

Meeting report

## Unraveling immunology

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A report on the 11th International Congress of Immunology, Stockholm, Sweden, 22-27 July 2001.

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The triennial International Congress of Immunology is the largest of its kind in the world, and the eleventh meeting was attended by some 5,500 delegates and 600 speakers. Almost all current areas of immunology were represented in detail, but a downside to a conference of such size was the necessity for parallel sessions and the possibility of being able to attend only a small proportion of the talks on offer. Presentations on regulatory T cells and the different subsets of dendritic cells were amongst the highlights, and I will attempt to present an overview of talks that discussed these cell types, as well as some other outstanding presentations about, for example, the immunological synapse.

### The return of the regulatory cell

Judged by the level of interest and discussion, it became readily apparent that studies of regulatory T ( $T_{reg}$ ) cells have become one of the hotbeds of immunological research. Although there were not that many talks dedicated purely to  $T_{reg}$  cells, many presenters featured them in some form or another, often trying to accommodate  $T_{reg}$  cells into their own particular hypotheses. Initially described in the early 1980s,  $T_{reg}$  cells languished for many years at the periphery of immunology, with many scientists doubting their very existence. The advent of new experimental approaches has, however, contributed to something of a renaissance for this cell type.

$T_{reg}$  cells are a subset of the  $CD4^+$  T-helper cell lineage and appear to have potent immunoregulatory functions; there is good evidence to suggest that these cells may play an important role in the maintenance of peripheral tolerance, which renders lymphocytes unresponsive to self antigens, and in the control of normal immune responses. One particularly

informative system for the study of  $T_{reg}$  cells has been a model for inflammatory bowel disease (IBD) developed by Fiona Powrie (Dunn School of Pathology, Oxford, UK). Using this model, Powrie has shown that the so-called 'adoptive' transfer of live cells expressing CD4 and high levels of the RB isoform of the tyrosine phosphatase CD45 ( $CD4^+CD45^{RB^{high}}$  cells) to a syngeneic recipient induced IBD in mice. In contrast,  $CD4^+CD45^{RB^{low}}$  cells were non-pathogenic; moreover, their co-transfer with  $CD45^{RB^{high}}$  cells actually suppressed the induction of IBD, and for this reason they were postulated to be  $T_{reg}$  cells. Other workers, foremost among them Shimon Sakaguchi (University of Kyoto, Japan), have shown that  $T_{reg}$  cells express CD25, a component of the interleukin-2 (IL-2) receptor, and CD152 (CTLA4), a receptor for the co-stimulatory molecules B7.1 and B7.2.

There is still some controversy over how  $T_{reg}$  cells actually exert their effects, with different workers pointing to cytokines and/or cell contact as the key requirement. The role of CD152 in  $T_{reg}$  cells has recently been the subject of intense research, with some reports suggesting that it signals their growth and/or differentiation whereas others suggest that it is necessary for the ability of  $T_{reg}$  cells to influence their targets. Powrie and one of her co-workers, Simon Read (Dunn School of Pathology, Oxford, UK), gave interesting talks addressing this question. Using the IBD model, they demonstrated that the administration of anti-CD152 antibody *in vivo* abolished the protection offered by  $T_{reg}$  cells. To further investigate the importance of this molecule, they examined the activity of  $T_{reg}$  cells isolated from CD152-knockout mice. Curiously,  $T_{reg}$  cells from the knockout mice functioned just as effectively as their wild-type counterparts. This somewhat paradoxical situation would, on the face of it, suggest that CD152 is both important and dispensable for  $T_{reg}$ -cell function. The issue may be resolved by proposing that CD152 is not in fact required for the effective differentiation and/or regulatory ability of  $T_{reg}$  cells, but that the anti-CD152 antibody may interfere with  $T_{reg}$ -cell function *in vivo* (for example, by the depletion or transmission of a component of a

negative signal) or, alternatively, might affect a functionally relevant population of CD152<sup>+</sup> cells in the host. In a workshop talk, Lukas Cederbom (University of Lund, Sweden) asked whether CD152 could instead exert its regulatory role by direct interaction with its costimulatory molecule ligands B7.1 and B7.2 (CD80 and CD86) on antigen-presenting cells (APCs) and thus alter their function. He showed that mixture of APCs (in this case dendritic cells, DCs) with CD4<sup>+</sup>CD25<sup>+</sup> T<sub>reg</sub> cells resulted in the surface downregulation of CD80 and CD86 and rendered the APCs ineffective at subsequently stimulating T cells. Even fixed DCs could be functionally modified by pre-treatment with T<sub>reg</sub> cells, raising the interesting possibility that T<sub>reg</sub> cells may be actively scavenging these costimulatory molecules from the APC surface.

