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(54) Title: GLYCOPHORIN BINDING PROTEIN (GBP130) FUSION COMPOSITIONS

(57) Abstract

Hybrid or fusion peptides formed by the fusion of two or more peptide components, where one component is derived from or is all or part of a malaria parasite red blood cell binding peptide, and the other peptide being a receptor for or capable of binding to a cytokine or other mediator of inflammation or immunity. The fusion peptides find a use in the treatment of septic shock, AIDS, and inflammatory conditions. The fusion peptides also serve as potential testing agents for use in inflammatory conditions and septic shock.

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GLYCOPHORIN BINDING PROTEIN (GBP130) FUSION COMPOSITIONS

The Field of the Invention:

The field of the present disclosure relates to hybrid therapeutic peptides having the property of lowering the levels of free Tumour Necrosis Factor α and β in the circulation and other harmful cytokines, thus, modifying the pathological damage caused by Tumour Necrosis Factor, and finding a use in the treatment of diseases especially but not only septic shock; bacterial meningitis' cerebral malaria, HIV, SVHD graft versus host disease and pulmonary fibrosis. The present disclosure is an extension the teachings of PCT 93/00505 Anti viral fusion peptides whose teachings are incorporated herein fully by reference, which PCT was published as WO93/18160 after the filing date of the priority document GB93 19350.7.

Background Art

Tumour necrosis factor herein after referred to as TNF is an extremely potent peptide produced in 2 forms, TNFα produced by activated macrophages and TNFβ produced by activated lymphocytes. Both α and β varieties have similar spectra of biological effects, however, TNFα is by far the more powerful of the two. The effects of TNF are mediated by binding to specific receptors found on the surface of most cells. As a naturally produced agent TNF has important biological roles to fulfil. Physiologically TNF is classified as a cytokine. It's effects on the immune system are to increase neutrophylia and activate macrophages, and increase the production of T cells in the thymus.

The term TNF tumour necroses factor was attributed to this peptide by Old arising from the observation that TNF can reduce necrosis and regression of experimental sarcomas in mice.

It is likely that TNF serves to eliminate small tumours from the host at an early stage in their development. Clinically cloned TNF has been used to treat human tumours especially melanoma. It has also been shown that TNF is more effective against tumours when used in combination with other cytokines IL2 or γIFN gamma interferon. Talmadge J et al Am.

J of Pathology, Vol 128, No 3, Sept 1987; 410-425.

After administration of TNF microembili and haemorrhagic necrosis are produced in the substrate of the tumour leading to it's regression. However, this endogenously produced potent peptide is not always helpful to the host and may be harmful.

Following intestinal surgery a number of patients succumb to endotoxic shock, a syndrome of refractory shock and small vessel changes. Shown experimentally to follow the administration of LPS, bacterial lipopolysaccharide constituent of the cell wall of gram negative bacteriae. Morrison D C et al, Am. J. Pathology, 93: 527-617: 1978. The syndrome of endotoxic shock shares many features in common with the effects seen after administration of TNF. It is now believed that LPS acts indirectly and causes shock via the production of TNF. Indeed, the administration of LPS to animals has been shown to cause a rise in TNF levels 200 minutes later. Mathison J et al, J. Clin. Invest., Vol 81: June 1988: 1925-1937.

The process of intestinal surgery or abdominal trauma leads to the release of gram negative organisms into the circulation. Gram negative cell wall lipopolysaccaride is a very potent agent capable of inducing a shock syndrome in low doses. Humans are exquisitely sensitive to LPS. LPS has 3 components: Lipid A - R core - polysaccharide. The polysaccharide part varies with the species and strain of the infecting organism. The active moiety of endotoxin is now believed to be Lipid A.

The clinical picture of 'septic shock' or 'endotoxic shock' is one of hopelessness. Some 100,000 North Americans die annually from this pathological process which occurs with an incidence of 200,000 to 400,000. Despite active management it is difficult to rescue a situation in which the clinical picture is one of descent from shock to multiple organ failure to death.

Not withstanding fluid support and pressor therapy with dopamine, cardiac output falls from direct cardiac suppression and low venous return. All fluid support provided redistributes into dilated capillary spaces where it sludges. The provision of such intensive treatment in a Critical Care Unit is expensive. A need exists for agents capable of preventing endotoxic shock, for treating septic shock, and also for diagnosing this entity so that treatment may be better planned. One is directed to the reviews of C J Schmeichel et al, Biotechnology, Vol 10, March 1992, 264-267 and to J Pavrillo et al, Annals of Internal Medicine, Vol 113, No 3, (1990) p227-242.

The rise of TNF levels seen in mice after injection of bacterial lipopolysaccharide LPS have also been seen in humans.

Similar experiments in healthy humans demonstrated a brief pulse of TNF production 90-180 minutes after the administration of endotoxin. Mitchie H R et al, N. Engl. J. Med., 1988: 318: 1481-6.

The observations of Mitchie are important in explaining the inconsistency of TNF assays in septic shock patients. Pulsed production of this cytokine ties in with the notion that TNF initiates the vascular responses in septic shock and explains why it is not always detected in serological assays. However, elevated TNF levels have been convincingly associated with mortality in the critically ill. J Bebets et al, Crit. Care Med., 1989, 17: 489. More convincingly Remick et al demonstrated and quantified an increase in TNF mRNA in mice after LPS administration. Remick D G et al, Am. J. Pathology, 1990; 136: 49-60.

Patients with septic shock exhibiting the Adult Respiratory Distress Syndrome, ARDS, have demonstrated higher plasma TNF levels - which in turn are associated with increased mortality. J D Marks et al, Am. Rev. Respir. Dis., 1990; 141: 94-97.

Evidence mounts for a role played by TNF in other pathological entities, such as rheumatoid arthritis; the rejection of transplants and GVHD graft venous host disease, Kunkel S L et al, 1991, Biotherapy 3, 135-141. In the case of malaria higher TNF levels are associated with cerebral malaria, see Grau G E et al (1987), Science 237, 1210-1212, and Grau G E, Eur. Cytokine Network 1, 203-210.

Further research suggests that TNF may produce a significant part of the pathological spectrum of AIDS.

The severe and rapid wasting of AIDS patients towards the end of their illness but not seen during years of asymptomatic viral carriage, led workers to suspect that some agent other than the virus itself may be responsible for this process. TNF already suspected as the cause of weight loss and cachexia in cancer and previously named "cachectin" was a prime suspect. Lahdevirta et al were able to demonstrate substantially raised serum TNF levels in AIDS patients several fold higher than in asymptomatic subjects. Lahdeverta J et al, Am. J. of Med., Vol 85, (1988) 289-291. Lahdeverta also pointed out that the raised TNF levels may be the result of persistent infection load seen in these patients harbouring at any one time chronic fungal, viral, parasitic and bacterial infestations. Indeed, other workers suggested that chronic sepsis raises TNF which in turn raises HIV viral titres thus creating a vicious circle. Osborn L et al proved this point, see Proc. Natl. Acad. Sci. USA, Vol 86, pp 2336-2340 (1989), by demonstrating that TNFα and also IL1 interleukin 1 increase HIV production in infected cells and that this effect is produced via NF-κB Nuclear Factor κappa B which intracellular messenger stimulates HIV production and also κappa immuno globulin light chain productions.

F Staal et al were able to demonstrate that intracellular thiols, more particularly GSH (gamma-glulamylcysteinglycine the most abundant), suppress NF-κB production and mitigate the effects of TNFα levels are elevated. Staal F, Proc. Nalt. Acad. Sci. Usa, Vol

87, pp 9943-9947, Dec 1990.

By blocking TNFα in vitro using anti-TNFα antibodies, the HIV production induced by TNFα can be reduced. Moreover, observers now suspect an amplification mechanism whereby TNFα leads to further production of it's own receptor and also production of IL6 (interleukin 6) which interleukin may prolong the process and continue to stimulate viral production when TNF is no longer available. Poli G et al, Proc. Nalt. Acad. Sci. USA, Vol 87, pp 782-785, Jan 90.

The agent methylxanthine pentoxyfylline is known to suppress TNFα levels in vivo. In vitro this agent has been demonstrated to reduce the replication of HIV in cultured cells. It's use in AIDS treatment in conjunction with the agent AZT was suggested by F Fazely et al, Blood, Vol 77, No 8, April 15 1991: pp 1653-1656.

The benefit of TNFα reduction in AIDS patients cannot be over stressed. TNFα is known to suppress haematopoiesis, of itself, and via IL2 interleukin 2, levels of which are raised by TNFα. Moreover TNFβ is a powerful suppressor of red cell production and this too is elevated in AIDS, as reviewed by J Doweiko in AIDS 1993, 7; 753-757. Anaemia is present in 35 to 75% of AIDS patients. It is difficult to treat and forces clinicians to lessen the dose of AZT or abort treatment with anti-viral agents.

Pursuant to the goal of inhibiting TNF both α and β forms researchers have focused on it's receptor interaction and mechanism of action.

TNFα and β binds with high affinity to 2 different receptors a 55 kilo-Dalton receptor and a 75 kilo-Dalton receptor. Each receptor produces different pharmacological affects thereby broadening the range of activity of TNF.

Significantly there are no TNF receptors on red cells. Indeed, the red cell is an exceptional cell in this respect. The teachings of the present disclosure enable TNF to bind harmlessly to red cells, thereby preventing it's deleterious effects.

The 55 kilo-Dalton TNF receptor has been cloned and sequenced and one is directed to Loetscher H, Pan Y-C E, et al, Cell 61, (1990) 351-359 and also directed to Schall T J et al, Cell 61, (1990) 361-370, incorporated fully herein by reference.

The 75 kilo-Dalton receptor has been cloned and sequenced and one is directed to Smith C A et al (1990) Science 248, 1019-1023 and to Dembic Z et al, 1990, Cytokine 2, 231-237, incorporated fully herein by reference. TNF binding proteins found in the blood stream are now believed to be free TNF receptors shed from cell membranes. Moreover, such natural 'soluble' receptors are believed to control or modify some of the ill effects produced by TNF as suggested by Dan Aderka et al, J. Exp. Med., Vol 175, Feb 92, pp 323-329, and by Endelmann H et al, J. Biol. Chemistry (1989), Vol 264, No 20, July 15, pp 11974-11960. That urinary proteins, TNF receptors, may be biologically useful was still further confirmed by Engelmann H et al, J. Biological Chemistry, Jan 25, pp 1531-1536 (1990) incorporated herein fully by reference.

Biological characterization of TNF-R (TNF-R55 and TNF-R75) shows the receptors to be homogenous and belong to a wider family of similar receptors including NGF-R nerve growth factor receptor, CD40 and CD27, see Peter Vanderbee et al, J. Exp. Med., Vol 176, Oct 1992, 1015-1024.

To lessen the effects of TNF and develop anti-septic shock agents, some workers have tried to administer TNF-R(s) soluble TNF receptors. Studies evaluating monomeric TNF-R both glycosylated and unglycosylated arising from expression in CHO cells and E.Coli respectively, showed monomeric forms of the receptor either glycosylated or unglycosylated

to have very low plasma half lives, 3.5 min and 11.6 min for T½α. Rapid renal clearance of the agent appeared to be a major obstacle for monomeric TNF-R as a therapeutic agent.

However, a TNF-R immunoadhesion a chimeric molecule developed by Gennentech demonstrated an improved ½ life with T½β at 20 mins clearance being mainly liver mediated.

Moreover by replacing the Fab of an antibody with TNF-R segments the affinity of the immunoadhesion agent for TNF is improved. It's chemical efficacy likely to be greater by virtue of the fact that TNF a trimer is normally twice bound to it's receptor therefore preventing dimer adhesion to cell surface receptors which can still occur in the case of singly inhibited TNF molecules.

One is directed to Avi Ashkenazi et al, Proc. Natl. Acad. Sci. USA, Vol 88, pp 10535-10539, Dec 1991, for an account of a TNF receptor immunoadhesion incorporated herein fully by reference. This particular construct used a human IGG Fc peptide fragment fused to two TGF-R fragments and was expressed in kidney cells.

A similar hybrid peptide was disclosed by K Peffel et al, J. Exp. Med., Vol 174, Dec 1991, pp 1483-1489 incorporated fully herein by reference. In this example a murine FC + hinge IGG fragment was fused to TNF-R fragments and expressed in CHO cells.

The present invention teaches molecules or molecular machines having an affinity for TNF and human red cells. Thus enabling cells to mop up TNF and causing TNF to adhere to the red cell surface. The disclosure emphasises that TNF is not associated with red cells as a natural phenomenon. The present disclosure teaches an unnatural union between red cells and TNF, by means of novel pharmaceutical protein agents.

A long half life is envisaged for the agents as the red cell surface protects the novel agents

from excretion by the kidney. Moreover, the red cell provides steric hinderance preventing a TNF so bound to itself from binding to a TNF-R in another cell.

The present invention derives from PCT 93/00505 and teaches a cytokine receptor, fused to a malaria parasite peptide having affinity for a red cell, or analogue there of, and this provides a molecular machine, a hybrid fusion peptide capable of binding a cytokine (TNFα or β or interferons or interleukins) to the red cell surface thereby inactivating it. The longer half life of such an agent allows greater clinical flexibility in drug administration and allows the agent to remain useful for longer periods.

The present disclosure provides the advantage of a macromolecule capable of dual function TNF binding and red cell adhesion without any separate laboratory procedures on red cells being required. The present disclosure is not confined to TNF or its receptors but teaches the fusion of other cytokine receptors to malaria parasite peptides to produce macromolecules capable of reducing levels of harmful cytokines.

The novel macromelecular agents of the present disclosure bind directly onto red cells in one step, and provide a novel use for modified peptides of the malaria parasite organism.

Of all parasites malaria must be the most damaging and successful. Many millions are infected with 1-2 million deaths per annum. The malaria parasite has evolved from earliest times and attacks not only humans but most varieties of animal. This serious parasite infests red blood cells. Various malaria species infect humans, plasmodium faciparium, and plasmodium vivax being the most important. The life cycle is complex with a short life cycle in the salivary gland of mosquitoes and following inoculation of a human the parasite object is ultimately the red cell. Merozotes bind to the red cell membrane, enter the cytoplasm and multiply.

The course of malaria is a variable one and may be characterised by a short acute illness which can bring death in a matter of hours; or a longer more chronic illness associated with debility and anaemia.

Other forms of malaria such as the plasmodium Knowlesi are well researched animal parasites which infects the Rhesus monkey. The preferred location for the malaria parasite is within the red cells of the infected host and for much of its life span it lives intracellularly protected from the host immune system.

Merozoites are thought to spend but a brief period free in the circulation. Accordingly, considerable research efforts have been expended to discover the means whereby the merozoite forms of the parasite gains attachment and gains entry into the human red cell.

Margaret E Perkins Journal Experimental Medicine 160 September 1984, 788-798 is responsible for formulation of a relationship between the plasmodium falsiparum binding molecule and glycophorin A and B two silao glycoproteins found on the surface of red cells.

More laterally, Holt and Perkins et al American Journal Tropical Medicine Hygiene 1989, p 245-251 disclose species and stain variations of plasmodium falciparum wherein some strains of the organism exhibit preference for sialo glycoproteins glycophorins A, B and C and also demonstrated was the varying requirements for the N-acetyl-neuramic acid residues (NeuNac).

The glycophorin A molecule is a highly glycosylated peptide. Pasvol has suggested that glycophorin binding peptide binds to the region of glycophorin close to the lipid bi-layer.

Pasvol G et al "Inhibition of Malaria Parasite Invasion of Monoclonical antibodies against glycophorin A correlates with a reduction in red cell membrane deformity." Blood, 74, No.

5, October 1985, 1836-1843.

Debate continues within the literature as to the requirement for sialic acid on the glycophorin molecule to affect invasion by merozoites.

Some strains of malaria are totally dependent on normally sialated glycophorin A to gain entry into the red cell, whereas other strains seem to be independent of sialic acid. See Mitchell et all 66, No 5, May 1986, 1519-1521. Perkins and Roco in Journal of Immunology 88, Vol 141, 3190-3196, No 9, again stress the importance of sialic acid where normally sialated glycophorin is necessary to achieve successful binding of merozoite peptides in particular pf200.

For several years a peptide called the glycophorin binding protein was believed to be the primary peptide responsible for binding merozoites to erythrocytes. A gene coding for GBP was isolated by M Ravetch J and Kochlan J and disclosed in Science Vol 227, pp 1953-1596, 29 March 1985 and incorporated herein fully by reference.

GBP 130 is characterised by a tandem repeated sequence coding for a 50 amino acid repeating sequence believed to be the site of erythrocyte binding, "A tandem repeated sequence determines the binding domain for an erythrocyte receptor binding protein of plasmodian falciparum". Cell, Vol 44, 689-696, March 14, 1986, Kochan J, Perkins M and Ravetch J. See Figure 2, p691, which also discloses the full sequence and genetic code of the GBP 130 molecule.

Other workers have challenged the supremacy of the GBP 130 as the primary binding molecule of the malaria merozoite. Orlandi P, Kim Lee Sim et al Molecular and Biochemical Parasitology, 40 (1990) 285-294 "Characterisation of the 175 kilodalton erythrocyte binding antigen of plasmodium falciparum" suggested a different peptide, the EBA 175 molecule,

as being responsible for merozoite binding or at least playing some role therein.

The EBA 175 molecule like the GBP 130 molecule has an affinity for the red blood cell surface and binds thereto.

It is known that the EBA 175 molecule has a prediction for olygosaccharides which are found on the surface of the red cell molecule. However, a problem arises in that the EBA 175 molecule does not bind effectively with the malaria merozoite parasite. Therefore, it is thought that the EBA 175 serves a function as a bridge. This disclosure proposes an alternative mechanism in that the EBA 175 molecule is responsible for bringing the merozoite closer to the RBC by binding with the base of the glycophorin A peptide; thus bringing the lipid bi layer of the malaria parasite into approximation with the lipid bilayer of the red cell membrane and thereby allowing the incorporation of the parasite into the erythrocyte itself. This disclosure suggests the merozoite is winched into the RBC cytoplasm.

