2 - Title: Intra-Bone Bone Marrow Transplant from Human CD47 Transgenic Swine as an Approach to Tolerance in Nonhuman Primates

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Background: Tolerance will be essential to optimal clinical xenotransplantation. Mixed xenogeneic chimerism achieves T cell, B cell and NK cell tolerance in human immune system mice. We aim to achieve mixed xenogeneic chimerism and tolerance using non-myeloablative intra-bone bone marrow transplantation (IBBMT) in baboons. Since pig bone marrow cells are rapidly destroyed by baboon macrophages, donors were transgenic swine expressing human CD47 (hCD47), which binds to SIRP-alpha on macrophages, transmitting a “don’t eat me” signal.

Methods: Four baboons (sp. papio hamadryas) received IBBMT from hCD47 and hCD55 transgenic GalT-KO swine following low-dose total body irradiation and thymic irradiation and induction with anti-CD20mAb and thymoglobulin. Maintenance immunosuppression was MMF, FK506, and anti-CD40mAb. Two animals (#3 and 4) also received anti-CD2mAb (LoCD2b) and cobra venom factor (CVF). 1-2x10^9 BM cells/kg were administered intravenously and intra-bone. Chimerism was determined by flow cytometry on peripheral blood,
and stained for baboon CD45, pCD45, pSLA1, pSWC3a, pCD3, pCD4, and pCD8. Non-Gal anti-swine antibody levels, mixed lymphocyte reactions (MLR) and ELISPOT responses were followed.

Results: Animals 1 and 2 demonstrated chimerism (>0.1% of pCD45+bCD45-) for <48 hours. Animals 3 and 4 demonstrated multi-lineage chimerism for approximately 20-30 days. MLR and ELISPOT did not demonstrate donor hyporesponsiveness, but anti-swine antibody levels decreased in animal 3 from the pre-transplant
levels. Studies in animal 4 are ongoing.

Conclusion: Enhancing addition cell depletion with anti-CD2mAb and inhibiting with CVF prolonged the
duration of porcine chimerism in baboons.