Immunology and Cell Biology (1997) **75**, 113–126

Review Article

Molecular mimicry: Can epitope mimicry induce autoimmune disease?

JANET M DAVIES

Biotechnology Programme, School of Biological and Environmental Science, Murdoch University, Murdoch, Perth, Western Australia and Department of Biochemistry and Molecular Biology, Monash University, Clayton, Victoria, Australia

Summary Mimicry of host antigens by infectious agents may induce cross-reactive autoimmune responses to epitopes within host proteins which, in susceptible individuals, may tip the balance of immunological response versus tolerance toward response and subsequently lead to autoimmune disease. Epitope mimicry may indeed be involved in the pathogenesis of several diseases such as post-viral myocarditis or Chagas disease, but for many other diseases in which it has been implicated, such as insulin-dependent diabetes mellitis or rheumatoid arthritis, convincing evidence is still lacking. Even if an epitope mimic can support a cross-reactive T or B cell response *in vitro*, its ability to induce an autoimmune disease *in vivo* will depend upon the appropriate presentation of the mimicked host antigen in the target tissue and, in the case of T cell mimics, the ability of the mimicking epitope to induce a proliferative rather than anergizing response upon engagement of the MHC–peptide complex with the T cell receptor. B cell presentation of mimicking foreign antigen to T cells is a possible mechanism for instigating an autoimmune response to self antigens that in turn can lead to autoimmune disease under particular conditions of antigen presentation, secondary signalling and effector cell repertoire. In this review evidence in support of epitope mimicry is examined in the light of the necessary immunological considerations of the theory.

Key words: altered peptide ligands, autoimmunity, cross-reactivity, epitope mimicry, molecular mimicry.

Introduction

Epitope mimicry is widely thought to be the mechanism for the induction of autoimmune disease. The theory is that an infectious agent (parasite, bacteria, yeast or virus) displays epitopes immunologically resembling host determinants and due to the minor antigenic differences between the two, the pathogen's epitope is able to induce an immune response that breaks tolerance to the host epitope. The cross-reactive T or B cell is then able to induce a pathogenic autoimmune response that leads to disease.[1] Bacterial urinary tract infections have been suggested to induce cross-reactive immune responses to antigens in the liver epithelium that contribute to the development of primary biliary cirrhosis (PBC).[2] Mimicry of a self antigen, the ZP3 zona pellucida antigen, by another unrelated self molecule, the nicotinic acetylcholine receptor delta chain, has even been proposed as an instigator of autoimmune reactivity to ovary cells.[3]

Molecular mimicry is a widely adopted term but it is more correct when considering the induction of autoimmune disease by mimicking pathogens to use the term epitope mimicry. This distinguishes it from other types of molecular mimicry such as ligand–receptor mimicry,[4] messenger RNA mimicry[5] and mimicry of cytokines and chemokines.[6] All types of mimicry may be strategies used by pathogens to gain entry to target cells, to manipulate inter- and intra-cellular processes or to avoid immune responses that limit their life cycle in the host. Autoimmunity resulting from epitope mimicry may be an unfortunate by-product of the anti-pathogen immune response that can lead to disease in pre-disposed individuals.

The scope of this review does not permit a comprehensive account of all studies on epitope mimicry that have emerged recently. Other reviews on mimicry[7] and its role in arthritis,[8] AIDS[9] and diabetes[10] are available. In this paper, the evidence needed to support the case for epitope mimicry in the induction of autoimmune disease will be addressed. The type of data which is presented to support the case for epitope mimicry and the necessary immunological considerations will be examined.

Cross-reactive auto-antibodies

There are three points to be made to establish the phenomenon of antibody cross-reactivity: (i) some antibodies can react with self; (ii) some auto-antibodies also react with a non-self antigen; and (iii) some antibodies to foreign antigens can cross-react to self antigens. It has been observed in a panel of 600 anti-viral mAb that as many as

Correspondence: Dr Janet M Davies, Department of Biochemistry and Molecular Biology, Monash University, Clayton Vic. 3168, Australia.

Received 19 June 1996; accepted 1 October 1996.

3.5% cross-react with mammalian proteins.[11] In experiments using mice constitutively expressing the *bcl-2* gene that inhibits apoptosis and hence, clonal deletion, antibodies to dsDNA were generated after immunization with the bacterial hapten pneumococcal cell wall.[12] Many experimental or clinical examples of auto-antibodies could have been cited here to support the existence of auto-antibodies in the peripheral B cell repertoire but this paper[12] is particularly pertinent to the topic of mimicry since the elicitor of the anti-dsDNA antibodies was a bacterial hapten. Among the normal human population there is a prevalence of natural auto-antibodies to intracellular molecules such as DNA, nuclear and cytoskeletal proteins which for the major part are not pathogenic but may contribute to the normal regulation of the immune system.[13]

Cross-reactive and auto-reactive T cells

The presence of auto-reactive T cells in the periphery is exemplified by the ability to expand T cells of multiple sclerosis (MS) patients to the auto-antigens of myelin, for example myelin basic protein (MBP).[14] A new study of Graves' disease has revealed γδ T cells reactive to self epitopes expressed by thyroid cells.[15] Demonstration of cross-reactivity of T cells is relatively new but several papers provide evidence for its occurrence. Plasticity in the recognition of MBP-specific T cell clones for various analogues of the immunodominant MBP epitope in MS has been shown by Bhardwaj *et al.*[16] Wucherpfennig and Strominger[17] tested the ability of 128 viral and bacterial peptides identified by data base searching as having sequence similarity to a motif of the immunodominant MBP epitope in MS for reactivity with T cell clones restricted by the MS-associated HLA DR2 presenting cells and found eight of these peptides induced cross-reactive proliferative responses.[17] These studies show that a degree of difference between peptides can be accommodated by the trimolecular TCR–MHC–peptide interaction.

Tolerance versus autoimmunity

The ability to find cross-reactive T cells or antibodies which can recognize self epitopes does not necessarily mean an autoimmune disease will develop. Immunological tolerance to self molecules is a balance that is normally maintained by mechanisms such as thymic and peripheral clonal deletion via apoptosis, direct T cell suppression, or antigen specific anergy.[18–20] The capability of cross-reactive immune responses to break tolerance and induce autoimmune disease depends on numerous intrinsic and extrinsic factors such as the ability of host MHC molecules to bind and present particular antigens, the likelihood of a peptide being processed for binding to the MHC, the existence in the periphery of B cells with antibody or T cells with receptors specific for self epitopes and the level of cytokines induced after an immune recognition event.

Epitope mimicry may be one means of breaking immunological non-responsiveness to an endogenous tissue antigen. The route by which a foreign antigen is presented may be quite different to that of an endogenous molecule which is likely to be presented on the cell surface in the groove of MHC class I. An antigen of an infectious agent is likely to be presented in the groove of MHC class II on the surface of a professional APC, such as a dendritic cell, or an activated B cell that could provide the appropriate secondary signalling, such as B7, for stimulating a proliferative response. This difference needs to be considered as does the effect of interaction of a peptide mimic with the TCR. The significance of T cell stimulation with epitope mimics or altered peptide ligands that fail to induce proliferation will be discussed later.

B cell and T cell responses contribute to autoimmune disease

Both cross-reactive antibody and T cell responses may contribute to the pathogenesis of an autoimmune disease. T cell pathogenesis is exemplified by several experimental models of autoimmune disease which can be transferred to naive laboratory animals using T cells primed *in vitro* to auto-antigens such as MBP for experimental allergic encephalitis[21] and heat shock protein (HSP) for adjuvant arthritis (AA).[22] B cell-mediated autoimmune pathogenesis and indeed epitope mimicry is demonstrated in a murine model of myocarditis. Antibodies generated after CMV infection were affinity purified against cardiac myosin. These antibodies cross-reacted with murine CMV polypeptides and could passively transfer myocarditis to naive mice.[23]

Besides their contribution to the pathogenesis of an autoimmune disease another link between B cell and T cell activity is in antigen presentation. Mamula *et al.*[24] showed that murine B cells primed *in vivo* to the human small nuclear ribonucleoprotein (snRNP) antigen can be transferred to naive mice whose T cells subsequently proliferated in response to both the human and the murine snRNP antigen. Presumably, the B cells reactive with the foreign snRNP antigen acted as APC, processing and presenting self snRNP to T cells in the recipients previously unable to proliferate to self snRNP and enabling their T cells to respond to self snRNP protein.

Investigation of epitope mimicry

An early experimental study of epitope mimicry by Fujinami and Oldstone[25] elucidates a number of important features of the theory of autoimmune disease induction by epitope mimicry. Rabbits were injected with a Hepatitis B virus polymerase peptide (IGC**YGSLPQE**) that mimicked an epitope of MBP (TTH**YGSLPQK**) and which was able to induce antibodies to MBP in five out of seven rabbits. Central nervous system lesions resembling some aspects of the demyelinating disease experimental allergic encephalomyelitis (EAE) were observed in some rabbits.

Since then several lines of evidence support the theory of epitope mimicry. The first is exemplified by a paper describing primary sequence homologies between various viruses and the peptides of the auto-antigen La (SS-B) that

were most frequently recognized by antibodies in sera of Sjögren's syndrome (SS) and SLE patients.[26] In this paper and many others, only primary sequence similarity is listed as a suggestion of epitope mimicry. Data on immune recognition of the potential mimic is lacking.

The second line of evidence is the demonstration of cross-reactivity of disease relevant mAb or affinity purified antibodies to a different antigen of unrelated origin. This is exemplified by another murine model of myocarditis. A mAb to *Streptococcus pyogenes* cross-reacts with high molecular weight cardiac and skeletal myosin and this reaction can be absorbed by *S. pyogenes*. Further to this a mAb to ventricular myosin was found to cross-react with *S. pyogenes* antigen.[27]

The third type of data presented for epitope mimicry is T cell cross-reaction. For example, the ability of the arthritogenic anti-HSP T cell clone of AA to cross-react with host proteoglycan.[22] Another is a recent paper presenting data on T cell lines from 14 MS patients which were raised *in vitro* against MBP, some of which cross-react with a coronavirus epitope.[28] Further examples of data in support of the theory of epitope mimicry are listed in Table 1.