The genetic sequence and the peptide sequence of EBA 175 was disclosed in J. Cell Biology 11, 1990, Kim Lee Sim, Orlandi P et al "Primary structure of the 175 K plasmodium falciparum erythrocyte binding antigen and identification of a peptide which elicits antibodies that inhibit malaria merozoite invasion" See Cell Biology Vol 111 (1990) p1877-1884, Figure 2 of p 1880 for the sequence of amino acids and DNA sequence.

To further complicate the picture Dagmar Nolte et al described two close relatives of the glycophorin binding peptide 130 molecule which they call GBPH or glycophorin binding peptide homologues. This molecule like the GBP molecule, displays several tandem repeat sequences and a high affinity for the erythrocyte surface membrane surface peptides. It has been proposed by Nolte and co-workers that it is the GBPH molecule and not the GBP molecule is released as an immunogenic decoy to distract the immune system from the real

binding peptide the GBPH.

The nucleotide sequence of one form of the peptide GPBH is disclosed by Dagmar Nolte et al in the Journal of Molecular and Biochemical Parasitology, 49, (1991), p 253-264. See Figure 2 of p 257 incorporated herein fully by reference. The peptide sequence is also disclosed.

See also Figure 3 of p 258 the same journal and paper which lists a comparison between GBP 130 and GBPH. Binding and entry of merozoites into RBC's involves several peptides of several alternatives as fail safes for the organism.

The picture is further complicated by other research notably by Peterson Gregory, who proposes PMMSA (Pre major merozoite surface antigen) as being responsible for erythrocyte binding either in this state or following fragmentation into smaller fragments. The genetic sequence and the peptide sequence of the PMMSA molecule is given in the Journal of Molecular and Biochemical Parasitology, 27 (1988), 291-302. See Figure 3 of p294 and 295. Peterson G et al.

Erythrocyte binding using different peptides and surface molecules is exhibited by other species of the malaria parasite in particular the plasmodium vivax organism. This organism can infect only persons expressing the Duffy marker. The Duffy antigen is a red cell surface marker and is one of many blood group markers and is carried by a percentage of the population.

Persons not expressing Duffy antigens are therefore immune from infection by plasmodium vivax. The plasmodium vivax expresses a Duffy binding receptor molecule P. vivax Duffy receptor was cloned and sequenced by Xiangdang Fang and disclosed in Molecular and Biochemical Parasitology, 44(1991) p125-132. See especially Figure 1 of p127 for the

genetic sequence and amino acid sequence.

Similar to plasmodium vivax is plasmodium Knowlesi which also uses the Duffy antigen. This organism parasitises Rhesus monkeys. Also in the same Journal, same figure, same page, is listed the genetic sequence of plasmodium Knowlesi Duffy receptor molecule which may find a use in the agents of the present disclosure.

When developing therapeutic agents directed against the malaria parasite itself, then it is clearly important to identify the precise molecule responsible for merozoite binding in the clinical context. However, where malaria peptides are to be employed as erythrocyte binding agents more generally, then it is not important to identify the precise peptide the malaria organism uses to effect invasion. Any malaria peptide capable of binding to an erythrocyte surface membrane may have a therapeutic use for other purposes such as the agents of the present disclosure and also segments of such a peptide.

Brief Summary

The present disclosure provides novel hybrid or fusion peptides having a minimum of 2 different peptide components each possessing different functionality. One peptide component will be derived from the malaria parasite or derivative or fragment or variation thereof and possess the ability to bind to a red cell surface. The other component of the fusion peptide will be a cytokine receptor or derivative or fragment thereof especially the TNF-R75 and 55 (Tumour Necrosis Factor Receptor 75 kilo-Dalton and 55 kilo-Dalton, the IL1-R (interleukin-1-receptor); the IL6-R (the interleukin 6-receptor); the IL8-R (the interleukin 8 receptor); IL2-R; IL4-R; IL3-R; IL5-R; IL7-R or the LIFR (leukaemia inhibitory factor)-R receptor or the γIFN-R gamma interferon receptor. It is envisaged that the fusion peptide will bind the target peptide to the red cell surface and mop up the free circulating target peptide (cytokine) thereby reducing it's deleterious effects.

In the clinical context the novel hybrid fusion peptides of the present disclosure will find therapeutic use in

(a) the prophylaxis and treatment of endotoxic shock (septic shock),

(b) the suppression of hyper-inflammatory states,

(c) as agents for the prevention and treatment of graft versus host disease, autoimmune disease, cerebralmalaria, transplant rejection, pulmonary fibrosis, ulcerative and degenerative diseases,

(d) as agents to treat or delay the onset of AIDS in HIV positive persons or as agents to minimize viral damage in HIV and other viral infections,

(e) as agents to treat cachexia and wasting caused by cancer.

DETAILED DISCLOSURE

The disclosure is best illustrated by reference to the exemplary embodiments described herein after which are non limiting.

EXEMPLARY EMBODIMENT GROUP 1

In this embodiment all or part of the peptide sequence comprising amino acid residues 201-774 of the GBP 130 (glycophorin binding peptide molecule 130) all or part or substitutional or deletional variations thereof or fragments thereof especially tandem repeats or modified fragments thereof are modified to form hybrid fusion peptide drugs as shown herein below.

The amino acid sequence of the glycophorin binding peptide 130 molecule was disclosed by Jarema Kochan et al in Cell Vol. 44: 689-696, March 14; 1986. See Figure 2, p691 and is incorporated fully herein by reference.

The general formula for the agents is as follows

NH_2—Ctk-R————————P————————COOH

or

NH_2—P—CtkR—COOH

a hybrid fusion peptide where Ctk-R represents a cytokine either TNF-R, IL1-R, IL2-R, IL4-R, IL8-R, IL6-R, IL3-R, IL5-R, IL7-R, LIF-R or γIFN-R or fragment thereof and where P represents the GBP130 molecule or fragment thereof, or other malaria derived red cell binding peptide.

Exemplary Embodiment 1(a). 1 of example group 1.

Exemplary embodiment 1(a). 1 is directed to a hybrid protein or fusion peptide capable of binding free TNFα or β to the red cell surface and comprising the fusion of two peptide components - a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally to the C terminal end or C terminally to the N terminal end by peptide bonds preferably, or by linkers to,

- a peptide component derived from all or part of the 55κd Tumour Necrosis Factor Receptor the sequence of which was disclosed by H Loetscher et al in Cell, Vol. 61, 351-359, April 20 1990, see p353, see Figure 2A for the amino acid sequence and see Figure B for the restriction map, disclosed and incorporated herein fully by reference.

Exemplary embodiment 1(a). 2 of example group 1

Exemplary embodiment 1 (a). 2 is directed to a hybrid protein or fusion peptide capable of binding free TNFα or β to the red cell surface and comprising the fusion of two peptide components

- a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally to the C terminal end or C terminally to the N terminal end by peptide bonds preferably or by linkers to,

- a peptide component derived from all or parts of a TNF receptor similar to example 1 (a).

1 but using the amino acid sequence disclosed by T J Schall et al in Cell, Vol 61, p 361-370, April 20 1990, see page 363, Figure 1A for the amino acid sequence disclosed and incorporated herein fully by reference.

Exemplary Embodiment 1(a). 3 of example group 1

Exemplary embodiment 1(a). 3 is directed to a hybrid protein or fusion peptide capable of binding free TNFα or β to the red cell surface and comprising the fusion of two peptide components

- a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally to the C terminal end or C terminally to the N terminal end by peptide bonds preferably or by linkers to,

- a peptide component derived from all or part of the Tumour Necrosis Factor Binding proteins I or II as isolated from human urine and sequenced by Yaran Norphor et al the sequence of which peptides are disclosed in Y Norphor et al EMBO Journal, Vol 9, No 10, pp 3269-3278 (1990) see page 3271, Figure 1D and p 3272, Table 1 which sequences are disclosed and incorporated herein fully by reference.

Exemplary Embodiment 1(b). 1 of group 1

Exemplary embodiment 1(b). 1 is directed to a hybrid protein or fusion peptide capable of binding free γIFN gamma interferon to the red cell surface and comprising the fusion of two peptide components

- a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally to the C terminal end or C terminally to the N terminal end by peptide bonds preferably or by linkers to,

- a peptide component derived from all or part of the γIFN receptor molecule the amino acid sequence of which was deduced and cloned by Auguet M et al and disclosed in Cell 55(1988), 273-280 and incorporated herein fully by reference.

Exemplary Embodiment 1(b). 2 of group 1

Exemplary embodiment 1(b). 2 is directed to a hybrid protein or fusion peptide capable of binding free γIFN gamma interferon to the red cell surface and comprising the fusion of two peptide components

- a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally to the C terminal end or C terminally to the N terminal end by peptide bonds preferably or by linkers to,

- a peptide component derived from a soluble γIFN receptor as cloned by GENTZ et al and disclosed in GENTZ R et al 1992, Eur. J. Biochem., and disclosed and incorporated herein fully by reference and also as disclosed in p140 of International Review of Experimental Pathology, Vol 34B, see Ozmen, Fountanalkis, Gentz and Garrotta, p137-1977.

The agents of type example 1(b). 1 and 1(b). 2 may be especially useful in the treatment of G.V.H.D. graft versus host disease.

Exemplary Embodiment 1(c). 1 of group 1

Exemplary embodiment 1(c). 1 is directed to a hybrid protein or fusion peptide capable of binding free IL2 interleukin 2 to the red cell surface and comprising the fusion of two peptide components

- a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally

to the C terminal end or C terminally to the N terminal end by peptide bonds preferably or by linkers to,

- a peptide component derived from the high affinity IL2 receptor ie. IL2β as characterized by Bich-Thuy et al 1987, J. Immunology, 139(5), 1550-1556; Dukovich M et al, Nature (London) 327, 518-522; Hatakeyama M et al, 1989, Science 244; 551-556; Robb R J et al, Proc. Natl. Acad. Sci. USA, 84(7) 2002-2006; Saragon H et al, 1990, Proc. Natl. Acad. Sci. USA, 87 (1), 11-15; T Sudo M et al, Proc. Natl. Acad. Schi. USA, 84 (12), 9215-9218 disclosed and incorporated herein fully by reference.

The agents of exemplary embodiment 1(c). 1 may be especially useful to reduce the expression of HIV virus in persons with AIDS.

Exemplary Embodiment 1(d). 1 of examples group 1

Exemplary embodiment 1(d). 1 is directed to a hybrid protein or fusion peptide capable of binding free Il-6 interleukin 6 to the red cell surface and comprising the fusion of two peptide components

- a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally to the C terminal end or C terminally to the N terminal end by peptide bonds preferably or by linkers to,

- a peptide component comprising or derived from either the high or low affinity IL6 receptor as cloned by Yamasaki K et al, Science (1988), 241, p825-828 and described also by Taga T et al, 1989, Cell 58 (3), 573-581; and disclosed and incorporated herein fully by reference.

Exemplary Embodiment 1(e). 1 of group 1

Exemplary embodiment 1(e). 1 is directed to a hybrid protein or fusion peptide capable of binding free IL1 interleukin one to the red cell surface and comprising the fusion of two

peptide components

- a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally to the C terminal end or C terminally to the N terminal end by peptide bonds preferably or by linkers to,

- a peptide component comprising all or part or derived from the IL-1 R interleukin one receptor as disclosed by Sims J E et al (1988), Science 241, 585-589 and disclosed and incorporated herein fully by reference. One is also directed to C J McMahon et al to EMBO Journal Vol 10; No 10' 1991; pp 2821-2832 for details and sequence of a type II IL-1 receptor disclosed and incorporated fully by reference.

Exemplary embodiment 1(f). 1 of group 1

Exemplary embodiment 1(f). 1 is directed to a hybrid protein or fusion peptide capable of binding free LIF leukaemia inhibitory factor to the red cell surface and comprising the fusion of two peptide components

- a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally to the C terminal end or C terminally to the N terminal end by peptide bonds preferably or by linkers to,

- a peptide component derived from all or part of the leukaemia inhibitory factor receptor as disclosed by Gearing D P et al EMBO. J., 10: 2839-2848 and also disclosed in Geraing D P et al, Polyfunctional cytokines 1L6 and LIF, Wiley Chichester (Ciba Foundation Symposium 167) p245 to p259, see especially 247, 248 and 249, Figure 1, where the amino acid sequence of LIF and IL6 are listed and compared, and are disclosed and incorporated herein fully by reference.

Exemplary embodiment 1(g). 1 of group 1

Exemplary embodiment 1(g). 1 is directed to a hybrid protein or fusion peptide capable of binding free Interleukin 3 to the red cell surface and comprising the fusion of two peptide components

- a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally to the C terminal end or C terminally to the N terminal end by peptide bonds preferably or by linkers to,

- a peptide component derived from all or part of the Interleukin 3 receptor as disclosed by Toshio Kitamura et al in Cell, Vol 66, 1165-1174, Sept 20, 1991, see Figure 1, p1167 incorporated fully herein by reference.

Exemplary embodiment 1(h). 1 of group 1

Exemplary embodiment 1(h). 1 is directed to a hybrid protein or fusion peptide capable of binding free Interleukin 5 to the red cell surface and comprising the fusion of two peptide components

- a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally to the C terminal end or C terminally to the N terminal end by peptide bonds preferably or by linkers to,

- a peptide component derived from all or part of the Interleukin 5 as disclosed by J Tavernier et al, Cell, Vol 66, Sept 20, pp1175-1184, see Fig 1, disclosed and incorporated herein fully by reference.

Exemplary embodiment 1(i). 1 of group 1

Exemplary embodiment 1(i). 1 is directed to a hybrid protein or fusion peptide capable of

binding free Interleukin 8 to the red cell surface and comprising the fusion of two peptide components

- a peptide component derived from all or part of the GBP 130 molecule (glycophorin binding peptide molecule as disclosed by Jarema Kochan et al in Cell, Vol 44, 689-696, Mar 14 1986, see Figure 2, p 691 and incorporated fully herein by reference fused N terminally to the C terminal end or C terminally to the N terminal end by peptide bonds preferably or by linkers to,

- a peptide component derived from all or part of the Interleukin 8 receptors type 1 and 2 as disclosed by R Gaylell et al, J. Biological Chemistry, Vol 268, No 10, April 5, pp7283-7289; 1993, disclosed and incorporated herein fully by reference.

Exemplary Embodiment 1(j). 1 of group 1

Exemplary Embodiment 1(j) is directed to a fusion peptide of a malaria parasite red blood cell binding peptide such as GBP130 fused to the IL4R interleukin 4 receptor all or part. The IL4 receptor was cloned and disclosed by R L Idzerda et al, J, Exp. Med., Vol 171, Mar. 1990, pp861-873, incorporated fully herein by reference.

EXAMPLE OF AGENTS GROUP 2

The agents of group 2 use the Glycophorin binding peptide homologue molecule for red cell binding.

The glycophorin binding peptide homologue molecule was cloned and disclosed by Dagmar Nolte et al Molecular and Biochem Parasitology, 49(1991) page 253-264. See especially Figure 2, p257 and is incorporated fully herein by reference.

Example 2(a); 2(b); 2(c); 2(d); 2(e); 2(f); 2(g); 2(h); 2(i);2(j)

The exemplified agents of group 2 are identical in every respect to group 1 except that in place of GBP 130 or segments thereof the malaria RBC binding component is provided by

GBPH glycophorin binding peptide homologue as referenced herein above especially peptide fragments comprising amino acid residues:

i residue 70 to 427 inclusive

ii residue 109 to 427 inclusive

iii residue 230 to 268 or any other tandem repeat or polymer thereof

of any fragment or species variation or substitution or deletional or inclusional variant thereof.

EXAMPLE OF AGENTS GROUP 3

The agents of group 3 use the EBA 175 erythrocyte binding antigen 175 for red cell binding.

The EBA 175 erythrocyte binding antigen 175 was cloned and disclosed by B Kim Lee Sim et al Journal Cell Biology, Vol. III, 1990, p1877-1884. See especially Figure 2, p1880 and is incorporated fully herein by reference.

Example 3(a); 3(b); 3(c); 3(d); 3(e); 3(f); 3(g); 3(h); 3(i), 3(j)

The exemplified agents of group 3 are identical in every respect to group 1 except that in place of GBP 130 or segments thereof the malaria RBC binding component is provided EBA 175 erythrocyte binding antigen 175 especially peptide fragments comprising amino acid residues

i residue 20 to 1435 inclusive

of any other fragment or species variation or substitution or deletional or inclusional variant thereof.

EXAMPLE OF AGENTS GROUP 4

The agents of group 4 use the Plasmodium Vivax Duffy Receptor for red cell binding.

The Plasmodium Vivax Duffy receptor was cloned and disclosed by Xiangdong Fong et al

Molecular Biochemical Parasitology, 44 (1991) 125-132. See especially Figure 2, p127 and is incorporated fully herein by reference.

Example 4(a); 4(b); 4(c); 4(d); 4(e); 4(f); 4(g); 4(h); 4(i); 4(j)

The exemplified agents of group 4 are identical in every respect to group 1 except that in place of GBP 130 or segments thereof the malaria RBC binding component is provided by Plasmodium Vivax Duffy Receptor especially peptide fragments comprising amino acid residues;

i residue 23 to 1051 inclusive

of any other fragment or species variation or substitution or deletional or inclusional variant thereof.

EXAMPLE OF AGENTS GROUP 5

As for group 1 except the malaria parasite peptides are twice represented.

EXAMPLE OF AGENTS GROUP 6

As for group 5 except that 2 different malaria parasite peptides are represented.

EXAMPLE OF AGENTS GROUP 7

These agents are as for examples 1, 2, 3, 4, 5 and 6 except the malaria parasite derived component is represented all or in part by

i an anti-ideotype Fab fragment

ii an antibody fragment binding to red cells in the same way as the malaria parasite components.

