



Shriners Hospitals for Children®
Boston, Massachusetts

FACTORS INFLUENCING TOLERANCE/REJECTION OF SKIN IN FACE/HAND TRANSPLANTATION

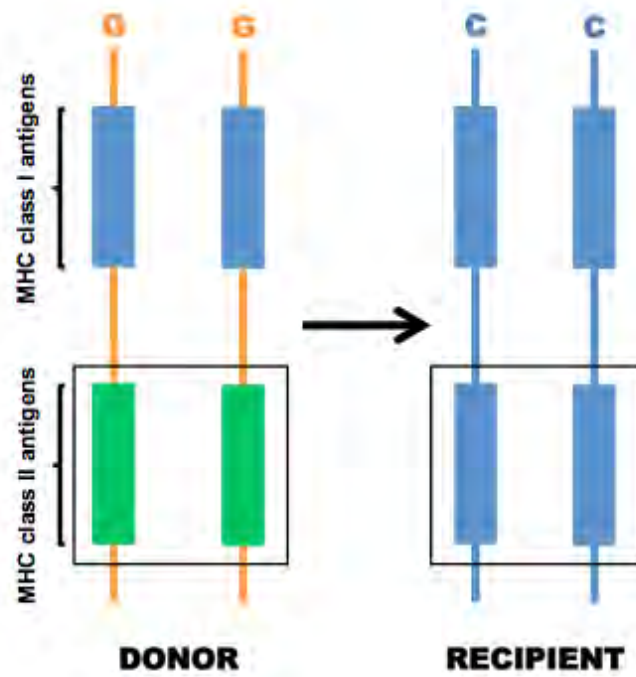
More than 100 upper extremity and 20 facial transplantations (vascularized composite allografts, VCAs) have been performed in patients with an unprecedented level of success following limb amputation, craniofacial trauma, and burns. Children are not exempt from such devastating injuries and complex congenital anomalies however and VCA represents an attractive treatment option. However, the current risks of life-long immunosuppression required severely limits application of VCA to the pediatric population.

Our group at Shriners Hospitals for Children – Boston was the first to demonstrate that the mixed chimerism approach can be successfully extended to large animal, pre-clinical models to achieve immunosuppression-free, indefinite survival of VCAs. Researchers used a special breed of swine for the studies that have since led to further insight with regard to the possibility of predicting acceptance or rejection of the skin component in VCAs through genetic analysis between the donor and recipient pairs. Having established the proof-of-principle model for mixed chimerism as a clinically-relevant approach for VCA tolerance, our current efforts are focused on translating our findings into clinically-applicable protocols to achieve tolerance of all components of a VCA (i.e. skin, muscle, bone etc.)

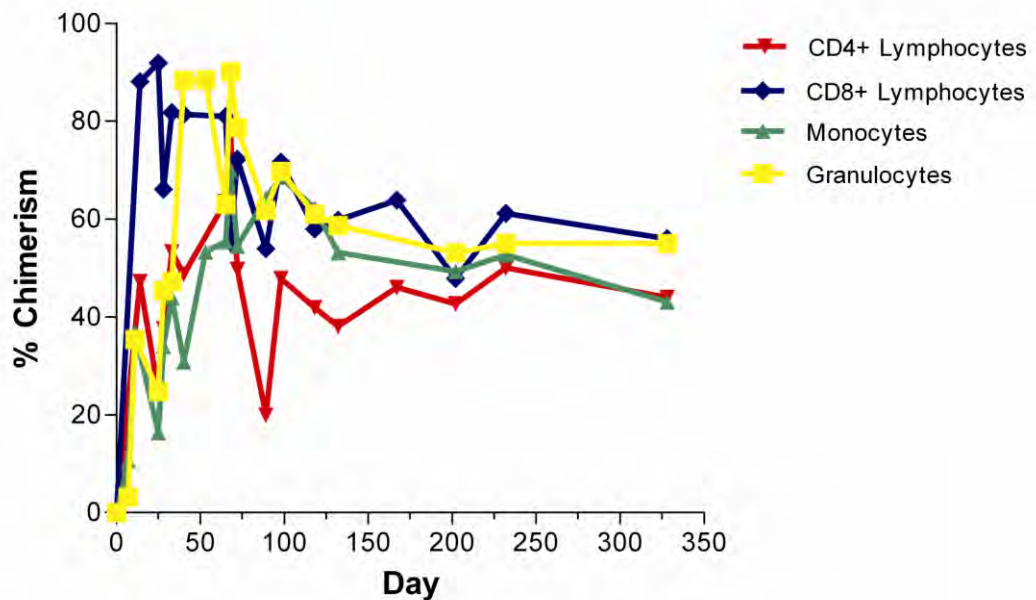
Recent Publications:

1. Madariaga ML, Shanmugarajah K, Michel SG, Villani V, La Muraglia GM 2nd, Torabi R, Leonard DA, Randolph MA, Colvin RB, Yamada K, Madsen JC, Cetrulo CL Jr, Sachs DH. Immunomodulatory strategies directed toward tolerance of vascularized composite allografts. *Transplantation*. 2015 Aug;99(8):1590-7.
2. Leto Barone AA, Kurtz JM, Albritton A, Mallard CA, Shanmugarajah K, Torabi R, Leonard DA, Randolph MA, Huang CA, Sachs DH, Cetrulo CL Jr. Effects of Transient Donor Chimerism on Rejection of MHC-Mismatched Vascularized Composite Allografts in Swine. *Vascularized Composite Allotransplantation*. 2015 Jan;2(1):1-8.
3. Shanmugarajah K, Leonard DA, Mallard C, Powell H, Albritton A, Randolph M, Harrington E, Sachs DH, Kurtz JM, Cetrulo CL Jr. MHC Class I Matching Between Donors and Recipients Influences the Skin Tolerance of Vascularized Composite Allografts. *Vascularized Composite Allotransplantation*. 2014 Dec;1(1-2):68.
4. Leonard DA, Kurtz JM, Mallard C, Albritton A, Duran-Struuck R, Farkash EA, Crepeau R, Matar A, Horner BM, Randolph MA, Sachs DH, Huang CA, Cetrulo CL Jr. Vascularized composite allograft tolerance across MHC barriers in a large animal model. *Am J Transplant*. 2014 Feb;14(2):343-55.
5. Leonard DA, Kurtz JM, Cetrulo CL Jr. Achieving immune tolerance in hand and face transplantation: a realistic prospect? *Immunotherapy*. 2014;6(5):499-502.
6. Leto Barone AA, Leonard DA, Torabi R, Mallard C, Glor T, Scalea JR, Randolph MA, Sachs DH, Cetrulo CL Jr. The gracilis myocutaneous free flap in swine: an advantageous preclinical model for vascularized composite allograft transplantation research. *Microsurgery*. 2013 Jan;33(1):51-5.

Hypothesis: MHC class I/class II antigen sharing between recipients and donors may influence VCA skin tolerance



MHC Class II Mismatched Chimeras Demonstrate Stable Mixed Chimerism



MHC class II mismatched chimeras demonstrate no significant clinical or histological signs of VCA rejection during the conditioning regimen or after cessation of immunosuppression.

