surface constituent of neurons and is encoded by a single gene. A modified form of prion protein, PrP^{Sc}, has been identified from scrapie-infected brains and is protease resistant. However, treatment of infected tissues with agents that destroy proteins caused a loss of infectivity. PrP^{Sc} is present in a monomeric form in scrapie-infected brain; in GSD a rare mutation of the human PrP gene leads to production of the pathogenic PrP^{Sc}. Thus this agent is both inherited and transmissible. Eighty-five per cent of CJD cases are sporadic, 15% are inherited, and there are occasional rare iatrogenic cases. An intriguing study of the PrP genes in iatrogenic cases of CJD shows that they have an unusual genotype that renders them susceptible to prion infection. The species barrier of prion disease which is perhaps vital to human protection from animal spongiform encephalopathies seems to be due to the inefficiency of different species in converting species specific PrP into pathogenic PrP^{Sc}.

The audience was disappointingly small, perhaps due to the meeting being held in July and the zoonoses being only a small part of most people's practice. Sadly, those who did come were not as questioning as one might have hoped. Although all the speakers spoke well a few took up more than their allotted span forcing others to shorten their talks, and restricting the time available for discussion. Some speakers should also look more closely at the title of the conference and make sure that their talks are relevant, rather than deliver their standard lecture-circuit seminar.

The meeting gave a wide perspective on the zoonoses. Animal health is important for all of us. There are many levels of interaction between animals, man, and the environment. As the environment changes different organisms will move into new niches and animals will alter their behaviour patterns. Changes in farming practices can have distant and unanticipated effects. As health care professionals we need to learn to recognise, understand, and respond to these changes.

The immunopathogenesis and immunotherapy of autoimmune disease

A conference entitled 'The Immunopathogenesis and Immunotherapy of Autoimmune Disease' was held at the Royal College of Physicians on 20 May 1992. Its aim was to consider advances in pathogenesis and their translation into therapeutic targets.

Current models of autoimmune disease are based on the concept that an autoantigenic peptide is presented by an appropriate human leucocyte antigen (HLA) to an autoantigen-specific T cell; these three components constitute the trimolecular complex. Activation of T cells specific for the autoantigen stimulates additional immune and non-immune effector mechanisms including antibodies, cytokines and other mediators which generate the pathology of the various diseases. It is still unclear whether the T cell response to autoantigens in humans is polyclonal or whether, as in some animal models, the T cell receptor (TCR) usage of the responder lymphocytes is restricted. The outcome of the trimolecular interaction is influenced by immunoregulatory processes and also by the hypothalamic-pituitary-adrenal axis.

Pathogenesis

The first three presentations concentrated on the HLA and non-HLA genes which contribute to autoimmune disease. **Dr J. Lanchbury** (United Medical and Dental Schools, London) reviewed the role of the major histocompatibility complex (MHC) in disease susceptibility using rheumatoid arthritis (RA) as a paradigm. He observed that only 30% of RA risk has a genetic basis, the rest being environmental, and that there were genetic influences outside the MHC: for example, chromosome 14. With regard to HLA associations, RA populations can be subdivided into three types: those like Northern Europeans who show the classical associations with DR4 and secondarily DR1; those like Jews, Indians, and Italians who have a primary association with DR1; and a group including Greeks without any

Rapporteurs:
GABRIELLE KINGSLEY, MRCP(UK)
Consultant Senior Lecturer, Rheumatology Unit, Guy's Hospital, London
RICHARD WATTS, MRCP(UK)
Senior Registrar in Rheumatology, Addenbrooke's Hospital, Cambridge

significant serological HLA association. Study of the latter is important in identifying non-HLA genetic influences and differences in disease expression. The association with DR4 and DR1 has been used to examine the mechanism by which these alleles are associated with RA Molecular techniques have enabled a structural comparison to be made between the various RA-associated (DR4Dw4, DR4Dw14, DR4Dw15, DR1Dw1 and DR6Dw16) and non-susceptibility alleles (DR4Dw10, DR4Dw13). The susceptibility, but not non-susceptibility, alleles share a similar structure in the third hypervariable region (HVR); this has given rise to the 'third HVR hypothesis', which proposes that an individual's susceptibility to RA is governed by possession of an allele with a particular third HVR structure. Support for this hypothesis came from molecular modelling studies which showed that the third HVR was included in the peptide binding region and could thus determine binding to a potential arthritogenic peptide. Although this hypothesis is attractive, it is probably an oversimplification. Studies of clinical heterogeneity in RA have shown that, for example, vasculitis is specifically associated with DR4Dw14, and that Felty's syndrome occurs more frequently in DR4Dw4/DR4Dw14 heterozygotes than in DR4Dw4 homozygotes; thus the contribution of the various susceptibility alleles may not be equivalent. It also remains unclear whether susceptibility alleles are associated with the development of RA or whether they determine progression; recent studies on early arthritis support the latter. Finally, mechanisms by which MHC susceptibility genes might act in RA were considered, including effects on the thymic T cell repertoire, on T cell usage in disease, and on the binding of disease-associated peptides.