EXAMPLES OF MANUFACTURING METHODS

The protein of the present disclosure are fabricated preferably in a stepwise fashion. Many different manufacturing strategies are available for each component any or all of which may

be applied in various combinations dictated largely by two factors.

(1) Existing manufacturing facilities for other products within a factory and the cost of alternative strategies.

COST

(2) The minimisation of byproducts which are expensive to produce and eliminate.

ie. COST

So many methods of manufacture are now available that economics rather than science dictates the choice.

Peptide Manufacture

The art continues to provide new techniques for applying the Merrifield synthesis of peptides on a scaled up basis useful for the large scale manufacture of peptides referred to as scale up of solid phase peptide synthesis, SPPS.

The chemical synthesis of even complex peptides such as an entire merozoite peptide falls well within the scope of the art.

In the interests of brevity a full account of Merrifield synthesis will not be given, however, one is directed to:

The Chemical Synthesis of Peptides, John Jones Clarendon Press, 1991; and to G B Fields and R Noble Solid Phase Synthesis Utilising Fluorenylmethoxycarbonyl amino acids. Int. J Peptides 35 1990 p161-214

as useful points of reference and are incorporated fully herein by reference.

The tandemly repeated architecture of some merozoite peptides render their chemical synthesis more economically viable than other large peptides.

Where variations in a peptide sequence are sought ie. substitutional, deletional or insertions of amino acids then it may be very helpful to use Merrifield synthesis for that segment alone.

Newer techniques for multicomponent peptide synthesis permit the simultaneous synthesis of oligo peptide segments in a single run thus reducing time and costs considerably. One is direct to Arpad Fucka et al Int. J Peptide Protein Es 37 1991, 487-493 for details disclosed of a method incorporated fully herein by reference.

The present art continues to provide refinements to old techniques and new techniques for peptide synthesis either small quantities for research or larger amounts for industrial purposes. These techniques being familiar to the skilled artisan are disclosed best in standard textbooks and reference texts, accordingly brief reference only will be made to interesting developments which are non limiting.

A recent development involves the use of a new anchoring moiety involving the bonding of (HYCRAM)® (Orpegen GMBh, Czernyring 22, D-6900 Heidelberg FRC) a 4-hydroxylcrotonoyl-amidomethyl grouping bonded to an aminomethyl-polyacrylamide gel via spacer molecules such as B-alanine, or sarcosine or the like. Fmoc-amino acids can be linked to the HYCRAM® by esterification. Also any Boc-amino acid or any Ddz-amino acid 3, 5-dimethoxyphenyl-2-propyl-2-oxycarbanyl-amino acid salt may be bonded to the HYCRAM® anchor.

Synthesis then proceeds using the Boc-/benzyl, the Ddz-/t-butyl or the Fmoc-/t-butyl protocols as usual.

Detachment of the peptide from the HYCRAM® support employs palladium tatra-kis (triphynyl-phosphane) a catalyst in a suitable solvent such as 50% (v/v) dimethylsulphoxide

with dimethyl formamide' N-methyppyrrolidine, tetrahydrofuran and water. Oxygen tetrahydrofuran must be excluded. Acceptor molecules, morpholine, dimedine or N, N'-dimethylbarbiturate may be added to take up the allylic group.

The Ddz-/t-butly amino acid protections are easier to cleave using with 1-5% (v/v) trifluroacetic acid in dichloromethane a process taking 10 to 30 minutes or by means of the more environmental friendly acetic acid or dioxane containing 1% (w/v) HCL gas.

The other useful protocol is the Fmoc-/t-butyl strategy. Cleavage of F moc can be achieved using 20-50% (v/v) piperidine/dimethyl formamide.

Deprotection can be monitored in both cases photometrically. The activation of Boc-; Fmoc-; or Ddz-amino acid derivatives may employ the inexpensive (Dcc diclohexylcarbodi-imide. Pre activation using HOBT (N-hydroxybenzotriazole) can be employed to form symmetric anhydrides of protected amino acids or their esters.

Other activating agents are the Castro Reagent or BOP' Benzotriazole-1-yl-oxy-tris (dimethyl amino) phosphonium hexa flurosphosphate; one is directed to CASTRO b et al (1957) Tetrahedron Lett. 15, 1219; and TBTU the Knorr reagent, Benzotriazole-1-yl-oxy-1, 1, 3-tetramethyluronioum tetrafluoroborate one is directed to Knorr R et al (1989) Tetrahedron Lett. 30, 1927.

Fragment condensation can be achieved using the BOP or the TBTU reagent with HOBT in excess. Protected peptides must also be in excess, however, solvents and excesses can often be recycled.

It will be appreciated that by blocking incomplete fragment condensations shorter by products can be discriminated from the desired polypeptide. Using this system high purity

polypeptides can be produced.

Monitoring of production process will usually involve U.V. absorbtion techniques.

A typical production process involve either the separate synthesis of peptide sequences by their expression in suitable hosts, and their subsequent purification; or chemical synthesis such as on a solid substrate for example by the sequential addition of amion acid residues or peptide fragments which are protected, the protection of the amino acid residues as required and the subsequent reacting of the peptide chains with linking agents before removing the peptide chains from the said solid substrates and the final purification by the various means is such as reverse phase chromatography; or any combination of the above.

In the case of some of the exemplary embodiments it may be convenient to manufacture the fusion peptides by means of a fused gene. A fused gene is a genetic sequence which codes both components of the hybrid component molecule. One is directed to Murphy United States Patent 4, 675, 382 for a detailed disclosure of the use of fused genes in the manufacture of hybrid peptides having the components MSH or Melanocyte Stimulating Hormone fused to diphtheria A toxins.

Alternatively peptide fragments may be manufactured by DNA cloning and expression in suitable hosts and recovery with subsequent condensation in vitro.

Generally cloned sequences useful for the production of fusion peptides will have the transmembrane domain and the cytoplasmic domain sequence removed.

For a useful general description of DNA cloning and molecular hybridization technology, one is directed to Maniatis et al Mollecular cloning, A Laboratory Manual, Cold Harbour Spring Laboratory (See Second Edition 1989); and to Horvath et al, An Automated DNA

synthesizer employing Deoxynucleoide 34 Phosphoramidites, methods in Enzymology 154: 313-326, 1987.

DNA may be made by the chemical synthesis of DNA polymer fragments using phosphotriester, phosphite or phosphoramidite chemistry. For a description of sold phase techniques one is directed to Chemical and Enzymatic Synthesis of Gene Fragments - A Laboratory manual ed H G Gassen and L Lang, Verlag Chemiee, Weinheim 1982; and Gait M J et al Nucleic Acids Research 1982, 10, 6243; Spoat B S et al Tetrahedron Letters, 1980, 21, 719; Matteuci M D et al J. American Chemical Society, 1983, 195, 661; Sinha N D et al Nucleic Acids Research, 1984, 12, 4539 and Matthes H W D et al Embo. Journal, 1984, 3, 801, whose teachings are incorporated herein fully by reference.

Reverse transcriptase techniques may also be used to generate a complimentary cDNA strand by means of the reverse transcription of malaria parasite derived mRNA. Kits are available for this purpose.

The DNA fragments may be ligated by either blunt-ended or staggered-ended termini after using restriction enzymes; digestion; filling in a required; and treatment with alkali and phosphatase for protection and subsequent ligation with suitable ligases.

Appropriate leader sequences may be chosen from the many available.

The cloning of the DNA sequence of the hybrid peptides of this invention may take place in prokaryotes such as E.Coli for example, K12 strain or E Coli B by way of non limiting examples or by means of the polymerase chain reaction.

Subsequent expression of the hybrid peptides may take place in any host cell, including mammalian host cells. Other useful cells are fungi, yeasts, insects and prokaryotes.

Signals suited to the chosen host cell are chosen as appropriate, in the case of prokaryotes one can chose from a large group including alkaline phosphatase, pemallinase and the like.

Where prokaryotes such as E Coli for example, are used to express the hybrid peptides, then they are transformed by an expression vector usually a plasmid such as PBR322 into which the DNA encoding the fusion peptide or fragment has been ligated such as plasmid will also feature suitable marker sequences, promoters, and Shine-Dalgarno sequences may be chosen as appropriate.

A prokaryote host such as E Coli may be transformed by treatment using a solution of $CaCl_2$ as described by Cohen et al PNAS 1973, 69, 2110 or by treatment with a solution comprising a mixture of RbCl, $MnCl_2$, potassium acetate and glycerol and then subsequently with 3-[N-morpholino]-propene-sulphonic acid and, RbCl and glycerol. One is described to "DNA Cloning" Vol II D M Gover ed, IRL press Ltd 1985 for a description of transforming techniques.

Where insect cells such as Lepidoptera cells are the chosen expression host a suitable vector would be Baculovirus. Such a system would contain the target peptide encoding sequence linked to a baculovirus promoter within a shuttle vector with sufficient baculovirus DNA flanking the target peptide encoding sequence to permit recombination. One is directed to Summers et al, TAES Bull (Texas Agricultural Experimental Station Bulletin) NR 1555 May 1987. One is also directed to Smithklein (WO/US/89/05550). Insect larvae can also be directed to PCT/WO/88/0200030 Miller et al. Other useful insects are Drosophila melanogasteric, and the like.

Where plant cells are the chosen host expression cells, the cowpea plant provides a suitable expression system. One is directed to the system developed by the Agriculture Genetics Company of Cambridge, UK, employing techniques involving the use of the

cowpea mosaic virus (CPMV). A general protocol for the cloning of foreign genes in plants (tomatoe) and the like may be obtained by consulting HORSC R B et al Science 227, 1229-31.

Alternatively where the chosen host is a yeast such as Saccharomyces cerevisiae the plasmid YRp7 as the expression vector may be used. One is directed to Stinchcomb et al Nature 282, 39, (1979), Kingsman et al, G7; 141 (1979); Tschemper et al, Gene 10; 1975 (1980).

A wide choice of promoters is available for use in yeast cell expression systems and include by way on non limiting examples 3-phosphoglycerate kinase and one is directed to Hitzman et al J. Biol. Chem. 255 2073 (1980); also enolase, glyceraldehyde-3-phosphate dehydroginase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triose phosphate isomerase, phospho glucose isomerase and glucokinaise being glycolytic enzymes and one is directed to Hess et al J. Adv. Enzyme Reg. 7, 149 (1968) and to Holland Biochemistry 17, 4900 91978.

Other promoters suitable for yeast expression systems include the promoter regions for alcohol dehydrogenase 2, 100 cytochrome C, acid phosphatase, also mettallothioneins, glycoraldehyde-3-phosphate dehydrogenase and others one is directed to Hitzman R et al European patent Publication No. 73, 657A.

Where mammalian cells are the chosen hosts for expression, these cells may be grown in vitro in tissue culture or suitable bioreactors or in vivo in animals.

Vectors useful for mammalian cells host systems involve the use of DNA derived from animal viruses such as SV40 virus; retroviruses such as RSV, MMTV, MOMLV,

baculovirus, Vaccinovirus, Andeovirus, polyoma or bovine papilloma virus.

Promoters suitable for mammalian cells systems may be chosen from the many available. One is directed to Friers et al Nature 273; 113 (1987) and Greenway P J et al Gene 18, 353-360 (1982) and Okayamah Mol Cell Biol. 3, 280 1 1983, by way of example.

Additionally suitable enhancers may be chosen from the many available. One is directed to Laimins L et al PNAS 78, 993 (1981) and Lusky M L et al MO. Cell Bio. 3, 1108 (1983) and Banerji J L et al Cel. 33, 729 (1983) and Osbourne T F et al Mol. Cel. Bio. 4, 1293 (1984).

For as description of some available selection techniques one is directed to Southern et al J. Molec. Appll. Genet. 1, 327 (1982) and to Mulligan et al Science 209; 1422 (1980) and to Sugden et al Mol. Cel. Biol. 5, 410-413 (1985).

Some techniques useful for the introduction of the expression vector into the host cell involve protoplast fusion, calcium phosphate precipitation, electroporation, and other techniques.

Mammalian host cells suitable for the expression of fragments of or in some cases the entire fusion peptides may now be chosen from the large number now available such as VERO or CHO-K1, a myloma cell line.

Other suitable eukaryotic host cells include COS cells, human embryonic kidney cells, mouse plasmoacytoma cells, mouse sertoli cells, baby hamster kidney cells (BHK cells), Chinese hamster ovary cells - DKFR(CHO), monkey kidney cells, African green monkey kidney cells, human cervical carcinoma cells (HELA cells), canine kidney cells, Buffalo rat liver cells, human lung cells, human liver cells and mouse mammary tumour cells, by way

of non limiting examples.

It will be appreciated that the chosen host cells will preferably express the minimum levels proteases within their cytoplasm. It will also be appreciated that amino acid sequence variations of the peptide sequences involved may be insertions, substitutional or deletional variations involving single amino acid residues or peptide fragments.

The purpose of such variations may be to increase the affinity of the components, to improve stability, to reduce the cost preparation or to increase the half life, or to lessen the severity of side effects such as atopic reactions. The final form of the agents of the present disclosures may involve any combination of substitutions, deletion or insertion of amino acid sequences, provided the binding ability of the epitopes or peptide sequence are retained.

It will be appreciated that also included in the present disclosure are glycosylation variations ie. variants completely unglycolated, variants having glycosyltaed amino acids other than those glycosylated in the natural peptides or variants having a greater number of amino acids residues glycosylated or fewer glycosylated residues or residues glycolated by oligosaccharides other than those oligosaccharides usually associated with the said sequences.

Following their expression by the host cell, the peptides are recovered and purified by means known to the ordinary skilled artisan.

Such methods may include acid extraction, ethanol precipitation using ammonium sulphate, anion or cation exchange chromatography phosphocellulose chromatography, immunoaffinity, chromatography hydroxyappetite chromatography and reverse phase chromatography.

Generally purification and processing involves four stages:

(1) extraction of peptides from host cell

(2) initial purification

(3) final purification

(4) production polishing

Extraction may be accomplished using sonication techniques or solid shear techniques - on a small scale.

Lysozyme based techniques are expensive. More usually in the case of bacterial hosts homogenizers or liquid shear techniques are employed.

Other useful techniques involve osmotic shock, freezing and thawing or alkali homogenisation.

In the case of where a product is expressed as an inclusion body cell paste may be solubilised by solvents such as 8M-guanidinium.

Centrifugation provides the removal cellular debris, and continuous flow centrifuges are preferred for large scale operations. As an alternative to centrifugation cross flow filtration using flat to tubular membranes and high shear forces may provide a useful alternative to centrifugation.

Initial purification involves mainly the removal of excess water and product concentration.

Precipitation using ammonium sulphate, organic solvents, polyethylene glycol or other polymers can be used to accomplish this step; with the addition of some variety of chromatography usually absorptive chromatography techniques employing ion exchange,

hydrophobic or bioaffinity interactions; followed by washing and desorption; chromatography is not restricted to columns but may take place in membranes or even in spirally wounded cartridges.

In cases where peptide fragments have been expressed as inclusion bodies an additional step of 'refolding' is required. Because of low yields after refolding inclusion body productions is often uneconomical. However, two approaches are practised to refold peptides into the natural or desired three dimensional state the empirical approach and the rationalist approach.

In the empirical approach multiple solvents are applied and an optimum strategy is determined using phase diagrams as disclosed by Ahmed and Biglow 1979 J. Mol. Biol. 131. 6097-617.

The rationalist approach seeks to produce conditions favouring the native state while at the same time keeping intermediates in solution.

A problem may arise in connection with disulphide bridges which may form in non-native configurations. A way around this problem is to oxidize disulphides under denaturing conditions, using gel filtration remove covalent aggregates and thereafter dilute the product in a non denaturing buffer. The peptide which collapses into an amorphous tangle often rearranges itself into the native form.

Highly resolving chromatography is the preferred technique for final purification. For large scale applications columns are preferred and techniques such as gel filtration, ion exchange, hydrophobic interaction or affinity chromatography may be used alone or in combination as dictated by economies of scale.

Gel filtration is best suited to small batch volumes and suffers from the disadvantage of slow speed.

Ion exchange chromatography techniques are very useful in early purification stages and can deal with large volumes at great speed, producing yields of high resolution.

Hydrophobic interaction chromatography provides both high resolution and high speed even at large batch volumes.

Bio affinity chromatography produces the highest resolution, at high speed, but batch size may require curtailment. This technique is an ideal late stage technique.

The increasing availability of monoclonal antibodies at lower prices has led to greater use of bio affinity chromatographic techniques.

A wide choice of chromatographic matrices is now available on the market suitable for large scale use.

Particle size is decreasing from the 90μm of traditional gels to approximately 40μm for newer gels such as Sepharose HR®, Suphacryl HR®, Superdex® (Pharmacia - LKB) or Fractogel® (Toso-Haas).

Other polymeric particles are Superose® (Pharmacia - LKB) or the TSKPW® varieties manufactured by (Toso Haas, Philadelphia USA), providing very low particle size.

It will be appreciated that the process of chromatography involves the choice and development of a strategy containing one or more steps ie. high resolution single step or a multistep procedure the final choice to be determined by

(1) the chosen peptide production process which determines the form of the starting material to be purified

(2) cost

Usually the first chromatography column will involve large diameter packings circa 100μm, which are often chosen so that they can be resanitized by sodium hydroxide to reduce costs. Low resolution steps to be followed by higher resolution steps until the desired product purity is obtained.

Step One Hydrophobic interaction chromatography at low ionic strength. Purpose to absorb proteinases. Target peptide not absorbed and collected. Alternative use proteinase inhibitors.

Step Two Re-run through h.l.c column adding salts to bind the target peptide to the h.l.c column. The objective is volume reduction. Alternatively employ ultra filtration as described. Use a step gradient to elute the target peptide.

Step Three A step gradient to a low ionic strength buffer will remove remaining salts. Alternatively employ polyethyleneimine precipitation, centrifugation and diafiltration.

