The long and winding road towards clinical transplantation tolerance

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The only currently effective treatment for end-stage organ failure is the use of an allogeneic organ transplant. However success is limited by the immune response to MHC molecules expressed by the graft (alloresponse), and by the morbidity and mortality associated with the immunosuppressive drugs that are used to control alloimmunity. The major goal in transplantation is to achieve tolerance. Data from experimental rodent models and from monitoring human transplant patients suggest that one of the keys to achieving and sustaining tolerance to an allogeneic transplant is the presence of regulatory T cells (Tregs). In additional experimental evidence and some clinical data now exist suggesting that adoptive therapy with Tregs is a successful strategy in promoting tolerance.

We have established in the laboratory protocols to expand Tregs in vitro either polyclonally or with specificity for the graft. The adoptive transfer of these cells in vivo in animal models have demonstrated that Tregs are safe and Tregs with specificity for the graft are superior compared to polyclonal Tregs, by injecting the same number of Tregs. However it is clear that to generate alloantigen-specific Tregs an initial high purity is necessary. We have recently moved to the GMP facility at Guy’s and by using the CliniMACS a purity of not more than 80% can be achieved. We have already obtained Treg lines from patients with either renal or liver diseases and we have demonstrated that after in vitro expansion they are functional and stable. We will start in the next few months two clinical trials in solid organ transplantation (kidney and liver).

Altogether the results obtained from our studies have important implication for cellular immunotherapy in preventing transplant rejection and autoimmune disease.