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OPEN POSITION

MICROBIOTA MUCOSAL IMMUNITY AND JAK INHIBITORS

DESCRIPTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic synovitis and bone damages, which consist of joint destruction and systemic osteoporosis. During the pathological process, pro-inflammatory cytokines such as TNF-alpha or IL-6 are central in the pathogenesis of RA. Biotherapies targeting these cytokines are current therapeutic strategies for RA and have drastically revolutionized healthcare of patients. However, at third of the patients are non-responders or lose response in the first months of treatment. These biotherapies are associated with more infections or neoplasia risks.

Janus kinase (JAK) is a family of intracellular, nonreceptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway. Indeed, upon cytokine receptor activation, JAK kinases (JAK-1, JAK-2, JAK-3 and Tyk-2) phosphorylate STAT proteins, which then translocate to the nucleus and regulate the expression of numerous genes that drive inflammatory response. Jak Inhibitor X is a potent and orally active inhibitor of the JAK family (with high selectivity to JAK-1 and JAK-3) which suppresses inflammatory signaling of γc-chain cytokines (IL-2, IL-4, IL-7, and IL-15), but also of IL-6 and interferon-γ[1] . Jak Inhibitor X represents a novel seducing therapy for RA. However, the effects of Jak inhibitor X, especially its influence on mucosal immunity and especially on innate lymphoid cells have not been explored.

Mucosal immunity acts as a double agent: a real firewall against pathogens, but also a collaborator that has coevolved to monitor, and exploit the normal microbiota. Commensal microorganisms impact the development of the immune system itself and help in maintenance of critical physiological processes including digestion, metabolism or host defense [2]. There are many recent arguments supporting the role of the gut microbiota in the pathogenesis of rheumatic diseases (reviewed in[3]). Experiments in germ-free or gnotobiotic conditions have provided a deeper understanding of host–microbial interactions and demonstrated that gut bacteria can induce autoimmunity in genetically predisposed animal models [4]. In human, commensals may contribute to RA and SpA pathogenesis by altering mucosal integrity, which could facilitate their migration or those of their products into the joints, or by impairing the ability of the mucosal immune system to induce protective immunity [5].

The immune system, and notably the innate compartment, plays an essential role in the regulation of host-microbiota interactions. Recently, additional innate lymphocytes have been discovered named **innate lymphoid cells** (ILCs) in human and mouse. ILCs are early effectors which do not express specific TCRs directed against a precise antigen neither develop a clonal selection and expansion when stimulated and are distinguished from T and B cells of the adaptive immune response. Three groups of ILCs are now described: ILC1, ILC2 and ILC3 mimicking type 1 (Th1-dependent, which protects against intracellular microbes through activation of mononuclear phagocytes), type 2(Th2-depedent, which induces mast cell, basophil, and eosinophil activation, as well as IgE antibody production, thus protecting against helminthes and venoms) and type 3 (Th17- dependent which activate mononuclear phagocytes but also recruit neutrophils and induce epithelial antimicrobial responses, thus protecting against extracellular bacteria and fungi) responses of the

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[1] "The Mechanism of Action of Tofacitinib - an Oral Janus Kinase Inhibitor for the Treatment of Rheumatoid Arthritis." *Clin Exp Rheumatol* 34, no. 2 : 318–28.
[2] "A New Vision of Immunity: Homeostasis of the Superorganism," *Mucosal Immunology* 3, no. 5: 450–60,
[3] "Review: Microbiome in Inflammatory Arthritis and Human Rheumatic Diseases" *Arthritis Rheum* 68, no. 1: 35–45,
[4] "The Microbiome and Rheumatoid Arthritis" *Nature Rheum* 7, no. 10 : 569–78,
[5] "Commensal Gut Bacteria and the Etiopathogenesis of Rheumatoid Arthritis.," *The Journal of Rheumatology* 35, no. 8: 1477–97.

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adaptative immune system. ILC1 consists of NK cells and other interferon-γ producing innate lymphocytes characterized by expression of the transcription factors T-bet and/Eomes. ILC2 secrete 'TH2-like' cytokines under the control of the transcription factors GATA-3 and RORα. ILC3 includes several phenotypically distinct cells that express and require the transcription factor RORγt in order to produce notably the cytokines IL-17 and IL-22.

