Master Project

A 3D microvascular *in vitro* model to mimic and predict transplant rejection in xenotransplantation

Cardiovascular Research Group, Department for BioMedical Research

Introduction / Aims:

Since more than 20 years there has been a chronic shortage of human donor organs for transplantation because the demand for organs is much higher than the availability. Xenotransplantation - the transplantation of organs between species, namely from pigs to humans, 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 human thrombomodulin have been produced and more genetic modifications are approaching thanks to the CRISPR-Cas9 technology.

Research Work:

After transplantation, graft EC are the first to come in contact with the recipient's blood. Students will work with porcine EC, either wildtype or genetically modified, using an *in vitro* microvasculature-on-chip model. Xenotransplantation is mimicked in this model by perfusing – in a closed, recirculating system – EC monolayers with human serum, plasma or eventually whole blood. Antibody deposition, cytokine secretion, as well as activation of the complement and coagulation systems will be the readouts. High resolution confocal microscopy will be used to visualize specific activation markers on the cell surface. Furthermore, the perfusate (serum, plasma or whole blood) will be analyzed using a multiplex-suspension array technique (Luminex system) to detect pro-inflammatory cytokines.

Relevance:

This project will allow the identification of a specific combination of transgenes which should be expressed by the xenograft endothelium in order to prevent rejection. Data from this project will directly influence the types of donor pigs used in preclinical pig-to-baboon xenotransplantation experiments performed by our collaborators in Munich.

Selected References:

Längin M et al., Nature 564(7736:430 (2018)
Sfriso R et al., Scientific Reports. 8:5898 (2018)
Sfriso, R., et al., Transplantation 102:S106 (2018)
Cowan PJ, Rieben R. Transplantation 100:485 (2016)
Bongoni AK et al., Transplantation 99:2061(2015)

Requirements:

Students selecting this project should be interested in xenotransplantation, advanced in vitro technologies, and innate immunity. A background knowledge on complement, coagulation and fibrinolytic systems is surely a plus. The topic involves no animal experimentation.

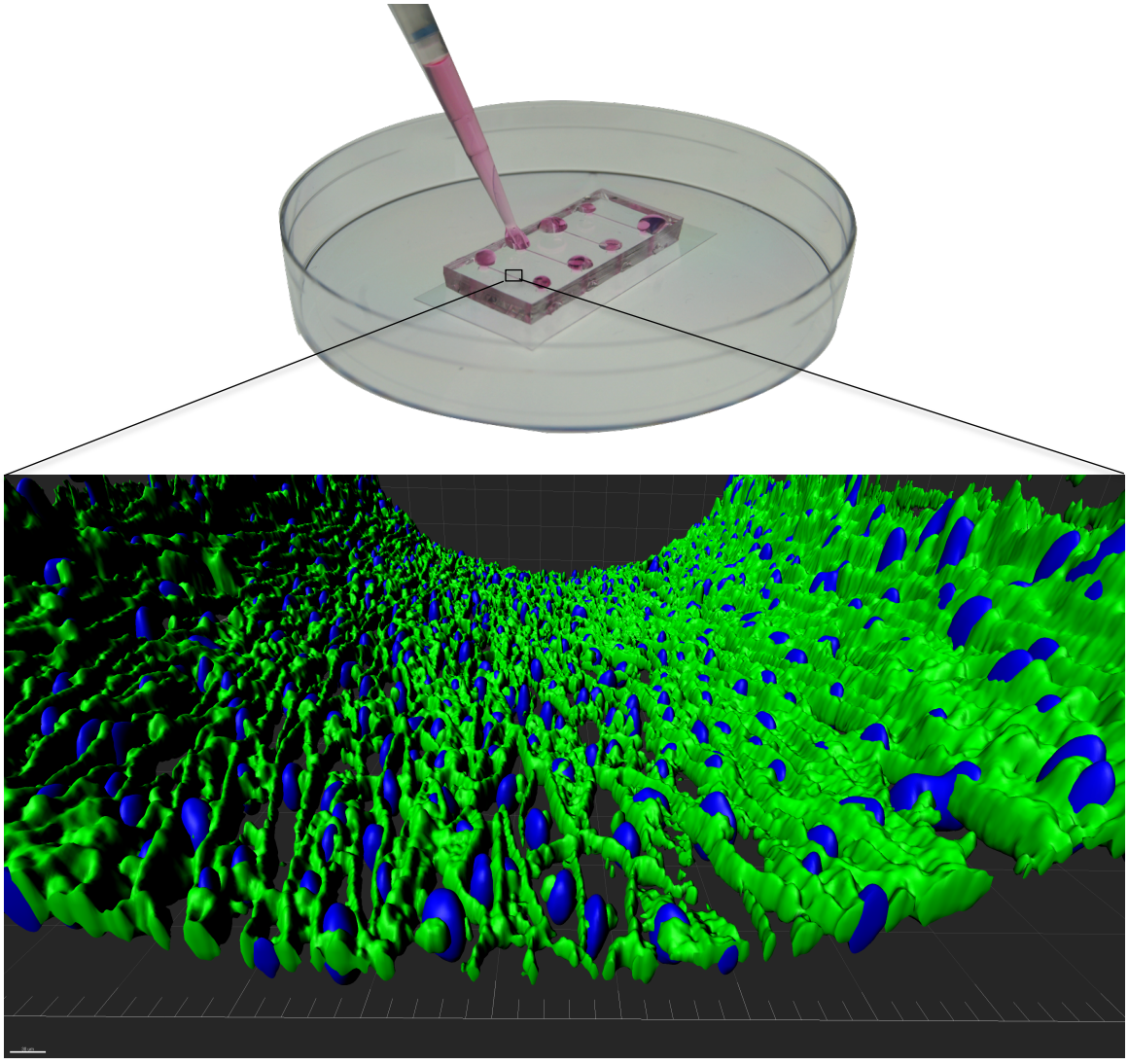
Specials:

Based on mutual agreement, a dissertation can be started following the master thesis work.

Contact:

Prof. Robert Rieben,
phone: 031 632 96 69
e-mail: robert.rieben@dbmr.unibe.ch

Department for BioMedical Research,
Cardiovascular Research,
Murtenstrasse 50,
CH-3008 Bern.



A) Microfluidic chip during cell seeding. B) 3D section of EC-coated microfluidic chip stained for VE-cadherin (green) and DAPI (blue) visualized under confocal microscope. Image processed using Imaris software. (Riccardo Sfriso)