A final talk on T<sub>reg</sub> cells was given by Toshiko Sakihama (University of Kyoto, Japan). She showed that, in mice, the transfer of isolated CD4<sup>+</sup>CD25<sup>+</sup> cells was able to prevent an alloresponse to skin transplants from allogeneic donors (mice that have a different major histocompatibility complex, MHC). This is a dramatic finding, given the highly immunogenic nature of skin allografts and the aggressive host response that normally ensues. Consistent with this finding, CD4<sup>+</sup>CD25<sup>+</sup> cells were also able to suppress the proliferation of cells in a mixed lymphocyte reaction (MLR), an experimental system in which reactive T cells from a donor can be detected. Finally, Sakihama was also able to show that co-culture of CD4<sup>+</sup>CD25<sup>+</sup> cells with allogeneic splenocytes and IL-2 for one week led to proliferation of the allospecific T<sub>reg</sub> cells and enhanced suppressive activity. There is still much to resolve, but it is clear from this conference that T<sub>reg</sub> cells have once more become an important paradigm in immunology and will doubtless receive much further attention in the future.

### **Dendritic cells: populations, function, and therapy**

For a few years now, DCs have been the focus of a highly productive area of research, and this conference amply reflected their popularity, with several sessions dedicated to them. Ken Shortman (Walter and Eliza Hall Institute, Melbourne, Australia) gave a very comprehensive talk elucidating the often confusing variability seen among DCs. In contrast to the majority of investigators currently active in this field, Shortman has focused his attention on mature peripheral murine DCs, as opposed to growing cells out from bone marrow or splenic progenitors. This kind of work is important because it enables characterization of the naturally differentiated cells actually involved in antigen presentation *in vivo*. Shortman demonstrated that there are essentially three discrete splenic DC populations, distinguished by their relative expressions of CD4, CD8 $\alpha$  and CD205 (a pattern recognition molecule, also called DEC205, that detects bacterial products). The CD4<sup>+</sup> population is

defined as 'myeloid' because it expresses the bone-marrow marker CD11b, a subunit of the adhesion molecule CR4, whereas the CD8 $\alpha$ <sup>+</sup> DCs are 'lymphoid' because they lack this marker. There has been some debate as to whether these DC subtypes actually represent distinct populations or are simply different stages of splenic DC maturation. Shortman was able to elegantly address this question in two ways. In the first approach he used a transgenic mouse expressing an anti-CD4 antibody, which depleted the CD4<sup>+</sup> population, and these mice nevertheless showed normal levels of the CD8 $\alpha$  subtype, suggesting that this subtype is not derived from the CD4<sup>+</sup> DC population. In the second approach, bromodeoxyuridine (BrdU) incorporation into replicating DNA showed that all three DC populations were dividing at approximately the same rate, implying that they were all potential progenitor populations. Shortman also described two cutaneous DC populations, which can be described as CD205<sup>+</sup>/Langerin<sup>+</sup> and CD205<sup>-</sup>/Langerin<sup>-</sup> (Langerin is a lectin specific to Langerhans cells), with the former actively dividing *in situ* and the latter being very stable. A complementary talk was given by Derek Hart (Mater Medical Research Institute, Brisbane, Australia), who further highlighted the phenotypic complexity of DCs, this time using those derived from human blood. Hart described five general DC subsets on the basis of the relative expression of the cell-surface markers MHC class II, CD11c, the metallo-peptidase CD13, and CD123 (IL3-R $\alpha$ ). The unraveling of the functions of the different DC populations described by Shortman, Hart and others will doubtless be a prominent topic of research for the future.

On a slightly different theme, Thomas Kupper (Brigham and Women's Hospital, Boston, USA) described DC migration using a radical approach. Kupper used an *in vivo* system that allowed him to analyze the migration of fluorescently labeled DCs in whole, intact animals by microscopic observation of capillaries in the ear, cremasteric muscle, or skin. He presented dramatic movie clips showing the rolling and tethering of DCs to endothelium, with tethering being dependent on the endothelial expression of the adhesion molecules E-selectin or P-selectin. Finally, he identified the cutaneous lymphocyte-associated antigen (CLA) on DCs as the key ligand for both these selectins.