Recent work has clarified the process by which T cell epitopes are generated from intact antigen. Unlike B cells, which recognise a conformational epitope, T cells see short linear peptides in the context of MHC molecules; these peptides are generated from intact antigen by the antigen presenting cell (APC). Endogenous proteins are processed into peptides which bind to MHC class I molecules in the APC endoplasmic reticulum (ER); the peptide-class I complex then travels to the APC surface to be presented to CD8+ T cells. Exogenous proteins enter the APC by endocytosis and are processed into peptides and bound to MHC class II molecules within endosomes; the complexes, expressed on the APC surface, are presented to CD4 cells. **Dr J. Trowsdale** (Imperial Cancer Research Fund, London) described the identification of new genes within the HLA class II region which encode molecules involved in antigen processing and presentation. These include proteasomes, involved in processing protein to peptides, transporters, required for transport of peptides into intracellular compartments like the ER, and some new and structurally rather distinct MHC molecules. Two proposed proteasome genes (LMP7 and LMP2) have been identified; their presumed function is based on structural comparisons with other similar molecules. The function of the transporter (TAP) gene products, located on the Golgi and ER, is also assigned from a structural analogy with cell-surface ATP-binding cassette (ABC) transporters such as the multi-drug resistance genes. The clustering of these genes within the MHC raises interesting possibilities for coevolution and coregulation of their function.

The final speaker on genetics was **Dr J. Todd** (John Radcliffe Hospital, Oxford) who discussed the genes involved in the development of diabetes mellitus (DM). He too noted an environmental influence (the concordance rate for DM in identical twins is 30%) which might even be protecting the non-diabetic twin. Somewhat controversially, he proposed that IDDM might be a form of maturity-onset DM accelerated by an autoimmune process since the effects of genes associated with maturity-onset and insulin dependent DM (IDDM) may overlap. IDDM is becoming commoner throughout the developed world, especially in young children; however, this could simply represent earlier presentation since most IDDM patients have islet cell antibodies by the age of five, suggesting that they are already programmed to develop disease. The main focus of the talk was the relative contribution to the genetic risk made by the various genes now known to be associated with IDDM. As well as the HLA region where DR3, DR4 and DQw8 are important, the insulin gene on chromosome 11 also contributes; there are probably many other susceptibility genes as, in mice, loci on eight different chromosomes appear to be relevant.

Professor J. Newsom-Davis (Institute of Molecular Medicine, John Radcliffe Hospital, Oxford) turned the audience's attention to autoimmune mechanisms in paraneoplastic neurological diseases, such as Lambert-Eaton myasthenic syndrome, myasthenia gravis, cerebellar degeneration, neuromytonia and sensory neuropathy, which are associated with a variety of malignancies, notably small cell lung cancer, thymoma, and ovarian cancer. In some of these syndromes the pathology is plainly antibody-mediated: eg the Lambert-Eaton syndrome which comprises weakness, mild ptosis, autonomic disturbance and, in 30%, associated autoimmune disease. The physiological defect is a reduction in the number of acetylcholine (ACh) packages ('quanta') released from nerve terminals in response to a nerve impulse, an event that is calcium-dependent. In support of a pathogenic role for antibodies, patients improve with plasmapheresis and passive transfer of patients' IgG to mice reduced the number of voltage-gated calcium channels at nerve terminals, thus decreasing ACh release. Electron microscopy studies have shown that in Lambert-Eaton syndrome there are fewer voltage-gated calcium channels and that their normal orderly array is disturbed. Experiments using patients' IgG showed that it could cross-link and down-regulate these channels in nerve endings and also inhibit their function in cancer cells

in culture. The data strongly suggest that the autoantibodies are provoked by tumour calcium channels. To date, the specific antibodies can be detected by radioimmunoassay in 30–50% of Lambert-Eaton patients, but the assay is currently being refined with the hope of improving sensitivity.

