TRANSPLANTATION STUDIES

Acute rejection still remains a major impediment to the success of transplant surgery and currently available methods often fail to detect rejection until late stages. Available diagnostic methods include the evaluation of clinical presentation, biochemical parameters, and tissue biopsies. Several immunosuppressants are currently available including the calcineurin inhibitors cyclosporine (CsA) and tacrolimus, the antiproliferatives sirolimus and everolimus, and anti-metabolites such as mycophenolate mofetil. Although its use was a landmark in allograft rejection treatment, cyclosporine has been found to result in nephrotoxicity and ultimately in chronic allograft dysfunction (CAD). Partly owing to this, immunotherapy now includes the use of multi-drug regimens to take advantage of synergistic effects of drugs and to lower dose requirements and hence decrease side effects.

Current strategies to overcome CI toxicity include stopping or reducing CsA and switching to sirolimus, everolimus, or mycophenolate mofetil. As new drugs continue to be developed, the identification of surrogate markers for detection of the onset of chronic nephrotoxicity will be essential. More detailed knowledge of the biochemistry underlying the toxicity of immunosuppressants alone and in combination will also be critical. We are employing proteomics to fulfill both of these needs; identifying biomarkers while providing crucial information regarding biochemical mechanism through identification of individual proteins and protein pathways involved in nephrotoxicity.

In comparison to biopsies, which are the best diagnostic alternative available today, biomarker analysis is non-invasive and is not associated with any risk for the patient. The development of a biomarker as a tool to diagnose and monitor immunosuppressant toxicity will also result in a better understanding of the biochemical mechanisms involved in immunosuppressant toxicity and the identification of diagnostic markers.