In the case of therapeutic peptides such as the agents of this disclosure where administration to a human is considered then the step of produce polishing is vital.

Product polishing involves the removal of polymers of the product and other pyrogens.

Techniques for product polishing involve additional gel filtration with or without a buffer exchange step; treatment with alhydrogel (aluminium hydroxide) or treatment with specific lecithins or anion exchanges.

EXAMPLE OF USE OF AGENTS IN TESTING KITS

A sample of patients blood 50ml is collected in a suitable container. It is desired to measure free TNFα or levels of circulating cytokines to determine elevation of these levels implying say endotoxic shock.

1mg of the hybrid fusion peptides of group 1a1, 1a2 or 2a1 or 3a or 4a or 5a are mixed with 10ml of blood to be assayed. Thereafter the antibodies directed against the complex TNF-TNF-R-malaria parasite peptide are added. These antibodies may be radiolabelled or labelled with luminescent groups or labelled by other means. The blood sample is then spun and rediluted, re-spun and rediluted. Thereafter the sample is put through an automated counter. The agents attach individual molecules of TNF to red cells and permit visualization and quantification of very small amounts, molecule by molecule of TNF on a red cell with very few laboratory steps. Moreover, as red cells lack TNF receptors the procedure should be accurate and permit measurement of very small amounts of TNF. As for TNF other cytokines may be assayed in the same way.

EXAMPLES OF AMINO ACID SEQUENCES

The invention will be further illustrated by an amino acid sequence listing of some of the exemplary embodiments, which are intended to be illustrative but not limiting. It will be appreciated by the skilled artisan that the sequence listed here under are but a few of the many possible variations in accordance with the teachings of the present disclosure, these other variations being obvious to the artisan of ordinary skill are accordingly omitted in the interest of brevity. It will also be appreciated that in the following sequence listings the signal and transmembrane and cytoplasmic domains of the disclosed peptides are deleted. However, they may be included to facilitate expression or extend half life if desired, in accordance with the teachings of the present disclosure.

It will also be appreciated that not all the cytokine receptor sequences can be listed and are excluded in the interest of brevity. Those cytokine receptor sequences not listed are well known to the skilled artisan and freely available in referenced texts and literature of the art. The substitution of such unlisted receptor sequences involves no intensive steps and falls within the skill of the ordinary skilled artisan.

A Examples of TNF-receptor malaria peptide fusion peptide.

In the following examples the TNF receptor sequence is in accordance with H Loetscher et al Cell, Vol. 61, 351-359, April 20; 1990, p353, Fig. 2A, the malaria parasite components as referenced herein before,

A1 NH_2-TNF-R - GBP 130-COOH

For an example of this peptide one is directed to the document of formal sequence listings.

A2 NH_2-TNF-R - GBPH-COOH (glycophorin binding peptide homologue)

For an example of this peptide one is directed to the document of formal sequence listings.

A3 NH_2-TNF-R - EBA 175-COOH

For an example of this peptide one is directed to the document of formal sequence listings.

A4 NH_2 TNF - Pl. Vivax Duffy R - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

A5 NH_2-TNF-R - GBP 130-COOH

An example of a polymer of an amino acid repeat sequence.

For an example of this peptide one is directed to the document of formal sequence listings.

A6 NH_2-TNF-R - GBPH-COOH (glycophorin binding peptide homologue)

An example of a polymer of an amino acid repeat sequence.

For an example of this peptide one is directed to the document of formal sequence listings.

B1 Example of one fusion peptide formed by the fusion of TNF-R tumour necrosis factor receptor with a malaria red cell binding peptide GBP130 the tumour necrosis factor receptor amino acid sequence as disclosed by Y Norphor et al, EMBO Journal Vol 9; No. 10;

pp3269-3278 (1990), see page 3271.

B1 NH_2 TNFR - GBP130-COOH

For an example of this peptide one is directed to the document of formal sequence listings.

C Example of one fusion peptide formed by fusion of TBPI tumour necrosis binding protein 1 with a malaria red cell binding peptide GBP130 already referenced herein TBPI being in accordance with Y NORPHOR et al EMBO Journal; Vol 9; No 10; pp3269-3278 (1990) see page 3271 Fif ID and p3272.

C1 NH_2 - TBPI - GBP130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

D1 Example of TBPII - GBP130 fusion peptide where TBPII is the tumour necrosis binding peptide type II as disclosed by NORPHOR et al EMBO. J. Vol 9; No 10; pp3269-3278 (1990) Fig 10 of p3271 and p3272 incorporated fully herein by reference.

D1 NH_2 - TBPII - GBP130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

D2 Example of a fusion peptide where the TNFR sequence is in accordance with all or part that disclosed by C A Smith and one is directed to Science, Vol. 248; 25 May 1990, P. 1021.

D2 NH_2 - TNFR - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

E Example of γIFN-R-GBP130 fusion peptide where γIFN-R is the γIFN gamma interferon receptor as disclosed by Auguet M et al Cell 55 (1988) pp273-280; Oct 21 1988; see Fig 2.

E1 NH_2 - γIFN-R - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

F Example of IL-1R-GBP 130 fusion protein where IL-1 is the type II receptor cloned and described by C J M Mahon et al EMBO Journal; Vol 10; No 10, pp2821-2832 (1991), see Fig 3.

F1 NH_2 - IL-1R type II - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

G Example of IL-1R type I - GBP 130 sequence of IL-IR type 1 as listed by M:Mahon et al EMBO J.; Vol 10; No 10; pp2821-2832 (1991); Fig 3.

G1 NH_2-IL1R type 1 - GBP130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

H Example of IL2-R - GBP 130 fusion proteins - COOH

H1 In this example the IL2-R molecule is in accordance with part of the IL2 molecule disclosed by T Nikaido et al, Nature, Vol 311, 18 Oct 1984, pp631 to P.635 incorporated fully herein by reference.

H1 NH_2 - IL2-R - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

H2 In this example the IL2 receptor molecule is in accordance with part of that molecule as disclosed by D Cosman et al, Nature, Vol 312; 20/27, December 1984, pp768-771 especially page 770 incorporated fully herein by reference.

H2 NH_2 - IL2-R - GPB 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

H3 In this example the IL2 receptor is formed by the IL2-R β chain as disclosed by Masanori Hatakeyama et al and one is directed to Science, Vol. 244, 5 May 1989, pp 551-556 see especially page 552 figure 1B.

H3 NH_2 - IL2-R - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

I Example of IL-3R-GBP130 fusion protein the IL-3R amino acid sequence is disclosed by Toshio Kitamura et al Cell, Vol 60, 1165-1174, Sept 20, 1991 and incorporated fully herein by reference.

I1 NH_2 - IL-3R - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

J Example of IL4-R-GPB 130 fusion protein where the amino acid sequence of IL4-R interleukin 4 receptor is in accordance with part of that IL4R sequence disclosed by R L Idzerda et al and one is directed to J. Exp. Med., Vol. 171: Mar 1990, pp861-873 especially to page 864 incorportated fully herein by reference.

J NH_2 - IL4-R - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

K Example of IL-5R - GBP130 fusion protein where the amino acid sequence of IL-5R is all or part of that sequence provided by Jan Tavernier et al, Cell, Vol 66, 1175-1184, Sept 20, 1991.

K1 NH_2 - IL-5R - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

L Example of IL-6R - GBP 130 fusion protein where the amino acid sequence of IL-6R is given by Katsuhiko Yamasaki et al Science, Vol 241; 12 Aug 1988; p825-827, see Fig 4, p826.

L1 NH_2-IL-6R - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

M Example of IL-8R-GBP 130 fusion peptide where the sequences of IL-9R type 1 and type II ar according to Richard Gayle III et al J. of Biological Chemistry, Vol 268, No 10, Apr 5, pp 7283-7289, see Fig 1.

M1 NH_2 - IL-8 R type 1 - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

M2 NH_2 - IL-8R type 2 - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

N Example of LIF-R-GBP 130 fusion protein where the LIF-R amino acid sequence is

in accordance with Gearing et al.

N1 NH_2 - LIF-R - GBP 130 - COOH

For an example of this peptide one is directed to the document of formal sequence listings.

In the preceeding examples of fusion peptides it will be appreciated that the signal and transmembrane and cytoplasmic domains have been deleted preserving only the functional extracellular domains. These deleted segments may be reintroduced or other peptide segments inserted without departing from the scope or spirt of this disclosure.

The Patent Cooperative Treaty

Title: Pharmaceutical Composition

Amino Acid Sequence Listing

Type: Hyptothetical

Agent: Dr J G Holdcroft

Agent's Reference: jgh:ec:10588

Inventor: K F PRENDERGAST

Service Address: Graham Watt & Co
Riverhead, Sevenoaks,
KENT TN13 2BN

A1 NH_2-TNF-R - GBP 130-COOH

NH_2 - Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg

20 Asp Ser Val Cys Pro Gln Gly Lys Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr

40 Lys Cys His Lys Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp

60 Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu Arg His Cys Leu

80 Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val Glu Ile Ser Ser Cys Thr Val Asp

100 Arg Asp Thr Val Cys Gly Cys Arg Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu

120 Phe Gln Cys Phe Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln

139 Glu Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu Asn Glu Cys

159 Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr Lys Leu Cys Leu Pro Gln Ile

179 Glu Asn Val Lys Gly Thr Glu Asp Ser Gly Thr Asn Ala Tyr Ile Cys Gly Asp Lys Tyr

299 Glu Lys Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp Thr

219 Cys Ala Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg Thr

239 Val Ala Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln Lys

259 Val Glu Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile Asn

279 Ile Gly Asp Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu Lys

300 Lys Lys Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys Lys

320 Lys Glu Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn Asn

340 Glu Val Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu Gly Gln

361 Ile Met Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile

382 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp

402 Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr

422 Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val

442 Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile

462 Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile

482 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp

502 Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg

523 Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu

543 Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met

563 Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr
584 Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu Thr Ser
604 Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His
624 Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg
644 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu
664 Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr
685 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser Ser
705 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu
725 Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn
745 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr
766 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp
787 Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp
806 Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile
827 Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp
847 Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala
867 Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro
887 Asn Asp Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

A2 $\underline{NH_2\text{-TNF-R - GBPH-COOH}}$ (glycophorin binding peptide homologue)

NH_2 - Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg
20 Asp Ser Val Cys Pro Gln Gly Lys Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr
40 Lys Cys His Lys Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
60 Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu Arg His Cys Leu
80 Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val Glu Ile Ser Ser Cys Thr Val Asp
100 Arg Asp Thr Val Cys Gly Cys Arg Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu
120 Phe Gln Cys Phe Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln
139 Glu Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu Asn Glu Cys
159 Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr Lys Leu Cys Leu Pro Gln Ile
179 Glu Asn Val Lys Gly Thr Glu Asp Ser Gly Thr Ser Gln Tyr Lys Gln Ala Ala Asp Tyr

199 Ser Phe Arg Glu Ser Arg Val Leu Ala Glu Gly Lys Ser Thr Ser Lys Lys Asn Ala Lys
219 Thr Ala Leu Arg Lys Thr Lys Gln Thr Thr Leu Th*r Ser Ala Asp Pro Glu Gly Gln Ile
239 Met Lys Ala Trp Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Asn Val Leu Tyr Gln Ile
259 Leu Asn Asn Thr Asp Pro Asn Asp Glu Leu Glu Th*r Ser Ala Asp Pro Glu Gly Gln
278 Ile Met Lys Ala Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Asn Val Leu Tyr Gln Ile
299 Leu Asn Asn Thr Asp Pro Asn Asp Glu Val Glu Se*r Ser Ala Asp Pro Glu Gly Gln Ile
319 Met Lys Ala Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Val Asn Val Leu Tyr Gln Ile Leu
340 Asn Asn Thr Asp Pro Asn Asp Glu Leu Glu Th*r Ser Ala Asp Pro Glu Gly Gln Ile Met
360 Lys Ala Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Val Asn Val Leu Tyr Gln Ile Leu Asn
381 His Thr Asp Ser Ser Glu Val Glu Th*r Ser Ala Asp Pro Glu Gly Gln Ile Met Lys Ala
401 Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Val Asn Val Leu Tyr Gln Ile Leu Asn His Thr
422 Asp Ser Ser Glu Val Glu Th*r Ser Ala Asp Pro Glu Gly Gln Ile Met Lys Ala Tyr Ala
442 Ala Asp Pro Glu Tyr Arg Lys His Val Asn Val Leu Tyr Gln Ile Leu Asn Asn Thr Asp
462 Pro Asn Asp Glu Leu Glu Th*r Ser Ala Asp Pro Glu Gly Gln Ile Met Lys Ala Tyr Ala
482 Ala Asp Pro Glu Tyr Arg Lys His Val Asn Val Leu Tyr Gln Ile Leu Asn Asn Thr Asp
502 Pro Asn Asp Glu Leu Glu Th*r Ser Ala Asp Pro Glu Gly Gln Ile Met Lys Ala Tyr Ala
522 Ala Asp Pro Glu Tyr Arg Lys His Val Asn Val Leu Tyr Gln Ile Leu Asn Asn Thr Asp
542 Pro Asn Asp Glu Ser Ser-COOH

A3 $\underline{NH_2\text{-TNF-R - EBA 175-COOH}}$

NH_2 - Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg
20 Asp Ser Val Cys Pro Gln Gly Lys Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr
40 Lys Cys His Lys Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
60 Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu Arg His Cys Leu
80 Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val Glu Ile Ser Ser Cys Thr Val Asp
100 Arg Asp Thr Val Cys Gly Cys Arg Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu
120 Phe Gln Cys Phe Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln
139 Glu Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu Asn Glu Cys
159 Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr Lys Leu Cys Leu Pro Gln Ile

