RA antigenic peptides

The present invention provides novel naturally-processed RA antigenic peptides which are candidate markers for erosive and non-erosive RA. These antigenic peptides are presented by human MHC class II HLA-DR molecules. Moreover, these antigenic peptides linked to MHC class II molecules, as well as antibodies reactive with said antigenic peptides, nucleic acids encoding said antigenic peptides, and nucleic acid constructs and host cells for expressing said antigenic peptides are provided. The antigenic peptides of the invention as well as the polypeptides they are derived from can be used as markers in diagnosis of RA and in therapy as anti-RA vaccines.

Rheumatoid Arthritis (RA), originally termed chronic polyarthritis, is a systemic autoimmune disease and one of the most debilitating forms of articular inflammation (Feldmann, M. et al., Cell 85 (1996) 307-310; Dedhia, H.V. & DiBartolomeo, A., Critical care clinics 18 (2002) 841-854). Typically, RA causes joint pain, deformities and severe joint stiffness. The disease can also have its manifestation outside the joints, especially in patients who are positive for an autoantibody, termed "rheumatoid factor" (RF) (Mageed, R.A., in: van Venrooij, W.J. & Maini, R.N. eds., Manual of biological markers of disease, Kluwer Academic Publishers (1996) 1-18). RA occurs quite frequently in the Caucasian population with the susceptibility to RA being influenced by genetic and environmental factors. Both have a crucial effect on the onset and the progression of this autoimmune disease. Approximately 4% of the total population has an increased genetic susceptibility to RA, roughly 20% of which (around 1% of the total population) develops RA as a result of, as yet, uncharacterized non-inheritable factors. Beyond that, RA shows a significant bias in the sex ratio: women have a three fold higher risk for RA than men, indicating that sex hormones may also be involved in the pathogenesis.

In the beginning, RA progresses slowly. Typical early stage symptoms are palm sweating, morning stiffness of fingers and symmetrical joint inflammation. In addition,

rheumatoid nodules can appear which is an indication for tissue affection outside the joints. In a simplified model, the immune system produces autoantibodies against healthy tissue. These autoantibodies attack the articular cartilage in the joint leading to its inflammation and later on to its destruction. This destruction stimulates the immune system to produce more autoantibodies. In addition, cytokines like tumor necrosis-factor alpha (TNF-α) and Interleukin-1 (IL-1) are produced which enhance the inflammatory reaction even further (Houssiau, F.A., Clin Rheumatol 14 Suppl 2 (1995) 10-13). The synovium begins to swell due to infiltration of additional cells of the immune system, such as macrophages and T cells. These cells are actively involved in causing further cell death and in driving joint inflammation (Fox, D.A., Arthritis Rheum 40 (1997) 598-609; Choy, E.H. & Panayi, G.S., N Engl J Med 344 (2001) 907-916). This process resembles a vicious circle of autoantibody production, joint inflammation and joint destruction.

Typically, RA progresses chronically, with 85-90% of all RA patients showing a mild to moderate disease development. Aggressive disease forms leading to complete loss of joint function up to the degree of invalidity is experienced by 10-15% of the patients. In this advanced RA state, patients have a permanent articular inflammation and display rheumatoid nodules. They suffer from strong chronical pain and the inflammation leads to severe finger stiffness and irreversible joint deformations or dislocations.

Diagnosis

There is growing evidence that therapeutic intervention early in the disease can reduce the extent of joint damage (Egsmose, C. et al., J Rheumatol 22 (1995) 2208-2213; Van der Heide, A. et al., Ann Intern Med 124 (1996) 699-707). Since treatment with disease-modifying antirheumatic drugs (DMARDs) is only justified when the risk:benefit or cost:effectiveness ratios are favorable, it is mandatory to be able to differentiate between RA and other forms of arthritis shortly after onset of the disease (Kirwan, J.R. & Quilty, B., Clin Exp Rheumatol 15 (1997) 15-25). The diagnosis is made by established criteria based on clinical history, physical examination and laboratory tests. The American Society of Rheumatism published a catalog of criteria to help gaining objective evidence for RA (Arnett, F.C. et al., Arthritis Rheum 31 (1987) 315-324). But so far, not a single test is available which is specific for RA. Several biological and biochemical markers, e.g. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA) or RF are utilized for the evaluation of RA. However, these markers are non-specific, as they appear in other inflammatory or autoimmune diseases as well. The RF, for instance, is an autoantibody that is present in the serum of approximately 50% of RA patients. Since increased levels of the same autoantibody can also be found in the context of other inflammatory diseases, such as Sjögren syndrome, endokarditis or chronical hepatitis, RF is

unsuitable to serve as a diagnostic marker for RA. Rather than being of diagnostic value *per se*, the above mentioned biochemical and biological markers are useful for assessing disease activity and prognosis as well as in the treatment and management of RA patients (Nakamura, R.M., J Clin Lab Anal 14 (2000) 305-313).

Recently, a diagnostic set of criteria was developed that consists of clinical and biochemical aspects which were claimed to discriminate, at an early state, between self-limiting, persistent non-erosive, and persistent erosive RA (Visser, H. et al., Arthritis Rheum 46 (2002) 357-365). Self-limiting arthritis was characterized by natural remission: there was no arthritis on examination in a patient for a certain period of time. Erosive arthritis was defined based on the presence of erosions on radiographs of the hands and/or feet. In particular, the use of antibodies recognizing cyclic citrullinated peptides appears to be promising and suggests an important role for citrullinated antigens in the early diagnosis and prognosis of erosive RA (Schellekens, G.A. et al., J Clin Invest 101 (1998) 273-281; Vincent, C. et al., J Rheumatol 25 (1998) 838-846). The early recognition of erosive RA allows early intervention with DMARDs, which will lead to earlier disease control and improvement of disease outcome (Symmons, D.P.M. et al., J Rheumatol 25 (1998) 1072-1077; Anderson, J.J. et al., Arthritis Rheum 43 (2000) 22-29). Likewise, early recognition of self-limiting and non-erosive arthritis will prevent unnecessary treatment with potentially toxic therapeutics (Fries, J.F. et al., Arthritis Rheum 36 (1993) 297-306.

Therapy

The goal of any anti-rheumatic therapy is to relieve pain in order to ease the activities of every day life. So far, complete healing of RA is not possible, but by applying modern therapies the progression of the disease can be slowed down or even stopped. Due to individual differences, each patient requires an individualized therapy and early diagnosis, as mentioned before, is desirable. RA therapy is complex and includes lifelong medicinal treatment as well as physio- and radiotherapy. DMARDs used in RA therapy are basic therapeutics (e.g. Methotrexate, Sulfasalazin, Hydroxychloroquin, Leflunomid, Azathioprin), cortisone, non-steroidal anti-inflammatory drugs (NSAID) or monoclonal antibodies against the pro-inflammatory cytokines TNF-α, IL-1β or their respective receptors (http://rheuma-online.de). These drugs have all in common that they are inhibitors of inflammation by suppressing the immune response. The main disadvantage is their lack of specificity for RA, their adverse effects and their inability to effectively target the causes of RA.

Autoimmunity

Autoimmunity starts when a specific adaptive immune response is initiated against self antigens (autoantigens) manifested by the development of self-reactive T or B cells. The normal consequence of an adaptive immune response against a foreign antigen is the clearance of the antigen from the body. When an adaptive immune response develops against a self antigen, however, the antigen can in most cases not be completely removed from the body, leading to a sustained immune response. As a consequence, the effector mechanisms of immunity cause chronic inflammatory injury to tissues. The mechanisms of tissue damage are essentially the same in autoimmune disease as those that operate in protective immunity and in hypersensitivity. Even though it is not well understood what triggers autoimmunity, several events which are nowadays believed to contribute to the induction of autoimmune diseases and selection of autoantigenic targets have been summarized most recently (Marrack, P. et al., Nat Med 7 (2001) 899-905).

Autoimmune diseases are controlled by properties of particular genes of each individual and environmental factor. The host's genes affect the susceptibility to autoimmunity at least at three levels. First, some of the genes affect the overall reactivity of the immune system and, thus, can predispose the individual to certain or to several different types of autoimmune diseases. Second, this altered immunoreactivity is funneled to particular autoantigens and tissues by other genes that affect recognition of antigenic peptides by T cells. Third, still other genes act on the ability of target tissues to modulate immune attack for instance by influencing the activity of effector cells of the immune system which are destined to initiate an autoaggressive attack. The latter two sets of genes dictate which antigens will be the targets of autoimmunity and hence which organs will be attacked and what damage will occur.

In addition, signals from the environment influence the development of autoimmunity at the same three levels, by affecting the overall reactivity of the immune system, the antigen-specificity and the state of the potential target tissue. And finally, there is cross-talk between genetic and environmental factors.

Major histocompatibility complex (MHC)

Population studies, genotyping and modern approaches at the molecular level have unanimously shown that certain genes encoded by the major histocompatibility complex (MHC) confer a significantly higher risk for the development of RA (Stastny, P., Tissue Antigens 4 (1974) 571-579; Wordsworth, P. et al., PNAS 86 (1989) 10049-10053; Wordsworth, P. & Bell, J., Springer Semin Immunopathol 14 (1992) 59-78). In particular, the class II MHC alleles *HLA-DRB1*0101*, **0401*, **0404* and **0405* in several ethnic groups increase the susceptibility to RA (Reveille, J., Curr Opin Rheumatol 10 (1998) 187-200). E.g. more than 90% of RF-positive RA patients carry one of these susceptibility alleles. HLA

class II molecules are MHC-surface proteins that bind antigenic peptides within the cell and present them on the surface of antigen-presenting cells for interaction with the T cell receptors of $CD4^+$ helper T lymphocytes, thereby initiating a cellular immune response (Banchereau, J. & Steinman, R.M., Nature 392 (1998) 245-252). The RA-association of particular HLA class II molecules together with the presence of large numbers of activated $CD4^+$ T cells in synovial tissue has supported the model of disease induction in which disease-associated HLA-DR molecules present disease-relevant (e.g. synovial) autoantigens and cause stimulation and expansion of synovial T cells, which then drive the inflammatory process (Striebich, C.C. et al., J Immunol 161 (1998) 4428-4436).

MHC class II HLA-DR (short: DR) proteins are heterodimers consisting of monomorphic α- and extremely polymorphic β-chains that bind peptide antigens in a peptide binding groove. This groove generally has four major pockets to accept side chains at relative positions 1, 4, 6 and 9 of the peptide (Stern, L.J. et al., Nature 368 (1994) 215-221). The allelic variations between HLA class II molecules account for the differential ability to bind antigenic peptides. This is the rationale why individuals differing in their HLA alleles have divergent antigenic peptide repertoirs, thereby leading to differences in the quality of immune responses (Messaoudi, I. et al., Science 298 (2002) 1797-1800).

Peptides bound by class II MHC molecules are typically longer and more heterogeneous in size (11-25 amino acids) than the peptides bound by class I MHC molecules (8-10 amino acids). This difference arises because the peptide binding groove of class II proteins is open and while peptides are gripped in the midle, their ends can extend out of the groove in a variable fashion (Jones, E.Y., Curr Opin Immunol 9 (1997) 75-79). As a consequence, class II molecules typically bind sets of overlapping peptides that share a common core sequence, termed "T cell epitope", but have different lengths.

More than a decade ago, it was recognized that the DRβ chains encoded by RA-linked DRB1 alleles, although exhibiting polymorphic differences, all share a stretch of identical or almost identical amino acids at positions 67-74, known as the "shared epitope" (Gregersen, P.K. et al., Arthritis Rheum 30 (1987) 1205-1213). Since immunity to autoantigens has been regarded central to the pathogenesis of RA, it was hypothesized that the shared epitope could impose disease linkage on the respective DR molecules by at least two different mechanisms: first, by selecting the relevant autoantigenic peptides for presentation, and second, by selecting the appropriate autoreactive T cell specificities during ontogeny. The three-dimensional structure of DR molecules has indeed revealed that the shared epitope is located in the center of the α-helix flanking one side of the peptide binding groove (Stern, L.J. et al., Nature 368 (1994) 215-221). Thus, strategically this shared epitope region is positioned in such a way that it can interact with both bound peptide and T cell receptor.

However, one of the unresolved mysteries in rheumatology research is the question what are the key arthritogenic antigens and epitopes in man that trigger the onset and the development of RA. Although autoantibodies of different specificity have been identified in serum and synovial fluid of patients it is often unclear whether the antigens which were released at the time of cartilage degradation, were initiating pathogenicity or whether they are merely a consequence of antigen spreading as a result of inflammation (Corrigall, V.M. & Panayi G.S., Crit Rev Immunol 22 (2002) 281-293). Furthermore it is difficult to define pathogenic mechanisms in which the antigen is present throughout the body, including the joint, but the pathology is targeted solely or predominately to the joint.

Autoantigens

The large number of possible autoantigens in RA is derived from studies using sera or, less frequently, T cells from patients with established chronic RA. One of the most convincing joint-specific antigen that has been proposed in the context of DR molecules, is type II collagen (CII), the predominant protein in articular cartilage. Autoantibodies against CII were found in elevated concentrations in the serum and joints of RA patients although it is not yet clear whether anti-CII antibodies are pathogenic in RA (Banerjee, S. et al., Clin Exp Rheumatol 6 (373-380). Snowden and coworkers have shown that peripheral blood T cells from RA patients proliferated to CII, most pronounced in those patients with anti-CII antibodies. However, the response was seen only in 50% of patients (Snowden, N. et al., Rheumatology 40 (1997) 1210-1218). In a mouse model immunization with CII was shown to induce arthritis in mice expressing the class II MHC alleles *DRB1*0401* and **0101* (Rosloniec, E.F. et al., J Exp Med 185 (1997) 1113-1122; Rosloniec, E.F. et al., J immunol 160 (1998) 2573-2578). The immunodominant epitope in both **0401* and **0101* transgenic mice was localized to peptides within residues 261-273 of human CII (Fugger, L. et al., Eur J Immunol 26 (1996) 928-933). The same epitope of CII was capable of stimulating a T cell response in RA patients, particularly in the early stages of disease. Synovial fluid T cells were especially responsive (Kim, H.Y. et al., Arthritis Rheum 42 (1999) 2085-2093).

Although other cartilage proteins have been proposed as RA candidate antigens, DR4-binding epitopes have been defined only for human cartilage glycoprotein 39 (HCgp39). This protein is secreted by synovial cells and articular chondrocytes and its expression is upregulated in plasma and joints during inflammation (Vos, K. et al., Ann Rheum Dis 59 (2000) 544-548). Similar to CII, HCgp39 treatment induces arthritis in mice. In addition a HCgp39 response of peripheral blood T cells from RA patients was detected (Verheijden, G.F. et al., Arthritis Rheum 40 (1997) 1115-1125). The predominant epitope recognized by T cells in DR4 patients was defined between residues 263-275 and identical to the immunodominant epitope found in *DRB1*0401*-transgenic mice after immunization with native HCgp39 (Cope, A.P. et al., Arthritis Rheum 42 (1999) 1497-

1507). Although not disease specific, responses to this peptide did correlate with disease activity in RA patients (Baeten, D. et al., Arthritis Rheum 43 (2000) 1233-1243). Antibodies to HCgp39, however, have also been detected in the sera of patients with inflammatory diseases, such as inflammatory bowel disease and systemic lupus erythematosus (SLE), albeit at a lower level than in RA.

In an attempt to track antigen-specific T cells in RA, soluble peptide-DR4 tetrameric complexes were used to detect synovial $CD4^+$ T cells reactive with CII or HCgp39 in $DR4^+$ patients (Kotzin, B.L. et al., PNAS 97 (2000) 291-296). The CII-DR4 complex bound in a specific manner to CII peptide-reactive T cell hybridomas, but did not stain a detectable fraction of synovial $CD4^+$ cells. Almost similar results were obtained with the HCgp39-DR4 complex suggesting that the major oligoclonal $CD4^+$ T cell expansions present in RA joints are not specific for the dominant CII and HCgp39 determinants described above.

In summary, despite some strong indications for a CII and HCgp39 association with RA, the evidence that they are important antigens in RA is scanty. A direct proof that peptides of CII or HCgp39 are presented in a class II MHC-restricted manner by antigen-presenting cells with subsequent stimulation and activation of synovial $CD4^+$ T cells is still lacking. Furthermore a major problem of animal models is their unknown relevance to RA as CII-induced arthritis by immunizing rats or mice differs in many respects from RA.

Naturally processed MHC class II-associated peptides

An alternative strategy to the identification of RA-specific autoantibodies and T cells relies on the sequence analysis of naturally processed peptide antigens bound to MHC class II molecules. With the help of monoclonal antibodies, class II MHC molecules conferring susceptibility to RA can be purified from cognate cells. RA-associated peptide antigens can be acid-eluted from purified HLA class II molecules. The mixture of small peptides can be separated by HPLC and the peptide sequence be determined by Edman sequencing or mass spectrometry. Due to limitations with peptide purification and sequencing techniques, peptide sequences were, as yet, only obtained from MHC molecules that have been isolated from cultured B cell lines or large amounts of tissue, and the analysis was restricted to a few abundant peptides (Kropshofer et al., J.Exp.Med. 175 (1992) 1799-1803; Chicz, R.M. et al., J Exp Med 178 (1993) 27-47). As a result of the development of high-resolution microcapillary HPLC columns and more sensitive mass spectrometers, MHC-bound peptides can be analyzed more efficiently (Dongre, A.R. et al., Eur J Immunol 31 (2001) 1485-1494; Engelhard, V.H. et al., Mol Immunol 39 (2002) 127-137).

Disclosed herein is a modified peptide isolation and sequencing technique was used to investigate the peptide antigen repertoire of HLA-DR4 molecules derived from

autologous dendritic cells (DCs) which were pulsed with serum or synovial fluid derived from RA patients. The main advantage of this innovative approach is the usage of human DCs that are professionals in RA-relevant antigen processing and presentation, instead of using transgenic animal models or artificial B cell lines.

DCs are enriched in rheumatoid synovial fluid and tissue and are derived from circulating immature precursors (Thomas, R. et al., J Immunol 152 (1994) 2613-2623). They are the most potent antigen-presenting cells which express high levels of MHC molecules together with a variety of accessory molecules (Mellman, I. et al., Trends Cell Biol 8 (1998) 231-237). In a most recent study, it was shown that *ex vivo* differentiated human DCs and macrophages that are phenotypically similar to antigen-presenting cells from RA synovial joints, were capable of generating and presenting immunodominant epitopes from CII and HCgp39 (Tsark, E.C. et al., J Immunol 169 (2002) 6625-6633). DC have the capacity to prime $CD4^+$ helper T cells and to effectively activate cytotoxic $CD8^+$ T cells (Ridge, T. et al., Nature 393 (1998) 474-478). Thus, peptides bound to MHC class II molecules and presented by DCs play a superior role in the pathogenesis of diseases involving T cell-driven immune responses.

Therefore, the problem posed by the lack of knowledge of MHC class II restricted antigenic peptides for RA is solved by providing novel naturally-processed MHC class II associated RA antigenic peptides and the polypeptides they are derived from as markers for RA.

The disclosure herein provides novel naturally-processed antigenic peptides which are candidate RA markers in erosive and non-erosive RA. These antigenic peptides are presented by human MHC class II HLA-DR molecules derived from dendritic cells which were pulsed with serum or synovial fluid derived from patients with established erosive or non-erosive RA. The MHC class II antigenic peptide of the invention are comprising (a) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, or (b) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122 with additional N-and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 39 or SEQ ID NOs. 58 to 102, and originate from interferon-γ-inducible lysosomal thiol reductase, integrin beta-2, phosphatitylinositol-4,5-bisphosphate 3-kinase, urokinase-type plasminogen activator, immunoglobulin heavy chain V-III region (V_H26), DJ-1 protein, apolipoprotein B-100, 26S proteasome non-ATPase regulatory subunit 8, interleukin-1 receptor, fibromodulin, GM-CSF/IL-3/IL-5 receptor, sorting nexin 3, inter-α-trypsin inhibitor heavy chain H4, complement C4, complement C3 (α-chain), complement C3 (β-chain), SH3 domain-binding glutamic acid-rich-like protein 3, interleukin-4-

induced protein 1, hemopexin, Hsc70- interacting protein, invariant chain (Ii), retinoic acid receptor responder protein 2, fibronectin, cathepsin B, tripeptidyl-peptidase II, legumain, platelet activating factor receptor, poly-alpha-2.8-sialyltransferase, and ras-leated protein Rab-11B. The present invention also provides these antigenic peptides and the proteins they are derived from as markers for erosive and/or non-erosive RA. Moreover, these antigenic peptides linked to MHC class II molecules, as well as antibodies reactive with said antigenic peptides, nucleic acids encoding said antigenic peptides, and nucleic acid constructs, host cells and methods for expressing said antigenic peptides are provided. Further methods are provided for isolating and identifying RA antigenic peptides.

In the first aspect, there is provided a MHC class II antigenic peptide comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 49, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 49 with additional N-and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 3.

In a second aspect, there is provided a diagnostic composition comprising an antibody reactive with an MHC class II antigenic peptide as defined above.

In a third aspect, there is provided the use of the MHC class II antigenic peptide comprising

(a) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID Nos. 49 to 57 and SEQ ID Nos. 103 to 122; or

(a) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID Nos. 49 to 57 and SEQ ID Nos. 103 to 122, with additional N- and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID Nos. 1 to 39 and SEQ ID Nos. 58 to 102;

wherein the antigenic peptide is a marker for erosive and/or non-erosive RA.

In a fourth aspect, there is provided the use of the MHC class II antigenic peptide as defined above, wherein the antigenic peptide is a marker for non-erosive RA.

In a fifth aspect, there is provided the use of the MHC class II antigenic peptide comprising:

(a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 109; or

(b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 109 with additional N-and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 68,

wherein the antigenic peptide is a marker for erosive RA.

In a sixth aspect, there is provided the use of the MHC class II antigenic peptide comprising:

(c) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 111; or

(d) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 111 with additional N-and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 72,

wherein the antigenic peptide is a marker for erosive RA.

Fig. 1: Diagram of Dendritic cell (DC)-mediated analysis of tissue samples: Dendritic cells (DCs), the most specialized antigen-presenting cells (APCs), are brought in contact with an antigen source (e.g. synovial fluid) under optimal conditions for antigen uptake and antigen processing. As a control, DCs are cultured under the same conditions in the absence of synovial fluid antigens. After maturation of DCs, antigen-loaded MHC class II molecules are purified and the respective MHC class II-associated antigenic peptides are isolated and identified.

Fig. 2A: ION-TRAP MS Base Peak Chromatogram of MHC class II-associated antigenic peptides that were isolated from dendritic cells pulsed with the serum of a RA patient. The peptides were eluted directly from a RP-C18-HPLC column into the ion trap mass spectrometer for immediate MS/MS identification. The numbers indicate the retention times (upper value) and the molecular masses (lower value) of the most prominent peptide peaks in the mixture at the respective time.

Fig. 2B: ION-TRAP MS spectrum of antigenic peptides at a retention time of 65.4 min. The marked peak was further fragmented and corresponded to a doubly charged peptide ion from the inter-alpha-trypsin inhibitor ITIH4 (cf. table 3).

Fig. 2C: ION-TRAP MS/MS spectrum of the doubly charged peptide ion at m/z 977.1. The fragmentation masses, together with the mass of the parent ion, were searched against a non-redundant human database by using the SEQUEST algorithm. The retrieved sequence MPKNVVFVIDKSGSMSGR (one-letter-code) corresponded to the dominant epitope ITIH4 (271-288) of the inter-alpha-trypsin inhibitor. The positions of the assigned series of N-terminal B-ions and C-terminal Y-ions are marked.

Fig. 3: Summary of the differential binding capacity of the tested candidate RA antigens in the context of binding to the *HLA-DRB1*0401* allele. The putative *HLA-DRB1*0401* binding motif is boxed in grey. and. As a measure for affinity, the peptide

concentration was determined that was needed to reduce binding of a fixed amount of biotinylated HA(307-319) peptide by 50% (IC_{50}) through competition. The reciprocal (1/ IC_{50}) directly correlates with peptide affinity. As a reporter biotinylated HA(307-319) peptide from influenza hemagglutinin (Rothbard, J.B. et al., Cell 52 (1988) 515-523) was included in the study.

The antigenic peptides of the invention are peptides, which are associated with and presented by MHC molecules and thereby can have the potential to activate or tolerize T cells. Antigenic peptides presented by MHC class II molecules are therefore MHC class II associated or MHC class II antigenic peptides, whereas antigenic peptides presented by MHC class I molecules are MHC class I associated or MHC class I antigenic peptides.

Peptides which are derived from proteins that are encoded in the genome of the body or an APC are denoted as "self-peptides". The main function of self-peptides presented by DCs in the peripheral lymphoid organs is thought to be the induction of T cell tolerance to self-proteins. Tolerance is the failure to respond to an antigen; when that antigen is borne by self tissues, tolerance is called self tolerance.

Antigens which are derived from an individual's own body are called "self antigens" or "autoantigens". An adaptive immune response directed against self antigens is called an autoimmune response. Likewise, adaptive immunity specific for self antigens is called autoimmunity. Autoreactivity describes immune responses directed against self antigens. RA is probably due to an autoimmune response that is based on the involvement of autoreactive T cells and/ or autoreactive antibodies. Immunogenic peptide includes, but is not limited to, an antigenic peptide capable of causing or stimulating a cellular or humoral immune response. Such peptides may also be reactive with antibodies.

Peptides derived from proteins encoded in the genome of bacteria, viruses or other foreign invaders and which differ from self-proteins are called "foreign antigenic" or "foreign" peptides. They are able to elicit a T cell response against foreign proteins they are derived from.

RA antigenic peptides are self-peptides that function as self antigens and as a consequence of the disease erroneously trigger autoreactivity against self tissues.

The present invention provides a MHC class II antigenic peptide comprising (a) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, or (b) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, with additional N-and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 39 and SEQ ID NOs. 58 to 102. Preferably, the MHC class II antigenic peptide has a length of less than 26 amino acids, more preferably a length of 11 to 25 amino acids. Even more preferred is the antigenic peptide of the invention with a length of 11 to 19 amino acids. Most preferred is the antigenic peptide of the invention consisting of the peptide binding motif comprising the four anchor amino acids.

The present invention also provides a MHC class II antigenic peptide comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 49, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 49 with additional N-and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 3.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 103, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 103 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NOs. 58 and 59.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 104, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 104 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 60.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 105, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 105 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 61.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 106, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 106 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 62.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 107, or (b) at least the

amino acid sequence of the peptide binding motif of SEQ ID NO. 107 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 63.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 50, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 50 with additional N-and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 5.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 108, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 108 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NOs. 64 to 67.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 109, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 109 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 68.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 110, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 110 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NOs. 69 and 70.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 111, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 111 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 72.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 112, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 112 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 73.

The MHC class II associated novel antigenic peptides of the invention originate from interferon-γ-inducible lysosomal thiol reductase (SEQ ID NOs. 1 to 3), integrin beta-2 (SEQ ID NOs. 58 and 59), phosphatitylinositol-4,5-bisphosphate 3-kinase (SEQ ID NO: 60), urokinase-type plasminogen activator (SEQ ID NO: 61), immunoglobulin heavy chain V-III region (V_H26) (SEQ ID NO: 62), DJ-1 protein (SEQ ID NO: 63), apolipoprotein B-100 (SEQ ID NOs. 4 and 5), 26S proteasome non-ATPase regulatory subunit 8 (SEQ ID

NOs. 64 to 67), interleukin-1 receptor (SEQ ID NO: 68), fibromodulin (SEQ ID NOs.: 69 and 70), GM-CSF/IL-3/IL-5 receptor (SEQ ID NOs. 71 and 72), sorting nexin 3 (SEQ ID NO: 73), inter-α-trypsin inhibitor heavy chain H4 (SEQ ID NOs. 6 to 12), complement C4 (SEQ ID NOs. 13 to 18), complement C3 (α-chain) (SEQ ID NOs. 19 to 23, 74 and 75), complement C3 (β-chain) (SEQ ID NOs. 76 and 77), SH3 domain-binding glutamic acid-rich-like protein 3 (SEQ ID NOs. 24 to 27), interleukin-4-induced protein 1 (SEQ ID NOs. 28 to 30), hemopexin (SEQ ID NOs. 31 to 35 and 78), Hsc70-interacting protein (SEQ ID NOs. 36 to 39), invariant chain (Ii) (SEQ ID NOs. 79 to 83), retinoic acid receptor responder protein 2 (SEQ ID NOs. 84 to 86), fibronectin (SEQ ID NOs. 87 to 91), cathepsin B (SEQ ID NO: 92), tripeptidyl-peptidase II (SEQ ID NOs. 93 and 94), legumain (SEQ ID NO: 95), platelet activating factor receptor (SEQ ID NO: 96), poly-alpha-2.8-sialyltransferase (SEQ ID NO: 97), and ras-leated protein Rab-11B (SEQ ID NOs. 98 to 102).

The single peptide binding groove of MHC class II molecules is about 25 Å long, but in contrast to MHC class I molecules, both sides are open (Stern LJ et al., Nature 1994; 368, 215-221). Thus, naturally processed antigenic peptides eluted from human MHC class II molecules have a minimal length of about 11 residues and attain a maximal length of about 25 residues (Chicz RM et al., J Exp Med 1993; 178, 27-47).

The stability of the MHC-peptide interaction is determined by more than a dozen hydrogen bonds involving the peptide backbone and the complementarity between specificity pockets of the binding groove and appropriately located amino acid side-chains of the peptide. The amino acids of the peptide fitting into the respective pockets were named "anchor" residues. With regard to most HLA-DR alleles, these anchors are located at relative positions P1, P4, P6 and P9. The combination of amino acids at these 4 anchor positions conferring high-stability binding to the respective HLA-DR allelic product and vary from allele to allele. The peptide binding motif is defined herein as the sequence of nine amino acids comprising the four anchor amino acids. The peptide binding motif of the MHC class II antigenic peptide of the invention is depicted in SEQ ID NO. 49 for the peptides derived from interferon-γ-inducible lysosomal thiol reductase (SEQ ID NOs. 1 to 3), in SEQ ID NO. 103 for the peptides derived from integrin beta-2 (SEQ ID NOs. 58 and 59), in SEQ ID NO. 104 for the peptides derived from phosphatitylinositol-4,5-bisphosphate 3-kinase (SEQ ID NO: 60), in SEQ ID NO. 105 for the peptides derived from urokinase-type plasminogen activator (SEQ ID NO: 61), in SEQ ID NO. 106 for the peptides derived from immunoglobulin heavy chain V-III region (V_H26) (SEQ ID NO: 62), in SEQ ID NO. 107 for the peptides derived from DJ-1 protein (SEQ ID NO: 63), in SEQ ID NO. 50 for the peptides derived from apolipoprotein B-100 (SEQ ID NOs. 4 and 5), in SEQ ID NO. 108 for the peptides derived from 26S proteasome non-ATPase regulatory

subunit 8 (SEQ ID NOs. 64 to 67), in SEQ ID NO. 109 for the peptides derived from interleukin-1 receptor (SEQ ID NO: 68), in SEQ ID NO. 110 for the peptides derived from fibromodulin (SEQ ID NOs.: 69 and 70), in SEQ ID NO. 111 for the peptides derived from GM-CSF/IL-3/IL-5 receptor (SEQ ID NOs. 71 and 72), in SEQ ID NO. 112 for the peptides derived from sorting nexin 3 (SEQ ID NO: 73), in SEQ ID NO. 51 for the peptides derived from inter-α-trypsin inhibitor heavy chain H4 (SEQ ID NOs. 6 to 12), in SEQ ID NO. 52 for the peptides derived from complement C4 (SEQ ID NOs. 13 to 18), in SEQ ID NO. 53 for the peptides derived from complement C3 (α-chain) (SEQ ID NOs. 19 to 23, 74 and 75), in SEQ ID NO. 113 for the peptides derived from complement C3 (β-chain) (SEQ ID NOs. 76 and 77), in SEQ ID NO. 54 for the peptides derived from SH3 domain-binding glutamic acid-rich-like protein 3 (SEQ ID NOs. 24 to 27), in SEQ ID NO. 55 for the peptides derived from interleukin-4-induced protein 1 (SEQ ID NOs. 28 to 30), in SEQ ID NO. 56 for the peptides derived from hemopexin (SEQ ID NOs. 31 to 35 and 78), in SEQ ID NO. 57 for the peptides derived from Hsc70-interacting protein (SEQ ID NOs. 36 to 39), in SEQ ID NO. 114 for the peptides derived from invariant chain (Ii) (SEQ ID NOs. 79 to 83), in SEQ ID NO. 115 for the peptides derived from retinoic acid receptor responder protein 2 (SEQ ID NOs. 84 to 86), in SEQ ID NO. 116 for the peptides derived from fibronectin (SEQ ID NOs. 87 to 91), in SEQ ID NO. 117 for the peptides derived from cathepsin B (SEQ ID NO: 92), in SEQ ID NO. 118 for the peptides derived from tripeptidyl-peptidase II (SEQ ID NOs.93 and 94), in SEQ ID NO. 119 for the peptides derived from legumain (SEQ ID NO: 95), in SEQ ID NO. 120 for the peptides derived from platelet activating factor receptor (SEQ ID NO: 96), in SEQ ID NO. 121 for the peptides derived from poly-alpha-2.8-sialyltransferase (SEQ ID NO: 97) and in SEQ ID NO. 122 for the peptides derived from Ras-related protein Rab-11B (SEQ ID NO: 98 to 102).

The peptide binding motif may also comprise at least one, at least two, at least three, at least four or at least five modifications of the amino acid sequence while still attaining the binding capacity of the non-modified peptide binding motif. Preferably, the modified peptide binding motif comprises at least three of the four anchor amino acids of the non-modified peptide binding motif. The amino acid modification may be a conservative amino acid substitution as described below.

Additional binding energy is provided by hydrogen bonds involving residues in front of the P1 anchor and behind the P9 anchor. In agreement with that, in most naturally processed peptides the nonameric core-region (P1-P9) is N- and C-terminally flanked by 3-4 residues. Hence, the majority of peptides are 15-17-mers. Longer peptides protrude from the groove, thereby allowing access of exopeptidases which are trimming both ends.

Therefore, the MHC class II antigenic peptide of the invention comprising (a) at least the amino acid sequence of the peptide binding motif selected from the group consisting of

SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, or (b) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122 with additional N- and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 39 and SEQ ID NOs. 58 to 102, preferably comprises additional N- and C- terminal flanking amino acid residues providing additional binding energy.

Preferably, the MHC class II antigenic peptide of the present invention has a binding capacity to the corresponding MHC class II molecule of between one tenth and ten-fold the IC_{50} of a corresponding peptide selected from the group consisting of SEQ ID NOs. 1 to 39 and SEQ. ID NOs. 58 to 102. The binding capacity of a peptide is measured by determining the concentration necessary to reduce binding of a labelled reporter peptide by 50%. This value is called IC_{50}. A MHC class II antigenic peptide of the invention maintains its binding capacity to the relevant HLA class II molecules as long as it attains IC_{50} values between one tenth and 10-fold the IC_{50} of the established reference peptides.

Since peptide trimming occurs in an individual fashion both before and after binding into the peptide binding groove, the occurrence of several truncation variants sharing a common nonameric core region is a common feature of MHC class II-bound peptides. Importantly, it was shown that C- or N-terminal truncation variants of the same epitope can trigger divergent T cell responses (Arnold et al., (2002) J. Immunol. 169, 739-749).

Several parameters can be envisaged that have an influence on the relative abundance of truncation variants of a particular epitope, e.g. the abundance and integrity of the antigen of relevance, antigen-associated proteins, the abundance of proteases, the type of proteases available and the supply with competitive antigens and/or peptides. Since the antigen supply is a major characteristic that may correlate with the origin of a sample, the ratio of particular truncation variants of an epitope can be of diagnostic value.

A peptide of the invention is a peptide which either has no naturally-occurring counterpart (e.g., such as an mutated peptide antigen), or has been isolated, i.e., separated or purified from components which naturally accompany it, e.g., in tissues such as pancreas, liver, spleen, ovary, testis, muscle, joint tissue, neural tissue, gastrointestinal tissue, or body fluids such as blood, serum, synovial fluid or urine. Typically, the peptide is considered "isolated" when a preparation comprising a peptide of the invention consists to at least 70%, by dry weight of said peptide and to less than 30% of the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, a

preparation of a peptide of the invention consists of at least 80%, more preferably at least 90%, and most preferably at least 99%, by dry weight, the peptide of the invention. Since a peptide that is chemically synthesized is, by its nature, separated from the components that naturally accompany it, the synthetic peptide is "isolated".

The invention further provides analogs of the antigenic peptide of the invention. The term analog includes any peptide which displays the functional aspects of these antigenic peptides comprising the binding capacity IC_{50} and the recognition by antibodies and cells of the immune system. Analogs exhibit essentially the same IC_{50} as the corresponding reference peptide. The term analog also includes conservative substitutions or chemical derivatives of the peptides.

The term "analog" includes any polypeptide having an amino acid residue sequence substantially identical to the sequences described herein in which one or more residues have been conservatively substituted with a functionally similar residue and which displays the functional aspects of the peptides as described herein. Examples of conservative substitutions include the substitution of one non-polar (hydrophobic) residue such as phenylalanine, tyrosine, isoleucine, valine, leucine or methionine for another, the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, between threonine and serine, the substitution of one basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue, such as aspartic acid or glutamic acid for another.

The phrase "conservative substitution" also includes the use of a chemically derivatized amino acid in place of a non-derivatized amino acid. "Chemical derivative" refers to a subject polypeptide having one or more amino acids chemically derivatized by reaction of a functional side group. Examples of such derivatized molecules include for example, those molecules in which free amino groups have been derivatized to form amine hydrochlorides, p-toluene sulfonyl groups, carbobenzoxy groups, t-butyloxycarbonyl groups, chloroacetyl groups, acetyl groups or formyl groups. Free carboxyl groups may be derivatized to form salts, methyl and ethyl esters or other types of esters or hydrazides. Free hydroxyl groups may be derivatized to form O-acyl or O-alkyl derivatives. The imidazole nitrogen of histidine may be derivatized to form N-im-benzylhistidine. Also included as chemical derivatives are those proteins or peptides, which contain one or more naturally-occurring amino acid derivative of the twenty standard amino acids. For examples: 4-hydroxyproline may be substituted for proline; 5-hydroxylysine may be substituted for lysine; 3-methylhistidine may be substituted for histidine; homoserine may be substituted for serine; and ornithine or citrulline may be substituted for lysine.

The MHC class II antigenic peptides of the invention and the proteins they are derived from can be used as markers in diagnosis of RA and in therapy as anti-RA vaccines. The term marker as used herein refers to a biomolecule, preferably a peptide or a polypeptide, which is expressed in a group of patients with a diagnosed disease, e.g. RA, and attains an abundance that is significantly increased or decreased as compared to a control group.

The marker of the present invention may be used as a prognostic marker to predict the susceptibility to a disease, e.g., to predict the susceptibility to RA, as a diagnostic marker for the diagnosis of a disease, e.g. for the diagnosis of RA, as a differential diagnostic marker to differentiate between different forms of a disease, e.g., to differentiate between different forms of RA, as a prognostic marker for the prediction of the outcome of a disease, e.g., for the prognosis of RA, and as a response marker to determine the efficacy of a therapeutic regime, e.g., as a response marker in the treatment of RA.

In a further embodiment, the MHC class II antigenic peptide comprising (a) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, or (b) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, with additional N-and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 39 and SEQ ID NOs. 58 to 102, is used as a marker for erosive and/or non-erosive RA.

In a further embodiment, the MHC class II antigenic peptide comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 49, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 49 with additional N-and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 3 is used as a marker for non-erosive RA.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 103, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 103 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NOs. 58 and 59 is used as a marker for non-erosive RA.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 104, or (b) at least the

amino acid sequence of the peptide binding motif of SEQ ID NO. 104 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 60 is used as a marker for non-erosive RA.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 105, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 105 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 61 is used as a marker for non-erosive RA.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 106, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 106 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 62 is used as a marker for non-erosive RA.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 107, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 107 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 63 is used as a marker for non-erosive RA.

In a further embodiment, the MHC class II antigenic peptide comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 50, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 50 with additional N-and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 5 is used as a marker for erosive RA.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 108, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 108 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NOs. 64 to 67 is used as a marker for erosive RA.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 109, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 109 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 68 is used as a marker for erosive RA.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 110, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 110 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NOs. 69 and 70 is used as a marker for erosive RA.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 111, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 111 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 72 is used as a marker for erosive RA.

Furthermore, a MHC class II antigenic peptide is provided comprising (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 112, or (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 112 with additional N- and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 73 is used as a marker for erosive RA.

In a further embodiment, the MHC class II antigenic peptides of the invention as described above are provided linked to a MHC class II molecule.

