Internship proposition 2025-2026

(One-page max)

Master 2 GP Medicine 4R (Repair, Replace, Regenerate, Reprogram)

Lab: INSERM UMR1229 Regenerative Medicine and Skeleton (RMeS), Nantes

Team: REJOINT Team (Regeneration and pathophysiology of joints

Name and position of the supervisor: VINATIER Claire (MCU) and MARANO Alexandre (post-doc)

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Candidate (if internship filled): TBD

Title of the internship: **Development of 3D *in vitro* models to study the role of CXCL12-CXCR4 axis in vascular invasion of articular cartilage**

Summary of the internship proposal:

Osteoarthritis (OA), is the most common joint disease impacting more than 500 million people worldwide. OA is characterized by inflammation of synovial membrane (synovitis), subchondral bone remodeling, and degradation of cartilage, leading to disability and ultimately pain. During OA, cartilage degradation is preceded by an abnormal increase in the number of hypertrophic chondrocytes through a process termed as “endochondral ossification like”. Briefly, endochondral ossification is a complex multiphasic process that normally took place during skeletal development. During this process, **chondrocytes undergoes maturation and become hypertrophic, thus, they will begin to secrete extracellular matrix degradation proteins (MMPs, ADAMTS) and pro-angiogenic factors (VEGFa) to initiate vascular invasion of cartilage**, resulting in its replacement by bone tissue.

Interestingly, new blood vessels formation has also been detected at osteochondral junction during OA development. More, in literature, strong correlations have been established between vascular invasion of cartilage and severity of OA patient score. Despite these observations, the exact mechanisms behind the step of vascular invasion remains largely understudied. Our preliminaries results suggest that hypertrophic chondrocytes may be implicated in the regulation of this step. *In vitro* experiments with Human Umbilical Vein Endothelial Cells (HUVECs) treated with conditioned medium indicated that hypertrophic chondrocytes can stimulate angiogenesis through the signaling axis CXCL12 (C-X-C motif chemokine ligand 12) - CXCR4 (C-X-C motif chemokine receptor 4). Moreover, it appears that CXCL12-CXCR4 axis is also promoting chondrocytes hypertrophy through a positive feedback loop. Thus, this M2 internship project aims **to gain insight regarding the role of CXCL12-CXCR4 in vascular invasion of OA cartilage.** We proposed to:

1. **Establish and characterize a robust 3D *in vitro model of vascular endothelium.*** To achieve this objective, HUVECs cell line will be used to develop spheroids through the simple method of cell droplet in a non-adherent surface. Thus, sprouting of the spheroid will be used to determine capacity of OA and healthy chondrocytes to promote angiogenesis through the use of conditioned medium
2. **Develop a robust 3D model of cartilage to assess role of CXCL12-CXCR4 in chondrocytes hypertrophy.** In this part of the project, we will produce pellet of healthy chondrocytes obtained from Bone marrows stromal cells (BMSCs) differentiation or primary chondrocytes retrieved from OA patients. Pellets will be incubated with either CXCL12, AMD3100 (CXCR4 specific inhibitor) or both to evaluate their effect on chondrocytes hypertrophy
3. **Determine the feasibility of HUVECs-chondrocytes spheroids fusion to develop a 3D coculture model.** Based on the results of the first two axis, we will consider fusion of HUVECs and OA/healthy chondrocytes pellets as a model that will partially reproduce vascular invasion of cartilage observed *in vivo*

Profile(s) linked to the project:

X Experimental Biology *(Recherche expérimentale)*

☐ Clinical Research *(Recherche clinique)*

☐ Research in data analysis (Recherche en analyse de données)