PHD PROJECT	Multi-scale mechano-biological characterization in space and time of articular cartilage substitutes (MecaBioCart)
INSTITUTION	University of Montpellier, France
RESEARCH UNIT	Institute for Regenerative Medicine and Biotherapy (IRMB), INSERM/UM, CHU Hôpital Saint Eloi, Montpellier, France
GRADUATE SCHOOL	ED 168 - Sciences Chimiques et Biologiques pour la Santé (CBS2)
PHD SUPERVISOR	Emeline Perrier-Groult
PHD CO-SUPERVISOR	Patrick Cañadas, Cristina Cavinato

- **Summary of the project:**

This project focuses on the multi-scale mechano-biological characterization of articular cartilage explants and 3D bio-printed cartilage constructs, and on the development of experimental methods for biomechanical characterization using imaging and microscopy techniques. The characterization will evaluate the extracellular matrix and, most importantly, the activity of mesenchymal stem cells and chondrocytes in the temporal and spatial mechano-biological evolution of the tissues, with the aim of multi-scale numerical modeling of their behavior. The challenge is to fill the gaps in the evaluation of tissue repair strategies and to create a comprehensive database for numerical models, based on a strongly interdisciplinary scientific collaboration.

- **Location:**

The main research sites will be the Institute of Regenerative Medicine and Biotherapies (IRMB, INSERM/UM, CHU Montpellier) and the Laboratory of Mechanics and Civil Engineering (LMGC) at the University of Montpellier (St Priest Campus).

- **Candidate profile:**

The candidate should hold a Master's degree in biology, biomechanics, biomedical engineering, mechanics or materials, or similar fields. They should have skills in bioengineering, biomechanics, and imaging, as well as cell biology. Knowledge of 3D printing would be an additional asset. The candidate should demonstrate rigor, motivation, and autonomy in managing an interdisciplinary project shared between two institutes. Knowledge of 3D printing would be a plus.

- **Detailed description of the project:**

The articular cartilage performs various functions such as transmitting mechanical stresses and repeatedly absorbing shocks, while maintaining a continuously lubricated surface. The constituent cells of the cartilage, chondrocytes, are mechanically stimulated to maintain tissue homeostasis. Thus, the determination of the evolution of microscopic stresses required to activate cells in their native substrate or in tissue engineering substitutes (created by 3D bioprinting, for example), and their spatial and temporal relationships with the stresses exerted at the joint level, is crucial to understand the development of degenerative diseases such as arthritis or osteoarthritis [1] and for the development of strategies for repairing articular cartilage. However, knowledge of these multi-scale mechanobiological mechanisms remains insufficient as experimental and numerical means are limited; overcoming these limits and achieving this goal requires significant multidisciplinarity. The collaboration between the "Stem Cell Biology and Cartilage Therapies" group at the Institute of Regenerative Medicine and Biotherapy (IRMB) and the

"Biomechanics of Tissue and Cell Interactions and Organization" team at the Laboratory of Mechanics and Civil Engineering (BIOTIC/LMGC) has already led to the characterization of chondrogenic differentiation of stem cells using in vitro and in silico methods on microsphere models subjected to different mechanical stimuli [2,3]. This collaboration has extended to the characterization of 3D bioprinted biomimetic scaffolds with sophisticated structure [4]. However, in line with international state-of-the-art [5,6], we have not yet achieved an adequate ability to characterize the mechanobiological evolution of the cell-matrix-tissue system, which makes it difficult to create scaffolds capable of achieving rigidity and rupture deformations similar to those of native tissues, favorable for cellular metabolism.

The proposed approach involves the development of new experimental methods to combine biomechanical characterization and imaging.

The analyzed structures will include: (i) native tissue from the murine femoro-tibial joint, with its native cells, (ii) Stem cells and neo-tissue microspheres, (iii) 3D bio-printed cartilage constructs based on gelatin, alginate, and fibrin, and mesenchymal stromal cells [7,8] (Figure 1a).

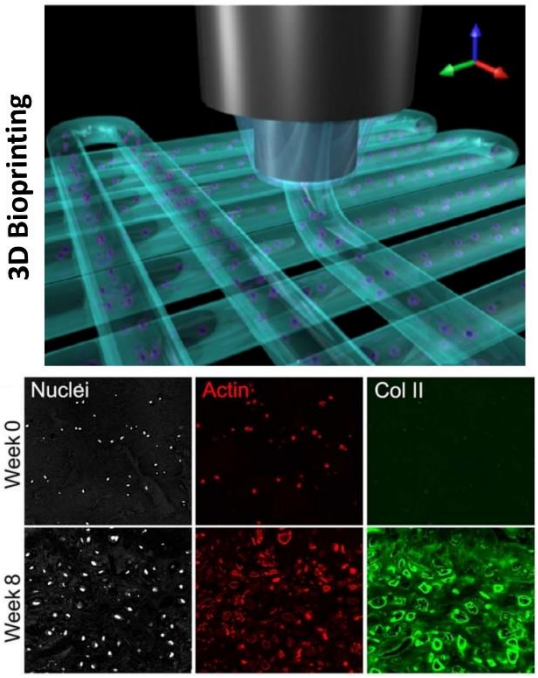

Figure 1 (a) Illustration of hydrogel deposition during 3D printing and (b) time-dependent microstructural remodeling in articular neocartilage constructs. Adapted from Constantini et al. and Onofrillo et al.[9,10].