Multimers (e.g., dimers, trimers, tetramers, pentamers, hexamers or oligomers) of a class II MHC molecule containing a covalently or non-covalently bound peptide according to the present invention, if conjugated with a detectable label (e.g., a fluorescent moiety, a radionuclide, or an enzyme that catalyzes a reaction resulting in a product that absorbs or emits light of a defined wavelength) can be used to quantify T cells from a subject (e.g., a human patient) bearing cell surface receptors that are specific for, and therefore will bind, such complexes. Relatively high numbers of such T cells are likely to be diagnostic of disease or an indication that the T cells are involved in immunity to the disease. In addition, continuous monitoring of the relative numbers of multimer-binding T cells can be useful in establishing the course of a disease or the efficacy of therapy. Such assays have been developed using tetramers of class I MHC molecules containing an HIV-l-derived or an influenza virus-15 derived peptide (Altman et al. (1996), Science 274:94-96; Ogg et al. (1998), Science 279:2103- 21061), and corresponding class II MHC multimers would be expected to be similarly useful. Such complexes could be produced by chemical cross-linking of purified class II MHC molecules assembled in the presence of a peptide of

interest or by modification of already established recombinant techniques for the production of class II MHC molecules containing a single defined peptide (Kazono et al. (1994), Nature 369:151-154; Gauthier et al. (1998), Proc. Natl. Acad. Sci. U.S.A. 95:11828-118331). The class II MHC molecule monomers of such multimers can be native molecules composed of full-length alpha and beta chains. Alternatively, they can be molecules containing either the extracellular domains of the alpha and beta chains or the alpha and beta chain domains that form the "walls" and "floor" of the peptide-binding cleft.

The invention also relates to an antibody, fragments or derivatives thereof, directed to and reactive with the above-described MHC class II antigenic peptides. The general methodology for producing antibodies is well known and is disclosed per example in Kohler and Milstein, 1975, Nature 256,494 or in J. G. R. Hurrel, Monoclonal Hybridoma Antibodies: Techniques and Applications, CRC Press Inc., Boco Raron, FL (1982). The antibodies can be polyclonal or, preferably, monoclonal, or antibody fragments like be F (ab') 2, Fab, Fv or scFv. The antibodies of the present invention may also be humanized (Merluzzi S. et al., (2000), Adv. Clin. Path., 4(2): 77-85) or human antibodies (Aujame L. et al., Hum. Antibodies, (1997), 8(4): 155-168).

The present invention also provides a nucleic acid molecule encoding a MHC class II antigenic peptide of the invention comprising (a) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, or (b) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, with additional N- and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 39 and SEQ. ID NOs. 58 to 102. Preferably, the nucleic acid molecule is a DNA molecule.

Furthermore, a nucleic acid molecule is provided encoding a MHC class II antigenic peptide of the invention linked to a MHC class II molecule.

This invention also provides a recombinant nucleic acid construct comprising the nucleic acid molecules as described above, operably linked to an expression vector. Expression vectors suitable for use in the present invention comprise at least one expression control element operably linked to the nucleic acid sequence encoding the antigenic peptide or the antigenic peptide linked to a MHC class II molecule. The recombinant expression construct may be a DNA construct.

The expression control elements are inserted in the vector to control and regulate the expression of the nucleic acid sequence encoding the antigenic peptide of the invention. Examples of expression control elements include, but are not limited to, lac system,

operator and promoter regions of phage lambda, yeast promoters and promoters derived from polyoma, adenovirus, retrovirus or SV40. Additional preferred or required operational elements include, but are not limited to, leader sequence, termination codons, polyadenylation signals and any other sequences necessary or preferred for the appropriate transcription and subsequent translation of the nucleic acid sequence in the host system. It will be understood by one skilled in the art that the correct combination of required or preferred expression control elements will depend on the host system chosen. It will further be understood that the expression vector should contain additional elements necessary for the transfer and subsequent replication of the expression vector containing the nucleic acid sequence in the host system. Examples of such elements include, but are not limited to, origins of replication and selectable markers. It will further be understood by one skilled in the art that such vectors are easily constructed using conventional methods ("DNA Isolation and Sequencing", Bruce A. Roe, Judy S. Crabtree and Akbar S. Khan, Published by John Wiley & Sons, 1996) or are commercially available.

Another aspect of this invention relates to a host organism or a host cell into which a recombinant nucleic acid construct comprising the nucleic acid molecules as described above, operably linked to an expression vector, has been inserted. The host cells transformed with the nucleic acid constructs encompassed by this invention include eukaryotes, such as animal, plant, insect and yeast cells and prokaryotes, such as E. coli. The means by which the nucleic acid construct carrying the nucleic acid sequence may be introduced into the cell include, but are not limited to, microinjection, electroporation, transduction, or transfection using DEAE-dextran, lipofection, calcium phosphate or other procedures known to one skilled in the art (Sambrook et al. (1989) in "Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Press, Plainview, New York).

In a preferred embodiment, eukaryotic expression vectors that function in eukaryotic cells are used. Examples of such vectors include, but are not limited to, retroviral vectors, vaccinia virus vectors, adenovirus vectors, herpes virus vector, fowl pox virus vector, plasmids, or the baculovirus transfer vectors. Preferred eukaryotic cell lines include, but are not limited to, COS cells, CHO cells, HeLa cells, NIH/3T3 cells, 293 cells (ATCC# CRL15731), T2 cells, dendritic cells, monocytes or Epstein-15 Barr Virus transformed B cells.

An antigenic peptide of the invention can be obtained, for example, by extraction from a natural source (e.g., elution from MHC II molecules); by expression of a recombinant nucleic acid encoding the peptide; or by chemical synthesis. A peptide that is produced in a cellular system different from the source from which it naturally originates is "isolated," because it will be separated from components which naturally accompany it. The recombinant peptide expressed by a host organism can be obtained as a crude lysate or can

be purified by standard protein purification procedures known in the art which may include differential precipitation, size exclusion chromatography, ion-exchange chromatography, isoelectric focusing, gel electrophoresis, affinity, and immunoaffinity chromatography and the like. The extent of isolation or purity can be measured by any appropriate method, e.g. mass spectrometry or HPLC analysis. The peptides may be prepared synthetically by procedures described in Merrifield, (1986) Science 232: 341-347, and Barany andMerrifield, The Peptides, Gross and Meienhofer, eds (N. Y., Academic Press), pp. 1-284 (1979). The synthesis can be carried out in solution or in solid phase or with an automatized synthesizer (Stewart and Young, Solid Phase Peptide Synthesis, 2nd ed., Rockford Ill., Pierce Chemical Co. (1984)).

Therefore, the present invention further provides a method for producing a MHC class II antigenic peptide comprising (a) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, or (b) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, with additional N-and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 39 and SEQ ID NOs. 58 to 102, comprising the steps of culturing the host cell containing a recombinant nucleic acid construct as described above under conditions allowing expression of said peptide and recovering the peptide from the cells or the culture medium.

In a further embodiment of the present invention, a method is provided for isolating and identifying MHC class II associated RA antigenic peptides in femtomolar amounts, which method comprises (a) providing immature dendritic cells in a number comprising 0.1 to 5 µg MHC class II molecules; (b) contacting the cells of (a) with serum or synovial fluid and inducing maturation of dendritic cells by adding TNFalpha; (c) isolating class II MHC molecule-antigenic peptide complexes from the cells with methods comprising solubilization of the cells and sequestration of the complexes of MHC class II molecules with antigenic peptides by immunoprecipitation or immunoaffinity chromatography; (d) washing the sequestered complexes of MHC class II molecules with antigenic peptides with water in an ultrafiltration tube; (e) eluting the associated antigenic peptides from the MHC class II molecules at 37°C with diluted trifluoro acetic acid, and (f) separating, detecting and identifying the isolated peptides by liquid chromatography and mass spectrometry. Furthermore, in step (f) of the method, the liquid chromatography comprises a first linear elution step from the reversed-phase material with a volume sufficient to elute the majority of contaminants prior to peptide elution. Moreover, the method may further comprise (g)

analyzing the identified peptides by methods comprising a database and a software developed to perform comparative data analysis across multiple datasets.

The amount of tissue or bodily fluid necessary to obtain e.g. 100 ng MHC class II molecules depends on the number of cells that do express MHC class II and on the expression rate of MHC class II molecules: e.g. 100 ng of MHC class II are equivalent to about 2 x 10^5 mature DCs or 5 to 10 x 10^6 peripheral blood monocytes or about 5 x 10^7 peripheral blood mononuclear cells which can be obtained from about 50 ml of blood.

For the purification of class II MHC molecule-antigenic peptide complexes from cells or tissue, the membranes of the cells or tissue have to be solubilized. Cell lysis may be carried out with methods known in the art, e.g. freeze-and-thaw cycles and the use of detergents, and combinations thereof. Preferred lysis methods are solubilization using detergents, preferably TX-100, NP40, n-octylglucoside, Zwittergent, Lubrol, CHAPS, most preferably TX-100 or Zwittergent 3-12. Cell debris and nuclei have to be removed from cell lysates containing the solubilized receptor-peptide complexes by centrifugation. Therefore, the complexes of class II MHC molecules with antigenic peptides are isolated from the cells with methods comprising solubilization with a detergent.

Furthermore, the MHC class II molecule-peptide complexes are purified from cell lysates by methods comprising immunoprecipitation or immunoaffinity chromatography. For the immunoprecipitation or immunoaffinity chromatography, antibodies specific for MHC class II molecules and suitable for these methods are used. The specific antibodies are preferably monoclonal antibodies, and are covalently or non-covalently e.g. via Protein A, coupled to beads, e.g. sepharose or agarose beads. A selection of the broad panel of anti-HLA antibodies used in the prior art comprises: anti-HLA-DR antibodies: L243, TU36, DA6.147, preferably L243; anti-HLA-DQ antibodies: SPVL3, TU22, TU169, preferably TU22 and TU169; anti-HLA-DP antibody B7/21 and anti-HLA-A,B,C antibodies W6/32 and B9.12.

Monoclonal antibodies specific for different MHC class II molecules may be commercially obtained (e.g. Pharmingen, Dianova) or purified from the supernatant of the respective hybridoma cells using Protein A- or Protein G- affinity chromatography. Purified monoclonal antibodies may be coupled by various methods known in the art, preferably by covalently coupling antibody amino groups to CNBr-activated sepharose.

Immunoisolation of MHC molecules may be performed by incubating the antibody-beads with the cell lysate under rotation for several hours or chromatographically by pumping the cell lysate through a micro-column. Washing of the antibody-beads may be performed in eppendorf tubes or in the microcolumn. The efficacy of the

immunoprecipitation may be analysed by SDS-PAGE and western blotting using antibodies recognizing denatured MHC molecules (anti-HLA-DRalpha: 1B5; anti-HLA class I: HC10 or HCA2).

The sequestered MHC class II molecule-peptide complexes are washed with water or low-salt buffer before elution in order to remove residual detergent contaminants. The low salt buffer may be a Tris, phosphate or acetate buffer in a concentration range of 0.5 – 10 mM, preferably in a concentration of 0.5 mM. In a more preferred embodiment, the MHC class II molecule -peptide complexes are washed with ultrapure water (sequencing grade) conventionally used for HPLC analysis, preferably with ultrapure (sequencing grade) water from MERCK. The washing step may be carried out by ultrafiltration. The ultrafiltration may be carried out in an ultrafiltration tube with a cut-off of 30 kD, 20 kD, 10 kD or 5 kD, preferably of 30 kD and a tube volume of 0.5 – 1.0 ml ("Ultrafree" tubes; Millipore). The washing in the ultrafiltration tube may be carried out 4 to 12 times, preferably 6 to 10 times, with a volume of 10 to 20 times the volume of the beads carrying the receptor-peptide complexes, preferably with a volume of 15 times the beads. The eluted peptides may be separated from the remaining MHC class II molecules using the same ultrafiltration tube. The eluted peptides may then be lyophilized.

By eluting the peptides from the MHC class II molecules, a complex mixture of naturally processed peptides derived from the source of potential antigen and from polypeptides of intra- or extracellular origin, is obtained. Only after elution, peptides can be separated and subjected to sequence analysis.

The antigenic peptides in the method of the present invention may be eluted by a variety of methods known in the art, preferably by using diluted acid, e.g., diluted acetonitrile (Jardetzky TS et al., Nature 1991 353, 326-329), diluted acetic acid and heating (Rudensky AY et al., Nature 1991, 353, 622-626; Chicz RM et al., Nature 1992, 358, 764-768) or diluted trifluoro acetic acid at 37°C (Kropshofer H et al., J Exp Med 1992, 175, 1799-1803). Most preferably, the peptides are eluted at 37°C with diluted trifluoro acetic acid.

The isolated antigenic peptides are then separated, detected and identified. By detecting it is understood that the amino acid sequence of the individual peptides in the mixture of isolated antigenic peptides is elucidated by methods adequate to detect and sequence femtomolar amounts of peptides. By identifying it is understood that it is established from which proteins or polypeptides the antigenic peptides are derived and which sequence they constitute within these proteins or polypeptides.

In a first step, the complex mixture of eluted peptides may be separated by one of a variety of possible chromatographic methods, e.g. by reversed phase, anion exchange, cation exchange chromatography or a combination thereof. Preferably, the separation is performed by C18-reverse phase chromatography or by reversed-phase / cation exchange two-dimensional HPLC, denoted as MudPit (Washburn MP et al., Nat Biotechnol., (2001), 19, 242-247).

The separation is done in a HPLC mode utilizing fused-silica micro-capillary columns which are either connected to a nano-flow electrospray source of a mass spectrometer or to a micro-fractionation device which spots the fractions onto a plate for MALDI analysis.

Liquid chromatography comprises peptide fractionation by the use of a strong ion exchange material and a hydrophobic reversed-phase material. For the elution of the peptides from the ion exchange and reversed-phase material different elution programs are run one after another comprising elutions with salt and with organic solvents, e.g., acetonitrile. The elution from the reversed-phase material is conducted in several steps of linear gradients of different lengths and slopes. A contamination in the sample to be fractionated may be any contamination whose elution competes with the detection of the peptide peaks in the mass spectrometer. Therefore, in order to prevent simultaneous elution, the contaminants have to be eluted with a sufficient solvent volume prior to the peptide elution step. Depending on the column used for liquid chromatography the solvent volume sufficient to elute the contaminants prior to the peptide elution step may be 100 to 200 times the column volume.

A variety of mass spectrometric techniques are suitable, preferably MALDI-post source decay (PSD) MS or electrospray ionization tandem mass spectrometry (ESI-MS), most preferably ion-trap ESI-MS.

The sequences of the individual peptides can be determined by means known in the art. Preferably, sequence analysis is performed by fragmentation of the peptides and computer-assisted interpretation of the fragment spectra using algorithms, e.g. MASCOT or SEQUEST. Both computer algorithms use protein and nucleotide sequence databases to perform cross-correlation analyses of experimental and theoretically generated tandem mass spectra. This allows automated high through-put sequence analysis.

The isolated and identified antigenic peptides of the invention can be validated by the MHC binding motif, the MHC binding capacity and/or by T cell recognition.

MHC binding motif

Peptides associated to a particular MHC molecule (allelic variant) have common structural characteristics, denoted as binding motifs, necessary to form stable complexes with MHC molecules. Peptide ligands eluted from MHC class I molecules are relatively short, ranging from 8-11 amino acids. Moreover, 2 or 3 side chains of the peptide are relevant for binding. The position of the respective amino acid side chains varies with the HLA allele, most often two of these so-called "anchor" residues are located at positions 2 and 9. With respect to a particular anchor position, only 1 or 2 amino acids normally can function as anchor amino acids e.g. leucine or valine V at position 2 in the case of HLA-A2.

In the case of MHC class II molecules, the peptide length varies from 11 to 25 amino acids, as longer peptides can bind since both ends of the peptide binding groove are open. Most HLA class II molecules accommodate up to 4 anchor residues at relative positions P1, P4, P6 and P9 contained in a nonameric core region. This core region, however, can have variable distance from the N-terminus of the peptide. In the majority of cases, 2-4 N-terminal residues precede the core region. Hence, the P1 anchor residues is located at positions 3, 4 or 5 in most HLA class II associated peptides. Peptides eluted from HLA-DR class II molecules share a big hydrophobic P1 anchor, represented by tyrosine, phenylalanine, tryptophane, methionine, leucine, isoleucine or valine.

The position and the exact type of anchor residues constitute the peptide binding motif which is known for most of the frequently occurring HLA class II allelic products. A computer algorithm allowing motif validation in peptide sequences is "Tepitope", available by vaccinome.

MHC binding capacity

Peptides identified by the method of the invention may be tested for their ability to bind to the appropriate MHC class II molecule by methods known in the art using, for example, isolated MHC class II molecules and synthetic peptides with amino acid sequences identical to those identified by the method of the invention (Kropshofer H et al., J. Exp. Med. 1992; 175, 1799-1803; Vogt AB et al., J. Immunol. 1994; 153, 1665-1673; Sloan VS et al., Nature 1995; 375, 802-806). Alternatively, a cellular binding assay using MHC class II expressing cell lines and biotinylated peptides can be used to verify the identified epitope (Arndt SO et al., EMBO J., 2000; 19, 1241-1251)

In both assays, the relative binding capacity of a peptide is measured by determining the concentration necessary to reduce binding of a labelled reporter peptide by 50%. This value is called IC_{50}. Peptide binding with a reasonable affinity to the relevant HLA class II

molecules attain IC_{50} values not exceeding 10-fold the IC_{50} of established reference peptides.

The same binding assays can also be used to test the ability of peptides to bind to alternative class II MHC molecules, i.e., class II MHC molecules other than those from which they were eluted using the method of the invention. The diagnostic methods of the invention using such peptides and therapeutic methods of the invention, using either the peptides or peptides derived from them, can be applied to subjects expressing such alternative class II MHC molecules.

T cell recognition

The epitope verification procedure may involve testing of peptides identified by the method of the invention for their ability to activate CD4+ T cell populations. Peptides with amino acid sequences either identical to those identified in the present invention or corresponding to a core sequence derived from a nested group of peptides identified in the present invention are synthesized. The synthetic peptides are then tested for their ability to activate CD4+ T cells from (a) test subjects expressing the MHC class II molecule of interest and having at least one symptom of the disease; and (b) control subjects expressing the MHC class II molecule of interest and having no symptoms of the disease. Additional control subjects can be those with symptoms of the disease and not expressing the MHC class II molecule of interest.

In some diseases (e.g., those with an autoimmune component) responsiveness in the CD4+ T cells of test subjects but not in CD4+ T cells of the control subjects described in (b) provides confirmatory evidence that the relevant peptide is an epitope that activates CD4+ T cells that can initiate, promote, or exacerbate the relevant disease. In other diseases (e.g., cancer or infectious diseases without an autoimmune component), a similar pattern of responsiveness and non-responsiveness to that described in the previous sentence would indicate that the relevant peptide is an epitope that activates CD4+ T cells that can mediate immunity to the disease or, at least, a decrease in the symptoms of the disease.

CD4+ T cell responses can be measured by a variety of *in vitro* methods known in the art. For example, whole peripheral blood mononuclear cells (PBMC) can be cultured with and without a candidate synthetic peptide and their proliferative responses measured by, e.g., incorporation of [^{3}H]-thymidine into their DNA. That the proliferating T cells are CD4+ T cells can be tested by either eliminating CD4+ T cells from the PBMC prior to assay or by adding inhibitory antibodies that bind to the CD4+ molecule on the T cells, thereby inhibiting proliferation of the latter. In both cases, the proliferative response will be inhibited only if CD4+ T cells are the proliferating cells. Alternatively, CD4+ T cells can be

purified from PBMC and tested for proliferative responses to the peptides in the presence of APC expressing the appropriate MHC class II molecule. Such APC can be B-lymphocytes, monocytes, macrophages, or dendritic cells, or whole PBMC. APC can also be immortalized cell lines derived from B-lymphocytes, monocytes, macrophages, or dendritic cells. The APC can endogenously express the MHC class II molecule of interest or they can express transfected polynucleotides encoding such molecules. In all cases the APC can, prior to the assay, be rendered non-proliferative by treatment with, e.g., ionizing radiation or mitomycin-C.

As an alternative to measuring cell proliferation, cytokine production by the CD4+ T cells can be measured by procedures known to those in art. Cytokines include, without limitation, interleukin-2 (IL-2), interferon-gamma (IFN-gamma), interleukin-4 (IL-4), TNF-alpha, interleukin-6 (IL-6), interleukin-10 (IL-l0), interleukin-12 (IL-12) or TGF-beta. Assays to measure them include, without limitation, ELISA, and bio-assays in which cells responsive to the relevant cytokine are tested for responsiveness (e.g., proliferation) in the presence of a test sample.

Alternatively, cytokine production by CD4+ lymphocytes can be directly visualized by intracellular immunofluorescence staining and flow cytometry.

Moreover, the MHC class II antigenic peptides of the present invention may be used in the diagnosis of RA. Therefore, a further embodiment of the invention is the use of an antigenic peptide according to the present invention as a marker for RA.

Preferably, a MHC class II antigenic peptide comprising (a) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, or (b) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, with additional N-and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 39 and SEQ ID NOs. 58 to 102, is used as a marker for RA.

In another embodiment, the antigenic peptides of the invention may be used as response markers to track the efficacy of a therapeutic regime. Essentially, a baseline value for an antigenic peptide can be determined, then a given therapeutic agent is administered, and the levels of the antigenic peptide are monitored subsequently, whereas a change in the level of the antigenic peptide is indicative of the efficacy of a therapeutic treatment.

Furthermore, the antigenic peptides which are only found in certain stages or phases of a disease, preferably of RA, may be utilized as stage-specific markers. Essentially, the levels of the antigenic peptides which have been linked to a certain disease stage are monitored regularly, thereby providing information about the stage of the disease and its progression.

The invention also includes the use of the polypeptides the RA antigenic peptides are derived from as markers for the diagnosis and monitoring of a disease, preferably of RA, and in particular, of erosive versus non-erosive RA. The rationale for the use of the respective proteins is that DCs reside in most tissues where they capture exogenous antigens via specific receptors and via specialized endocytotic mechanisms (e.g. macropinocytosis) followed by presentation of the processed antigens as peptides on MHC class II molecules. Previous studies have shown that the frequency of a peptide epitope found in the context of MHC class II molecules, e.g. the RA antigenic peptides, in the majority of cases mirrors the abundance of the protein from which this particular peptide was derived from. Therefore, not only the RA antigenc peptides but also the corresponding proteins can serve as markers for RA.

Therefore, in a further embodiment of the present invention, the use of a polypeptide selected from the group consisting of interferon-gamma-inducible lysosomal thiol reductase (SEQ ID NO: 40), integrin beta-2 (SEQ ID NO. 123), phosphatitylinositol-4,5-bisphosphate 3-kinase (SEQ ID NO: 124), urokinase-type plasminogen activator (SEQ ID NO. 125), immunoglobulin heavy chain V-III region (V_H26) (SEQ ID NO. 126), DJ-1 protein (SEQ ID NO. 127), apolipoprotein B-100 (SEQ ID NO: 41), 26S proteasome non-ATPase regulatory subunit 8 (SEQ ID NO. 128), interleukin-1 receptor (SEQ ID NO: 129), fibromodulin (SEQ ID NO. 130), GM-CSF/IL-3/IL-5 receptor (SEQ ID NO. 131), sorting nexin 3 (SEQ ID NO. 132), inter-alpha-trypsin inhibitor heavy chain H4 (SEQ ID NO: 42), complement C4 (SEQ ID NO: 43), complement C3 (SEQ ID NO: 44), SH3 domain-binding glutamic acid-rich-like protein 3 (SEQ ID NO: 45), interleukin-4-induced protein 1 (SEQ ID NO: 46), hemopexin (SEQ ID NO: 47), Hsc70-interacting protein (SEQ ID NO: 48), invariant chain (Ii) (SEQ ID NO. 133), retinoic acid receptor responder protein 2 (SEQ ID NO. 134), fibronectin (SEQ ID NO. 135), cathepsin B (SEQ ID NO: 136), tripeptidyl-peptidase II (SEQ ID NO. 137), legumain (SEQ ID NO. 138), platelet activating factor receptor (SEQ ID NO. 139), poly-alpha-2.8-sialyltransferase (SEQ ID NO. 140), ras-leated protein Rab-11B (SEQ ID NO. 141) as a marker for RA is provided. Preferably, the polypeptide is used as a marker for erosive RA. It is also preferred to use the polypetide as a marker for non-erosive RA. Especially preferred is the use of interleukin-4-induced protein 1 (SEQ ID NO: 46) as a marker for RA. The Fig1 polypeptide has not been known as a marker for RA until now, and is considered as an important candidate marker for RA.

The diagnosis of RA can be made by examining expression and/or composition of a polypeptide or peptide marker for RA, by a variety of methods, including enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. A test sample from an individual is assessed for the presence of an alteration in the expression and/or an alteration in composition of a polypeptide or a peptide of the present invention. An alteration in expression of a polypeptide or peptide can be, for example, an alteration in the quantitative polypeptide expression (*i.e.*, the amount of polypeptide produced); an alteration in the composition of a polypeptide is an alteration in the qualitative polypeptide expression (*e.g.*, expression of a mutant polypeptide or of a different splicing variant).

Both such alterations (quantitative and qualitative) can also be present. An "alteration" in the polypeptide expression or composition, as used herein, refers to an alteration in expression or composition in a test sample, as compared with the expression or composition of the peptide or polypeptide in a control sample. A control sample is a sample that corresponds to the test sample (e.g., is from the same type of cells), and is from an individual who is not affected by RA. An alteration in the expression or composition of the peptide or polypeptide in the test sample, as compared with the control sample, is indicative of RA or a susceptibility to RA. Various means of examining expression or composition of a peptide or polypeptide of the present invention can be used, including spectroscopy, colorimetry, electrophoresis, isoelectric focusing, and immunoassays (*e.g.*, David *et al.*, U.S. Pat. No. 4,376,110) such as immunoblotting (see also Current Protocols in Molecular Biology, particularly chapter 10). For example, in one embodiment, an antibody capable of binding to the polypeptide (*e.g.*, as described above), preferably an antibody with a detectable label, can be used. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

Western blotting analysis, using an antibody as described above that specifically binds to a peptide or polypeptide of the present invention, may be used to measure the level or amount of a peptide or polypeptide in a test sample and comparing it with the level or amount of the peptide or polypeptide in a control sample. Preferably the peptide or polypeptide in a test sample is measured in a homogenous or a heterogenous immuno

assay. A level or amount of the polypeptide in the test sample that is higher or lower than the level or amount of the polypeptide in the control sample, such that the difference is statistically significant, is indicative of an alteration in the expression of the polypeptide, and is diagnostic for a RA or a susceptibility to RA.

Therefore, the present invention also relates to a diagnostic composition comprising an antibody reactive with a MHC class II antigenic peptide of the invention.

In a further embodiment the antigenic peptides of the invention or the proteins they are derived from may be used in the prevention and treatment of a disease, preferably of RA.

One aspect of the invention is a therapeutic purpose, wherein one or more of the identified antigenic peptides are used to vaccinate patients against RA, preferably against erosive and/or non-erosive RA. In the course of the vaccination the antigenic peptide would induce an antigen-specific T cell tolerance in the patient which would ultimately lead to regression of the disease or to an attenuation of disease development.

A promising strategy to induce specific immune tolerance in future clinical trials is the use of DNA tolerizing vaccines. DNA tolerizing vaccines encoding autoantigens alone were shown to reduce T cell proliferative responses (Ruiz, P. et al., J Immunol 162 (1999) 3336-3341), while DNA tolerizing vaccines co-delivering autoantigen plus IL-4 also induced protective T_H2 responses (Garren, H. et al., Immunity 15 (2001) 15-22). Examples of non-polynucleotide-specific tolerizing therapies under development include protein antigens, naturally processed peptides, altered peptide ligands, other biomolecules, such as DNA, or proteins and peptides containing posttranslational modifications, and antigens delivered orally to induce "oral tolerance" (reviewed in: Robinson, W.H. et al., Clin Immunol 103 (2002) 7-12). A potential adverse effect with regard to tolerizing therapies is the development of autoimmunity.

To this end, the relevant RA antigenic peptides may be directly administered to the patient in an amount sufficient for the peptides to bind to the MHC molecules, and provoke peripheral tolerance of T cells.

Alternatively, the antigenic peptides of the invention may be utilized for the generation of vaccines based on DCs. In this case, autologous DCs derived from patients' monocytes may be pulsed with the relevant peptides or recombinant proteins containing the relevant peptide sequences.

Therefore, the present invention provides a pharmaceutical composition comprising a MHC class II antigenic peptide comprising (a) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, or (b) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID NOs. 49 to 57 and SEQ ID NOs. 103 to 122, with additional N-and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 39 and SEQ ID NOs. 58 to 102, an antibody reactive with said antigenic peptide, or a polypeptide selected from the group consisting of SEQ ID NOs 40 to 48 and SEQ. ID NOs. 123 to 141, and optionally a pharmaceutically acceptable excipient, diluent or carrier. The antigenic peptide has to be present in an amount sufficient to tolerize specific lymphocytes. Such an amount will depend on the peptide used, the administration, the severity of the disease to be treated and the general conditions of the patient and will usually range from 1 to 50 mg/ml, for example in case of peptides being loaded on dendritic cells.

An acceptable excipient, diluent or carrier may be phosphate buffered saline for *in vitro* studies and physiological salt solutions for *in vivo* applications.

"Vaccination" herein means both active immunization, i. e. the *in vivo* administration of the peptides to elicit an *in vivo* immune tolerance directly in the patient and passive immunization, i. e. the use of the peptides to tolerize *in vitro* CD4+ T lymphocytes or to stimulate autologous or allogeneic dendritic cells, which are subsequently re-inoculated into the patient.

The present invention also provides the antigenic peptides, antibodies, nucleic acids, host cells, methods, compositions and uses substantially as herein before described especially with reference to the Examples.

Having now generally described this invention, the same will become better understood by reference to the specific examples, which are included herein for purpose of illustration only and are not intended to be limiting unless otherwise specified, in connection with the following figures.

Examples

The examples below are illustrated in connection with the figures described above and based on the methodology summarized in Fig 1, as described in the following. Commercially available reagents referred to in the examples, were used according to manufacturer's instructions unless otherwise indicated.

Methodology of the invention

Dendritic cells and culturing

The study was performed with human dendritic cells which were differentiated from monocytes, as described below. Monocytes were purified from human peripheral blood. The blood was taken from healthy donors with the following haplotypes: (1) *HLA-DRB1*0401, *03011*, (2) *HLA-DRB1*0401, *0304*, (3) *HLA-DRB1*0401, *1301*, (4) *HLA-DRB1*0401, *0701, HLA-DRB1*0401, *0407.*

All cells were cultured in RPMI 1640 medium (short: RPMI) supplemented with 1 mM Pyruvate, 2 mM Glutamine and 10% heat-inactivated fetal calf serum (Gibco BRL, Rockville, MD).

Isolation of peripheral blood mononuclear cells (PBMCs)

Peripheral blood was obtained from the blood bank in Mannheim, Germany as standard buffy coat preparations from healthy donors. Heparin (200 I.U./ml blood, Liquemine, Roche) was used to prevent clotting. Peripheral blood mononuclear cells (PBMCs) were isolated by centrifugation in LSM® (1.077-1.080 g/ml; ICN, Aurora, OH) at 800g (room temperature) for 30 min. PBMCs were collected from the interphase and washed twice in RPMI containing 20 mM Hepes (500g for 15 min, 300g for 5 min). In order to remove erythrocytes, PBMCs were treated with ALT buffer (140 mM ammonium chloride, 20 mM Tris, pH 7.2) for 3 min at 37°C. PBMCs were washed twice with RPMI containing 20 mM Hepes (200g for 5 min).

Generation of dendritic cells from peripheral blood monocytes.

Monocytes were isolated from PBMCs by positive sorting using anti-CD14 magnetic beads (Miltenyi Biotech, Auburn, CA) according to the manufacturer's protocol. Monocytes were cultured in RPMI supplemented with 1% non-essential amino acids (Gibco, BRL, Rockville, MD), 50 ng/ml recombinant human granulocyte macrophage-colony stimulating factor (GM-CSF; S.A. 1.1×10^7 U/mg) (Leucomax; Novartis, Basel

Switzerland) and 3 ng/ml recombinant human IL-4 (S.A. $2.9x10^4$ U/µg) (R&D Systems, Minneapolis, MN). Monocytes were seeded at 0.3 x 10^6/ml in 6-well plates (Costar) for 5 days to obtain immature dendritic cells.

The quality of monocyte-derived immature dendritic cells was routinely monitored by flow-cytometric analysis and assessed to be appropriate when they displayed the following phenotype: CD1a (high), CD3 (neg.), CD14 (low), CD19 (neg.), CD56 (neg.), CD80 (low), CD83 (neg.), CD86 (low) and HLA-DR (high). In contrast, mature dendritic cells (cf. below) display the following phenotype: CD1a (low), CD80 (high), CD83 (high), CD86 (high) and HLA-DR (high). Monoclonal antibodies against CD1a, CD3, CD14, CD19, CD56, CD80, CD83, CD86 as well as the respective isotype controls were purchased from Pharmingen (San Diego, CA).

Exposure of dendritic cells to serum or synovial fluid

Serum and synovial fluid were irradiated for 30 min with ^{137}Cs (70 TBq). To feed dendritic cells with serum- or synovia-derived antigen, 6 x 10^6 immature dendritic cells were pulsed with either 1 ml serum or 0.6 ml synovial fluid. At the same time maturation of dendritic cells was induced by adding 10 ng/ml recombinant human tumor necrosis factor alpha (TNFα; S.A. $1.1x10^5$ U/µg). As a control, 6 x 10^6 immature dendritic cells were incubated with TNFα alone.

After 24 hrs in culture, mature dendritic cells were harvested by centrifugation at 300g for 10 min. Cells were washed with PBS and transferred to an eppendorf tube. After centrifugation at 400g for 3 min, the supernatant was completely removed and the cells were frozen at -70°C.

Generation of anti-HLA class II beads

The anti-HLA-DR monoclonal antibody (mAb) L243 (ATCC, Manassas, VA) was produced by culturing the respective mouse hybridoma cell line. mAb L243 was purified using ProteinA sepharose (Pharmacia, Uppsala, Sweden) and immobilized to CNBr-activated sepharose beads (Pharmacia) at a final concentration of 2.5 mg/ml, according to the manufacturer's protocol. L243 beads were stored in PBS containing 0.1% Zwittergent 3-12 (Calbiochem, La Jolla, CA).

Nano-scale purification of HLA-DR-peptide complexes

Pellets of frozen dendritic cells were resuspended in 10-fold volume of ice cold lysis buffer (1% Triton-X-100, 20 mM Tris, pH 7.8, 5 mM $MgCl_2$, containing protease inhibitors chymostatin, pepstatin, PMSF and leupeptin (Roche, Mannheim, Germany)) and lysed in a horizontal shaker at 1000 rpm, 4°C for 1 h. The cell lysate was cleared from cell debris and nuclei by centrifugation at 10000g, 4°C for 10 min. The lysate was co-incubated with L243 beads (5-10 µl L243 beads per 100 µl cell lysate) in a horizontal shaker at 1000 rpm, 4°C for 2 hrs. Immunoprecipitated HLA-DR-peptide complexes bound to L243 beads were sedimented by centrifugation at 1000g, 4°C for 1 min and washed four times with 500 µl 0.1% Zwittergent 3-12 (Calbiochem) in PBS.

The efficacy of depletion of HLA-DR-peptide complexes was monitored by analyzing the respective cell lysates before and after immunoprecipitation and aliquots of the beads by western blotting using the anti-HLA-DRα-specific mAb 1B5 (Adams, T.E. et al., Immunology 50 (1983) 613-624).

Elution of HLA-DR-associated peptides

HLA-DR-peptide complexes bound to L243 beads were resuspended in 100 µl H_2O (HPLC-grade; Merck, Darmstadt, Germany), transferred to an ultrafiltration tube, Ultrafree MC, 30 kD cut-off (Millipore, Bedford, MA) and washed 10 times with 100 µl H_2O (HPLC-grade) by centrifugation for 1-2 min at 10000g at RT. For eluting the bound peptides, 60 µl 0.1% trifluoracetic acid (Fluka, Buchs, Switzerland) in H_2O (HPLC-grade) was added and incubation was performed for 30 min at 37°C. Eluted peptides were collected in a new eppendorf tube by centrigugation of the Ultrafree unit at 10000g for 3 min at RT and immediately lyophilized in a Speed-Vac™ vacuum centrifuge.

Fractionation by two-dimensional nanoflow LC

To perform high-throughput sequencing of complex peptide mixtures, the MudPIT (multidimensional protein identification technology) was used (Washburn, M.P. et al., Nat Biotechnol 19 (2001), 242-247) which is based on liquid chromatographic fractionation followed by mass spectrometric sequence determination.

To this end, lyophilized peptides eluted from HLA molecules were resuspended in a buffer containing 5% (v/v) acetonitrile (ACN), 0.5% (v/v) acetic acid, 0.012% (v/v) heptafluoro butyric acid (HFBA) and 1% (v/v) formic acid. The peptide mixture was fractionated on a fused-silica microcapillary column (100 µm i.d. × 375 µm) generated by a Model P-2000 laser puller (Sutter Instrument Co., Novato, CA). The microcolumn was packed with 3 µm / C18 reversed-phase material (C18-ACE 3 µm [ProntoSIL 120-3-C18

ACE-EPS, Leonberg, Germany]) followed by 3 cm of 5 µm cation exchange material (Partisphere SCX; Whatman, Clifton, USA).

A fully automated 8-step gradient separation on a LC Packings UltiMate HPLC (LC Packings, San Francisco, USA) was carried out, using the following buffers: 5% ACN / 0.012% HFBA / 0.5% acetic acid (buffer A), 80% ACN / 0.012% HFBA / 0.5% acetic acid (buffer B), 250 mM ammonium acetate / 5% ACN / 0.012% HFBA / 0.5% acetic acid (buffer C), and 1.5 M ammonium acetate / 5% ACN / 0.012% HFBA / 0.5% acetic acid (buffer D). The first 116 min step consisted of a 75 min gradient from 0 to 40% buffer B followed by a 10 min gradient from 40 to 80% buffer B, a 6 min hold at 80% buffer B and a 10 min equilibration step with 100% buffer A. The next 5 steps (146 min each) were characterized by the following profile: 5 min 100% buffer A, 5 min gradient from 0 to x% buffer C, 5 min 100% buffer A, 30 min gradient from 0 to 10% buffer B, 55 min gradient from 10 to 35% buffer B, 20 min gradient from 35 to 50% buffer B, 10 min gradient from 50 to 80% buffer B, a 6 min hold at 80% buffer B, and a 10 min equilibration step with 100% buffer A. The buffer C percentages (x) in steps 2-6 were as follows: 20, 40, 60, 80, and 90%. The 30 min gradient from 0 to 10% buffer B, which is the first linear elution step from the reversed-phase material, was needed in order to sufficiently separate peptide elution from the elution of a major contaminant (m/z=945) which otherwise would have led to the loss of the more hydrophilic peptide peaks. Step 7 consisted of the following profile: 5 min 100% buffer A, 20 min 100% buffer C, 5 min gradient from 0 to 10% buffer B, 35 min gradient from 10 to 35% buffer B, 50 min gradient from 35 to 50% buffer B, 10 min gradient from 50 to 80% buffer B, a 5 min hold at 80% buffer B and a 10 min equilibration step with 100% buffer A. Step 8 was identical to step 7 with the exception of using buffer D instead of buffer C.

Ion trap MS/MS mass spectrometry

The HPLC column was directly coupled to a Finnigan LCQ Deca XP Plus ion trap mass spectrometer (Thermo Finnigan, San Jose, USA) equipped with a nano-LC electrospray ionization source. Mass spectrometry in the MS/MS mode was performed according to the manufacturer's protocol. Peptides were identified by the SEQUEST algorithm (U.S. patents 6,017,693 and 5,538,897).

MALDI-TOF mass spectrometry

Peptides spotted onto an AnchorChip plate were co-cristallized with matrix (5 mg/ml; α-cyano-4-hydroxy-cinnamic acid (Merck, Darmstadt, Germany), 50% acetonitrile, 0.1% trifluoroacetic acid). For qualitative analysis of the whole peptide repertoire, samples were analyzed on an Ultraflex™ MALDI-TOF mass spectrometer (Bruker, Bremen, Germany), according to the manufacturer's protocol.

Sequence identification by SEQUEST and differential dataset analysis.

MS/MS fragmentation data were analyzed with the software SEQUEST (Thermo Finnigan, San Jose, USA). From an in-house protein database, which was created based on the public databases Swiss-Prot and TrEMBL, SEQUEST extracted for each spectrum all peptide sequences that corresponded to the molecular mass of the parent ion and measured the degree of similarity between the experimental spectrum and the theoretical, *in silico* generated, spectrum. Only the top-scoring candidate sequence was listed.

The peptide sequences derived from the SEQUEST analysis and their accompanying information on mass accuracy, scoring parameters and peptide origin were stored in an appropriately designed relational database and further processed. Certain constraints were enforced in order to guarantee the storage of only significant sequences with satisfying SEQUEST scores. The two most important constraints were: (i) keep only those sequences that have a cross correlation coefficient (CC) higher than a certain value and (ii) from the remaining sequences keep those ones which have a predefined delta cross correlation coefficient (ΔCC). For both criteria the minimum chosen values are based on empirical knowledge of interpreting SEQUEST results.

