Master Project

Evaluation of local, on-demand immunosuppression in a pig model of vascularized composite allotransplantation (hand transplantation)

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Introduction / Aims:

Vascularized composite allotransplantations (VCA), such as face- and hand transplantations, are emerging as novel therapeutic options for individuals who have suffered severe tissue loss. Currently, the widespread adoption of this "life-enhancing" rather than "life-saving" intervention is prevented by considerable side effects associated with the use of systemic immunosuppression. Local delivery of the immunosuppressive drugs might help to minimize the use of systemic immunosuppression, reducing adverse effects on kidneys and liver. To this aim, we designed an on-demand drug delivery system in which the immunosuppressive drug Tacrolimus is encapsulated in triglycerol-monostearate hydrogel (TGMS-TAC). Subcutaneously injected TGMS-TAC gel is able to release Tacrolimus in response to rejection episodes. Using hind limb allotransplantation in rats we could show that TGMS-TAC injected under the skin of the grafted limb significantly prolonged graft survival. Before translating this protocol into the clinical setting we will perform VCA in pigs and test the possibility to prevent rejection using TGMS-TAC. We hypothesize that, similar to what was demonstrated in the rat model, site-specific immunosuppression will be effective in maintaining VCA survival, promoting high intra-graft drug levels and reduced systemic toxicity.

Research Work:

As a model for limb transplantation, vascularized osteomyocutaneous flaps (a piece of tissue containing bone, muscle and skin which can be perfused using an artery and a vein) will be transplanted into the groin of pigs. TGMS-TAC will be injected under the skin of this transplant to prevent rejection. The grafts will be monitored for up to 90 days or until rejection. The master student will be involved in laboratory analyses of tissue and blood samples using confocal microscopy, FACS, and multiplexed suspension arrays (Luminex technique).

Relevance:

Successful completion of the proposed project would pave the way for clinical use of local, on-demand immunosuppression in VCA, particularly in hand transplantation. Local delivery of the drug directly to the allograft will lead to reduced (nephro)toxicity and may therefore lead to a paradigm shift in clinical immunosuppressive therapy in VCA.

Selected References:

Gajanayake T et al., Sci Transl Med 6:249ra110 (2014)
Dzhonova D et al., Transplantation 102:1684 (2018)
Dzhonova D et al., PLOS ONE:13:e0203409 (2018)

Requirements:

Students selecting this project should be interested in performing translational research in close collaboration with surgeon-scientists. Basics in immunology are a plus and the interest to learn state-

of-the-art immunological techniques is a must. The students will have the possibility to observe the surgical procedures in the OR and they will be involved in monitoring the transplanted pigs, which will live on a farm. The project will include education in animal experimentation (LTK 1 course) and special training to work with large animals. No prior knowledge in this field is required.

Specials:

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

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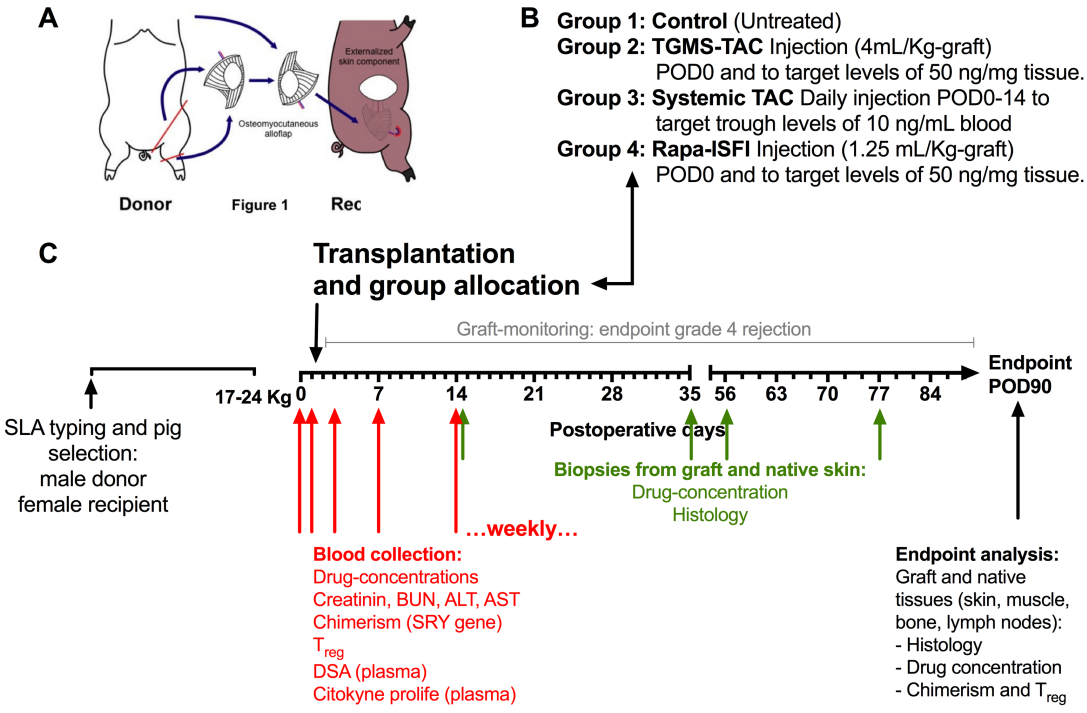

Experimental design and group description. A) Schematic diagram of the swine heterotopic VCA model11: An osteomyocutaneous flap is taken from the donor hind limb and transplanted to a subcutaneous pocket along the abdominal wall of the recipient. B) Group description C) Timeline of the experiment for a single recipient. Rapa-ISFI is an additional type of local immunosuppression system which is not mentioned in the text above.