In a clinically oriented talk, Lawrence Fong (Stanford University School of Medicine, USA) described the use of DCs as vehicles for cancer immunotherapy. The method exploited the highly stimulatory ability of DCs to present tumor-derived peptides, essentially using DCs as natural adjuvants to enhance the antigenic effect of the peptides. The protocol involved removing autologous DCs from a patient's blood, incubating them with tumor biopsies or tumor-specific peptides *ex vivo*, and then re-injecting them into the patient. The use of the cytokine Flt3 ligand *in vitro* encouraged the expansion and activation of DCs, thereby maximizing their stimulatory capability. Some promising clinical results were

seen in prostate-cancer patients, with clinical stabilization (as measured by prostate-specific antigen) observed for more than two years. Encouragingly, these clinical regimens did not result in any deleterious side-effects such as the breakage of tolerance, resulting in autoimmunity. Further clinical studies using this technique are ongoing.

### Molecular interactions in infection and immunity

Several interesting talks focused on molecular interactions during infections and immune reactions to them. Alan Sher (National Institute of Allergy and Infectious Diseases, Bethesda, USA) described the influence of microbial exposure on the outcome of an immune response, focusing in particular on the role of DCs and IL-12 production. Using the intracellular parasite *Toxoplasma gondii*, Sher was able to show that this organism strongly and consistently shifted the host response to a Th1 T-helper-cell phenotype, which is manifested in production of interferon  $\gamma$  (IFN  $\gamma$ ) and IL-12. The key cells in this response appeared to be lymphoid CD8 $\alpha^+$  splenic DCs, which respond directly to *T. gondii* antigens by the production of IL-12 and massive migration of DCs into lymphoid organs. The parasite antigens appear to act as chemokine mimics, given that exposure resulted in down-regulation of the chemokine receptor CCR5. Interestingly, the IL-12 production was transient (peaking approximately six hours after antigen exposure *in vivo*) and the DCs were left 'paralyzed' and not capable of being re-triggered *in vivo* to produce further IL-12. This paralysis (referred to as 'exhaustion' by other workers, such as Antonio Lanzavecchia (Institute for Research in Biomedicine, Bellinzona, Switzerland)) could be circumvented by culturing the DCs for a period *in vitro*, suggesting that there is some factor *in vivo* that is responsible for de-sensitizing the DCs. Data presented by Sher pointed to the parasite inducing production of the anti-inflammatory molecule lipoxin A4 as a crucial step in DC paralysis. This idea was backed up by experiments showing that treatment with lipoxin A4 diminished CCR5 expression on DCs.

André Capron (INSERM, Lille, France) examined host-parasite interactions in schistosomiasis. The parasitic helminth *Schistosoma mansoni* uses a startling array of mechanisms to evade the immune response, eliciting no evidence of inflammation at any stage of infection. Capron highlighted that one of the most important mechanisms is the subversion of the host endothelium to an anti-inflammatory phenotype, for example by down-regulation of E-selectin and VCAM (vascular cell adhesion molecule). A second mechanism is the blockade of migration of Langerhans cells (skin-resident DCs), modeled by the *ex vivo* culture of epidermal sheets with *S. mansoni* antigens. Although IL-10 is induced by parasite exposure, it did not seem to be responsible for this blockade: mice treated with anti-IL-10 antibody and IL-10 $^{-/-}$  mice responded identically to untreated and wild-type mice that had been exposed to *S. mansoni*. Instead, Capron purified

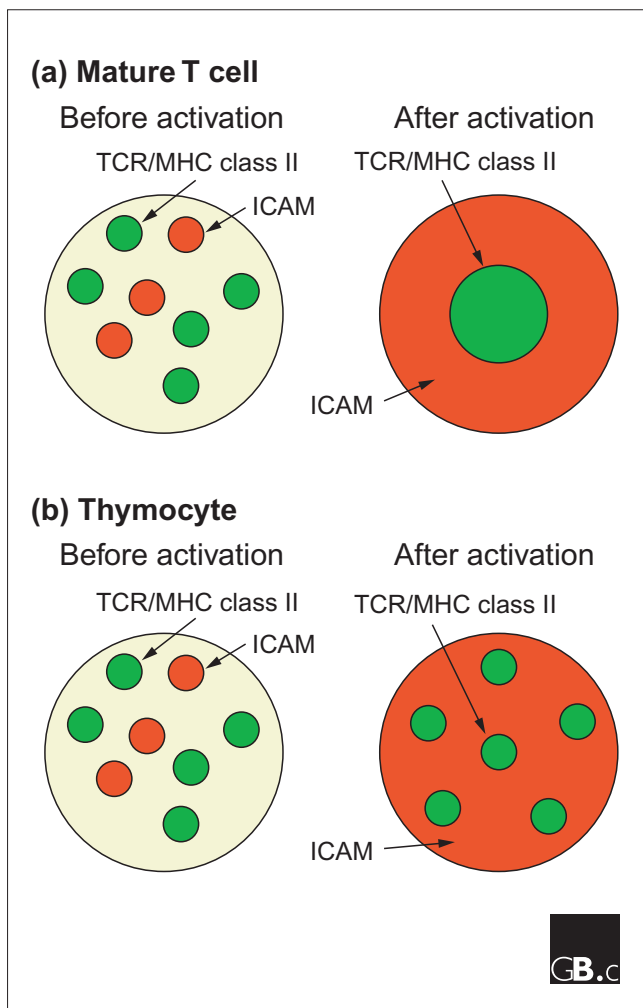
the lipophilic factors prostaglandin D2 and E2 from *S. mansoni* and identified these as the primary bioactive factors in the inhibition of Langerhans-cell migration. Capron finally described some preliminary clinical data obtained from field studies using the schistosome vaccine Bilhavax<sup>TM</sup>. These studies appeared fairly encouraging, demonstrating a reduction in worm burden and fecundity. The immune response included a strong Th2 helper-cell response, with IgG1 being the major antibody isotype. Such a Th2 response would be effective at controlling some of the stages of a Schistosome infection.