A dataset was defined as the sum of data from a particular set of spectra. The design of database and software allowed queries on a single dataset as well as comparisons of multiple datasets. Such a database and software design enables comparative sample analysis, which is not provided by SEQUEST. For instance, possible queries on a single dataset could provide information on the score distribution among the stored spectra, on the existence of further sequence length variants or common subsequences, or on the protein origin of peptide sequences. Since the occurrence of truncation variants of the same epitope is a general characteristic of class II MHC-bound peptides, the existence of length variants in a dataset provides additional strong evidence for the presence of an epitope in a set of spectra.

The most important feature in the analysis of multiple datasets is the possibility to extract a common subset of sequences that satisfies a given criterion. Such a criterion could be based on sequence similarity, e.g., within all sequences of a collection of datasets, those

sequences were selected that had at least one subsequence in common with any other sequence. Such comparisons across different datasets constitute the differential approach (RA samples versus control samples) and thereby optimize the search for candidate RA marker peptides.

The pairwise similarity scores between sequences were calculated by a software routine, which is an implementation of a standard string-comparison algorithm. Subsequently, these scores were used to group closely-related sequences (sequences sharing a common subsequence) in well-separated clusters by an additionally developed software routine, which is based on a well-established algorithm (hierarchical clustering, UPGMA).

The generated clusters (e.g. of peptide truncation variants) were then used to identify closely-related sequences across different datasets.

Overall, the data evaluation software provided the ability to perform swiftly and reproducibly the following:

-Select from the sequence output generated by SEQUEST those sequences that satisfy reliable empirical criteria.

- Store the data in a database appropriately designed for the discovery process at hand.

-Extract information about the sequence content of each stored dataset. This information is valuable in assessing the importance of individual sequences within the given dataset and, consequently, across multiple datasets.

-Provide, by virtue of the multiple dataset comparisons, a tool that realizes the differential approach, namely the study of the actual sequence content of one sample versus other(s).

Purification of HLA-DR molecules

HLA-DR molecules were purified from 10^{10} EBV-transformed B cell lines or T2-transfectants by affinity chromatography, using anti-DR monoclonal antibody L243, as previously described (Kropshofer H. et al., PNAS 92 (1995) 8313-8317).

In vitro peptide binding assay

HA(307-319), PKYVKQNTLKLAT, is an immunodominant epitope from influenza virus hemagglutinin that binds well to HLA-DR4 molecules and was used as a reporter peptide in an *in vitro* peptide binding assay (Rothbard, J.B. et al., Cell (1988) 52:515-523).

Purified detergent-solubilized HLA-DR4 molecules (200 nM) were co-incubated with biotinylated HA(307-319) peptide (200 nM) and graded amounts of competitor peptide (100 nM – 10 μM) for 24 hrs at 37°C in binding buffer (50 nM sodium phosphate, 50 mM sodium citrate, pH 4.8, 0.1% Zwittergent 3-12) in a total volume of 50 μl. The competitor peptides were derived from the candidate RA antigens identified in this study and purchased as synthetic peptides from Medprobe (Lund, Sweden).

3 x 10 μl were then diluted 10-fold in PBS containing 0.05% Tween-20 and 1% BSA and incubated for 2 hrs in a microtiterplate (Nalge Nunc), which has been coated over night with anti-DR monoclonal antibody L243. Afterwards the samples were developed by incubation with 0.1 μg/ml EU-labeled streptavidin (Wallay Oy, Turku, Finland) for 45 min according to the manufacturer's protocol. After intensive washing with 0.05% Tween-20 in PBS, Europium fluorescence was measured with a time-resolved fluorometer (VICTOR 1420, Wallac/Perkin Elmer Life Sciences) to quantify the binding of biotinylated HA(307-319) peptide to HLA-DR4 molecules (Arndt, S.O. et al., EMBO J. 19 (2000) 1241-1251).

Example 1

In this example, the technique mentioned in Figure 1 was used to identify novel HLA-DR-associated peptide markers derived from serum and synovial fluid of patients with non-erosive RA.

6×10^6 immature dendritic cells were pulsed with either 1 ml serum (5 samples) or 0.6 ml synovial fluid (2 samples) of patients with non-erosive RA and cultured for 24 hrs in the presence of 10 ng/ml TNFα. As a control, 6×10^6 dendritic cells were cultured in the presence of TNFα (10 ng/ml) without adding serum but 1 ml of PBS. In an additional experiment 6×10^6 dendritic cells were pulsed with 1 ml serum from 2 healthy test persons and cultured for 24 hrs in the presence of TNFα (10 ng/ml).

Dendritic cells were lysed in detergent TX-100 and HLA-DR molecules were isolated using mAb L243. HLA-DR-associated peptides were eluted with 0.1% TFA and analyzed by high-throughput 2D-LC-MS/MS technology. Peptide identification was achieved by using the SEQUEST algorithm. The peptide sequences derived from the SEQUEST analysis and accompanying information on mass accuracy, scoring parameters and peptide origin were stored in a database and further processed.

The peptide sequences identified from unpulsed DCs (control 1) and from DCs pulsed with the serum of healthy test persons (control 2) were compared with the peptide sequences identified from DCs pulsed with the serum of non-erosive RA patients. Among the RA-specific sequences, only those peptides were selected for further evaluation that re-occurred in at least three of five non-erosive RA samples.

In each serum sample roughly 600±150 individual peptide sequences (cross correlation coefficient $CC > 3.0$ and $\Delta CC > 0.15$) were identified. In the synovia samples the number of individual peptide sequences was slightly smaller (400±30). Approximately 80-85% of the peptides found in RA samples were also identified in control samples, underlining the high reproducibility of the analysis. In the majority of cases, several length variants of the same epitope could be identified which is a typical characteristic of class II MHC-bound antigens and supports the validity of the results (Jones, E.Y., Curr Opin Immunol 9 (1997) 75-79). Further confidence in the quality of the data relies on the fact that several of the identified peptides or proteins have already been described in the context of MHC class II molecules: epitopes derived from ubiquitous proteins like Hsp70, enolase, annexin II, cathepsin C or collagen II, as well as from MHC molecules (HLA-A, -B, -C, -E, -G, and β_2-microglobulin) and CLIP (Chicz, R.M. et al., J Exp Med 178 (1993) 27-47; Sinigaglia, F. & Hammer, J., Curr Opin Immunol 6 (1994) 52-56; Arnold-Schild, D. et al., J

Immunol 162 (1999) 3757-3760; Vogt, A.B. & Kropshofer, H., Trends Biochem Sci 4 (1999) 150-154) were frequently detected.

RA-specific peptide sequences were further validated with regard to binding to the RA susceptibility allele *DRB1*0401* by using the TEPITOPE software (Hammer, J. et al., Adv Immunol 66 (1997) 67-100). This software provides means for the qualitative and quantitative prediction of T cell epitopes.

The output of the study consists of an epitope that occurred, apart from one exception, only in non-erosive RA samples (Table 1).

Interferon-gamma-inducible lysosomal thiol reductase

A very interesting epitope which was identified in 3 out of 7 non-erosive RA samples from serum and synovia is derived from the interferon-gamma-inducible lysosomal thiol reductase (GILT): the 16-mer GILT (192-207) with the amino acid sequence of SEQ ID NO: 3 (Table 1). Further length variants in three other samples support the relevance of this epitope (Table 1): the 14-mer GILT (192-205; SEQ ID NO: 1) and the 17-mer GILT (192-208; SEQ ID NO: 2).

As judged from the shortest length variant, GILT (192-205), the epitope contains a suitable binding motif, with regard to binding to the RA susceptibility allele *DRB1*0401*: 196M serves as a P1 anchor, 199M as a P4 anchor and 201A as a P6 anchor. According to TEPITOPE scoring, the epitope has a binding score (threshold value) of 1% which is similar to the binding score of an epitope from influenza haemagglutinin (307-319) that was shown to be a strong *DRB1*0401* binder (Table 1) (Rothbard, J.B. et al., Cell 52 (1988) 515-523).

GILT is constitutively expressed in antigen-presenting cells, such as dendritic cells, macrophages and B cells, and facilitates unfolding of endocytosed antigens in MHC class II-containing compartments (MIIC) by enzymatically reducing disulfide bonds (Phan, U.T. et al., J Biol Chem 275 (2000) 25907-25914). Direct binding of GILT to HLA-DR molecules has been reported for B cells (Arunachalam, B. et al., J Immunol 160 (1998) 5797-5806). A rather long second epitope of GILT was found to bind to HLA-DR3 molecules: the 22-mer GILT (38-59) having the amino acid sequence SPLQALDFFGNGPPVNYKTGNL (Chicz, R.M. et al., J Exp Med 178 (1993) 27-47).

In addition to GILT (192-207), another epitope of the same protein was identified in several RA samples, but also in control samples: GILT (210-227) with the amino acid

sequence QPPHEYVPWVTVNGKPLE. This epitope was accompanied by 3 other length variants: the 16-mer GILT (210-225), the 17-mer GILT (210-226) and the 19-mer GILT (210-228).

As indicated by its name, GILT expression can be induced by the pro-inflammatory cytokine interferon gamma (IFN-γ) in various types of cells, including macrophages, endothelial cells and fibroblasts (Luster, A.D. et al., J Biol Chem 263 (1988) 12036-12043). As IFN-γ is known to be present in inflamed joints of RA patients, GILT could become over-expressed in synovia and serum and, hence, could be taken up by DCs as an exogenous antigen. GILT (192-207) may be derived from exogenous GILT. The other GILT epitope, which is also present in the control samples, may be derived from endogenous GILT, expressed by DCs. Alternatively, both GILT (192-207) and GILT (210-227) may be derived from endogenous GILT, in case that GILT processing and GILT-derived epitope presentation by DCs were critically altered upon contact with RA-associated material.

The identified epitope of Interferon-gamma-inducible lysosomal thiol reductase GILT (192-205) which has been described already in detail, was further analysed in an *in vitro* binding assay using synthetic GILT (192-205) peptide and purified HLA-DR4 molecules (Fig. 3): In agreement with TEPITOPE scoring, the peptide was shown to bind to HLA-DR4 with high affinity, comparable to the viral HA(307-319) peptide.

Integrin beta-2

The extended analysis revealed the presence of an epitope which was identified in two out of seven non-erosive RA samples from serum and synovia and which is derived from the beta subunit of Integrin (ITB2): the 17-mer ITB2 (315-331; SEQ. ID NO: 58) with the amino acid sequence NIQPIFAVTSRMVKTYE (Table 1). One length variant was found: the 19-mer ITB2 (313-331; SEQ. ID NO: 59) supporting the validity of the identified epitope (Table 1).

The peptide sequence contains a moderate *HLA-DRB1*0401* binding motif with 316I and 319I serving as P1 and P4 anchor, respectively (TEPITOPE binding score: 2%).

Integrins are a family of cell surface receptors that play important roles in embryogenesis, wound healing, immune responses, and cell adhesion. ITB2 is a heterodimeric receptor for intercellular and vascular adhesion molecules (ICAMs and VCAMs) and exclusively expressed on leukocytes. ICAMs and VCAMs are members of the immunoglobulin superfamily that has a central function in humoral and cell-mediated immune responses. Many cytokines, such as interferon-γ, IL-1 and TNFα, which are

upregulated in inflammatory diseases like RA, induce expression of ICAMs on the surface of endothelial cells. It was shown that the expression of ICAM-1 and VCAM-1 is higher in synovial tissue of RA patients as compared to osteoarthritis patients (Furuzawa-Carballeda, J. et al., Scand J Immunol 50 (1999) 215-222).

Binding of ITB2 and other integrins to ICAMs allows leukocytes to infiltrate into their target tissues, e.g. the sites of inflammation. In order to function in a non-adherent or circulating mode, leukocytes constitutively express ITB2 and other integrins with low ligand-binding capacity. The ITB2/ICAM-1 interaction has become an important strategic target to approach inflammation, autoimmune diseases and cancer (Yusuf-Makagiansar, H. et al., Med Res Rev 22 (2002) 146-167), hence these findings strongly support the validity of the identified ITB2 epitope as a candidate marker for RA.

Phosphatidylinositol-4,5-bisphosphate 3-kinase

Another epitope with a moderate *HLA-DRB1*0401* binding motif was identified in two non-erosive serum samples: the 17-mer PI3K (792-808; SEQ. ID NO: 60) with the amino acid sequence NKVFGEDSVGVIFKNGD derived from Phosphatidylinositol 3-kinase (PI3K) (Table 1). In this peptide 794V could serve as a hydrophobic P1 anchor, 797E as a negatively charged P4 anchor, and 799S as a typical DR4-P6 anchor (TEPITOPE binding score: 3%).

PI3K is ubiquitously expressed in many cell types and phosphorylates lipids, predominantly phosphatidylinositol-4,5-bisphosphate. The protein has emerged as a key signal transducer for survival factor receptors, including growth factors, cytokines, and integrins (reviewed by Toker, A. & Cantley, L., Nature 387 (1997) 673-676). In addition, PI3K plays an important role in the signaling pathway of Toll-like receptors (TLRs) that recognize a variety of microbial products, collectively termed pathogen-associated molecular patterns (PAMPs) (Fukao, T. & Koyasu, S., Trends Immunol 24 (2003) 358-363). Stimulation through TLRs by PAMPs, such as lipopolysaccharide (LPS) (endotoxin) triggers production of various cytokines, including IL-12, which is a key cytokine in TLR-mediated Th1 responses. It was shown that PI3K is an endogenous suppressor of TLR-mediated IL-12 production and limits excessive Th1 polarization. Thus PI3K was suggested to be a negative regulator of innate immune responses in order to prevent prolonged activation of innate immunity harmful to the host. The knowledge that autoimmune responses in RA rely on Th1 cytokines, ultimately links PI3K with RA. Although no specific pathogen has been consistently linked to the development of RA, it is believed that RA develops in two stages in which an initial response induced by foreign antigens,

subsequently develops into a self-sustaining autoimmune response (Klinman, D., Arthritis Rheum 48 (2003) 590-593).

Urokinase-type plasminogen activator

Another epitope which was only found in non-erosive RA samples was derived from a urokinase-type plasminogen activator (uPA): the 16-mer uPA (328-343; SEQ. ID NO: 61) with the amino acid sequence YPEQLKMTVVKLISHR (Table 1). With regard to *HLA-DRB1*0401* binding, the sequence reveals a moderate binding motif: 332L, 335T and 337V are putative P1, P4 and P6 anchors, respectively (TEPITOPE binding score: 2%).

Plasminogen activators (PAs) are highly specific serine proteases generating plasmin from plasminogen. Two types of PAs, a urokinase-type (uPA) and a tissue-type (tPA) have been identified in mammals. The activities of PAs are controlled by natural inhibitors (PAIs). Plasmin is involved in inflammatory reactions by inducing cytokines such as TGFβ, and in cartilage and fibrin degradation. Evidences for ongoing coagulation within the rheumatoid joint together with an enhancement of uPA synthesis and activation in arthritic joints have led to the hypothesis that the PA/plasmin system is associated with the clinical severity of arthritis (reviewed by Busso, N. & Hamilton, J.A., Arthritis Rheum 46 (2002) 2268-2279). Based on *in vitro* studies, there are several cell types present in the inflamed joints of RA patients, in particular monocytes and synovial fibroblasts which can express PAs and PAIs and which therefore could contribute to the *in vivo* levels. The activity of PAs (i.e. uPA) is stimulated by cytokines, such as IL-1 and TNFα, which are known to be highly upregulated in serum as well as in synovial fluid of RA patients. These lines of evidence render uPA (328-343) a putative peptide marker for RA.

Immunglobulin heavy chain V-III region (V_H26)

One of the identified epitopes that display a very strong binding motif with regard to *HLA-DRB1*0401* binding, is derived from the V_H26 gene segment of the immunglobulin heavy chain: the 16-mer V_H26 (95-110; SEQ. ID NO: 62) with the amino acid sequence KNTLYLQMNSLRAEDT (Table 1). The high TEPITOPE binding score (1%) is substantiated by 99Y functioning as a very potent P1 anchor, 102M as a moderate P4 anchor and 104S as a typical HLA-DR4 P6 anchor.

Immunglobulins (Ig) are responsible for antigen binding and stimulate further immune reactions, e.g. by binding to isotope-specific Fc receptors. Interestingly, the

human V_H26 gene segment appears to encode a high-avidity synovial rheumatoid factor and thus seems to have an impact on RA progression (Wong, A. et al., Autoimmunity 20 (1995) 191-199). The fact that the identified epitope V_H26 (95-110) was found in the serum of two seropositive RA patients (Table 1) correlates with the above observation.

DJ-1 protein

In two non-erosive RA samples our continued studies revealed the presence of an epitope which is derived from a protein termed DJ-1: the 16-mer DJ-1 (135-150; SEQ. ID NO: 63) with the amino acid sequence NGGHYTYSENRVEKDG (Table 1). According to TEPITOPE scoring the peptide contains a rather weak *HLA-DRB1*0401* binding motif with 139Y serving as a P1 anchor, 142S as a P4 anchor and 144N as a possible P6 anchor (binding score: 8%).

DJ-1 belongs to the ThiJ/PfpI protein family whose members are evolutionary distributed from Archaea to Eukarya. ThiJ/PfpI proteins share a conserved ThiJ domain that is structurally related to the type I glutamine amidotransferase domain (Lee, S.J. et al., J Biol Chem 25 (2003) Epub ahead of print).

DJ-1, which is preferentially expressed in testis and moderately in other tissues, was first identified as a novel candidate of the oncogene product that transformed mouse NIH3T3 cells in cooperation with *ras*. In the mean time additional physiological roles of DJ-1 were revealed including a strong correlation to Parkinson disease and sperm fertilization. DJ-1 seems to have multiple functions – here we provide the first indication for an association of DJ-1 with RA.

Example 2

In this example, the same technology was used that has been described in detail in example 1. Serum (6 samples) and synovial fluid (2 samples) of patients with diagnosed erosive RA were utilized in this case to identify candidate markers specific for erosive RA.

The peptide sequences found in the erosive RA samples were compared with the sequences identified in unpulsed DCs (control 1) and in DCs pulsed with the serum of healthy test persons (control 2). Among the RA-specific sequences, only those peptides were selected for further evaluation that re-occurred in at least three of six erosive RA samples.

In this study one epitope was discovered which occurred, apart from one exception, only in erosive RA samples.

Apolipoprotein B-100

The epitope which was mainly found in erosive RA sera (4 out of 8 erosive RA samples) is derived from apolipoprotein B-100: the 16-mer ApoB (2877-2892) with the amino acid sequence of SEQ ID NO: 4 (Table 2). In addition a length variant of the same epitope was identified (Table 2): the 17-mer ApoB (2877-2893; SEQ ID NO: 5). The following *DRB1*0401* binding motif can be predicted: 2881L as a P1 anchor, 2884D as a P4 anchor and 2886N as a P6 anchor (binding score 3%).

In an earlier study on EBV-B cells, the epitope ApoB (2885-2900), which partly overlaps with the epitope described here, has been found in the context of HLA-DR4 (Chicz, R.M. et al., J Exp Med 178 (1993) 27-47).

Apolipoprotein B-100 is a constituent of very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) and functions as a recognition signal for the cellular binding and internalization of LDL particles by the ApoB/E receptor (Yang, C.Y. et al., Nature 323 (1986) 738-742). Interestingly, an increased ratio of LDL cholesterol to HDL cholesterol was observed among newly diagnosed RA patients (Park, Y.B. et al., J Rheumatol 26 (1999) 1701-1704). The adverse lipid profile in active RA could be improved by treating RA patients with DMARDs without the use of lipid-lowering agents (Park, Y.B. et al., Am J Med 113 (2002) 188-193). Since an increased cardiovascular mortality among patients with chronic inflammatory diseases, such as RA, is well documented (Symmons, D.P. et al., J Rheumatol 25 (1998) 1072-1077) it was suggested that local inflammation in RA leads to altered blood lipid levels, thereby increasing the risk of atherosclerosis. The question whether components of the lipoprotein metabolism are causal for pathogenesis or merely affected by ongoing immune reactions during RA development cannot be answered yet. However, the observation of adverse lipid profiles in RA patients supports the validity of the presented ApoB epitope as a serum-derived RA candidate marker.

The length variant ApoB (2877-2892), but not ApoB (2877-2893), has been identified in samples of two healthy controls (Table 2). Since Apolipoprotein B constitutes 1% of all plasma proteins, the presence of ApoB epitopes in healthy control samples is not surprising. The results suggest that only the length variant ApoB (2877-2893; SEQ ID NO: 5) is specific for erosive RA.

26S proteasome non-ATPase regulatory subunit 8

An epitope which was quite frequently identified in mostly erosive RA samples both from serum and synovia, is derived from the regulatory subunit 8 of the 26S proteasome (PSMD8): the 15-mer PSMD8 (218-232; SEQ. ID NO: 64) with the amino acid sequence GPNNYYSFASQQQKP (Table 2). Three additional length variants were identified: the 16-mer PSMD8 (218-233; SEQ. ID NO: 65), the 17-mer PSMD8 (218-234; SEQ. ID NO: 66) and the 18-mer PSMD8 (218-234; SEQ. ID NO: 67) (Table 2). The presence of length variants supports the validity of the identified epitope as a class II MHC-derived antigenic peptide. The peptide displays a moderate binding motif with respect to *DRB1*0401* binding (TEPITOPE binding score: 3%). Binding to HLA-DR4 could be confirmed in an *in vitro* binding assay using synthetic PSMD8 (218-233) peptide and purified HLA-DR4 molecules (Fig. 3): According to its IC_{50} value against the reporter peptide HA(308-319), PSMD8 (218-233; SEQ. ID NO: 65) binds to HLA-DR4 with a moderate affinity, confirming the TEPITOPE prediction. The 15-mer PSMD8 (218-232; SEQ. ID NO: 64) was identified once in an unpulsed control sample.

The proteasome accouts for about 1% of the cytoplasmic protein pool and is involved in ATP-dependent degradation of ubiquitinated proteins. Moreover, the proteasome is responsible for the processing of several transcription factors (i.e. nuclear factor-κB), for cell cycle control and the generation of MHC class I restricted antigens. The regulatory subunits of the proteasome are important for the selectivity of protein degradation. The non-ATPase regulatory subunit 8, in particular, is known to be necessary for the activation of the cell division control protein 28 (Cdc28), an essential cell cycle regulator in yeast.

Importantly, strongly increased levels of circulating proteasomes (cProteasomes) were detected in serum samples obtained from patients with different systemic autoimmune diseases, including RA (Egerer, K. et al., J Reumatol 29 (2002) 2045-2052). There appears to be a close correlation between the levels of cProteasome and disease activity and concentrations of C-reactive protein in patients with severe RA. cProteasome is discussed to trigger subsequent immune responses, which would indicate an antigen-driven mechanism. The concentration of released Proteasome antigen seems to reflect the magnitude of cellular damage in autoimmune diseases. From their findings Egerer and coworkers concluded that cProteasomes could represent a novel marker for disease severity in autoimmune processes. Since the epitope PSMD8 (218-232; SEQ. ID NO: 64) was mainly identified in erosive RA samples our analysis supports this conclusion.

Interleukin-1 receptor

Another candidate marker for erosive RA is the Interleukin-1 receptor (IL-1R) which was identified in two erosive serum samples via its peptide IL-1R (79-94; SEQ. ID NO: 68) with the amino acid sequence EKLWFVPAKVEDSGHY (Table 2). IL-1R (79-94; SEQ. ID NO: 68), with 83F as a P1 anchor, 86A as a P4 anchor and 88V as a P6 anchor, contains a strong binding motif with regard to binding to the RA susceptibility allele *DRB1*0401* (TEPITOPE binding score: 1%). In an *in vitro* binding assay the synthetic peptide was shown to bind to HLA-DR4 molecules with high affinity (Fig. 3), similar to HA(309-319) peptide.

Interleukin-1 (IL-1) is a proinflammatory cytokine and implicated in a variety of infectious immune responses as well as in RA and other inflammatory diseases (Dinarello, C., Blood 87 (1996) 2095-2147). It binds to its respective receptor which functions as a signal transducer to trigger cell proliferation or to stimulate protein synthesis. Increased IL-1 production has been observed in RA patients and plays a pivotal role in its clinical manifestations (Dayer, J.M., Rheumatology 42 (2003) ii3-ii19). IL-1 is viewed as a key mediator in RA through activation of macrophages and T- and B- lymphocytes. In addition, IL-1 contributes to inflammation by inducing the expression of cell-adhesion molecules, other cytokines and chemokines. Furthermore IL-1 is also pivotal in the destruction of bone and cartilage in RA by stimulating the production of matrix metalloproteinases. Thus, the IL-1/IL-1R complex is a first class target for anti-inflammatory therapeutics. The use of a recombinant human IL-1 receptor antagonist (IL-1RA) has been approved for the treatment of RA patients.

Fibromodulin

Three erosive RA samples gave rise to an epitope derived from the secreted matrix protein fibromodulin (FM): the 13-mer FM (178-190; SEQ. ID NO: 70) with the amino acid sequence LRELHLDHNQISR (Table 2). Furthermore, the 14-mer FM (177-190; SEQ. ID NO: 69) was identified, which was also found once in an unpulsed control experiment. The epitope depicts a strong *DRB1*0401* binding motif with 181L serving as a P1 anchor, 184D as a P4 anchor and 186N as a P6 anchor (TEPITOPE binding score: 1%).

Fibromodulin belongs to a family of small leucine-rich proteoglycans (SLRPs) that bind to TGFβs and collagens and other extracellular matrix molecules. *In vitro*, SLRPs were shown to regulate collagen fibrillogenesis, a process essential in development, tissue repair and metastasis. To better understand the function of SLRPs *in vivo*, SLRP-deficient mice were generated and shown to develop a wide array of diseases (e.g. osteoporosis and osteoarthritis), most of them resulting primarily from an abnormal collagen fibrillogenesis

(Ameye, L. & Young, M.F., Glycobiology 12 (2002) 107R-116R). Since collagen formation and degradation is highly enhanced in the inflamed joints of RA patients, an increased level of fibromodulin can be envisaged. In accord with this consideration is the fact that the identified FM epitope was primarily found in RA samples of synovial origin (3 out of 4 synovia samples).

GM-CSF/IL-3/IL-5 receptor

In 5 out of 8 samples from erosive RA patients an epitope from the β-chain of the multiple cytokine receptor CYRB could be identified: the 15-mer CYRB (359-373; SEQ. ID NO: 71) with the amino acid sequence ETMKMRYEHIDHTFE and its length variant, the 17-mer CYRB (359-375; SEQ. ID NO: 72) (Table 2). In an *in vitro* binding assay the synthetic CYRB (359-375) peptide was shown to bind to HLA-DR4 molecules with moderate affinity (Fig. 3). This is in agreement with TEPITOPE which predicted a moderate peptide binding motif with respect to *DRB1*0401* binding (TEPITOPE binding score: 3%). The epitope was clearly overrepresented in the RA samples since it was identified in the serum of only one healthy test person.

The GM-CSF/IL-3/IL-5 receptor is a type I membrane protein and differentially expressed throughout the hematopoietic system (reviewed by Geijsen, N. et al., Cytokine Growth Factor Rev 12 (2001) 19-25). Its ligands, IL-3 and GM-CSF, are secreted by CD4+ T cells and important stimuli for the formation of dendritic cells originating from progenitor cells in the bone marrow. The critical role of dendritic cells in the initiation and development of an immune response suggests that they play a key role in the development of autoimmune inflammatory disorders, such as RA, by transporting autoantigen to the draining lymph node where DCs encounter and prime naïve T cells. The activity of GM-CSF has been linked to proinflammatory effects in RA supporting the identified receptor epitope CYRB (359-373; SEQ. ID NO: 71) as a putative candidate peptide marker for the diagnosis of RA.

Sorting nexin 3

Another epitope which appears to be indicative for erosive RA is derived from a protein termed sorting nexin 3 (SNX3): the 16-mer SNX3 (142-157; SEQ. ID NO: 73) having the amino acid sequence HMFLQDEIIDKSYTPS (Table 2). In this epitope 144F, 147D and 149I could serve as P1, P4 and P6 anchors, respectively, in the peptide-binding groove of the RA susceptibility allele *DRB1*0401* (TEPITOPE binding score: 2%).

Sorting nexins are a diverse group of cellular trafficking proteins that share a common phospholipid-binding motif (reviewed by Worby, C.A. & Dixon, J.E., Nat Rev Mol Cell Biol 3 (2002) 919-31). The ability of these proteins to bind specific phospholipids, as well as their propensity to form protein-protein complexes, points to the involvement of these proteins in membrane trafficking and protein sorting. Sorting nexin 3 in particular is present in the cytosol and in endosomes and appears to be involved in membrane trafficking from early to recycling endosomes. Whether sorting nexin 3 plays a role in RA, e.g. by influencing antigen presentation routes, remains unknown at the moment. The epitope SNX3 (142-157; SEQ. ID NO: 73) identified in this study suggests a link between sorting nexins and autoimmunity.

Example 3

All peptide sequences identified in examples 1 and 2 from non-erosive and erosive RA samples were used in this example to search for common markers relevant for both RA types. The RA-specific sequences were again compared with peptide sequences of the control samples (unpulsed DCs and DCs pulsed with the serum of two healthy test persons) and only those peptides were selected for further evaluation that re-occurred in at least three of altogether fifteen RA samples (erosive and non-erosive RA).

Inter-alpha-trypsin inhibitor

Ten out of eleven serum samples (erosive & non-erosive RA) gave rise to an epitope derived from the heavy chain H4 of the inter-alpha-trypsin inhibitor: ITIH4 (271-287) with the amino acid sequence of SEQ ID NO: 8 (Table 3). Apart from this major length variant of the ITIH4 epitope, six length variants of the same ITIH4 epitope could be identified (Table 3): the 19-mer ITIH4 (271-289; SEQ ID NO: 6), the 18-mer ITIH4 (271-288; SEQ ID NO: 7), the 16-mer ITIH4 (274-289; SEQ ID NO: 12), the 15-mer ITIH4 (273-287; SEQ ID NO: 10), the 15-mer (274-288; SEQ ID NO: 11) and the 14-mer ITIH4 (274-287; SEQ ID NO: 9).

As judged from the shortest length variant, ITIH4 (274-287), the epitope contains a very strong binding motif, with regard to binding to the RA susceptibility allele *DRB1*0401*: 277F serves as a P1 anchor, 280D as a P4 anchor and 282S as a P6 anchor (binding score: 1%).

ITIH4 belongs to the Inter-alpha-inhibitor (IαI) family which is a group of serum protease inhibitors that bind to hyaluronic acid (HA) and appear to be involved in acute-phase reactions (Salier, J.P. et al., Biochemical Journal 315 (1996) 1-9).

HA is a polysaccharide found in all tissues of the body, in particular, in loose connective tissue, e.g. joint fluid (Evered, D. & Whelan, J. eds., The Biology of Hyaluronan, John Wiley & Sons (1989)). HA has an important structural function in cartilage and other tissues where it stabilizes the extracellular matrix by forming aggregates with proteoglycans. It has also been assigned important biological functions by regulating cellular activities via binding to cell surface proteins, such as CD44 and ICAM-1 (Knudson, C.B. & Knudson, W., FASEB J 7 (1993) 1233-1241; Hall, C.L. et al., J Cell Biol 126 (1994) 575-588). RA is accompanied by a large increase in total HA in the joint fluid as well as in the serum, suggesting that circulating HA originates from rheumatoid joints (Engström-Laurent, A. et al., Scand J Clin Lab Invest 45 (1985) 497-504).

Complexes of HA and some IαI family members were observed in large amounts in the synovial fluid of RA patients (Jessen, T.E. et al., Biological Chemistry Hoppe-Seyler 375 (1994) 521-526). The role of the IαI-HA complex in inflammatory reactions might be to modify the CD44-HA interaction that mediates leukocyte activation and invasion (Isacke, C.M. & Yarwood, H., Int J Biochem Cell Biol 34 (2002) 718-721). Additionally, synovial fluid of RA patients contains elevated levels of TSG-6, an anti-inflammatory glycoprotein and a member of the hyaladherin family of HA-binding proteins (Wisniewski, H.G. et al., J Immunol 151 (1993) 6593-6601). It has been shown that a complex of TSG-6 with IαI family members inhibits the activity of plasmin, a central molecule in the activation of inflammation-associated enzymes (Wisniewski, H.G. et al., J Immunol 156 (1996) 1609-1615). A regulation of plasmin activity by several acute-phase plasma proteins, namely TSG-6 and IαI family members, may prove to be important in RA, given the high contents of HA, TSG-6 and IαI family members in synovial fluid of inflamed joints.

This evidence, together with the identification of multiple length variants of the same epitope and a strong HLA-DR4 binding motif, convincingly support the validity of the presented ITIH4 epitope as a serum-derived RA candidate marker.

Complement C4

In eight out of eleven RA sera (erosive and non-erosive) tested, another dominant epitope was identified which is derived from complement C4: the 15-mer C4 (1697-1711) with the amino acid sequence of SEQ ID NO: 13 (Table 3). Five additional length variants of the same epitope could be found (Table 3): the 12-mer C4 (1697-1708; SEQ ID NO: 18),

the 13-mer C4 (1698-1710; SEQ ID NO: 17), the 14-mer C4 (1697-1710; SEQ ID NO: 15), the 16-mer C4 (1697-1712; SEQ ID NO: 14) and the 18-mer C4 (1697-1714; SEQ ID NO: 16). Moreover, the presented epitope displays a very strong *DRB1*0401* binding motif: 1700Y as P1 anchor, 1704D as P2 anchor and 1706N as P6 anchor (binding score: 1%).

C4 which constitutes approximately 0.5% of plasma protein mass plays a critical role in the triggering of the central pathway of the complement system. The protein is synthesized as a single-chain precursor and, prior to secretion, is enzymatically cleaved to form a trimer of non-identical α-, β-, and γ-chains. The identified epitope C4 (1697-1711) is located at the very C-terminus of the C4 γ-chain. The C4 α-chain is further proteolytically degraded by activated C1 to form the C4a anaphylatoxin, which is a mediator of local inflammatory processes (Moon, K.E. et al., J Biol Chem 256 (1981) 8685-8692).

In general, the complement cascade is involved in the induction and progression of inflammatory reactions and is a major defense system against various pathogenic agents, including bacteria, viruses and other antigens (Morgan, B.P., Methods Mol Biol 150 (2000) 1-13). Inappropriate activation, however, can lead to tissue damage and manifestation of disease (Speth, C. et al., Wien Klin Wochenschr 111 (1999) 378-391).

Activation of the complement system has been repeatedly implicated in the pathogenesis of RA, based on studies showing increased levels of complement metabolites, including C4 and C4a, in plasma, synovial fluid and synovial tissue of RA patients (Neumann, E. et al., Arthritis Rheum 46 (2002) 934-945). In addition collagen-induced arthritis (CIA) in mice is characterized by the presence of complement activation products (Linton, S.M. & Morgan, B.P., Mol Immunol 36 (1999) 905-914). CIA is prevented after treatment with anti-C5 monoclonal antibodies (Wang, Y. et al., PNAS 92 (1995) 8955-8959) or with soluble CR1, an inhibitor of the complement system, delivered by gene therapy (Dreja, H. et al., Arthritis Rheum 43 (2000) 1698-1709). Activation of complement factors in joints is possibly induced by the presence of various immune complexes and it was hypothesized that stimulation of the innate immune system by infectious agents and cytokines may contribute to the initiation of RA (Friese, M.A. et al., Clin Exp Immunol 121 (2000) 406-414).

Two of the six presented C4 epitopes, the 15- and the 18-mer, were also identified in healthy control samples (Table 3) indicating that only some length variants of this C4 epitope are RA-specific, namely the antigenic peptides of SEQ ID NOs: 14, 15, 17, and 18.

Complement C3

Another epitope that was found in erosive and non-erosive RA samples is derived from complement C3 (alpha-chain): the 14-mer C3 (1431-1444) with the amino acid sequence of SEQ ID NO: 21 (Table 3). Six additional length variants of the same epitope were identified in serum (Table 3): the 13-mer C3 (1431-1443; SEQ ID NO: 23), the 14-mer C3 (1429-1442; SEQ ID NO: 74), the 15-mer C3 (1431-1445; SEQ ID NO: 22), the 15-mer C3 (1429-1443; SEQ ID NO: 20), the 17-mer C3 (1427-1443; SEQ ID NO:75) and the 19-mer C3 (1426-1444; SEQ ID NO: 19). As judged from the shortest length variant, C3 (1431-1443), a *DRB1*0401* binding motif can be postulated: 1434Y serves as a P1 anchor, 1437D as a P4 anchor and 1439A as a P6 anchor.

In erovise and non-erosive RA samples a further epitope was found, which is derived from complement C3 (beta-chain): the 19 mer C3 (157-175) with the amino acid sequence of SEQ. ID NO: 76 (Table 3). One additional length variant of the same epitope was identified in serum (Table 3): 20-mer C3 (157-176; SEQ. ID NO: 77)

Complement C3 which constitutes about 1-2% of plasma protein mass plays a central role in the activation of the complement system and belongs to the family of the acute-phase proteins. Its processing by C3 convertase to C3a anaphylatoxin and C3b is the central step in both the classical and alternative complement pathways (Barrington, R. et al., Immunol Rev 180 (2001) 5-15). After activation, C3b can bind covalently, via a reactive thiolester, to cell surface carbohydrates or immune aggregates (Isaac, L. & Isenman, D.E., J Biol Chem 267 (1992) 10062-10069). The identified epitope C3 (1431-1444) is located at the C-terminus of C3b.

As already discussed in the context of complement epitope C4 (1697-1711), there is increasing evidence for an important role of components of the complement cascade in the pathophysiology of RA. The result of this study, in which two major epitopes derived from complement C3 and C4 were identified in serum of RA patients, underlines the close link between the activated complement system and pathogenesis of RA. This coincidence makes a strong argument for the validity of the presented C3 / C4 epitopes as serum-derived candidate RA markers.

SH3 domain-binding glutamic acid-rich-like protein 3

Another epitope which was elucidated quite frequently in serum of RA patients (six out of eleven erosive and non-erosive RA samples), is derived from the SH3 domain-binding glutamic acid-rich-like protein 3 (SH3BGRL3): SH3BGRL3 (15-26) with the amino acid sequence of SEQ ID NO: 25 (Table 3). Three length variants of the same epitope were identified (Table 3): the 14-mer SH3BGRL3 (13-26; SEQ ID NO: 26), the 14-

mer SH3BGRL3 (15-28; SEQ ID NO: 27) and the 16-mer SH3BGRL3 (13-28; SEQ ID NO: 24). The *DRB1*0401* binding motif is: 17I as P1 anchor, 20Q as P4 anchor and 22S as P6 anchor (binding score 4%).

SH3BGRL3 is a small 10 kD protein that belongs to the SH3BGR family. The precise function of the protein is unknown but a role as a modulator of glutaredoxin biological activity is postulated (Mazzocco, M. et al., Biochem Biophys Res Commun 285 (2001) 540-545). So far, SH3BGRL3 has not been described in the context of RA.

Interestingly, the analysis elucidated a second epitope of the same protein, which was highly abundant in all RA and control samples: the 16-mer SH3BGRL3 (29-44) with the amino acid sequence DGKRIQYQLVDISQDN. In addition multiple length variants of the same epitope were found in most samples as well. As judged from the shortest length variant, SH3BGRL3 (31-42), the epitope contains almost similar *DRB1*0401* anchor residues compared with SH3BGRL3 (15-26): 33I serves as a P1 anchor, 36Q as a P4 anchor and 38V as a P6 anchor (binding score -2). This similarity is reflected by comparable binding scores.

The presence of this second SH3BGRL3 epitope supports the validity of the SH3BGRL3 (15-26) epitope because both peptides are derived from the same protein, however, only one of them, epitope SH3BGRL3 (15-26), appears to be generated in a RA-specific manner. A similar observation has been described already for GILT in example 1.

Among the four SH3BGRL3 length variants the longest variant, SH3BGRL3 (13-28), was also identified in a healthy control sample (Table 3). However, this particular length variant was found only one time, which indicates a significant enrichment of the SH3BGRL3 epitope in the context of RA.

Interleukin-4 (IL-4) induced protein 1

In all the investigated synovial fluids (erosive & non-erosive RA) and in eight out of eleven sera (erosive & non-erosive RA), one highly dominant epitope was identified which is derived from the human homolog of the IL-4 induced protein 1 (Fig1): Fig1 (293-309) with the amino acid sequence of SEQ ID NO: 28 (Table 3). The validity of the epitope was further supported by the presence of additional length variants in several samples (Table 3): the 16-mer Fig1 (293-308; SEQ ID NO: 30) and the 19-mer Fig1 (293-311; SEQ ID NO: 29). Moreover, the amino acid sequence displays a typical *DRB1*0401* binding motif: 299V serves as P1 anchor, 302E as P4 anchor and 304S as P6 anchor (binding score 1%).

Two length variants of the same epitope, Fig1 (293-308) and Fig1 (293-309), were identified in one unpulsed sample and in one healthy control sample as well (Table 3). However, the presence of the Fig1 epitope in almost all RA samples but not in all of the control samples tested strongly indicates an enrichment in the context of RA.

