JAMES RENNIE BEQUEST

REPORT ON EXPEDITION/PROJECT/CONFERENCE

Expedition/Project/Conference Title:
Keystone Symposium: Mechanisms of Immunologic Tolerance and its Breakdown

Travel Dates: 7-12 January 2003.....

Location: Snowbird, Utah, USA.....

Group Member(s): Kristin Hochweller and Mandy McGeachy.....

Aims: To be updated on current research in the field and present our work in the form of a poster.....

OUTCOME (not less than 300 words):

In accordance with the original idea of the Keystone Symposia, which is to "organize meetings on biomedical and life sciences in secluded, relaxed atmospheres that encourage interaction and networking", this Keystone meeting was held in Snowbird, a small skiing resort about an hour drive from Salt Lake City. The conference aimed to discuss tolerance and its breakdown, but with emphasis on bridging the gap between basic, pre-clinical and clinical studies. The first couple of days therefore focused on the mechanisms of tolerance induction, both peripheral and central, and how these may be breached to allow autoimmunity. Maintenance of tolerance by regulatory cells was a popular topic throughout the meeting, and an extra evening workshop reflected the large number of abstracts on these now-favoured cells. Towards the end of the week, the focus shifted towards mouse models of human autoimmune diseases as a way of elucidating both mechanisms of tolerance failure and intervention strategies. Finally, several exciting clinical studies were described, reminding us all of the ultimate goal of research in this field.

Although T cell tolerance was the focus of the majority of talks in the first plenary session, Mark Shlomchik (Yale University, USA) gave an interesting start to the meeting by discussing the regulation of autoreactive, rheumatoid factor producing B cells in an Ig transgenic system. He described how, in autoimmune-prone mice, a chronic autoimmune state may be the result of defective B cell activation outside germinal centres. Moving on to a molecular level, Josef Penninger (IMBA, Austria) and Garisson Fathman (Stanford University, USA) described newly identified genes, which appear to be required for T cell tolerance induction (*cbl-b* and *grail* respectively), while Mark Anderson (Joslin Diabetes Centre, USA) presented *aire*, a gene which controls the transcription of organ-specific antigens in the thymus. Defects in expression of these genes result in a variety of autoimmune symptoms. The first day ended with a plenary talk by Mark Jenkins (University of Minnesota, USA). He summarised years of research employing the ovalbumin-specific T cell adoptive transfer system, which was originally developed in his lab, and gave a great overview of the fate of naïve T cells after injection of soluble antigen with or without adjuvant.

After a desperately needed night of sleep, the second day moved on to the genetics behind a variety of autoimmune diseases. The importance of allelic variations in a number of autoimmune conditions, for example diabetes, lupus, asthma and allergies, was discussed. One of the recurring themes during the meeting was the effect of specific gene knock-outs on immunity and tolerance. Christopher Goodnow (Australia National University, Australia) described in the second plenary talk how researchers are trying to identify genes solely required for either immunogenic or tolerogenic signalling. His talk followed on well from the first day, in which such genes were also described. Identification of these genes, for example *unmodulated*, which is required for immunogenic signalling only, may lead to important new advances in the development of pharmaceutical agents which specifically block the immunogenic signalling, or enhance the tolerogenic signal, to prevent or treat autoimmune diseases.

These days no discussion on tolerance would be complete without regulatory T cells, and there were several excellent talks and posters on this interesting topic. Using time-lapse confocal microscopy, the "Kiss of Suppression" by $CD4^+CD25^+$ regulatory T cells on stimulated T cells in culture was beautifully demonstrated by Ethan Shevach (National Institue of Health, USA). Fiona Powrie (Sir William Dunn School of Pathology, UK) discussed the ability of $CD25^+$ cells to suppress inflammation by acting directly on cells of the innate immune system using a T-independent model of colitis, and also showed the potential therapeutic benefits of these cells to ameliorate established colitis in a T-dependent model. The role of cells other than T cells to regulate immune responses was not forgotten, with NKT cells (Terry Delovitch, John P. Roberts Research Institute and University of Western Ontario, Canada) and NKDC in diabetes (Matthias von Herrath, La Jolla Institute for Allergy and Immunology, USA), and even B cells in experimental autoimmune encephalomyelitis (EAE) (Stephen Anderton, University of Edinburgh, UK).

Plenary speaker Anne O'Garra (The National Institute for Medical Research, UK) elaborated further on the generation and functions of IL-10 producing TR1 cells, with insightful data on their relation to TH1/TH2 cells. Using vitamin D3 and dexamethasone to induce TR1, she showed that by blocking TH1- and TH2-inducing cytokines a far purer population of IL-10 producers could be obtained. Also, neither TH1- nor TH2-specific signalling pathways appeared to be activated in TR1 cells.

The discussion then switched to mouse models of autoimmunity and development of therapeutic intervention strategies. David Scott (American Red Cross, USA) described the IgG carrier system for induction of tolerance to antigen incorporated in IgG fusion proteins. This system was shown to have beneficial effects with MBP in EAE, and was also used by Rachel Caspi (NIH, USA) who demonstrated its efficacy in preventing experimental autoimmune uveoretinis (EAU) induced by immunisation with antigen as well as by transfer of activated cells. Caspi also showed data from elegant experiments comparing the roles of peripheral versus central tolerance in mouse strains susceptible or resistant to EAU, concluding that central mechanisms play a more important role than previously thought. Anne Cooke (Cambridge University, UK) switched tack to describe the perhaps undervalued benefits of nematode infections in mice (and man). Finally, the induction of TR1 cells by intranasal administration of peptide was described as a possible mechanism for the efficacy of peptide therapy by David Wraith (University of Bristol, UK). A workshop of short talks allowed further discussion on the various approaches to immunotherapy, and their potential (or lack thereof) to treat human disease.

Having spent the week discussing potential strategies for treating or preventing autoimmunity, the final session looked at studies going on in human disease, mainly diabetes and multiple sclerosis (MS). David Hafler (Harvard Medical School, USA) described an innovative admixture study to find genes associated with MS susceptibility. His group looked for European-ancestry genes common to African people with MS, based on the very low incidence of MS in

people of African heritage compared to Europeans. Two studies demonstrated different approaches to the treatment of Type 1 diabetes: Jeffrey Bluestone (UCSF, USA) showed that anti-CD3 given at the onset of clinical symptoms significantly delayed further β cell destruction, while David Harlan (NIH, USA) gave an interesting talk on "The Edmonton Experience" of islet cell transplantation. This session was an exciting reminder of the types of therapeutic applications coming out of studies in the lab.

The meeting ended on a high note, when Hugh McDevitt and Ray Owen were honoured with the Special Life Time Achievement Award. Unfortunately, only Ray Owen was able to accept the award in person, but his entertaining portrayal of immunological tolerance in its infancy was an excellent reminder of how far we have come since Edward Jenner developed the first vaccine. The organisers, David Scott, Rachel Caspi, Anne Cooke and Terry Delovitch, provided an excellent meeting, which left us travelling home enthusiastic, motivated and with a positive attitude towards the potential benefits our research may at some time have for future therapy of autoimmune diseases.