Evidence is needed for epitope mimicry

If epitope mimicry by an infectious agent is to trigger an autoimmune response that leads to an autoimmune disease then several facts need to be established: (i) the presence of the pathogen needs to associate with the onset of symptoms or disease in a convincing proportion of cases; (ii) a clinically detectable immune response to the pathogen should be demonstrable at least at the onset of the disease and this response should be shown to cross-react with host antigens of the affected tissue; (iii) also, the pathology of the disease ought to be consistent with the proposed immune response. These criteria are often hard to fulfil since the pathology inducing autoimmune disease may have commenced long before the onset of clinical symptoms which hampers research into the triggers of autoimmunity.

Epitope mimicry in human disease

Epitope mimicry in parasitic diseases

A disease in which there is convincing evidence for epitope mimicry is Chagas disease induced by the parasite *Trypanosoma cruzi*. First there is a real association of the parasite with the disease. During infection of the host, various antibody idiotypes are elicited by a parasite, some of which directly cross-react with host proteins and may contribute to the pathogenicity of the infection.[37] Autoantibodies and T cell responses are directed against both cardiac and nervous tissue antigens.[38,39] The prevalence of antibody cross-reactivity is high; 30 out of 30 chronic and 11 out of 13 acute Chagas patients have antibodies to a 150 kDa parasitic antigen which lyses the blood stage of the parasite and cross-reacts with human and murine striated and smooth muscle.[40] More than one epitope of a 160 kDa parasite antigen induces cross-reactive antibodies to different epitopes of a 48 kDa antigen of myentric and sciatic nerve cells.[41] Since an autoimmune inflammatory pathology is evident in Chagas patients, the pathology occurs in the absence of parasites in the local region and since there are several parasitic antigens which appear to induce antibodies to nerve and muscle antigens[37,41] it is reasonable to suggest that molecular mimicry may be an initiating mechanism.

There is a similarly strong case for mimicry of the 'S'

Table 1 Evidence for epitope mimicry

Disease	Evidence described	Reference
Lyme disease	mAb to flagellin of *Borrelia burgdorferi* X-R with human axons. Patient sera react with axons.	29
Myasthenia gravis	Active site peptide of acetyl choline receptor (AChR) has sequence similarity with the HSV gpD and antibodies to the gpD peptide X-R with AChR and inhibit binding of ligand to AChR.	30
TMEV in mice	mAb to TMEV VP-1 protein X-R with oligodendrocytes and augments demyelination.	31
Viral myocarditis	mAb to coxsackie B4 VP-1 protein X-R with mouse α-cardiac myosin.	32
	Neutralizing antibodies to conformational epitopes of the coxsackie B3 capsid protein induce myocarditis in naive mice; these neutralizing antibodies X-R with the surface of cultured cardiac fibroblasts and induce complement mediated lysis *in vitro*.	33
Peripheral demyelinating neuropathy	mAb to HSV 1 ribonucleotide reductase X-R with P_o myelin protein.	34
	Patient derived IgM mAb to myelin associated glycoprotein X-R with 90–100 kDa protein of *Citrobacter diversus* and *Proteus morgani*.	35
Systemic lupus erythematosus	23 of 63 patients' antibody reacts with ribonucleoprotein smD peptide 95–119 with sequence similarity to EBV nuclear antigen 1 (EBNA1) polypeptide. Three patient sera affinity purified against the smD peptide X-R with the EBNA1 polypeptide and EBV transfected cells.	36

EBV Epstein Barr virus, HSV herpes simplex virus, TMEV Theilers murine encephalitis virus, X-R cross-reacts.

antigen of the optic nerve and the retina being the cause of the eye pathology of river blindness in *Onchocerca volvulus* patients. Antibodies to the Ov39 antigen of the parasite, which is recognized by *O. volvulus* patient sera, cross-react with a 44 kDa antigen isolated from a human cDNA library that localizes to neural tissue in the retina. The two mimicking antigens are also able to stimulate cross-reactive T cell responses.[42] The case for the epitope mimicry leading to the pathogenesis of the eye disease is supported by the work with experimental uveitis in which a similar disease can be induced in Lewis rats by immunization with the S antigen epitope[43] and T cells specific for the epitope can adoptively transfer the disease.[44]

Epitope mimicry in GBS

The disease Guillain-Barre syndrome (GBS) deserves attention here since: (i) it fulfils the first criterion for epitope mimicry—association with the pathogen; (ii) it is not frequently considered despite the observation that the post-infectious syndrome is clearly associated with antibodies to peripheral nerves; and (iii) it exemplifies the fact that epitope mimicry need not be confined to peptide epitopes but may include molecules such as glycolipids. There is a good association with intestinal infection with *Campylobacter jejuni* and the onset of GBS, a disease of the peripheral nervous system involving T cell and antibody reactivity to the myelin antigens P_0, P_1 and gangliosides GM_1, GD_{1a} and GD_{1b}, GT and/or GQ_{1b} as well as increased expression of MHC class II molecules on Schwann cells, IFNγ, ICAM-1, and increased macrophage infiltration.[45] Mimicry of the myelin gangliosides by the LPS of the intestinal bacteria *C. jejuni* which can be isolated from patients with GBS, has been postulated to cause the anti-myelin autoimmunity.[46] Yuki *et al.*[47] described the association of prior infection with *C. jejuni* serotype 19 and the development of GBS and noted that the carbohydrate of its LPS is structurally identical to part of the GM_1 ganglioside. They also showed that *C. jejuni* can be isolated from patients with Fisher syndrome (FS), the acute onset form of GBS which is characterized by antibodies to the GQ_{1b} ganglioside, and that mAb to the GQ_{1b} ganglioside and auto-antibodies to GQ_{1b} from FS cross-react to *C. jejuni* LPS. Antibodies from *C. jejuni* infected enteritis patients without neurological symptoms did not react with gangliosides. In a high percentage of GBS patients (9 out of 11) with previous *C. jejuni* infections antibodies to GM1 can be competitively inhibited by two strains of *C. jejuni*.[48] This data provides good circumstantial support for the hypothesis of mimicry inducing the neurological symptoms that develop after intestinal infection with *C. jejuni*. An observation that some people who had clinical signs of enteritis but no neurological symptoms were infected with the same strain as those who develop FS[49] implies that induction of neurological pathology is restricted by host factors, such as HLA type, which would be in keeping with an autoimmunological mechanism of disease. The ability to show that antibodies to the glycolipids can cause the pathology of GBS would be necessary to support the case for epitope mimicry.

Epitope mimicry in insulin-dependent diabetes mellitis

A case for epitope mimicry in insulin-dependent diabetes mellitis (IDDM) is emerging in the literature but reasonable association of the purported agent, Coxsackie B virus and IDDM has been difficult to establish. The 65 kDa isoform of glutamic acid decarboxylase (GAD) is believed to be the primary target antigen in IDDM and auto-antibodies to GAD are well documented in IDDM[50] and sequence homology to the P2-C replication protein of Coxsackie B enteroviruses has been noted.[51] The Coxsackie viruses have been associated with IDDM by the ability to demonstrate T cell proliferation to three Coxsackie strains in about 50% of 22 newly diagnosed IDDM patients[52] and increased prevalence of anti-Coxsackie antibodies in newly diagnosed children with IDDM.[53] T cell proliferation and antibodies to both the GAD 65 in the region of amino acids 247–279 which encodes the sequence similar to the Coxsackie P2-C antigen and the P2-C mimic have been demonstrated in four IDDM patients.[54] Antibodies to both the GAD 65 and similar P2-C peptides have been found in both Coxsackie B4 infected diabetic mice and IDDM patients and response to each antigen can be competitively inhibited by the other.[55] Other studies found that the T cell epitope of GAD 65 lies in the region of amino acids 473–555, which is inconsistent with the hypothesis of mimicry of GAD amino acids 250–273[56] and MAb to GAD derived from one patient with IDDM were not cross-reactive with the proposed mimicking sequences.[57] Rabbit antisera against the Coxsackie virus B4 P2-C peptide can cross-react and precipitate GAD 65, however, these authors also showed that only 18% of IDDM chidren and 10% of normal subjects have antibodies to this peptide.[58] None the less, Coxsackie B viruses can potentiate diabetes in laboratory animals, anti-P2-C peptide antibodies react with GAD 65 and prior infection with Coxsackie B viruses, and in particular strain B4, is found in a number of IDDM patients.[54,59] It has been proposed that expression of P2-C during Coxsackie virus infection primes T cells to both the exogenous and endogenous GAD antigen on β-cells of the pancreas. Whether GAD is presented on the surface of β-cells in MHC molecules such that T cells could access and bind them has yet to be shown.

Epitope mimicry in rheumatic fever

Microbial infections have long been blamed for the development of rheumatic fever via the induction of cross-reactive antibodies to heart antigens.[60–62] A popular theory which has subsequently been partially substantiated[27,63] that molecular mimicry by so called prominent group A streptococcal antigens, now known to be epitopes in the M surface protein were inducing cross-reactions to antigens in human tissue.[61] This is further supported by a report describing structural similarity between the *Streptococci* sialyl Lewis oligosaccharide and host cardiac selectin which could facilitate binding of bacteria to the heart endocardium[64] and possibly be a target for autoimmunity. Expansion of the epidemiological evidence for the

involvement of bacteria in rheumatic fever has been reviewed in Smiley and Hoffman.[65]

Epitope mimicry by bacteria in reactive arthritis and ankylosing spondylitis

In the 1980s extensive investigation was undertaken to show that mimicry by antigens of a number of enteric bacteria such as *Klebsiella*, *Shigella* and *Streptococcus* caused the pathogenesis of reactive arthritis or ankylosing spondylitis. This area has been thoroughly reviewed elsewhere (for example Smith *et al.*[8]) and is not discussed here. However, it is noteworthy that the suspected target of mimicry was the HLA–B27 molecule and this is the first implication that the target of mimicry was a molecule directly involved in antigen presentation. It is fair to state that a firm link between arthritic diseases and enteric bacteria remains controversial.