The project consists of implementing biomechanical tests aimed at characterizing the biomechanical behavior of cell culture over long periods of time (Figure 1b). The tests will take into account the solid extracellular matrix, whether fibrous or not, as well as the fluid phase [11,12] under guidance by millimeter and micrometer level imaging [13,14]. The biomechanical behavior will be influenced by the structural properties of the materials undergoing remodeling. In parallel, the immunohistochemical properties of tissue components as well as genetic expression will be analyzed. This will allow us to analyze the ability of each type of structure to guide cells towards the chondrocyte phenotype and to specify key mechanical properties at the tissue and cellular scales, enabling optimization of this guidance. The objective of acquiring such a rich multi-scale database is to inform numerical models with a specific constitutive framework, motivated by our experimental observations, which will gradually incorporate cellular activity in a simulation of tissue growth and remodeling [15].

➢ Application:

A CV, a cover letter, and a transcript of grades must be sent to emeline.groult@inserm.fr and cristina.cavinato@umontpellier.fr before May 8th, 2023. Letters of recommendation in support of your application are also welcome.

➢ Bibliography:

[1] D.L. Robinson, M.E. Kersh, N.C. Walsh, D.C. Ackland, R.N. de Steiger, M.G. Pandy, J. Mech. Behav. Biomed. Mater. 61 (2016) 96–109.
[2] G. Dusfour, M. Maumus, P. Cañadas, D. Ambard, C. Jorgensen, D. Noël, S. Le Floc'h, Mater. Sci. Eng. C Mater. Biol. Appl. 112 (2020) 110808.
[3] N. Petitjean, G. Dusfour, P. Cañadas, M. Maumus, P. Valorge, S. Devic, J. Berthelot, E. Belamie, P. Royer, C. Jorgensen, D. Noël, S. Le Floc'h, Mater. Sci. Eng. C 121 (2021) 111800.
[4] T. Brossier, G. Volpi, J. Vasquez-Villegas, N. Petitjean, O. Guillaume, V. Lapinte, S. Blanquer, Biomacromolecules (2021).
[5] C.F. Guimarães, L. Gasperini, A.P. Marques, R.L. Reis, Nat. Rev. Mater. 5 (2020) 351–370.
[6] W. Wei, H. Dai, Bioact. Mater. 6 (2021) 4830–4855.
[7] M. Dufaud, S. Lilian, M. Maumus, M. Simon, E. Perrier-Groult, G. Subra, C. Jorgensen, D. Noël, Bioprinting 28 (2022) e00253.
[8] M. Simon, M. Maumus, B. Legrand, L. Sole, M. Dufaud, A. Mehdi, C. Jorgensen, D. Noël, G. Subra, Biomater. Adv. 147 (2023) 213321.
[9] C. Onofrillo, S. Duchi, C.D. O'Connell, R. Blanchard, A.J. O'Connor, M. Scott, G.G. Wallace, P.F.M. Choong, C.D. Bella, Biofabrication 10 (2018) 045006.
[10] M. Costantini, J. Idaszek, K. Szöke, J. Jaroszewicz, M. Dentini, A. Barbetta, J.E. Brinchmann, W. Święszkowski, Biofabrication 8 (2016) 035002.
[11] J.M. Patel, B.C. Wise, E.D. Bonnevie, R.L. Mauck, Tissue Eng. Part C Methods 25 (2019) 593–608.
[12] N. Petitjean, P. Canadas, P. Royer, D. Noël, S. Le Floc'h, J. Biomed. Mater. Res. A (2022) 1–23.
[13] F. Maier, C.G. Lewis, D.M. Pierce, Osteoarthritis Cartilage 27 (2019) 810–822.
[14] C. Cavinato, M. Chen, D. Weiss, M.J. Ruiz-Rodríguez, M.A. Schwartz, J.D. Humphrey, Front. Cardiovasc. Med. 8 (2021).
[15] E.K. Moo, M. Ebrahimi, S.C. Sibole, P. Tanska, R.K. Korhonen, Acta Biomater. 153 (2022) 178–189.