Dr D. Mason (Sir William Dunn School of Pathology, Oxford), introduced the topic of control of the immune response by the hypothalamic-pituitary-adrenal (HPA) axis. Experimental allergic encephalomyelitis (EAE) is a murine model for multiple sclerosis (MS) induced by injection of myelin basic protein (MPB). The Lewis rat is susceptible to EAE; the MHC-compatible PVG rat, bred in the same environment, is not. In Lewis rats with EAE there is normally a single severe attack of paralysis, associated with a peak steroid level, after which the animal recovers and is then refractory to EAE induction. If a rat is adrenalectomised prior to EAE induction, it does not recover but dies; death can be prevented by a steroid implant. Even more convincingly, the normally non-susceptible PVG rat can be made susceptible by adrenalectomy and this can also be reversed by implanted steroid. Adrenalectomy has an effect only if performed before the onset of paralysis. A similar role for the HPA axis in controlling disease expression has been demonstrated in other rodent autoimmune diseases, notably adjuvant arthritis. The interaction between the immune system and the HPA axis occurs in the hypothalamus where interleukin-1 (IL-1) stimulates production of corticotrophin releasing factor (CRF) and thence ACTH and adrenal steroids; the latter suppress the cell-mediated immune response by effects on T cells and macrophages. Dr Mason went on to discuss cytokine regulation of the immune system in different rodent strains. Animals which primarily developed a cell-mediated immune response (stimulated by interferon (IFN)-gamma and IL-2 and inhibited by IL-4 and IL-10) would be predisposed to develop autoimmune diseases but would be protected against certain infections. By contrast, those with a poor cell-mediated response but good humoral responses (stimulated by IL-4 and inhibited by IL-10 and IFN-gamma) would not develop autoimmune disease but would be predisposed to infection. Manipulation of cytokines, for example the treatment of leishmaniasis-susceptible mice with antibody to IL-4, can render them resistant. Animals with a naturally relatively suppressed HPA axis would have active cell-mediated immunity and be prone to autoimmune disease. A similar defect in HPA response has been identified in human RA.

Professor A. Weetman (Clinical Sciences Centre, University of Sheffield), then turned to the autoantigens themselves. He discussed autoimmune thyroid disease where, unusually, the major autoantigens are known: thyroglobulin, thyroid peroxidase, and thyroid stimulating hormone receptor. As noted above, T and B cell epitopes differ. T cell epitopes are linear peptides of nine amino acid residues (class I presentation) and 12 residues (class II presentation) which can, to an extent, be predicted from the primary sequence. Primary B cell epitopes are conformational, depending on the tertiary structure of the antigen; the sequential B cell epitopes (unfoldons, cryptotopes), which appear as proteins unfold, are unlikely to be relevant in disease initiation. Thyroglobulin (Tg), a 660kd glycoprotein composed of two 330kd subunits, has four to six major B cell epitopes which, like Tg T cell epitopes, must be iodinated for antigenicity; it is not known whether non-thyroxine epitopes exist. Thyroid peroxidase (TPO) is a 933 amino acid haem-containing enzyme responsible for iodinating and coupling tyrosine residues on Tg. Reactivity to TPO depends heavily on tertiary structure since only up to 50% of microsomal antibody positive sera react with reduced TPO on immunoblotting; functional inhibition of TPO by these sera also varies. At least six B cell epitopes have been identified, including the sites which catalyse peroxidation, but it is uncertain whether this contributes to hypothyroidism by blocking T3 and T4 synthesis. Of current interest is whether TPO-inhibiting antibodies are present in Hashimoto's disease and, if so, whether they are also cytotoxic. The T cell response to TPO is heterogeneous, both within and between patients. Yet T cell lines from Graves disease patients recognised only two of 28 linear TPO peptides (residues 535-551 and 632-645); a TPO-responsive T cell line has been used to transfer disease. The thyroid stimulating hormone (TSH) receptor, an 87kd molecule homologous to the luteinising hormone receptor, comprises an extracellular domain with five glycosylation sites and a carboxyterminal domain with seven transmembrane regions. TSH, thyroid stimulating antibodies and thyroid blocking antibodies bind to distinct sites on the extracellular domain. The T cell response is again heterogeneous but 50% of Graves patients respond to one or more TSH receptor peptides. The question of whether responses to these various antigenic epitopes help to identify subsets of patients remains open. Finally Professor Weetman discussed a recent paper which had shown that in Graves disease, intrathyroidal lymphocytes used only two to five TCR Vα genes, a highly restricted usage suggestive of an oligoclonal T cell response. His group has, however, been unable to replicate this work using whole thyroid, thyroid lymphocytes or IL-2 receptor positive T cells. In 11 patients, 14 of the 18 Vα genes tested were present.