A subsequent study has revealed two further candidates for mimicry by *K. pneumoniae* for the pathogenesis of ankylosing spondylitis (AS). Fielder *et al.*[66] propose that the observed sequence similarity between the pulD gene product and B27, and the pulA gene product and type I and IV collagen are involved via epitope mimicry, in the induction of AS. A significant IgG and IgA response to synthetic peptides corresponding to these regions of similarity was demonstrated by ELISA with AS patient sera but it can be noted that the antibody response to collagen was low.

MHC mimicry and autoimmune pathogenesis

Many have noted that the target of mimicry may be the HLA molecules themselves. Rheumatoid factor IgM has been shown to recognize peptides of HLA class I A2 α2 peptides and 53% of 30 RF positive RA patients reacted with these peptides.[67] T cells specific for *M. leprae* HSP 3–13 epitope are also activated by the V3 peptide of the HLA class II DR2 chain.[68]

Of the tens of thousands of peptides associated with MHC class II molecules on the surface of B cells, peptides derived from MHC domains are dominant.[69,70] It is plausible that MHC peptides would make good targets of autoimmune reactions because of this relatively high level of expression on the cell surface. An organism wishing to evade an immune response may seek to mimic epitopes which should be tolerized by the host (i.e. its own tissue type antigens). The fact that an attempted mimicry is incomplete and only similarity results, the epitope created by a mimic may be sufficient to overcome the tolerance mechanisms and prime the immune response against self. The puzzle for this theory being the scenario for the induction of organ specific or non-systemic disease such as rheumatoid arthritis (RA) and IDDM is that the target HLA antigen would be expressed on cells systemically.

Epitope mimicry of the HLA–DR4 susceptibility locus in RA

It has been suggested that a viral antigen or bacterial HSP which mimics host HSP could be the initiating RA by molecular mimicry.[71] Initially the proposed mimic was mycobacterial HSP 65 and the target was the human homologue HSP 65. Now there is another level of complexity to the mimicry since not only is the host HSP 65 a target but there is also proposed mimicry by bacterial HSP and other antigens of infectious agents and the HLA DR4 β-chain allele associated with RA susceptibility in the region where this allele differs from other non-RA associated alleles (EQRRAA).[72]

One mimic postulated to be involved in the development of RA is the epitope of the *E. coli* HSP *dnaJ* (QKRAA) which has been used to induce rabbit antibodies that recognize the HLA protein.[73] During microbial infection, the immunological responses against the infectious agent generate expression of HSP of host origin and HSP of the infectious agent may also be expressed and responded to by auto-reactive T cells.[74] This process could initiate an autoimmune response against host synovium and thus commence the pathogenesis of RA. In the experimental model AA, responses to an epitope of mycobacterial HSP 65 by a specific T cell clone induces arthritis in Lewis rats presumably by mimicry of the host HSP 65.[22] Numerous studies have shown that patients with RA have both humoral[75] and cell-mediated immune responses to HSP 65 from both mycobacterial and human origin.[76–78] In support of a pathogenic role for immune responses to HSP in arthritis, Born et al.[74] show that the recognition of HSP 65 is by γδ T cells and antibodies to HSP have been observed to react with synovial tissues of arthritic rats and rheumatoid and osteoarthritis in humans.[79] A case against the role of either microbial HSP mimicry of HSP and/or of HLA epitopes is made in an extensive study using ELISA with HSP antigens of various sources. Jarjour *et al.*[80] found increased reactivity to human HSP60 only in 20% of patients with mixed connective tissue disease not AS, Reiter's syndrome (RS) or RA patients. Similarly, Karopoulos *et al.*[81] found no difference in the serum antibody response to HSP 65 between RA, SLE, mycobacterially infected and multisystemic autoimmune disease patients and normal control subjects. In contrast, Albani *et al.*[82] report that T cells from 18 out of 21 RA patients proliferated in response to the *dnaJ*p1 peptide that contains the region of similarity to the HLA molecule and that RA patient antibody but not control subject antibody responses to *dnaJ* were inhibited by the *dnaJ*p1 peptide. However, it should be noted that in their study anti-HSP antibodies were found in both RA and normal sera. It is possible that different epitopes are recognized by RA than other sera but in the study of Karopoulos *et al.*[81] no difference between the two sera sets was found in the recognition of truncated forms of the HSP gene expressed in *E. coli* and therefore this seems an unlikely explanation.

The second sequence similarity with the RA-associated DR4 haplotype (EQKRAA) is with the 110 kDa glycoprotein of EBV (BALF-4). Affinity purified antibodies from EBV-infected mononucleosis patients will cross-react with the HLA DR4 antigen.[83] EBV is a virus often implicated in the pathogenesis of RA and other rheumatic autoimmune diseases like SLE due to serological reactivity to EBV antigens in some patients.[84] Also epitope mim-

icry between EBNA-1 and type I collagen has also been suggested as being implicated in the pathogenesis of RA.[85] Wilson *et al.*[86] report two further examples of sequence similarity and antibody reactivity to peptides mimicking HLA DR4*0401 and not DR4*0402. RA patient sera and not AS or normal sera reacted with peptides of: (i) *P. mirabilis* haemolysin (ESRRAL) and the RA susceptibility sequence of DR4*0401 (EQRRAA); and (ii) *P. mirabilis* urease (LRREI) and collagen XI (LRRET).

The implications of these studies are that HLA association with RA may be more than simply the effect of HLA differences on antigen presentation[87] and linkage to other unknown co-segregating genes. However the case for epitope mimicry in the pathogenesis of arthritis is hindered by the fact that the proposed pathogens are fairly common and it is difficult to establish an exclusive association of specific infections with the disease.

MHC mimicry and the induction of AIDS

There is increasing evidence that mimicry of MHC molecules by the HIV contributes to the depletion of T cells in AIDS. Many examples of mimicry between the HIV *env* proteins and HLA molecules have been found and some of these are described in Table 2. It has also been shown that monoclonal anti-idiotypes against the gp120 of HIV were able to compete with the peptide antigen defining the epitope and inhibit binding of the peptide with its antibody.[92] It is feasible that gp120 itself could induce idiotypes that bind to the host cell determinants like the MHC and initiate an immune response to the cells bearing those molecules.

If mimicry of MHC class II is occurring in AIDS, as patients develop antibodies to the HIV *env*, T cells could be destroyed by autoimmune reactions. Evidence for this aspect of pathogenesis is supported by the observation that the frequency of antibodies to β2 microglobulin free HLA increase with higher disease severity scores.[93] Similarly, Silvestris *et al.*[9] report that antibodies to the HLA molecule correlate with lymphocytopenia. Evidence to support an alternative theory of direct viral effects is that plasma virons incorporate MHC molecules from their host cell into their envelope. The virus particle may then be seen as self and avoid immune response, or act to prime the immune system against the aberrantly expressed MHC.[94] Mimicry of the MHC class II molecule at the CD4 binding site by gp120 may result in partial stimulation of T cells binding through CD4 to the gp120 without co-stimulation of T cell CD3 or CD28 by other normal APC molecules thus resulting in anergy or apoptosis of the T cell.[95]

Considerations for the investigation of epitope mimicry

The results discussed so far has arisen from either: (i) primary sequence similarities between autoimmune epitopes or key proteins; or (ii) discovery of cross-reactive antibody or T cell reactions involved in the autoimmune disease. There are uncertainties in interpreting these results and other sequence similarities listed in the literature as evidence for epitope mimicry.

Determining the significance of primary sequence similarities

The degree of similarity in mimicking peptides necessary for interaction of epitopes with antibody or TCR and MHC molecule, and the degree of divergence that will allow the mimic to escape the normal down-regulating mechanisms are the unknown entities. Though the effects of amino acid substitutions in linear epitopes can to an extent be predicted by use of matrices such as that prepared for antibody recognition by Geysen *et al.*[96] or for isomorphic amino acid substitutions in protein by Tudos *et al.*,[97] their success is not universal. When conducting a retrospective analysis of T cell amino acid substitutions described in the literature it was found that only 63.4% of amino acid substitutions in 213 examples of T cell–epitope–MHC interactions complied with the predicted outcome of the amino acid substitution based on the Tudos matrix.[98] For T cell epitopes the matrices do not

Table 2 Epitope mimicry between HIV and MHC proteins

Protein	Sequence	Experimental result	Reference
HLA class II β-domain and gp41	N**GTERVR** E**GTDRVI**	mAb to peptide reacts with gp41 and HLA proteins. 35% of HIV patient sera reacted with the MHC II molecule.	88
HLA DQ, DR and DP β-chains and *Nef* Bru protein	**QEE**T-T**GVVSTP** **QEE**EEV**GFPVTP**	Not tested.	89
HLA DR β-chain and gp120	**VVSTGLIHNG** **VVSTQLLLNG**	41.6% of HIV patients recognize both peptides.	90
HLA DR α-chain and gp120	**EEHVIIQAEFYLN** **EEVVIRSANFTDN**	48.2% of HIV patients recognize both peptides.	90
HLA DR α-chain and gp41	**VEHWGLDQPL** **VERYLKDQQL**	28.5% of HIV patients recognize both peptides.	90
Common region of HLA class I and gp120	conformation epitope of gp120 amino acids 490–492 and 505–508	The gp120 epitope is immunodominant in HIV patients. mAb cross-reactivity.	91

The letters in bold type represent identical amino acids present in both sequences.

