

Internship proposition 2026-2027
Master 2 GP Medicine 4R (Repair, Replace, Regenerate, Reprogram)



Lab: Inserm U1229 RMeS- Regenerative Medicine and Skeleton
Team: REJOINT groupe Age-OA

Name and position of the supervisor: Claire Vinatier and Romain Guiho

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Candidate (if internship filled):

Title of the internship: β -catenin O-GlcNAcylation as a potential therapeutic target in Osteoarthritis and Intervertebral disc degeneration

Summary of the internship proposal:

The most common degenerative joint diseases are intervertebral disc disease (IVDD) and osteoarthritis (OA). These two chronic conditions, which are both characterized by pain and an absence of a known cure, are highly prevalent in modern societies, particularly among the elderly and individuals with low levels of physical activity. These two diseases contribute significantly to work-related disabilities and long-term health burdens, with their prevalence expected to rise in the coming year, placing an increasing strain on both patients and society. This growing impact underscores the urgent need for improved management strategies, making it a key priority for the World Health Organization, as reflected in the Decade of Healthy Aging initiative (2021-2030).

Despite the anatomical, architectural, and embryonic differences in the tissues that constitute synovial and fibrocartilaginous joints, the degenerative processes in IVDD and OA share striking similarities. Both diseases exhibit overlapping tissue alterations, including degradation of the extracellular matrix and disruption of cellular homeostasis. Additionally, they involved dysregulations of common molecular pathways related to inflammation, autophagy, oxidative stress, apoptosis, and cellular senescence. Among these pathways, the Wnt/ β -catenin signaling is particularly affected. Aberrant activation of this pathway has been implicated in both disease progression by promoting tissue degradation and inflammation, ultimately disrupting the homeostasis of articular cartilage and nucleus pulposus, the central part of IVD, leading to fibrosis and calcification. Recent studies have revealed that β -catenin undergoes O-GlcNAcylation, a reversible post-translational modification that stabilizes it and enhances its interaction with EZH2, a methyltransferase whose activity is also involved in the catabolic processes of OA and IVDD. Moreover, high levels of O-GlcNAcylation have been detected in the degenerated tissues of patients with OA and IVDD. Based on this evidence, we hypothesize that O-GlcNAcylation, particularly of β -catenin, plays a key role in the pathological mechanisms underlying both diseases. Supported by a consortium with complementary expertise, the ArNAc project aims to: i) investigate the O-GlcNAcylation status of β -catenin and its molecular effects; ii) identify other O-GlcNAcylated proteins in human and murine OA and IVDD; iii) develop therapeutic tools specifically targeting the O-GlcNAcylation of relevant proteins such as β -catenin; and iv) evaluate the therapeutic potential of modulating β -catenin O-GlcNAcylation in preclinical models of OA and IVDD.

By integrating research on both OA and IVDD and focusing on the Wnt/ β -catenin signaling pathway, the ArNAc project seeks to deepen our understanding of the pathophysiology of these two diseases, identifying both shared and disease-specific regulatory mechanisms. Furthermore, ArNAc aspires to establish a pioneering therapeutic concept that aims to

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modulate the O-GlcNAcylation of key proteins, such as β -catenin, paving the way for novel treatment strategies for OA and IVDD patients.

Profile(s) linked to the project:

- Experimental Biology (*Recherche expérimentale*)
- Clinical Research (*Recherche clinique*)
- Research in data analysis (*Recherche en analyse de données*)