179 Glu Asn Val Lys Gly Thr Glu Asp Ser Gly Thr Ala Arg Asn Glu Tyr Asp Ile Lys Glu

199 Asn Glu Lys Phe Leu Asp Val Tyr Lys Glu Lys Phe Asn Glu Leu Asp Lys Lys Lys Tyr

219 Gly Asn Val Gln Lys Thr Asp Lys Lys Ile Phe Thr Phe Ile Glu Asn Lys Leu Asp Ile

239 Leu Asn Asn Ser Lys Phe Asn Lys Arg Trp Lys Ser Tyr Gly Thr Pro Asp Asn Ile Asp

259 Lys Asn Met Ser Leu Ile Asn Lys His Asn Asn Glu Glu Met Phe Asn Asn Asn Tyr Gln

279 Ser Phe Leu Ser Thr Ser Ser Leu Ile Lys Gln Asn Lys Tyr Val Pro Ile Asn Ala Val Arg

300 Val Ser Arg Ile Leu Ser Phe Leu Asp Ser Arg Ile Asn Asn Gly Arg Asn Thr Ser Ser

320 Asn Asn Glu Val Leu Ser Asn Cys Arg Glu Lys Arg Lys Gly Met Lys Trp Asp Cys Lys

340 Lys Lys Asn Asp Arg Ser Asn Tyr Val Cys Ile Pro Asp Arg Arg Ile Gln Leu Cys Ile Val

361 Asn Leu Ser Ile Ile Lys Thr Tyr Thr Lys Glu Thr Met Lys Asp His Phe Ile Glu Ala Ser

382 Lys Lys Glu Ser Gln Leu Leu Leu Lys Lys Asn Asp Asn Lys Tyr Asn Ser Lys Phe

401 Cys Asn Asp Leu Lys Asn Ser Phe Leu Asp Tyr Gly His Leu Ala Met Gly Asn Asp

420 Met Asp Phe Gly Gly Tyr Ser Thr Lys Ala Glu Asn Lys Ile Gln Glu Val Phe Lys Gly

440 Ala His Gly Glu Ile Ser Glu His Lys Ile Lys Asn Phe Arg Lys Glu Trp Trp Asn Glu Phe

461 Arg Glu Lys Leu Trp Glu Ala Met Leu Ser Glu His Lys Asn Asn Ile Asn Asn Cys Lys

481 Asn Ile Pro Gln Glu Glu Leu Gln Ile Thr Gln Trp Ile Lys Glu Trp His Gly Glu Phe Leu

502 Leu Glu Arg Asp Asn Arg Ser Lys Leu Pro Lys Ser Lys Cys Lys Asn Asn Thr Leu Tyr

522 Glu Ala Cys Glu Lys Glu Cys Ile Asp Pro Cys Met Lys Tyr Arg Asp Trp Ile Ile Arg Ser

543 Lys Phe Glu Trp His Thr Leu Ser Lys Glu Tyr Glu Thr Gln Lys Val Pro Lys Glu Asn

563 Ala Glu Asn Tyr Leu Ile Lys Ile Ser Glu Asn Lys Asn Asp Ala Lys Val Ser Leu Leu

583 Leu Asn Asn Cys Asp Ala Glu Tyr Ser Lys Tyr Cys Asp Cys Lys His Thr Thr Thr Leu

603 Val Lys Ser Val Leu Asn Gly Asn Asp Asn Thr Ile Lys Glu Lys Arg Glu His Ile Asp

623 Leu Asp Asp Phe Ser Lys Phe Gly Cys Asp Lys Asn Ser Val Asp Thr Asn Thr Lys

642 Val Trp Glu Cys Lys Asn Pro Tyr Ile Leu Ser Thr Lys Asp Val Cys Val Pro Pro Arg

662 Arg Gln Glu Leu Cys Leu Gly Asn Ile Asp Arg Ile Tyr Asp Lys Asn Leu Leu Met Ile

682 Lys Glu His Ile Leu Ala Ile Ala Ile Tyr Glu Ser Arg Ile Leu Lys Arg Lys Tyr Lys Asn

703 Lys Asp Asp Lys Glu Val Cys Lys Ile Ile Asn Lys Thr Phe Ala Asp Ile Arg Asp Ile Ile

724 Gly Gly Thr Asp Tyr Trp Asn Asp Leu Ser Asn Arg Lys Leu Val Gly Lys Ile Asn Thr

744 Asn Ser Lys Tyr Val His Arg Asn Lys Lys Asn Asp Lys Leu Phe Arg Asp Glu Trp Trp

764 Lys Val Ile Lys Lys Asp Val Trp Asn Val Ile Ser Trp Val Phe Lys Asp Lys Thr Val Cys

785 Lys Glu Asp Asp Ile Glu Asn Ile Pro Gln Phe Phe Arg Trp Phe Ser Glu Trp Gly Asp

805 Asp Tyr Cys Gln Asp Lys Thr Lys Met Ile Glu Thr Leu Lys Val Glu Cys Lys Glu Lys

825 Pro Cys Glu Asp Asp Asn Cys Lys Ser Lys Cys Asn Ser Tyr Lys Glu Trp Ile Ser Lys

845 Lys Lys Glu Glu Tyr Asn Lys Gln Ala Lys Gln Tyr Gln Glu Tyr Gln Lys Gly Asn Asn

865 Tyr Lys Met Tyr Ser Glu Phe Lys Ser Ile Lys Pro Glu Val Tyr Leu Lys Lys Tyr Ser Glu

886 Lys Cys Ser Asn Leu Asn Phe Glu Asp Glu Phe Lys Glu Glu Leu His Ser Asp Tyr

905 Lys Asn Lys Cys Thr Met Cys Pro Glu Val Lys Asp Val Pro Ile Ser Ile Ile Arg Asn Asn

926 Glu Gln Thr Ser Gln Glu Ala Val Pro Glu Glu Asn Thr Glu Ile Ala His Arg Thr Glu Thr

947 Pro Ser Ile Ser Glu Gly Pro Lys Gly Asn Glu Gln Lys Glu Arg Asp Asp Asp Ser Leu

967 Ser Lys Ile Ser Val Ser Pro Glu Asn Ser Arg Pro Glu Thr Asp Ala Lys Asp Thr Ser

987 Asn Leu Leu Lys Leu Lys Gly Asp Val Asp Ile Ser Met Pro Lys Ala Val Ile Gly Ser

1007 Ser Pro Asn Asp Asn Ile Asn Val Thr Glu Gln Gly Asp Asn Ile Ser Gly Val Asn Ser

1027 Lys Pro Leu Ser Asp Asp Val Arg Pro Asp Lys Lys Glu Leu Glu Asp Gln Asn Ser Asp

1047 Glu Ser Glu Glu Thr Val Val Asn His Ile Ser Lys Ser Pro Ser Ile Asn Asn Gly Asp Asp

1068 Ser Gly Ser Gly Ser Ala Thr Val Ser Glu Ser Ser Ser Ser Asn Thr Gly Leu Ser Ile

1088 Asp Asp Asp Arg Asn Gly Asp Thr Phe Val Arg Thr Gln Asp Thr Ala Asn Thr Glu Asp

1108 Val Ile Arg Lys Glu Asn Ala Asp Lys Asp Glu Asp Glu Lys Gly Ala Asp Glu Glu Arg

1028 His Ser Thr Ser Glu Ser Leu Ser Ser Pro Glu Glu Lys Met Leu Thr Asp Asn Glu Gly

1048 Gly Asn Ser Leu Asn His Glu Glu Val Lys Glu His Thr Ser Asn Ser Asp Asn Val Gln

1068 Gln Ser Gly Gly Ile Val Asn Met Asn Val Glu Lys Glu Leu Lys Asp Thr Leu Glu Asn

1088 Pro Ser Ser Ser Leu Asp Glu Gly Lys Ala His Glu Glu Leu Ser Glu Pro Asn Leu Ser

1108 Ser Asp Gln Asp Met Ser Asn Thr Pro Gly Pro Leu Asp Asn Thr Ser Glu Glu Thr Thr

1128 Glu Arg Ile Ser Asn Asn Glu Tyr Lys Val Asn Glu Arg Glu Asp Glu Arg Thr Leu Thr

1148 Lys Glu Tyr Glu Asp Ile Val Leu Lys Ser His Met Asn Arg Glu Ser Asp Asp Gly Glu

1168 Leu Tyr Asp Glu Asn Ser Asp Leu Ser Thr Val Asn Asp Glu Ser Glu Asp Ala Glu Ala

1188 Lys Met Lys Gly Asn Asp Thr Ser Glu Met Ser His Asn Ser Ser Gln His Ile Glu Ser

1208 Asp Gln Gln Lys Asn Asp Met Lys Thr Val Gly Asp Leu Gly Thr Thr His Val Gln Asn

1228 Glu Ile Ser Val Pro Val Thr Gly Glu Ile Asp Glu Lys Leu Arg Glu Ser Lys Glu Ser Lys

1249 Ile His Lys Ala Glu Glu Glu Arg Leu Ser His Thr Asp Ile His Lys Ile Asn Pro Glu Asp
1270 Arg Asn Ser Asn Thr Leu His Leu Lys Asp Ile Arg Asn Glu Glu Asn Glu Arg His Leu
1290 Thr Asn Gln Asn Ile Asn Ile Ser Gln Glu Arg Asp Leu Gln Lys His Gly Phe His Thr
1310 Met Asn Asn Leu His Gly Asp Gly Val Ser Glu Arg Ser Gln Ile Asn His Ser His His
1330 Gly Asn Arg Gln Asp Arg Gly Gly Asn Ser Gly Asn Val Leu Asn Met Arg Ser Asn Asn
1350 Asn Asn Phe Asn Asn Ile Pro Ser Arg Tyr Asn Leu Tyr Asp Lys Lys Leu Asp Leu Asp
1370 Leu Tyr Glu Asn Arg Asn Asp Ser Thr Thr Lys Glu Leu Ile Lys Lys Leu Ala Glu Ile
1390 Asn Lys Cys Glu Asn Glu Ile Ser Val Lys Tyr Cys Asp His Met Ile His Glu Glu Ile Pro
1411 Leu Lys Thr Cys Thr Lys Glu Lys Thr Arg Asn Leu Cys Cys Ala Val Ser Asp Tyr Cys
1431 Met Ser Tyr Phe Thr Tyr Asp Ser Glu Glu Tyr Tyr Asn Cys Thr Lys Arg Glu Phe Asp
1451 Asp Pro Ser Tyr Thr Cys Phe Arg Lys Glu Ala Phe Ser Ser Met Ile Phe Lys Phe Leu
1471 Ile Thr Asn Lys Ile Tyr Tyr Tyr Phe Tyr Thr Tyr Lys Thr Ala Lys Val Thr Ile Lys Lys
1492 Ile Asn Phe Ser Leu Ile Phe Phe Phe Phe Phe Ser Phe-COOH

A4 <u>NH_2 TNF - Pl. Vivax Duffy R - COOH</u>

NH_2 - Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg
20 Asp Ser Val Cys Pro Gln Gly Lys Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr
40 Lys Cys His Lys Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
60 Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu Arg His Cys Leu
80 Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val Glu Ile Ser Ser Cys Thr Val Asp
100 Arg Asp Thr Val Cys Gly Cys Arg Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu
120 Phe Gln Cys Phe Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln
139 Glu Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu Asn Glu Cys
159 Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr Lys Leu Cys Leu Pro Gln Ile
179 Glu Asn Val Lys Gly Thr Glu Asp Ser Gly Thr Lys Asp Asp Phe Ser Ile Thr Leu Ile
199 Asn Tyr His Glu Gly Lys Lys Tyr Leu Ile Ile Leu Lys Arg Lys Leu Glu Lys Ala Asn Asn
220 Arg Asp Val Cys Asn Phe Phe Leu His Phe Ser Gln Val Asn Asn Val Leu Leu Glu
239 Arg Thr Ile Glu Thr Leu Leu Glu Cys Lys Asn Glu Tyr Val Lys Gly Glu Asn Gly Lys
259 Tyr Leu Ala Lys Gly His His Cys Val Glu Glu Asp Asn Leu Glu Arg Trp Leu Gln Gly

279 Thr Asn Glu Arg Arg Ser Glu Glu Asn Ile Lys Tyr Lys Tyr Gly Val Thr Glu Leu Lys Ile

300 Lys Tyr Ala Gln Met Asn Gly Lys Arg Ser Ser Arg Ile Leu Lys Glu Ser Ile Tyr Gly Ala

321 His Asn Phe Gly Gly Asn Ser Tyr Met Glu Gly Lys Asp Gly Gly Asp Lys Thr Gly Glu

341 Glu Lys Asp Gly Glu His Lys Thr Asp Ser Lys Thr Asp Asn Gly Lys Gly Ala Asn Asn

361 Leu Val Met Leu Asp Tyr Glu Thr Ser Ser Asn Gly Gln Pro Ala Gly Thr Leu Asp Asn

381 Val Leu Glu Phe Val Thr Gly His Glu Gly Asn Ser Arg Lys Asn Ser Ser Asn Gly Gly

401 Asn Pro Tyr Asp Ile Asp His Lys Lys Thr Ile Ser Ser Ala Ile Ile Asn His Ala Phe Leu

422 Gln Asn Thr Val Met Lys Asn Cys Asn Tyr Lys Arg Lys Arg Arg Glu Arg Asp Trp Asp

442 Cys Asn Thr Lys Lys Asp Val Cys Ile Pro Asp Arg Arg Tyr Gln Leu Cys Met Lys Glu

462 Leu Thr Asn Leu Val Asn Asn Thr Asp Thr Asn Phe His Arg Asp Ile Thr Phe Arg Lys

482 Leu Tyr Leu Lys Arg Lys Leu Ile Tyr Asp Ala Ala Val Glu Gly Asp Leu Leu Leu Lys

502 Leu Asn Asn Tyr Arg Tyr Asn Lys Asp Phe Cys Lys Asp Ile Arg Trp Ser Leu Gly Asp

522 Phe Gly Asp Ile Ile Met Gly Thr Asp Met Glu Ile Gly Tyr Ser Lys Val Val Glu Asn Asn

543 Leu Arg Ser Ile Phe Gly Thr Asp Glu Lys Ala Gln Gln Arg Arg Lys Gln Trp Trp Asn

563 Glu Ser Lys Ala Gln Ile Trp Thr Ala Met Met Tyr Ser Val Lys Lys Arg Leu Lys Gly Asn

584 Phe Ile Trp Ile Cys Lys Leu Asn Val Ala Val Asn Ile Glu Pro Gln Ile Tyr Arg Trp Ile

605 Arg Glu Trp Gly Arg Asp Tyr Val Ser Glu Leu Pro Thr Glu Val Gln Lys Leu Lys Glu

625 Lys Cys Asp Gly Lys Ile Asn Tyr Thr Asp Lys Lys Val Cys Lys Val Pro Pro Cys Gln

645 Asn Ala Cys Lys Ser Tyr Asp Gln Trp Ile Thr Arg Lys Lys Asn Gln Trp Asp Val Leu

665 Ser Asn Lys Phe Ile Ser Val Lys Asn Ala Glu Lys Val Gln Thr Ala Gly Ile Val Thr Pro

686 Tyr Asp Ile Leu Lys Gln Glu Leu Asp Glu Phe Asn Glu Val Ala Phe Glu Asn Glu Ile

706 Asn Lys Arg Asp Gly Ala Tyr Ile Glu Leu Cys Val Cys Ser Val Glu Glu Ala Lys Lys

726 Asn Thr Gln Glu Val Val Thr Asn Val Asp Asn Ala Ala Lys Ser Gln Ala Thr Asn Ser

746 Asn Pro Ile Ser Gln Pro Val Asp Ser Ser Lys Ala Glu Lys Val Pro Gly Asp Ser Thr

766 His Gly Asn Val Asn Ser Gly Gln Asp Ser Ser Thr Thr Gly Lys Ala Val Thr Gly Asp

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

806 Ser Val Ser Ala Lys Asn Val Asp Pro Gln Lys Ser Val Ser Lys Arg Ser Asp Asp Thr

826 Ala Ser Val Thr Gly Ile Ala Glu Ala Gly Lys Glu Asn Leu Gly Ala Ser Asn Ser Arg Pro

847 Ser Glu Ser Thr Val Glu Ala Asn Ser Pro Gly Asp Asp Thr Val Asn Ser Ala Ser Ile

867 Pro Val Val Ser Gly Glu Asn Pro Leu Val Thr Pro Tyr Asn Gly Leu Arg His Ser Lys
887 Asp Asn Ser Asp Ser Asp Gly Pro Ala Glu Ser Met Ala Asn Pro Asp Ser Asn Ser Lys
907 Gly Glu Thr Gly Lys Gly Gln Asp Asn Asp Met Ala Lys Ala Thr Lys Asp Ser Ser Asn
927 Ser Ser Asp Gly Thr Ser Ser Ala Thr Gly Asp Thr Thr Asp Ala Val Asp Arg Glu Ile
947 Asn Lys Gly Val Pro Glu Asp Arg Asp Lys Thr Val Gly Ser Lys Asp Gly Gly Gly Glu
967 Asp Asn Ser Ala Asn Lys Asp Ala Ala Thr Val Val Gly Glu Asp Arg Ile Arg Glu Asn
987 Ser Ala Gly Gly Ser Thr Asn Asp Arg Ser Lys Asn Asp Thr Glu Lys Asn Gly Ala Ser
1007 Thr Pro Asp Ser Lys Gln Ser Glu Asp Ala Thr Ala Leu Ser Lys Thr Glu Ser Leu Glu
1027 Ser Thr Glu Ser Gly Asp Arg Thr Thr Asn Asp Thr Thr Asn Ser Leu Glu Asn Lys Asn
1047 Gly Gly Lys Glu Lys Asp Leu Gln Lys His Asp Phe Lys Ser Asn Asp Thr Pro Asn Glu
1067 Glu Pro Asn Ser Asp Gln Thr Thr Asp Ala Glu Gly His Asp Arg Asp Ser Ile Lys Asn
1087 Asp Lys Ala Glu Arg Arg Lys His Met Asn Lys Asp Thr Phe Thr Lys Asn Thr Asn Ser
1107 His His Leu Asn Ser Asn Asn Asn Leu Ser Asn Gly Lys Leu Asp Ile Lys Glu Tyr Lys
1127 Tyr Arg Asp Val Lys Ala Thr Arg Glu Asp Ile Ile Leu Met Ser Ser Val Arg Lys Cys Asn
1148 Asn Asn Ile Ser Leu Glu Tyr Cys Asn Ser Val Glu Asp Lys Ile Ser Ser Asn Thr Cys
1168 Ser Arg Glu Lys Ser Lys Asn Leu Cys Cys Ser Ile Ser Asp Phe Cys Leu Asn Tyr Phe
1188 Asp Val Tyr Ser Tyr Glu Tyr Leu Ser Cys Met Lys Lys Glu Phe Glu Asp Pro Ser Tyr
1208 Lys Cys Phe Thr Lys Gly Gly Phe Lys Ile Asp Lys Thr Tyr Phe Ala Ala Ala Gly Ala
1228 Leu Leu Ile Leu Leu Leu Leu Ile Ala Ser Arg Lys Met Ile Lys Asn Asp Ile-COOH

A5 Examples of TNF-receptor malaria peptide fusion peptide.

In the following example the TNF receptor sequence is in accordance with H Loetscher et al Cell, Vol. 61, 351-359, April 20; 1990, p353, Fig. 2A, the malaria parasite components as referenced herein before,

A5 NH_2-TNF-R - GBP 130-COOH

An example of a polymer of an amino acid repeat sequence.

NH_2 - Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg
20 Asp Ser Val Cys Pro Gln Gly Lys Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr

40 Lys Cys His Lys Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp

60 Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu Arg His Cys Leu

80 Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val Glu Ile Ser Ser Cys Thr Val Asp

100 Arg Asp Thr Val Cys Gly Cys Arg Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu

120 Phe Gln Cys Phe Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln

139 Glu Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu Asn Glu Cys

159 Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr Lys Leu Cys Leu Pro Gln Ile

179 Glu Asn Val Lys Gly Thr Glu Asp Ser Gly Thr Asn Ala Tyr Ile Cys Gly Asp Lys Tyr

299 Glu Lys Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp Thr

219 Cys Ala Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg Thr

239 Val Ala Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln Lys

259 Val Glu Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile Asn

279 Ile Gly Asp Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu Lys

300 Lys Lys Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys Lys

320 Lys Glu Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn Asn

340 Glu Val Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr[Leu Thr Ser Ala Asp Pro Glu Gly

360 Gln Ile Met Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys

381 Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu

419 Asp]$_n$ Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu

nnn Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu

nnn Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

A6 NH_2-TNF-R - GBPH-COOH (glycophorin binding peptide homologue)

An example of a polymer of an amino acid repeat sequence.

NH_2 - Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg

20 Asp Ser Val Cys Pro Gln Gly Lys Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr

40 Lys Cys His Lys Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp

60 Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu Arg His Cys Leu

80 Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val Glu Ile Ser Ser Cys Thr Val Asp

100 Arg Asp Thr Val Cys Gly Cys Arg Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu

120 Phe Gln Cys Phe Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln

139 Glu Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu Asn Glu Cys

159 Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr Lys Leu Cys Leu Pro Gln Ile

179 Glu Asn Val Lys Gly Thr Glu Asp Ser Gly Thr Ser Gln Tyr Lys Gln Ala Ala Asp Tyr

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

219 Thr Ala Leu Arg Lys Thr Lys Gln Thr Thr Leu [Thr Ser Ala Asp Pro Glu Gly Gln Ile

239 Met Lys Ala Trp Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Asn Val Leu Tyr Gln Ile

259 Leu Asn Asn Thr Asp Pro Asn Asp Glu Leu Glu]$_n$ Thr Ser Ala Asp Pro Glu Gly Gln

nnn Ile Met Lys Ala Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Val Asn Val Leu Tyr Gln Ile

nnn Leu Asn Asn Thr Asp Pro Asn Asp Glu Ser Ser-COOH

Where n = a real number.

