

**Title:** Local delivered immunosuppression in vascularized composite allotransplantation

**Summary:** Vascularized composite allotransplantations (VCAs) such as facial and hand- allotransplantation 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 (SI). Local delivery of the anti-rejection drugs might help to minimize the use of SI, reducing global collateral or end-organ adverse effects. Our research is aiming at developing innovative delivery systems for site-specific immunosuppression in VCA. Using an *in vivo* model of VCA, the Brown Norway (BN)–to–Lewis rat hind-limb transplantations, we are currently evaluating the clinical efficacy of two different delivery systems: 1) hydrogels loaded with the immunosuppressive drug tacrolimus (TAC) and 2) *in situ* forming implants (ISFI) loaded with the immunomodulatory drug Rapamycin. The first system should have the advantage to release the drug “on-demand” under inflammatory condition, the latter to modulate the milieu within the graft promoting a “regulatory” and tolerogenic environment. After injection of local delivered immunosuppression into the transplanted hind-limb, the rats are routine monitored for evaluating the graft survival and measuring the plasma and tissue levels of the immunosuppressive drugs by ELISA or HPLC/MS. Several immunological parameters (e.g., presence of donor lymphocytes, number and phenotype of T-regulatory cells, presence of donor specific antibodies) are analyzed by FACS in peripheral blood and tissues (i.e., skin, bone marrow, spleen), and *in situ* by immunofluorescence and immunohistochemistry analysis. Moreover, mixed lymphocyte reaction (MLR) using Lewis responder-cells and BN stimulator-cells is preformed in order to analyzed the induction of tolerance to alloantigen. The effect of the therapies is also evaluated by analysis of complement and immunoglobulin deposition in the tissues by immunofluorescence and by analysis of the plasma and tissue levels of inflammatory and anti-inflammatory cytokines using bioplex analysis.

**Requirements:** Students selecting this module are interested both in transplantation immunology and in getting an introduction to state of the art methodologies for assessing graft survival and for characterizing the immunological response to local-delivered immunosuppression. The topic involves animal experimentation as well as organ experiments.

**Literature:** Gajanayake et al. Sci. Transl. Med. 2014; 6, 249ra110  
Schnider. et al. J Clin Dev Immunol. 2013; 2013:495212.

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

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