take into account the position of anchor residues for MHC binding or TCR binding sites which are more constrained than other amino acids in the epitope. The method of discovering mimics of an epitope defined by a primary sequence involves database searching for similar sequences then consideration as to the likely significance of the similar sequences. Database search programs such as FASTP[99] were originally devised to find evolutionary-related protein families, hence matches with low level similarity over longer stretches rank higher than high levels of homology over short sequences. A factor to consider is the bias of the databases for human, *E. coli* and viral genomes. Hence the sequences in the data bases, though they are constantly expanding in number, are limited to targets of interest to researchers. An essential consideration to be made when database searching for epitope similarity is that of the significance of the similarity. The probability of chance similarity in primary sequences decreases in proportion with the length over which the similarity extends. The probability of incorporating by chance the same six amino acids in a row in two unrelated proteins is 1 in 20^6 if each amino acid is considered equally likely to be associated next to any other amino acid. However, amino acids tend to pair together and not associate by random assortment.[97,100] Many short oligopeptide motifs ranging in length from di- to octapeptides have been abundantly found in protein similarity searches of totally unrelated sequences.[101,102] The frequency of homologous pentamers found in databases was determined to be 7.9×10^{-7} [101] and of all possible tetrapeptides, 20% did not occur at all and 20% only occurred once in databases. Weise and Carnegie chose the value of greater than 60% similar over 6–15 amino acids for consideration as a peptide with potential physiological mimicry.[103]

The likelihood of a linear sequence of amino acids being an epitope

Not all linear sequence similarities give rise to antibody or T cell reactivity to the similar or mimicked sequence despite the ability to generate cross-reactive antibodies in experimental animals. For example, similar peptides with conservative amino acid substitutions of MBP and human T cell leukaemia virus-I (HTLV-I) which induces a demyelinating encephalitis named HTLV-I associated myelopathy (HAM) were able to induce cross-reactive antibodies in rabbits yet neither peptide was recognized by HAM patient sera or T cells.[104] A similar study investigating the role of MBP sequence similarity in the pathogenesis of the encephalitic condition of visna in maedi visna virus (MVV) infected sheep demonstrated cross-reactivity of antibodies raised against the MVV peptide to the similar MBP peptide and sheep MBP but only the MBP peptide was recognized by the MVV-infected sheep antibodies and no T cell response could be detected to either peptide.[105] In the study of Dyrberg *et al.* serological cross-reactivity was generated between some but not all HSV gpD peptides that shared sequence similarity with the acetylcholine receptor α-chain.[106]

In the previously mentioned study of Wucherpfennig and Strominger only 8 out of 128 peptides that had primary sequence similarity to the MBP epitope motif were able to stimulate the T cell line, despite peptide selection based on structurally conserative amino acid substitutions.[17] Peptides with 9 out of 12 identical amino acids of the Grave's disease antigen thyroid peroxidase (TPO) did not support cross-reactivity of T cell clones specific for the TPO antigen because anchor residues binding to the MHC (DQB1*0602/DQA1*0102) groove resulted in a different conformation presented to the T cell clone.[107] These data demonstrate that factors other than primary sequence similarity are needed for the generation of cross-reactive B and T cell responses.

The suspected mimics need to elicit T or B cells specific for their potential epitope. Epitope prediction strategies have been designed for B cell epitopes[108] and T cell epitopes[109] based on MHC binding motifs, amphipathy of alpha helices, surface probability, flexibility and hydropathy which may provide an indication as to the epitopes within a protein sequence. Epitope prediction programs are not universally applicable or reliable.[110]

The need for epitope presentation and antigen accessibility

For T cell epitopes the similar sequences need to be presented in the appropriate MHC molecule associated with disease. HLA binding studies have now enabled the prediction of peptides that will bind particular MHC motifs.[111] The HLA associations for particular autoimmune diseases are well characterized now and part of this association can be attributed to the ability of particular MHC haplotype to bind key epitopes through specific anchor residues.[112,113] The RA-associated and non-associated DR types differ at four sites in the β-chain and binding specificity to peptides also differ.[87] The non-RA DRB1*0402 MHC allele which is associated with the autoimmune skin disease pemphigus vulgaris, differs in the P4 pocket of the MHC from the RA-associated DRB1 allele and this results in its ability to present the skin disease antigen desmoglein 3.[114] The binding of HLA A 0201 and B27 to EBV EBNA-1 protein peptides was found to be limited not because there are no MHC binding motifs present in EBNA-1 but for other reasons not accounted for by the ability of the MHC to bind the peptides.[115] After examination of the data in the paper by Stuber *et al.*[115] it was evident that prediction of peptides which might bind the particular MHC does not always correspond to the experimental result of binding studies. More than MHC binding is necessary for effective presentation of antigen to T cells. As well as an epitope being able to bind an MHC molecule, factors such as the proteolytic processing of the antigen in the specific cell and the resulting conformation of the MHC and bound peptide are important. In line with this, Englehard and colleagues observed that the frequency of peptides eluted from MHC molecules did not correlate with the affinity of those peptides for the MHC.[116]

Effects of amino acid substitution in T cell epitopes

Some amino acid changes in epitopes have been shown to actually enhance the reactivity of T cells.[117,118] Alternatively, T cell recognition of an epitope bound in MHC need not result in a proliferative immune response that is auto-degenerative. The effect of amino acid substitutions in sequence similarities is dependent upon numerous factors which need to be determined empirically for each sequence similarity identified or epitope being assessed for mimicry. For example, an epitope of MBP which induces EAE in mice was substituted with alanine in up to five places and the corresponding peptide was still able to induce disease[119] which is convincing evidence in support of a degree of flexibility in the interaction of TCR for MHC class II–epitope complexes.

Amino acid substitutions may alternatively result in analogues of the epitope which are presented by the MHC molecule, bind the TCR but deliver only partial secondary signals resulting in altered cytokine production and inhibition of proliferation.[120,121]. Analogues of the influenza haemagglutinin 301–319 epitope bound the MHC class II complex but T cell response was specifically and non-competitively inhibited due to lack of induction of intracellular inositol phosphate production, calcium accumulation and IL-2 production.[122] Substitution of an anchor residue in the influenza matrix protein epitope resulted in the analogue's ability to bind the HLA-B35 MHC complex but it was not able to induce T cell proliferation and also antagonized the proliferation of the T cells presented with the original epitope.[123] Therefore epitope mimics, which are effectively analogues of self epitopes, may likewise inhibit a reaction or fail to induce proliferation of T cells.

Analogues may act antagonistically and much lower concentrations of the analogue may inhibit the response normally resulting from the original epitope. Epitope analogues of the HSP 65 180–188[124] for AA and a combination of antagonist peptides of the encephalitic proteolipid protein epitope 139–151[125] or MBP epitope 97–99[126] for EAE have been used in therapy for prevention of the autoimmune disease at concentrations up to 10-fold lower than the original epitope concentration required to induce disease. Mimicking peptide epitopes from pathogens may therefore act to anergize or down-regulate a response to self epitope. There are natural examples of viruses which contain and express altered epitopes that abrogate the immune response to its natural or dominant antigen version. Natural antagonistic epitope analogues have been found in isolates of HIV[127,128] and HBV.[129] The ability to induce a cross-reactive T cell response to an HLA allele by an EBV peptide[130] was found to result in absence of a particular T cell response to that epitope in individuals with that particular HLA allele.[131] Therefore rather than a proliferative response being induced by the presence of a similar epitope in the virus, the response had been abrogated and the people were tolerant to that epitope. Page *et al.*[132] showed that though an altered peptide ligand was unable to stimulate T cell proliferation it was functional in the ability to induce negative selection of T cells in the thymus. In the light of the research presented in this paragraph it is evident that primary sequence similarity and even T cell recognition of similar peptides should be considered with guarded optimism when searching for potential instigators of autoimmunity through cross-reactive immune responses. A mimic may be as likely to tolerize as to induce a proliferative response depending on other factors such as the genetic haplotype and presence of co-stimulatory signals.

Cross-reactions with non-linear or non-protein epitopes

A further consideration for the theory of mimicry is that the mimicking antigen need not be similar at the primary amino acid sequence level. Cross-reactivity of T cells between peptides from unrelated proteins with only marginal sequence similarity has been shown.[107,133] Antibody cross-reactivity is often demonstrated without primary sequence similarity. A similar antigenic surface can be made up of associations of amino acids from distal regions of the same or different peptide chains of a complex protein antigen or totally dissimilar molecules such as carbohydrate or nucleotide structures, or linear stretches of amino acids which display the same conformation to the antibody or TCR. For example, synthetic peptide libraries have been used to define the polyspecificity of mAb to an oncogene peptide and it was found that certain peptides were mimotopes but had no amino acid homology to the original epitope and some peptides even had higher affinity binding to the mAb than the original antigen.[134] In mice, the *in vivo* expression of the polyoma virus T antigen from a plasmid carrying the T antigen gene was sufficient to generate antibodies reactive to double strand DNA and histones.[135] The mechanism by which expression of a viral DNA binding protein induced antibodies to either DNA and DNA binding proteins was not elucidated but it was stated by the authors that anti-DNA antibodies in some SLE patients are expressed simultaneously with polyoma virus production. Another study showed that the anti-DNA antibodies in SLE may be directed against protein antigens or at least be cross-reactive with a protein, HP8, selected from a cDNA library by antibodies to DNA.[136] Hence there is molecular mimicry between the shape of the DNA and this protein to which these antibodies also bind. It may be possible that the polyoma T antigen and other viral proteins act as mimics of host DNA and are a priming target for the development of auto-antibodies in diseases like SLE and SS.