B1 NH_2 TNFR - GBP130-COOH

NH_2 - Gly Leu Val Pro His Leu Gly Asp Arg Glu Leu Arg Asp Ser Val Cys Pro Gln Gly

20 Lys Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys Gly Thr Tyr Leu

41 Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp Cys Arg Glu Cys Glu Ser Gly Ser

61 Phe Thr Ala Ser Glu Asn His Leu Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu

81 Met Gly Gln Val Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg

101 Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe Asn Cys Ser Leu

121 Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu Lys Gln Asn Thr Val Cys Thr Cys

141 His Ala Gly Phe Phe Leu Arg Glu Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser

161 Leu Glu Cys Thr Lys Leu Cys Leu Pro Gln Ile Glu Asn Asn Ala Tyr Ile Cys Gly Asp

181 Lys Tyr Glu Lys Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu

201 Asp Thr Cys Ala Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr

221 Arg Thr Val Ala Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu

241 Gln Lys Val Glu Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln

261 Ile Asn Ile Gly Asp Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys

282 Glu Lys Lys Lys Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser

302 Lys Lys Lys Glu Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser

322 Asn Asn Glu Val Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro

342 Glu Gly Gln Ile Met Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe

363 Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn

383 Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp

403 Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn

423 Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu

443 Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His

464 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys

484 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro

504 Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

524 Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly

544 Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys

564 Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu

584 Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr

604 Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val

624 Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile

644 Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu

665 Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu

685 Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys

706 His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg

726 Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg

746 Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn

767 Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser

787 Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His

807 Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg

827 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu

847 Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr

868 Asp Pro Asn Asp Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

C1 NH_2 - TBPI - GBP130 - COOH

NH_2 - Asp Ser Val Cys Pro Gln Gly Lys Tyr Ile His Pro Gln Gly Gln Val Glu Ile Ser

20 Ser Cys Thr Val Asp Arg Asp Thr Val Ile Glu Asn Asn Ala Tyr Ile Cys Gly Asp Lys

40 Tyr Glu Lys Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp

60 Thr Cys Ala Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg

80 Thr Val Ala Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln

100 Lys Val Glu Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile

120 Asn Ile Gly Asp Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu

141 Lys Lys Lys Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys

161 Lys Lys Glu Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn

181 Asn Glu Val Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu

201 Gly Gln Ile Met Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr

222 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys

242 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro

262 Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

282 Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly

302 Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys

323 Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu

343 Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu

363 Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu

383 Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln

403 Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile

424 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu

444 Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys

465 His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg

485 Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg

505 Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn

526 Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser

546 Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His

566 Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg

586 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu

606 Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr

627 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala

647 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu

667 Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn

687 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr

707 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp

728 Pro Asn Asp Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

D1 $\underline{NH_2 - TBPII - GBP130 - COOH}$

NH_2 - Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg

20 Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys Ser Thr Ser Asp Thr Val Cys Asp Ser

40 Cys Glu Asp Ser Thr Tyr Thr Gln Leu Trp Asn Ile Cys Thr Cys Arg Pro Gly Trp Tyr

60 Cys Ala Leu Ser Cys Arg Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp

80 Val Val Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Ala Tyr Ile Cys Gly Asp Lys

100 Tyr Glu Lys Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp

120 Thr Cys Ala Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg

140 Thr Val Ala Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln

160 Lys Val Glu Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile

180 Asn Ile Gly Asp Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu

201 Lys Lys Lys Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys

221 Lys Lys Glu Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn

241 Asn Glu Val Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu

261 Gly Gln Ile Met Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr

282 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys

302 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro

322 Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

342 Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly

362 Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys
403 Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu
423 Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu
443 Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu
463 Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln
483 Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile
504 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu
524 Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys
545 His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg
565 Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg
585 Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn
606 Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser
626 Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His
646 Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg
666 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu
686 Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr
707 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala
727 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu
747 Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn
767 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr
787 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp
808 Pro Asn Asp Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

D2 NH_2 - TNFR - GBP 130 - COOH

NH_2 - Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg
20 Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys Ser Thr Ser Asp Thr Val Cys Asp Ser
40 Cys Glu Asp Ser Thr Tyr Thr Gln Leu Trp Asn Ile Cys Thr Cys Arg Pro Gly Trp Tyr
60 Cys Ala Leu Ser Cys Arg Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Thr
80 Val Val Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Ala Tyr Ile Cys Gly Asp Lys

100 Tyr Glu Lys Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp

120 Thr Cys Ala Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg

140 Thr Val Ala Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln

160 Lys Val Glu Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile

180 Asn Ile Gly Asp Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu

201 Lys Lys Lys Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys

221 Lys Lys Glu Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn

241 Asn Glu Val Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu

261 Gly Gln Ile Met Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr

282 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys

302 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro

322 Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

342 Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly

362 Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys

383 Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu

403 Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu

423 Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu

443 Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln

463 Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile

484 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu

504 Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys

525 His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg

545 Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg

565 Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn

586 Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser

606 Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His

626 Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg

646 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu

666 Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr

687 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala

707 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu

727 Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn

747 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr

767 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp

788 Pro Asn Asp Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

E1 NH_2 - γIFN-R - GBP 130 - COOH

NH_2 Ser Arg Ala Glu Met Gly Thr Ala Asp Leu Gly Pro Ser Ser Val Pro Thr Pro Thr

20 Asn Val Thr Ile Glu Ser Tyr Asn Met Asn Pro Ile Val Tyr Trp Glu Tyr Gln Ile Met

40 Pro Gln Val Pro Val Phe Thr Val Glu Val Lys Asn Tyr Gly Val Lys Asn Ser Glu Trp

60 Ile Asp Ala Cys Ile Asn Ile Ser His His Tyr Cys Asn Ile Ser Asp His Val Gly Asp Pro

81 Ser Asn Ser Leu Trp Val Arg Val Lys Ala Arg Val Gly Gln Lys Glu Ser Ala Tyr Ala Lys

102 Ser Glu Glu Phe Ala Val Cys Arg Asp Gly Lys Ile Gly Pro Pro Lys Leu Asp Ile Arg

122 Lys Glu Glu Lys Gln Ile Met Ile Asp Ile Phe His Pro Ser Val Phe Val Asn Gly Asp Glu

143 Gln Glu Val Asp Tyr Asp Pro Glu Thr Thr Cys Tyr Ile Arg Val Tyr Asn Val Tyr Val Arg

164 Met Asn Gly Ser Glu Ile Gln Tyr Lys Ile Leu Thr Gln Lys Glu Asp Asp Cys Asp Glu

184 Ile Gln Cys Gln Leu Ala Ile Pro Val Ser Ser Leu Asn Ser Gln Tyr Cys Val Ser Ala Glu

205 Gly Val Leu His Val Trp Gly Val Thr Thr Glu Lys Ser Lys Glu Val Cys Ile Thr Ile Phe

226 Asn Ser Ser Ile Lys Gly Asn Ala Tyr Ile Cys Gly Asp Lys Tyr Glu Lys Ala Val Asp Tyr

247 Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp Thr Cys Ala Arg Lys Glu Lys

267 Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg Thr Val Ala Thr Gln Thr Lys

287 Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln Lys Val Glu Ser Asp Ser Glu

307 Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile Asn Ile Gly Asp Thr Glu Asn Gln

328 Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu Lys Lys Lys Glu Glu Ser Gly Lys

349 Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys Lys Lys Glu Pro Lys Ala Ser Lys

369 Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn Asn Glu Val Lys Ile Arg Ala Ala Ser

390 Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Thr Ala Ala

410 Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro

430 Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro

450 Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe

471 Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn

491 Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp

511 Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn

531 Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu

551 Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His

572 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys

592 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro

611 Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

631 Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln

651 Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile

671 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp

691 Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg

712 Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu

732 Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met

752 Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr

773 Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr

793 Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His

814 Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg

834 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu

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

875 Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala

895 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu

915 Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Gln Asn

935 Ala Asp Asn Asn Glu Ala-COOH

F1 NH_2 - IL-1R type II - GBP 130 - COOH

NH_2 - Met Leu Arg Leu Tyr Val Leu Val Met Gly Val Ser Ala Phe Thr Leu Gln Pro Ala

20 Ala His Thr Gly Ala Ala Arg Ser Cys Arg Phe Arg Gly Arg His Tyr Lys Arg Glu Phe

40 Arg Leu Glu Gly Glu Pro Val Ala Leu Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala

60 Ser Val Ser Pro Arg Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val Pro

80 Gly Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp Leu Leu Pro Ala Leu

100 Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr Arg Asn Ala Ser Tyr Cys Asp Lys Met

120 Ser Ile Glu Ile Leu Arg Val Phe Glu Asn Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro

141 Asp Ile Leu Thr Leu Ser Thr Ser Gly Val Leu Val Cys Phe Asp Leu Ser Glu Phe Thr

161 Arg Asp Lys Thr Asp Val Lys Ile Asp Trp Tyr Lys Asp Ser Leu Leu Leu Asp Lys Asp

181 Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr His Leu Leu Val His Asp Val Ala Leu

201 Glu Asp Arg Gly Tyr Tyr Arg Cys Val Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn

221 Ile Thr Arg Ser Ile Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro His Ile Ile Ser

243 Pro Leu Lys Thr Ile Ser Arg Ser Leu Gly Ser Arg Leu Thr Ile Pro Cys Lys Val Phe

263 Leu Gly Thr Gly Thr Pro Leu Thr Thr Met Leu Trp Trp Thr Ala Asn Asp Thr His Ile

283 Glu Ser Ala Tyr Pro Gly Gly Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn

303 Asn Glu Asn Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu Asp Leu His

323 Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe Gln Thr Leu Arg Thr Thr Val

343 Lys Glu Asn Ala Tyr Ile Cys Gly Asp Lys Tyr Glu Lys Ala Val Asp Tyr Gly Phe Arg

363 Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp Thr Cys Ala Arg Lys Glu Lys Thr Thr Leu

383 Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg Thr Val Ala Thr Gln Thr Lys Lys Asp Glu

403 Glu Asn Lys Ser Val Val Thr Glu Glu Gln Lys Val Glu Ser Asp Ser Glu Lys Gln Lys

423 Arg Thr Lys Lys Val Val Lys Lys Gln Ile Asn Ile Gly Asp Thr Glu Asn Gln Lys Glu Gly

444 Lys Asn Val Lys Lys Val Ile Lys Lys Glu Lys Lys Lys Glu Glu Ser Gly Lys Pro Glu Glu

465 Asn Lys His Ala Asn Glu Ala Ser Lys Lys Lys Glu Pro Lys Ala Ser Lys Val Ser Gln

485 Lys Pro Ser Thr Ser Thr Arg Ser Asn Asn Glu Val Lys Ile Arg Ala Ala Ser Asn Gln

505 Glu Thr Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Thr Ala Ala Asp Pro

525 Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

545 Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly

565 Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys

586 Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu

606 Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu

626 Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu

646 Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln

666 Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile

687 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp

707 Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg

727 Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu

747 Arg Arg Asn Ala Asp Asn Lys Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg

767 Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn

788 Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser

808 Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu

829 Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn

849 Ala Asp Asn Lys Glu Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr

869 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp

890 Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp

910 Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile

931 Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp

951 Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser

971 Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro

991 Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro

1010 Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe

1030 His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Gln Asn Ala Asp Asn

1050 Asn Glu Ala-COOH

G1 <u>NH_2-IL1R type 1 - GBP130 - COOH</u>

NH_2 - Met Lys Val Leu Leu Arg Leu Ile Cys Phe Ile Ala Leu Leu Ile Ser Ser Leu Glu

20 Ala Asp Lys Cys Lys Glu Arg Glu Glu Lys Ile Ile Leu Val Ser Ser Ala Asn Glu Ile Asp

41 Val Arg Pro Cys Pro Leu Asn Pro Asn Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp
61 Asp Ser Lys Thr Pro Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys Glu Lys Leu
82 Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr Tyr Cys Val Val Arg Asn Ser
102 Ser Tyr Cys Leu Arg Ile Lys Ile Ser Ala Lys Phe Val Glu Asn Glu Pro Asn Leu Cys
122 Tyr Asn Ala Gln Ala Ile Phe Lys Asp Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val
142 Cys Phe Tyr Met Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu Trp Tyr
161 Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe Ser Gly Val Lys Asp Arg Leu
181 Ile Val Met Asn Val Arg Glu Lys His Arg Gly Asn Tyr Thr Cys His Ala Ser Tyr Thr Tyr
202 Leu Gly Lys Gln Tyr Pro Ile Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro
223 Thr Arg Pro His Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val Asp Leu Gly Ser Gln Ile
244 Gln Leu Ile Cys Asn Val Thr Gly Gln Leu Ser Asp Ile Ala Tyr Trp Lys Trp Asn Gly Ser
265 Val Ile Asp Glu Asp Asp Pro Val Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala
285 Asn Lys Arg Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu Ser Arg Phe Tyr
305 Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile Asp Ala Ala Tyr Ile Gln Leu
326 Ile Tyr Pro Val Thr Asn Phe Gln Lys Asn Ala Tyr Ile Cys Gly Asp Lys Tyr Glu Lys Ala
347 Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp Thr Cys Ala Arg
367 Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg Thr Val Ala Thr
387 Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln Lys Val Glu Ser
407 Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile Asn Ile Gly Asp Thr
428 Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu Lys Lys Lys Glu
448 Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys Lys Lys Glu Pro
468 Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn Asn Glu Val Lys
488 Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu Gly Ile Met Arg Glu
509 Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr
530 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala
550 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu
570 Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn
590 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr
610 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr

630 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala

650 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu

670 Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn

690 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr

710 Ala Ala Asp Pro Glu Thr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr

730 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu Thr Ser Ser Asp

750 Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile

771 Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp

791 Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala

811 Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro

831 Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser Ser Asp Pro

851 Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe

872 His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn

892 Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp

912 Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn

932 Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu

952 Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr

973 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys

993 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro

1013 Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

1033 Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

H1 <u>NH_2 - IL2-R - GBP 130 - COOH</u>

NH_2-Glu Leu Cys Asp Asp Asp Pro Pro Glu Ile Pro His Ala Thr Phe Lys Ala Met Ala

20 Tyr Lys Glu Gly Thr Met Leu Asn Cys Glu Cys Lys Arg Gly Phe Arg Arg Ile Lys Ser

40 Gly Ser Leu Tyr Met Leu Cys Thr Gly Asn Ser Ser His Ser Ser Trp Asp Asn Gln Cys

60 Gln Cys Thr Ser Ser Ala Thr Arg Asn Thr Thr Lys Gln Val Thr Pro Gln Pro Glu Glu

80 Gln Lys Glu Arg Lys Thr Thr Glu Met Gln Ser Pro Met Gln Pro Val Asp Gln Ala Ser

100 Leu Pro Gly His Cys Arg Glu Pro Pro Pro Trp Glu Asn Glu Ala Thr Glu Arg Ile Tyr His

121 Phe Val Val Gly Gln Met Val Tyr Tyr Gln Cys Val Gln Gly Tyr Arg Ala Leu His Arg
141 Gly Pro Ala Glu Ser Val Cys Lys Met Thr His Gly Lys Thr Arg Trp Thr Gln Pro Gln
161 Leu Ile Cys Thr Gly Glu Met Glu Thr Ser Gln Phe Pro Gly Glu Glu Lys Pro Gln Ala
181 Ser Pro Glu Gly Arg Pro Glu Ser Glu Thr Ser Cys Leu Val Thr Thr Thr Asp Phe Gln
201 Ile Gln Thr Glu Met Ala Ala Thr Met Glu Thr Ser Ile Phe Thr Thr Glu Tyr Gln Asn Ala
222 Tyr Ile Cys Gly Asp Lys Tyr Glu Lys Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu
243 Ala Glu Gly Glu Asp Thr Cys Ala Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln
263 Lys Thr Ser Thr Arg Thr Val Ala Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val
283 Val Thr Glu Glu Gln Lys Val Glu Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val
303 Val Lys Lys Gln Ile Asn Ile Gly Asp Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys
324 Val Ile Lys Lys Glu Lys Lys Lys Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala
344 Asn Glu Ala Ser Lys Lys Lys Glu Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr
364 Ser Thr Arg Ser Asn Asn Glu Val Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr
384 Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His
405 Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg
425 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu
445 Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr
466 Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala
486 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu
506 Glu Val Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn
526 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr
546 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp
567 Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp
587 Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val
608 Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp
628 Asn Lys Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp
648 Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn
669 Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu
689 Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr

710 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys
730 Glu Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro
750 Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp
770 Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly
790 Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys
811 Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu
831 Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu
851 Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp
871 Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln
891 Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile
911 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu
930 Ala-COOH

H2 NH_2 - IL2-R - GPB 130 - COOH

NH_2-Ala Glu Leu Cys Asp Asp Asp Pro Pro Glu Ile Pro His Ala Thr Phe Lys Ala Met
20 Ala Tyr Lys Glu Gly Thr Met Leu Asn Cys Glu Cys Lys Arg Gly Phe Arg Arg Ile Lys
40 Ser Gly Ser Leu Tyr Met Leu Cys Thr Gly Asn Ser Ser His Ser Ser Trp Asp Asn Gln
60 Cys Gln Cys Thr Ser Ser Ala Thr Arg Asn Thr Thr Lys Gln Val Thr Pro Gln Pro Glu
80 Glu Gln Lys Glu Arg Lys Thr Thr Lys Ile Gln Ser Pro Met Gln Pro Val Asp Gln Ala
100 Ser Leu Pro Gly His Cys Arg Glu Pro Pro Pro Trp Glu Asn Glu Ala Thr Glu Arg Ile
120 Tyr His Phe Val Val Gly Gln Met Val Tyr Tyr Gln Cys Val Gln Gly Tyr Arg Ala Leu His
141 Arg Gly Pro Ala Glu Ser Val Cys Lys Met Thr His Gly Lys Thr Arg Trp Thr Gln Pro
161 Gln Leu Ile Cys Thr Gly Glu Met Glu Thr Ser Gln Phe Pro Gly Glu Glu Lys Pro Gln
181 Ala Ser Pro Glu Gly Arg Pro Glu Ser Glu Thr Ser Cys Leu Val Thr Thr Thr Asp Phe
201 Gln Ile Gln Thr Glu Met Ala Ala Thr Met Glu Thr Ser Ile Phe Thr Thr Glu Tyr Asn Ala
222 Tyr Ile Cys Gly Asp Lys Tyr Glu Lys Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu
243 Ala Glu Gly Glu Asp Thr Cys Ala Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln
263 Lys Thr Ser Thr Arg Thr Val Ala Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val
283 Val Thr Glu Glu Gln Lys Val Glu Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val