The human *fig1* gene was first identified in IL-4-stimulated B cell cultures (Chu, C.C. & Paul, W.E., PNAS 94 (1997) 2507-2512). The human *fig1* resides on chromosome 19q13.3-19q13.4, a region previously identified to be involved in susceptibility to autoimmune diseases, including SLE, arthritis, multiple sclerosis, and insulin-dependent diabetes mellitus (Becker K.G. et al., PNAS 95 (1998) 9979-9984). Since its expression is largely limited to immune tissues and its regulation is dependent on IL-4, a key modulator of the immune response, *fig1* is thus an attractive candidate gene for autoimmune disease susceptibility (Chavan, S.S. et al., Biochim Biophys Acta 1576 (2002) 70-80). The HLA-DR4-restricted presentation of a Fig1 epitope provides the first indication that Fig1 protein is produced and possibly involved in the disease development of RA. The Fig1 polypeptide has not been known as a marker for RA until now, and is considered as an important candidate marker for RA.

Hemopexin

Another RA candidate marker which was frequently identified in serum samples (ten out of eleven samples) and in synovia samples (two out of four samples) (erosive & non-erosive RA) is derived from hemopexin (HPX): HPX (351-367) with the amino acid sequence of SEQ ID NO: 32 (Table 3). Several length variants were found which support the validity of this epitope (Table 3): the 13-mer HPX (351-363; SEQ ID NO: 33), the 14-mer HPX (350-363; SEQ ID NO: 34), the 15-mer HPX (351-365; SEQ ID NO: 35), the 18-mer HPX (351-368; SEQ ID NO: 31) and the 18-mer HPX (350-367; SEQ ID NO: 78). Furthermore, the epitope contains a very strong *DRB1*0401* binding motif: 355I serves as a P1 anchor, 358D as a P4 anchor and 360V as a P6 anchor (binding score: 1%).

Two length variants of the same epitope, HPX (351-367; SEQ ID NO: 32) and HPX (351-365; SEQ ID NO: 35), could also be identified in healthy control samples (Table 3) indicating that only some length variants are specific for RA, namely the antigenic peptides of SEQ ID NOs. 31, 33, 34 and 78.

HPX is a 60 kD plasma glycoprotein with a high binding affinity to heme (Müller-Eberhard, U., Methods Enzymol 163 (1988) 536-565). It is mainly expressed in the liver, and belongs to the acute-phase proteins the synthesis of which is induced in an inflammatory situation. RA is a chronic inflammatory autoimmune disease and elevated

levels of several acute-phase proteins, including C-reactive protein and serum amyloid A, have been reported (Nakamura, R., J Clin Lab Anal 14 (2000) 305-313). HPX is responsive to the cytokines IL-1 and IL-6, which are upregulated in patients suffering from RA (Feldmann, M. & Maini, R.N., Rheumatology 38, Suppl 2 (1999) 3-7).

HPX is the major vehicle for the transportation of heme in the plasma and its principal role is to prevent heme-mediated oxidative stress and loss of heme-bound iron (Tolosano, E. & Altruda, F., DNA Cell Biol 21 (2002) 297-306). It can protect cells against oxidative stress by inducing the expression of intracellular antioxidants such as heme oxygenase, metallothioneins and ferritin. Metallothioneins are cytosolic proteins that are expressed particularly in synovial fibroblasts (Backman, J.T. et al., Virchows Arch 433 (1998) 153-160). There is significant experimental evidence for the presence of oxidative stress in the synovial tissue of RA patients (reviewed in: Schett, G. et al., Arthritis Res 3 (2000) 80-86). Furthermore HPX was reported to promote proliferation of human T lymphocytes (Smith, A. et al., Exp Cell Res 232 (1997) 246-254). These studies render it likely that HPX belongs to the up-regulated proteins in serum and synovia of RA patients, thereby providing a rationale for the relevance of HPX (351-367) as a RA-specific candidate marker.

Hsc70-interacting protein

An epitope which was mostly identified in serum samples (4 out of eleven erosive and non-erosive RA samples) and which is also related to stress responses is derived from the Hsc70-interacting protein Hip: Hip (83-98) with the amino acid sequence of SEQ ID NO: 38 (Table 3). Two length variants of this epitope were identified (Table 3): the 18-mer Hip (83-100; SEQ ID NO: 36) and the 15-mer Hip (84-98; SEQ ID NO: 39). An additional length variant was discovered in one erosive synovia sample (Table 3): the 15-mer Hip (85-99; SEQ ID NO: 37). As judged from the shortest length variant Hip (84-98) a *DRB1*0401* binding motif attaining a moderate score of 8%, can be postulated: 89I as P1 anchor, 92D as P4 anchor, 94D as P6 anchor.

In the cytosol of eukaryotic cells, Hip and Hop proteins associate with Hsc70 in order to participate in the regulation of Hsc70 chaperone activity (Frydman, J. & Höhfeld, J., Trends Biochem Sci 22 (1997) 87-92). The 42 kD Hip protein binds to the ATPase domain of Hsc70. It was postulated that Hip might increase the half-life of the chaperone-substrate complex providing the molecular basis for an efficient cooperation of Hsc70 with downstream chaperone systems. Hsc70 and Hsp90 have been shown to cooperate during protein folding *in vitro* (Jakob, U. & Buchner, J., Trends Biochem Sci 19 (1994) 205-211;

Freeman, B.C. & Morimoto, R.I., EMBO J 15 (1996) 2969-2979) and to play a role in thermal denaturation (Schneider, C. et al., PNAS 93 (1996) 14536-14541). The Hsc70 and Hsp90 association with stress-adaptation ultimately links Hip to stress responses, including the induction of heat shock proteins, in the synovial tissue of RA patients (reviewed in: Schett, G. et al., Arthritis Res 3 (2001) 80-86).

Binding properties of ITIH4, C4, C3, SH3BGRL3, Fig1, HPX and Hip

In order to further investigate the binding properties of the above described antigenic peptides of ITIH4, C4, C3, SH3BGRL3, Fig1, HPX and Hip to HLA-DR4 molecules, *in vitro* binding assays were performed (Fig. 3): According to their IC_{50} values against the reporter peptide HA (309-317), the synthetic peptides ITIH4 (274-287), SH3BGRL3 (13-26), and Fig1 (293-309) bind to HLA-DR4 with high affinity (Fig. 3). Moderate binding to HLA-DR4 was measured for the synthetic peptides C4 (1696-1709) and HPX (351-365). The synthetic peptide C3 (1431-1444) bound only weakly to HLA-DR4 which is in agreement with TEPITOPE scoring (9%). No binding was measured for the Hip (84-98) peptide (data not shown).

Invariant chain (Ii)

Among the candidate marker peptides that appear to be indicative for erosive and non-erosive RA is an epitope which is derived from the HLA-DR-associated invariant chain (Ii): the 15-mer Ii (110-124; SEQ. ID NO: 83) with the amino acid sequence ATPLLMQALPMGALP (Table 3). Moreover, four length variants were identified: the 16-mer Ii (109-124; SEQ. ID NO: 81), the 17-mer Ii (109-125; SEQ. ID NO: 80), the 18-mer Ii (109-126; SEQ. ID NO: 79) and the 21-mer Ii (109-129; SEQ. ID NO: 82) (Table 3). The presence of length variants gives confidence in the identified peptide sequence which displays a moderate *DRB1*0401* binding motif (TEPITOPE binding score: 5%) with 114L serving as a P1 anchor, 117A as a P4 anchor and 119P as a P6 anchor. The epitope was identified in two erosive and three non-erosive RA samples. Two Ii length variants were found in one unpulsed sample and two samples of healthy test persons.

Peptide loading of MHC class II molecules is regulated by two accessory molecules in the class II pathway, invariant chain Ii and HLA-DM (reviewed by Bakke, O. & Nordeng T.W., Immunol Rev 172 (1999) 171-187 and Kropshofer, H. et al., Immunol Today 18 (1997) 77-82). Ii trimers bind to nascent MHC class II molecules in the rough endoplasmic reticulum (ER) and block the peptide-binding groove, stabilizing the class II molecule and

preventing the binding of ligands available in the ER. Class II/Ii complexes are transported via the Golgi apparatus to endosomes, where Ii is degraded to a nested set of class II-associated Ii peptides (CLIP). The release of CLIP enables endosomal peptides to bind to the MHC class II molecules which are presented to T cell receptors on the cell surface. The identified epitope Ii (110-124) overlaps with the C-terminal part of CLIP. Interestingly, a reduced interaction of CLIP with RA-associated HLA-DR alleles was described (Patil, N.S. et al., J Immunol 167 (2001) 7157-7168), indicating that a reduced interaction may contribute to the pathophysiology of autoimmunity in RA.

Retinoic acid receptor responder protein 2

In 4 out of 11 serum samples (erosive & non-erosive RA) an epitope was identified which is derived from retinoic acid receptor responder protein 2 (RARRES2): the 22-mer RARRES2 (40-61; SEQ. ID NO: 86) with the amino acid sequence HPPVQWAFQETSVESAVDTPFP (Table 3). In the C-terminal part of the epitope two length variants could have been identified: the 23-mer RARRES2 (40-62; SEQ. ID NO: 84) and the 24-mer RARRES2 (40-63; SEQ. ID NO: 85) (Table 3). With 45W as P1 anchor, 48Q as P4 anchor and 50T as P6 anchor, the epitope displays a moderate binding motif in the context of *DRB1*0401* (TEPITOPE binding score: 3%).

RARRES2 is a small 18.6 kD protein and mostly expressed in the endothelium and epidermis. The expression appears to be hormone dependent and a response to retinoic acid in skin and some osteotrophic hormones in marrow-derived stromal cells was identified (Nagpal, S. et al., J Invest Dermatol 109 (1997) 91-95 and Adams, A.E. et al., J Cell Biochem 74 (1999) 587-595). The function of RARRES2 is largely unknown and an association with RA, for instance through impaired osteoclastogenesis, is imaginable.

Fibronectin

Another HLA-DR4 associated peptide which was exclusively found in 3 out of 4 synovia samples (erosive & non-erosive RA) is derived from fibronectin (Fn), a major glycoprotein in blood plasma and in the extracellular matrix: the 15-mer Fn (1881-1895; SEQ. ID NO: 90) with the amino acid sequence IYLYTLNDNARSSPV (Table 3). The epitope appears to be a very good *DRB1*0401* binder with 1885Y serving as a hydrophobic P1 anchor, 1888N as a P4 anchor and 1890N as a P6 anchor (TEPITOPE binding score: 1%). Four length variants were additionally identified: the 16-mer Fn (1881-1896; SEQ. ID NO: 91), the 16-mer Fn (1880-1895; SEQ. ID NO: 88), the 17-mer Fn (1881-1897; SEQ. ID

NO: 89) and the 17-mer Fn (1880-1896; SEQ. ID NO: 87), strongly supporting the validity of the identified Fn epitope (Table 3).

Fibronectin plays an important role in cell adhesion, cell motility and in opsonization. It binds collagen and fibrin and mediates adhesion of fibroblasts to collagen fibrils. Fibronectin is strongly expressed in the synovial lining layer of both RA and osteoarthritis patients and correlates with hyperplasia of diseased joints. The identification of epitope Fn (1881-1895) in only samples of synovial origin is in line with these findings and points to a putative role of highly abundant fibronectin in autoimmunity.

Cathepsin B

Three out of fifteen RA samples (erosive & non-erosive RA) gave rise to an epitope which originates from Cathepsin B (CatB): the 15-mer CatB (227-241; SEQ. ID NO: 92) with the amino acid sequence YNSYSVSNSEKDIMA (Table 3). The peptide displays a moderate *DRB1*0401* binding motif with 230Y as a hydrophobic P1 anchor and the serine residues at positions 233 and 235 as putative P4 and P6 anchors (TEPITOPE binding score: 6%).

Cathepsin B is a thiol peptidase and believed to participate in intracellular degradation and turnover of proteins, e.g. collagen. It is located in lysosomes of different cell types including leukocytes. In the context of inflammation and disease it was shown that Cathepsin B contributes to cartilage destruction in osteoarthritis and pathological proteolysis in RA and cancer (Cunnane, G. et al., Arthritis Rheum 44 (2001) 1744-1753). Enzyme activities of Cathepsin B and other lysosomal peptidases correlate with RA progression which supports the validity of epitope CatB (227-241) as a putative RA marker peptide (Sohar, N. et al., Biol Chem 383 (2002) 865-869).

Tripeptidyl-peptidase II

Another peptidase-derived epitope which was found in three out of fifteen RA samples (erosive & non-erosive RA) is derived from tripeptidyl-peptidase II (TPP2): the 15-mer TPP2 (970-984; SEQ. ID NO: 93) having the amino acid sequence AGSLTLSKTELGKKA (Table 3). Additionally, the length variant TPP2 (970-985; SEQ. ID NO: 94) was identified. The peptidase epitope contains a typical *DRB1*0401* binding motif with 973L, 976S and 978T as P1, P4 and P6 anchors respectively (TEPITOPE binding score: 3%).

Similar to Cathepsin B, tripeptidyl-peptidase II is involved in lysosomal protein degradation. The identification of epitope TPP2 (970-984) in the context of RA provides the first indication that TPP2 might be implicated in impaired protein degradation in the context of inflammation and RA.

Legumain

Legumain (LGMN) completes the set of three peptidases which were found in this investigation. The identified epitope LGMN (99-112; SEQ. ID NO: 95) with the amino acid sequence VPKDYTGEDVTPQN (Table 3) displays a typical binding motif with respect to the HLA allele *DRB1*0401* in which 103Y could serve as a P1 anchor, 106E as a P4 anchor and 108V as a P6 anchor (TEPITOPE binding score: 1%).

Legumain occurs in endosomal and lysosomal fractions of antigen-presenting cells such as dendritic cells (Schwarz, G. et al., Biol Chem 383 (2002) 1813-1816). It has a strict specificity for the hydrolysis of asparaginyl bonds and was shown to play an important role in the processing of bacterial antigens for MHC class II presentation (Manoury, B. et al., Nature 396 (1998) 695-699). Whether Legumain is involved in autoimmune diseases, such as RA, remains unknown but the fact that three lysosomal peptidases together with GILT and the 26S proteasome were identified in this investigation suggests that the protein degradation machinery facilitating antigen processing might be significantly altered in the context of RA.

Platelet activating factor receptor

An epitope which was identified in three out of eleven serum RA samples (erosive & non-erosive RA) is derived from a receptor for platelet activating factor (PAFR): the 13-mer PAFR (264-276; SEQ. ID NO: 96) with the amino acid sequence DSKFHQAINDAHQ (Table 3). According to TEPITOPE scoring (3%) the epitope contains a moderated *DRB1*0401* binding motif with 267F as P1 anchor, 270A as P4 anchor and 272N as P6 anchor (Table 3).

Platelet activating factor (PAF) is a pro-inflammatory lipid mediator which binds to a G-protein-coupled seven transmembrane receptor on the surface of a broad range of cell types. By receptor binding, PAF transduces pleiotrophic functions which include cell motility, smooth muscle contraction, and synthesis and release of cytokines (reviewed by Honda, Z. et al., J Biochem 131 (2002) 773-779). Pharmacological studies and the

establishment of PAFR (-/-) mice have suggested that PAF functions in a variety of settings including allergy, inflammation, neural functions, reproduction, and atherosclerosis. Interestingly, PAF was found in elevated levels in the synovial fluid of RA patients and shown to induce neoangiogenesis, which is frequently observed in rheumatoid synovitis (Lupia, E. et al., Eur J Immunol 26 (1996) 1690-1694). This type of evidence gives further confidence in epitope PAFR (264-276) being a RA-associated marker peptide.

Poly-alpha-2,8-sialyltransferase

Another epitope which was found in three out of eleven serum samples (erosive & non-erosive RA) originates from Polysialyltransferase (PST): the 15-mer PST (333-347; SEQ. ID NO: 97), MPLEFKTLNVLHNRG (Table 3), displays a moderate binding motif with respect to *DRB1*0401* binding (TEPITOPE scoring: 2%). 337F could serve as a P1 anchor, 340L as a P4 anchor and 342V as a P6 anchor.

Polysialic acid is a carbohydrate composed of a linear homopolymer of α-2,8-linked sialic acid residues. The glycan is mainly attached to the neural cell adhesion molecule (N-CAM) and implicated in many morphogenic processes of the neural cells by modulating the adhesive property of N-CAM. The membrane protein polysialyltransferase catalyzes the polycondensation of sialic acid residues and is highly expressed in fetal brain, lung and kidney, in adult heart, spleen and thymus, and to a lesser extent in peripheral blood leukocytes (Nakayama, J. et al., Proc Natl Acad Sci 92 (1995) 7031-7035). Elevated PST levels were observed in serum of patients with metastatic tumors and an increased enzyme activity was also associated with rheumatoid arthritis (Berge, P.G. et al., Klin Wochenschr 60 (1982) 445-449). The identification of epitope PST (333-347) in several RA samples is in line with these observations and supports the putative role of PST in RA.

Ras-related protein Rab-11B

The last epitope presented in this analysis of RA samples is derived from the Ras-related protein Rab-11B: the 13-mer Rab-11B (51-63; SEQ. ID NO: 102) with the amino acid sequence RSIQVDGKTIKAQ (Table 3, the peptide sequence were validated with regard to binding to the RA susceptibility allele *DRB1**0301 by using the TEPITOPE software (Hammer, J. et al., Adv Immunol 66 (1997) 67-100)). This epitope and four additional lenght variants, the 14-mer Rab-11B (50-63; SEQ. ID NO: 100), the 15-mer Rab-11B (49-63; SEQ. ID NO: 98), the 17-mer Rab-11B (49-65; SEQ. ID NO: 101) and the 18-mer Rab-11B (49-66; SEQ. ID NO: 99) were found in three erosive and two non-erosive

RA samples (Table 3). The 15-mer Rab-11B (49-63) was identified in 1 out of 12 control samples.

.Rab proteins are small GTPases that play an important role in membrane trafficking along the endo- and exocytic pathway. Rab-11B is assumed to be essential for the transport of internalized transferrin from the recycling compartment to the plasma membrane. Furthermore Rab-11B was identified in rat osteoclasts and might play an additional role in bone resorption. The epitope Rab-11B (51-63) provides the first indication of a role of Rab-11B in RA development.

Table 1: HLA-DR associated peptide antigens from serum and synovial fluid of patients with mostly non-erosive RA.

SEQ. ID. NO.	RA-type[a]	RF[b] (IU/ml)	Sample[c]	Haplo-type[d]	Length	Sequence[e]	*DRB1*0401*-binding score[f]	Protein source[g]
1	N	-	S	1	14	GDRGMQLMHANAQR	1%	Interferon-gamma-inducible lysosomal thiol reductase (192-205)
2	N	6.8	S	3	17	GDRGMQLMHANAQRTDA		
3	N	6.8	S	3	16	GDRGMQLMHANAQRTD		
2	N	9.1	Syn	4	17	GDRGMQLMHANAQRTDA		
3	N	9.1	Syn	4	16	GDRGMQLMHANAQRTD		
3	E	20.7	S	3	16	GDRGMQLMHANAQRTD		
58	N	9.1	Syn	4	17	NIQPIFAVTSRMVKTYE	2%	Integrin beta-2 (315-331)
58	N	9.1	S	4	17	NIQPIFAVTSRMVKTYE		
59	N	9.1	S	4	19	ENNIQPIFAVTSRMVKTYE		
60	N	153	S	5	17	NKVFGEDSVGVIFKNGD	3%	Phosphatidylinositol-4,5-bisphosphate 3-kinase (792-808)
60	N	88	S	5	17	NKVFGEDSVGVIFKNGD		
61	N	9.1	S	4	16	YPEQLKMTVVKLISHR	2%	Urokinase-type plasminogen activator (328-343)
61	N	9.1	Syn	4	16	YPEQLKMTVVKLISHR		
62	N	153	S	5	16	KNTLYLQMNSLRAEDT	1%	Immunglobulin heavy chain

62	N	88	S	5	16	KNTLYLQMNSLRAEDT		V-III region (V_H26) (95-110)
63	N	153	S	5	16	NGGHYTYSENRVEKDG	8%	DJ-1 protein (135-150)
63	N	88	S	5	16	NGGHYTYSENRVEKDG		
	strong HLA-DRB1*0401 binder					PKYVKQNTLKLAT[h (i)]	1%	Influenza Haemagglutinin (307-319)
	moderate HLA-DRB1*0401 binder					KHKVYACEVTHQGLS[h (ii)]	2%	Immunglobuline kappa (188-202)
	weak HLA-DRB1*0401 binder					KTIAYDEEARR[h (iii)]	> 10%	*M. tuberculosis* Hsp65 (3-13)

[a]RA-type of the patient based on clinical diagnosis: persistant erosive (E) or persistent non-erosive (N) RA

[b]Rheumatoid factor

[c]Sample description: dendritic cells pulsed with serum (S) or synovial fluid (Syn)

[d]Haplotype of the buffy coat: (1) *HLA-DRB1*0401, *03011*; (2) *HLA-DRB1*0401, *0304*; (3) *HLA-DRB1*0401, *1301*; (4) *HLA-DRB1*0401, *0701*; (5) *HLA-DRB1*0401, *0407 *0401, *1301*; (4) *HLA-DRB1*0401, *0701*

[e]Sequences of the RA-derived peptides in one-letter-code. The *HLA-DRB1*0401* binding motif is boxed in grey.

[f]Score of the epitope in context of the *HLA-DRB1*0401* allele based on the TEPITOPE program (Hammer, J. et al., Adv Immunol 66 (1997) 67-100).

[g]Protein name according to the Swiss-Prot / TrEMBL database. The numbers in brackets represent the shortest length variant of the respective epitope.

[h (i)] Rothbard, J.B. et al., Cell 52 (1988) 515-523. [h (ii)] Chicz, R.M. et al., J Exp Med 178 (1993) 27-47. [h (iii)] van Schooten, W.C. et al., Eur J Immunol 19 (1989) 2075-2079.

Table 2: HLA-DR associated peptide antigens from serum and synovial fluid of patients with mostly erosive RA.

SEQ. ID. NO.	RA-type[a]	RF[b] (IU/ml)	Sample[c]	Haplo-type[d]	Length	Sequence[e]	*DRB1*0401*-binding score[f]	Protein source[g]
4	E	-	S	1	16	INNQLTLDSNTKYFHK**	3%	Apolipoprotein B-100 (2877-2892)
4	E	+	S	2	16	INNQLTLDSNTKYFHK**		
4	E	134	S	3	16	INNQLTLDSNTKYFHK**		
4	E	20.7	S	3	16	INNQLTLDSNTKYFHK**		
5	E	20.7	S	3	17	INNQLTLDSNTKYFHKL		
4	N	-	S	1	16	INNQLTLDSNTKYFHK**		
64	E	134	S	3	15	GPNNYYSFASQQQKP	3%	26S proteasome non-ATPase regulatory subunit 8 (218-232)
64	E	0	S	5	15	GPNNYYSFASQQQKP		
64	E	401	S	5	15	GPNNYYSFASQQQKP		
65	E	134	Syn	3	16	GPNNYYSFASQQQKPE		
66	E	134	Syn	3	17	GPNNYYSFASQQQKPED		
66	N	6.8	Syn	3	17	GPNNYYSFASQQQKPED		
67	N	6.8	Syn	3	18	GPNNYYSFASQQQKPEDT		
68	E	0	S	5	16	EKLWFVPAKVEDSGHY	1%	Interleukin-1 receptor (79-94)
68	E	401	S	5	16	EKLWFVPAKVEDSGHY		

69	E	-	S	1	14	SLRELHLDHNQISR	1%	Fibromodulin (178-190)
70	E	20.7	Syn	3	13	LRELHLDHNQISR		
69	E	20.7	Syn	3	14	SLRELHLDHNQISR		
70	E	134	Syn	3	13	LRELHLDHNQISR		
69	N	6.8	Syn	3	14	SLRELHLDHNQISR		
70	N	6.8	Syn	3	13	LRELHLDHNQISR		
71	E	134	S	3	15	ETMKMRYEHIDHTFE*	3%	GM-CSF/IL-3/IL-5 receptor (359-373)
71	E	20.7	S	3	15	ETMKMRYEHIDHTFE*		
71	E	0	S	5	15	ETMKMRYEHIDHTFE*		
72	E	401	S	5	17	ETMKMRYEHIDHTFEIQ		
72	E	134	Syn	3	17	ETMKMRYEHIDHTFEIQ		
71	N	6.8	S	3	15	ETMKMRYEHIDHTFE*		
71	N	6.8	Syn	3	15	ETMKMRYEHIDHTFE*		
73	E	0	S	5	16	HMFLQDEIIDKSYTPS	2%	Sorting nexin 3 (142-157)
73	E	401	S	5	16	HMFLQDEIIDKSYTPS		

[a]RA-type of the patient based on clinical diagnosis: persistant erosive (E) or persistent non-erosive (N) RA

[b]Rheumatoid factor

[c]Sample description: dendritic cells pulsed with serum (S) or synovial fluid (Syn)

[d]Haplotype of the buffy coat: (1) *HLA-DRB1*0401, *03011*; (2) *HLA-DRB1*0401, *0304*; (3) *HLA-DRB1*0401, *1301*; (4) *HLA-DRB1*0401, *0701*; (5) *HLA-DRB1*0401, *0407*

[e]Sequences of the RA-derived peptides in one-letter-code. The *HLA-DRB1*0401* binding motif is boxed in grey.

[f]Score of the epitope in context of the *HLA-DRB1*0401* allele based on the TEPITOPE program (Hammer, J. et al., Adv Immunol 66 (1997) 67-100).

[g]Protein name according to the Swiss-Prot / TrEMBL database. The numbers in brackets represent the shortest length variant of the respective epitope.

* Length variant of the respective epitope which was identified in 1 healthy control sample as well.

** Length variant of the respective epitope, which was identified in 2 healthy control samples as well.

Table 3: HLA-DR associated peptide antigens from serum or synvial fluid of patients with erosive and non-erosive RA.

SEQ. ID No.	RA-type[a]	RF[b] (IU/ml)	Sample[c]	Haplo-type[d]	Length	Sequence[e]	*DRB1*0401*-binding score[f]	Protein source[g]
6	E	-	S	3	19	MPKNVVFVIDKSGSMSGRK	1%	Inter-alpha-trypsin inhibitor heavy chain H4 (274-287)
7	E	+	S	3	18	MPKNVVFVIDKSGSMSGR		
8	E	+	S	3	17	MPKNVVFVIDKSGSMSG*		
8	E	134	S	3	17	MPKNVVFVIDKSGSMSG*		
9	E	134	S	3	14	NVVFVIDKSGSMSG		
8	E	134	S	2	17	MPKNVVFVIDKSGSMSG*		
10	E	134	S	2	15	KNVVFVIDKSGSMSG		
8	E	20.7	S	1	17	MPKNVVFVIDKSGSMSG*		
11	E	20.7	S	1	15	NVVFVIDKSGSMSGR		
6	N	-	S	3	19	MPKNVVFVIDKSGSMSGRK		
7	N	6.8	S	3	18	MPKNVVFVIDKSGSMSGR		
8	N	6.8	S	3	17	MPKNVVFVIDKSGSMSG*		
8	N	6.8	S	3	17	MPKNVVFVIDKSGSMSG*		
12	N	6.8	S	3	16	NVVFVIDKSGSMSGRK		
8	N	6.8	S	1	17	MPKNVVFVIDKSGSMSG*		
8	N	153	S	5	17	MPKNVVFVIDKSGSMSG*		
8	N	88	S	5	17	MPKNVVFVIDKSGSMSG*		
10	E	0	S	5	15	KNVVFVIDKSGSMSG		
8	E	0	S	5	17	MPKNVVFVIDKSGSMSG*		
7	E	0	S	5	18	MPKNVVFVIDKSGSMSGR		

8	E	401	S	5	17	MPKNVVFVIDKSGSMSG*		
7	E	401	S	5	18	MPKNVVFVIDKSGSMSGR		
13	N	-	S	1	15	GHPQYLLDSNSWIEE**	1%	Complement C4 (1697-1708)
14	N	-	S	1	16	GHPQYLLDSNSWIEEM		
15	N	-	S	1	14	GHPQYLLDSNSWIE		
13	N	6.8	S	3	15	GHPQYLLDSNSWIEE**		
16	N	9.1	S	4	18	GHPQYLLDSNSWIEEMPS*		
17	N	9.1	S	4	13	HPQYLLDSNSWIE		
13	N	9.1	S	4	15	GHPQYLLDSNSWIEE**		
18	N	9.1	S	4	12	GHPQYLLDSNSW		
14	E	-	S	1	16	GHPQYLLDSNSWIEEM		
13	E	-	S	1	15	GHPQYLLDSNSWIEE**		
18	E	-	S	1	12	GHPQYLLDSNSW		
13	E	+	S	2	15	GHPQYLLDSNSWIEE**		
13	E	134	S	3	15	GHPQYLLDSNSWIEE**		
15	E	134	S	3	14	GHPQYLLDSNSWIE		
16	E	134	S	3	18	GHPQYLLDSNSWIEEMPS*		
13	E	20.7	S	3	15	GHPQYLLDSNSWIEE		
16	E	20.7	S	3	18	GHPQYLLDSNSWIEEMPS*		
13	E	0	S	5	15	GHPQYLLDSNSWIEE**		
19	N	9.1	S	4	19	GVDRYISKYELDKAFSDRN	9%	Complement C3 (α-chain) (1431-1443)
20	N	-	S	1	15	RYISKYELDKAFSDR		
21	N	-	S	1	14	ISKYELDKAFSDRN		

22	N	-	S	1	15	ISKYELDKAFSDRNT		
23	N	-	S	1	13	ISKYELDKAFSDR		
21	E	+	S	2	14	ISKYELDKAFSDRN		
74	N	88	S	5	17	VDRYISKYELDKAFSDR		
75	E	0	S	5	14	RYISKYELDKAFSD*		
76	N	153	S	5	19	LPVGRTVMVNIENPEGIPV	3%	Complement C3 (β-chain) (157-175)
76	N	88	S	5	19	LPVGRTVMVNIENPEGIPV		
76	E	0	S	5	19	LPVGRTVMVNIENPEGIPV		
77	E	0	S	5	20	LPVGRTVMVNIENPEGIPVK		
76	E	401	S	5	19	LPVGRTVMVNIENPEGIPV		
77	E	401	S	5	20	LPVGRTVMVNIENPEGIPVK		
24	N	6.8	S	3	16	GSREIKSQQSEVTRIL*	4%	SH3 domain-binding glutamic acid-rich-like protein 3 (15-26)
25	N	-	S	1	12	REIKSQQSEVTR		
26	N	-	S	1	14	GSREIKSQQSEVTR		
24	N	-	S	1	16	GSREIKSQQSEVTRIL*		
27	N	-	S	1	14	REIKSQQSEVTRIL		
26	E	-	S	1	14	GSREIKSQQSEVTR		
25	E	-	S	1	12	REIKSQQSEVTR		
25	E	134	S	3	12	REIKSQQSEVTR		
25	E	20.7	S	3	12	REIKSQQSEVTR		
24	E	20.7	S	3	16	GSREIKSQQSEVTRIL*		
26	E	401	S	5	14	GSREIKSQQSEVTR		
25	E	401	S	5	12	REIKSQQSEVTR		

28	E	20.7	Syn	3	17	GPHDVHVQIETSPPARN	1%	Interleukin-4-induced protein 1 (293-308)
29	E	20.7	Syn	3	19	GPHDVHVQIETSPPARNLK		
29	E	134	Syn	3	19	GPHDVHVQIETSPPARNLK		
28	E	-	S	1	17	GPHDVHVQIETSPPARN		
28	E	+	S	2	17	GPHDVHVQIETSPPARN		
28	E	134	S	3	17	GPHDVHVQIETSPPARN		
30	E	134	S	3	16	GPHDVHVQIETSPPAR*		
30	E	20.7	S	3	16	GPHDVHVQIETSPPAR*		
28	N	6.8	S	3	17	GPHDVHVQIETSPPARN		
28	N	9.1	S	4	17	GPHDVHVQIETSPPARN		
30	N	9.1	S	4	16	GPHDVHVQIETSPPAR*		
28	N	-	S	1	17	GPHDVHVQIETSPPARN		
28	N	9.1	Syn	4	17	GPHDVHVQIETSPPARN		
28	N	6.8	Syn	3	17	GPHDVHVQIETSPPARN		
28	E	0	S	5	17	GPHDVHVQIETSPPARN	1%	Interleukin-4-induced protein 1 (293-309)
31	N	-	S	1	18	TPHGIILDSVDAAFICPG	1%	Hemopexin (351-363)
32	N	9.1	S	4	17	TPHGIILDSVDAAFICP**		
33	N	9.1	S	4	13	TPHGIILDSVDAA**		
32	N	6.8	Syn	3	17	TPHGIILDSVDAAFICP**		
32	N	9.1	Syn	4	17	TPHGIILDSVDAAFICP**		
33	N	9.1	Syn	4	13	TPHGIILDSVDAA**		
34	N	9.1	Syn	4	14	GTPHGIILDSVDAA		

35	N	6.8	S	3	15	TPHGIILDSVDAAFI*		
32	N	6.8	S	3	17	TPHGIILDSVDAAFICP**		
31	E	+	S	2	18	TPHGIILDSVDAAFICPG		
35	E	134	S	3	15	TPHGIILDSVDAAFI*		
32	E	134	S	3	17	TPHGIILDSVDAAFICP**		
35	E	20.7	S	3	15	TPHGIILDSVDAAFI*		
32	E	20.7	S	3	17	TPHGIILDSVDAAFICP**		
78	N	153	S	5	18	GTPHGIILDSVDAAFICP**		
35	N	88	S	5	15	TPHGIILDSVDAAFI**		
33	N	88	S	5	13	TPHGIILDSVDAA**		
32	N	88	S	5	17	TPHGIILDSVDAAFICP**		
78	E	0	S	5	18	GTPHGIILDSVDAAFICP**		
35	E	0	S	5	15	TPHGIILDSVDAAFI**		
33	E	401	S	5	13	TPHGIILDSVDAA**		
35	E	401	S	5	15	TPHGIILDSVDAAFI**		
32	E	401	S	5	17	TPHGIILDSVDAAFICP**		
36	E	134	Syn	3	18	IDKEGVIEPDTDAPQEMG	8%	Hsc70-interacting protein (84-98)
37	E	134	Syn	3	15	KEGVIEPDTDAPQEM		
38	E	-	S	1	16	IDKEGVIEPDTDAPQE		
39	E	-	S	1	15	DKEGVIEPDTDAPQE		
36	N	9.1	S	4	18	IDKEGVIEPDTDAPQEMG		
38	N	-	S	1	16	IDKEGVIEPDTDAPQE		
38	N	6.8	S	3	16	IDKEGVIEPDTDAPQE		

79	E	+	S	2	18	MATPLLMQALPMGALPQG	5%	Invariant chain (Ii) (110-124)
80	E	+	S	2	17	MATPLLMQALPMGALPQ**		
81	E	+	S	2	16	MATPLLMQALPMGALP		
80	E	134	Syn	3	17	MATPLLMQALPMGALPQ**		
82	N	9.1	S	4	21	MATPLLMQALPMGALPQGPMQ**		
83	N	6.8	S	3	15	ATPLLMQALPMGALP		
82	N	6.8	Syn	3	21	MATPLLMQALPMGALPQGPMQ**		
84	E	0	S	5	23	HPPVQWAFQETSVESAVDTPFPA	3%	Retinoic acid receptor responder protein 2 (40-61)
85	E	0	S	5	24	HPPVQWAFQETSVESAVDTPFPAG		
86	E	0	S	5	22	HPPVQWAFQETSVESAVDTPFP		
84	E	401	S	5	23	HPPVQWAFQETSVESAVDTPFPA		
85	E	401	S	5	24	HPPVQWAFQETSVESAVDTPFPAG		
84	N	153	S	5	23	HPPVQWAFQETSVESAVDTPFPA		
86	N	153	S	5	22	HPPVQWAFQETSVESAVDTPFP		
85	N	153	S	5	24	HPPVQWAFQETSVESAVDTPFPAG		
84	N	88	S	5	23	HPPVQWAFQETSVESAVDTPFPA		
85	N	88	S	5	24	HPPVQWAFQETSVESAVDTPFPAG		
87	E	20.7	Syn	3	17	KIYLYTLNDNARSSPVV	1%	Fibronectin (1881-1895)
88	E	20.7	Syn	3	16	KIYLYTLNDNARSSPV		
89	E	20.7	Syn	3	17	IYLYTLNDNARSSPVVI		
90	E	20.7	Syn	3	15	IYLYTLNDNARSSPV		
91	E	20.7	Syn	3	16	IYLYTLNDNARSSPVV		
90	E	134	Syn	3	15	IYLYTLNDNARSSPV		

90	N	6.8	Syn	3	15	IYLYTLNDNARSSPV		
92	E	134	S	3	15	YNSYSVSNSEKDIMA	6%	Cathepsin B (227-241)
92	E	134	Syn	3	15	YNSYSVSNSEKDIMA		
92	N	6.8	S	3	15	YNSYSVSNSEKDIMA		
93	E	0	S	5	15	AGSLTLSKTELGKKA	3%	Tripeptidyl-peptidase II (970-984)
93	E	401	S	5	15	AGSLTLSKTELGKKA		
94	E	401	S	5	16	AGSLTLSKTELGKKAD		
94	N	153	S	5	16	AGSLTLSKTELGKKAD		
95	E	-	S	1	14	VPKDYTGEDVTPQN	1%	Legumain (99-112)
95	N	-	S	1	14	VPKDYTGEDVTPQN		
95	N	9.1	Syn	4	14	VPKDYTGEDVTPQN		
96	E	0	S	5	13	DSKFHQAINDAHQ	3%	Platelet activating factor receptor (264-276)
96	E	401	S	5	13	DSKFHQAINDAHQ		
96	N	88	S	5	13	DSKFHQAINDAHQ		
97	E	0	S	5	15	MPLEFKTLNVLHNRG	2%	Poly-alpha-2,8-sialyltransferase (333-347)
97	E	401	S	5	15	MPLEFKTLNVLHNRG		
97	N	88	S	5	15	MPLEFKTLNVLHNRG		
98	E	-	S	1	15	ATRSIQVDGKTIKAQ†	1%†	Ras-related protein Rab-11B (51-63)
98	E	+	S	2	15	ATRSIQVDGKTIKAQ†		

98	E	20.7	S	3	15	ATRSIQVDGKTIKAQ†
99	E	20.7	S	3	18	ATRSIQVDGKTIKAQIWD†
100	N	6.8	S	3	14	TRSIQVDGKTIKAQ†
99	N	6.8	S	3	18	ATRSIQVDGKTIKAQIWD†
101	N	6.8	S	3	17	ATRSIQVDGKTIKAQIW†
98	N	-	S	1	15	ATRSIQVDGKTIKAQ†
102	N	-	S	1	13	RSIQVDGKTIKAQ†

[a]RA-type of the patient based on clinical diagnosis: persistant erosive (E) or persistent non-erosive (N) RA

[b]Rheumatoid factor

[c]Sample description: dendritic cells pulsed with serum (S) or synovial fluid (Syn)

[d]Haplotype of the buffy coat: (1) *HLA-DRB1*0401, *03011*; (2) *HLA-DRB1*0401, *0304*; (3) *HLA-DRB1*0401, *1301*; (4) *HLA-DRB1*0401, *0701*; (5) *HLA-DRB1*0401, *0407*

[e]Sequences of the RA-derived peptides in one-letter-code. The putative *HLA-DRB1*0401* († **0301*) binding motif is boxed in grey.

[f]Score of the epitope in context of the *HLA-DRB1*0401* († **0301*) allele based on the TEPITOPE program (Hammer, J. et al., Adv Immunol 66 (1997) 67-100).

[g]Protein name according to the Swiss-Prot / TrEMBL database. The numbers in brackets represent the shortest length variant of the respective epitope.

*(**) Length variant of the respective epitope which was identified in 1 (2) healthy control sample(s) as well.

Table 4: Summary of the candidate RA markers.