B cells as presenters of epitope mimics

Much of the data on mimicry is in reference to antibody cross-reactivity and one criticism of the theory of mimicry is that T cells mediate many of the autoimmune diseases. An hypothesis could be that B cells are intrinsically involved in autoimmune pathogenesis mediated by mimicry due to their role as APC and thus cross-reactive B cell responses may be crucial to the pathogenesis of autoimmune disease because they present mimicking epitopes to T cells. Mamula and colleagues described two experi-

ments in which either human snRNP or cytochrome C was used to prime an immune response in mice against the non-self protein and as a result, an immune response to the self protein was elicited. Immunization with the murine protein could not induce a T or B cell response to the murine protein but immunization with the human homologue caused antibody production to the murine protein. Transfer of self reactive B cells to naive mice facilitated a T cell response to the murine protein in recipients.[24,137] The importance of this research is that an autoimmune response was induced by a foreign molecule with only slight antigenic differences from the self molecule. Similarly, mimicking epitopes of pathogens could in theory induce a B cell response to the mimic that can present antigen to T cells and break the mechanisms that are normally maintaining the self tolerance. James *et al.*[138] injected a single peptide of auto-antigen RNP Sm B/B′ into numerous rabbits and antibodies to a range of epitopes from that molecule and other RNP were induced over time. It has been noted that six regions of the 60 kDa Ro antigen in SLE share sequence similarity with the nucleocapsid (N) protein of the vesicular stomatitis virus (VSV) purported to be implicated in SLE. Immunization of rabbits with the VSV N protein induced antibodies reactive with the N protein and the similar Ro antigen. Repeated immunization with the N protein induced antibodies to numerous Ro peptides including ones that did not share sequence similarity.[139] It was inferred that the N protein activated cross-reactive B cells that recognized the Ro antigen and then acted as antigen presenting cells priming T cells to other Ro peptides which in turn provided help to other B cells thus resulting in epitope spreading. It would follow then that a mimicking antigen, similar in only one epitope, may initiate a primary cross-reactive response to that epitope that subsequently results in recognition of numerous epitopes in the mimicked host protein. If this were to be the case, one would expect that autoimmune diseases would be characterized by responses to many epitopes and the initial target would be difficult to determine. Recognition of multiple antigens and epitopes is evident in IDDM, SLE, RA, PBC and probably most autoimmune diseases. Clinical studies are usually conducted in the phase of pathogenesis when multiple epitopes and antigens are recognized by polyclonal T and B cell responses. It is conceivably difficult to investigate the hypothesis of mimicry at this stage since the initial event leading to autoimmunity may have long since passed.

A model of autoimmune pathogenesis mediated by epitope mimicry

A useful model for the induction of autoimmune disease based on the observations presented in this review is shown in Figure 1. A mimicking antigen sufficiently different from self proteins as to avoid tolerance, yet similar enough to self epitopes as to cross-react, primes a B cell that may produce antibodies that cross-react with a self protein. In addition or alternatively, the primed B cell presents the mimicking epitope bound in MHC class II to

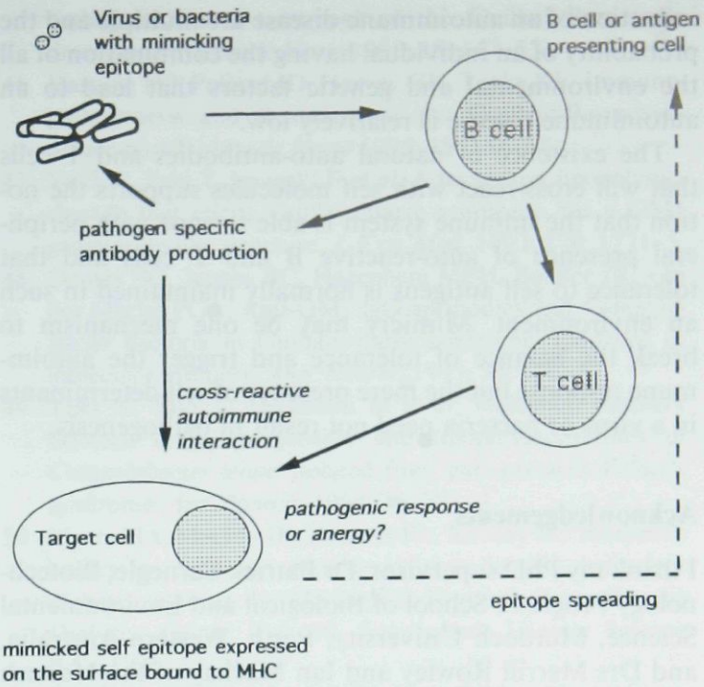

Figure 1 Mechanisms of autoimmune disease induced by epitope mimicry. B cells present mimicking epitopes of infectious agents to T cells via a MHC class II pathway. In addition, they produce antibodies with specificity for the instigating epitope that cross-react with host proteins containing the mimicked epitope. T cells interact with host tissue expressing the mimicked self epitope in the context of MHC class I and, depending on the appropriate secondary signalling, a pathogenic autoimmune response develops. As the immune response persists new epitopes are processed from the target tissue and epitope spreading occurs.

T cells in a manner that results in stimulation of the T cells that then interact with the antigen bound by MHC class I *in situ*. In this way a disease process could be initiated. As the disease progresses, new epitopes from the original and related molecules may emerge and mask the response to the instigating epitope. This model would account for the oligo or polyclonality seen in the T cell responses of autoimmune disease patients, for example MS or RA patients.[140,141] This model does not explain why disease develops in a particular tissue if the target auto-antigen is common to all cells such as the mitochondrial pyruvate dehydrogenase complex which is the primary auto-antigen in PBC.[142] This model depends on a self epitope being expressed in the context of MHC class I on the cell surface with the necessary secondary signalling for T cell reactivity or in the instance of antibody cross-reactivity the accessibility of a B cell epitope. It is known that stimulation of inactive T cells with peptide epitopes complexed with soluble MHC class II and no secondary signals undergo apoptosis.[143] The 'out clause' in this model, then, is that T cells inappropriately stimulated with antigen mimics would be likely to apoptose, or anergize, and thus an autoimmune response would not ensue. A combination of factors such as local increased expression of cytokines, vascular adhesion molecules, HSP and MHC induced by infection may create an environment in which mimicry of host epitopes could initiate an ongoing autoimmune response in patients with the permissive genetic background. Fortunately, the requirements for the

induction of an autoimmune disease are multiple and the probability of an individual having the combination of all the environmental and genetic factors that lead to an autoimmune disease is relatively low.

The existence of natural auto-antibodies and T cells that will cross-react with self molecules supports the notion that the immune system is able to cope with peripheral presence of auto-reactive B and T cells and that tolerance to self antigens is normally maintained in such an environment. Mimicry may be one mechanism to break the balance of tolerance and trigger the autoimmune response but the mere presence of self determinants in a virus or bacteria need not result in pathogenesis.

Acknowledgements

I thank my PhD supervisor, Dr Patrick Carnegie, Biotechnology Program, School of Biological and Environmental Science, Murdoch University, Perth, Western Australia, and Drs Merrill Rowley and Ian Mackay of the Monash University, Melbourne, Victoria, for their informative discussions during preparation of this manuscript. I am grateful for support from the National Multiple Sclerosis Society of Australia and the National Health and Medical Research Council during preparation of this review.

References

1 Oldstone MBA. Molecular mimicry and autoimmune disease. *Cell* 1987; **50**: 819–820.

2 Bulter P, Hamilton-Miller J, Baum H, Burroughs AK. Detection of M2 antibodies in patients with recurrent urinary tract infection using an ELISA and purified PBC specific antigens. Evidence for a molecular mimicry mechanism in the pathogenesis of primary biliary cirrhosis? *Biochem. Mol. Biol. Int.* 1995; **35**: 473–85.

3 Luo A-M, Garza KM, Hunt D, Tung KSK. Antigen mimicry in autoimmune disease sharing of amino acid residues critical for pathogenic T cell activation. *J. Clin. Invest.* 1993; **92**: 2117–23.

4 Neurath AR, Strick N. Antigenic mimicry of an immunoglobulin A epitope by a hepatitis B virus cell attachment site. *Virology* 1990; **178**: 631–4.

5 Carnegie PR, Lawson MA. Viral mimicry and disease. *Today's Life Sci.* 1990; **2**: 14–20.

6 Gao J-L, Murphy PM. Human cytomegalovirus open reading frame *US28* encodes a functional β chemokine receptor. *J. Biol. Chem.* 1994; **269**: 28 539–42.

7 Fujinami RS. Molecular Mimicry. In: Rose NR and Mackay IR (eds) *The Autoimmune Diseases II.* San Diego: Academic Press Inc., 1992; 153–69.

8 Smith JL, Palumbo SA, Walls I. Relationship between foodborne bacterial pathogens and the reactive arthritides. *J. Food Safety* 1993; **13**: 209–36.

9 Silvestris F, Williams RC Jr, Dammacco F. Autoreactivity in HIV-1 infection: Role of molecular mimicry. *Clin. Immunol. Immunopathol.* 1995; **75**: 197–205.

10 Solimena M, de Camilli P. Coxsackieviruses and diabetes. *Nature Med.* 1995; **1**: 25–26.

11 Srinivasappa J, Saegusa J, Prabhakar BS *et al.* Molecular mimicry: Frequency of reactivity of monoclonal antiviral antibodies with normal tissues. *J. Virol.* 1986; **57**: 397–401.

12 Ray SK, Putterman C, Diamond B. Pathogenic autoantibodies are routinely generated during the response to foreign antigen: A paradigm for autoimmune disease. *Proc. Natl Acad. Sci. USA* 1996; **93**: 2019–24.

13 Coutinho A, Kazatchkine MD, Avrameas S. Natural autoantibodies. *Curr. Opin. Immunol.* 1995; **7**: 812–18.

14 Allegretta M, Nicklas JA, Sriram S, Albertini RJ. T cells responsive to myelin basic protein in patients with multiple sclerosis. *Science* 1990; **247**: 718–21.

15 Catalfamo M, Roura-Mir C, Sospedra M *et al.* Self-reactive cytotoxic γδ T lymphocytes in Graves' Disease specifically recognize thyroid epithelial cells. *J. Immunol.* 1996; **156**: 804–11.

16 Bhardwaj V, Kumar V, Geysen H, Sercarz E. Degenerate recognition of a dissimilar antigenic peptide by myelin basic protein-reactive T cells. *J. Immunol.* 1993; **151**: 5000–10.

17 Wucherpfennig KW, Strominger JL. Molecular mimicry in T cell-mediated autoimmunity: Viral petides activate human T cell clones specific for myelin basic protein. *Cell* 1995; **80**: 695–705.

18 Matzinger P. Tolerance, danger and the extended family. *Annu. Rev. Immunol.* 1994; **12**: 720–41.

19 Ramsdell F, Fowlkes BJ. Clonal deletion versus clonal anergy: The role of the thymus in inducing self tolerance. *Science* 1990; **248**: 1342–8.