303 Val Lys Lys Gln Ile Asn Ile Gly Asp Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys

324 Val Ile Lys Lys Glu Lys Lys Lys Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala

344 Asn Glu Ala Ser Lys Lys Lys Glu Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr

364 Ser Thr Arg Ser Asn Asn Glu Val Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr

384 Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His

404 Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg

424 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu

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

465 Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala

585 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu

505 Glu Val Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn

525 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr

545 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp

566 Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp

586 Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val

607 Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp

627 Asn Lys Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp

647 Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn

667 Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu

687 Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr

708 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys

728 Glu Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro

748 Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

768 Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly

788 Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys

809 Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu

829 Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu

849 Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp

869 Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln

889 Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile
910 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu
929 Ala-COOH

H3 NH_2 - IL2-R - GBP 130 - COOH

NH_2-Ala Val Asn Gly Thr Ser Gln Phe Thr Cys Phe Tyr Asn Ser Arg Ala Asn Ile Ser
20 Cys Val Trp Ser Gln Asp Gly Ala Leu Gln Asp Thr Ser Cys Gln Val His Ala Trp Pro
40 Asp Arg Arg Arg Trp Asn Gln Thr Cys Glu Leu Leu Pro Val Ser Gln Ala Ser Trp Ala
60 Cys Asn Leu Ile Leu Gly Ala Pro Asp Ser Gln Lys Leu Thr Thr Val Asp Ile Val Thr
80 Leu Arg Val Leu Cys Arg Glu Gly Val Arg Trp Arg Val Met Ala Ile Gln Asp Phe Lys
100 Pro Phe Glu Asn Leu Arg Leu Met Ala Pro Ile Ser Leu Gln Val Val His Val Glu Thr
120 His Arg Cys Asn Ile Ser Trp Glu Ile Ser Gln Ala Ser His Tyr Phe Glu Arg His Leu Glu
141 Phe Glu Ala Arg Thr Leu Ser Pro Gly His Thr Trp Glu Glu Ala Pro Leu Leu Thr Leu
161 Lys Gln Lys Gln Glu Trp Ile Cys Leu Glu Thr Leu Thr Pro Asp Thr Gln Tyr Glu Phe
181 Gln Val Arg Val Lys Pro Leu Gln Gly Glu Phe Thr Thr Trp Ser Pro Trp Ser Gln Pro
201 Leu Ala Phe Arg Thr Lys Pro Ala Ala Leu Gly Lys Asp Thr Asn Ala Tyr Ile Cys Gly
221 Asp Lys Tyr Glu Lys Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly
241 Glu Asp Thr Cys Ala Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser
261 Thr Arg Thr Val Ala Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu
281 Glu Gln Lys Val Glu Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys
301 Gln Ile Asn Ile Gly Asp Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys
322 Lys Glu Lys Lys Lys Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala
342 Ser Lys Lys Lys Glu Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg
362 Ser Asn Asn Glu Val Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp
382 Pro Glu Gly Gln Ile Met Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile
403 Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp
423 Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser
443 Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro
463 Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro

483 Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe
504 His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn
524 Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp
544 Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn
564 Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu
584 Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His
605 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys
625 Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu
645 Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu
665 Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln
685 Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile
706 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu
726 Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr
747 Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val
767 Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile
787 Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu
808 Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu
828 Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys
849 His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg
869 Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg
889 Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn
910 Thr Asp Pro Asn Asp Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

I1 $\underline{NH_2 - IL\text{-}3R - GBP\ 130 - COOH}$

NH_2 - Thr Lys Glu Asp Pro Asn Pro Pro Ile Thr Asn Leu Arg Met Lys Ala Lys Ala Gln
20 Gln Leu Thr Trp Asp Leu Asn Arg Asn Val Thr Asp Ile Glu Cys Val Lys Asp Ala Asp
40 Tyr Ser Met Pro Ala Val Asn Asn Ser Tyr Cys Gln Phe Gly Ala Ile Ser Leu Cys Glu
60 Val Thr Asn Tyr Thr Val Arg Val Ala Asn Pro Pro Phe Ser Thr Trp Ile Leu Phe Pro
80 Glu Asn Ser Gly Lys Pro Trp Ala Gly Ala Glu Asn Leu Thr Cys Trp Ile His Asp Val

100 Asp Phe Leu Ser Cys Ser Trp Ala Val Gly Pro Gly Ala Pro Ala Asp Val Gln Tyr Asp

120 Leu Tyr Leu Asn Val Ala Asn Arg Arg Gln Gln Tyr Glu Cys Leu His Tyr Lys Thr Asp

140 Ala Gln Gly Thr Arg Ile Gly Cys Arg Phe Asp Asp Ile Ser Arg Leu Ser Ser Gly Ser

160 Gln Ser Ser His Ile Leu Val Arg Gly Arg Ser Ala Ala Phe Gly Ile Pro Cys Thr Asp

180 Lys Phe Val Val Phe Ser Gln Ile Glu Ile Leu Thr Pro Pro Asn Met Thr Ala Lys Cys

200 Asn Lys Thr His Ser Phe Met His Trp Lys Met Arg Ser His Phe Asn Arg Lys Phe Arg

220 Tyr Glu Leu Gln Ile Gln Lys Arg Met Gln Pro Val Ile Thr Glu Gln Val Arg Asp Arg Thr

241 Ser Phe Gln Leu Leu Asn Pro Gly Thr Tyr Thr Val Gln Ile Arg Ala Arg Glu Arg Val

261 Tyr Glu Phe Leu Ser Ala Trp Ser Thr Pro Gln Arg Phe Glu Cys Asp Gln Glu Glu Gly

281 Ala Asn Thr Arg Ala Trp Arg Asn Ala Tyr Ile Cys Gly Asp Lys Tyr Glu Lys Ala Val Asp

302 Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp Thr Cys Ala Arg Lys Glu

322 Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg Thr Val Ala Thr Gln Thr

342 Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln Lys Val Glu Ser Asp Ser

362 Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile Asn Ile Gly Asp Thr Glu Asn

383 Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu Lys Lys Lys Glu Glu Ser Gly

404 Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys Lys Lys Glu Pro Lys Ala Ser

424 Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn Asn Glu Val Lys Ile Arg Ala Ala

445 Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Thr Ala

465 Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro

486 Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro

506 Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe

527 Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn

547 Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp

567 Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn

587 Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu

607 Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His

628 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys

648 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro

668 Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

688 Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln
708 Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile
729 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp
749 Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg
770 Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu
790 Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met
810 Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr
831 Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr
851 Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His
872 Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg
892 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu
912 Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr
933 Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala
953 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu
973 Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Gln Asn
993 Ala Asp Asn Asn Glu Ala-COOH

J1 <u>NH_2 - IL-5R - GBP 130 - COOH</u>

NH_2-Met Lys Val Leu Gln Glu Pro Thr Cys Val Ser Asp Thr Met Ser Ile Ser Thr Cys
20 Glu Trp Lys Met Asn Gly Pro Thr Asn Cys Ser Thr Glu Leu Arg Leu Leu Tyr Gln Leu
40 Val Phe Leu Leu Ser Glu Ala His Thr Cys Ile Pro Glu Asn Asn Gly Gly Ala Gly Cys
60 Val Cys His Leu Leu Met Asp Asp Val Val Ser Ala Asp Asn Tyr Thr Leu Asp Leu Trp
80 Ala Gly Gln Gln Leu Leu Trp Lys Gly Ser Phe Lys Pro Ser Glu His Val Lys Pro Arg
100 Ala Pro Gly Asn Leu Thr Val His Thr Asn Val Ser Asp Thr Leu Leu Leu Thr Trp Ser
120 Asn Pro Tyr Pro Pro Asp Asn Tyr Leu Tyr Asn His Leu Thr Tyr Ala Val Asn Ile Trp
140 Ser Glu Asn Asp Pro Ala Asp Phe Arg Ile Tyr Asn Val Thr Tyr Leu Glu Pro Ser Leu
160 Arg Ile Ala Ala Ser Thr Leu Lys Ser Gly Ile Ser Tyr Arg Ala Arg Val Arg Ala Trp Ala
181 Gln Cys Tyr Asn Thr Thr Trp Ser Glu Trp Ser Pro Ser Thr Lys Trp His Asn Ser Tyr
201 Arg Glu Pro Phe Glu Gln His Asn Ala Tyr Ile Cys Gly Asp Lys Tyr Glu Lys Ala Val

221 Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp Thr Cys Ala Arg Lys

241 Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg Thr Val Ala Thr Gln

261 Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln Lys Val Glu Ser Asp

281 Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile Asn Ile Gly Asp Thr Glu

302 Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu Lys Lys Lys Glu Glu

322 Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys Lys Lys Glu Pro Lys

342 Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn Asn Glu Val Lys Ile Arg

363 Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu

383 Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr

404 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala

420 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu

444 Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn

464 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr

484 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr

504 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala

524 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu

544 Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn

564 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr

584 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr

604 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu Thr Ser Ser Asp

624 Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile

645 Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp

665 Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala

685 Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro

705 Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser Ser Asp Pro

725 Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe

746 His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn

766 Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp

786 Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn

806 Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu
826 Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr
847 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys
867 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro
887 Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp
907 Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

K1 NH_2-IL-6R - GBP 130 - COOH

NH_2 - Asp Leu Leu Pro Asp Glu Lys Ile Ser Leu Leu Pro Pro Val Asn Phe Thr Ile Lys
20 Val Thr Gly Leu Ala Gln Val Leu Leu Gln Trp Lys Pro Asn Pro Asp Gln Glu Gln Arg
40 Asn Val Asn Leu Glu Tyr Gln Val Lys Ile Asn Ala Pro Lys Glu Asp Asp Tyr Glu Thr
61 Arg Ile Thr Glu Ser Lys Cys Val Thr Ile Leu His Lys Gly Phe Ser Ala Ser Val Arg Thr
82 Ile Leu Gln Asn Asp His Ser Leu Leu Ala Ser Ser Trp Ala Ser Ala Glu Leu His Ala
102 Pro Pro Gly Ser Pro Gly Thr Ser Ile Val Asn Leu Thr Cys Thr Thr Asn Thr Thr Glu
122 Asp Asn Tyr Ser Arg Leu Arg Ser Tyr Gln Val Ser Leu His Cys Thr Trp Leu Val Gly
142 Thr Asp Ala Pro Glu Asp Thr Gln Tyr Phe Leu Tyr Tyr Arg Tyr Gly Ser Trp Thr Glu
162 Glu Cys Gln Glu Tyr Ser Lys Asp Thr Leu Gly Arg Asn Ile Ala Cys Trp Phe Pro Arg
182 Thr Phe Ile Leu Ser Lys Gly Arg Asp Trp Leu Ser Val Leu Val Asn Gly Ser Ser Lys
202 His Ser Ala Ile Arg Pro Phe Asp Gln Leu Phe Ala Leu His Ala Ile Asp Gln Ile Asn Pro
223 Pro Leu Asn Val Thr Ala Glu Ile Glu Gly Thr Arg Leu Ser Ile Gln Trp Glu Lys Pro Val
244 Ser Ala Phe Pro Ile His Cys Phe Asp Tyr Glu Val Lys Ile His Asn Thr Arg Asn Gly Tyr
265 Leu Gln Ile Glu Lys Leu Met Thr Asn Ala Phe Ile Ser Ile Ile Asp Asp Leu Ser Lys Tyr
286 Asp Val Gln Val Arg Ala Ala Val Ser Ser Met Cys Arg Glu Ala Gly Leu Trp Ser Glu
306 Trp Ser Gln Pro Ile Tyr Val Gly Phe Ser Arg Asn Ala Tyr Ile Cys Gly Asp Lys Tyr Glu
327 Lys Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp Thr Cys
347 Ala Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg Thr Val
367 Ala Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln Lys Val
387 Glu Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile Asn Ile Gly
408 Asp Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu Lys Lys

428 Lys Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys Lys Lys

448 Glu Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn Asn Glu

468 Val Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile

489 Met Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu

510 Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu

530 Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys

551 His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg

571 Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg

591 Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr

611 Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr

631 Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His

652 Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg

672 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu

692 Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr

713 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu Thr Ser Ser Asp

733 Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile

754 Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp

774 Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala

794 Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro

814 Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser Ser Asp Pro

834 Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe

855 His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn

875 Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp

896 Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn

916 Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu

936 Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr

957 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys

977 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro

997 Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

1017 Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

L1 NH_2 - IL-8 R type 1 - GBP 130 - COOH

NH_2 - Leu Ala Pro Arg Arg Cys Pro Ala Gln Glu Val Ala Arg Gly Val Leu Thr Ser Leu

20 Pro Gly Asp Ser Val Thr Leu Thr Cys Pro Gly Val Glu Pro Glu Asp Asn Ala Thr Val

40 His Trp Val Leu Arg Lys Pro Ala Ala Gly Ser His Pro Ser Arn Trp Ala Gly Met Gly Arg

61 Arg Leu Leu Leu Arg Ser Val Gln Leu His Asp Ser Gly Asn Tyr Ser Cys Tyr Ala Gly

81 Arg Pro Ala Gly Thr Val His Leu Leu Val Asp Val Pro Pro Glu Glu Pro Gln Leu Ser

101 Cys Phe Arg Lys Ser Pro Leu Ser Asn Val Val Cys Glu Trp Gly Pro Arg Ser Thr Pro

121 Ser Leu Thr Thr Lys Ala Val Leu Leu Val Arg Lys Phe Gln Asn Ser Pro Ala Glu Asp

141 Phe Gln Glu Ser Gln Lys Phe Ser Cys Gln Leu Ala Val Pro Glu Gly Asp Ser Ser Phe

161 Tyr Ile Val Ser Met Cys Val Ala Ser Ser Val Gly Ser Lys Phe Ser Lys Thr Gln Thr

181 Phe Gln Gly Cys Gly Ile Leu Gln Pro Asp Pro Pro Ala Asn Ile Thr Val Thr Ala Val Ala

202 Arg Asn Pro Arg Trp Leu Ser Val Thr Trp Gln Asp Pro His Ser Trp Asn Ser Ser Phe

222 Tyr Arg Leu Arg Phe Glu Leu Arg Tyr Arg Ala Glu Arg Ser Lys Thr Phe Thr Thr Trp

242 Met Val Lys Asp Leu Gln His His Cys Val Ile His Asp Ala Trp Ser Gly Leu Arg His Val

263 Val Gln Leu Arg Ala Gln Glu Glu Phe Gly Gln Gly Glu Trp Ser Glu Trp Ser Pro Glu

283 Ala Met Gly Thr Pro Trp Thr Glu Ser Arg Ser Pro Pro Ala Glu Asn Glu Val Ser Thr

303 Pro Met Gln Ala Leu Thr Thr Asn Lys Asp Asp Asp Asn Ile Leu Phe Arg Asp Ser Ala

323 Asn Ala Thr Ser Leu Pro Val Gln Asp Asn Ala Tyr Ile Cys Gly Asp Lys Tyr Glu Lys

343 Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp Thr Cys Ala

363 Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg Thr Val Ala

383 Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln Lys Val Glu

404 Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile Asn Ile Gly Asp

425 Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu Lys Lys Lys

445 Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys Lys Lys Glu

465 Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn Asn Glu Val

485 Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met

506 Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr

527 Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr
547 Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His
568 Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg
588 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu
608 Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr
629 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala
649 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu
669 Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn
689 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr
709 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr
729 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu Thr Ser Ser Asp
749 Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile
770 Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp
790 Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala
810 Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro
830 Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser Ser Asp Pro
850 Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe
871 His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn
891 Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp
911 Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn
931 Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu
951 Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr
972 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys
992 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro
1011 Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp
1031 Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

M1 NH_2 - IL-8 R type 1 - GBP 130 - COOH

NH_2-Met Ser Asn Ile Thr Asp Pro Gln Met Trp Asp Phe Asp Asp Leu Asn Phe Thr Gly

20 Met Pro Pro Ala Asp Glu Asp Tyr Ser Pro Cys Met Leu Glu Thr Glu Thr Leu Asn Lys

40 Tyr Val Val Ile Ile Ala Tyr Ala Leu Val Phe Leu Leu Ser Leu Leu Gly Asn Ser Leu Val

61 Met Leu Val Ile Leu Tyr Ser Arg Val Gly Arg Ser Val Thr Asp Val Tyr Leu Leu Asn

81 Leu Ala Leu Ala Asp Leu Leu Phe Ala Leu Thr Leu Pro Ile Trp Ala Ala Ser Lys Val

101 Asn Gly Trp Ile Phe Gly Thr Phe Leu Cys Lys Val Val Ser Leu Leu Lys Glu Val Asn

121 Phe Tyr Ser Gly Ile Leu Leu Leu Ala Cys Ile Ser Val Asp Arg Tyr Leu Ala Ile Val His

142 Ala Thr Arg Thr Leu Thr Gln Lys Arg His Leu Val Lys Phe Val Cys Leu Gly Cys Trp

162 Gly Leu Ser Met Asn Leu Ser Leu Pro Phe Phe Leu Phe Arg Gln Ala Tyr His Pro Asn

182 Asn Ser Ser Pro Val Cys Tyr Glu Val Leu Gly Asn Asp Thr Ala Lys Trp Arg Met Val

202 Leu Arg Ile Leu Pro His Thr Phe Gly Phe Ile Val Pro Leu Phe Val Met Leu Phe Cys

222 Tyr Gly Phe Thr Leu Arg Thr Leu Phe Lys Ala His Met Gly Gln Lys His Arg Ala Met

242 Arg Val Ile Phe Ala Val Val Leu Ile Phe Leu Leu Cys Trp Leu Pro Tyr Asn Leu Val

262 Leu Leu Ala Asp Thr Leu Met Arg Thr Gln Val Ile Gln Glu Thr Cys Glu Arg Arg Asn

282 Asn Ile Gly Arg Ala Leu Asp Ala Thr Glu Ile Leu Gly Phe Leu His Ser Cys Leu Asn

302 Pro Ile Ile Tyr Ala Phe Ile Gly Gln Asn Phe Arg His Gly Phe Leu Lys Ile Leu Ala Met

322 His Gly Leu Val Ser Lys Glu Phe Leu Ala Arg His Arg Val Thr Ser Tyr Thr Ser Ser

342 Ser Val Asn Val Ser Ser Asn Leu Asn Ala Tyr Ile Cys Gly Asp Lys Tyr Glu Lys Ala

362 Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp Thr Cys Ala Arg

382 Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg Thr Val Ala Thr

402 Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln Lys Val Glu Ser

423 Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile Asn Ile Gly Asp Thr

443 Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu Lys Lys Lys Glu

463 Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys Lys Lys Glu Pro

483 Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn Asn Glu Val Lys

503 Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu Gly Ile Met Arg Glu

524 Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr

545 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala

565 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu

585 Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn

605 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr

625 Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr

645 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala

665 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu

685 Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn

705 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr

725 Ala Ala Asp Pro Glu Thr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr

745 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu Thr Ser Ser Asp

765 Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile

786 Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp

806 Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala

826 Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro

846 Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser Ser Asp Pro

866 Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe

887 His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn

907 Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp

927 Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn

947 Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu

967 Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr

988 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys

1008 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro

1028 Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

1049 Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

M2 NH_2 - IL-8R type 2 - GBP 130 - COOH

NH_2 - Met Glu Ser Asp Ser Phe Glu Asp Phe Trp Lys Gly Glu Asp Leu Ser Asn Tyr Ser

