**Introduction: immunoregulation: harnessing T cell biology for therapeutic benefit**

Of the various organ systems within the human body, the immune system is arguably the most powerful. The potential to destroy specific targets is combined with an exquisite ability to discriminate between ‘self’ and ‘non-self’, where destructive activity is limited to foreign targets including pathogenic microorganisms, genetically disparate cells, and certain cancer cells. Occasionally, immune dysfunction results in self-antigens being recognized as foreign, and the crippling consequence of autoimmune disease bears witness to the power of immune attack. To be able to harness the power of the immune system would have profound implications for clinical application, including control of infectious diseases, targeting of tumour metastases, use of foreign tissue and organ transplants in tissue repair and organ replacement therapies, and conversion of autoimmune self-aggressive activity to a self-tolerant state. The fluid nature of the immune system within the blood and lymphatics would enable such therapies to be deeply penetrating, while the intrinsic memory of immunity would perpetuate the beneficial effects of therapy to prevent disease recurrence. Immune discrimination is qualified by the adaptive immune response where specificity is driven by antigen and the phenotypic fate of the responding lymphocyte is guided by micro-environmental cues to result in either aggression, or tolerance.

It was the study of inherited immune dysregulation that eventually revealed that expression of a single gene, foxp3, is able to orchestrate differentiation of the naive T lymphocyte into a regulatory T lymphocyte for immune tolerance. Three reports provided the first definitive evidence for foxp3 being an immune regulatory ‘master’ switch that is nodal for tolerance (Rudensky 2005), a discovery that has greatly advanced the quest to harness the immune response. Encoding a winged helix transcriptional repressor protein (illustrated on the front cover of the printed journal), the foxp3 gene has recently been genetically engineered to enable direct visualisation of regulatory T cells in vivo (Fontenot et al. 2005; Rudensky 2005). This issue of Philosophical Transactions of the Royal Society B picks up at the level of the regulatory T cell and integrates an immune regulatory theme with recent data on molecular events that regulate the developmental fate of T lymphocytes, on how such regulation might be harnessed in vivo, and on preclinical and clinical outcomes where extrapolation of our understanding of the immune response is providing novel immune-modulatory therapies.

Alexander Rudensky introduces the discovery of foxp3 (Rudensky 2005), and is followed by Fehervari & Sakaguchi (2005) who discuss the regulatory T cell and how CD4+ regulatory cells might be developed in vivo or ex vivo for therapy, identifying some major hurdles that need to be overcome prior to realizing the full potential of regulatory T cells in the clinic. Given that signalling through the immune synapse may be guided to produce donor-specific regulatory T cells, Meiri (2005) next reviews molecular communication at the level of the T cell immune synapse, where critical interactions between lipid rafts and the cytoskeleton trigger the downstream fate of the responding cell. The immune and nervous systems share many regulatory mechanisms, including the semaphorins that in neuronal development mediate positive and negative axonal guidance cues during migration. Takegahara et al. (2005) describe how semaphorins and their receptors also modulate homeostasis in the immune system and influence activation and differentiation of T lymphocytes. The TIM proteins represent another family of cell surface immune regulators and are remarkable for their selective influence on either Th1, or Th2, responses. Mariat et al. (2005) present TIM-3, TIM-2, and TIM-1 and explain how each plays a discrete role during development and termination of the adaptive immune response. My own contribution (Metcalfe 2005) develops a theory that the naive T cell is sensitive to ‘stemness’ signals that may guide development towards a relatively undifferentiated, non-aggressive regulatory phenotype; here fate determination signalling in the naive T cell, leading to epigenetic stabilisation of the regulatory T cell. I also introduce axotrophin, a neural stem cell gene recently discovered to have profound effects on T cells including T cell expression of foxp3. Axotrophin is thus a potential new target for therapeutic manipulation of the immune response. Harnessing molecular communication cues for immune tolerance has exploited the extracellular accessibility of functional molecules, using monoclonal antibodies or immune-constructs for therapy. The pioneering work of Stephen Cobbold’s group (Cobbold 2005) has shown that antibody-mediated interception of critical cell surface molecules is able to reprogram the mature immune repertoire for specific tolerance—not only to transplant antigens but also in autoimmune disease. An alternative use of antibody is to deplete target cells, and a fascinating story by Waldmann & Hale (2005) tells how CAMPATH was developed and eventually introduced as a successful therapeutic agent: a guiding light to us all.