### The immunological synapse

Paul Allen (Washington University School of Medicine, St Louis, USA) presented some fascinating unpublished data on the ever-popular immunological synapse. The term 'immunological synapse' was first coined by Allen and co-workers a couple of years ago and is used to describe the highly organized junction formed between a T cell and an APC during antigen presentation. The immunological synapse is typically rich in signaling and adhesion molecules and provides a stable platform for the activation of T cells. Allen has previously published data on synapse formation using mature T cells stimulated by surrogate APCs in the form of lipid bilayers, but nothing was known about what occurs with thymocytes (developing immature T cells in the thymus). Allen managed to fill this gap by describing experiments using exactly the same model system to examine double-positive (CD4 $^+$  CD8 $^+$ ) developing thymocytes (these cells subsequently mature into single-positive CD4 $^+$  or CD8 $^+$  cells). During activation by APCs, mature T cells show rearrangement of MHC class II molecules and T-cell receptors (TCRs) on their surface to a single activation cluster (the synapse), which is surrounded by the adhesion molecule ICAM. Thymocytes, on the other hand, gave a very different pattern, showing multiple discrete islands of TCR-MHC class II complexes surrounded by a 'sea' of ICAM (see Figure 1). Thymocytes therefore seemed unable to coalesce their receptors into a single synapse; the consequences of this distinctive pattern for thymocyte activation currently remain a matter for speculation. Allen also presented some data aimed at elucidating the roles of CD4 and CD28 in synapse formation using mice lacking these molecules. He showed that CD4 was important for the kinetics of activation, with synapse formation occurring only very slowly in its absence. In contrast, CD28 did not influence synapse kinetics but was required for the long-term maintenance of the immunological synapse once formed.

### Regulation of autoimmunity

Edward Wakeland (University of Dallas, USA) gave an impressive talk on the regulation of autoimmunity, demonstrating a model approach to dissecting the genetics of systemic lupus erythematosus (SLE), a systemic autoimmune



**Figure 1**

The differences in immunological synapse formation between mature T cells and immature thymocytes during activation. **(a)** Following activation of a mature T cell, ICAM molecules (red) are 'pushed' to the periphery and T-cell receptors (TCRs) and MHC class II molecules are clustered and form a single synapse (green). **(b)** In contrast, on a thymocyte, TCRs and MHC class II molecules form multiple discrete synapses and do not cluster into a single focus. The biological consequences of these patterns are unclear.

B cells - the key cells mediating autoimmunity in SLE - and found polymorphism only in the gene encoding CD48, which has been shown to be necessary for CD4<sup>+</sup> T-cell activation. Further experiments are ongoing to determine what other genes or clusters of genes are critical for the development of SLE. Wakeland's talk and the others described here provided fine examples of the way that fundamental insights into immunology and, potentially, human disease, are coming from careful molecular analysis of each step of the immune response, whether autoimmune or a response to infection. We can expect further significant studies to have been made before the twelfth International Congress.

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disease caused by chronic production of IgG antibodies. Wakeland took the audience from the earliest stages of generating congenic mice to examining their phenotypes. By making congenic mice from normal C57BL/6 (B6) and SLE-prone NZM2410 mice and comparing the two, Wakeland identified three susceptibility loci, designated SLE-1-SLE-3. SLE-1 played the most critical role in breaking tolerance and the candidate gene was mapped to a region of 0.5 centiMorgan. As a sobering note to anyone involved in the genetics of autoimmunity, the 'relatively small' SLE-1 region harbored 33 known 'candidate' genes. Mapping this area in detail, Wakeland examined the genes that are known to be expressed in