RA-type	Protein source[a]	Frequency in the RA samples[b]	Accession number[c]
mostly non-erosive	Interferon-γ-inducible lysosomal thiol reductase	3 of 7 N	P13284
	Integrin beta-2	2 of 7 N	P05107
	Phosphatidylinositol-4,5-bisphosphate 3-kinase	2 of 7 N	P42338
	Urokinase-type plasminogen activator	2 of 7 N	P00749
	Immunglobulin heavy chain V-III region (V_H26)	2 of 7 N	P01764
	DJ-1 protein	2 of 7 N	Q99497
mostly erosive	Apolipoprotein B-100	4 of 8 E	P04114
	26S proteasome non-ATPase regulatory subunit 8	4 of 8 E	P48556
	Interleukin-1 receptor	2 of 8 E	P14778

	Fibromodulin	3 of 8 E	Q06828
	GM-CSF/IL-3/IL-5 receptor	5 of 8 E	P32927
	Sorting nexin 3	2 of 8 E	O60493
erosive and non-erosive	Inter-α-trypsin inhibitor heavy chain H4	6 of 8 E / 4 of 7 N	Q14624
	Complement C4	5 of 8 E / 3 of 7 N	P01028
	Complement C3	2 of 8 E / 3 of 7 N	P01024
	SH3 domain-binding glutamic acid-rich-like protein 3	4 of 8 E / 2 of 7 N	Q9H299
	Interleukin-4-induced protein 1	7 of 8 E / 5 of 7 N	Q96RQ9
	Hemopexin	5 of 8 E / 7 of 7 N	P02790
	Hsc70-interacting protein	2 of 8 E / 3 of 7 N	P50502
	Invariant chain (Ii)	2 of 8 E / 3 of 7 N	P04233
	Retinoic acid receptor responder protein 2	2 of 8 E / 2 of 7 N	Q99969
	Fibronectin	2 of 8 E / 1 of 7 N	P02751

Cathepsin B	2 of 8 E / 1 of 7 N	P07858
Tripeptidyl-peptidase II	2 of 8 E / 1 of 7 N	P29144
Legumain	1 of 8 E / 2 of 7 N	Q99538
Platelet activating factor receptor	2 of 8 E / 1 of 7 N	P25105
Alpha-2,8-sialyltransferase	2 of 8 E / 1 of 7 N	Q92187
Ras-related protein Rab-11B	3 of 8 E / 2 of 7 N	Q15907

[a]Protein name according to the Swiss-Prot / TrEMBL database.

[b]Frequency of the identified epitope in the RA samples. The RA-type of the patient was based on clinical diagnosis: persistant erosive (E) or persistent non-erosive (N) RA.

[c]relates to the Swiss-Prot databas

Claims

1. A MHC class II antigenic peptide comprising

(a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 49, or

(b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 49 with additional N-and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID NOs. 1 to 3.

2. The MHC class II antigenic peptide according to claim 1 linked to a MHC class II molecule.

3. A diagnostic composition comprising an antibody reactive with an MHC class II antigenic peptide according to claim 1.

4. The use of the MHC class II antigenic peptide comprising

   (a) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID Nos. 49 to 57 and SEQ ID Nos. 103 to 122; or

   (b) at least the amino acid sequence of the peptide binding motif selected from the group consisting of SEQ ID Nos. 49 to 57 and SEQ ID Nos. 103 to 122, with additional N- and C-terminal flanking sequences of a corresponding sequence selected from the group consisting of SEQ ID Nos. 1 to 39 and SEQ ID Nos. 58 to 102;

   wherein the antigenic peptide is a marker for erosive and/or non-erosive RA.

5. The use of the MHC class II antigenic peptide according to claim 1, wherein the antigenic peptide is a marker for non-erosive RA.

6. The use of the MHC class II antigenic peptide comprising:

   (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 109; or

   (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 109 with additional N-and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 68,

   wherein the antigenic peptide is a marker for erosive RA.

7. The use of the MHC class II antigenic peptide comprising:

   (a) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 111; or

   (b) at least the amino acid sequence of the peptide binding motif of SEQ ID NO. 111 with additional N-and C-terminal flanking sequences of the corresponding sequence of SEQ ID NO. 72,

   wherein the antigenic peptide is a marker for erosive RA.

***

SEQUENCE LISTING

<110> F. Hoffmann-La Roche AG

<120> RA antigenic peptides

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Tyr Ala Pro Gly Leu Ser Pro Asp Thr Ile Met Glu Cys Ala Met Gly
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Pro Glu Lys Asp Glu Pro Thr Tyr Ile Leu Asn Ile Lys Arg Gly Ile
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Trp Val Asn Gly Gln Val Pro Asp Gly Val Ser Lys Val Leu Val Asp
725 730 735

His Phe Gly Tyr Thr Lys Asp Asp Lys His Glu Gln Asp Met Val Asn
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Ser Ser Ser Gly Val Ile Ala Pro Gly Ala Lys Ala Gly Val Lys Leu
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Pro Lys Arg Pro Val Lys Leu Leu Ser Gly Gly Asn Thr Leu His Leu
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Ile Asp Met Ser Thr Asn Tyr Asn Ser Asp Ser Leu His Phe Ser
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Ala Phe Thr Phe Ser His Asp Tyr Lys Gly Ser Thr Ser His His
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Leu Val Ser Arg Lys Ser Ile Ser Ala Ala Leu Glu His Lys Val
1955 1960 1965

Ser Ala Leu Leu Thr Pro Ala Glu Gln Thr Gly Thr Trp Lys Leu
1970 1975 1980

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1985 1990 1995

Tyr Asn Thr Lys Asp Lys Ile Gly Val Glu Leu Thr Gly Arg Thr
2000 2005 2010

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2015 2020 2025

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Val Gly Gln Val Tyr Ser Thr Leu Val Thr Tyr Ile Ser Asp Trp
2540 2545 2550

Trp Thr Leu Ala Ala Lys Asn Leu Thr Asp Phe Ala Glu Gln Tyr
2555 2560 2565

Ser Ile Gln Asp Trp Ala Lys Arg Met Lys Ala Leu Val Glu Gln
2570 2575 2580

Gly Phe Thr Val Pro Glu Ile Lys Thr Ile Leu Gly Thr Met Pro
2585 2590 2595

Ala Phe Glu Val Ser Leu Gln Ala Leu Gln Lys Ala Thr Phe Gln
2600 2605 2610

Thr Pro Asp Phe Ile Val Pro Leu Thr Asp Leu Arg Ile Pro Ser
2615 2620 2625

Val Gln Ile Asn Phe Lys Asp Leu Lys Asn Ile Lys Ile Pro Ser
2630 2635 2640

Arg Phe Ser Thr Pro Glu Phe Thr Ile Leu Asn Thr Phe His Ile
2645 2650 2655

Pro Ser Phe Thr Ile Asp Phe Val Glu Met Lys Val Lys Ile Ile
2660 2665 2670

Arg Thr Ile Asp Gln Met Gln Asn Ser Glu Leu Gln Trp Pro Val
2675 2680 2685

Pro Asp Ile Tyr Leu Arg Asp Leu Lys Val Glu Asp Ile Pro Leu
2690 2695 2700

Ala Arg Ile Thr Leu Pro Asp Phe Arg Leu Pro Glu Ile Ala Ile
2705 2710 2715

Pro Glu Phe Ile Ile Pro Thr Leu Asn Leu Asn Asp Phe Gln Val
2720 2725 2730

Pro Asp Leu His Ile Pro Glu Phe Gln Leu Pro His Ile Ser His
2735 2740 2745

Thr Ile Glu Val Pro Thr Phe Gly Lys Leu Tyr Ser Ile Leu Lys
2750 2755 2760

Ile Gln Ser Pro Leu Phe Thr Leu Asp Ala Asn Ala Asp Ile Gly
2765 2770 2775

Asn Gly Thr Thr Ser Ala Asn Glu Ala Gly Ile Ala Ala Ser Ile
2780 2785 2790

Thr Ala Lys Gly Glu Ser Lys Leu Glu Val Leu Asn Phe Asp Phe
2795 2800 2805

Gln Ala Asn Ala Gln Leu Ser Asn Pro Lys Ile Asn Pro Leu Ala
2810 2815 2820

Leu Lys Glu Ser Val Lys Phe Ser Ser Lys Tyr Leu Arg Thr Glu
2825 2830 2835

His Gly Ser Glu Met Leu Phe Phe Gly Asn Ala Ile Glu Gly Lys
2840 2845 2850

Ser Asn Thr Val Ala Ser Leu His Thr Glu Lys Asn Thr Leu Glu
2855 2860 2865

Leu Ser Asn Gly Val Ile Val Lys Ile Asn Asn Gln Leu Thr Leu

2870 2875 2880

Asp Ser Asn Thr Lys Tyr Phe His Lys Leu Asn Ile Pro Lys Leu
2885 2890 2895

Asp Phe Ser Ser Gln Ala Asp Leu Arg Asn Glu Ile Lys Thr Leu
2900 2905 2910

Leu Lys Ala Gly His Ile Ala Trp Thr Ser Ser Gly Lys Gly Ser
2915 2920 2925

Trp Lys Trp Ala Cys Pro Arg Phe Ser Asp Glu Gly Thr His Glu
2930 2935 2940

Ser Gln Ile Ser Phe Thr Ile Glu Gly Pro Leu Thr Ser Phe Gly
2945 2950 2955

Leu Ser Asn Lys Ile Asn Ser Lys His Leu Arg Val Asn Gln Asn
2960 2965 2970

Leu Val Tyr Glu Ser Gly Ser Leu Asn Phe Ser Lys Leu Glu Ile
2975 2980 2985

Gln Ser Gln Val Asp Ser Gln His Val Gly His Ser Val Leu Thr
2990 2995 3000

Ala Lys Gly Met Ala Leu Phe Gly Glu Gly Lys Ala Glu Phe Thr
3005 3010 3015

Gly Arg His Asp Ala His Leu Asn Gly Lys Val Ile Gly Thr Leu
3020 3025 3030

Lys Asn Ser Leu Phe Phe Ser Ala Gln Pro Phe Glu Ile Thr Ala
3035 3040 3045

Ser Thr Asn Asn Glu Gly Asn Leu Lys Val Arg Phe Pro Leu Arg
3050 3055 3060

Leu Thr Gly Lys Ile Asp Phe Leu Asn Asn Tyr Ala Leu Phe Leu
3065 3070 3075

Ser Pro Ser Ala Gln Gln Ala Ser Trp Gln Val Ser Ala Arg Phe
3080 3085 3090

Asn Gln Tyr Lys Tyr Asn Gln Asn Phe Ser Ala Gly Asn Asn Glu
3095 3100 3105

Asn Ile Met Glu Ala His Val Gly Ile Asn Gly Glu Ala Asn Leu
3110 3115 3120

Asp Phe Leu Asn Ile Pro Leu Thr Ile Pro Glu Met Arg Leu Pro
3125 3130 3135

Tyr Thr Ile Ile Thr Thr Pro Pro Leu Lys Asp Phe Ser Leu Trp
3140 3145 3150

Glu Lys Thr Gly Leu Lys Glu Phe Leu Lys Thr Thr Lys Gln Ser
3155 3160 3165

Phe Asp Leu Ser Val Lys Ala Gln Tyr Lys Lys Asn Lys His Arg
3170 3175 3180

His Ser Ile Thr Asn Pro Leu Ala Val Leu Cys Glu Phe Ile Ser
3185 3190 3195

Gln Ser Ile Lys Ser Phe Asp Arg His Phe Glu Lys Asn Arg Asn
3200 3205 3210

Asn Ala Leu Asp Phe Val Thr Lys Ser Tyr Asn Glu Thr Lys Ile
3215 3220 3225

Lys Phe Asp Lys Tyr Lys Ala Glu Lys Ser His Asp Glu Leu Pro
3230 3235 3240

Arg Thr Phe Gln Ile Pro Gly Tyr Thr Val Pro Val Val Asn Val
3245 3250 3255

Glu Val Ser Pro Phe Thr Ile Glu Met Ser Ala Phe Gly Tyr Val
3260 3265 3270

Phe Pro Lys Ala Val Ser Met Pro Ser Phe Ser Ile Leu Gly Ser
3275 3280 3285

Asp Val Arg Val Pro Ser Tyr Thr Leu Ile Leu Pro Ser Leu Glu
3290 3295 3300

Leu Pro Val Leu His Val Pro Arg Asn Leu Lys Leu Ser Leu Pro
3305 3310 3315

His Phe Lys Glu Leu Cys Thr Ile Ser His Ile Phe Ile Pro Ala
3320 3325 3330

Met Gly Asn Ile Thr Tyr Asp Phe Ser Phe Lys Ser Ser Val Ile
3335 3340 3345

Thr Leu Asn Thr Asn Ala Glu Leu Phe Asn Gln Ser Asp Ile Val
3350 3355 3360

Ala His Leu Leu Ser Ser Ser Ser Ser Val Ile Asp Ala Leu Gln
3365 3370 3375

Tyr Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys Arg Gly Leu
3380 3385 3390

Lys Leu Ala Thr Ala Leu Ser Leu Ser Asn Lys Phe Val Glu Gly

3395 3400 3405

Ser His Asn Ser Thr Val Ser Leu Thr Thr Lys Asn Met Glu Val
3410 3415 3420

Ser Val Ala Lys Thr Thr Lys Ala Glu Ile Pro Ile Leu Arg Met
3425 3430 3435

Asn Phe Lys Gln Glu Leu Asn Gly Asn Thr Lys Ser Lys Pro Thr
3440 3445 3450

Val Ser Ser Ser Met Glu Phe Lys Tyr Asp Phe Asn Ser Ser Met
3455 3460 3465

Leu Tyr Ser Thr Ala Lys Gly Ala Val Asp His Lys Leu Ser Leu
3470 3475 3480

Glu Ser Leu Thr Ser Tyr Phe Ser Ile Glu Ser Ser Thr Lys Gly
3485 3490 3495

Asp Val Lys Gly Ser Val Leu Ser Arg Glu Tyr Ser Gly Thr Ile
3500 3505 3510

Ala Ser Glu Ala Asn Thr Tyr Leu Asn Ser Lys Ser Thr Arg Ser
3515 3520 3525

Ser Val Lys Leu Gln Gly Thr Ser Lys Ile Asp Asp Ile Trp Asn
3530 3535 3540

Leu Glu Val Lys Glu Asn Phe Ala Gly Glu Ala Thr Leu Gln Arg
3545 3550 3555

Ile Tyr Ser Leu Trp Glu His Ser Thr Lys Asn His Leu Gln Leu
3560 3565 3570

Glu Gly Leu Phe Phe Thr Asn Gly Glu His Thr Ser Lys Ala Thr
3575 3580 3585

Leu Glu Leu Ser Pro Trp Gln Met Ser Ala Leu Val Gln Val His
3590 3595 3600

Ala Ser Gln Pro Ser Ser Phe His Asp Phe Pro Asp Leu Gly Gln
3605 3610 3615

Glu Val Ala Leu Asn Ala Asn Thr Lys Asn Gln Lys Ile Arg Trp
3620 3625 3630

Lys Asn Glu Val Arg Ile His Ser Gly Ser Phe Gln Ser Gln Val
3635 3640 3645

Glu Leu Ser Asn Asp Gln Glu Lys Ala His Leu Asp Ile Ala Gly
3650 3655 3660

Ser Leu Glu Gly His Leu Arg Phe Leu Lys Asn Ile Ile Leu Pro
3665 3670 3675

Val Tyr Asp Lys Ser Leu Trp Asp Phe Leu Lys Leu Asp Val Thr
3680 3685 3690

Thr Ser Ile Gly Arg Arg Gln His Leu Arg Val Ser Thr Ala Phe
3695 3700 3705

Val Tyr Thr Lys Asn Pro Asn Gly Tyr Ser Phe Ser Ile Pro Val
3710 3715 3720

Lys Val Leu Ala Asp Lys Phe Ile Thr Pro Gly Leu Lys Leu Asn
3725 3730 3735

Asp Leu Asn Ser Val Leu Val Met Pro Thr Phe His Val Pro Phe
3740 3745 3750

Thr Asp Leu Gln Val Pro Ser Cys Lys Leu Asp Phe Arg Glu Ile
3755 3760 3765

Gln Ile Tyr Lys Lys Leu Arg Thr Ser Ser Phe Ala Leu Asn Leu
3770 3775 3780

Pro Thr Leu Pro Glu Val Lys Phe Pro Glu Val Asp Val Leu Thr
3785 3790 3795

Lys Tyr Ser Gln Pro Glu Asp Ser Leu Ile Pro Phe Phe Glu Ile
3800 3805 3810

Thr Val Pro Glu Ser Gln Leu Thr Val Ser Gln Phe Thr Leu Pro
3815 3820 3825

Lys Ser Val Ser Asp Gly Ile Ala Ala Leu Asp Leu Asn Ala Val
3830 3835 3840

Ala Asn Lys Ile Ala Asp Phe Glu Leu Pro Thr Ile Ile Val Pro
3845 3850 3855

Glu Gln Thr Ile Glu Ile Pro Ser Ile Lys Phe Ser Val Pro Ala
3860 3865 3870

Gly Ile Val Ile Pro Ser Phe Gln Ala Leu Thr Ala Arg Phe Glu
3875 3880 3885

Val Asp Ser Pro Val Tyr Asn Ala Thr Trp Ser Ala Ser Leu Lys
3890 3895 3900

Asn Lys Ala Asp Tyr Val Glu Thr Val Leu Asp Ser Thr Cys Ser
3905 3910 3915

Ser Thr Val Gln Phe Leu Glu Tyr Glu Leu Asn Val Leu Gly Thr

3920 3925 3930

His Lys Ile Glu Asp Gly Thr Leu Ala Ser Lys Thr Lys Gly Thr
3935 3940 3945

Leu Ala His Arg Asp Phe Ser Ala Glu Tyr Glu Glu Asp Gly Lys
3950 3955 3960

Phe Glu Gly Leu Gln Glu Trp Glu Gly Lys Ala His Leu Asn Ile
3965 3970 3975

Lys Ser Pro Ala Phe Thr Asp Leu His Leu Arg Tyr Gln Lys Asp
3980 3985 3990

Lys Lys Gly Ile Ser Thr Ser Ala Ala Ser Pro Ala Val Gly Thr
3995 4000 4005

Val Gly Met Asp Met Asp Glu Asp Asp Asp Phe Ser Lys Trp Asn
4010 4015 4020

Phe Tyr Tyr Ser Pro Gln Ser Ser Pro Asp Lys Lys Leu Thr Ile
4025 4030 4035

Phe Lys Thr Glu Leu Arg Val Arg Glu Ser Asp Glu Glu Thr Gln
4040 4045 4050

Ile Lys Val Asn Trp Glu Glu Glu Ala Ala Ser Gly Leu Leu Thr
4055 4060 4065

Ser Leu Lys Asp Asn Val Pro Lys Ala Thr Gly Val Leu Tyr Asp
4070 4075 4080

Tyr Val Asn Lys Tyr His Trp Glu His Thr Gly Leu Thr Leu Arg
4085 4090 4095

Glu Val Ser Ser Lys Leu Arg Arg Asn Leu Gln Asn Asn Ala Glu
4100 4105 4110

Trp Val Tyr Gln Gly Ala Ile Arg Gln Ile Asp Asp Ile Asp Val
4115 4120 4125

Arg Phe Gln Lys Ala Ala Ser Gly Thr Thr Gly Thr Tyr Gln Glu
4130 4135 4140

Trp Lys Asp Lys Ala Gln Asn Leu Tyr Gln Glu Leu Leu Thr Gln
4145 4150 4155

Glu Gly Gln Ala Ser Phe Gln Gly Leu Lys Asp Asn Val Phe Asp
4160 4165 4170

Gly Leu Val Arg Val Thr Gln Lys Phe His Met Lys Val Lys His
4175 4180 4185

Leu Ile Asp Ser Leu Ile Asp Phe Leu Asn Phe Pro Arg Phe Gln
4190 4195 4200

Phe Pro Gly Lys Pro Gly Ile Tyr Thr Arg Glu Glu Leu Cys Thr
4205 4210 4215

Met Phe Ile Arg Glu Val Gly Thr Val Leu Ser Gln Val Tyr Ser
4220 4225 4230

Lys Val His Asn Gly Ser Glu Ile Leu Phe Ser Tyr Phe Gln Asp
4235 4240 4245

Leu Val Ile Thr Leu Pro Phe Glu Leu Arg Lys His Lys Leu Ile
4250 4255 4260

Asp Val Ile Ser Met Tyr Arg Glu Leu Leu Lys Asp Leu Ser Lys
4265 4270 4275

Glu Ala Gln Glu Val Phe Lys Ala Ile Gln Ser Leu Lys Thr Thr
4280 4285 4290

Glu Val Leu Arg Asn Leu Gln Asp Leu Leu Gln Phe Ile Phe Gln
4295 4300 4305

Leu Ile Glu Asp Asn Ile Lys Gln Leu Lys Glu Met Lys Phe Thr
4310 4315 4320

Tyr Leu Ile Asn Tyr Ile Gln Asp Glu Ile Asn Thr Ile Phe Asn
4325 4330 4335

Asp Tyr Ile Pro Tyr Val Phe Lys Leu Leu Lys Glu Asn Leu Cys
4340 4345 4350

Leu Asn Leu His Lys Phe Asn Glu Phe Ile Gln Asn Glu Leu Gln
4355 4360 4365

Glu Ala Ser Gln Glu Leu Gln Gln Ile His Gln Tyr Ile Met Ala
4370 4375 4380

Leu Arg Glu Glu Tyr Phe Asp Pro Ser Ile Val Gly Trp Thr Val
4385 4390 4395

Lys Tyr Tyr Glu Leu Glu Glu Lys Ile Val Ser Leu Ile Lys Asn
4400 4405 4410

Leu Leu Val Ala Leu Lys Asp Phe His Ser Glu Tyr Ile Val Ser
4415 4420 4425

Ala Ser Asn Phe Thr Ser Gln Leu Ser Ser Gln Val Glu Gln Phe
4430 4435 4440

Leu His Arg Asn Ile Gln Glu Tyr Leu Ser Ile Leu Thr Asp Pro

4445 4450 4455

Asp Gly Lys Gly Lys Glu Lys Ile Ala Glu Leu Ser Ala Thr Ala
4460 4465 4470

Gln Glu Ile Ile Lys Ser Gln Ala Ile Ala Thr Lys Lys Ile Ile
4475 4480 4485

Ser Asp Tyr His Gln Gln Phe Arg Tyr Lys Leu Gln Asp Phe Ser
4490 4495 4500

Asp Gln Leu Ser Asp Tyr Tyr Glu Lys Phe Ile Ala Glu Ser Lys
4505 4510 4515

Arg Leu Ile Asp Leu Ser Ile Gln Asn Tyr His Thr Phe Leu Ile
4520 4525 4530

Tyr Ile Thr Glu Leu Leu Lys Lys Leu Gln Ser Thr Thr Val Met
4535 4540 4545

Asn Pro Tyr Met Lys Leu Ala Pro Gly Glu Leu Thr Ile Ile Leu
4550 4555 4560

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<309> 1998-07-15
<313> (1)..(930)

<400> 42

Met Lys Pro Pro Arg Pro Val Arg Thr Cys Ser Lys Val Leu Val Leu
1 5 10 15

Leu Ser Leu Leu Ala Ile His Gln Thr Thr Thr Ala Glu Lys Asn Gly
20 25 30

Ile Asp Ile Tyr Ser Leu Thr Val Asp Ser Arg Val Ser Ser Arg Phe
35 40 45

Ala His Thr Val Val Thr Ser Arg Val Val Asn Arg Ala Asn Thr Val
50 55 60

Gln Glu Ala Thr Phe Gln Met Glu Leu Pro Lys Lys Ala Phe Ile Thr
65 70 75 80

Asn Phe Ser Met Asn Ile Asp Gly Met Thr Tyr Pro Gly Ile Ile Lys
85 90 95

Glu Lys Ala Glu Ala Gln Ala Gln Tyr Ser Ala Ala Val Ala Lys Gly
100 105 110

Lys Ser Ala Gly Leu Val Lys Ala Thr Gly Arg Asn Met Glu Gln Phe
115 120 125

Gln Val Ser Val Ser Val Ala Pro Asn Ala Lys Ile Thr Phe Glu Leu
130 135 140

Val Tyr Glu Glu Leu Leu Lys Arg Arg Leu Gly Val Tyr Glu Leu Leu
145 150 155 160

Leu Lys Val Arg Pro Gln Gln Leu Val Lys His Leu Gln Met Asp Ile
165 170 175

His Ile Phe Glu Pro Gln Gly Ile Ser Phe Leu Glu Thr Glu Ser Thr
180 185 190

Phe Met Thr Asn Gln Leu Val Asp Ala Leu Thr Thr Trp Gln Asn Lys
195 200 205

Thr Lys Ala His Ile Arg Phe Lys Pro Thr Leu Ser Gln Gln Gln Lys
210 215 220

Ser Pro Glu Gln Gln Glu Thr Val Leu Asp Gly Asn Leu Ile Ile Arg
225 230 235 240

Tyr Asp Val Asp Arg Ala Ile Ser Gly Gly Ser Ile Gln Ile Glu Asn
245 250 255

Gly Tyr Phe Val His Tyr Phe Ala Pro Glu Gly Leu Thr Thr Met Pro
260 265 270

Lys Asn Val Val Phe Val Ile Asp Lys Ser Gly Ser Met Ser Gly Arg
275 280 285

Lys Ile Gln Gln Thr Arg Glu Ala Leu Ile Lys Ile Leu Asp Asp Leu
290 295 300

Ser Pro Arg Asp Gln Phe Asn Leu Ile Val Phe Ser Thr Glu Ala Thr
305 310 315 320

Gln Trp Arg Pro Ser Leu Val Pro Ala Ser Ala Glu Asn Val Asn Lys
325 330 335

Ala Arg Ser Phe Ala Ala Gly Ile Gln Ala Leu Gly Gly Thr Asn Ile
340 345 350

Asn Asp Ala Met Leu Met Ala Val Gln Leu Leu Asp Ser Ser Asn Gln
355 360 365

Glu Glu Arg Leu Pro Glu Gly Ser Val Ser Leu Ile Ile Leu Leu Thr
370 375 380

Asp Gly Asp Pro Thr Val Gly Glu Thr Asn Pro Arg Ser Ile Gln Asn

385 390 395 400

Asn Val Arg Glu Ala Val Ser Gly Arg Tyr Ser Leu Phe Cys Leu Gly
405 410 415

Phe Gly Phe Asp Val Ser Tyr Ala Phe Leu Glu Lys Leu Ala Leu Asp
420 425 430

Asn Gly Gly Leu Ala Arg Arg Ile His Glu Asp Ser Asp Ser Ala Leu
435 440 445

Gln Leu Gln Asp Phe Tyr Gln Glu Val Ala Asn Pro Leu Leu Thr Ala
450 455 460

Val Thr Phe Glu Tyr Pro Ser Asn Ala Val Glu Glu Val Thr Gln Asn
465 470 475 480

Asn Phe Arg Leu Leu Phe Lys Gly Ser Glu Met Val Val Ala Gly Lys
485 490 495

Leu Gln Asp Arg Gly Pro Asp Val Leu Thr Ala Thr Val Ser Gly Lys
500 505 510

Leu Pro Thr Gln Asn Ile Thr Phe Gln Thr Glu Ser Ser Val Ala Glu
515 520 525

Gln Glu Ala Glu Phe Gln Ser Pro Lys Tyr Ile Phe His Asn Phe Met
530 535 540

Glu Arg Leu Trp Ala Tyr Leu Thr Ile Gln Gln Leu Leu Glu Gln Thr
545 550 555 560

Val Ser Ala Ser Asp Ala Asp Gln Gln Ala Leu Arg Asn Gln Ala Leu
565 570 575

Asn Leu Ser Leu Ala Tyr Ser Phe Val Thr Pro Leu Thr Ser Met Val
580 585 590

Val Thr Lys Pro Asp Asp Gln Glu Gln Ser Gln Val Ala Glu Lys Pro
595 600 605

Met Glu Gly Glu Ser Arg Asn Arg Asn Val His Ser Gly Ser Thr Phe
610 615 620

Phe Lys Tyr Tyr Leu Gln Gly Ala Lys Ile Pro Lys Pro Glu Ala Ser
625 630 635 640

Phe Ser Pro Arg Arg Gly Trp Asn Arg Gln Ala Gly Ala Ala Gly Ser
645 650 655

Arg Met Asn Phe Arg Pro Gly Val Leu Ser Ser Arg Gln Leu Gly Leu
660 665 670

Pro Gly Pro Pro Asp Val Pro Asp His Ala Ala Tyr His Pro Phe Arg
675 680 685

Arg Leu Ala Ile Leu Pro Ala Ser Ala Pro Pro Ala Thr Ser Asn Pro
690 695 700

Asp Pro Ala Val Ser Arg Val Met Asn Met Lys Ile Glu Glu Thr Thr
705 710 715 720

Met Thr Thr Gln Thr Pro Ala Pro Ile Gln Ala Pro Ser Ala Ile Leu
725 730 735

Pro Leu Pro Gly Gln Ser Val Glu Arg Leu Cys Val Asp Pro Arg His
740 745 750

Arg Gln Gly Pro Val Asn Leu Leu Ser Asp Pro Glu Gln Gly Val Glu
755 760 765

Val Thr Gly Gln Tyr Glu Arg Glu Lys Ala Gly Phe Ser Trp Ile Glu
770 775 780

Val Thr Phe Lys Asn Pro Leu Val Trp Val His Ala Ser Pro Glu His
785 790 795 800

Val Val Val Thr Arg Asn Arg Arg Ser Ser Ala Tyr Lys Trp Lys Glu
805 810 815

Thr Leu Phe Ser Val Met Pro Gly Leu Lys Met Thr Met Asp Lys Thr
820 825 830

Gly Leu Leu Leu Leu Ser Asp Pro Asp Lys Val Thr Ile Gly Leu Leu
835 840 845

Phe Trp Asp Gly Arg Gly Glu Gly Leu Arg Leu Leu Leu Arg Asp Thr
850 855 860

Asp Arg Phe Ser Ser His Val Gly Gly Thr Leu Gly Gln Phe Tyr Gln
865 870 875 880

Glu Val Leu Trp Gly Ser Pro Ala Ala Ser Asp Asp Gly Arg Arg Thr
885 890 895

Leu Arg Val Gln Gly Asn Asp His Ser Ala Thr Arg Glu Arg Arg Leu
900 905 910

Asp Tyr Gln Glu Gly Pro Pro Gly Val Glu Ile Ser Cys Trp Ser Val
915 920 925

Glu Leu
930

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<309> 1986-07-21
<313> (1)..(1744)

<400> 43

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Ser Leu Gln Lys Pro Arg Leu Leu Leu Phe Ser Pro Ser Val Val His
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Leu Gly Val Pro Leu Ser Val Gly Val Gln Leu Gln Asp Val Pro Arg
35 40 45

Gly Gln Val Val Lys Gly Ser Val Phe Leu Arg Asn Pro Ser Arg Asn
50 55 60

Asn Val Pro Cys Ser Pro Lys Val Asp Phe Thr Leu Ser Ser Glu Arg
65 70 75 80

Asp Phe Ala Leu Leu Ser Leu Gln Val Pro Leu Lys Asp Ala Lys Ser
85 90 95

Cys Gly Leu His Gln Leu Leu Arg Gly Pro Glu Val Gln Leu Val Ala
100 105 110

His Ser Pro Trp Leu Lys Asp Ser Leu Ser Arg Thr Thr Asn Ile Gln
115 120 125

Gly Ile Asn Leu Leu Phe Ser Ser Arg Arg Gly His Leu Phe Leu Gln
130 135 140

Thr Asp Gln Pro Ile Tyr Asn Pro Gly Gln Arg Val Arg Tyr Arg Val
145 150 155 160

Phe Ala Leu Asp Gln Lys Met Arg Pro Ser Thr Asp Thr Ile Thr Val
165 170 175

Met Val Glu Asn Ser His Gly Leu Arg Val Arg Lys Lys Glu Val Tyr
180 185 190

Met Pro Ser Ser Ile Phe Gln Asp Asp Phe Val Ile Pro Asp Ile Ser
195 200 205

Glu Pro Gly Thr Trp Lys Ile Ser Ala Arg Phe Ser Asp Gly Leu Glu
210 215 220

Ser Asn Ser Ser Thr Gln Phe Glu Val Lys Lys Tyr Val Leu Pro Asn
225 230 235 240

Phe Glu Val Lys Ile Thr Pro Gly Lys Pro Tyr Ile Leu Thr Val Pro
245 250 255

Gly His Leu Asp Glu Met Gln Leu Asp Ile Gln Ala Arg Tyr Ile Tyr
260 265 270

Gly Lys Pro Val Gln Gly Val Ala Tyr Val Arg Phe Gly Leu Leu Asp
275 280 285

Glu Asp Gly Lys Lys Thr Phe Phe Arg Gly Leu Glu Ser Gln Thr Lys
290 295 300

Leu Val Asn Gly Gln Ser His Ile Ser Leu Ser Lys Ala Glu Phe Gln
305 310 315 320

Asp Ala Leu Glu Lys Leu Asn Met Gly Ile Thr Asp Leu Gln Gly Leu
325 330 335

Arg Leu Tyr Val Ala Ala Ala Ile Ile Glu Ser Pro Gly Gly Glu Met
340 345 350

Glu Glu Ala Glu Leu Thr Ser Trp Tyr Phe Val Ser Ser Pro Phe Ser
355 360 365

Leu Asp Leu Ser Lys Thr Lys Arg His Leu Val Pro Gly Ala Pro Phe
370 375 380

Leu Leu Gln Ala Leu Val Arg Glu Met Ser Gly Ser Pro Ala Ser Gly
385 390 395 400

Ile Pro Val Lys Val Ser Ala Thr Val Ser Ser Pro Gly Ser Val Pro
405 410 415

Glu Val Gln Asp Ile Gln Gln Asn Thr Asp Gly Ser Gly Gln Val Ser
420 425 430

Ile Pro Ile Ile Ile Pro Gln Thr Ile Ser Glu Leu Gln Leu Ser Val
435 440 445

Ser Ala Gly Ser Pro His Pro Ala Ile Ala Arg Leu Thr Val Ala Ala
450 455 460

Pro Pro Ser Gly Gly Pro Gly Phe Leu Ser Ile Glu Arg Pro Asp Ser
465 470 475 480

Arg Pro Pro Arg Val Gly Asp Thr Leu Asn Leu Asn Leu Arg Ala Val
485 490 495

Gly Ser Gly Ala Thr Phe Ser His Tyr Tyr Tyr Met Ile Leu Ser Arg
500 505 510

Gly Gln Ile Val Phe Met Asn Arg Glu Pro Lys Arg Thr Leu Thr Ser

515 520 525

Val Ser Val Phe Val Asp His His Leu Ala Pro Ser Phe Tyr Phe Val
530 535 540

Ala Phe Tyr Tyr His Gly Asp His Pro Val Ala Asn Ser Leu Arg Val
545 550 555 560

Asp Val Gln Ala Gly Ala Cys Glu Gly Lys Leu Glu Leu Ser Val Asp
565 570 575

Gly Ala Lys Gln Tyr Arg Asn Gly Glu Ser Val Lys Leu His Leu Glu
580 585 590

Thr Asp Ser Leu Ala Leu Val Ala Leu Gly Ala Leu Asp Thr Ala Leu
595 600 605

Tyr Ala Ala Gly Ser Lys Ser His Lys Pro Leu Asn Met Gly Lys Val
610 615 620

Phe Glu Ala Met Asn Ser Tyr Asp Leu Gly Cys Gly Pro Gly Gly Gly
625 630 635 640

Asp Ser Ala Leu Gln Val Phe Gln Ala Ala Gly Leu Ala Phe Ser Asp
645 650 655

Gly Asp Gln Trp Thr Leu Ser Arg Lys Arg Leu Ser Cys Pro Lys Glu
660 665 670

Lys Thr Thr Arg Lys Lys Arg Asn Val Asn Phe Gln Lys Ala Ile Asn
675 680 685

Glu Lys Leu Gly Gln Tyr Ala Ser Pro Thr Ala Lys Arg Cys Cys Gln
690 695 700

Asp Gly Val Thr Arg Leu Pro Met Met Arg Ser Cys Glu Gln Arg Ala
705 710 715 720

Ala Arg Val Gln Gln Pro Asp Cys Arg Glu Pro Phe Leu Ser Cys Cys
725 730 735

Gln Phe Ala Glu Ser Leu Arg Lys Lys Ser Arg Asp Lys Gly Gln Ala
740 745 750

Gly Leu Gln Arg Ala Leu Glu Ile Leu Gln Glu Glu Asp Leu Ile Asp
755 760 765

Glu Asp Asp Ile Pro Val Arg Ser Phe Phe Pro Glu Asn Trp Leu Trp
770 775 780

Arg Val Glu Thr Val Asp Arg Phe Gln Ile Leu Thr Leu Trp Leu Pro
785 790 795 800

Asp Ser Leu Thr Thr Trp Glu Ile His Gly Leu Ser Leu Ser Lys Thr
805 810 815

Lys Gly Leu Cys Val Ala Thr Pro Val Gln Leu Arg Val Phe Arg Glu
820 825 830

Phe His Leu His Leu Arg Leu Pro Met Ser Val Arg Arg Phe Glu Gln
835 840 845

Leu Glu Leu Arg Pro Val Leu Tyr Asn Tyr Leu Asp Lys Asn Leu Thr
850 855 860

Val Ser Val His Val Ser Pro Val Glu Gly Leu Cys Leu Ala Gly Gly
865 870 875 880

Gly Gly Leu Ala Gln Gln Val Leu Val Pro Ala Gly Ser Ala Arg Pro
885 890 895

Val Ala Phe Ser Val Val Pro Thr Ala Ala Ala Ala Val Ser Leu Lys
900 905 910

Val Val Ala Arg Gly Ser Phe Glu Phe Pro Val Gly Asp Ala Val Ser
915 920 925

Lys Val Leu Gln Ile Glu Lys Glu Gly Ala Ile His Arg Glu Glu Leu
930 935 940

Val Tyr Glu Leu Asn Pro Leu Asp His Arg Gly Arg Thr Leu Glu Ile
945 950 955 960

Pro Gly Asn Ser Asp Pro Asn Met Ile Pro Asp Gly Asp Phe Asn Ser
965 970 975

Tyr Val Arg Val Thr Ala Ser Asp Pro Leu Asp Thr Leu Gly Ser Glu
980 985 990

Gly Ala Leu Ser Pro Gly Gly Val Ala Ser Leu Leu Arg Leu Pro Arg
995 1000 1005

Gly Cys Gly Glu Gln Thr Met Ile Tyr Leu Ala Pro Thr Leu Ala
1010 1015 1020

Ala Ser Arg Tyr Leu Asp Lys Thr Glu Gln Trp Ser Thr Leu Pro
1025 1030 1035

Pro Glu Thr Lys Asp His Ala Val Asp Leu Ile Gln Lys Gly Tyr
1040 1045 1050

Met Arg Ile Gln Gln Phe Arg Lys Ala Asp Gly Ser Tyr Ala Ala
1055 1060 1065

Trp Leu Ser Arg Asp Ser Ser Thr Trp Leu Thr Ala Phe Val Leu

1070 1075 1080

Lys Val Leu Ser Leu Ala Gln Glu Gln Val Gly Gly Ser Pro Glu
1085 1090 1095

Lys Leu Gln Glu Thr Ser Asn Trp Leu Leu Ser Gln Gln Gln Ala
1100 1105 1110

Asp Gly Ser Phe Gln Asp Pro Cys Pro Val Leu Asp Arg Ser Met
1115 1120 1125

Gln Gly Gly Leu Val Gly Asn Asp Glu Thr Val Ala Leu Thr Ala
1130 1135 1140

Phe Val Thr Ile Ala Leu His His Gly Leu Ala Val Phe Gln Asp
1145 1150 1155

Glu Gly Ala Glu Pro Leu Lys Gln Arg Val Glu Ala Ser Ile Ser
1160 1165 1170

Lys Ala Asn Ser Phe Leu Gly Glu Lys Ala Ser Ala Gly Leu Leu
1175 1180 1185

Gly Ala His Ala Ala Ala Ile Thr Ala Tyr Ala Leu Ser Leu Thr
1190 1195 1200

Lys Ala Pro Val Asp Leu Leu Gly Val Ala His Asn Asn Leu Met
1205 1210 1215

Ala Met Ala Gln Glu Thr Gly Asp Asn Leu Tyr Trp Gly Ser Val
1220 1225 1230

Thr Gly Ser Gln Ser Asn Ala Val Ser Pro Thr Pro Ala Pro Arg
1235 1240 1245

Asn Pro Ser Asp Pro Met Pro Gln Ala Pro Ala Leu Trp Ile Glu
1250 1255 1260

Thr Thr Ala Tyr Ala Leu Leu His Leu Leu Leu His Glu Gly Lys
1265 1270 1275

Ala Glu Met Ala Asp Gln Ala Ser Ala Trp Leu Thr Arg Gln Gly
1280 1285 1290

Ser Phe Gln Gly Gly Phe Arg Ser Thr Gln Asp Thr Val Ile Ala
1295 1300 1305

Leu Asp Ala Leu Ser Ala Tyr Trp Ile Ala Ser His Thr Thr Glu
1310 1315 1320

Glu Arg Gly Leu Asn Val Thr Leu Ser Ser Thr Gly Arg Asn Gly
1325 1330 1335

Phe Lys Ser His Ala Leu Gln Leu Asn Asn Arg Gln Ile Arg Gly
1340 1345 1350

Leu Glu Glu Glu Leu Gln Phe Ser Leu Gly Ser Lys Ile Asn Val
1355 1360 1365

Lys Val Gly Gly Asn Ser Lys Gly Thr Leu Lys Val Leu Arg Thr
1370 1375 1380

Tyr Asn Val Leu Asp Met Lys Asn Thr Thr Cys Gln Asp Leu Gln
1385 1390 1395

Ile Glu Val Thr Val Lys Gly His Val Glu Tyr Thr Met Glu Ala
1400 1405 1410

Asn Glu Asp Tyr Glu Asp Tyr Glu Tyr Asp Glu Leu Pro Ala Lys
1415 1420 1425

Asp Asp Pro Asp Ala Pro Leu Gln Pro Val Thr Pro Leu Gln Leu
1430 1435 1440

Phe Glu Gly Arg Arg Asn Arg Arg Arg Arg Glu Ala Pro Lys Val
1445 1450 1455

Val Glu Glu Gln Glu Ser Arg Val His Tyr Thr Val Cys Ile Trp
1460 1465 1470

Arg Asn Gly Lys Val Gly Leu Ser Gly Met Ala Ile Ala Asp Val
1475 1480 1485

Thr Leu Leu Ser Gly Phe His Ala Leu Arg Ala Asp Leu Glu Lys
1490 1495 1500

Leu Thr Ser Leu Ser Asp Arg Tyr Val Ser His Phe Glu Thr Glu
1505 1510 1515

Gly Pro His Val Leu Leu Tyr Phe Asp Ser Val Pro Thr Ser Arg
1520 1525 1530

Glu Cys Val Gly Phe Glu Ala Val Gln Glu Val Pro Val Gly Leu
1535 1540 1545

Val Gln Pro Ala Ser Ala Thr Leu Tyr Asp Tyr Tyr Asn Pro Glu
1550 1555 1560

Arg Arg Cys Ser Val Phe Tyr Gly Ala Pro Ser Lys Ser Arg Leu
1565 1570 1575

Leu Ala Thr Leu Cys Ser Ala Glu Val Cys Gln Cys Ala Glu Gly
1580 1585 1590

Lys Cys Pro Arg Gln Arg Arg Ala Leu Glu Arg Gly Leu Gln Asp

1595 1600 1605

Glu Asp Gly Tyr Arg Met Lys Phe Ala Cys Tyr Tyr Pro Arg Val
1610 1615 1620

Glu Tyr Gly Phe Gln Val Lys Val Leu Arg Glu Asp Ser Arg Ala
1625 1630 1635

Ala Phe Arg Leu Phe Glu Thr Lys Ile Thr Gln Val Leu His Phe
1640 1645 1650

Thr Lys Asp Val Lys Ala Ala Ala Asn Gln Met Arg Asn Phe Leu
1655 1660 1665

Val Arg Ala Ser Cys Arg Leu Arg Leu Glu Pro Gly Lys Glu Tyr
1670 1675 1680

Leu Ile Met Gly Leu Asp Gly Ala Thr Tyr Asp Leu Glu Gly His
1685 1690 1695

Pro Gln Tyr Leu Leu Asp Ser Asn Ser Trp Ile Glu Glu Met Pro
1700 1705 1710

Ser Glu Arg Leu Cys Arg Ser Thr Arg Gln Arg Ala Ala Cys Ala
1715 1720 1725

Gln Leu Asn Asp Phe Leu Gln Glu Tyr Gly Thr Gln Gly Cys Gln
1730 1735 1740

Val

<210> 44
<211> 1663
<212> PRT
<213> Homo sapiens

<300>
<308> Swiss-Prot/P01024
<309> 1986-07-21
<313> (1)..(1663)

