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Host laboratory:
Lab : Biosanté

Host group/team:
équipe BRM (biomimetism and regenerative medicine)

Title of the M2 research internship:

Biomimetic polymeric brushes presenting BMPs to induce stem cells osteogenic differentiation

Project summary:

Regenerative medicine for the repair of bone defects is an active field of research in particular since a big demographical challenge is the population aging. With aging, there is more bone resorption and less bone formation. This combination of bone mass deficiency and reduction in strength ultimately results in osteoporosis and fractures [1]. Today, several clinical trials have been approved to repair critical bone defects with biomaterials which naturally form bone (osteoinductive) [2]. In particular, biomaterial-based mimetic (biomimetic) approaches aim to mimic the natural extracellular matrix – the 3D environment surrounding cells – that supports and regulates cell growth, differentiation, and migration [3, 4]. In this project biomimetic materials will present bone morphogenetic proteins (BMPs) and adhesion ligands (cRGD) to activate cellular receptors and to potentiate the osteogenic differentiation [5] for an innovative future application in regenerative medicine. Our group has developed biomaterials that present specific components of the extracellular matrix to drive osteogenic differentiation of stem cells. We have shown that the glycosaminoglycan heparan sulfate (HS), which is present on all mammalian cell surfaces and in the extracellular matrix, regulates the activity of BMP2 [5, 6], a very potent osteogenic growth factor used on osteoinductive biomaterials. On the contrary, the glycosaminoglycan chondroitin sulfate, structurally very similar to HS, does not improve BMP2 signaling, probably due to the low affinity of its binding (paper under submission). Employing HS-presenting biomaterials for future *in vivo* applications is not a sustainable strategy since HS encounters short life time if placed in an injured site due to its degradation by the enzymes heparinases which are released by cells involved in the immunity response (Eming, Krieg, and Davidson 2007). GAG mimetics based on chemically engineered polymers have been developed to be injected in the injured site and to replace the degraded HS (Barritault et al. 2017). These polymers are however difficult to synthetize and remain difficult to access. Polymer brushes are an attractive approach for tissue engineering, thanks to their simple fabrication, extracellular matrix-like structure and in vivo stability (Kim and Jung 2016). Depending on their charges, surface density and length, polymeric brushes can be used to immobilize proteins and peptides (Krishnamoorthy et al. 2014). The group of J. Gautrot has developed an international track record in the synthesis, characterization and chemical functionalization of polymer brushes. His group focuses on the characterization of their physico-chemistry and interaction with proteins and cells, for application in regenerative medicine. The interaction of polymer brushes and the delivery of growth factors for regenerative medicine applications has received relatively little attention (Psarra et al. 2015; Ren et al. 2011). Together, we have already demonstrated that sulfonate polymer brushes mimicking sulfated GAGs, can bind BMPs stably, and we have identified key structural features regulating this binding. Moreover, we found that

this biomaterial is highly cell resistant, preventing adhesion. Although this is desirable to limit bacterial adhesion and infections [7] promoting specific adhesion and migration from tissue resident cells is essential to orchestrate tissue repair. In collaboration with D. Boturyn's group, who has developed peptide bioconjugation strategies, we propose to control cell adhesion by chemically functionalizing sulfonate brushes with different types of adhesion peptides. In this way, it will be possible to use these biomimetic materials for *in vitro* and, in the future*, in vivo* studies.

Keywords:
Polymeric brushes, bone morphogenetic proteins, glycosaminoglycans, osteogenic differentiation, adhesion peptides

Relevant publications of the team:

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M.H. Marchena, E. Lambert, B. Bogdanović, F. Quadir, C.E. Neri-Cruz, J. Luo, C. Nadal, E. Migliorini, J.E. Gautrot, BMP-Binding Polysulfonate Brushes to Control Growth Factor Presentation and Regulate Matrix Remodelling, ACS Appl Mater Interfaces 16(31) (2024) 40455-40468.

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