20 Nossal GJV. Negative selection of lymphocytes. *Cell* 1994; **76**: 229–39.

21 Vandenbark AA, Gill T, Offner H. A myelin basic protein specific T lymphocyte line which mediates experimental autoimmune encephalomyelitis. *J. Immunol.* 1985; **135**: 223–8.

22 van Eden W, Hogervorst EJM, Hensen EJ, van der Zee R, van Embden JDA, Cohen IR. A cartilage-mimicking T-cell epitope on a 65 K mycobacterial heat-shock protein: Adjuvant arthritis as a model for human rheumatoid arthritis. *Curr. Top. Microbiol. Immunol.* 1989a; **145**: 27–43.

23 Lawson CM, O'Donoghue HL, Reed WD. Mouse cytomegalovirus infection induces antibodies which cross-react with virus and cardiac myosin: A model for the study of molecular mimicry in the pathogensis of viral myocarditis. *Immunology* 1992; **75**: 513–19.

24 Mamula MJ, Fatenejad S, Craft J. B cells process and present lupus autoantigens that initiate autoimmune T cell responses. *J. Immunol.* 1994; **152**: 1453–61.

25 Fujinami RS, Oldstone MBA. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: Mechanism for autoimmunity. *Science* 1985; **230**: 1043–5.

26 Haaheim LR, Halse A-K, Kvakestad R, Stern B, Normann O, Jonsson R. Serum antibodies from patients with primary Sjogren's syndrome and systemic lupus erythematosus recognise multiple epitopes on the La(SS-B) autoantigen resembling viral protein sequences. *Scand. J. Immunol.* 1996; **43**: 115–21.

27 Krisher K, Cunningham MW. Myosin: A link between *Streptococci* and heart. *Science* 1985; **227**: 413–15.

28 Talbot PJ, Paquette J-S, Ciurli C, Antel JP, Ouellet F. Myelin basic protein and human coronavirus 229E cross-reactive T cells in multiple sclerosis. *Ann. Neurol.* 1996; **39**: 23–240.

29 Sigal LH. Molecular mimicry and Lyme Borreliosis. *Ann. Neurol.* 1990; **28**: 195–6.

30 Schwimmbeck PL, Dyrberg T, Drachman DB, Oldstone

MBA. Molecular mimicry and myasthenia gravis: An autoantigenic site of the acetylcholine receptor α-subunit that has biological activity and reacts immunologically with *Herpes simplex* virus. *J. Clin. Invest.* 1989; **84**: 1174–80.

31 Yamada M, Zurbriggen A, Fujinami RS. Monoclonal antibody to Theiler's murine encephalomyelitis virus defines a determinant on myelin and oligodendrocytes, and augments demyelination in experimental allergic encephalomyelitis. *J. Exp. Med.* 1990; **171**: 1893–907.

32 Beisel KW, Scrinivasappa J, Prabhakar BS. Identification of a putative shared epitope between coxsackie virus B4 and alpha cardiac myosin heavy chain. *Clin. Exp. Immunol.* 1991; **86**: 49–55.

33 Gauntt CJ, Aizpe JM, Higdon AL *et al.* Molecular mimicry, anti-coxsackievirus B3 neutralizing monoclonal antibodies, and myocarditis. *J. Immunol.* 1995; **154**: 2983–95.

34 Hojeberg B, Ingemarsson R, Kristensson K, Lycke E, Olsson T. A monoclonal antibody against HSV type 1 ribonucleotide reductase cross-reacts with the P_o protein of peripheral nerve myelin. *J. Neurol. Sci.* 1991; **106**: 91–5.

35 Brouet J-C, Mariette X, Gendron M-C, Dubreuil M-L. Monoclonal IgM from patients with peripheral demyelinating neuropathies cross-react with bacterial polypeptides. *Clin. Exp. Immunol.* 1994; **96**: 466–9.

36 Sabbatini A, Bombardieri S, Migliorini P. Autoantibodies from patients with systemic lupus erythematosus bind a shared sequence of SmD and Epstein-Barr virus-encoded nuclear antigen EBNA-1. *Eur. J. Immunol.* 1993; **23**: 1146–52.

37 Ferrari I, Levin MJ, Wallukat G *et al.* Molecular mimicry between the immunodominant ribosomal protein P0 of *Trypanosoma cruzi* and a functional epitope on the human β_1-adrenergic receptor. *J. Exp. Med.* 1995; **182**: 59–65.

38 van Voorhis WC, Schlekewy L, Trong HL. Molecular mimicry by *Trypanosoma cruzi*: The F1–160 epitope that mimics mammalian nerve can be mapped to a 12-amino acid peptide. *Proc. Natl Acad. Sci. USA* 1991; **88**: 5993–7.

39 Grauert MR, Houdayer M, Hontebeyrie-Joskowciz M. *Trypanosoma cruzi* infection enhances polyreactive antibody response in an acute case of human Chagas' disease. *Clin. Exp. Immunol.* 1993; **93**: 85–92.

40 Zwirner NW, Malchiodi EL, Chiaramonte MG, Fossati CA. A lytic monoclonal antibody to *Trypanosoma cruzi* bloodstream trypomastigotes which recognizes an epitope expressed in tissue affected in Chagas' disease. *Infect. Immun.* 1994; **62**: 2483–9.

41 Van Voorhis W, Barrett L, Koelling R, Farr AG. FL-160 proteins of *Trypanosoma cruzi* are expressed from a multigene family and contain two distinct epitopes that mimic nervous tissues. *J. Exp. Med.* 1993; **178**: 681–94.

42 Braun G, McKechnie NM, Gurr W. Molecular and immunological characterization of hr44, a human ocular component immunologically cross-reactice with antigen Ov39 of *Onchocerca volvulus*. *J. Exp. Med.* 1995; **182**: 1121–32.

43 Donoso LA, Gregerson DS, Fling SP, Merryman C, Sery TW. The use of synthetic peptides in the study of experimental autoimmune uveitis. *Curr. Eye Res.* 1990; **9**: 155–61.

44 Singh VK, Yamaki K, Abe T, Shinohara T. Molecular mimicry between uveitopathogenic site of retinal S-antigen and *Escherichia coli* protein: Induction of experimental autoimmune uveitis and lymphocyte cross-reaction. *Cell. Immunol.* 1989b; **122**: 262–73.

45 Hartung HP, Pollard JD, Harvey GK, Toyka KV. Immunopathogenesis and treatment of the Guillain-Barre syndrome-part I. *Muscle Nerve* 1995; **18**: 147–53.

46 Hartung HP, Pollard JD, Harvey GK, Toyka KV. Immunopathogenesis and treatment of the Guillain-Barre syndrome-part II. *Muscle Nerve* 1995; **18**: 154–64.

47 Yuki N, Taki T, Imagaki F *et al.* A bacterium lipopolysaccharide that elicits Guillain-Barre syndrome has a GM1 ganglioside-like structure. *J. Exp. Med.* 1993; **178**: 1771–5.

48 Oomes PG, Jacobs BC, Hazenberg MPH, Banffer JR, van der Meche FGA. Anti-GM_1 IgG antibodies and *Campylobacter* bacteria in Guillain-Barre syndrome: Evidence of molecular mimicry. *Ann. Neurol.* 1995; **38**: 170–5.

49 Yuki N, Taki T, Takahashi M *et al.* Molecular mimicry between GQ_{1b} ganglioside and lipopolysaccharides of *Campylobacter jejuni* isolated from patients with Fisher's syndrome. *Ann. Neurol.* 1994; **36**: 791–3.

50 Myers MA, Mackay IR, Zimmet PA, Rowley MJ. Autoantibodies to glutamate decarboxylase in insulin dependent diabetes mellitus. In: Marshall S, Home P, Rizza R (eds) *Diabetes Annual*, Vol. 10. Amsterdam: Elsevier Science B.V., 1996; 15–36.

51 Kaufman DL, Erlander MG, Clare-Salzler M, Atkinson MA, Maclaren NK, Tobin AJ. Autoimmunity to two forms of glutamate decarboxylase in insulin-dependent diabetes mellitus. *J. Clin. Invest.* 1992; **89**: 283–92.

52 Jones DB, Amstrong N. Proliferative lymphocyte responses to viruses containing sequence similarity to glutamic acid decarboxylase in insulin-dependent diabetes. *Diabetic Med.* 1994; **11** (Suppl. 2): S17.

53 Hyoty H, Hiltunen M, Knip M *et al.* A prospective study of the role of Coxsackie B and other enterovirus infections in the pathogenesis of IDDM. *Diabetes* 1995; **44**: 652–7.

54 Atkinson MA, Bowman MA, Campbell L, Darrow BL, Kaufman DL, Maclaren NK. Cellular immunity to a determinant common to glutamate decarboxylase and coxsackie virus in insulin-dependent diabetes. *J. Clin. Invest.* 1994; **94**: 2125–9.

55 Hou J, Said C, Franchi D, Dockstader P, Chatterjee NK. Antibodies to glutamic acid decarboxylase and P2-C peptides in sera from coxsackie virus B4 infected mice and IDDM patients. *Diabetes* 1994; **43**: 1260–6.

56 Lohmann T, Leslie RD, Hawa M, Geysen M, Rodda S, Londei M. Immunodominant epitopes of glutamic acid decarboxylase 65 and 67 in insulin-dependent diabetes mellitus. *Lancet* 1994; **343**: 1607–8.

57 Richter W, Mertens T, Schoel B *et al.* Sequence homology of the diabetes-associated autoantigen glutamate decarboxylase with coxsackie B4–2C protein and heat shock protein 60 mediates no molecular mimicry of autoantibodies. *J. Exp. Med.* 1994; **180**: 721–6.

58 Lonnrot M, Hyoty H, Knip M *et al.* Antibody cross-reactivity induced by the homologous regions in glutamic acid decarboxylase (GAD_{65}) and 2C protein of coxsackievirus B4. *Clin. Exp. Immunol.* 1996; **104**: 398–405.

59 Clements GB, Galbraith DN, Taylor KW. Coxsackie B virus infection and onset of childhood diabetes. *Lancet* 1995; **346**: 221–3.

