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Background: Despite improvements in short-term results following solid organ allotransplantation, long-term results have not been significantly altered over the past decade. Vasculopathy, infections, and malignancies that develop in chronically suppressed recipients of otherwise successful allografts and emphasize the limitations of current immunosuppressive approaches. Therefore, induction of specific transplantation tolerance remains a major goal of clinical organ transplantation. The long-term goal of our studies is to develop reliable clinical regimens that can induce allograft tolerance in various organ transplants without the need for immunosuppression. Previous work from the mentor's laboratory at the Massachusetts General Hospital, Boston, MA, has demonstrated that the combination of bone marrow plus organ transplantation (kidney) can lead to allogeneic tolerance in cynomolgus monkeys without permanent immunosuppression. This model is successfully adapted and translated to a clinical study¹ resulting in the first successful intentional clinical tolerance study. We now would like to apply this protocol to liver transplantation using a similar cynomolgus monkey model. Once successful this regimen will be translated to human liver transplantation to induce immunological tolerance without prolonged administration of immunosuppressive agents.

Material and Methods: Five pairs of feral monkeys (5 recipients and 5 donors, Charles River Laboratory, Houston, TX) will be selected based on their mismatches for both at class I and class II MHC loci using class I allele-specific mAb and proliferation assay in combination². They will be matched for ABO blood group antigens. Recipients will be conditioned as described, using thymic irradiation (7Gy) day -1, low dose total body irradiation (TBI 1.5 Gy days -6 and -5), equine anti-thymocyte globulin (ATGAM) 50mg/kg days -2, -1, 0, anti-CD154 mAb 20mg/kg days 0 and 2 or up to day 10. Cyclosporine will begin from day 1 and will be continued for 28 days following the transplant and then permanently discontinued. Liver transplantation will be performed using standard liver transplantation procedures for humans. Unmodified donor bone marrow (approximately 2×10^8 nucleated cells/kg) will be administered at the time of liver transplantation on day 0. Liver function will be followed by serial liver function tests (AST, ALT), LDH, bilirubin, coagulation parameters and serum albumin as well as protocol biopsies at regular intervals (in collaboration with the Department of Pathology). Recipients' white blood cells (WBCs) will be followed for multilineage chimerism (i.e. donor and recipient lymphocytes, monocytes and granulocytes) as previously described². Flow cytometry analysis will study T cell, B cell, and NK cell chimerism using donor class I-specific mAb in combination with anti-CD3, CD20, CD56 and CD16 mAbs and cellular proliferation assays will evaluate in vitro tolerance to donor antigen.

Statistical Analysis: Animal numbers have been discussed with Antai Wang at ICRC Biostatistics Department and found to be sufficient. Anticipated Result: It is expected that liver allografts will be accepted permanently without chronic immunosuppression and lead to tolerance to the organ.