11th. World Congress on Computational Mechanics (WCCM XI)
5th. European Conference on Computational Mechanics (ECCM V)
6th. European Conference on Computational Fluid Dynamics (ECFD VI)
July 20 - 25, 2014, Barcelona, Spain

MICROMECHANICAL ENVIRONMENT OF MESENCHYMAL STEM CELLS IN A BIOREACTOR

Magali Cruel[1]*, Morad Bensidhoum[2], Pierre Becquart[2], Cécile Nouguier-Lehon[1], Hervé Petite[2] and Thierry Hoc[1]

[1]LTDS, CNRS UMR 5513, Ecole Centrale de Lyon, 36 av Guy de Collongue, F-69134 Ecully
magali.cruel@ec-lyon.fr ; cecile.nouguier@ec-lyon.fr ; thierry.hoc@ec-lyon.fr

[2]B2OA, CNRS UMR 7052, Université Paris Diderot, 10 av de Verdun, F-75010 Paris
morad.bensidhoum@univ-paris-diderot.fr ; pierre.becquart@univ-paris-diderot.fr ; herve.petite@univ-paris-diderot.fr

Key Words: *bone tissue engineering, flow-induced shear stress, mechanotransduction, computational fluid dynamics.*

The treatment of large bone defects raises important clinical issues. The current solution has several drawbacks and these have prompted an on-going search for alternative methods. Tissue engineering offers an attractive alternative. The principle is to use the patient's own stem cells extracted from bone marrow in order to generate bone tissue in vitro. The proof of concept was established in a large animal model of clinical relevance [1].

The three-dimensional biochemical and mechanical micro-environment of the cells is provided by a bioreactor. It is well known that the mechanical stresses, especially shear stresses, play a fundamental role in the growth of cells and tissues [2] through the so-called process of mechanotransduction. This mechanism links the mechanical loading to a biological response of the cells such as proliferation, differentiation, extracellular matrix production... The aim of this study is to optimize the design of this bioreactor in terms of mechanical stimulation of cells.

The first part of the present study consisted in the determination of the most efficient shear stresses in terms of cell response. For that purpose, mesenchymal stem cells (MSCs) seeded on different biomaterials (Plexiglas®, coral and hydroxyapatite) were submitted to different flow-induced shear stresses in a home-made device. The genic expression of mechanotransduction-related genes and the phosphorylation of the protein ERK 1/2 were analyzed. This enabled to identify a range of ideal shear stresses for cell stimulation of the order of 1 Pa, for all materials.

The second part of this work was dedicated to the numerical study of the current perfusion bioreactor used in the B2OA laboratory [3]. It is composed of a Plexiglas® tube filled with coral cubic particles on which MSCs are seeded. Culture medium circulates from bottom to top of the bioreactor at a flow of 10mL/min. Granular packings of cubes were generated with the software LMGC90® to model the actual assemblies of coral particles. Computational fluid dynamics simulations were performed using the software Comsol Multiphysics®. Other scaffold geometries and inlet flows were also computed. Velocity and wall shear stress

distributions were analyzed from the simulations (cf figure 1). It appeared that the initial configuration with cubic particles and a flow of 10mL/min created very low mechanical stimulation levels for cells, typically two orders of magnitude lower than the efficient shear stress found in the first part. This work highlights the necessity to change the scaffold geometry and the inlet flow.

These results enabled to determine a better three-dimensional configuration based on a new scaffold shape leading to a more homogeneous and appropriate loading of cells. These numerical results will then be tested experimentally: bioreactor cultures will be performed and followed by biological analyses of gene expression and protein production.

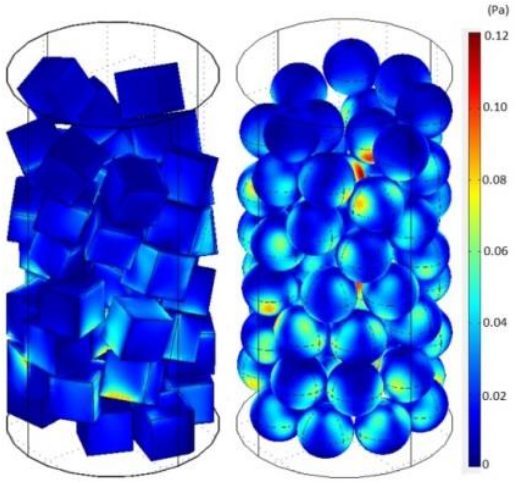

Figure 1: wall shear stress with an inlet flow of 10mL/min with two geometries of scaffolds (Pa)

REFERENCES

[1] H. Petite, V. Viateau, W. Bensaïd, A. Meunier, C. De Pollak, M. Bourguignon, K. Oudina, L. Sedel, and G. Guillemin, Tissue-engineered bone regeneration. *Nature Biotechnology*, Vol. **18**, pp. 959-963, 2000.

[2] T.N. McAllister, T. Du and J.A. Frangos, Fluid shear stress stimulates prostaglandin and nitric oxide release in bone marrow-derived preosteoclast-like cells. *Biochemical and Biophysical Research Communications*, Vol. **270**, pp. 643–648, 2000.

[3] B. David, D. Bonnefont-Rousselot, K. Oudina, M.C. Degat, M. Deschepper, V. Viateau, M. Bensidhoum, C. Oddou, and H. Petite, A perfusion bioreactor for engineering bone constructs: An in vitro and in vivo study. *Tissue Engineering*, Vol. **17**, pp. 505–516, 2011.