60 Adams DD. A theory of the pathogenesis of rheumatic fever, glomerulo-nephritis and other autoimmune disease triggered by infection. *Clin. Exp. Immunol.* 1969; **5**: 105–15.

61 Williams RC. Rheumatic fever and the *Streptococcus*. Another look at molecular mimicry. *Am. J. Med.* 1983; **75**: 727–30.

62 Dale JB, Beachy EH. Sequence of myosin-crossreactive epitopes of streptococcal M protein. *J. Exp. Med.* 1986; **164**: 1785–90.

63 Cunningham MW, Antone SM, Gulizia JM, McManus BM, Fischetti VA, Guantt CJ. Cytotoxic and viral neutralizing antibodies crossreact with streptococcal M protein, enteroviruses, and human cardiac myosin. *Proc. Natl Acad. Sci. USA* 1992; **89**: 1320–4.

64 Hirota K, Kanitani H, Nemoto K, Ono T, Miyake Y. Cross-reactivity between human sialyl Lewis oligosaccharide and common causative oral bacteria of infective endocarditis. *FEMS Immunol. Med. Microbiol.* 1995; **12**: 159–64.

65 Smiley JD, Hoffman WL. Southwestern internal medicine conference: The role of infections in the rheumatic diseases: Molecular mimicry between bacterial and human stress proteins? *Am. J. Med. Sci.* 1991; **301**: 138–49.

66 Fielder M, Pirt SJ, Tarpey I *et al.* Molecular mimicry and ankylosing spondylitis: possible role of a novel sequence in pullulanase of *Klebsiella pneumoniae*. *FEBS Lett.* 1995; **369**: 243–8.

67 Williams RC, Malone CC, Kao K-J. IgM rheumatoid factors react with human class I HLA molecules. *J. Immunol.* 1996; **156**: 1684–94.

68 Haanen JBAG, Ottenhoff THM, Lai A Fat RFM, Soebono H, Spits H, de Vries RRP. *Mycobacterium leprae*-specific T cells from a tuberculoid leprosy patient suppress HLA-DR3-restricted T cell responses to an immunodominant epitope in 65-kDa hsp of Mycobacteria. *J. Immunol.* 1990; **145**: 3898–904.

69 Engelhard VH. Structure of peptides associated with class I and class II MHC molecules. *Annu. Rev. Immunol.* 1994; **12**: 181–207.

70 Chicz RM, Lane WS, Robinson RA, Rucco M, Strominger JL, Gorga JC. Self-peptides bound to the type I diabetes associated class II MHC molecules HLA-DQ1 and HLA-DQ8. *Int. Immunol.* 1994; **6**: 1639–49.

71 Albani S, Roudier J. Molecular basis for the association between HLA DR4 and rheumatoid arthritis. From the shared epitope hypothesis to a peptidic model of rheumatoid arthritis. *Clin. Biochem.* 1992; **25**: 209–12.

72 McCusker CT, Reid B, Green D, Gladman DD, Buchanan WW, Singal DP. HLA-D region antigens in patients with rheumatoid arthritis. *Arthritis Rheum.* 1991; **34**: 192–7.

73 Albani S, Tuckwell JE, Esparza L, Carson DA, Roudier J. The susceptibility sequence to rheumatoid arthritis is a cross-reactive B cell epitope shared by the *Escherichia coli* heat shock protein dnaJ and the histocompatibility leukocyte antigen DRB10401 molecule. *J. Clin. Invest.* 1992; **89**: 327–31.

74 Born W, Hall L, Dallas A *et al.* Recognition of a peptide antigen by heat-shock-reactive γδ T lymphocytes. *Science* 1990; **249**: 67–9.

75 Bhar GM, Rook GAW, Al-saffar M, van Embden J, Stanford JL, Behbehani K. Antibody levels to mycobacteria in relation to HLA type: Evidence for non-HLA-linked high levels of antibody to the 65 kD heat shock protein of *M. bovis* in rheumatoid arthritis. *Clin. Exp. Immunol.* 1988; **74**: 211–15.

76 Hermann E, Mayet W-J, Lohse AW, Grevenstein J, Meyer zum Buschenfelde K-H, Fleischer B. Proliferative response to synovial fluid and peripheral blood mononuclear cells to arthritogenic and non-arthritogenic microbial antigens and to the 65-kDa mycobacterial heat-shock protein. *Med. Microbiol. Immunol.* 1990; **179**: 215–24.

77 Burmester GR, Altstidl U, Kalden JR, Emmrich F. Stimulatory response towards the 65 kDa heat shock protein and other mycobacterial antigens in patients with rheumatoid arthritis. *J. Rheumatol.* 1991; **18**: 171–6.

78 de Graeff-Meeder ER, van der Zee R, Rijkers GT *et al.* Recognition of human 60 kD heat shock protein by mononuclear cells from patients with juvenile chronic arthritis. *Lancet* 1991; **337**: 1368–72.

79 de Graeff-Meeder ER, Voorhorst M, van Eden W *et al.* Antibodies to the mycobacterial 65-kd heat-shock protein are reactive with synovial tissue of adjuvant arthritic rats and patients with rheumatoid arthritis and osteoarthritis. *Am. J. Pathol.* 1990; **137**: 1013–17.

80 Jarjour WN, Jefferies BD, Davis JS, Welch WJ, Mimura T, Winfield JB. Autoantibodies to human stress proteins: A survey of various rheumatic and other inflammatory diseases. *Arth. Rheum.* 1991; **34**: 1133–8.

81 Karopoulos C, Rowley MJ, Handley CJ, Strugnell RA. Antibody reactivity to mycobacterial 65 kDa heat shock protein: Relevance to autoimmunity. *J. Autoimmunity.* 1995; **8**: 235–48.

82 Albani S, Keystone EC, Nelson JL *et al.* Positive selection in autoimmunity: abnormal immune responses to a bacterial dnaj antigenic determinant in patients with early rheumatoid arthritis. *Nature Med.* 1995; **1**: 448–52.

83 Roudier J, Petersen J, Rhodes GH, Luka J, Carson DA. Susceptibility to rheumatoid arthritis maps to a T-cell epitope shared by the HLA-Dw4 DR β-1 chain and the Epstein-Barr virus glycoprotein gp110. *Proc. Natl Acad. Sci. USA* 1989; **86**: 5104–8.

84 Fox RI, Luppi M, Pisa P, Kang H-I. Potential role of Epstein-Barr virus in Sjogren's syndrome and rheumatoid arthritis. *J. Rheumatol.* 1992; **19** (Suppl. 32): 18–24.

85 Birkenfeld P, Haratz N, Klein G, Sulitzeanu D. Cross-reactivity between the EBNA-1 p107 peptide, collagen, and keratin: Implications for the pathogenesis of rheumatoid arthritis. *Clin. Immunol. Immunopathol.* 1990; **54**: 14–25.

86 Wilson C, Ebringer A, Ahmadi K *et al.* Shared amino acid sequences between major histocompatibility complex class II glycoproteins, type XI collagen and *Proteus mirabilis* in rheumatoid arthritis. *Ann. Rheum. Dis.* 1995; **54**: 216–20.

87 Hammer J, Gallazzi F, Bono E *et al.* Peptide binding specificity of HLA-DR4 molecules: correlation with rheumatoid arthritis association. *J. Exp. Med.* 1995; **181**: 1847–55.

88 Golding H, Robey FA, Gates FTI *et al.* Identification of homologous regions in human immunodeficiency virus I gp41 and human MHC class II β 1 domain. *J. Exp. Med.* 1988; **167**: 914–23.

89 Vega MA, Guigo R, Smith TF. Autoimmune response in AIDS. *Nature* 1990; **345**: 26.

90 Zaitseva MB, Moshnikov SA, Kozhich AT *et al.* Antibodies to MHC class II peptides are present in HIV-1-positive sera. *Scand. J. Immunol.* 1992; **35**: 267–73.

91 Lopalco L, De Santis C, Meneveri R *et al.* Human immunodeficiency virus type 1 gp120 C5 region mimics the HLA class I α1 peptide-binding domain. *Eur. J. Immunol.* 1993; **23**: 2016–21.

92 Zaghouani H, Goldstein D, Shah H *et al.* Induction of antibodies to the envelope protein of the human immunodeficiency virus by immunization with monoclonal anti-idiotypes. *Proc. Natl Acad. Sci. USA* 1991; **88**: 5645–9.

93 Borghi MO, De Santis C, Barcellini W *et al.* Autoantibodies

against β2-microglobulin-free HLA antigens in AIDS patients. *J. Acq. Immune Def. Syndr.* 1993; **6**: 1114–19.

94 Rossio JL, Bess J Jr, Henderson LE, Cresswell P, Arthur LO. HLA class II on HIV particles is functional in superantigen presentation to human T cells: implications for HIV pathogenesis. *AIDS Res. Hum. Retroviruses* 1995; **11**: 1433–9.

95 Bisset LR. Molecular mimicry in the pathogenesis of AIDS: The HIV/MHC/mycoplasma triangle. *Med. Hypoth.* 1994; **43**: 388–96.

96 Geysen HM, Mason TJ, Rodda SJ. Cognitive features of continuous antigenic determinants. *J. Mol. Recog.* 1988a; **1**: 32–41.

97 Tudos E, Cserzo M, Simon I. Predicting isomorphic residue replacements for protein design. *Int. J. Pept. Protein Res.* 1990; **36**: 236–9.

98 Davies JM. Searching for molecular mimicry in lentiviral diseases of sheep and goats. PhD Thesis, Murdoch University, Western Australia, Australia, 1993.

99 Lipman DJ, Pearson WR. Rapid and sensitive protein similarity searches. *Science* 1985; **227**: 1435–41.

100 McLachlan AD. Repeating sequences and gene duplication in proteins. *J. Mol. Biol.* 1972; **64**: 417–37.

101 McCaldon P, Argos P. Oligopeptide biases in protein sequences and their use in predicting protein coding regions in nucleotide sequences. *Proteins Struct. Funct. Genet.* 1988; **4**: 99–122.

