jeudi, juillet 28, 2022

# INTERNATIONAL PhD PROPOSAL

**PhD Supervisor full name** **Sven KRACKER**

## PhD PROPOSAL IDENTIFICATION

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| **PhD Project title** | Characterization of a novel inborn error of immunity associated to antibody deficiencies |
| **Project Acronym** | NOVEL- PAD |
| **Project Keyword** | B lymphocyte homeostasis |

## LABORATORY PRESENTATION

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| **Laboratory Team Name** | Laboratory of Human Lymphohematopoiesis |
| **Department IP** | Imagine |
| **Doctoral school** | École Doctorale « Hématologie, Oncogenèse et Biothérapies » - n° 561 |
| **University** | Université Paris Cité |
| **Laboratory website** | https://www.institutimagine.org/fr/isabelle-andre-175 |

## PhD PROPOSAL

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| **PhD Supervisor full name** | Sven KRACKER |
| **PhD Supervisor position** | research director |
| **PhD Supervisor email** | sven.kracker@inserm.fr |

## PhD Proposal abstract (1000 characters maximum)

Inborn errors of immunity associated to antibody deficiencies also known as primary antibody deficiencies (PADs) constitute a heterogeneous group of primary immune deficiencies diagnosed in childhood or in adulthood, which remain not well understood. This PhD project proposal aims at studying molecular, genetic and pathophysiological mechanisms associated to monogenic primary antibody deficiencies. This will be achieved by combining whole exome sequencing analysis with in depth immune phenotyping and specifically gene/mutation tailored functional studies. Within this frame we will take advantage of a recently identified de novo variant in a gene involved in intracellular signaling and implicated in survival and maintenances of mature B cells. This project is expected to provide unique fundamental insights of regulating crucial intracellular signaling pathways important for adaptive immune responses and to improve the diagnosis and care of rare but severe diseases.

## PhD Proposal (4000 characters maximum)

Primary antibody deficiencies (PADs) are the most common type of primary immunodeficiency and arise either alone or in combination with immunodeficiencies affecting other aspects of immunity against pathogens[1]. Depending on their underlying cause, PADs have been associated with various pathologies, including susceptibility to microbial infections, autoinflammatory and autoimmune diseases and some types of cancer. PADs are not solely due to B cell-intrinsic defects; they can also result from impairments in other cell lineages. The team has expertise in deciphering molecular consequences of mono-genetic defects responsible for the pathogenesis of PADs (see[2,3]) and is interested in the characterization of molecular pathways involved in B cell development and function. We veryrecently identified a *de novo*variant in a gene involved in intracellular signaling and implicated in survival and maintenances of mature B cells. The PhD thesis project aims to investigate the pathophysiological mechanism of the identified mutation with a variety of functional assays in *in vitro*, *ex vivo*and *in vivo*models specifically tailored for the gene of interest.

The PhD candidate will characterize expression of the variant at RNA and protein level in primary patient's cells, patient derived cells lines and ectopic expression systems. The candidate will investigate the impact of the variant on protein-protein interactions with a variety of molecular and imagine technics, e.g., protein immune precipitation, fluorescence resonance energy transfer microscopy and proximity ligation assay. Furthermore, the PhD candidate will investigate the impact of the variant on different intracellular signaling pathways. A particular attention will be given to NFkB signaling.

In parallel, to obtain additional insights into the pathophysiological mechanism of the disease,the PhD candidate will participate to the generation of knock-in mice, carrying the same variant as identified in the patient, using CRISPR/CAS9 technology (taking advantage of the excellent mouse transgeneses platform at Imagine). The generation and characterization of this animal model is part of the PhD project. The PhD candidate will investigate to what extend the generated mouse model replicates the patient phenotype. The candidate will compare the immune phenotype of lymphocyte populations in bone marrow, spleen, thymus and lymph nodes focusing especially on B and T lymphocytes.

The candidate will have the opportunity to work with several cutting-edge platforms located within the Imagine Institute and Necker campus, with a collaborative team and an enthusiastic mentor (PhD supervisor).

The project will not only identify and describe a novel primary antibody deficiency but in addition should provide novel insights on the control/regulation of intracellular signaling pathways at different stages of B and T lymphocyte development in humans and mice.

Durandy, A., Kracker, S. & Fischer, A. Primary antibody deficiencies. *Nat. Rev. Immunol.***13**, 519–533 (2013).

Deau, M.-C. *et al.*A human immunodeficiency caused by mutations in the PIK3R1 gene. *J. Clin.*

*Invest.***124**, 3923–3928 (2014).

Bouafia, A. *et al.* Loss of ARHGEF1 causes a human primary antibody deficiency. *J. Clin. Invest.***129**, 1047–1060 (2019).

## Expected profile of the candidate

The ideal candidate will be highly motivated and hard-working with a strong background in immunology and/or molecular biology. The Applicant should be interested in fundamental and translational research. Previous training in cell culture, biochemistry, molecular cell biology and cell imaging techniques is a plus.