Immunotherapy

Dr D. Wraith (Cambridge University) postulated that pathological autoimmunity might arise from several mechanisms: breakdown of suppression, cross-reactivity between autoantigen and foreign antigen, presentation of sequestered antigen, and breakthrough of 'rogue' clones. He considered the possibility of basing

strategies for immunotherapy on T cell recognition in studies of PLJ mice with MBP-induced EAE, a self-limiting demyelinating disease mediated by TCR-Vβ8+ T cells. Interestingly, the immune response recognises not only MBP but also other brain antigens, notably proteolipid (PLP). T cell clones specific for the N-terminal 11 amino acids (Ac1-11) of MBP, the dominant epitope in PLJ mice, can transfer EAE to naive animals. In Ac1-11, residues 3 and 6 bind to the TCR while residue 4 interacts with the MHC. Substitution of alanine for lysine at residue 4 (Ac1-11[4A]) results in increased binding to the MHC and enhanced T cell activation. In fact, it emerges that Ac1-11 binding affinity is proportional to the hydrophobicity of the amino acid at residue 4 and, unexpectedly, the naturally occurring Ac1-11 peptide is among those with the lowest affinity to the MHC. Dr Wraith proposed that, whereas for foreign antigens the immunodominant epitopes were usually those with the highest affinity for MHC, for self antigens reactivity would be found mainly to relatively weakly binding peptides since high-affinity peptides would have induced tolerance. This idea is clearly contentious; in discussion, **Dr H. Grey** (Cytel, San Diego) stated that in his studies of PLP-induced EAE in SJL mice, the relevant peptides were high affinity binders although these may not have been naturally processed epitopes. It is clearly possible that epitopes on autoantigens may not obey the same rules for recognition as foreign antigens and that perhaps only epitopes with a low MHC affinity can break tolerance.

Turning to the use of altered peptides in therapy, Dr Wraith has shown that treatment with Ac1-11[4A] can both prevent and treat EAE induced by Ac1-11. Although these two peptides do compete at the MHC binding site, the therapeutic effect of Ac1-11[4A] is not simply due to MHC blockade. Changing the residues on Ac1-11[4A] which interact with the TCR abrogates the ability of the peptide to induce tolerance but its binding to the MHC remains unaltered. The requirement for adjuvant in parenteral therapy with Ac1-11[4A] would be a major disadvantage in humans; Dr Wraith's demonstration that inhalation of peptide is a very potent means of inducing tolerance, even in the absence of adjuvant, is very exciting. This, and the apparently analogous oral induction of tolerance reported by other groups, clearly merit further study. Finally, Dr Wraith considered the nature of T cell receptor (TCR) recognition of peptide. Classically it has been considered that the capacity of a TCR to recognise a peptide is highly specific, if not unique, for that peptide. However, studying changes made to the residues Ac1-11 which interact with the TCR, it became apparent that, while there was a high degree of specificity for proline at residue 6, substitutions which permitted T cell recognition could be made at residue 3. Some of these 3-substituted peptides, despite substitution with chemically very different amino acids, could induce EAE; thus they presumably interacted with the same T cells as the naturally occurring Ac1-11 peptide.