102 Ohno S. To be or not to be a responder in T-cell responses: Ubiquitous oligopeptides in all proteins. *Immunogenetics* 1991; **34**: 215–21.

103 Weise MJ, Carnegie PR. An approach to searching protein sequences for superfamily relationships or chance similarities relevant to the molecular mimicry hypothesis: Application to the basic protein of myelin. *J. Neurochem.* 1988; **51**: 1267–73.

104 Davies JM, Sonoda S, Yashiki S, Osame M, Carnegie PR. Mimicry between HTLV-I and myelin basic protein: No response in HTLV-I-associated myelopathy patients. *J. Neuroimmunol.* 1992; **41**: 239–44.

105 Davies JM, Watt NJ, Torsteindottir S, Carnegie PR. Mimicry of a 21.5 kDa myelin basic protein peptide by a maedi visna virus polymerase peptide does not contribute to the pathogenesis of encephalitis in sheep. *Vet. Immunol. Immunopathol.* (in press).

106 Dyrberg T, Oldstone MBA. Peptides as probes to study molecular mimicry and virus-induced autoimmunity. *Curr. Top. Microbiol. Immunol.* 1986; **130**: 25–37.

107 Quarantino S, Thorpe CJ, Travers PJ, Londei M. Similar antigenic surfaces, rather than sequence homology, dictate T-cell epitope molecular mimicry. *Proc. Natl Acad. Sci. USA* 1995; **92**: 10 398–402.

108 Jameson B, Wolf H. The antigenic index: A novel algorithm for predicting antigenic deteminants. *CABIOS* 1988; **4**: 181–6.

109 Delisi C, Berzofsky JA. T-cell antigenic sites tend to be amphipathic structures. *Proc. Natl Acad. Sci. USA* 1985; **82**: 7042–52.

110 Stern PS. Predicting antigenic sites on proteins. *Trends Biotechnol.* 1991; **9**: 163–9.

111 Hammer J. New methods to predict MHC-binding sequences within protein antigens. *Curr. Opin. Immunol.* 1995; **7**: 263–9.

112 DiBrino M, Parker KC, Shiloach J *et al.* Endogenous peptides bound to HLA-A3 possess a specific combination of anchor residues that permit identification of potential antigenic peptides. *Proc. Natl Acad. Sci. USA* 1993; **90**: 1508–12.

113 Hammer J, Belunis C, Bolin D *et al.* High-affinity binding of short peptides to major histocompatibility complex class II molecules by anchor combinations. *Proc. Natl Acad. Sci. USA.* 1994; **91**: 4456–60.

114 Wucherpfennig KW, Yu B, Bhol K *et al.* Structural basis for major histocompatibility complex (MHC)-linked susceptibility to autoimmunity: Charged residues of a single MHC binding pocket confer selective presentation of self-peptides in pemphigus vulgaris. *Proc. Natl Acad. Sci. USA* 1995; **92**: 11 935–9.

115 Stuber G, Dillner J, Modrow S *et al.* HLA-A0201 and HLA-B7 binding peptides in the EBV-encoded EBNA-1, EBNA-2 and BZLF-1 proteins detected in the MHC class I alleles in EBNA-1. *Int. Immunol.* 1995; **7**: 653–63.

116 Chen Y, Sidney J, Southwood S *et al.* Naturally processed peptides longer than nine amino acid residues bind to the class I MHC molecule HLA-A2.1 with high affinity and in different conformations. *J. Immunol.* 1994; **152**: 2874–81.

117 Smilek DE, Wraith DC, Hodgkinson S, Dwivedy S, Steinman L, McDevitt HO. A single amino acid change in a myelin basic protein peptide confers the capacity to prevent rather than induce experimental autoimmune encephalomyelitis. *Proc. Natl Acad. Sci. USA* 1991; **88**: 9633–7.

118 Boehncke W-H, Takeshita T, Pendleton CD *et al.* The importance of dominant negative effects of amino acid side chain substitution in peptide-MHC molecule interactions and T cell recognition. *J. Immunol.* 1993; **150**: 331–41.

119 Gautam AM, Pearson CI, Smilek DE, Stainman L, McDevitt HO. A polyalanine peptide with only five native myelin basic protein residues induces autoimmune encephalitis. *J. Exp. Med.* 1992; **176**: 605–9.

120 Racioppi L, Ronchese F, Matis LA, Germain RN. Peptide-major histocompatibility complex class II complexes with mixed agonist/antagonist properties provide evidence for ligand-related differences in T cell receptor-dependent intracellular signaling. *J. Exp. Med.* 1993; **177**: 1047–60.

121 Sloan-Lancaster J, Allen PM. Significance of T-cell stimulation by altered peptide ligands in T cell biology. *Curr. Opin. Immunol.* 1995; **7**: 103–9.

122 De Magistris MT, Alexander J, Coggeshall M *et al.* Antigen analog-major histocompatibility complexes act as antagonists of the T cell receptor. *Cell* 1992; **68**: 625–34.

123 Dong T, Boyd D, Rosenberg W *et al.* An HLA-B35-restricted epitope modified at an anchor residue results in an antagonist peptide. *Eur. J. Immunol.* 1996; **26**: 335–9.

124 Wauben MHM, Boog CJP, van der Zee R, Joosten I, Schlief A, van Eden W. Disease inhibition by major histocompatibility complex binding peptide analogues of disease-associated epitopes: More than blocking alone. *J. Exp. Med.* 1992; **176**: 667–77.

125 Franco A, Southwood S, Arrhenius T *et al.* T cell receptor antagonist peptides are highly effective inhibitors of experimental allergic encephalomyelitis. *Eur. J. Immunol.* 1994; **24**: 940–6.

126 Brocke S, Gijbels K, Allegretta M *et al.* Treatment of experimental encephalomyelitis with a peptide analgoue of myelin basic protein. *Nature* 1996; **379**: 343–6.

127 Callahan KM, Fort MM, Obah EA, Reinherz EL, Siliciano RF. Genetic variability in HIV-1 gp120 affects interactions with HLA molecules and T cell receptor. *J. Immunol.* 1990; **144**: 3341–6.

128 Klenerman P, Rowland-Jones S, McAdam S *et al.* Cytotoxic T-cell activity antagonized by naturally occurring HIV-1 Gag variants. *Nature* 1994; **369**: 403–7.

129 Bertoletti A, Sette A, Chisari F *et al.* Natural variants of cytotoxic epitopes are T-cell receptor antagonists for antiviral cytotoxic T cells. *Nature* 1994; **369**: 407–10.

130 Burrows SR, Khanna R, Burrows JM, Moss DJ. An alloresponse in humans is dominated by cytotoxic T lymphocytes (CTL) cross-reactive with a single Epstein-Barr virus CTL epitope: Implications for graft-verus-host disease. *J. Exp. Med.* 1994; **179**: 1155–61.

131 Burrows SR, Silins SL, Moss DJ, Khanna R, Misko IS, Argaet VP. T cell receptor repertoire for a viral epitope in humans is diversified by tolerance to background major histocompatibility complex antigen. *J. Exp. Med.* 1995; **182**: 1703–15.

132 Page DM, Alexander J, Snoke K *et al.* Negative selection of $CD4^+CD8^+$ thymocytes by T-cell receptor peptide antagonists. *Proc. Natl Acad. Sci. USA* 1994; **91**: 4057–61.

133 Harris DP, Vordermeier H-M, Singh M, Moreno C, Jurcevic S, Ivanyi J. Cross-recognition by T cells of an epitope shared by two unrelated mycobacterial antigens. *Eur. J. Immunol.* 1995; **25**: 3173–9.

134 Pinilla C, Chendra S, Appel JR, Houghten RA. Elucidation of monoclonal antibody polyspecificity using a synthetic combinatorial library. *Pept. Res.* 1995; **8**: 250–7.

135 Moens U, Seternes O-M, Hey AW *et al. In vivo* expression of a single viral DNA-binding protein generates systemic lupus erythematosus-related autoimmunity to double-stranded DNA and histones. *Proc. Natl Acad. Sci. USA* 1995; **92**: 12 393–7.

136 Zack DJ, Yamamoto K, Wong AL, Stempniak M, French C, Weisbart RH. DNA mimics a self-protein that may be a target for some anti-DNA antibodies in synthetic lupus erythematosus. *J. Immunol.* 1995; **154**: 1987–94.

137 Mamula MJ, Lin R-H, Janeway CJ, Hardin JA. Breaking T cell tolerance with foreign and self co-immunogens: A study of autimmune B and T cell epitopes of cytochrome c. *J. Immunol.* 1992; **149**: 789–95.

138 James JA, Gross T, Scofield H, Harley JB. Immunoglobulin epitope spreading and autoimmune disease after peptide immunization: Sm B/B′-derived PPPGMRPP and PPPGIRGP induce spliceosome autoimmunity. *J. Exp. Med.* 1995; **181**: 453–561.

139 Huang S-C, Pan Z, Kurien BT, James JA, Harley JB, Scofield, RH. Immunisation with vesicular stomatitis virus nucleocapsid protein induces autoantibodies to the 60 kD Ro ribonucleoprotein particle. *J. Investig. Med.* 1995; **43**: 151–8.

140 Richert JR, Robinson ED, Johnson, AH *et al.* Heterogeneity of the T-cell receptor β gene rearrangements generated in myelin basic protein-specific T-cell clones isolated from a patient with multiple sclerosis. *Ann. Neurol.* 1991; **29**: 299–306.

141 Bucht A, Oksenberg JR, Lindblad S, Gronberg A, Steinman L, Klareskog L. Characterization of T-cell receptor αβ repertoire in synovial tissue from different temporal phases of rheumatoid arthritis. *Scand. J. Immunol.* 1992a; **35**: 159–65.

142 Bjorkland A, Totterman TH. Is primary biliary cirrhosis an autoimmune disease. *Scand. J. Gastroenterol.* 1994; **29** (Suppl. 204): 32–9.

143 Arimilli S, Mumm J, Nag B. Antigen-specific apoptosis in immortalized T cells by soluble MHC class II-peptide complexes. *Immunol. Cell Biol.* 1996; **74**: 96–105.