Title: **Endothelial cell protection in xenotransplantation: Assessing the effect of multiple transgenes and the pathophysiological role of the plasma cascade systems.**

Introduction: The demand of organ transplantation has rapidly increased over the last 10-20 years because the supply of organs from optimal deceased donors has remained low and insufficient to meet the need. Xenotransplantation – the transplantation of organs between species, namely from pig to human – could provide a solution if immunological and other associated problems could be solved. However, organs from normal, wildtype pigs are rejected hyperacutely by binding human preformed antibodies to antigens expressed on the porcine endothelium followed by activation of the complement system and finally the coagulation cascade. One of the key mechanisms of hyperacute and acute vascular rejection in pig to-human xenotransplantation is the activation of endothelial cells (EC) that leads to vascular leakage, edema and thrombus formation. To overcome these limitations, pigs (over)expressing one or more human endothelial protective genes have been produced using genetic engineering techniques. Animals lacking the major antigen responsible for hyperacute rejection, Gal alpha-1,3 Gal, as well as expressing the human complement regulatory protein CD46 and/or thrombomodulin, have been produced and are currently studied to test whether these modifications may help to overcome the incompatibilities in the immunological and coagulation systems between pig and human.

Research work: The main aim of this study is to explore pig-to-human molecular incompatibilities *in vitro* with a particular focus on the complement and coagulation systems and the current genetic strategies to overcome these incompatibilities. Students will work with porcine EC in a xenotransplantation setting by using a microfluidic *in vitro* model. Porcine EC will be cultured into round diameter microfluidic channels, which mimic small vessels, and then perfused with human serum, plasma or whole human blood by using a peristaltic pump. Immunofluorescence staining will be performed in order to characterize the EC, quantify new transgenes and assess EC activation, complement deposition and coagulation activation.

References:
Cowan PJ, Rieben R. Transplantation. 2016; 100(3):485-6.
Bongoni AK et al., Transplantation. 2015; 99(10):2061-9.

Requirements: Students selecting this module should be interested in innate immunity, xenotransplantation and the plasma cascade systems. A background knowledge on complement, coagulation and fibrinolytic systems is surely a plus. The topic involves no animal experimentation.

Time-slots & # of students:
Elective module series I : 1-2 students
Elective module series II: 1-2 students

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