Proposed *Ph.D.* Project - GI IVID (2026-2029)

Title: **Ubiquitin-proteasome system dysfunction and susceptibility to intracellular respiratory pathogens in VEXAS syndrome**

Supervision:

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Scientific background and rational:
VEXAS syndrome is a recently described acquired autoinflammatory disease caused by somatic loss-of-function mutations in UBA1, encoding the E1 enzyme of the ubiquitin-proteasome system (UPS). In addition to severe systemic inflammation and hematological defects, recent clinical studies have revealed a high burden of severe infections in VEXAS patients, often occurring independently of immunosuppressive treatments. These infections disproportionately involve intracellular respiratory bacterial pathogens, notably *Legionella pneumophila*. The UPS is a central regulator of innate immune signaling, autophagy, vesicular trafficking, and host defense against intracellular pathogens. *L. pneumophila* actively exploits host ubiquitination pathways to establish its replicative niche within macrophages, making it a highly relevant model to investigate the consequences of UPS dysfunction on antibacterial immunity. Our preliminary data indicate that UBA1 knock-out macrophages display increased permissiveness to *L. pneumophila* replication, associated with defects in intracellular control mechanisms. Together, these observations support the hypothesis that VEXAS syndrome represents a unique human model of acquired immunodeficiency linked to ubiquitination defects, offering a rare opportunity to dissect UPS-dependent host-pathogen interactions in a clinically relevant context.

Objectives and feasibility:
This project aims to determine how UBA1 mutations impair macrophage-mediated control of intracellular respiratory pathogens, and to establish VEXAS syndrome as a model of acquired susceptibility to respiratory infections. Human cellular models carrying UBA1 mutations and primary macrophages from VEXAS patients (French VEXAS Group) will be combined, using *Legionella pneumophila* as the main intracellular pathogen model. Approaches will include analyses of intracellular replication, imaging of pathogen-containing vacuoles, assessment of endosomal, autophagic, and inflammatory pathways, and transcriptomic/proteomic profiling. Experiments will be conducted at the CIRI, which provides state-of-the-art facilities and direct access to the French National Reference Center for *Legionella*, ensuring feasibility and strong translational relevance.

Keywords:
VEXAS syndrome, intracellular pathogens, ubiquitination, innate immunity, macrophages, host-pathogen interactions

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