<400> 44

Met Gly Pro Thr Ser Gly Pro Ser Leu Leu Leu Leu Leu Leu Thr His
1 5 10 15

Leu Pro Leu Ala Leu Gly Ser Pro Met Tyr Ser Ile Ile Thr Pro Asn
20 25 30

Ile Leu Arg Leu Glu Ser Glu Glu Thr Met Val Leu Glu Ala His Asp
35 40 45

Ala Gln Gly Asp Val Pro Val Thr Val Thr Val His Asp Phe Pro Gly
50 55 60

Lys Lys Leu Val Leu Ser Ser Glu Lys Thr Val Leu Thr Pro Ala Thr
65 70 75 80

Asn His Met Gly Asn Val Thr Phe Thr Ile Pro Ala Asn Arg Glu Phe
85 90 95

Lys Ser Glu Lys Gly Arg Asn Lys Phe Val Thr Val Gln Ala Thr Phe
100 105 110

Gly Thr Gln Val Val Glu Lys Val Val Leu Val Ser Leu Gln Ser Gly
115 120 125

Tyr Leu Phe Ile Gln Thr Asp Lys Thr Ile Tyr Thr Pro Gly Ser Thr
130 135 140

Val Leu Tyr Arg Ile Phe Thr Val Asn His Lys Leu Leu Pro Val Gly
145 150 155 160

Arg Thr Val Met Val Asn Ile Glu Asn Pro Glu Gly Ile Pro Val Lys
165 170 175

Gln Asp Ser Leu Ser Ser Gln Asn Gln Leu Gly Val Leu Pro Leu Ser
180 185 190

Trp Asp Ile Pro Glu Leu Val Asn Met Gly Gln Trp Lys Ile Arg Ala
195 200 205

Tyr Tyr Glu Asn Ser Pro Gln Gln Val Phe Ser Thr Glu Phe Glu Val
210 215 220

Lys Glu Tyr Val Leu Pro Ser Phe Glu Val Ile Val Glu Pro Thr Glu
225 230 235 240

Lys Phe Tyr Tyr Ile Tyr Asn Glu Lys Gly Leu Glu Val Thr Ile Thr
245 250 255

Ala Arg Phe Leu Tyr Gly Lys Lys Val Glu Gly Thr Ala Phe Val Ile
260 265 270

Phe Gly Ile Gln Asp Gly Glu Gln Arg Ile Ser Leu Pro Glu Ser Leu
275 280 285

Lys Arg Ile Pro Ile Glu Asp Gly Ser Gly Glu Val Val Leu Ser Arg
290 295 300

Lys Val Leu Leu Asp Gly Val Gln Asn Leu Arg Ala Glu Asp Leu Val
305 310 315 320

Gly Lys Ser Leu Tyr Val Ser Ala Thr Val Ile Leu His Ser Gly Ser
325 330 335

Asp Met Val Gln Ala Glu Arg Ser Gly Ile Pro Ile Val Thr Ser Pro

340 345 350

Tyr Gln Ile His Phe Thr Lys Thr Pro Lys Tyr Phe Lys Pro Gly Met
355 360 365

Pro Phe Asp Leu Met Val Phe Val Thr Asn Pro Asp Gly Ser Pro Ala
370 375 380

Tyr Arg Val Pro Val Ala Val Gln Gly Glu Asp Thr Val Gln Ser Leu
385 390 395 400

Thr Gln Gly Asp Gly Val Ala Lys Leu Ser Ile Asn Thr His Pro Ser
405 410 415

Gln Lys Pro Leu Ser Ile Thr Val Arg Thr Lys Lys Gln Glu Leu Ser
420 425 430

Glu Ala Glu Gln Ala Thr Arg Thr Met Gln Ala Leu Pro Tyr Ser Thr
435 440 445

Val Gly Asn Ser Asn Asn Tyr Leu His Leu Ser Val Leu Arg Thr Glu
450 455 460

Leu Arg Pro Gly Glu Thr Leu Asn Val Asn Phe Leu Leu Arg Met Asp
465 470 475 480

Arg Ala His Glu Ala Lys Ile Arg Tyr Tyr Thr Tyr Leu Ile Met Asn
485 490 495

Lys Gly Arg Leu Leu Lys Ala Gly Arg Gln Val Arg Glu Pro Gly Gln
500 505 510

Asp Leu Val Val Leu Pro Leu Ser Ile Thr Thr Asp Phe Ile Pro Ser
515 520 525

Phe Arg Leu Val Ala Tyr Tyr Thr Leu Ile Gly Ala Ser Gly Gln Arg
530 535 540

Glu Val Val Ala Asp Ser Val Trp Val Asp Val Lys Asp Ser Cys Val
545 550 555 560

Gly Ser Leu Val Val Lys Ser Gly Gln Ser Glu Asp Arg Gln Pro Val
565 570 575

Pro Gly Gln Gln Met Thr Leu Lys Ile Glu Gly Asp His Gly Ala Arg
580 585 590

Val Val Leu Val Ala Val Asp Lys Gly Val Phe Val Leu Asn Lys Lys
595 600 605

Asn Lys Leu Thr Gln Ser Lys Ile Trp Asp Val Val Glu Lys Ala Asp
610 615 620

Ile Gly Cys Thr Pro Gly Ser Gly Lys Asp Tyr Ala Gly Val Phe Ser
625 630 635 640

Asp Ala Gly Leu Thr Phe Thr Ser Ser Ser Gly Gln Gln Thr Ala Gln
645 650 655

Arg Ala Glu Leu Gln Cys Pro Gln Pro Ala Ala Arg Arg Arg Arg Ser
660 665 670

Val Gln Leu Thr Glu Lys Arg Met Asp Lys Val Gly Lys Tyr Pro Lys
675 680 685

Glu Leu Arg Lys Cys Cys Glu Asp Gly Met Arg Glu Asn Pro Met Arg
690 695 700

Phe Ser Cys Gln Arg Arg Thr Arg Phe Ile Ser Leu Gly Glu Ala Cys
705 710 715 720

Lys Lys Val Phe Leu Asp Cys Cys Asn Tyr Ile Thr Glu Leu Arg Arg
725 730 735

Gln His Ala Arg Ala Ser His Leu Gly Leu Ala Arg Ser Asn Leu Asp
740 745 750

Glu Asp Ile Ile Ala Glu Glu Asn Ile Val Ser Arg Ser Glu Phe Pro
755 760 765

Glu Ser Trp Leu Trp Asn Val Glu Asp Leu Lys Glu Pro Pro Lys Asn
770 775 780

Gly Ile Ser Thr Lys Leu Met Asn Ile Phe Leu Lys Asp Ser Ile Thr
785 790 795 800

Thr Trp Glu Ile Leu Ala Val Ser Met Ser Asp Lys Lys Gly Ile Cys
805 810 815

Val Ala Asp Pro Phe Glu Val Thr Val Met Gln Asp Phe Phe Ile Asp
820 825 830

Leu Arg Leu Pro Tyr Ser Val Val Arg Asn Glu Gln Val Glu Ile Arg
835 840 845

Ala Val Leu Tyr Asn Tyr Arg Gln Asn Gln Glu Leu Lys Val Arg Val
850 855 860

Glu Leu Leu His Asn Pro Ala Phe Cys Ser Leu Ala Thr Thr Lys Arg
865 870 875 880

Arg His Gln Gln Thr Val Thr Ile Pro Pro Lys Ser Ser Leu Ser Val
885 890 895

Pro Tyr Val Ile Val Pro Leu Lys Thr Gly Leu Gln Glu Val Glu Val

900 905 910

Lys Ala Ala Val Tyr His His Phe Ile Ser Asp Gly Val Arg Lys Ser
915 920 925

Leu Lys Val Val Pro Glu Gly Ile Arg Met Asn Lys Thr Val Ala Val
930 935 940

Arg Thr Leu Asp Pro Glu Arg Leu Gly Arg Glu Gly Val Gln Lys Glu
945 950 955 960

Asp Ile Pro Pro Ala Asp Leu Ser Asp Gln Val Pro Asp Thr Glu Ser
965 970 975

Glu Thr Arg Ile Leu Leu Gln Gly Thr Pro Val Ala Gln Met Thr Glu
980 985 990

Asp Ala Val Asp Ala Glu Arg Leu Lys His Leu Ile Val Thr Pro Ser
995 1000 1005

Gly Cys Gly Glu Gln Asn Met Ile Gly Met Thr Pro Thr Val Ile
1010 1015 1020

Ala Val His Tyr Leu Asp Glu Thr Glu Gln Trp Glu Lys Phe Gly
1025 1030 1035

Leu Glu Lys Arg Gln Gly Ala Leu Glu Leu Ile Lys Lys Gly Tyr
1040 1045 1050

Thr Gln Gln Leu Ala Phe Arg Gln Pro Ser Ser Ala Phe Ala Ala
1055 1060 1065

Phe Val Lys Arg Ala Pro Ser Thr Trp Leu Thr Ala Tyr Val Val
1070 1075 1080

Lys Val Phe Ser Leu Ala Val Asn Leu Ile Ala Ile Asp Ser Gln
1085 1090 1095

Val Leu Cys Gly Ala Val Lys Trp Leu Ile Leu Glu Lys Gln Lys
1100 1105 1110

Pro Asp Gly Val Phe Gln Glu Asp Ala Pro Val Ile His Gln Glu
1115 1120 1125

Met Ile Gly Gly Leu Arg Asn Asn Asn Glu Lys Asp Met Ala Leu
1130 1135 1140

Thr Ala Phe Val Leu Ile Ser Leu Gln Glu Ala Lys Asp Ile Cys
1145 1150 1155

Glu Glu Gln Val Asn Ser Leu Pro Gly Ser Ile Thr Lys Ala Gly
1160 1165 1170

Asp Phe Leu Glu Ala Asn Tyr Met Asn Leu Gln Arg Ser Tyr Thr
1175 1180 1185

Val Ala Ile Ala Gly Tyr Ala Leu Ala Gln Met Gly Arg Leu Lys
1190 1195 1200

Gly Pro Leu Leu Asn Lys Phe Leu Thr Thr Ala Lys Asp Lys Asn
1205 1210 1215

Arg Trp Glu Asp Pro Gly Lys Gln Leu Tyr Asn Val Glu Ala Thr
1220 1225 1230

Ser Tyr Ala Leu Leu Ala Leu Leu Gln Leu Lys Asp Phe Asp Phe
1235 1240 1245

Val Pro Pro Val Val Arg Trp Leu Asn Glu Gln Arg Tyr Tyr Gly
1250 1255 1260

Gly Gly Tyr Gly Ser Thr Gln Ala Thr Phe Met Val Phe Gln Ala
1265 1270 1275

Leu Ala Gln Tyr Gln Lys Asp Ala Pro Asp His Gln Glu Leu Asn
1280 1285 1290

Leu Asp Val Ser Leu Gln Leu Pro Ser Arg Ser Ser Lys Ile Thr
1295 1300 1305

His Arg Ile His Trp Glu Ser Ala Ser Leu Leu Arg Ser Glu Glu
1310 1315 1320

Thr Lys Glu Asn Glu Gly Phe Thr Val Thr Ala Glu Gly Lys Gly
1325 1330 1335

Gln Gly Thr Leu Ser Val Val Thr Met Tyr His Ala Lys Ala Lys
1340 1345 1350

Asp Gln Leu Thr Cys Asn Lys Phe Asp Leu Lys Val Thr Ile Lys
1355 1360 1365

Pro Ala Pro Glu Thr Glu Lys Arg Pro Gln Asp Ala Lys Asn Thr
1370 1375 1380

Met Ile Leu Glu Ile Cys Thr Arg Tyr Arg Gly Asp Gln Asp Ala
1385 1390 1395

Thr Met Ser Ile Leu Asp Ile Ser Met Met Thr Gly Phe Ala Pro
1400 1405 1410

Asp Thr Asp Asp Leu Lys Gln Leu Ala Asn Gly Val Asp Arg Tyr
1415 1420 1425

Ile Ser Lys Tyr Glu Leu Asp Lys Ala Phe Ser Asp Arg Asn Thr

1430 1435 1440

Leu Ile Ile Tyr Leu Asp Lys Val Ser His Ser Glu Asp Asp Cys
1445 1450 1455

Leu Ala Phe Lys Val His Gln Tyr Phe Asn Val Glu Leu Ile Gln
1460 1465 1470

Pro Gly Ala Val Lys Val Tyr Ala Tyr Tyr Asn Leu Glu Glu Ser
1475 1480 1485

Cys Thr Arg Phe Tyr His Pro Glu Lys Glu Asp Gly Lys Leu Asn
1490 1495 1500

Lys Leu Cys Arg Asp Glu Leu Cys Arg Cys Ala Glu Glu Asn Cys
1505 1510 1515

Phe Ile Gln Lys Ser Asp Asp Lys Val Thr Leu Glu Glu Arg Leu
1520 1525 1530

Asp Lys Ala Cys Glu Pro Gly Val Asp Tyr Val Tyr Lys Thr Arg
1535 1540 1545

Leu Val Lys Val Gln Leu Ser Asn Asp Phe Asp Glu Tyr Ile Met
1550 1555 1560

Ala Ile Glu Gln Thr Ile Lys Ser Gly Ser Asp Glu Val Gln Val
1565 1570 1575

Gly Gln Gln Arg Thr Phe Ile Ser Pro Ile Lys Cys Arg Glu Ala
1580 1585 1590

Leu Lys Leu Glu Glu Lys Lys His Tyr Leu Met Trp Gly Leu Ser
1595 1600 1605

Ser Asp Phe Trp Gly Glu Lys Pro Asn Leu Ser Tyr Ile Ile Gly
1610 1615 1620

Lys Asp Thr Trp Val Glu His Trp Pro Glu Glu Asp Glu Cys Gln
1625 1630 1635

Asp Glu Glu Asn Gln Lys Gln Cys Gln Asp Leu Gly Ala Phe Thr
1640 1645 1650

Glu Ser Met Val Val Phe Gly Cys Pro Asn
1655 1660

<210> 45
<211> 93
<212> PRT
<213> Homo sapiens

<300>
<308> Swiss-Prot/Q9H299

<309> 2003-02-28
<313> (1)..(93)

<400> 45

Met Ser Gly Leu Arg Val Tyr Ser Thr Ser Val Thr Gly Ser Arg Glu
1 5 10 15

Ile Lys Ser Gln Gln Ser Glu Val Thr Arg Ile Leu Asp Gly Lys Arg
20 25 30

Ile Gln Tyr Gln Leu Val Asp Ile Ser Gln Asp Asn Ala Leu Arg Asp
35 40 45

Glu Met Arg Ala Leu Ala Gly Asn Pro Lys Ala Thr Pro Pro Gln Ile
50 55 60

Val Asn Gly Asp Gln Tyr Cys Gly Asp Tyr Glu Leu Phe Val Glu Ala
65 70 75 80

Val Glu Gln Asn Thr Leu Gln Glu Phe Leu Lys Leu Ala
85 90

<210> 46
<211> 567
<212> PRT
<213> Homo sapiens

<300>
<308> Swiss-Prot/Q96RQ9
<309> 2003-02-28
<313> (1)..(567)

<400> 46

Met Ala Pro Leu Ala Leu His Leu Leu Val Leu Val Pro Ile Leu Leu
1 5 10 15

Ser Leu Val Ala Ser Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro
20 25 30

Phe Glu Lys Cys Met Gln Asp Pro Asp Tyr Glu Gln Leu Leu Lys Val
35 40 45

Val Thr Trp Gly Leu Asn Arg Thr Leu Lys Pro Gln Arg Val Ile Val
50 55 60

Val Gly Ala Gly Val Ala Gly Leu Val Ala Ala Lys Val Leu Ser Asp
65 70 75 80

Ala Gly His Lys Val Thr Ile Leu Glu Ala Asp Asn Arg Ile Gly Gly
85 90 95

Arg Ile Phe Thr Tyr Arg Asp Gln Asn Thr Gly Trp Ile Gly Glu Leu
100 105 110

Gly Ala Met Arg Met Pro Ser Ser His Arg Ile Leu His Lys Leu Cys

115 120 125

Gln Gly Leu Gly Leu Asn Leu Thr Lys Phe Thr Gln Tyr Asp Lys Asn
130 135 140

Thr Trp Thr Glu Val His Glu Val Lys Leu Arg Asn Tyr Val Val Glu
145 150 155 160

Lys Val Pro Glu Lys Leu Gly Tyr Ala Leu Arg Pro Gln Glu Lys Gly
165 170 175

His Ser Pro Glu Asp Ile Tyr Gln Met Ala Leu Asn Gln Ala Leu Lys
180 185 190

Asp Leu Lys Ala Leu Gly Cys Arg Lys Ala Met Lys Lys Phe Glu Arg
195 200 205

His Thr Leu Leu Glu Tyr Leu Leu Gly Glu Gly Asn Leu Ser Arg Pro
210 215 220

Ala Val Gln Leu Leu Gly Asp Val Met Ser Glu Asp Gly Phe Phe Tyr
225 230 235 240

Leu Ser Phe Ala Glu Ala Leu Arg Ala His Ser Cys Leu Ser Asp Arg
245 250 255

Leu Gln Tyr Ser Arg Ile Val Gly Gly Trp Asp Leu Leu Pro Arg Ala
260 265 270

Leu Leu Ser Ser Leu Ser Gly Leu Val Leu Leu Asn Ala Pro Val Val
275 280 285

Ala Met Thr Gln Gly Pro His Asp Val His Val Gln Ile Glu Thr Ser
290 295 300

Pro Pro Ala Arg Asn Leu Lys Val Leu Lys Ala Asp Val Val Leu Leu
305 310 315 320

Thr Ala Ser Gly Pro Ala Val Lys Arg Ile Thr Phe Ser Pro Pro Leu
325 330 335

Pro Arg His Met Gln Glu Ala Leu Arg Arg Leu His Tyr Val Pro Ala
340 345 350

Thr Lys Val Phe Leu Ser Phe Arg Arg Pro Phe Trp Arg Glu Glu His
355 360 365

Ile Glu Gly Gly His Ser Asn Thr Asp Arg Pro Ser Arg Met Ile Phe
370 375 380

Tyr Pro Pro Pro Arg Glu Gly Ala Leu Leu Leu Ala Ser Tyr Thr Trp
385 390 395 400

Ser Asp Ala Ala Ala Ala Phe Ala Gly Leu Ser Arg Glu Glu Ala Leu
405 410 415

Arg Leu Ala Leu Asp Asp Val Ala Ala Leu His Gly Pro Val Val Arg
420 425 430

Gln Leu Trp Asp Gly Thr Gly Val Val Lys Arg Trp Ala Glu Asp Gln
435 440 445

His Ser Gln Gly Gly Phe Val Val Gln Pro Pro Ala Leu Trp Gln Thr
450 455 460

Glu Lys Asp Asp Trp Thr Val Pro Tyr Gly Arg Ile Tyr Phe Ala Gly
465 470 475 480

Glu His Thr Ala Tyr Pro His Gly Trp Val Glu Thr Ala Val Lys Ser
485 490 495

Ala Leu Arg Ala Ala Ile Lys Ile Asn Ser Arg Lys Gly Pro Ala Ser
500 505 510

Asp Thr Ala Ser Pro Glu Gly His Ala Ser Asp Met Glu Gly Gln Gly
515 520 525

His Val His Gly Val Ala Ser Ser Pro Ser His Asp Leu Ala Lys Glu
530 535 540

Glu Gly Ser His Pro Pro Val Gln Gly Gln Leu Ser Leu Gln Asn Thr
545 550 555 560

Thr His Thr Arg Thr Ser His
565

<210> 47
<211> 462
<212> PRT
<213> Homo sapiens

<300>
<308> Swiss-Prot/P02790
<309> 1986-07-21
<313> (1)..(462)

<400> 47

Met Ala Arg Val Leu Gly Ala Pro Val Ala Leu Gly Leu Trp Ser Leu
1 5 10 15

Cys Trp Ser Leu Ala Ile Ala Thr Pro Leu Pro Pro Thr Ser Ala His
20 25 30

Gly Asn Val Ala Glu Gly Glu Thr Lys Pro Asp Pro Asp Val Thr Glu
35 40 45

Arg Cys Ser Asp Gly Trp Ser Phe Asp Ala Thr Thr Leu Asp Asp Asn

50 55 60

Gly Thr Met Leu Phe Phe Lys Gly Glu Phe Val Trp Lys Ser His Lys
65 70 75 80

Trp Asp Arg Glu Leu Ile Ser Glu Arg Trp Lys Asn Phe Pro Ser Pro
85 90 95

Val Asp Ala Ala Phe Arg Gln Gly His Asn Ser Val Phe Leu Ile Lys
100 105 110

Gly Asp Lys Val Trp Val Tyr Pro Pro Glu Lys Lys Glu Lys Gly Tyr
115 120 125

Pro Lys Leu Leu Gln Asp Glu Phe Pro Gly Ile Pro Ser Pro Leu Asp
130 135 140

Ala Ala Val Glu Cys His Arg Gly Glu Cys Gln Ala Glu Gly Val Leu
145 150 155 160

Phe Phe Gln Gly Asp Arg Glu Trp Phe Trp Asp Leu Ala Thr Gly Thr
165 170 175

Met Lys Glu Arg Ser Trp Pro Ala Val Gly Asn Cys Ser Ser Ala Leu
180 185 190

Arg Trp Leu Gly Arg Tyr Tyr Cys Phe Gln Gly Asn Gln Phe Leu Arg
195 200 205

Phe Asp Pro Val Arg Gly Glu Val Pro Pro Arg Tyr Pro Arg Asp Val
210 215 220

Arg Asp Tyr Phe Met Pro Cys Pro Gly Arg Gly His Gly His Arg Asn
225 230 235 240

Gly Thr Gly His Gly Asn Ser Thr His His Gly Pro Glu Tyr Met Arg
245 250 255

Cys Ser Pro His Leu Val Leu Ser Ala Leu Thr Ser Asp Asn His Gly
260 265 270

Ala Thr Tyr Ala Phe Ser Gly Thr His Tyr Trp Arg Leu Asp Thr Ser
275 280 285

Arg Asp Gly Trp His Ser Trp Pro Ile Ala His Gln Trp Pro Gln Gly
290 295 300

Pro Ser Ala Val Asp Ala Ala Phe Ser Trp Glu Glu Lys Leu Tyr Leu
305 310 315 320

Val Gln Gly Thr Gln Val Tyr Val Phe Leu Thr Lys Gly Gly Tyr Thr
325 330 335

Leu Val Ser Gly Tyr Pro Lys Arg Leu Glu Lys Glu Val Gly Thr Pro
340 345 350

His Gly Ile Ile Leu Asp Ser Val Asp Ala Ala Phe Ile Cys Pro Gly
355 360 365

Ser Ser Arg Leu His Ile Met Ala Gly Arg Arg Leu Trp Trp Leu Asp
370 375 380

Leu Lys Ser Gly Ala Gln Ala Thr Trp Thr Glu Leu Pro Trp Pro His
385 390 395 400

Glu Lys Val Asp Gly Ala Leu Cys Met Glu Lys Ser Leu Gly Pro Asn
405 410 415

Ser Cys Ser Ala Asn Gly Pro Gly Leu Tyr Leu Ile His Gly Pro Asn
420 425 430

Leu Tyr Cys Tyr Ser Asp Val Glu Lys Leu Asn Ala Ala Lys Ala Leu
435 440 445

Pro Gln Pro Gln Asn Val Thr Ser Leu Leu Gly Cys Thr His
450 455 460

<210> 48
<211> 369
<212> PRT
<213> Homo sapiens

<300>
<308> Swiss-Prot/P50502
<309> 1996-10-02
<313> (1)..(369)

<400> 48

Met Asp Pro Arg Lys Val Asn Glu Leu Arg Ala Phe Val Lys Met Cys
1 5 10 15

Lys Gln Asp Pro Ser Val Leu His Thr Glu Glu Met Arg Phe Leu Arg
20 25 30

Glu Trp Val Glu Ser Met Gly Gly Lys Val Pro Pro Ala Thr Gln Lys
35 40 45

Ala Lys Ser Glu Glu Asn Thr Lys Glu Glu Lys Pro Asp Ser Lys Lys
50 55 60

Val Glu Glu Asp Leu Lys Ala Asp Glu Pro Ser Ser Glu Glu Ser Asp
65 70 75 80

Leu Glu Ile Asp Lys Glu Gly Val Ile Glu Pro Asp Thr Asp Ala Pro
85 90 95

Gln Glu Met Gly Asp Glu Asn Ala Glu Ile Thr Glu Glu Met Met Asp

100 105 110

Gln Ala Asn Asp Lys Lys Val Ala Ala Ile Glu Ala Leu Asn Asp Gly
115 120 125

Glu Leu Gln Lys Ala Ile Asp Leu Phe Thr Asp Ala Ile Lys Leu Asn
130 135 140

Pro Arg Leu Ala Ile Leu Tyr Ala Lys Arg Ala Ser Val Phe Val Lys
145 150 155 160

Leu Gln Lys Pro Asn Ala Ala Ile Arg Asp Cys Asp Arg Ala Ile Glu
165 170 175

Ile Asn Pro Asp Ser Ala Gln Pro Tyr Lys Trp Arg Gly Lys Ala His
180 185 190

Arg Leu Leu Gly His Trp Glu Glu Ala Ala His Asp Leu Ala Leu Ala
195 200 205

Cys Lys Leu Asp Tyr Asp Glu Asp Ala Ser Ala Met Leu Lys Glu Val
210 215 220

Gln Pro Arg Ala Gln Lys Ile Ala Glu His Arg Arg Lys Tyr Glu Arg
225 230 235 240

Lys Arg Glu Glu Arg Glu Ile Lys Glu Arg Ile Glu Arg Val Lys Lys
245 250 255

Ala Arg Glu Glu His Glu Arg Ala Gln Arg Glu Glu Glu Ala Arg Arg
260 265 270

Gln Ser Gly Ala Gln Tyr Gly Ser Phe Pro Gly Gly Phe Pro Gly Gly
275 280 285

Met Pro Gly Asn Phe Pro Gly Gly Met Pro Gly Met Gly Gly Gly Met
290 295 300

Pro Gly Met Ala Gly Met Pro Gly Leu Asn Glu Ile Leu Ser Asp Pro
305 310 315 320

Glu Val Leu Ala Ala Met Gln Asp Pro Glu Val Met Val Ala Phe Gln
325 330 335

Asp Val Ala Gln Asn Pro Ala Asn Met Ser Lys Tyr Gln Ser Asn Pro
340 345 350

Lys Val Met Asn Leu Ile Ser Lys Leu Ser Ala Lys Phe Gly Gly Gln
355 360 365

Ala

<210> 49
<211> 9
<212> PRT
<213> Homo sapiens

<400> 49

Met Gln Leu Met His Ala Asn Ala Gln
1 5

<210> 50
<211> 9
<212> PRT
<213> Homo sapiens

<400> 50

Leu Thr Leu Asp Ser Asn Thr Lys Tyr
1 5

<210> 51
<211> 9
<212> PRT
<213> Homo sapiens

<400> 51

Phe Val Ile Asp Lys Ser Gly Ser Met
1 5

<210> 52
<211> 9
<212> PRT
<213> Homo sapiens

<400> 52

Tyr Leu Leu Asp Ser Asn Ser Trp Ile
1 5

<210> 53
<211> 9
<212> PRT
<213> Homo sapiens

<400> 53

Tyr Glu Leu Asp Lys Ala Phe Ser Asp
1 5

<210> 54
<211> 9
<212> PRT
<213> Homo sapiens

<400> 54

Ile Lys Ser Gln Gln Ser Glu Val Thr
1 5

<210> 55
<211> 9
<212> PRT

<213> Homo sapiens

<400> 55

Val Gln Ile Glu Thr Ser Pro Pro Ala
1 5

<210> 56
<211> 9
<212> PRT
<213> Homo sapiens

<400> 56

Ile Ile Leu Asp Ser Val Asp Ala Ala
1 5

<210> 57
<211> 9
<212> PRT
<213> Homo sapiens

<400> 57

Ile Glu Pro Asp Thr Asp Ala Pro Gln
1 5

<210> 58
<211> 17
<212> PRT
<213> Homo sapiens

<400> 58

Asn Ile Gln Pro Ile Phe Ala Val Thr Ser Arg Met Val Lys Thr Tyr
1 5 10 15

Glu

<210> 59
<211> 19
<212> PRT
<213> Homo sapiens

<400> 59

Glu Asn Asn Ile Gln Pro Ile Phe Ala Val Thr Ser Arg Met Val Lys
1 5 10 15

Thr Tyr Glu

<210> 60
<211> 17
<212> PRT
<213> Homo sapiens

<400> 60

Asn Lys Val Phe Gly Glu Asp Ser Val Gly Val Ile Phe Lys Asn Gly
1 5 10 15

Asp

<210> 61
<211> 16
<212> PRT
<213> Homo sapiens

<400> 61

Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile Ser His Arg
1 5 10 15

<210> 62
<211> 16
<212> PRT
<213> Homo sapiens

<400> 62

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
1 5 10 15

<210> 63
<211> 16
<212> PRT
<213> Homo sapiens

<400> 63

Asn Gly Gly His Tyr Thr Tyr Ser Glu Asn Arg Val Glu Lys Asp Gly
1 5 10 15

<210> 64
<211> 15
<212> PRT
<213> Homo sapiens

<400> 64

Gly Pro Asn Asn Tyr Tyr Ser Phe Ala Ser Gln Gln Gln Lys Pro
1 5 10 15

<210> 65
<211> 16
<212> PRT
<213> Homo sapiens

<400> 65

Gly Pro Asn Asn Tyr Tyr Ser Phe Ala Ser Gln Gln Gln Lys Pro Glu
1 5 10 15

<210> 66
<211> 17
<212> PRT
<213> Homo sapiens

<400> 66

Gly Pro Asn Asn Tyr Tyr Ser Phe Ala Ser Gln Gln Gln Lys Pro Glu
1 5 10 15

Asp

<210> 67
<211> 18
<212> PRT
<213> Homo sapiens

<400> 67

Gly Pro Asn Asn Tyr Tyr Ser Phe Ala Ser Gln Gln Gln Lys Pro Glu
1 5 10 15

Asp Thr

<210> 68
<211> 16
<212> PRT
<213> Homo sapiens

<400> 68

Glu Lys Leu Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr
1 5 10 15

<210> 69
<211> 14
<212> PRT
<213> Homo sapiens

<400> 69

Ser Leu Arg Glu Leu His Leu Asp His Asn Gln Ile Ser Arg
1 5 10

<210> 70
<211> 13
<212> PRT
<213> Homo sapiens

<400> 70

Leu Arg Glu Leu His Leu Asp His Asn Gln Ile Ser Arg
1 5 10

<210> 71
<211> 15
<212> PRT
<213> Homo sapiens

<400> 71

Glu Thr Met Lys Met Arg Tyr Glu His Ile Asp His Thr Phe Glu
1 5 10 15

<210> 72
<211> 17
<212> PRT
<213> Homo sapiens

<400> 72

Glu Thr Met Lys Met Arg Tyr Glu His Ile Asp His Thr Phe Glu Ile
1 5 10 15

Gln

<210> 73
<211> 16
<212> PRT
<213> Homo sapiens

<400> 73

His Met Phe Leu Gln Asp Glu Ile Ile Asp Lys Ser Tyr Thr Pro Ser
1 5 10 15

<210> 74
<211> 17
<212> PRT
<213> Homo sapiens

<400> 74

Val Asp Arg Tyr Ile Ser Lys Tyr Glu Leu Asp Lys Ala Phe Ser Asp
1 5 10 15

Arg

<210> 75
<211> 14
<212> PRT
<213> Homo sapiens

<400> 75

Arg Tyr Ile Ser Lys Tyr Glu Leu Asp Lys Ala Phe Ser Asp
1 5 10

<210> 76
<211> 19
<212> PRT
<213> Homo sapiens

<400> 76

Leu Pro Val Gly Arg Thr Val Met Val Asn Ile Glu Asn Pro Glu Gly
1 5 10 15

Ile Pro Val

<210> 77
<211> 20
<212> PRT
<213> Homo sapiens

<400> 77

Leu Pro Val Gly Arg Thr Val Met Val Asn Ile Glu Asn Pro Glu Gly
1 5 10 15

Ile Pro Val Lys
20

<210> 78
<211> 18
<212> PRT
<213> Homo sapiens

<400> 78

Gly Thr Pro His Gly Ile Ile Leu Asp Ser Val Asp Ala Ala Phe Ile
1 5 10 15

Cys Pro

<210> 79
<211> 18
<212> PRT
<213> Homo sapiens

<400> 79

Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro Met Gly Ala Leu Pro
1 5 10 15

Gln Gly

<210> 80
<211> 17
<212> PRT
<213> Homo sapiens

<400> 80

Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro Met Gly Ala Leu Pro
1 5 10 15

Gln

<210> 81
<211> 16
<212> PRT
<213> Homo sapiens

<400> 81

Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro Met Gly Ala Leu Pro
1 5 10 15

<210> 82
<211> 21
<212> PRT
<213> Homo sapiens

<400> 82

Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro Met Gly Ala Leu Pro

1 5 10 15

Gln Gly Pro Met Gln
20

<210> 83
<211> 15
<212> PRT
<213> Homo sapiens

<400> 83

Ala Thr Pro Leu Leu Met Gln Ala Leu Pro Met Gly Ala Leu Pro
1 5 10 15

<210> 84
<211> 23
<212> PRT
<213> Homo sapiens

<400> 84

His Pro Pro Val Gln Trp Ala Phe Gln Glu Thr Ser Val Glu Ser Ala
1 5 10 15

Val Asp Thr Pro Phe Pro Ala
20

<210> 85
<211> 24
<212> PRT
<213> Homo sapiens

<400> 85

His Pro Pro Val Gln Trp Ala Phe Gln Glu Thr Ser Val Glu Ser Ala
1 5 10 15

Val Asp Thr Pro Phe Pro Ala Gly
20

<210> 86
<211> 22
<212> PRT
<213> Homo sapiens

<400> 86

His Pro Pro Val Gln Trp Ala Phe Gln Glu Thr Ser Val Glu Ser Ala
1 5 10 15

Val Asp Thr Pro Phe Pro
20

<210> 87
<211> 17
<212> PRT
<213> Homo sapiens

<400> 87

Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val
1 5 10 15

Val

<210> 88
<211> 16
<212> PRT
<213> Homo sapiens

<400> 88

Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val
1 5 10 15

<210> 89
<211> 17
<212> PRT
<213> Homo sapiens

<400> 89

Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val Val
1 5 10 15

Ile

<210> 90
<211> 15
<212> PRT
<213> Homo sapiens

<400> 90

Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val
1 5 10 15

<210> 91
<211> 16
<212> PRT
<213> Homo sapiens

<400> 91

Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val Val
1 5 10 15

<210> 92
<211> 15
<212> PRT
<213> Homo sapiens

<400> 92

Tyr Asn Ser Tyr Ser Val Ser Asn Ser Glu Lys Asp Ile Met Ala
1 5 10 15

<210> 93
<211> 15
<212> PRT

<213> Homo sapiens

<400> 93

Ala Gly Ser Leu Thr Leu Ser Lys Thr Glu Leu Gly Lys Lys Ala
1 5 10 15

<210> 94
<211> 16
<212> PRT
<213> Homo sapiens

<400> 94

Ala Gly Ser Leu Thr Leu Ser Lys Thr Glu Leu Gly Lys Lys Ala Asp
1 5 10 15

<210> 95
<211> 14
<212> PRT
<213> Homo sapiens

<400> 95

Val Pro Lys Asp Tyr Thr Gly Glu Asp Val Thr Pro Gln Asn
1 5 10

<210> 96
<211> 13
<212> PRT
<213> Homo sapiens

<400> 96

Asp Ser Lys Phe His Gln Ala Ile Asn Asp Ala His Gln
1 5 10

<210> 97
<211> 15
<212> PRT
<213> Homo sapiens

<400> 97

Met Pro Leu Glu Phe Lys Thr Leu Asn Val Leu His Asn Arg Gly
1 5 10 15

<210> 98
<211> 15
<212> PRT
<213> Homo sapiens

<400> 98

Ala Thr Arg Ser Ile Gln Val Asp Gly Lys Thr Ile Lys Ala Gln
1 5 10 15

<210> 99
<211> 18
<212> PRT
<213> Homo sapiens

<400> 99

Ala Thr Arg Ser Ile Gln Val Asp Gly Lys Thr Ile Lys Ala Gln Ile
1 5 10 15

Trp Asp

<210> 100
<211> 14
<212> PRT
<213> Homo sapiens

<400> 100

Thr Arg Ser Ile Gln Val Asp Gly Lys Thr Ile Lys Ala Gln
1 5 10

<210> 101
<211> 17
<212> PRT
<213> Homo sapiens

<400> 101

Ala Thr Arg Ser Ile Gln Val Asp Gly Lys Thr Ile Lys Ala Gln Ile
1 5 10 15

Trp

<210> 102
<211> 13
<212> PRT
<213> Homo sapiens

<400> 102

Arg Ser Ile Gln Val Asp Gly Lys Thr Ile Lys Ala Gln
1 5 10

<210> 103
<211> 9
<212> PRT
<213> Homo sapiens

<400> 103

Ile Gln Pro Ile Phe Ala Val Thr Ser
1 5

<210> 104
<211> 9
<212> PRT
<213> Homo sapiens

<400> 104

Val Phe Gly Glu Asp Ser Val Gly Val
1 5

<210> 105
<211> 9
<212> PRT

<213> Homo sapiens

<400> 105

Leu Lys Met Thr Val Val Lys Leu Ile
1 5

<210> 106
<211> 9
<212> PRT
<213> Homo sapiens

<400> 106

Tyr Leu Gln Met Asn Ser Leu Arg Ala
1 5

<210> 107
<211> 9
<212> PRT
<213> Homo sapiens

<400> 107

Tyr Thr Tyr Ser Glu Asn Arg Val Glu
1 5

<210> 108
<211> 9
<212> PRT
<213> Homo sapiens

<400> 108

Tyr Tyr Ser Phe Ala Ser Gln Gln Gln
1 5

<210> 109
<211> 9
<212> PRT
<213> Homo sapiens

<400> 109

Phe Val Pro Ala Lys Val Glu Asp Ser
1 5

<210> 110
<211> 9
<212> PRT
<213> Homo sapiens

<400> 110

Leu His Leu Asp His Asn Gln Ile Ser
1 5

<210> 111
<211> 9
<212> PRT
<213> Homo sapiens

<400> 111

Met Arg Tyr Glu His Ile Asp His Thr
1 5

<210> 112
<211> 9
<212> PRT
<213> Homo sapiens

<400> 112

Phe Leu Gln Asp Glu Ile Ile Asp Lys
1 5

<210> 113
<211> 9
<212> PRT
<213> Homo sapiens

<400> 113

Met Val Asn Ile Glu Asn Pro Glu Gly
1 5

<210> 114
<211> 9
<212> PRT
<213> Homo sapiens

<400> 114

Leu Met Gln Ala Leu Pro Met Gly Ala
1 5

<210> 115
<211> 9
<212> PRT
<213> Homo sapiens

<400> 115

Trp Ala Phe Gln Glu Thr Ser Val Glu
1 5

<210> 116
<211> 9
<212> PRT
<213> Homo sapiens

<400> 116

Tyr Thr Leu Asn Asp Asn Ala Arg Ser
1 5

<210> 117
<211> 9
<212> PRT
<213> Homo sapiens

<400> 117

Tyr Ser Val Ser Asn Ser Glu Lys Asp
1 5

<210> 118
<211> 9
<212> PRT
<213> Homo sapiens

<400> 118

Leu Thr Leu Ser Lys Thr Glu Leu Gly
1 5

<210> 119
<211> 9
<212> PRT
<213> Homo sapiens

<400> 119

Tyr Thr Gly Glu Asp Val Thr Pro Gln
1 5

<210> 120
<211> 9
<212> PRT
<213> Homo sapiens

<400> 120

Phe His Gln Ala Ile Asn Asp Ala His
1 5

<210> 121
<211> 9
<212> PRT
<213> Homo sapiens

<400> 121

Phe Lys Thr Leu Asn Val Leu His Asn
1 5

<210> 122
<211> 9
<212> PRT
<213> Homo sapiens

<400> 122

Ile Gln Val Asp Gly Lys Thr Ile Lys
1 5

<210> 123
<211> 769
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P05107
<309> 1987-08-13
<313> (1)..(769)

