PhD project No. 24, Prof. Warnatz

Scientific Area	Immune-related diseases
Two project titles	A) The stroma niche of disturbed germinal center. B) Extrafollicular plasma cell responses in patients with primary immunodeficiency
Host country	Germany, France
Supervisor, institution	Prof. Klaus Warnatz, Medical Center - University of Freiburg, Germany
Co-Supervisor, institution	A) + B) Christoph Mueller, University of Strasbourg, France
Mentor, institution	A) and B) Kai Michael Toellner, U Birmingham UK (to be confirmed)
Secondment institution	A) and B) Novartis (to be confirmed)

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

The Warnatz lab is interested in understanding underlying pathomechanisms of human immunodeficiency and autoimmunity. Previous work has led to the discovery of novel human monogenetic immunodeficiency disorders, contributed to our comprehension of the altered humoral immune system in common variable immunodeficiency (CVID), the differentiation of human T-Bet^{hi}CD21^{low} B cells and associated organ disease. The recent focus is the understanding of disturbed germinal centre (GC) function as the hub of high affinity antibody responses.

Topic description, including techniques to be used

Project A)

We plan to visualize the niche which is required to allow for the proper formation of GCs in secondary lymphoid organs (SLO) of patients with disturbed GC function in comparison to SLO of immunocompetent donors. The focus of this project is on the non-hematopoietic stroma. In parallel to immunohistochemical visualization, stromal cells shall be characterized phenotypically, transcriptionally and by functional in-vitro assay in co-culture with GC T and B cells in order to characterize their role in support of T-B cell differentiation during immune responses. The effect of known monogenic causes of disturbed GC function on stromal cells can be studied by CRISPR-Cas9 induced genetic variants in stromal cells.

Techniques: Multiple epitope ligand cartography (MELC), imaging mass cytometry, CyTOF, Flow cytometry, RNAseq

Project B)

Increasingly, the role of extrafollicular responses after activation of the adaptive immune system are rediscovered. Key players of such responses are potentially T-bet^{hi}CD21^{low} B cells and T peripheral helper cells (T_{PH}) which provide the precursors for a plasma cell response. In this project we will investigate podoplanin^{+} CD157^{high} stromal cells providing the niche for the plasma cell response. In parallel to immunohistochemical visualization, stromal cells shall be characterized phenotypically, transcriptionally and by functional in vitro assay in co-culture with activated T and B cells in order to characterize their role in support of plasma cells. The effect of known monogenic causes of disturbed GC function on stromal cells can be studied by CRISPR-Cas9 induced genetic variants in stromal cells.

Techniques: Multiple epitope ligand cartography (MELC), imaging mass cytometry, CyTOF, Flow cytometry, RNAseq

Recommended applicant's training (technical expertise and knowledge)

Techniques: Cell culture, multidimensional flow cytometry, immunohistochemistry, analysis of transcriptomes, CRISPR Cas9

Knowledge: adaptive immunity, humoral immunity, germinal centre function, signalling, system biology

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.

Maximum two relevant publications
Unger et al., 2018, JACI: TH1 phenotype of T follicular helper cells indicates an IFNgamma-associated immune dysregulation in CD21low CVID patients Klocperk et al., 2018, JACI: Exhausted phenotype of follicular CD8 T cells in CVID

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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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