Program in Therapeutic Cell Transfer for Transplant Tolerance: An Update

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Successful solid organ, vascularized composite tissue, and islet transplantation currently requires nonspecific immunosuppressive agents indefinitely for graft maintenance. Dependence on immunosuppression tempers the substantial benefit obtained from transplantation. The typical regimens are relatively complex and expensive. More importantly, they increase the risk of opportunistic infection and malignancy and have many non-immune side effects that hamper their tolerability. Specifically, the drugs cyclosporine and tacrolimus are nephrotoxic, a side effect of significant concern in renal transplantation. Steroids exacerbate osteoporosis and hyperlipidemia and cause avascular osteonecrosis. Both classes of agents worsen glucose tolerance and hypertension and are associated with cosmetic effects causing non-compliance. As such, methods of transplantation that lessen the dependence on chronic immunosuppression stand to reduce the risk and expense of transplantation. They must, however, also prevent rejection. The development of alternate therapies that help to minimize the need for lifelong immunosuppression or eliminate the need for drugs entirely through the induction of tolerance are, therefore, of great interest.

Therapeutic cell transfer for the control of the human immune system represents a compelling approach to reduce or eliminate the need for anti-rejection drugs. The Program in Therapeutic Cell Transfer in the Northwestern Comprehensive Transplant Center (CTC) is currently conducting paradigm-shifting clinical trials of tolerance induction using donor-derived stem cell infusions in kidney transplant recipients. We are also developing strategies to harness the immunomodulatory potential of regulatory T cells (Tregs) for the prevention of allograft rejection.

It has been known for over 50 years that bone marrow chimerism induces tolerance to transplanted organs, cells, and tissues. However, the requirement for close HLA matching and the toxicity of ablative hematopoietic stem cell transplantation (HSCT) has limited the widespread application of this approach. Only limited success has been reported using combined kidney and HSCT for tolerance induction, with reliable withdrawal of IS only possible in HLA-identical donor/recipient pairs. Achieving successful induction of donor-specific tolerance through durable chimerism in mismatched recipients, while avoiding graft versus host disease (GVHD), would represent a paradigm-shifting achievement for organ and tissue recipients. Since 2009, the CTC has conducted a Phase 2 trial of combined HSCT and living donor kidney transplantation for tolerance induction under my direction. Our unique approach depends upon the transplantation of donor-derived CD8+ T cell receptor negative (TCR-) facilitating cells (FC) along with donor stem cells into the transplant recipient the day after a kidney transplant. FC have been shown to promote stem cell engraftment and durable chimerism, and also prevent GVHD. This “FCRx” technology was developed by Dr. Leventhal’s collaborator, Dr. Suzanne Ildstad, who directs the Institute for Cellular Therapeutics at the University of Louisville. Twenty patients are currently enrolled in this trial, with 12 subjects having achieved durable donor chimerism and have been completely withdrawn from immunosuppression. The initial results of this ground breaking trial were recently published in Science Translational Medicine and Transplantation. Importantly, the FCRx technology has just been licensed by Novartis Pharmaceuticals, which intends to launch a Phase 3 trial in kidney transplant recipients in 2014. The FCRx approach to tolerance induction will hopefully become a “standard of care” treatment in selected kidney transplant recipients within the next decade.

Increasing evidence suggests that transplantation tolerance can also be achieved through peripheral mechanisms, particularly immune regulation. The observation that HSC have immunomodulatory potential is the foundation of another ongoing clinical trial of tolerance induction at Northwestern, under the direction of Joshua Miller, MD. In this trial, patients receive sequential infusions of donor derived HSC after an HLA-identical kidney transplant. Results of this trial were recently published in the Journal of the American Society of Nephrology. Fifty percent of patients enrolled into this trial have been successfully withdrawn from all immunosuppression. Mechanistic studies of subjects hold the promise of identifying a biomarker signature in the blood and urine of operational transplant tolerance.

Research over the past two decades has highlighted the ability of a particular subpopulation of T cells, termed Tregs, to suppress immune responses. For several years, the laboratories of the CTC have explored the use of Tregs to control organ transplant rejection. We have shown in preclinical animal models that a subgroup of these cells, CD4+CD25+Foxp3+ Tregs, can potently prevent rejection in a donor-specific manner, avoiding undesirable nonspecific immunosuppression. We have developed the capacity to isolate and expand human Tregs with potent suppressive capacity. We can now expand large quantities of Tregs in the laboratory for re-introduction into organ transplant recipients. Over the next calendar year we intend to launch first-in-human trials of expanded autologous Tregs in kidney transplant recipients. If successful, this would establish Treg Adoptive Cell Transfer (TRACT) in organ transplantation as a therapeutic modality uniquely introduced and available at Northwestern. Northwestern Memorial Hospital possesses a unique resource, the Matthew Center for Cellular Therapy (MCCT), which has been utilized to develop and validate the protocols for clinical scale isolation and expansion of human Tregs. A productive collaboration between Dr. Leventhal and Dr. Ann LeFever, Director of the MCCT, has been in place to achieve large scale isolation and expansion of clinical grade human Tregs from potential renal transplant recipients.

For more information on the Program in Therapeutic Cell Transfer, please contact the CTC at 312-685-3555 or ctc@northwestern.edu.