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Technical Abstract

Background: The overall goal of composite tissue allotransplantation(CTA) is improvement of quality of life (QoL). Correction of the tissue defect gives the patient a 'sense of self', as well as an integer body image and well-being, facilitating social interaction and enabling a patient to function within society. Ultimately, patients have to decide whether the risks associated with CTA justifies the benefits of a non-life sustaining hand and face allotransplantation. Overall, 70% of patients receiving a CTA reported a significant improvement in their QoL. It is therefore crucial to assess current immunosuppressive options, quantify their perceived risks and explore novel research methods attempting to shift the balance in favor of CTA. The solution to the risks and failures of CTA lies in the induction of donor-specific tolerance. Mixed chimerism is associated with donor specific transplantation tolerance and has been shown to effectively induce donor-specific tolerance to a variety of allografts such as skin, heart, lung, islet, trachea, esophagus in rodent and non-human primate animal models. The risk associated with bone marrow transplantation, include a pre-conditioning regimen which is not benign and graft-vs.-host disease (GVHD).

Over the last several decades, cells of the placenta have become the focal point for research involving regenerative medicine and cell replacement therapies. A proprietary amnion-derived multipotent progenitor (AMP) cells which are non-immunogenic and possess significant immunomodulatory characteristics will be examined. A recent study showed that in a rodent skin transplant model, AMP cells facilitate the engraftment of allogeneic bone marrow cells, thus promoting the induction of a durable mixed hematopoietic chimerism and tolerance to donor skin grafts.

Focus Area: Immune Rejection: Immune modulation approaches

Objective/Hypothesis: Co-infusion of an Amnion derived multipotent progenitor cell with donor bone marrow cells will induce durable chimerism and donor specific tolerance. Previous studies in a rodent transplant model has demonstrated efficacy of this approach.

Specific Aim: To determine if the addition of AMP cells can permit the achievement of durable chimerism in a well characterized large animal bone marrow transplant (BMT) model that otherwise achieves only transient chimerism without GVHD across MHC barriers

Study Design: We propose to study the effects of AMP cells on a non-myeloablative BMT protocol which achieves only transient chimerism. AMP cells will first be assessed at a high dose, and then de-escalated (Subaim 1a) in order to achieve life-long chimerism and tolerance to skin allografts placed on day+90 post BMT. Subaim 1b will focus on making the preparatory regimen clinically relevant for cadaveric donors. The skin graft will be placed within 24-36 hours after starting the regimen. Control animals will not receive AMP cells.

Impact: The data from small animal studies have shown the ability to establish a long lasting mixed chimerism and donor specific tolerance. The elimination of immune suppressing drugs will revolutionize composite tissues and solid organ transplantation. Furthermore, we envisage the technology being applied to the field of bone marrow transplants. The ability to do a complete bone marrow replacement with mismatched bone marrow will transform cancer therapy.

Translation: The non-human primate data will be used as part of a package to include tumorigenicity and safety/toxicology studies to seek an IND for a phase I clinical trial.

Military Relevance: This technology will be applicable to the treatment of extremity and craniofacial injuries as well as other types of injuries to solid organs and tissues such as abdominal wall and pelvic floor reconstruction. The technology will also allow for the transplantation of full thickness skin for enhanced burn care.