We therefore propose to study in experimental arthritis in mice the consequence of Jak inhibitor X ® treatment:

- on arthritis severity (control of efficacy)

- on mucosal immunity and especially on ILCs

- on gut microbiota

This project will benefit from complementarity between scientist with a unique expertise in both rheumatology and immunology and in the field of gut microbiota, having a direct access to corresponding laboratory skills. Dr David MOULIN, 39 years old, the coordinator of this project is senior scientist in UMR7365 IMoPA (Nancy). He is working in the field of rheumatology since his PhD 2005. DM has coordinated 15 grants (Fondation arthritis, SFR, BQR Région Lorraine). He is supervising a PhD student working on the microbiota influence on articular phenotype in deficient mice. He has gathered worldwide-recognized scientists in the fields of immunology and microbiota to run this project.

Koufany M *et al.* The peroxisome proliferator-activated receptor γ agonist pioglitazone preserves bone microarchitecture in experimental arthritis by reducing the interleukin-17-dependent osteoclastogenic pathway. **Arthritis Rheum**. 2013;65(12):3084-95.
Paquet J *et al.* Cytokines profiling by multiplex analysis in experimental arthritis: which pathophysiological relevance for articular versus systemic mediators? **Arthritis Res Ther.** 2012;14(2):R60.

Prof Harry SOKOL, Professor in the Gastroenterology (APHP), is the head of AVENIR Team, Gut Microbiota and Immunity, INSERM U1157/UMR CNRS 7203, UPMC, Paris. He has published over 100 original papers (h-index=28). He received an ERC starting grants in 2016. References

Sokol H et al. Fungal microbiota dysbiosis in IBD. **Gut**. 2016. pii: gutjnl-2015-310746.
Lamas N et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. **Nat Med**. 2016;22(6):598-605.
Sarrabayrouse G et al. CD4CD8 α α lymphocytes, a novel human regulatory T cell subset induced by colonic bacteria and deficient in patients with inflammatory bowel disease. **PLoS Biol**. 2014;12(4):e1001833.

Prof Gérard EBERL, the head of microenvironment and Immunity Lab at the Pasteur Institute (Paris) has proposed his scientific advice to characterize ILCs by FACS and IHC in this project. He is one of the most considered scientists in the field of mucosal immunity (h-index=46). References:

Eberl G. RORγt, a multitask nuclear receptor at mucosal surfaces. **Mucosal Immunol**. 2016 doi:10.1038/mi.2016.86.
Ohnmacht C et al. The microbiota regulates type 2 immunity through RORγt⁺ T cells. **Science**. 2015;349(6251):989-93.
Gury-BenAri M *et al.*. The Spectrum and Regulatory Landscape of Intestinal ILC Are Shaped by the Microbiome. **Cell**. 2016;166(5):1231-1246.e13.

Partners involved: UMR 7365 CNRS-UL IMoPA, collaboration with team "Micro-environnement et Immunité" (Inserm U 1224, Institut Pasteur-Paris), collaboration with team "

TERMS AND TENURE

The postdoctoral scientist will work in the Inflammation group of Team 4 of ***IMoPA Lab*** (see http://www.imopa.cnrs.fr/spip.php?article170 for publications) and in close collaboration with the team of Pr Gérard EBERL (https://research.pasteur.fr/en/team/microenvironment-and-immunity/) at **Institut Pasteur**.

The position is vacant from April 2019 on a full-time basis and is integrated in an ambitious funded project.

Minimal Duration of the contract: 12 months.

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HOW TO APPLY

Applicants are requested to submit the following materials:
• A cover letter applying for the position
• Full CV and list of publications
• Academic transcripts (unofficial versions are fine)

Deadline for application is ***2019 April 1th***. Applicants will be interviewed by an Ad Hoc Commission.

Applications are only accepted through email. All documents must be sent to ***David.moulin@univ-lorraine.fr***

JOB LOCATION

Main : Nancy, Lorraine, France

REQUIREMENTS

DOCUMENTS

- Curriculum Vitae - Your most recently updated C.V. including list of publications
- Cover Letter
- Statement of Research