<400> 123

Met Leu Gly Leu Arg Pro Pro Leu Leu Ala Leu Val Gly Leu Leu Ser
1 5 10 15

Leu Gly Cys Val Leu Ser Gln Glu Cys Thr Lys Phe Lys Val Ser Ser
20 25 30

Cys Arg Glu Cys Ile Glu Ser Gly Pro Gly Cys Thr Trp Cys Gln Lys
35 40 45

Leu Asn Phe Thr Gly Pro Gly Asp Pro Asp Ser Ile Arg Cys Asp Thr
50 55 60

Arg Pro Gln Leu Leu Met Arg Gly Cys Ala Ala Asp Asp Ile Met Asp
65 70 75 80

Pro Thr Ser Leu Ala Glu Thr Gln Glu Asp His Asn Gly Gly Gln Lys
85 90 95

Gln Leu Ser Pro Gln Lys Val Thr Leu Tyr Leu Arg Pro Gly Gln Ala
100 105 110

Ala Ala Phe Asn Val Thr Phe Arg Arg Ala Lys Gly Tyr Pro Ile Asp
115 120 125

Leu Tyr Tyr Leu Met Asp Leu Ser Tyr Ser Met Leu Asp Asp Leu Arg
130 135 140

Asn Val Lys Lys Leu Gly Gly Asp Leu Leu Arg Ala Leu Asn Glu Ile
145 150 155 160

Thr Glu Ser Gly Arg Ile Gly Phe Gly Ser Phe Val Asp Lys Thr Val
165 170 175

Leu Pro Phe Val Asn Thr His Pro Asp Lys Leu Arg Asn Pro Cys Pro
180 185 190

Asn Lys Glu Lys Glu Cys Gln Pro Pro Phe Ala Phe Arg His Val Leu
195 200 205

Lys Leu Thr Asn Asn Ser Asn Gln Phe Gln Thr Glu Val Gly Lys Gln
210 215 220

Leu Ile Ser Gly Asn Leu Asp Ala Pro Glu Gly Gly Leu Asp Ala Met
225 230 235 240

Met Gln Val Ala Ala Cys Pro Glu Glu Ile Gly Trp Arg Asn Val Thr
245 250 255

Arg Leu Leu Val Phe Ala Thr Asp Asp Gly Phe His Phe Ala Gly Asp
260 265 270

Gly Lys Leu Gly Ala Ile Leu Thr Pro Asn Asp Gly Arg Cys His Leu
275 280 285

Glu Asp Asn Leu Tyr Lys Arg Ser Asn Glu Phe Asp Tyr Pro Ser Val

290 295 300

Gly Gln Leu Ala His Lys Leu Ala Glu Asn Asn Ile Gln Pro Ile Phe
305 310 315 320

Ala Val Thr Ser Arg Met Val Lys Thr Tyr Glu Lys Leu Thr Glu Ile
325 330 335

Ile Pro Lys Ser Ala Val Gly Glu Leu Ser Glu Asp Ser Ser Asn Val
340 345 350

Val His Leu Ile Lys Asn Ala Tyr Asn Lys Leu Ser Ser Arg Val Phe
355 360 365

Leu Asp His Asn Ala Leu Pro Asp Thr Leu Lys Val Thr Tyr Asp Ser
370 375 380

Phe Cys Ser Asn Gly Val Thr His Arg Asn Gln Pro Arg Gly Asp Cys
385 390 395 400

Asp Gly Val Gln Ile Asn Val Pro Ile Thr Phe Gln Val Lys Val Thr
405 410 415

Ala Thr Glu Cys Ile Gln Glu Gln Ser Phe Val Ile Arg Ala Leu Gly
420 425 430

Phe Thr Asp Ile Val Thr Val Gln Val Leu Pro Gln Cys Glu Cys Arg
435 440 445

Cys Arg Asp Gln Ser Arg Asp Arg Ser Leu Cys His Gly Lys Gly Phe
450 455 460

Leu Glu Cys Gly Ile Cys Arg Cys Asp Thr Gly Tyr Ile Gly Lys Asn
465 470 475 480

Cys Glu Cys Gln Thr Gln Gly Arg Ser Ser Gln Glu Leu Glu Gly Ser
485 490 495

Cys Arg Lys Asp Asn Asn Ser Ile Ile Cys Ser Gly Leu Gly Asp Cys
500 505 510

Val Cys Gly Gln Cys Leu Cys His Thr Ser Asp Val Pro Gly Lys Leu
515 520 525

Ile Tyr Gly Gln Tyr Cys Glu Cys Asp Thr Ile Asn Cys Glu Arg Tyr
530 535 540

Asn Gly Gln Val Cys Gly Gly Pro Gly Arg Gly Leu Cys Phe Cys Gly
545 550 555 560

Lys Cys Arg Cys His Pro Gly Phe Glu Gly Ser Ala Cys Gln Cys Glu
565 570 575

Arg Thr Thr Glu Gly Cys Leu Asn Pro Arg Arg Val Glu Cys Ser Gly
580 585 590

Arg Gly Arg Cys Arg Cys Asn Val Cys Glu Cys His Ser Gly Tyr Gln
595 600 605

Leu Pro Leu Cys Gln Glu Cys Pro Gly Cys Pro Ser Pro Cys Gly Lys
610 615 620

Tyr Ile Ser Cys Ala Glu Cys Leu Lys Phe Glu Lys Gly Pro Phe Gly
625 630 635 640

Lys Asn Cys Ser Ala Ala Cys Pro Gly Leu Gln Leu Ser Asn Asn Pro
645 650 655

Val Lys Gly Arg Thr Cys Lys Glu Arg Asp Ser Glu Gly Cys Trp Val
660 665 670

Ala Tyr Thr Leu Glu Gln Gln Asp Gly Met Asp Arg Tyr Leu Ile Tyr
675 680 685

Val Asp Glu Ser Arg Glu Cys Val Ala Gly Pro Asn Ile Ala Ala Ile
690 695 700

Val Gly Gly Thr Val Ala Gly Ile Val Leu Ile Gly Ile Leu Leu Leu
705 710 715 720

Val Ile Trp Lys Ala Leu Ile His Leu Ser Asp Leu Arg Glu Tyr Arg
725 730 735

Arg Phe Glu Lys Glu Lys Leu Lys Ser Gln Trp Asn Asn Asp Asn Pro
740 745 750

Leu Phe Lys Ser Ala Thr Thr Thr Val Met Asn Pro Lys Phe Ala Glu
755 760 765

Ser

<210> 124
<211> 1070
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P42338
<309> 1995-11-01
<313> (1)..(1070)

<400> 124

Met Cys Phe Ser Phe Ile Met Pro Pro Ala Met Ala Asp Ile Leu Asp
1 5 10 15

Ile Trp Ala Val Asp Ser Gln Ile Ala Ser Asp Gly Ser Ile Pro Val

20 25 30

Asp Phe Leu Leu Pro Thr Gly Ile Tyr Ile Gln Leu Glu Val Pro Arg
35 40 45

Glu Ala Thr Ile Ser Tyr Ile Lys Gln Met Leu Trp Lys Gln Val His
50 55 60

Asn Tyr Pro Met Phe Asn Leu Leu Met Asp Ile Asp Ser Tyr Met Phe
65 70 75 80

Ala Cys Val Asn Gln Thr Ala Val Tyr Glu Glu Leu Glu Asp Glu Thr
85 90 95

Arg Arg Leu Cys Asp Val Arg Pro Phe Leu Pro Val Leu Lys Leu Val
100 105 110

Thr Arg Ser Cys Asp Pro Gly Glu Lys Leu Asp Ser Lys Ile Gly Val
115 120 125

Leu Ile Gly Lys Gly Leu His Glu Phe Asp Ser Leu Lys Asp Pro Glu
130 135 140

Val Asn Glu Phe Arg Arg Lys Met Arg Lys Phe Ser Glu Glu Lys Ile
145 150 155 160

Leu Ser Leu Val Gly Leu Ser Trp Met Asp Trp Leu Lys Gln Thr Tyr
165 170 175

Pro Pro Glu His Glu Pro Ser Ile Pro Glu Asn Leu Glu Asp Lys Leu
180 185 190

Tyr Gly Gly Lys Leu Ile Val Ala Val His Phe Glu Asn Cys Gln Asp
195 200 205

Val Phe Ser Phe Gln Val Ser Pro Asn Met Asn Pro Ile Lys Val Asn
210 215 220

Glu Leu Ala Ile Gln Lys Arg Leu Thr Ile His Gly Lys Glu Asp Glu
225 230 235 240

Val Ser Pro Tyr Asp Tyr Val Leu Gln Val Ser Gly Arg Val Glu Tyr
245 250 255

Val Phe Gly Asp His Pro Leu Ile Gln Phe Gln Tyr Ile Arg Asn Cys
260 265 270

Val Met Asn Arg Ala Leu Pro His Phe Ile Leu Val Glu Cys Cys Lys
275 280 285

Ile Lys Lys Met Tyr Glu Gln Glu Met Ile Ala Ile Glu Ala Ala Ile
290 295 300

Asn Arg Asn Ser Ser Asn Leu Pro Leu Pro Leu Pro Pro Lys Lys Thr
305 310 315 320

Arg Ile Ile Ser His Val Trp Glu Asn Asn Asn Pro Phe Gln Ile Val
325 330 335

Leu Val Lys Gly Asn Lys Leu Asn Thr Glu Glu Thr Val Lys Val His
340 345 350

Val Arg Ala Gly Leu Phe His Gly Thr Glu Leu Leu Cys Lys Thr Ile
355 360 365

Val Ser Ser Glu Val Ser Gly Lys Asn Asp His Ile Trp Asn Glu Pro
370 375 380

Leu Glu Phe Asp Ile Asn Ile Cys Asp Leu Pro Arg Met Ala Arg Leu
385 390 395 400

Cys Phe Ala Val Tyr Ala Val Leu Asp Lys Val Lys Thr Lys Lys Ser
405 410 415

Thr Lys Thr Ile Asn Pro Ser Lys Tyr Gln Thr Ile Arg Lys Ala Gly
420 425 430

Lys Val His Tyr Pro Val Ala Trp Val Asn Thr Met Val Phe Asp Phe
435 440 445

Lys Gly Gln Leu Arg Thr Gly Asp Ile Ile Leu His Ser Trp Ser Ser
450 455 460

Phe Pro Asp Glu Leu Glu Glu Met Leu Asn Pro Met Gly Thr Val Gln
465 470 475 480

Thr Asn Pro Tyr Thr Glu Asn Ala Thr Ala Leu His Val Lys Phe Pro
485 490 495

Glu Asn Lys Lys Gln Pro Tyr Tyr Tyr Pro Pro Phe Asp Lys Ile Ile
500 505 510

Glu Lys Ala Ala Glu Ile Ala Ser Ser Asp Ser Ala Asn Val Ser Ser
515 520 525

Arg Gly Gly Lys Lys Phe Leu Pro Val Leu Lys Glu Ile Leu Asp Arg
530 535 540

Asp Pro Leu Ser Gln Leu Cys Glu Asn Glu Met Asp Leu Ile Trp Thr
545 550 555 560

Leu Arg Gln Asp Cys Arg Glu Ile Phe Pro Gln Ser Leu Pro Lys Leu
565 570 575

Leu Leu Ser Ile Lys Trp Asn Lys Leu Glu Asp Val Ala Gln Leu Gln

580 585 590

Ala Leu Leu Gln Ile Trp Pro Lys Leu Pro Pro Arg Glu Ala Leu Glu
595 600 605

Leu Leu Asp Phe Asn Tyr Pro Asp Gln Tyr Val Arg Glu Tyr Ala Val
610 615 620

Gly Cys Leu Arg Gln Met Ser Asp Glu Glu Leu Ser Gln Tyr Leu Leu
625 630 635 640

Gln Leu Val Gln Val Leu Lys Tyr Glu Pro Phe Leu Asp Cys Ala Leu
645 650 655

Ser Arg Phe Leu Leu Glu Arg Ala Leu Gly Asn Arg Arg Ile Gly Gln
660 665 670

Phe Leu Phe Trp His Leu Arg Ser Glu Val His Ile Pro Ala Val Ser
675 680 685

Val Gln Phe Gly Val Ile Leu Glu Ala Tyr Cys Arg Gly Ser Val Gly
690 695 700

His Met Lys Val Leu Ser Lys Gln Val Glu Ala Leu Asn Lys Leu Lys
705 710 715 720

Thr Leu Asn Ser Leu Ile Lys Leu Asn Ala Val Lys Leu Asn Arg Ala
725 730 735

Lys Gly Lys Glu Ala Met His Thr Cys Leu Lys Gln Ser Ala Tyr Arg
740 745 750

Glu Ala Leu Ser Asp Leu Gln Ser Pro Leu Asn Pro Cys Val Ile Leu
755 760 765

Ser Glu Leu Tyr Val Glu Lys Cys Lys Tyr Met Asp Ser Lys Met Lys
770 775 780

Pro Leu Trp Leu Val Tyr Asn Asn Lys Val Phe Gly Glu Asp Ser Val
785 790 795 800

Gly Val Ile Phe Lys Asn Gly Asp Asp Leu Arg Gln Asp Met Leu Thr
805 810 815

Leu Gln Met Leu Arg Leu Met Asp Leu Leu Trp Lys Glu Ala Gly Leu
820 825 830

Asp Leu Arg Met Leu Pro Tyr Gly Cys Leu Ala Thr Gly Asp Arg Ser
835 840 845

Gly Leu Ile Glu Val Val Ser Thr Ser Glu Thr Ile Ala Asp Ile Gln
850 855 860

Leu Asn Ser Ser Asn Val Ala Ala Ala Ala Ala Phe Asn Lys Asp Ala
865 870 875 880

Leu Leu Asn Trp Leu Lys Glu Tyr Asn Ser Gly Asp Asp Leu Asp Arg
885 890 895

Ala Ile Glu Glu Phe Thr Leu Ser Cys Ala Gly Tyr Cys Val Ala Ser
900 905 910

Tyr Val Leu Gly Ile Gly Asp Arg His Ser Asp Asn Ile Met Val Lys
915 920 925

Lys Thr Gly Gln Leu Phe His Ile Asp Phe Gly His Ile Leu Gly Asn
930 935 940

Phe Lys Ser Lys Phe Gly Ile Lys Arg Glu Arg Val Pro Phe Ile Leu
945 950 955 960

Thr Tyr Asp Phe Ile His Val Ile Gln Gln Gly Lys Thr Gly Asn Thr
965 970 975

Glu Lys Phe Gly Arg Phe Arg Gln Cys Cys Glu Asp Ala Tyr Leu Ile
980 985 990

Leu Arg Arg His Gly Asn Leu Phe Ile Thr Leu Phe Ala Leu Met Leu
995 1000 1005

Thr Ala Gly Leu Pro Glu Leu Thr Ser Val Lys Asp Ile Gln Tyr
1010 1015 1020

Leu Lys Asp Ser Leu Ala Leu Gly Lys Ser Glu Glu Glu Ala Leu
1025 1030 1035

Lys Gln Phe Lys Gln Lys Phe Asp Glu Ala Leu Arg Glu Ser Trp
1040 1045 1050

Thr Thr Lys Val Asn Trp Met Ala His Thr Val Arg Lys Asp Tyr
1055 1060 1065

Arg Ser
1070

<210> 125
<211> 431
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P00749
<309> 1986-07-21
<313> (1)..(431)

<400> 125

Met Arg Ala Leu Leu Ala Arg Leu Leu Leu Cys Val Leu Val Val Ser

1 5 10 15

Asp Ser Lys Gly Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp
20 25 30

Cys Leu Asn Gly Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile
35 40 45

His Trp Cys Asn Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile
50 55 60

Asp Lys Ser Lys Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly
65 70 75 80

Lys Ala Ser Thr Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser
85 90 95

Ala Thr Val Leu Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu
100 105 110

Gln Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg
115 120 125

Arg Arg Pro Trp Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln
130 135 140

Glu Cys Met Val His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro
145 150 155 160

Pro Glu Glu Leu Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg
165 170 175

Phe Lys Ile Ile Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp
180 185 190

Phe Ala Ala Ile Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val
195 200 205

Cys Gly Gly Ser Leu Met Ser Pro Cys Trp Val Ile Ser Ala Thr His
210 215 220

Cys Phe Ile Asp Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly
225 230 235 240

Arg Ser Arg Leu Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val
245 250 255

Glu Asn Leu Ile Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His
260 265 270

His Asn Asp Ile Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys
275 280 285

Ala Gln Pro Ser Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr
290 295 300

Asn Asp Pro Gln Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys
305 310 315 320

Glu Asn Ser Thr Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val
325 330 335

Val Lys Leu Ile Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly
340 345 350

Ser Glu Val Thr Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys
355 360 365

Thr Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu
370 375 380

Gln Gly Arg Met Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys
385 390 395 400

Ala Leu Lys Asp Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu
405 410 415

Pro Trp Ile Arg Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
420 425 430

<210> 126
<211> 117
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P01764
<309> 1986-07-21
<313> (1)..(117)

<400> 126

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Gly
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn

85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Lys
115

<210> 127
<211> 189
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/Q99497
<309> 1997-05-01
<313> (1)..(189)

<400> 127

Met Ala Ser Lys Arg Ala Leu Val Ile Leu Ala Lys Gly Ala Glu Glu
1 5 10 15

Met Glu Thr Val Ile Pro Val Asp Val Met Arg Arg Ala Gly Ile Lys
20 25 30

Val Thr Val Ala Gly Leu Ala Gly Lys Asp Pro Val Gln Cys Ser Arg
35 40 45

Asp Val Val Ile Cys Pro Asp Ala Ser Leu Glu Asp Ala Lys Lys Glu
50 55 60

Gly Pro Tyr Asp Val Val Val Leu Pro Gly Gly Asn Leu Gly Ala Gln
65 70 75 80

Asn Leu Ser Glu Ser Ala Ala Val Lys Glu Ile Leu Lys Glu Gln Glu
85 90 95

Asn Arg Lys Gly Leu Ile Ala Ala Ile Cys Ala Gly Pro Thr Ala Leu
100 105 110

Leu Ala His Glu Ile Gly Phe Gly Ser Lys Val Thr Thr His Pro Leu
115 120 125

Ala Lys Asp Lys Met Met Asn Gly Gly His Tyr Thr Tyr Ser Glu Asn
130 135 140

Arg Val Glu Lys Asp Gly Leu Ile Leu Thr Ser Arg Gly Pro Gly Thr
145 150 155 160

Ser Phe Glu Phe Ala Leu Ala Ile Val Glu Ala Leu Asn Gly Lys Glu
165 170 175

Val Ala Ala Gln Val Lys Ala Pro Leu Val Leu Lys Asp
180 185

<210> 128
<211> 257
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P48556
<309> 1996-02-01
<313> (1)..(257)

<400> 128

Met Tyr Glu Gln Leu Lys Gly Glu Trp Asn Arg Lys Ser Pro Asn Leu
1 5 10 15

Ser Lys Cys Gly Glu Glu Leu Gly Arg Leu Lys Leu Val Leu Leu Glu
20 25 30

Leu Asn Phe Leu Pro Thr Thr Gly Thr Lys Leu Thr Lys Gln Gln Leu
35 40 45

Ile Leu Ala Arg Asp Ile Leu Glu Ile Gly Ala Gln Trp Ser Ile Leu
50 55 60

Arg Lys Asp Ile Pro Ser Phe Glu Arg Tyr Met Ala Gln Leu Lys Cys
65 70 75 80

Tyr Tyr Phe Asp Tyr Lys Glu Gln Leu Pro Glu Ser Ala Tyr Met His
85 90 95

Gln Leu Leu Gly Leu Asn Leu Leu Phe Leu Leu Ser Gln Asn Arg Val
100 105 110

Ala Glu Phe His Thr Glu Leu Glu Arg Leu Pro Ala Lys Asp Ile Gln
115 120 125

Thr Asn Val Tyr Ile Lys His Pro Val Ser Leu Glu Gln Tyr Leu Met
130 135 140

Glu Gly Ser Tyr Asn Lys Val Phe Leu Ala Lys Gly Asn Ile Pro Ala
145 150 155 160

Glu Ser Tyr Thr Phe Phe Ile Asp Ile Leu Leu Asp Thr Ile Arg Asp
165 170 175

Glu Ile Ala Gly Cys Ile Glu Lys Ala Tyr Glu Lys Ile Leu Phe Thr
180 185 190

Glu Ala Thr Arg Ile Leu Phe Phe Asn Thr Pro Lys Lys Met Thr Asp
195 200 205

Tyr Ala Lys Lys Arg Gly Trp Val Leu Gly Pro Asn Asn Tyr Tyr Ser
210 215 220

Phe Ala Ser Gln Gln Gln Lys Pro Glu Asp Thr Thr Ile Pro Ser Thr

225 230 235 240

Glu Leu Ala Lys Gln Val Ile Glu Tyr Ala Arg Gln Leu Glu Met Ile
245 250 255

Val

<210> 129
<211> 569
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P14778
<309> 1990-04-01
<313> (1)..(569)

<400> 129

Met Lys Val Leu Leu Arg Leu Ile Cys Phe Ile Ala Leu Leu Ile Ser
1 5 10 15

Ser Leu Glu Ala Asp Lys Cys Lys Glu Arg Glu Glu Lys Ile Ile Leu
20 25 30

Val Ser Ser Ala Asn Glu Ile Asp Val Arg Pro Cys Pro Leu Asn Pro
35 40 45

Asn Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser Lys Thr
50 55 60

Pro Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys Glu Lys
65 70 75 80

Leu Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr Tyr Cys
85 90 95

Val Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser Ala Lys
100 105 110

Phe Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala Ile Phe
115 120 125

Lys Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys Pro Tyr
130 135 140

Met Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu Gln Trp
145 150 155 160

Tyr Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe Ser Gly
165 170 175

Val Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His Arg Gly
180 185 190

Asn Tyr Thr Cys His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln Tyr Pro
195 200 205

Ile Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro Thr
210 215 220

Arg Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val Asp Leu
225 230 235 240

Gly Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu Ser Asp
245 250 255

Ile Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp Asp Pro
260 265 270

Val Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn Lys Arg
275 280 285

Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu Ser Arg
290 295 300

Phe Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile
305 310 315 320

Asp Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Phe Gln Lys
325 330 335

His Met Ile Gly Ile Cys Val Thr Leu Thr Val Ile Ile Val Cys Ser
340 345 350

Val Phe Ile Tyr Lys Ile Phe Lys Ile Asp Ile Val Leu Trp Tyr Arg
355 360 365

Asp Ser Cys Tyr Asp Phe Leu Pro Ile Lys Ala Ser Asp Gly Lys Thr
370 375 380

Tyr Asp Ala Tyr Ile Leu Tyr Pro Lys Thr Val Gly Glu Gly Ser Thr
385 390 395 400

Ser Asp Cys Asp Ile Phe Val Phe Lys Val Leu Pro Glu Val Leu Glu
405 410 415

Lys Gln Cys Gly Tyr Lys Leu Phe Ile Tyr Gly Arg Asp Asp Tyr Val
420 425 430

Gly Glu Asp Ile Val Glu Val Ile Asn Glu Asn Val Lys Lys Ser Arg
435 440 445

Arg Leu Ile Ile Ile Leu Val Arg Glu Thr Ser Gly Phe Ser Trp Leu
450 455 460

Gly Gly Ser Ser Glu Glu Gln Ile Ala Met Tyr Asn Ala Leu Val Gln

465 470 475 480

Asp Gly Ile Lys Val Val Leu Leu Glu Leu Glu Lys Ile Gln Asp Tyr
485 490 495

Glu Lys Met Pro Glu Ser Ile Lys Phe Ile Lys Gln Lys His Gly Ala
500 505 510

Ile Arg Trp Ser Gly Asp Phe Thr Gln Gly Pro Gln Ser Ala Lys Thr
515 520 525

Arg Phe Trp Lys Asn Val Arg Tyr His Met Pro Val Gln Arg Arg Ser
530 535 540

Pro Ser Ser Lys His Gln Leu Leu Ser Pro Ala Thr Lys Glu Lys Leu
545 550 555 560

Gln Arg Glu Ala His Val Pro Leu Gly
565

<210> 130
<211> 376
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/Q06828
<309> 1994-06-01
<313> (1)..(376)

<400> 130

Met Gln Trp Thr Ser Leu Leu Leu Leu Ala Gly Leu Phe Ser Leu Ser
1 5 10 15

Gln Ala Gln Tyr Glu Asp Asp Pro His Trp Trp Phe His Tyr Leu Arg
20 25 30

Ser Gln Gln Ser Thr Tyr Tyr Asp Pro Tyr Asp Pro Tyr Pro Tyr Glu
35 40 45

Thr Tyr Glu Pro Tyr Pro Tyr Gly Val Asp Glu Gly Pro Ala Tyr Thr
50 55 60

Tyr Gly Ser Pro Ser Pro Pro Asp Pro Arg Asp Cys Pro Gln Glu Cys
65 70 75 80

Asp Cys Pro Pro Asn Phe Pro Thr Ala Met Tyr Cys Asp Asn Arg Asn
85 90 95

Leu Lys Tyr Leu Pro Phe Val Pro Ser Arg Met Lys Tyr Val Tyr Phe
100 105 110

Gln Asn Asn Gln Ile Thr Ser Ile Gln Glu Gly Val Phe Asp Asn Ala
115 120 125

Thr Gly Leu Leu Trp Ile Ala Leu His Gly Asn Gln Ile Thr Ser Asp
130 135 140

Lys Val Gly Arg Lys Val Phe Ser Lys Leu Arg His Leu Glu Arg Leu
145 150 155 160

Tyr Leu Asp His Asn Asn Leu Thr Arg Met Pro Gly Pro Leu Pro Arg
165 170 175

Ser Leu Arg Glu Leu His Leu Asp His Asn Gln Ile Ser Arg Val Pro
180 185 190

Asn Asn Ala Leu Glu Gly Leu Glu Asn Leu Thr Ala Leu Tyr Leu Gln
195 200 205

His Asn Glu Ile Gln Glu Val Gly Ser Ser Met Arg Gly Leu Arg Ser
210 215 220

Leu Tyr Leu Leu Asp Leu Ser Tyr Asn His Leu Arg Lys Val Pro Asp
225 230 235 240

Gly Leu Pro Ser Ala Leu Glu Gln Leu Tyr Met Glu His Asn Asn Val
245 250 255

Tyr Thr Val Pro Asp Ser Tyr Phe Arg Gly Ala Pro Lys Leu Leu Tyr
260 265 270

Val Arg Leu Ser His Asn Ser Leu Thr Asn Asn Gly Leu Ala Ser Asn
275 280 285

Thr Phe Asn Ser Ser Ser Leu Leu Glu Leu Asp Leu Ser Tyr Asn Gln
290 295 300

Leu Gln Lys Ile Pro Pro Val Asn Thr Asn Leu Glu Asn Leu Tyr Leu
305 310 315 320

Gln Gly Asn Arg Ile Asn Glu Phe Ser Ile Ser Ser Phe Cys Thr Val
325 330 335

Val Asp Val Val Asn Phe Ser Gln Leu Gln Val Val Arg Leu Asp Gly
340 345 350

Asn Glu Met Lys Arg Ser Ala Met Pro Ala Glu Ala Pro Leu Cys Leu
355 360 365

Arg Leu Ala Ser Leu Ile Glu Ile
370 375

<210> 131
<211> 897
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P32927
<309> 1993-10-01
<313> (1)..(897)

<400> 131

Met Val Leu Ala Gln Gly Leu Leu Ser Met Ala Leu Leu Ala Leu Cys
1 5 10 15

Trp Glu Arg Ser Leu Ala Gly Ala Glu Glu Thr Ile Pro Leu Gln Thr
20 25 30

Leu Arg Cys Tyr Asn Asp Tyr Thr Ser His Ile Thr Cys Arg Trp Ala
35 40 45

Asp Thr Gln Asp Ala Gln Arg Leu Val Asn Val Thr Leu Ile Arg Arg
50 55 60

Val Asn Glu Asp Leu Leu Glu Pro Val Ser Cys Asp Leu Ser Asp Asp
65 70 75 80

Met Pro Trp Ser Ala Cys Pro His Pro Arg Cys Val Pro Arg Arg Cys
85 90 95

Val Ile Pro Cys Gln Ser Phe Val Val Thr Asp Val Asp Tyr Phe Ser
100 105 110

Phe Gln Pro Asp Arg Pro Leu Gly Thr Arg Leu Thr Val Thr Leu Thr
115 120 125

Gln His Val Gln Pro Pro Glu Pro Arg Asp Leu Gln Ile Ser Thr Asp
130 135 140

Gln Asp His Phe Leu Leu Thr Trp Ser Val Ala Leu Gly Ser Pro Gln
145 150 155 160

Ser His Trp Leu Ser Pro Gly Asp Leu Glu Phe Glu Val Val Tyr Lys
165 170 175

Arg Leu Gln Asp Ser Trp Glu Asp Ala Ala Ile Leu Leu Ser Asn Thr
180 185 190

Ser Gln Ala Thr Leu Gly Pro Glu His Leu Met Pro Ser Ser Thr Tyr
195 200 205

Val Ala Arg Val Arg Thr Arg Leu Ala Pro Gly Ser Arg Leu Ser Gly
210 215 220

Arg Pro Ser Lys Trp Ser Pro Glu Val Cys Trp Asp Ser Gln Pro Gly
225 230 235 240

Asp Glu Ala Gln Pro Gln Asn Leu Glu Cys Phe Phe Asp Gly Ala Ala
245 250 255

Val Leu Ser Cys Ser Trp Glu Val Arg Lys Glu Val Ala Ser Ser Val
260 265 270

Ser Phe Gly Leu Phe Tyr Lys Pro Ser Pro Asp Ala Gly Glu Glu Glu
275 280 285

Cys Ser Pro Val Leu Arg Glu Gly Leu Gly Ser Leu His Thr Arg His
290 295 300

His Cys Gln Ile Pro Val Pro Asp Pro Ala Thr His Gly Gln Tyr Ile
305 310 315 320

Val Ser Val Gln Pro Arg Arg Ala Glu Lys His Ile Lys Ser Ser Val
325 330 335

Asn Ile Gln Met Ala Pro Pro Ser Leu Asn Val Thr Lys Asp Gly Asp
340 345 350

Ser Tyr Ser Leu Arg Trp Glu Thr Met Lys Met Arg Tyr Glu His Ile
355 360 365

Asp His Thr Phe Glu Ile Gln Tyr Arg Lys Asp Thr Ala Thr Trp Lys
370 375 380

Asp Ser Lys Thr Glu Thr Leu Gln Asn Ala His Ser Met Ala Leu Pro
385 390 395 400

Ala Leu Glu Pro Ser Thr Arg Tyr Trp Ala Arg Val Arg Val Arg Thr
405 410 415

Ser Arg Thr Gly Tyr Asn Gly Ile Trp Ser Glu Trp Ser Glu Ala Arg
420 425 430

Ser Trp Asp Thr Glu Ser Val Leu Pro Met Trp Val Leu Ala Leu Ile
435 440 445

Val Ile Phe Leu Thr Ile Ala Val Leu Leu Ala Leu Arg Phe Cys Gly
450 455 460

Ile Tyr Gly Tyr Arg Leu Arg Arg Lys Trp Glu Glu Lys Ile Pro Asn
465 470 475 480

Pro Ser Lys Ser His Leu Phe Gln Asn Gly Ser Ala Glu Leu Trp Pro
485 490 495

Pro Gly Ser Met Ser Ala Phe Thr Ser Gly Ser Pro Pro His Gln Gly
500 505 510

Pro Trp Gly Ser Arg Phe Pro Glu Leu Glu Gly Val Phe Pro Val Gly
515 520 525

Phe Gly Asp Ser Glu Val Ser Pro Leu Thr Ile Glu Asp Pro Lys His

530 535 540

Val Cys Asp Pro Pro Ser Gly Pro Asp Thr Thr Pro Ala Ala Ser Asp
545 550 555 560

Leu Pro Thr Glu Gln Pro Pro Ser Pro Gln Pro Gly Pro Pro Ala Ala
565 570 575

Ser His Thr Pro Glu Lys Gln Ala Ser Ser Phe Asp Phe Asn Gly Pro
580 585 590

Tyr Leu Gly Pro Pro His Ser Arg Ser Leu Pro Asp Ile Leu Gly Gln
595 600 605

Pro Glu Pro Pro Gln Glu Gly Gly Ser Gln Lys Ser Pro Pro Pro Gly
610 615 620

Ser Leu Glu Tyr Leu Cys Leu Pro Ala Gly Gly Gln Val Gln Leu Val
625 630 635 640

Pro Leu Ala Gln Ala Met Gly Pro Gly Gln Ala Val Glu Val Glu Arg
645 650 655

Arg Pro Ser Gln Gly Ala Ala Gly Ser Pro Ser Leu Glu Ser Gly Gly
660 665 670

Gly Pro Ala Pro Pro Ala Leu Gly Pro Arg Val Gly Gly Gln Asp Gln
675 680 685

Lys Asp Ser Pro Val Ala Ile Pro Met Ser Ser Gly Asp Thr Glu Asp
690 695 700

Pro Gly Val Ala Ser Gly Tyr Val Ser Ser Ala Asp Leu Val Phe Thr
705 710 715 720

Pro Asn Ser Gly Ala Ser Ser Val Ser Leu Val Pro Ser Leu Gly Leu
725 730 735

Pro Ser Asp Gln Thr Pro Ser Leu Cys Pro Gly Leu Ala Ser Gly Pro
740 745 750

Pro Gly Ala Pro Gly Pro Val Lys Ser Gly Phe Glu Gly Tyr Val Glu
755 760 765

Leu Pro Pro Ile Glu Gly Arg Ser Pro Arg Ser Pro Arg Asn Asn Pro
770 775 780

Val Pro Pro Glu Ala Lys Ser Pro Val Leu Asn Pro Gly Glu Arg Pro
785 790 795 800

Ala Asp Val Ser Pro Thr Ser Pro Gln Pro Glu Gly Leu Leu Val Leu
805 810 815

Gln Gln Val Gly Asp Tyr Cys Phe Leu Pro Gly Leu Gly Pro Gly Pro
820 825 830

Leu Ser Leu Arg Ser Lys Pro Ser Ser Pro Gly Pro Gly Pro Glu Ile
835 840 845

Lys Asn Leu Asp Gln Ala Phe Gln Val Lys Lys Pro Pro Gly Gln Ala
850 855 860

Val Pro Gln Val Pro Val Ile Gln Leu Phe Lys Ala Leu Lys Gln Gln
865 870 875 880

Asp Tyr Leu Ser Leu Pro Pro Trp Glu Val Asn Lys Pro Gly Glu Val
885 890 895

Cys

<210> 132
<211> 261
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/Q60493
<309> 1996-11-01
<313> (1)..(261)

<400> 132

Met Ile Tyr Lys Cys Pro Met Cys Arg Glu Phe Phe Ser Glu Arg Ala
1 5 10 15

Asp Leu Phe Met His Gln Lys Val His Thr Ala Glu Lys Pro His Lys
20 25 30

Cys Asp Lys Cys Asp Lys Gly Phe Phe His Ile Ser Glu Leu His Ile
35 40 45

His Trp Arg Asp His Thr Gly Glu Lys Val Tyr Lys Cys Asp Asp Cys
50 55 60

Gly Lys Asp Phe Ser Thr Thr Thr Lys Leu Asn Arg His Lys Lys Ile
65 70 75 80

His Thr Val Glu Lys Pro Tyr Lys Cys Tyr Glu Cys Gly Lys Ala Phe
85 90 95

Asn Trp Ser Pro His Leu Gln Ile His Met Arg Val His Thr Gly Glu
100 105 110

Lys Pro Tyr Val Cys Ser Glu Cys Gly Arg Gly Phe Ser Asn Ser Ser
115 120 125

Asn Leu Cys Met His Gln Arg Val His Thr Gly Glu Lys Pro Phe Lys

130 135 140

Cys Glu Glu Cys Gly Lys Ala Phe Arg His Thr Ser Ser Leu Cys Met
145 150 155 160

His Gln Arg Val His Thr Gly Glu Lys Pro Tyr Lys Cys Tyr Glu Cys
165 170 175

Gly Lys Ala Phe Ser Gln Ser Ser Ser Leu Cys Ile His Gln Arg Val
180 185 190

His Thr Gly Glu Lys Pro Tyr Arg Cys Cys Gly Cys Gly Lys Ala Phe
195 200 205

Ser Gln Ser Ser Ser Leu Cys Ile His Gln Arg Val His Thr Gly Glu
210 215 220

Lys Pro Phe Lys Cys Asp Glu Cys Gly Lys Ala Phe Ser Gln Ser Thr
225 230 235 240

Ser Leu Cys Ile His Gln Arg Val His Thr Lys Glu Arg Asn His Leu
245 250 255

Lys Ile Ser Val Ile
260

<210> 133
<211> 296
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P04233
<309> 1987-03-20
<313> (1)..(296)

<400> 133

Met His Arg Arg Arg Ser Arg Ser Cys Arg Glu Asp Gln Lys Pro Val
1 5 10 15

Met Asp Asp Gln Arg Asp Leu Ile Ser Asn Asn Glu Gln Leu Pro Met
20 25 30

Leu Gly Arg Arg Pro Gly Ala Pro Glu Ser Lys Cys Ser Arg Gly Ala
35 40 45

Leu Tyr Thr Gly Phe Ser Ile Leu Val Thr Leu Leu Leu Ala Gly Gln
50 55 60

Ala Thr Thr Ala Tyr Phe Leu Tyr Gln Gln Gln Gly Arg Leu Asp Lys
65 70 75 80

Leu Thr Val Thr Ser Gln Asn Leu Gln Leu Glu Asn Leu Arg Met Lys
85 90 95

Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro
100 105 110

Leu Leu Met Gln Ala Leu Pro Met Gly Ala Leu Pro Gln Gly Pro Met
115 120 125

Gln Asn Ala Thr Lys Tyr Gly Asn Met Thr Glu Asp His Val Met His
130 135 140

Leu Leu Gln Asn Ala Asp Pro Leu Lys Val Tyr Pro Pro Leu Lys Gly
145 150 155 160

Ser Phe Pro Glu Asn Leu Arg His Leu Lys Asn Thr Met Glu Thr Ile
165 170 175

Asp Trp Lys Val Phe Glu Ser Trp Met His His Trp Leu Leu Phe Glu
180 185 190

Met Ser Arg His Ser Leu Glu Gln Lys Pro Thr Asp Ala Pro Pro Lys
195 200 205

Val Leu Thr Lys Cys Gln Glu Glu Val Ser His Ile Pro Ala Val His
210 215 220

Pro Gly Ser Phe Arg Pro Lys Cys Asp Glu Asn Gly Asn Tyr Leu Pro
225 230 235 240

Leu Gln Cys Tyr Gly Ser Ile Gly Tyr Cys Trp Cys Val Phe Pro Asn
245 250 255

Gly Thr Glu Val Pro Asn Thr Arg Ser Arg Gly His His Asn Cys Ser
260 265 270

Glu Ser Leu Glu Leu Glu Asp Pro Ser Ser Gly Leu Gly Val Thr Lys
275 280 285

Gln Asp Leu Gly Pro Val Pro Met
290 295

<210> 134
<211> 163
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/Q99969
<309> 2000-05-30
<313> (1)..(163)

