

Skin Mycobiota, Digital Profiling and Immune Networks in Psoriasis: an Environmental and Technology-Driven Systems Medicine Approach

Context and Global Health Positioning. Psoriasis is a chronic inflammatory dermatosis affecting around 60 million people worldwide ¹. Beyond its cutaneous manifestations and association with psoriatic arthritis, psoriasis is a major public health issue, with significant impact on quality of life, comorbidities (cardiovascular, metabolic), and healthcare costs. Increasing evidence supports the role of the human microbiota as an environmental determinant of chronic inflammatory diseases. In psoriasis, several studies suggest a fungal dysbiosis of the skin, with over-representation of specific species such as *Candida spp.* ^{2,3}, a commensal fungus associated with systemic immune activation ^{4,5}. Within this framework, we propose to dissect how the **cutaneous and intestinal mycobiota**, as components of the exposome, contribute to psoriatic inflammation through CD4⁺ TH17 cell responses. Our project explicitly adopts a **global health perspective**, considering commensal fungi of the skin and gut as key **environmental exposures** shaping immune homeostasis and disease risk across populations. The project is anchored in the horizontal axis “**Health and Environment**”, by integrating microbial ecology, host immunity, and clinical phenotype, and in the vertical axis “**Digital Health and Technologies**”, by relying on advanced sequencing, bioinformatics, and data-integration pipelines for multi-omic analysis.

Objectives of the doctoral research program. This doctoral project will be coordinated by **Dr Alicia Moreno Sabater** (CIMI, Sorbonne University, Study and manipulation of tolerance in Immunopathology), in close collaboration with **Pr Boualem Sendid** (University of Lille, Inserm U1285 & CNRS UMR 8576, « Glycobiology in Fungal Pathogenesis and Clinical Application »). The doctoral research project embedded in our ANR PsoFungi initiative ([ANR-24-CE17-2730](#)), pursues two main objectives: 1) **Environmental mycobiota signatures in psoriasis**: to characterize and compare skin and gut fungal communities in psoriatic patients and healthy controls, and to define psoriasis-specific “environmental” fungal signatures at both anatomical sites. 2) **Digital integration of mycobiota–immunity networks**: to analyse the functional interactions between dominant fungal taxa and resident cutaneous CD4⁺ T cells (activation, cytokine profiles, TCR repertoire) and to integrate these datasets using digital tools (metagenomic pipelines, statistical modelling, multivariate integration). Beyond descriptive profiling, the ambition is to construct **data-driven models** linking fungal exposure, local immune responses, and disease phenotype, to identify candidate fungal antigens and immune pathways amenable to targeted interventions in a global health context.

Methods and Digital/Technological Dimensions. To carry out this project, we have established a **collaboration** with clinicians specialized in **psoriasis** from the **Dermatology and Allergology Department (Dr J.-B. Montfort and Dr C. Bachmeyer)** and the **Plastic, Reconstructive and Aesthetic Surgery Department (Dr L. Litrico and Prof. M. Atlan)** at **Tenon Hospital, Paris, France**. Clinicians from these departments see approximately **200 patients per year**. Psoriasis patients attending **specialized consultations** at this hospital have **not responded to topical treatments** and require **systemic therapy**. Clinicians frequently perform **skin biopsies** to confirm the **diagnosis of psoriasis** and collect **blood samples** to assess patients’ **overall health status** prior to initiating systemic treatment. In this context, we have applied for the necessary **ethical approvals** to conduct these **non-interventional research protocols** involving **human participants**. Our project proposal has been reviewed by the **Clinical Research Unit at Saint Antoine Hospital** and by the **Committee for the Protection of Persons (Research Ethics Committee)**. The available biological material (skin scales, lesional and non-lesional biopsies, faecal samples, peripheral blood) enables a **multi-level analysis** of the environment–host interface.

1) Digital mycobiota profiling to characterise fungal communities in psoriasis. Fungal DNA will be extracted from skin and faecal samples and analysed by high-throughput sequencing of the ITS2 region. The resulting data will be processed using bioinformatic pipelines (quality control, clustering, taxonomic

assignment) running on Sorbonne University platforms. We will compute alpha and beta diversity indices, identify taxa that differ between patients and controls, and define psoriasis-associated fungal signatures at skin and gut levels. When possible, methods from computational ecology and machine learning will be applied to link mycobiota composition and structure to clinical parameters and immunological readouts, thereby integrating environmental exposure and host response within a digital health framework, as previously described^{4,6}.

2) *Ex vivo immune functional assays and digital immunoprofiling.* To this aim, we will characterise how commensal and environmental fungi shape local T cell responses in psoriasis. Resident CD4⁺ T cells will be isolated from lesional and control skin biopsies, then stimulated *in vitro* with fungal extracts selected based on prior digital mycobiota analyses. Their functional profile will be assessed by multiparametric flow cytometry to quantify TH17/TH1-like responses (IL-17A, IL-22, IFN- γ , IL-10, IL-4) and chemokine receptor expression (CCR6, CXCR3)⁵. When feasible, TCR repertoire sequencing (V β -seq) will be performed, followed by computational analysis to detect antigen-driven clonal expansions. Together, these approaches will provide a high-resolution, digitally analysable map of fungus-specific T cell immunity in psoriatic skin.

3) *Integrated data analysis and systems-level modelling.* Integration of data obtained will bring together metagenomic, immunological, and clinical datasets to build a comprehensive view of the mycobiota–immunity–psoriasis network⁷. Using R-based statistical frameworks, multivariate models and network analysis, we will integrate sequencing data, immune phenotypes and patient characteristics to identify correlations and potential causal pathways linking environmental fungal exposure (skin and gut), resident immune responses, and psoriasis severity. This systems approach aims to define candidate fungal antigens and immune signatures that could serve as biomarkers or therapeutic targets in a precision-medicine and global health perspective.

Impact and Global Health Perspective. This project aligns with the “**Global Health – Health and Environment**” horizontal axis by considering commensal fungi as a modifiable environmental factor in chronic inflammatory skin disease, analysing the gut–skin axis as a systemic interface between microbial exposure and distant organ inflammation, and identifying environmental fungal signatures linked to disease onset, flares or treatment response to inform population-level prevention. By characterising the environmental mycobiota in a human cohort and mapping its impact on host immunity, it clarifies how microbial exposures shape global inflammatory burden. It also fits the “**Digital Health and Technologies**” vertical axis through systematic use of high-throughput sequencing, the development of dedicated bioinformatic pipelines and statistical tools, and the integration of multi-source data (omics, cytometry, clinical) into digital models of the mycobiota–immunity–disease network, in a systems biology and precision-medicine framework, while training the doctoral candidate in core digital skills. The project will clarify how skin and gut mycobiota contribute to psoriasis, identify fungal antigens and immune signatures as potential targets to develop a framework applicable to other microbiota-driven inflammatory diseases. In the longer term, its results could inform digital decision-support tools integrating microbiota and immune biomarkers for risk stratification and therapeutic guidance in psoriasis and related conditions.

References:

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