PhD project description (to be shown on the URI-website)

Scientific Area	Innate and adaptive effector functions
Project Title	„Targeting drivers of disease progression in hemophagocytic lymphohistiocytosis (HLH)"
Host country	Germany
Supervisor, institution	Prof. Stephan Ehl, Medical Center - University of Freiburg, Germany
Co-Supervisor, institution	Prof. Daniel Pinschewer, University of Basel, Switzerland
Mentor, institution	to be determined later
Secondment institution	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

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening immunohematologic disorder caused by hyperactivated T cells and macrophages, leading to excessive inflammation and multi-organ failure. In primary HLH, uncontrolled immune activation is the result of gene defects affecting perforin-dependent cytotoxicity of NK and CD8 T cells. HLH patients present with prolonged fever, hepatosplenomegaly, cytopenia, often liver disease and neurological manifestations. Primary HLH is commonly a disease of early childhood and, if untreated, the outcome is generally fatal. Clinical management focusses on initial aggressive immunosuppression. These remission-inducing therapies suppress hyperinflammation, eliminate activated immune cells and dampen the cytokine storm, stabilizing the patients for allogeneic hematopoietic stem cell transplantation (HSCT). Novel therapeutic approaches target key disease driving cytokines like IFNγ (emapalumab) or cytokine receptor signalling pathways, like ruxolitinib (JAK1/2 inhibitor). However, overall survival of HLH patients is not satisfactory (about 60%), due to uncontrolled disease activity, treatment toxicity, relapses before transplantation and opportunistic infections. Hence, alternative strategies to improve HLH outcome are needed.

We aim at novel therapeutic approaches to achieve remission in HLH by silencing disease-driving T cells and macrophages without physical elimination and stopping the hyperinflammatory process. In the case of disease-driving T cells this may be achieved by enhancing negative signals (e.g. via inhibitory receptors or inhibitory cytokines) or by blocking positive signals (e.g. costimulation, activating cytokines or activating receptors) thereby downregulating effector functions to promote T cell exhaustion or to force apoptosis. Such therapeutic approaches would dampen hyperinflammation and disease symptoms. Robust preclinical mouse models for FHL2 (Perforin deficiency), FHL3 (Munc13-4 deficiency), and FHL4 (Syntaxin-11 deficiency) that reliably replicate the clinical picture of HLH patients upon viral infection are well established and available to test such novel therapeutic concepts.

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. A distinct CD38+CD45RA+ population of CD4+, CD8+, and double-negative T cells is controlled by FAS. J Exp Med. 2021 Feb 1;218(2):e20192191.

Kögl T et al. Hemophagocytic lymphohistiocytosis in syntaxin-11-deficient mice: T-cell exhaustion limits fatal disease. Blood. 2013 Jan 24;121(4):604-1.

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

Name of the supervisor
Stephan Ehl
PhD project title
„Targeting drivers of disease progression in hemophagocytic lymphohistiocytosis (HLH)"
Ethics self-assessment
Study with patient material is approved by the Ethics committee of the University of Freiburg (protocol numbers 610/15; 409/16) Mouse experiments are approved by the *Regierungspraesidium* Freiburg (G-18/160, G-20/109)

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Ethics self-assessment

1. Human Embryos/Foetus	
Does your research involve Human Embryonic Stem Cells (hESCs)?	YES ☐ / NO ☒
Does your research involve the use of human embryos?	YES ☐ / NO ☒
Does your research involve the use of human foetal tissues / cells?	YES ☐ / NO ☒
2. Humans	
Does your research involve human participants?	YES ☒ / NO ☐
Does your research involve physical interventions on the study participants?	YES ☐ / NO ☒
3. Human Cells /Tissues	
Does your research involve human cells or tissues (other than from Human Embryos/ Foetuses, i.e. section 1)?	YES ☒ / NO ☐
4. Personal Data	
Does your research involve personal data collection and/or processing?	YES ☐ / NO ☒
Does your research involve further processing of previously collected personal data (secondary use)?	YES ☐ / NO ☒
5. Animals	
Does your research involve animals?	YES ☒ / NO ☐
6. Third Countries	
In case non-EU countries are involved, do the research related activities undertaken in these countries raise potential ethics issues?	YES ☐ / NO ☒
Do you plan to use local resources (e.g. animal and/or human tissue samples, genetic material, live animals, human remains, materials of historical value, endangered fauna or flora samples, etc.)?	YES ☐ / NO ☒
Do you plan to import any material - including personal data - from non-EU countries into the EU?	YES ☐ / NO ☒
Do you plan to export any material - including personal data - from the EU to non-EU countries?	YES ☐ / NO ☒
In case your research involves low and/or lower middle income countries, are any benefits-sharing actions planned? List available here: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519	YES ☐ / NO ☒
Could the situation in the country put the individuals taking part in the research at risk?	YES ☐ / NO ☒

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7. **Environment & Health and Safety**	
Does your research involve the use of elements that may cause harm to the Environment, to animals or plants?	YES ☐ / NO ☒
Does your research deal with endangered fauna and/or flora and/or protected areas?	YES ☐ / NO ☒
Does your research involve the use of elements that may cause harm to humans, including research staff?	YES ☐ / NO ☒
8. Dual Use	
Does the research have potential for military applications?	YES ☐ / NO ☒
10. Misuse	
Does this research have the potential for malevolent/criminal/terrorist abuse?	YES ☐ / NO ☒
11. Other Ethics Issues	
Are there any other ethics issues that should be taken into consideration? If yes, please specify in your ethics statement (see below)	YES ☐ / NO ☒

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