

Indices of Tolerance – Aims and Objectives

Renal transplantation can revolutionise the quality of life and life expectancy of patients with end stage renal failure. However, such patients are required to take immunosuppressive medication for the rest of their lives. These drugs have a significant incidence of adverse effects, including infection and malignancy, which may be life-threatening. In addition, these drugs are very expensive.

However, there are anecdotal reports of occasional patients who have discontinued their immunosuppressive drugs without losing their transplants. These patients are described as being “tolerant” of their grafts. Unfortunately, there has been no reliable way of differentiating these individuals from the majority who have discontinued their medication and subsequently rejected their grafts.

Recent advances in basic immunology have permitted the development of targeted, *ex vivo* tests of immunological reactivity whose clinical applicability has been demonstrated in a number of contexts. However, there remains a “validation gap” to be bridged which will allow these tests to be transformed into tests appropriate for the routine prospective management of transplant patients.

There are two ways in which this project may bridge that gap. First, it will bring together a range of several different *ex vivo* approaches to the analysis of immunological tolerance in carefully defined patients. Second, by applying these tests, to spontaneously tolerant patients who are taking no immunosuppressive drugs, it will be using a group of patients who are ideal to address this question but who are too rare to be studied in anything other than a large multi-centre project such as this.

The use of these tests in this group of patients will lead to the validation of the concept of an “immunological fingerprint” of the tolerant state. So successful has recent progress in transplant immunotherapy been that there is now a realistic expectation of being able to manipulate the immune response towards immunological tolerance. Hence, our demonstration of the validity of these tests in identifying the spontaneously tolerant state will also allow us to use them to identify potentially successful therapeutic manipulations that will generate tolerance. Real clinical advantage will accrue when these tests can be applied prospectively to patients, to identify those in whom discontinuation of immunosuppressive medication will not result in rejection.

Once the blood samples have been collected and sent to the relevant centres the following tests will be carried out:

- The frequency of cells specific for donor antigen, using three distinct tests: limiting dilution analysis, ELISPOT and CFSE proliferation,
- Donor-reactivity in a trans-vivo delayed type hypersensitivity assay
- Frequency of T cell receptor gene usage and length polymorphism,
- Expression of activation markers and transcription of cytokine genes using real-time PCR and
- Transcription of immune-related genes by cDNA array chip analysts.

All these assays will be performed in parallel on samples from control non-tolerant patients. Not all the tests will be carried out in the same centre: each lab will perform individual testing and the results will be collated at King's College . This information will then be integrated with a view to defining an “immunological fingerprint” of transplantation tolerance. This will then be disseminated to propagate awareness of and progress in applicability of these assays amongst interested groups. As a result of this study, we hope to undertake a trial of drug withdrawal in patients deemed to be tolerant.