Internship Proposition
(one page max)

Master 2 GP Immunology & ImmunoIntervention (I^3)
2026-2027

Lab: CR2TI
Team: I
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Title of the internship: Functional Characterization of CD8 T Cell Dysregulation in Patients with *IKZF1* Haploinsufficiency

Summary of the internship proposal:

Background

Heterozygous loss-of-function variants in *IKZF1*, encoding the transcription factor IKAROS, are responsible for a spectrum of inborn errors of immunity. While the impact of IKAROS haploinsufficiency on B cell development and humoral immunity has been extensively documented, recent observations suggest that mature T cell compartments are also profoundly affected. In particular, patients carrying the *IKZF1* H195Q and R184W variants display marked CD8 T cell activation and expansion, raising important questions regarding the mechanisms underlying these abnormalities and their functional consequences.

Project Objectives

The objective of this project is to characterize the mechanisms driving T cell activation in patients carrying the *IKZF1* H195Q and R184W variants.

The central hypothesis is that CD8 T cells from *IKZF1*-mutated patients exhibit an exaggerated cytotoxic response following stimulation, accompanied by accelerated differentiation toward dysfunctional or exhausted states. Understanding these alterations will provide new insights into the role of IKAROS in regulating peripheral T cell function and immune homeostasis.

Scientific Strategy

The project will combine advanced immunophenotyping and functional analyses of patient-derived T cells.

Flow cytometry will be used to characterize CD4, CD8, and γδ T cell subsets, with particular emphasis on activation, differentiation, and exhaustion-associated markers. Functional studies will investigate the cytotoxic properties of CD8 T cells using intracellular cytokine staining, co-culture systems, and cytotoxicity assays following stimulation.

Experimental work will be conducted on the CIMNA immunomonitoring platform in close collaboration with the Immunology Laboratory of Nantes University Hospital under the supervision of Dr. Cécile Braudeau. In parallel, the student will explore and analyze existing single-cell RNA sequencing datasets generated from *IKZF1*-deficient patients at the CR2TI (Centre de Recherche en Transplantation et Immunologie, Inserm UMR 1064, Nantes Université) under the supervision of Dr. Thomas Laurent, using dedicated interactive analysis tools developed within the laboratory.

Expected Outcomes

We anticipate identifying profound alterations in CD8 T cell cytotoxic programs associated with accelerated acquisition of exhaustion-related phenotypes, consistent with a cell-intrinsic role of IKAROS in regulating T cell activation and differentiation.

These findings will provide mechanistic insight into T cell dysfunction in IKZF1 haploinsufficiency and may have important implications for the long-term clinical management of affected individuals. In particular, they may raise questions regarding the ability of these patients to sustain effective antiviral and antitumor immune responses during aging.

Option(s) linked to the project:

☐ Clinical Research Profile (Recherche Clinique)
☐ Data Analyst Profile (Recherche et Analyse de Données Omiques)
x Experimental Biology Profile (Recherche Expérimentale)

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