Year 2022/2023

DOCTORAT BIOLOGIE BRETAGNE SANTE LOIRE

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☐ **Requested** ☒ **Acquired**	**Funding origin: ANR LabCom – HTL Region Pays de la Loire**
Thesis title: **Combining viscosupplementation and cartilage engineering to treat osteoarthritis**		3 keywords: **Osteoarthritis, Hydrogel, Cartilage engineering**
Unit / team: **INSERM U1229 – RMeS Lab (REJOINT TEAM)**		
Supervisor's name: **Claire Vinatier** Co-supervisor's name: **Vianney Delplace**		Phone number: **06 61 44 35 87** Email address: claire.vinatier@univ-nantes.fr vianney.delplace@univ-nantes.fr

Socio-economic and scientific context:

Osteoarthritis (OA) is the most common debilitating joint disease, affecting more than 500 million people worldwide. Together with the other musculoskeletal conditions, it is the leading cause of disability. OA is now known to be a multifaceted disease that can result from a variety of factors, including traumatic injury and osteochondral defects. Viscosupplementation, i.e., the intra-articular injection of a viscous solution of hyaluronic acid (HA) able to restore joint lubrication, has long been shown to be limited by the rapid clearance of HA. In parallel, hydrogels offering relevant bioactivity properties for cartilage engineering remain limited. In this context, we envisioned the development of a new generation of injectable hydrogels for long-term viscosupplementation and cartilage tissue engineering.

Working hypotheses and aims:

In the RMeS laboratory, we recently discovered and patented a new crosslinking method to synthesize injectable hydrogels that is based on the use of a reversible interaction between a boronic acid derivative and a polyol. In parallel, HTL Biotechnology, has successfully developed a new approach for the industrial production of heparosan, a natural bioprecursor of heparin that resembles HA but is more resistance to biodegradation. Based on these strong preliminary data, we hypothesize that an intra-articularly injectable boronic hydrogel made of heparosan would lead to prolonged viscosupplementation compared to HA viscous solutions. We also hypothesize that heparosan may exhibit growth factors (TGF-b, FGF,….) binding properties similar to heparin, which could be of interest for cartilage tissue engineering. The overall goal of this project is to develop a new generation of injectable heparosan-based hydrogels that allows both prolonged viscosupplementation in OA joint and improved cartilage engineering.

Main milestones of the thesis:

The student will first synthesize and optimize an heparosan-based dynamic hydrogel, using the reversible interaction between a boronic acid derivative and a polyol. As controls, an HA-based dynamic hydrogel, a silanized (non-dynamic) HA-based hydrogel and a silanized heparosan-based hydrogel will be designed. The cytocompatibility of the different hydrogels will be evaluated in vitro by measuring the viability (live/dead staining), metabolic activity (CCK-8 assay) and proliferation (PicoGreen assay) of encapsulated cells of interest (chondrocytes from OA patients). In collaboration with the Nantes Veterinary School (ONIRIS), the viscosupplementation benefits of these gels will be tested and compared in a small animal model of OA (rabbit), with a complete assessment of disease severity and cartilage matrix remodeling.

In parallel, the student will validate the growth factors binding properties of heparosan-based hydrogels. A series of heparosan-based hydrogels will be tested, investigating the effects of hydrogel composition (e.g., polymer content, degree of substitution, crosslinking density) on the growth factors binding properties. The ability of the selected hydrogels to support cartilage formation will be investigated, using either chondrocytes or mesenchymal stromal cells (MSC) in vitro and in vivo.

Scientific and technical skills required by the candidate:

We expect the candidate to have a strong biomedical engineering background, with some knowledge in organic chemistry, materials science (macromolecular synthesis and physicochemical characterization), and biology (cell culture, basic biological characterization). Ideally, the candidate would also have a previous experience in the field of hydrogel design and/or tissue engineering.

3 publications from the team related to the topic:

V. Delplace, M.-A. Boutet, C. Le Visage, Y. Maugars, J. Guicheux, and **C. Vinatier**, "Osteoarthritis: From upcoming treatments to treatments yet to come.," Jt. bone spine, vol. 88, no. 5, p. 105206, Oct. 2021, doi: 10.1016/j.jbspin.2021.105206.

E. Rederstorff, G. Rethore, P. Weiss, S. Sourice, S. Beck-Cormier, E. Mathieu, M. Maillasson, Y. Jacques, S. Colliec-Jouault, B. H. Fellah, J. Guicheux, **C. Vinatier**. Enriching a cellulose hydrogel with a biologically active marine exopolysaccharide for cell-based cartilage engineering. Journal of Tissue Engineering and Regenerative Medicine. 2017 Apr ;11(4):1152-1164. doi: 10.1002/term.2018.

C. Lesage, M. Lafont, Y. Maugars, P. Guihard, P. Weiss, J. Guicheux, **V. Delplace**, "Material-Assisted Bioengineering Strategies for Osteochondral Defect Repair", Advanced Science. 2022, 9, 2200050. doi: 10.1002/advs.202200050

National collaborations:

HTL Biotechnology, industrial partner, Javené (France)