PhD project description No. 13, Prof. Bengsch

Scientific Area	Innate and adaptive effector functions Immune-mediated diseases
Two project titles	A) Profiling the cellular metabolic landscape of human T cell differentiation in chronic infection and cancer B) Role of cellular stress pathways in exhausted T cells
Host country	Germany
Supervisor, institution	Prof. Dr. Dr. Bertram Bengsch, University Medical Center Freiburg, Germany,
Co-Supervisor, institution	Prof. Dr. Christoph Hess, University of Basel, Switzerland
Mentor, institution	To be determined later
Secondment institution	To be determined later

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

We study how the immune system responds to chronic inflammation aiming to understand cellular mechanisms controlling immune function that can inform therapeutic decisions, for example during cancer immunotherapy. Advanced single-cell profiling approaches including mass cytometry and imaging mass cytometry are used in combination with algorithmic deconvolution of the dense data sets. We focus on understanding exhausted T cells (TEX), which constitute a T cell lineage distinct from functional memory and effector cells characterized by co-expression of immunoregulatory molecules, an altered transcriptional and epigenetic landscape and reduced functionality. We demonstrated that bioenergetic regulation through immune checkpoints (e.g., PD-1) is an important driver of exhaustion.

Topic description, including techniques to be used

Project A) We plan to identify metabolic programs expressed by T cells responding to different antigens in chronic infection and cancer. A focus will be on metabolic pathways expressed in different exhausted T cell subsets, as identified by transcriptional and epigenetic profiling. We will use high-content profiling of metabolic targets at the single cell level by mass cytometry combined with imaging mass cytometry of human tissue sections. Individual pathways will be investigated using metabolomic approaches and pathway inhibition.

Project B) Exhausted T cells are subject to cellular stress driving mitochondrial dysfunction. In this project we will investigate external cues driving T cell cellular stress pathways. We will focus on cues present in the inflammatory environment during chronic infection and cancer and determine their effect on autophagic flux, the unfolded protein response, oxidative stress response and DNA damage response in different subtypes of human T cells, including different subtypes of exhausted T cells and residential memory T cells. Changes in cellular stress responses will be further investigated during immunotherapy.

Techniques: Mass and flow cytometry, imaging mass cytometry, cell culture, T cell stimulation and cytokine assays, transcriptome profiling, metabolic flux analysis, metabolomics, bioinformatics

Recommended applicant's training (technical expertise and knowledge)

Techniques: cell culture, DNA cloning, flow cytometry, SDS-PAGE, Western blotting

Knowledge: T cell immunology, immunometabolism, metabolic signaling, virology, cell biology,

Maximum two relevant publications

Schwabenland/Salie et al 2021, preprint http://dx.doi.org/10.2139/ssrn.3765620 Deep spatial profiling of COVID19 brains reveals neuroinflammation by compartmentalized local immune cell interactions and targets for intervention.

Bengsch et al. 2018, Immunity: Epigenomic-Guided Mass Cytometry Profiling Reveals Disease-Specific Features of Exhausted CD8 T Cells.

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	
The research involves human participants.	YES ☐ / NO ☒
The 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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