role of Ikaros in the regulation of T-cell pathogenicity
Host country	France
Supervisor, institution	Dr. Susan Chan and Dr. Céline Charvet, University of Strasbourg, France
Co-Supervisor, institution	Dr. Ulrich Maurer, University of Freiburg, Germany
Mentor, institution	To be determined later
Secondment institution	University of Freiburg, Germany

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

The laboratory of Susan Chan and Philippe Kastner is interested in understanding how transcription factors regulate lymphocyte differentiation, including T cells. $CD4^+$ Th17 cells are essential to clear fungi and extracellular bacterial infections (conventional (c) Th17 cells). Yet, they can also acquire pathogenic properties and be actively involved in viral infections, as well as in autoimmune and inflammatory diseases, such as multiple sclerosis. The factors that control this paradigm are only partially understood. We recently described that, on one hand, the transcription factor Ikaros (1) is essential to promote the polarization of $CD4^+$ T cells into the IL-17-producing cTh17 lineage and on the other hand, it inhibits the pathogenic signature of $CD4^+$ T cells, by repressing the expression of the cytokine GM-CSF (2). How does Ikaros exert its antagonist function on conventional and pathogenic T cells remains unclear.

Topic description, including techniques to be used

Project A) Role of Ikaros in Th17 cell development

We will explore whether Ikaros binds to Th17 hallmark genes and/or modifies the chromatin accessibility landscape in Th17 cells. We will determine whether Ikaros is required to help the transcription factor RORγt, essential for Th17 cell polarization, to bind on its target genes, such as IL-17, using WT and Ikaros KO mice. We will analyze whether Ikaros regulates the activation of molecular cascades that are critical for the development of Th17 cells.

Project B) Role of Ikaros in the regulation of T-cell pathogenicity

We will investigate how Ikaros regulates GM-CSF expression, either directly by binding on regulatory sequences of the *Csf2* gene, or indirectly, by controlling the production of cytokines, such as IL-2, that could act in an autocrine way. We will determine how to reverse the pathogenic signature observed in Ikaros deficient $CD4^+$ T cells by testing different pharmacological inhibitors. We will explore whether Ikaros deficient $CD4^+$ T cells possess a pathogenic potential to induce a murine model of multiple sclerosis.

Techniques: molecular biology, cell culture, retroviral transduction of primary murine T cells, flow cytometry, quantitative real-time PCR, Western blots, ChIP-seq, ATAC-seq, RNA-seq, bioinformatic analysis, mouse models.

Recommended applicant's training (technical expertise and knowledge)

Techniques: cell culture, molecular biology, flow cytometry, Western blots, qRT-PCR
Knowledge: immunology, cell biology, signalling pathways, mouse genetic

One or maximum two relevant publication(s)

Heizmann et al., 2018, Current opinion in Immunology: The Ikaros family in lymphocyte development.
Bernardi et al., 2021, Proc Natl Acad Sci.: $CD4^+$ T cells require Ikaros to inhibit their differentiation towards a pathogenic cell fate.

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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