Professor J. Lamb (St Mary's Hospital London) considered the control of autoimmune disease through modulation of the TCR by conventional peptide antigens and by superantigens. Superantigens are a diverse group of molecules which, unlike normal peptides, do not bind in the conventional peptide binding groove created by TCR-Vα, TCR-Vβ and MHC but rather to exposed surfaces of the TCR-Vβ chain and MHC. Hence, they activate all T cells that possess the appropriate Vβ chain; most superantigens interact with only one or a limited number of Vβ chains but, even so, will stimulate a much higher proportion of the T cell repertoire than a conventional peptide. There are two types of superantigen: endogenous (demonstrated to date only in mice) produced by portions of viral DNA incorporated in the host genome: and exogenous, which are relevant both in rodents and man. The latter are proteins produced by a range of pathogenic organisms including mycoplasma, streptococci and staphylococci; among the most investigated are the staphyloccocal enterotoxins (SE) and the toxic shock syndrome toxin (TSST-1), both of which are responsible for clearly identifiable illnesses in humans. In the normal situation, tolerance to autoantigens is maintained in part centrally, by deletion of autoreactive T cells in the thymus, and in part peripherally, by suppressing or anergising potentially self-reactive T cells. Professor Lamb investigated mechanisms of peripheral T cell tolerance using an *in vitro* model in which an influenza haemagglutinin specific DR-restricted human T cell clone was treated for 24 hours with various potentially anergising stimuli; its proliferative response to rechallenge with haemagglutinin plus antigen presenting cells (APC) was then measured. Anergy can be induced by high-dose haemagglutinin peptides given without APC, by superantigen (staphyloccocal enterotoxin B which recognises Vβ3.1 used by the clone), and by anti-CD2 and anti-TCR antibodies. Antigen and superantigen induced anergy is antigen specific and long-lasting; antigen but not superantigen-induced anergy is MHC class II dependent. The mechanisms of anergy involve downregulation of cell surface CD3 expression although expression of CD2 and CD25 is increased in both anergising and activating interactions. Expression of CD28 is also marginally downregulated in anergy but upregulated in activation where cross-linking of CD28 is associated with stabilisation of cytokine mRNA. Expression of adhesion proteins such as CD29 and CD43 may also be downregulated in anergy albeit transiently. Lymphokine production is also modulated in established anergy with decreased production of several cytokines, including IL2, IL4 and IL5. To assess the relevance of these findings to autoimmune T cells, a panel of rheumatoid synovial T cell clones, which respond to an unknown synovial fluid antigen, were then investigated. Again, a superantigen which binds

to the TCR-Vβ used by a particular clone of T cells can tolerise it. Thus, if the T cell response in a human autoimmune disease involved either T cells expressing a limited range of TCRs or T cells with a restricted Vβ usage, the fascinating possibility arises that a superantigen which recognised the relevant Vβ chain might be used therapeutically to tolerise the patient to the pathogenic T cells.

Dr H. Grey (Cytel, San Diego) returned to the theme of the therapeutic use of MHC binding antigenic peptides. In studies of PLP-induced EAE in SJL mice, his group have shown that KM peptide, a non-homologous blocker (structurally unrelated to PLP) can protect against EAE if administered before or at the time of disease induction. Such non-homologous blockade appears to be mediated exclusively by competition with PLP at the MHC. The group, however, noted that blockers made by altering the sequence of the autoantigenic peptides (analogous blockers) were a hundredfold more effective than non-homologous blockers even if their affinity to the MHC was the same. Furthermore, tetanus toxoid analogues inhibited the T cell response to tetanus toxoid much more effectively than the response to haemagglutinin (and vice versa), even though both were restricted by the same MHC. These findings showed that analogous blockers had effects beyond MHC blockade, perhaps involving competition at the TCR. Dr Grey envisaged three outcomes for the interaction between the MHC-peptide complex and the TCR; activation of the T cell (the normal outcome), antagonist/partial agonist activity, or no T cell response. The latter would most likely follow binding of a complex with low affinity for the TCR. To investigate the mechanisms of analogue peptide inhibition in a system where the effect on MHC binding was eliminated, the prepulse assay was devised. APC, preincubated with a suboptimal dose of antigen which left some HLA-DR molecules free, were cultured with inhibitor peptides which bound to the free DR sites. These APC, in which some MHC were complexed to antigenic and some to inhibitory peptides, were then used to stimulate a haemagglutinin specific T cell clone. Inhibition occurred only with an analogue not a non-homologous blocker and was entirely antigen specific. Substitution of a single TCR contact residue of the haemagglutinin peptide resulted in TCR antagonism, not activation. To enable the effect of resubstitution of TCR contact residues to be explored in detail, a peptide was synthesised with a polyalanine backbone but preserved MHC contact residues. Substitution in the backbone with only one residue able to interact with the TCR was insufficient to lead to antagonism in the prepulse assay but substitution with two or three TCR contact residues resulted in increasing antagonism. Substitution of four residues rendered the peptide antigenic. Antagonism was only observed if the antigen was presented by cells and not by planar membranes, suggesting that molecules other than those of the trimolecular complex were required. Furthermore, the antagonist had to be on the same cell as the antigen. Finally, these antagonists inhibit early events in T cell activation such as calcium flux but do not inhibit the very earliest event, conjugate formation. The prospect of such an antigen specific and sensitive method of inhibiting autoimmune disease is very encouraging but it can only be applied where the pathogenic autoantigenic peptide is known, which is rarely the case in human disease