The intrinsic regulatory mechanisms of the immune system in vivo may be influenced by therapy and Hickman & Turk (2005) describe how T cell depletion therapies trigger homeostatic control...
mechanisms to reconstitute the peripheral lymphoid compartment and, in so doing, may distort proper representation of naive and memory T cells. Awareness of this potential barrier to therapeutic tolerance induction has led the authors to suggest combination therapies to favour development of allo-responsive regulatory T cell populations. The overview by Hale et al. (2005) sets the scene for clinical transplantation tolerance by identifying developmental progression of therapies from rodent models through to preclinical non-human primates. Here the various routes towards tolerance induction together with their limitations in preclinical models are expertly woven together with early phase clinical work that has directly facilitated translational and proof-of-concept trials in man. A complementary overview by Knechtle (2005) discusses development of tolerogenic strategies in the clinic on three fronts: mechanistic, prospective clinical trials, and assays for tolerance. Mechanistically, microchimerism studies and the search for tolerance-inducing cells of donor origin are providing valuable data in the rare patient where clinical tolerance arises, usually following bone marrow transplantation. Clinical trials using co-stimulation blockade or T cell depletion—more recently by CAMPATH—are revealing that clinical use of calcineurin inhibitors can be reduced with concomitant reduction of associated nephrotoxicity. Indeed, it is possible that some patients might have become fully tolerant to their graft and here there is need for a molecular/cellular phenotype unique to transplant tolerance to allow their safe weaning off all immunosuppression. In bone marrow transplantation, an integral component is introduction of haematopoietic stem cells that develop into a competent, donor-derived immune system: when the graft is not of recipient origin, development of lethal graft versus host disease (GVHD) must be avoided. Blazar & Murphy (2005) review GVHD and approaches to avoid development of GVHD while preserving development of immune competence towards pathogens. By exploiting endogenous regulatory pathways revealed in molecular/cellular studies, a long-term aim is to guide the development of host-reactive T cells towards the regulatory tolerant phenotype that will be capable of specific suppression of GVHD.

Non-immune cell transplantation to treat disease is an attractive concept, especially for diabetes, and Roy Calne’s overview (Calne 2005a) sets in context the progression of our understanding of, and then treatment of, diabetes. Despite successful outcomes of both vascularized pancreas and pancreatic islet transplantation, the incidence of diabetes far outweighs availability of donors and there is a great need for alternative sources of functional islets. Here the emerging field of stem cells as a resource in regenerative medicine becomes highly pertinent. Similarly, use of stem cells or precursor cells as a potential source of graft for demyelinating neuronal disease is being explored and the studies reported by Tepavčević & Blakemore (2005) reveal that tissue matching may not be a prerequisite for transplantation of oligodendrocyte precursor cells. Here, inflammation associated with the allo-immune response has a stimulatory effect on remyelination, including remyelination by endogenous cells that then take over the repair process. In his summary, Calne (2005b) presents a lively personal insight into the development of clinical transplantation ranging through the surgery, the sources of organs, different eras of therapeutic strategy, and finally bringing us back to the ethical and legal matters that remain to be addressed.

In summary, these transactions draw together a range of disciplines that cross-inform each upon the other, where we foresee an enabling interaction towards harnessing fate determination in T cell immunity for therapeutic manipulation. After drawing up a wish-list of contributors, both my co-editors and I were delighted when so many responded positively and we warmly thank all who have joined us in this endeavour.

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REFERENCES


