PhD project No. 14, Prof. Pinschewer

Scientific Area	Innate and adaptive immunity
Two project titles	A) Affinity maturation in chronic viral infection B) Clonal competition of B cells in chronic viral infection
Host country	Switzerland
Supervisor, institution	Prof. Daniel Pinschewer, University of Basel, Dept. of Biomedicine
Co-Supervisor, institution	A) and B) Prof. Stephan Ehl, Medical Center - University of Freiburg
Mentor, institution	A) and B) To be determined later
Secondment institution	A) and B) University of Freiburg, Germany

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

The Pinschewer laboratory combines mouse models of viral infection with viral reverse genetics to investigate immunity, pathogenesis and vaccination in the context of viral infection.

Topic description, including techniques to be used

Background: The importance of antibody-producing B cells for immune control of persistent viral diseases such as hepatitis C virus in man or lymphocytic choriomeningitis virus (LCMV) in mice has become increasingly appreciated. Still, the functioning of B cell responses in the chronic viral infection context remains ill-defined. One of the hallmarks and a fundamental principle of B cell immunity consists in the cells' affinity maturation. Evidence suggests that the Darwinian selection process of affinity maturation is perturbed in persistent viral diseases, facilitating viral persistence.

Project A) This project aims to longitudinally follow at single cell resolution the affinity maturation and differentiation of B cells in the context of acute versus chronic viral infection: It combines reverse genetic virus engineering, single cell RNA sequencing technology and cutting-edge B cell transfer studies in acutely and chronically LCMV-infected mice. A range of viral variants will be engineered, exhibiting differential affinity for a monoclonal antiviral B cell. These viruses will be used to infect mice, in which the aforementioned B cells are engrafted. Upon evolution of the transferred B cells in either acute or chronic infection, the B cells will be characterized for their differentiation, transcriptome and, importantly, for the mutational landscape in their B cell receptor. Thereby, the project is designed to decipher the mechanisms accounting for subversion of clonal selection and B cell affinity maturation in the context of persistent viral diseases.

Project B) This project aims to define and compare B cell affinity thresholds as determinants of B cell responses in acute versus chronic viral infection. A library of reverse engineered antibodies will be generated, recapitulating the evolutionary tree of a high-affinity LCMV-neutralizing antibody from its unmutated common ancestor, and the affinity of each antibody in the library will be determined by biolayer interferometry. A set of CrispR/Cas-based immunoglobulin knock-in mice will be generated spanning the range of affinities in the antibody library. The resulting monoclonal B cells will be used in adoptive transfer studies to compare their behavior in acutely versus chronically infected recipient mice. This work will allow to systematically assess affinity-dependent clonal expansion and differentiation of B cells in an infection context-dependent manner.

Recommended applicant's training (technical expertise and knowledge)

Techniques: Eagerness to learn and work hard; Knowledge: Immunology, molecular biology

Maximum two relevant publications

Fallet et al., 2016, Sci Immunol: Interferon-driven deletion of antiviral B cells at the onset of chronic infection.
Fallet et al. Chronic, 2020, Cell Rep.: Viral Infection Promotes Efficient Germinal Center B Cell Responses.

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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