Following the promising theoretical prospects outlined in previous talks, **Dr G. Kingsley** (Guy's Hospital, London) discussed the use of biological response modifiers in RA. Since the initiating antigen in RA is unknown, antigen-specific therapy is not feasible. Because of the strong HLA association, RA is one of the first targets for therapy with MHC-binding peptides; DR4/DR1 binding peptides have been made but not yet used. The third member of the trimolecular complex, the T cell, is the focus of most current immunotherapy. The relevance of the T cell as a target is supported by the effect of therapies such as thoracic duct drainage, total lymphoid irradiation, lymphopheresis and cyclosporin. Considerable experience has been gained with the use of anti-T cell monoclonal antibodies (mAbs). Initial studies used murine mAbs; because of side-effects due to the development of human anti-mouse responses and because different mAb isotypes may show disparate efficacy, recent work has used chimerised mAbs in which a murine FAb is complexed to a human Fc. Humanised mAbs where, except for the antigen-binding site itself, the entire molecule is human have also been constructed. Since it is not known whether the T cell response in RA is oligoclonal, specific anti-TCR mAbs cannot be used. Instead, the targets have been T cell activation markers, such as CD25 (interleukin 2 receptor) and CD7, antigens like CD4 which identify a critical T cell subset or pan T cell markers, like CD5. Studies with murine and chimerised anti-CD7 in mAbs in RA have shown a marked reduction of CD7+ cells in the blood and synovium but no significant clinical effect. Three patients given murine anti-CD25 mAb showed a transient benefit. CD5 Plus, comprising anti-CD5 conjugated to ricin, was designed to produce more effective depletion than anti-CD5 mAb alone, but no direct comparison between the two has been made. Improvement occurred in longstanding patients but there was a better response in early RA; the clinical effect persisted after normalisation of CD5+ cells in the blood. With anti CD4 mAb, overall results of several uncontrolled studies, in patients refractory to other treatments, show that 50–60% improve although the effect may be transient; a small number have a longlasting benefit. A chimeric anti-CD4 mAb has also shown some benefit and is currently being studied in early RA. The mechanism of action of anti-CD4 mAb remains uncertain. Despite clinical improvement, no change in acute phase reactants is induced and, although the blood CD4 count falls, it returns to normal before clinical

relapse. Supporting the idea that depletion of peripheral blood CD4 cells is not sufficient for therapeutic benefit, a controlled study, using a single pulse of chimeric anti-CD4 or four pulses at weekly intevals, demonstrated a marked reduction in CD4 levels but no clinical effect. Adverse effects, including infection, have been infrequent except in patients receiving other immunosuppressive drugs. Murine anti-CD4 therapy also results in less sensitisation than other mAb, perhaps because of a tolerising effect on the response to neoantigens; chimeric anti-CD4-mAb therapy leads to only very low levels of anti-mouse antibody of uncertain clinical significance.

Alternatives to mAb treatment include T cell vaccination (TCV) with intact T cells and vaccination with TCR peptides. The aim of TCV is to induce specific immunity to the disease-related T cells by immunising patients with these T cells in an attenuated form. In murine autoimmune disease, vaccination with attenuated disease-inducing T cell lines can protect against and suppress disease mainly by invoking an anti-TCR response. There are problems in transferring TCV to humans including choice of dose and regime and, more fundamentally, the lack of disease-inducing T cell lines. The former may be solved by current primate studies; with regard to the latter, unpurified splenic T cells from primed rodents can provide an effective vaccine. In humans, preliminary TCV studies have been performed in RA and MS; no toxicity has been observed but further studies, preferably in a disease with a known antigen, are needed to assess the clinical and immunological effects. In the long term, TCV may not prove to be generally applicable for practical reasons, but a similar anti-TCR response can be produced by vaccination with TCR peptides. Two groups have shown that TCR peptide vaccination, using peptides derived from the TCR V region, is effective in protecting against and treating murine EAE. A study in MS is in progress; immune responses against the immunising peptides have been found but no clinical results are yet available.

The feeling at the end of the meeting was that novel therapies, based on the approaches discussed at this meeting, are slowly moving from the laboratory to the patient. The current front runner is anti-T cell mAb therapy, but there are many unanswered questions with regard to efficacy and long-term safety, including opportunistic infection and the potential for lymphoid malignancy as seen with anti-CD3 mAb. Furthermore, such therapy cannot be disease specific since these T cell antigens are used in all immune responses. However, increasing knowledge of MHC and TCR restriction in human autoimmune disease may provide more selective avenues of attack. One thing is clear; for those interested in the immunopathogenesis and immunotherapy of autoimmune disease, the future holds many exciting discoveries.

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