Contrat doctoral – ED Galilée

Titre du sujet : Development of a hybrid scaffold to engineer an in vitro model recapitulating the complexity of the blood vasculature

- Unité de recherche : LVTS Inserm U1148
- Discipline : sciences pour l'ingénieur
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- Domaine de recherche : bioingénierie cardiovasculaire
- Mots clés : tissue engineering, vascular graft, polysaccharide-based scaffold, polyvinylalcohol

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Vascularization of 3D models represents a major challenge of tissue engineering and a key prerequisite for their clinical and industrial application. The use of prevascularized models built from dedicated materials could solve some of the actual limitations, and would provide more in vivo-like perfusable tissue and organ-specific platforms. To fully recapitulate the properties of the tissue vasculature, a prerequisite is to consider the complexity of the vascular network, including the different types of vessels such as arteries, capillaries and veins. Current strategies frequently focus only in one type of vessel, mainly the capillaries. One of the challenges to reunite in one material the different types of blood vessels relate to their different mechanical properties, that demands the design of hybrid materials with adapted properties to match the different elasticity of the vessels.
The LVTS has large experience in the formation of vessels of small diameter, in the range of capillaries and venules, within polysaccharide scaffolds. The goal of this project will be to increase the level of complexity by engineering a polysaccharide scaffold that includes also an artery-like tissue. This will increase the physiological relevance of the engineered tissue and will allow to apply arterial flow using a microfluidic pump to mimic the arterial perfusion. The strategy chosen in the project involves developing such arterial-like vessel by associating two types of polymers, a polysaccharide which will be customized to avoid thrombogenicity and promote endothelialization, and the PVA (Polyvinyl alcohol – largely used in biomaterials) to ensure appropriate mechanical properties. This engineered artery will be integrated in a polysaccharide scaffold in which small diameter channels and micropores allow the organization of endothelial cells in capillaries and venules.

PROJECT METHODOLOGY AND WORK SEQUENCING:

Task 1: Manufacturing and testing of new vascular grafts (M1-M10):

Objective: Determine PVA and polysaccharide combinations to obtain the substitutes.

a) **Tubes manufacturing:** tube manufacturing will be performed using a novel process which is currently developed at U1148.
b) **Physico-chemical characterizations** of the grafts: FTIR, SEM, surface microscopies…

Task 2: Determination of the mechanical specifications (M3-M10 months):

a) ***In vivo* strain characterizations:** The strain will be compared to human small arteries (typically femoral arteries) in Bichat hospital (Paris) following a specific protocol.
b) **Biomechanical tests:** Oscillatory measurements at this peculiar strain will allow to obtain the storage E' and loss E'' moduli. This peculiar "in vivo-like" protocol, is to our knowledge highly original. The results will be compared to the values found in the literature for the same arteries.

Task 3: Integration in polysaccharide scaffolds (M8-18)

a) **Hybrid material:** A manufacture process will be established to obtain a polysaccharide porous scaffold with microchannels to host the capillaries and venules and integrating the arterial graft.
b) **Characterization of the hybrid scaffold** will include 3D imaging, mechanical properties evaluation, in vitro degradation, swelling.

Task 4: In vitro tests (M16-M33)

Co-culture studies: adhesion and proliferation of endothelial progenitor cells in the presence of support cells (smooth muscle cells for the arterial graft, pericytes for the venules). The extracellular matrix secreted by the cells will be evaluated through immunofluorescence and quantified using Luminex. 3D imaging of the immunostained constructs will be done with confocal and light-sheet microscopes. Haemocompatibility will be assessed through platelet adhesion and blood clot formation.

Task 4: Writing of thesis manuscript and scientific articles (3 months).

At least three communications (preferentially oral presentations) in national and international congress (Biomat, European Society for Biomaterials, EVBO conference) are planned.