<400> 134

Met Arg Arg Leu Leu Ile Pro Leu Ala Leu Trp Leu Gly Ala Val Gly
1 5 10 15

Val Gly Val Ala Glu Leu Thr Glu Ala Gln Arg Arg Gly Leu Gln Val

20 25 30

Ala Leu Glu Glu Phe His Lys His Pro Pro Val Gln Trp Ala Phe Gln
35 40 45

Glu Thr Ser Val Glu Ser Ala Val Asp Thr Pro Phe Pro Ala Gly Ile
50 55 60

Phe Val Arg Leu Glu Phe Lys Leu Gln Gln Thr Ser Cys Arg Lys Arg
65 70 75 80

Asp Trp Lys Lys Pro Glu Cys Lys Val Arg Pro Asn Gly Arg Lys Arg
85 90 95

Lys Cys Leu Ala Cys Ile Lys Leu Gly Ser Glu Asp Lys Val Leu Gly
100 105 110

Arg Leu Val His Cys Pro Ile Glu Thr Gln Val Leu Arg Glu Ala Glu
115 120 125

Glu His Gln Glu Thr Gln Cys Leu Arg Val Gln Arg Ala Gly Glu Asp
130 135 140

Pro His Ser Phe Tyr Phe Pro Gly Gln Phe Ala Phe Ser Lys Ala Leu
145 150 155 160

Pro Arg Ser

<210> 135
<211> 2386
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P02751
<309> 1986-07-21
<313> (1)..(2386)

<400> 135

Met Leu Arg Gly Pro Gly Pro Gly Leu Leu Leu Leu Ala Val Gln Cys
1 5 10 15

Leu Gly Thr Ala Val Pro Ser Thr Gly Ala Ser Lys Ser Lys Arg Gln
20 25 30

Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val Ala Val Ser Gln Ser
35 40 45

Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln
50 55 60

Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr Gly
65 70 75 80

Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr
85 90 95

Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr
100 105 110

Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly Ala
115 120 125

Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly
130 135 140

Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu Thr
145 150 155 160

Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly Glu
165 170 175

Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala Gly
180 185 190

Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly Trp
195 200 205

Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile Thr
210 215 220

Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser Tyr
225 230 235 240

Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu Leu
245 250 255

Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu Arg
260 265 270

His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr Asp
275 280 285

Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro Pro
290 295 300

Tyr Gly His Cys Val Thr Asp Ser Gly Val Val Tyr Ser Val Gly Met
305 310 315 320

Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met Leu Cys Thr Cys Leu
325 330 335

Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val Thr Gln Thr Tyr Gly
340 345 350

Gly Asn Ser Asn Gly Glu Pro Cys Val Leu Pro Phe Thr Tyr Asn Gly

355 360 365

Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg Gln Asp Gly His Leu
370 375 380

Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp Gln Lys Tyr Ser Phe
385 390 395 400

Cys Thr Asp His Thr Val Leu Val Gln Thr Gln Gly Gly Asn Ser Asn
405 410 415

Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr Thr
420 425 430

Asp Cys Thr Ser Glu Gly Arg Arg Asp Asn Met Lys Trp Cys Gly Thr
435 440 445

Thr Gln Asn Tyr Asp Ala Asp Gln Lys Phe Gly Phe Cys Pro Met Ala
450 455 460

Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly Val Met Tyr Arg Ile
465 470 475 480

Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly His Met Met Arg Cys
485 490 495

Thr Cys Val Gly Asn Gly Arg Gly Glu Trp Thr Cys Ile Ala Tyr Ser
500 505 510

Gln Leu Arg Asp Gln Cys Ile Val Asp Asp Ile Thr Tyr Asn Val Asn
515 520 525

Asp Thr Phe His Lys Arg His Glu Glu Gly His Met Leu Asn Cys Thr
530 535 540

Cys Phe Gly Gln Gly Arg Gly Arg Trp Lys Cys Asp Pro Val Asp Gln
545 550 555 560

Cys Gln Asp Ser Glu Thr Gly Thr Phe Tyr Gln Ile Gly Asp Ser Trp
565 570 575

Glu Lys Tyr Val His Gly Val Arg Tyr Gln Cys Tyr Cys Tyr Gly Arg
580 585 590

Gly Ile Gly Glu Trp His Cys Gln Pro Leu Gln Thr Tyr Pro Ser Ser
595 600 605

Ser Gly Pro Val Glu Val Phe Ile Thr Glu Thr Pro Ser Gln Pro Asn
610 615 620

Ser His Pro Ile Gln Trp Asn Ala Pro Gln Pro Ser His Ile Ser Lys
625 630 635 640

Tyr Ile Leu Arg Trp Arg Pro Lys Asn Ser Val Gly Arg Trp Lys Glu
645 650 655

Ala Thr Ile Pro Gly His Leu Asn Ser Tyr Thr Ile Lys Gly Leu Lys
660 665 670

Pro Gly Val Val Tyr Glu Gly Gln Leu Ile Ser Ile Gln Gln Tyr Gly
675 680 685

His Gln Glu Val Thr Arg Phe Asp Phe Thr Thr Thr Ser Thr Ser Thr
690 695 700

Pro Val Thr Ser Asn Thr Val Thr Gly Glu Thr Thr Pro Phe Ser Pro
705 710 715 720

Leu Val Ala Thr Ser Glu Ser Val Thr Glu Ile Thr Ala Ser Ser Phe
725 730 735

Val Val Ser Trp Val Ser Ala Ser Asp Thr Val Ser Gly Phe Arg Val
740 745 750

Glu Tyr Glu Leu Ser Glu Glu Gly Asp Glu Pro Gln Tyr Leu Asp Leu
755 760 765

Pro Ser Thr Ala Thr Ser Val Asn Ile Pro Asp Leu Leu Pro Gly Arg
770 775 780

Lys Tyr Ile Val Asn Val Tyr Gln Ile Ser Glu Asp Gly Glu Gln Ser
785 790 795 800

Leu Ile Leu Ser Thr Ser Gln Thr Thr Ala Pro Asp Ala Pro Pro Asp
805 810 815

Pro Thr Val Asp Gln Val Asp Asp Thr Ser Ile Val Val Arg Trp Ser
820 825 830

Arg Pro Gln Ala Pro Ile Thr Gly Tyr Arg Ile Val Tyr Ser Pro Ser
835 840 845

Val Glu Gly Ser Ser Thr Glu Leu Asn Leu Pro Glu Thr Ala Asn Ser
850 855 860

Val Thr Leu Ser Asp Leu Gln Pro Gly Val Gln Tyr Asn Ile Thr Ile
865 870 875 880

Tyr Ala Val Glu Glu Asn Gln Glu Ser Thr Pro Val Val Ile Gln Gln
885 890 895

Glu Thr Thr Gly Thr Pro Arg Ser Asp Thr Val Pro Ser Pro Arg Asp
900 905 910

Leu Gln Phe Val Glu Val Thr Asp Val Lys Val Thr Ile Met Trp Thr

915 920 925

Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val Asp Val Ile Pro Val
930 935 940

Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro Ile Ser Arg Asn Thr
945 950 955 960

Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val Thr Tyr Tyr Phe Lys
965 970 975

Val Phe Ala Val Ser His Gly Arg Glu Ser Lys Pro Leu Thr Ala Gln
980 985 990

Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu Gln Phe Val Asn Glu
995 1000 1005

Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro Pro Arg Ala Gln
1010 1015 1020

Ile Thr Gly Tyr Arg Leu Thr Val Gly Leu Thr Arg Arg Gly Gln
1025 1030 1035

Pro Arg Gln Tyr Asn Val Gly Pro Ser Val Ser Lys Tyr Pro Leu
1040 1045 1050

Arg Asn Leu Gln Pro Ala Ser Glu Tyr Thr Val Ser Leu Val Ala
1055 1060 1065

Ile Lys Gly Asn Gln Glu Ser Pro Lys Ala Thr Gly Val Phe Thr
1070 1075 1080

Thr Leu Gln Pro Gly Ser Ser Ile Pro Pro Tyr Asn Thr Glu Val
1085 1090 1095

Thr Glu Thr Thr Ile Val Ile Thr Trp Thr Pro Ala Pro Arg Ile
1100 1105 1110

Gly Phe Lys Leu Gly Val Arg Pro Ser Gln Gly Gly Glu Ala Pro
1115 1120 1125

Arg Glu Val Thr Ser Asp Ser Gly Ser Ile Val Val Ser Gly Leu
1130 1135 1140

Thr Pro Gly Val Glu Tyr Val Tyr Thr Ile Gln Val Leu Arg Asp
1145 1150 1155

Gly Gln Glu Arg Asp Ala Pro Ile Val Asn Lys Val Val Thr Pro
1160 1165 1170

Leu Ser Pro Pro Thr Asn Leu His Leu Glu Ala Asn Pro Asp Thr
1175 1180 1185

Gly Val Leu Thr Val Ser Trp Glu Arg Ser Thr Thr Pro Asp Ile
1190 1195 1200

Thr Gly Tyr Arg Ile Thr Thr Thr Pro Thr Asn Gly Gln Gln Gly
1205 1210 1215

Asn Ser Leu Glu Glu Val Val His Ala Asp Gln Ser Ser Cys Thr
1220 1225 1230

Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr Asn Val Ser Val Tyr
1235 1240 1245

Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile Ser Asp Thr Ile
1250 1255 1260

Ile Pro Ala Val Pro Pro Pro Thr Asp Leu Arg Phe Thr Asn Ile
1265 1270 1275

Gly Pro Asp Thr Met Arg Val Thr Trp Ala Pro Pro Pro Ser Ile
1280 1285 1290

Asp Leu Thr Asn Phe Leu Val Arg Tyr Ser Pro Val Lys Asn Glu
1295 1300 1305

Glu Asp Val Ala Glu Leu Ser Ile Ser Pro Ser Asp Asn Ala Val
1310 1315 1320

Val Leu Thr Asn Leu Leu Pro Gly Thr Glu Tyr Val Val Ser Val
1325 1330 1335

Ser Ser Val Tyr Glu Gln His Glu Ser Thr Pro Leu Arg Gly Arg
1340 1345 1350

Gln Lys Thr Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp
1355 1360 1365

Ile Thr Ala Asn Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala
1370 1375 1380

Thr Ile Thr Gly Tyr Arg Ile Arg His His Pro Glu His Phe Ser
1385 1390 1395

Gly Arg Pro Arg Glu Asp Arg Val Pro His Ser Arg Asn Ser Ile
1400 1405 1410

Thr Leu Thr Asn Leu Thr Pro Gly Thr Glu Tyr Val Val Ser Ile
1415 1420 1425

Val Ala Leu Asn Gly Arg Glu Glu Ser Pro Leu Leu Ile Gly Gln
1430 1435 1440

Gln Ser Thr Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala

1445 1450 1455

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val
1460 1465 1470

Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
1475 1480 1485

Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys Ser Thr Ala
1490 1495 1500

Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
1505 1510 1515

Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys Pro
1520 1525 1530

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln Met
1535 1540 1545

Gln Val Thr Asp Val Gln Asp Asn Ser Ile Ser Val Lys Trp Leu
1550 1555 1560

Pro Ser Ser Ser Pro Val Thr Gly Tyr Arg Val Thr Thr Thr Pro
1565 1570 1575

Lys Asn Gly Pro Gly Pro Thr Lys Thr Lys Thr Ala Gly Pro Asp
1580 1585 1590

Gln Thr Glu Met Thr Ile Glu Gly Leu Gln Pro Thr Val Glu Tyr
1595 1600 1605

Val Val Ser Val Tyr Ala Gln Asn Pro Ser Gly Glu Ser Gln Pro
1610 1615 1620

Leu Val Gln Thr Ala Val Thr Asn Ile Asp Arg Pro Lys Gly Leu
1625 1630 1635

Ala Phe Thr Asp Val Asp Val Asp Ser Ile Lys Ile Ala Trp Glu
1640 1645 1650

Ser Pro Gln Gly Gln Val Ser Arg Tyr Arg Val Thr Tyr Ser Ser
1655 1660 1665

Pro Glu Asp Gly Ile His Glu Leu Phe Pro Ala Pro Asp Gly Glu
1670 1675 1680

Glu Asp Thr Ala Glu Leu Gln Gly Leu Arg Pro Gly Ser Glu Tyr
1685 1690 1695

Thr Val Ser Val Val Ala Leu His Asp Asp Met Glu Ser Gln Pro
1700 1705 1710

Leu Ile Gly Thr Gln Ser Thr Ala Ile Pro Ala Pro Thr Asp Leu
1715 1720 1725

Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr
1730 1735 1740

Pro Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro
1745 1750 1755

Lys Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp
1760 1765 1770

Ser Ser Ser Val Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr
1775 1780 1785

Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro
1790 1795 1800

Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg
1805 1810 1815

Arg Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile Thr Ile Ser
1820 1825 1830

Trp Arg Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala
1835 1840 1845

Val Pro Ala Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro
1850 1855 1860

Asp Val Arg Ser Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr Asp
1865 1870 1875

Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser
1880 1885 1890

Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp Ala Pro Ser Asn
1895 1900 1905

Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu Val Ser Trp
1910 1915 1920

Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys Tyr Glu
1925 1930 1935

Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg Pro
1940 1945 1950

Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu
1955 1960 1965

Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu

1970 1975 1980

Pro Leu Ile Gly Arg Lys Lys Thr Asp Glu Leu Pro Gln Leu Val
1985 1990 1995

Thr Leu Pro His Pro Asn Leu His Gly Pro Glu Ile Leu Asp Val
2000 2005 2010

Pro Ser Thr Val Gln Lys Thr Pro Phe Val Thr His Pro Gly Tyr
2015 2020 2025

Asp Thr Gly Asn Gly Ile Gln Leu Pro Gly Thr Ser Gly Gln Gln
2030 2035 2040

Pro Ser Val Gly Gln Gln Met Ile Phe Glu Glu His Gly Phe Arg
2045 2050 2055

Arg Thr Thr Pro Pro Thr Thr Ala Thr Pro Ile Arg His Arg Pro
2060 2065 2070

Arg Pro Tyr Pro Pro Asn Val Gly Glu Glu Ile Gln Ile Gly His
2075 2080 2085

Ile Pro Arg Glu Asp Val Asp Tyr His Leu Tyr Pro His Gly Pro
2090 2095 2100

Gly Leu Asn Pro Asn Ala Ser Thr Gly Gln Glu Ala Leu Ser Gln
2105 2110 2115

Thr Thr Ile Ser Trp Ala Pro Phe Gln Asp Thr Ser Glu Tyr Ile
2120 2125 2130

Ile Ser Cys His Pro Val Gly Thr Asp Glu Glu Pro Leu Gln Phe
2135 2140 2145

Arg Val Pro Gly Thr Ser Thr Ser Ala Thr Leu Thr Gly Leu Thr
2150 2155 2160

Arg Gly Ala Thr Tyr Asn Ile Ile Val Glu Ala Leu Lys Asp Gln
2165 2170 2175

Gln Arg His Lys Val Arg Glu Glu Val Val Thr Val Gly Asn Ser
2180 2185 2190

Val Asn Glu Gly Leu Asn Gln Pro Thr Asp Asp Ser Cys Phe Asp
2195 2200 2205

Pro Tyr Thr Val Ser His Tyr Ala Val Gly Asp Glu Trp Glu Arg
2210 2215 2220

Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln Cys Leu Gly Phe
2225 2230 2235

Gly Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp Cys His Asp
2240 2245 2250

Asn Gly Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg Gln Gly
2255 2260 2265

Glu Asn Gly Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly Lys
2270 2275 2280

Gly Glu Phe Lys Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp
2285 2290 2295

Gly Lys Thr Tyr His Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu
2300 2305 2310

Gly Ala Ile Cys Ser Cys Thr Cys Phe Gly Gly Gln Arg Gly Trp
2315 2320 2325

Arg Cys Asp Asn Cys Arg Arg Pro Gly Gly Glu Pro Ser Pro Glu
2330 2335 2340

Gly Thr Thr Gly Gln Ser Tyr Asn Gln Tyr Ser Gln Arg Tyr His
2345 2350 2355

Gln Arg Thr Asn Thr Asn Val Asn Cys Pro Ile Glu Cys Phe Met
2360 2365 2370

Pro Leu Asp Val Gln Ala Asp Arg Glu Asp Ser Arg Glu
2375 2380 2385

<210> 136
<211> 339
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P07858
<309> 1988-08-01
<313> (1)..(339)

<400> 136

Met Trp Gln Leu Trp Ala Ser Leu Cys Cys Leu Leu Val Leu Ala Asn
1 5 10 15

Ala Arg Ser Arg Pro Ser Phe His Pro Val Ser Asp Glu Leu Val Asn
20 25 30

Tyr Val Asn Lys Arg Asn Thr Thr Trp Gln Ala Gly His Asn Phe Tyr
35 40 45

Asn Val Asp Met Ser Tyr Leu Lys Arg Leu Cys Gly Thr Phe Leu Gly
50 55 60

Gly Pro Lys Pro Pro Gln Arg Val Met Phe Thr Glu Asp Leu Lys Leu

65 70 75 80

Pro Ala Ser Phe Asp Ala Arg Glu Gln Trp Pro Gln Cys Pro Thr Ile
85 90 95

Lys Glu Ile Arg Asp Gln Gly Ser Cys Gly Ser Cys Trp Ala Phe Gly
100 105 110

Ala Val Glu Ala Ile Ser Asp Arg Ile Cys Ile His Thr Asn Ala His
115 120 125

Val Ser Val Glu Val Ser Ala Glu Asp Leu Leu Thr Cys Cys Gly Ser
130 135 140

Met Cys Gly Asp Gly Cys Asn Gly Gly Tyr Pro Ala Glu Ala Trp Asn
145 150 155 160

Phe Trp Thr Arg Lys Gly Leu Val Ser Gly Gly Leu Tyr Glu Ser His
165 170 175

Val Gly Cys Arg Pro Tyr Ser Ile Pro Pro Cys Glu His His Val Asn
180 185 190

Gly Ser Arg Pro Pro Cys Thr Gly Glu Gly Asp Thr Pro Lys Cys Ser
195 200 205

Lys Ile Cys Glu Pro Gly Tyr Ser Pro Thr Tyr Lys Gln Asp Lys His
210 215 220

Tyr Gly Tyr Asn Ser Tyr Ser Val Ser Asn Ser Glu Lys Asp Ile Met
225 230 235 240

Ala Glu Ile Tyr Lys Asn Gly Pro Val Glu Gly Ala Phe Ser Val Tyr
245 250 255

Ser Asp Phe Leu Leu Tyr Lys Ser Gly Val Tyr Gln His Val Thr Gly
260 265 270

Glu Met Met Gly Gly His Ala Ile Arg Ile Leu Gly Trp Gly Val Glu
275 280 285

Asn Gly Thr Pro Tyr Trp Leu Val Ala Asn Ser Trp Asn Thr Asp Trp
290 295 300

Gly Asp Asn Gly Phe Phe Lys Ile Leu Arg Gly Gln Asp His Cys Gly
305 310 315 320

Ile Glu Ser Glu Val Val Ala Gly Ile Pro Arg Thr Asp Gln Tyr Trp
325 330 335

Glu Lys Ile

<210> 137
<211> 1249
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P29144
<309> 1992-12-01
<313> (1)..(1249)

<400> 137

Met Ala Thr Ala Ala Thr Glu Glu Pro Phe Pro Phe His Gly Leu Leu
1 5 10 15

Pro Lys Lys Glu Thr Gly Ala Ala Ser Phe Leu Cys Arg Tyr Pro Glu
20 25 30

Tyr Asp Gly Arg Gly Val Leu Ile Ala Val Leu Asp Thr Gly Val Asp
35 40 45

Pro Gly Ala Pro Gly Met Gln Val Thr Thr Asp Gly Lys Pro Lys Ile
50 55 60

Val Asp Ile Ile Asp Thr Thr Gly Ser Gly Asp Val Asn Thr Ala Thr
65 70 75 80

Glu Val Glu Pro Lys Asp Gly Glu Ile Val Gly Leu Ser Gly Arg Val
85 90 95

Leu Lys Ile Pro Ala Ser Trp Thr Asn Pro Ser Gly Lys Tyr His Ile
100 105 110

Gly Ile Lys Asn Gly Tyr Asp Phe Tyr Pro Lys Ala Leu Lys Glu Arg
115 120 125

Ile Gln Lys Glu Arg Lys Glu Lys Ile Trp Asp Pro Val His Arg Val
130 135 140

Ala Leu Ala Glu Ala Cys Arg Lys Gln Glu Glu Phe Asp Val Ala Asn
145 150 155 160

Asn Gly Ser Ser Gln Ala Asn Lys Leu Ile Lys Glu Glu Leu Gln Ser
165 170 175

Gln Val Glu Leu Leu Asn Ser Phe Glu Lys Lys Tyr Ser Asp Pro Gly
180 185 190

Pro Val Tyr Asp Cys Leu Val Trp His Asp Gly Glu Val Trp Arg Ala
195 200 205

Cys Ile Asp Ser Asn Glu Asp Gly Asp Leu Ser Lys Ser Thr Val Leu
210 215 220

Arg Asn Tyr Lys Glu Ala Gln Glu Tyr Gly Ser Phe Gly Thr Ala Glu

225 230 235 240

Met Leu Asn Tyr Ser Val Asn Ile Tyr Asp Asp Gly Asn Leu Leu Ser
245 250 255

Ile Val Thr Ser Gly Gly Ala His Gly Thr His Val Ala Ser Ile Ala
260 265 270

Ala Gly His Phe Pro Glu Glu Pro Glu Arg Asn Gly Val Ala Pro Gly
275 280 285

Ala Gln Ile Leu Ser Ile Lys Ile Gly Asp Thr Arg Leu Ser Thr Met
290 295 300

Glu Thr Gly Thr Gly Leu Ile Arg Ala Met Ile Glu Val Ile Asn His
305 310 315 320

Lys Cys Asp Leu Val Asn Tyr Ser Tyr Gly Glu Ala Thr His Trp Pro
325 330 335

Asn Ser Gly Arg Ile Cys Glu Val Ile Asn Glu Ala Val Trp Lys His
340 345 350

Asn Ile Ile Tyr Val Ser Ser Ala Gly Asn Asn Gly Pro Cys Leu Ser
355 360 365

Thr Val Gly Cys Pro Gly Gly Thr Thr Ser Ser Val Ile Gly Val Gly
370 375 380

Ala Tyr Val Ser Pro Asp Met Met Val Ala Glu Tyr Ser Leu Arg Glu
385 390 395 400

Lys Leu Pro Ala Asn Gln Tyr Thr Trp Ser Ser Arg Gly Pro Ser Ala
405 410 415

Asp Gly Ala Leu Gly Val Ser Ile Ser Ala Pro Gly Gly Ala Ile Ala
420 425 430

Ser Val Pro Asn Trp Thr Leu Arg Gly Thr Gln Leu Met Asn Gly Thr
435 440 445

Ser Met Ser Ser Pro Asn Ala Cys Gly Gly Ile Ala Leu Ile Leu Ser
450 455 460

Gly Leu Lys Ala Asn Asn Ile Asp Tyr Thr Val His Ser Val Arg Arg
465 470 475 480

Ala Leu Glu Asn Thr Ala Val Lys Ala Asp Asn Ile Glu Val Phe Ala
485 490 495

Gln Gly His Gly Ile Ile Gln Val Asp Lys Ala Tyr Asp Tyr Leu Val
500 505 510

Gln Asn Thr Ser Phe Ala Asn Lys Leu Gly Phe Thr Val Thr Val Gly
515 520 525

Asn Asn Arg Gly Ile Tyr Leu Arg Asp Pro Val Gln Val Ala Ala Pro
530 535 540

Ser Asp His Gly Val Gly Ile Glu Pro Val Phe Pro Glu Asn Thr Glu
545 550 555 560

Asn Ser Glu Lys Ile Ser Leu Gln Leu His Leu Ala Leu Thr Ser Asn
565 570 575

Ser Ser Trp Val Gln Cys Pro Ser His Leu Glu Leu Met Asn Gln Cys
580 585 590

Arg His Ile Asn Ile Arg Val Asp Pro Arg Gly Leu Arg Glu Gly Leu
595 600 605

His Tyr Thr Glu Val Cys Gly Tyr Asp Ile Ala Ser Pro Asn Ala Gly
610 615 620

Pro Leu Phe Arg Val Pro Ile Thr Ala Val Ile Ala Ala Lys Val Asn
625 630 635 640

Glu Ser Ser His Tyr Asp Leu Ala Phe Thr Asp Val His Phe Lys Pro
645 650 655

Gly Gln Ile Arg Arg His Phe Ile Glu Val Pro Glu Gly Ala Thr Trp
660 665 670

Ala Glu Val Thr Val Cys Ser Cys Ser Ser Glu Val Ser Ala Lys Phe
675 680 685

Val Leu His Ala Val Gln Leu Val Lys Gln Arg Ala Tyr Arg Ser His
690 695 700

Glu Phe Tyr Lys Phe Cys Ser Leu Pro Glu Lys Gly Thr Leu Thr Glu
705 710 715 720

Ala Phe Pro Val Leu Gly Gly Lys Ala Ile Glu Phe Cys Ile Ala Arg
725 730 735

Trp Trp Ala Ser Leu Ser Asp Val Asn Ile Asp Tyr Thr Ile Ser Phe
740 745 750

His Gly Ile Val Cys Thr Ala Pro Gln Leu Asn Ile His Ala Ser Glu
755 760 765

Gly Ile Asn Arg Phe Asp Val Gln Ser Ser Leu Lys Tyr Glu Asp Leu
770 775 780

Ala Pro Cys Ile Thr Leu Lys Asn Trp Val Gln Thr Leu Arg Pro Val

785 790 795 800

Ser Ala Lys Thr Lys Pro Leu Gly Ser Arg Asp Val Leu Pro Asn Asn
805 810 815

Arg Gln Leu Tyr Glu Met Val Leu Thr Tyr Asn Phe His Gln Pro Lys
820 825 830

Ser Gly Glu Val Thr Pro Ser Cys Pro Leu Leu Cys Glu Leu Leu Tyr
835 840 845

Glu Ser Glu Phe Asp Ser Gln Leu Trp Ile Ile Phe Asp Gln Asn Lys
850 855 860

Arg Gln Met Gly Ser Gly Asp Ala Tyr Pro His Gln Tyr Ser Leu Lys
865 870 875 880

Leu Glu Lys Gly Asp Tyr Thr Ile Arg Leu Gln Ile Arg His Glu Gln
885 890 895

Ile Ser Asp Leu Glu Arg Leu Lys Asp Leu Pro Phe Ile Val Ser His
900 905 910

Arg Leu Ser Asn Thr Leu Ser Leu Asp Ile His Glu Asn His Ser Phe
915 920 925

Ala Leu Leu Gly Lys Lys Lys Ser Ser Asn Leu Thr Leu Pro Pro Lys
930 935 940

Tyr Asn Gln Pro Phe Phe Val Thr Ser Leu Pro Asp Asp Lys Ile Pro
945 950 955 960

Lys Gly Ala Gly Pro Gly Cys Tyr Leu Ala Gly Ser Leu Thr Leu Ser
965 970 975

Lys Thr Glu Leu Gly Lys Lys Ala Asp Val Ile Pro Val His Tyr Tyr
980 985 990

Leu Ile Pro Pro Pro Thr Lys Thr Lys Asn Gly Ser Lys Asp Lys Glu
995 1000 1005

Lys Asp Ser Glu Lys Glu Lys Asp Leu Lys Glu Glu Phe Thr Glu
1010 1015 1020

Ala Leu Arg Asp Leu Lys Ile Gln Trp Met Thr Lys Leu Asp Ser
1025 1030 1035

Ser Asp Ile Tyr Asn Glu Leu Lys Glu Thr Tyr Pro Asn Tyr Leu
1040 1045 1050

Pro Leu Tyr Val Ala Arg Leu His Gln Leu Asp Ala Glu Lys Glu
1055 1060 1065

Arg Met Lys Arg Leu Asn Glu Ile Val Asp Ala Ala Asn Ala Val
1070 1075 1080

Ile Ser His Ile Asp Gln Thr Ala Leu Ala Val Tyr Ile Ala Met
1085 1090 1095

Lys Thr Asp Pro Arg Pro Asp Ala Ala Thr Ile Lys Asn Asp Met
1100 1105 1110

Asp Lys Gln Lys Ser Thr Leu Val Asp Ala Leu Cys Arg Lys Gly
1115 1120 1125

Cys Ala Leu Ala Asp His Leu Leu His Thr Gln Ala Gln Asp Gly
1130 1135 1140

Ala Ile Ser Thr Asp Ala Glu Gly Lys Glu Glu Glu Gly Glu Ser
1145 1150 1155

Pro Leu Asp Ser Leu Ala Glu Thr Phe Trp Glu Thr Thr Lys Trp
1160 1165 1170

Thr Asp Leu Phe Asp Asn Lys Val Leu Thr Phe Ala Tyr Lys His
1175 1180 1185

Ala Leu Val Asn Lys Met Tyr Gly Arg Gly Leu Lys Phe Ala Thr
1190 1195 1200

Lys Leu Val Glu Glu Lys Pro Thr Lys Glu Asn Trp Lys Asn Cys
1205 1210 1215

Ile Gln Leu Met Lys Leu Leu Gly Trp Thr His Cys Ala Ser Phe
1220 1225 1230

Thr Glu Asn Trp Leu Pro Ile Met Tyr Pro Pro Asp Tyr Cys Val
1235 1240 1245

Phe

<210> 138
<211> 433
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/Q99538
<309> 1997-11-01
<313> (1)..(433)

<400> 138

Met Val Trp Lys Val Ala Val Phe Leu Ser Val Ala Leu Gly Ile Gly
1 5 10 15

Ala Val Pro Ile Asp Asp Pro Glu Asp Gly Gly Lys His Trp Val Val

20 25 30

Ile Val Ala Gly Ser Asn Gly Trp Tyr Asn Tyr Arg His Gln Ala Asp
35 40 45

Ala Cys His Ala Tyr Gln Ile Ile His Arg Asn Gly Ile Pro Asp Glu
50 55 60

Gln Ile Val Val Met Met Tyr Asp Asp Ile Ala Tyr Ser Glu Asp Asn
65 70 75 80

Pro Thr Pro Gly Ile Val Ile Asn Arg Pro Asn Gly Thr Asp Val Tyr
85 90 95

Gln Gly Val Pro Lys Asp Tyr Thr Gly Glu Asp Val Thr Pro Gln Asn
100 105 110

Phe Leu Ala Val Leu Arg Gly Asp Ala Glu Ala Val Lys Gly Ile Gly
115 120 125

Ser Gly Lys Val Leu Lys Ser Gly Pro Gln Asp His Val Phe Ile Tyr
130 135 140

Phe Thr Asp His Gly Ser Thr Gly Ile Leu Val Phe Pro Asn Glu Asp
145 150 155 160

Leu His Val Lys Asp Leu Asn Glu Thr Ile His Tyr Met Tyr Lys His
165 170 175

Lys Met Tyr Arg Lys Met Val Phe Tyr Ile Glu Ala Cys Glu Ser Gly
180 185 190

Ser Met Met Asn His Leu Pro Asp Asn Ile Asn Val Tyr Ala Thr Thr
195 200 205

Ala Ala Asn Pro Arg Glu Ser Ser Tyr Ala Cys Tyr Tyr Asp Glu Lys
210 215 220

Arg Ser Thr Tyr Leu Gly Asp Trp Tyr Ser Val Asn Trp Met Glu Asp
225 230 235 240

Ser Asp Val Glu Asp Leu Thr Lys Glu Thr Leu His Lys Gln Tyr His
245 250 255

Leu Val Lys Ser His Thr Asn Thr Ser His Val Met Gln Tyr Gly Asn
260 265 270

Lys Thr Ile Ser Thr Met Lys Val Met Gln Phe Gln Gly Met Lys Arg
275 280 285

Lys Ala Ser Ser Pro Val Pro Leu Pro Pro Val Thr His Leu Asp Leu
290 295 300

Thr Pro Ser Pro Asp Val Pro Leu Thr Ile Met Lys Arg Lys Leu Met
305 310 315 320

Asn Thr Asn Asp Leu Glu Glu Ser Arg Gln Leu Thr Glu Glu Ile Gln
325 330 335

Arg His Leu Asp Ala Arg His Leu Ile Glu Lys Ser Val Arg Lys Ile
340 345 350

Val Ser Leu Leu Ala Ala Ser Glu Ala Glu Val Glu Gln Leu Leu Ser
355 360 365

Glu Arg Ala Pro Leu Thr Gly His Ser Cys Tyr Pro Glu Ala Leu Leu
370 375 380

His Phe Arg Thr His Cys Phe Asn Trp His Ser Pro Thr Tyr Glu Tyr
385 390 395 400

Ala Leu Arg His Leu Tyr Val Leu Val Asn Leu Cys Glu Lys Pro Tyr
405 410 415

Pro Leu His Arg Ile Lys Leu Ser Met Asp His Val Cys Leu Gly His
420 425 430

Tyr

<210> 139
<211> 342
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/P25105
<309> 1992-05-01
<313> (1)..(342)

<400> 139

Met Glu Pro His Asp Ser Ser His Met Asp Ser Glu Phe Arg Tyr Thr
1 5 10 15

Leu Phe Pro Ile Val Tyr Ser Ile Ile Phe Val Leu Gly Val Ile Ala
20 25 30

Asn Gly Tyr Val Leu Trp Val Phe Ala Arg Leu Tyr Pro Cys Lys Lys
35 40 45

Phe Asn Glu Ile Lys Ile Phe Met Val Asn Leu Thr Met Ala Asp Met
50 55 60

Leu Phe Leu Ile Thr Leu Pro Leu Trp Ile Val Tyr Tyr Gln Asn Gln
65 70 75 80

Gly Asn Trp Ile Leu Pro Lys Phe Leu Cys Asn Val Ala Gly Cys Leu

85 90 95

Phe Phe Ile Asn Thr Tyr Cys Ser Val Ala Phe Leu Gly Val Ile Thr
100 105 110

Tyr Asn Arg Phe Gln Ala Val Thr Arg Pro Ile Lys Thr Ala Gln Ala
115 120 125

Asn Thr Arg Lys Arg Gly Ile Ser Leu Ser Leu Val Ile Trp Val Ala
130 135 140

Ile Val Gly Ala Ala Ser Tyr Phe Leu Ile Leu Asp Ser Thr Asn Thr
145 150 155 160

Val Pro Asp Ser Ala Gly Ser Gly Asn Val Thr Arg Cys Phe Glu His
165 170 175

Tyr Glu Lys Gly Ser Val Pro Val Leu Ile Ile His Ile Phe Ile Val
180 185 190

Phe Ser Phe Phe Leu Val Phe Leu Ile Ile Leu Phe Cys Asn Leu Val
195 200 205

Ile Ile Arg Thr Leu Leu Met Gln Pro Val Gln Gln Gln Arg Asn Ala
210 215 220

Glu Val Lys Arg Arg Ala Leu Trp Met Val Cys Thr Val Leu Ala Val
225 230 235 240

Phe Ile Ile Cys Phe Val Pro His His Val Val Gln Leu Pro Trp Thr
245 250 255

Leu Ala Glu Leu Gly Phe Gln Asp Ser Lys Phe His Gln Ala Ile Asn
260 265 270

Asp Ala His Gln Val Thr Leu Cys Leu Leu Ser Thr Asn Cys Val Leu
275 280 285

Asp Pro Val Ile Tyr Cys Phe Leu Thr Lys Lys Phe Arg Lys His Leu
290 295 300

Thr Glu Lys Phe Tyr Ser Met Arg Ser Ser Arg Lys Cys Ser Arg Ala
305 310 315 320

Thr Thr Asp Thr Val Thr Glu Val Val Val Pro Phe Asn Gln Ile Pro
325 330 335

Gly Asn Ser Leu Lys Asn
340

<210> 140
<211> 359
<212> PRT

<213> Homo sapiens

<300>
<308> Swissprot/Q92187
<309> 1997-11-01
<313> (1)..(359)

<400> 140

Met Arg Ser Ile Arg Lys Arg Trp Thr Ile Cys Thr Ile Ser Leu Leu
1 5 10 15

Leu Ile Phe Tyr Lys Thr Lys Glu Ile Ala Arg Thr Glu Glu His Gln
20 25 30

Glu Thr Gln Leu Ile Gly Asp Gly Glu Leu Ser Leu Ser Arg Ser Leu
35 40 45

Val Asn Ser Ser Asp Lys Ile Ile Arg Lys Ala Gly Ser Ser Ile Phe
50 55 60

Gln His Asn Val Glu Gly Trp Lys Ile Asn Ser Ser Leu Val Leu Glu
65 70 75 80

Ile Arg Lys Asn Ile Leu Arg Phe Leu Asp Ala Glu Arg Asp Val Ser
85 90 95

Val Val Lys Ser Ser Phe Lys Pro Gly Asp Val Ile His Tyr Val Leu
100 105 110

Asp Arg Arg Arg Thr Leu Asn Ile Ser His Asp Leu His Ser Leu Leu
115 120 125

Pro Glu Val Ser Pro Met Lys Asn Arg Arg Phe Lys Thr Cys Ala Val
130 135 140

Val Gly Asn Ser Gly Ile Leu Leu Asp Ser Glu Cys Gly Lys Glu Ile
145 150 155 160

Asp Ser His Asn Phe Val Ile Arg Cys Asn Leu Ala Pro Val Val Glu
165 170 175

Phe Ala Ala Asp Val Gly Thr Lys Ser Asp Phe Ile Thr Met Asn Pro
180 185 190

Ser Val Val Gln Arg Ala Phe Gly Gly Phe Arg Asn Glu Ser Asp Arg
195 200 205

Glu Lys Phe Val His Arg Leu Ser Met Leu Asn Asp Ser Val Leu Trp
210 215 220

Ile Pro Ala Phe Met Val Lys Gly Gly Glu Lys His Val Glu Trp Val
225 230 235 240

Asn Ala Leu Ile Leu Lys Asn Lys Leu Lys Val Arg Thr Ala Tyr Pro

245 250 255

Ser Leu Arg Leu Ile His Ala Val Arg Gly Tyr Trp Leu Thr Asn Lys
260 265 270

Val Pro Ile Lys Arg Pro Ser Thr Gly Leu Leu Met Tyr Thr Leu Ala
275 280 285

Thr Arg Phe Cys Asp Glu Ile His Leu Tyr Gly Phe Trp Pro Phe Pro
290 295 300

Lys Asp Leu Asn Gly Lys Ala Val Lys Tyr His Tyr Tyr Asp Asp Leu
305 310 315 320

Lys Tyr Arg Tyr Phe Ser Asn Ala Ser Pro His Arg Met Pro Leu Glu
325 330 335

Phe Lys Thr Leu Asn Val Leu His Asn Arg Gly Ala Leu Lys Leu Thr
340 345 350

Thr Gly Lys Cys Val Lys Gln
355

<210> 141
<211> 218
<212> PRT
<213> Homo sapiens

<300>
<308> Swissprot/Q15907
<309> 1998-07-15
<313> (1)..(218)

<400> 141

Met Gly Thr Arg Asp Asp Glu Tyr Asp Tyr Leu Phe Lys Val Val Leu
1 5 10 15

Ile Gly Asp Ser Gly Val Gly Lys Ser Asn Leu Leu Ser Arg Phe Thr
20 25 30

Arg Asn Glu Phe Asn Leu Glu Ser Lys Ser Thr Ile Gly Val Glu Phe
35 40 45

Ala Thr Arg Ser Ile Gln Val Asp Gly Lys Thr Ile Lys Ala Gln Ile
50 55 60

Trp Asp Thr Ala Gly Gln Glu Arg Tyr Arg Ala Ile Thr Ser Ala Tyr
65 70 75 80

Tyr Arg Gly Ala Val Gly Ala Leu Leu Val Tyr Asp Ile Ala Lys His
85 90 95

Leu Thr Tyr Glu Asn Val Glu Arg Trp Leu Lys Glu Leu Arg Asp His
100 105 110

Ala Asp Ser Asn Ile Val Ile Met Leu Val Gly Asn Lys Ser Asp Leu
115 120 125

Arg His Leu Arg Ala Val Pro Thr Asp Glu Ala Arg Ala Phe Ala Glu
130 135 140

Lys Asn Asn Leu Ser Phe Ile Glu Thr Ser Ala Leu Asp Ser Thr Asn
145 150 155 160

Val Glu Glu Ala Phe Lys Asn Ile Leu Thr Glu Ile Tyr Arg Ile Val
165 170 175

Ser Gln Lys Gln Ile Ala Asp Arg Ala Ala His Asp Glu Ser Pro Gly
180 185 190

Asn Asn Val Val Asp Ile Ser Val Pro Pro Thr Thr Asp Gly Gln Lys
195 200 205

Pro Asn Lys Leu Gln Cys Cys Gln Asn Leu
210 215