20 Tyr Ser Ser Thr Leu Pro Pro Phe Leu Leu Asp Ala Ala Pro Cys Glu Pro Glu Ser Leu

40 Glu Ile Asn Lys Tyr Phe Val Val Ile Ile Tyr Ala Leu Val Phe Leu Leu Ser Leu Leu Gly

61 Asn Ser Leu Val Met Leu Val Ile Leu Tyr Ser Arg Val Gly Arg Ser Val Thr Asp Val

81 Tyr Leu Leu Asn Leu Ala Leu Ala Asp Leu Leu Phe Ala Leu Thr Leu Pro Ile Trp Ala

101 Ala Ser Lys Val Asn Gly Trp Ile Phe Gly Thr Phe Leu Cys Lys Val Val Ser Leu Leu

121 Lys Glu Val Asn Phe Tyr Ser Gly Ile Leu Leu Leu Ala Cys Ile Ser Val Asp Arg Tyr

141 Leu Ala Ile Val His Ala Thr Arg Thr Leu Thr Gln Lys Arg Tyr Leu Val Lys Phe Ile Cys

162 Leu Ser Ile Trp Gly Leu Ser Leu Leu Leu Ala Leu Pro Val Leu Leu Phe Arg Arg Thr

182 Val Tyr Ser Ser Asn Val Ser Pro Ala Cys Tyr Glu Asp Met Gly Asn Asn Thr Ala Asn

202 Trp Arg Met Leu Leu Arg Ile Leu Pro Gln Ser Phe Gly Phe Ile Val Pro Leu Leu Ile

222 Met Leu Phe Cys Tyr Gly Phe Thr Leu Arg Thr Leu Phe Lys Ala His Met Gly Gln Lys

242 His Arg Ala Met Arg Val Ile Phe Ala Val Val Leu Ile Phe Leu Leu Cys Trp Leu Pro Tyr

263 Asn Leu Val Leu Leu Ala Asp Thr Leu Met Arg Thr Gln Val Ile Gln Glu Thr Cys Glu

283 Arg Arg Asn His Ile Asp Arg Ala Leu Asp Ala Thr Glu Ile Leu Gly Ile Leu His Ser Cys

304 Leu Asn Pro Leu Ile Tyr Ala Phe Ile Gly Gln Lys Phe Arg His Gly Leu Leu Lys Ile Leu

325 Ala Ile His Gly Leu Ile Ser Lys Asp Ser Leu Pro Lys Asp Ser Arg Pro Ser Phe Val Gly

346 Ser Ser Ser Gly His Thr Ser Thr Thr Leu Asn Ala Tyr Ile Cys Gly Asp Lys Tyr Glu Lys

367 Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu Gly Glu Asp Thr Cys Ala

387 Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr Ser Thr Arg Thr Val Ala

407 Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr Glu Glu Gln Lys Val Glu

427 Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys Lys Gln Ile Asn Ile Gly Asp

448 Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile Lys Lys Glu Lys Lys Lys

468 Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu Ala Ser Lys Lys Lys Glu

488 Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr Arg Ser Asn Asn Glu Val

508 Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala Asp Pro Glu Gly Ile Met Arg

529 Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn

550 Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser

570 Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His

590 Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg

610 Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu

630 Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr

650 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala

670 Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu

690 Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn

710 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr

730 Ala Ala Asp Pro Glu Thr Arg Lys His Leu Glu Val Phe His Lys Ile Leu Thr Asn Thr

750 Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Leu Thr Ser Ser Asp

770 Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile

791 Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp

811 Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala

831 Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro

851 Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Glu Leu Thr Ser Ser Asp Pro

871 Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe

892 His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn

912 Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp

932 Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn

952 Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu

972 Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr

993 Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys

1013 Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro

1033 Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

1053 Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-COOH

N1 NH_2 - LIF-R - GBP 130 - COOH

NH_2-Met Arg Thr Ala Ser Asn Phe Gln Trp Leu Leu Ser Thr Phe Ile Leu Leu Tyr Leu

20 Met Asn Gln Val Asn Ser Gln Lys Lys Gly Ala Pro His Asp Leu Lys Cys Val Thr Asn

40 Asn Leu Gln Val Trp Asn Cys Ser Trp Lys Ala Pro Ser Gly Thr Gly Arg Gly Thr Asp

60 Tyr Glu Val Cys Ile Glu Asn Arg Ser Arg Ser Cys Tyr Gln Leu Glu Lys Thr Ser Ile Lys

81 Ile Pro Ala Leu Ser His Gly Asp Tyr Glu Ile Thr Ile Asn Ser Leu His Asp Phe Gly Ser

102 Ser Thr Ser Lys Phe Thr Leu Asn Glu Gln Asn Val Ser Leu Ile Pro Asp Thr Pro Glu

122 Ile Leu Asn Leu Ser Ala Asp Phe Ser Thr Ser Thr Leu Tyr Leu Lys Trp Asn Asp Arg

142 Gly Ser Val Phe Pro His Arg Ser Asn Val Ile Trp Glu Ile Lys Val Leu Arg Lys Glu Ser

163 Met Glu Leu Val Lys Leu Val Thr His Asn Thr Thr Leu Asn Gly Lys Asp Thr Leu His

183 His Trp Ser Trp Ala Ser Asp Met Pro Leu Glu Cys Ala Ile His Phe Val Glu Ile Arg Cys

204 Tyr Ile Asp Asn Leu His Phe Ser Gly Leu Glu Glu Trp Ser Asp Trp Ser Pro Val Lys

224 Asn Asn Ser Trp Ile Pro Asp Ser Gln Thr Lys Val Phe Pro Gln Asp Lys Val Ile Leu

244 Val Gly Ser Asp Ile Thr Phe Cys Cys Val Ser Gln Glu Lys Val Leu Ser Ala Leu Ile Gly

265 His Thr Asn Cys Pro Leu Ile His Leu Asp Gly Glu Asn Val Ala Ile Lys Ile Arg Asn Ile

286 Ser Val Ser Ala Ser Ser Gly Thr Asn Val Val Phe Thr Thr Glu Asp Asn Ile Phe Gly

306 Thr Val Ile Phe Ala Gly Tyr Pro Pro Asp Thr Pro Gln Gln Leu Asn Cys Glu Thr His

326 Asp Leu Lys Glu Ile Ile Cys Ser Trp Asn Pro Gly Arg Val Thr Ala Leu Val Gly Pro Arg

347 Ala Thr Ser Tyr Thr Leu Val Glu Ser Phe Ser Gly Lys Tyr Val Arg Leu Lys Arg Ala

367 Glu Ala Pro Thr Asn Glu Ser Tyr Gln Leu Leu Phe Gln Met Leu Pro Asn Gln Glu Ile

387 Tyr Asn Phe Thr Leu Asn Ala His Asn Pro Leu Gly Arg Ser Gln Ser Thr Ile Leu Val

407 Asn Ile Thr Glu Lys Val Tyr Pro His Thr Pro Thr Ser Phe Lys Val Lys Asp Ile Asn Ser

428 Thr Ala Val Lys Leu Ser Trp His Leu Pro Gly Asn Phe Ala Lys Ile Asn Phe Leu Cys

448 Glu Ile Glu Ile Lys Lys Ser Asn Ser Val Gln Glu Gln Arg Asn Val Thr Ile Gln Gly Val

469 Glu Asn Ser Ser Tyr Leu Val Ala Leu Asp Lys Leu Asn Pro Tyr Thr Leu Tyr Thr Phe

489 Arg Ile Arg Cys Ser Thr Glu Thr Phe Trp Lys Trp Ser Lys Trp Ser Asn Lys Lys Gln

509 His Leu Thr Thr Glu Ala Ser Pro Ser Lys Gly Pro Asp Thr Trp Arg Glu Trp Ser Ser

529 Asp Gly Lys Asn Leu Ile Ile Tyr Trp Lys Pro Leu Pro Ile Asn Glu Ala Asn Gly Lys Ile

550 Leu Ser Tyr Asn Val Ser Cys Ser Ser Asp Glu Glu Thr Gln Ser Leu Ser Glu Ile Pro

570 Asp Pro Gln His Lys Ala Glu Ile Arg Leu Asp Lys Asn Asp Tyr Ile Ile Ser Val Val Ala

591 Lys Asn Ser Val Gly Ser Ser Pro Pro Ser Lys Ile Ala Ser Met Glu Ile Pro Asn Asp

611 Asp Leu Lys Ile Glu Gln Val Val Gly Met Gly Lys Gly Ile Leu Leu Thr Trp His Tyr Asp

632 Pro Asn Met Thr Cys Asp Tyr Val Ile Lys Trp Cys Asn Ser Ser Arg Ser Glu Pro Cys

653 Leu Met Asp Trp Arg Lys Val Pro Ser Asn Ser Thr Glu Thr Val Ile Glu Ser Asp Glu

672 Phe Arg Pro Gly Ile Arg Tyr Asn Phe Phe Leu Tyr Gly Cys Arg Asn Gln Gly Tyr Gln

692 Leu Leu Arg Ser Met Ile Gly Tyr Ile Glu Glu Leu Ala Pro Ile Val Ala Pro Asn Phe Thr

713 Val Glu Asp Thr Ser Ala Asp Ser Ile Leu Val Lys Trp Glu Asp Ile Pro Val Glu Glu Leu

734 Arg Gly Phe Leu Arg Gly Tyr Leu Phe Tyr Phe Gly Lys Gly Glu Arg Asp Thr Ser Lys

754 Met Arg Val Leu Glu Ser Gly Arg Ser Asp Ile Lys Val Lys Asn Ile Thr Asp Ile Ser Gln

775 Lys Thr Leu Arg Ile Ala Asp Leu Gln Gly Lys Thr Ser Tyr His Leu Val Leu Arg Ala Tyr

796 Thr Asp Gly Gly Val Gly Pro Glu Lys Ser Met Tyr Val Val Thr Lys Asn Ala Tyr Ile Cys

816 Gly Asp Lys Tyr Glu Lys Ala Val Asp Tyr Gly Phe Arg Glu Ser Arg Ile Leu Ala Glu

836 Gly Glu Asp Thr Cys Ala Arg Lys Glu Lys Thr Thr Leu Arg Lys Ser Lys Gln Lys Thr

856 Ser Thr Arg Thr Val Ala Thr Gln Thr Lys Lys Asp Glu Glu Asn Lys Ser Val Val Thr

876 Glu Glu Gln Lys Val Glu Ser Asp Ser Glu Lys Gln Lys Arg Thr Lys Lys Val Val Lys

896 Lys Gln Ile Asn Ile Gly Asp Thr Glu Asn Gln Lys Glu Gly Lys Asn Val Lys Lys Val Ile

917 Lys Lys Glu Lys Lys Lys Glu Glu Ser Gly Lys Pro Glu Glu Asn Lys His Ala Asn Glu

937 Ala Ser Lys Lys Lys Glu Pro Lys Ala Ser Lys Val Ser Gln Lys Pro Ser Thr Ser Thr

957 Arg Ser Asn Asn Glu Val Lys Ile Arg Ala Ala Ser Asn Gln Glu Thr Leu Thr Ser Ala

977 Asp Pro Glu Gly Gln Ile Met Arg Glu Thr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu

997 Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn

1017 Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr

1037 Ala Ser Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp

1058 Pro Asn Asp Asp Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp

1078 Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val

1099 Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp

1119 Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala

1139 Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro

1159 Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro

1179 Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Val Phe

1200 His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn

1220 Lys Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro

1240 Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp

1260 Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly

1280 Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys
1301 Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu
1321 Glu Leu Thr Ser Ser Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu
1341 Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Glu
1361 Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln
1381 Ile Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe Tyr Lys Ile
1402 Leu Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp
1422 Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile Met Arg Glu Tyr Ala Ser Asp Pro Glu Tyr
1442 Arg Lys His Leu Glu Ile Phe Tyr Lys Ile Leu Thr Asn Thr Asp Pro Asn Asp Asp Val
1462 Glu Arg Arg Asn Ala Asp Asn Lys Glu Asp Leu Thr Ser Ala Asp Pro Glu Gly Gln Ile
1482 Met Arg Glu Tyr Ala Ala Asp Pro Glu Tyr Arg Lys His Leu Glu Ile Phe His Lys Ile Leu
1503 Thr Asn Thr Asp Pro Asn Asp Glu Val Glu Arg Gln Asn Ala Asp Asn Asn Glu Ala-
COOH

CLAIMS

What is claimed is;

1) The hybrid peptides formed by the fusion of two or more components, one component being derived from all or part of a malaria parasite peptide capable of binding to a red blood cell and the other component being a cytokine receptor or receptor capable of binding to an inflammatory mediator or part thereof or substitutional or deletional variation there of.

2) The hybrid peptide according to claim 1 where all or part of the 55kd TNF-R Tumour Necrosis factor receptor or the 75kd TNF-R is joined C terminally to the N terminal of the GBP 130 molecule glycophorin binding peptide molecule or where the N terminal of the TNF-R molecule is joined to the C terminal of the GBP 130 molecule.

3) The hybrid peptide according to claim 1 where all or part of the TBPI Tumour Necrosis factor binding peptide type 1 or TBPII is joined C terminally to the N terminal of the GBP 130 molecule glycophorin binding peptide molecule or where the N terminal of the TBPI or TBPII molecule is joined to the C terminal of the GBP 130 molecule.

4) The hybrid peptide according to claim 1 where all or part of the γIFN-R gamma interferon receptor is joined C terminally to the N terminal of the GBP 130 molecule glycophorin binding peptide molecule all or part or where the N terminal of the γIFN-R molecule is joined to the C terminal of the GBP 130 molecule all or part.

5) The hybrid peptide according to claim 1 where all or part of the IL1-R interleukin high or low affinity receptor is joined C terminally to the N terminal of the GBP 130

molecule glycophorin binding peptide molecule all or part or where the N terminal of the IL1-R molecule is joined to the C terminal of the GBP 130 molecule.

6) The hybrid peptide according to claim 1 where all or part of the IL2-R interleukin high or low affinity receptor is joined C terminally to the N terminal of the GBP 130 molecule glycophorin binding peptide molecule all or part or where the N terminal of the IL2-R molecule is joined to the C terminal of the GBP 130 molecule.

7) The hybrid peptide according to claim 1 where all or part of the IL3-R interleukin high or low affinity receptor is joined C terminally to the N terminal of the GBP 130 molecule glycophorin binding peptide molecule or where the N terminal of the IL3-R molecule is joined to the C terminal of the GBP 130 molecule.

8) The hybrid peptide according to claim 1 where all or part of the IL4-R interleukin receptor is joined C terminally to the N terminal of the GBP 130 molecule glycophorin binding peptide molecule or where the N terminal of the IL4-R molecule is joined to the C terminal of the GBP 130 molecule.

9) The hybrid peptide according to claim 1 where all or part of the IL5-R interleukin receptor is joined C terminally to the N terminal of the GBP 130 molecule glycophorin binding peptide molecule or where the N terminal of the IL5-R molecule is joined to the C terminal of the GBP 130 molecule.

10) The hybrid peptide according to claim 1 where all or part of the IL6-R interleukin receptor is joined C terminally to the N terminal of the GBP 130 molecule glycophorin binding peptide molecule or where the N terminal of the IL6-R molecule is joined to the C terminal of the GBP 130 molecule.

11) The hybrid peptide according to claim 1 where all or part of the IL7-R interleukin receptor is joined C terminally to the N terminal of the GBP 130 molecule glycophorin binding peptide molecule or where the N terminal of the IL7-R molecule is joined to the C terminal of the GBP 130 molecule.

12) The hybrid peptide according to claim 1 where all or part of the IL8-R interleukin receptor is joined C terminally to the N terminal of the GBP 130 molecule glycophorin binding peptide molecule or where the N terminal of the IL8-R molecule is joined to the C terminal of the GBP 130 molecule.

13) The hybrid peptide according to claim 1 where all or part of the LIF-R leukaemia inhibitory factor receptor is joined C terminally to the N terminal of the GBP 130 molecule glycophorin binding peptide molecule or where the N terminal of the LIF-R molecule is joined to the C terminal of the GBP 130 molecule.

14) The hybrid fusion peptide according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13 where the malaria parasite derived peptide component is all or part of the GBPH glycophorin binding peptide homologue molecule preferably residues 70 to 427 or part of thereof joined C or N terminally to the cytokine receptor of claims 2,3,4,5,6,7,8,9,10,11,12,13.

15) The hybrid fusion peptide according to claims 1,2,3,4,5,6,7,8,9,10.11.12,13 where the malaria parasite derived peptide component is all or part of the EBA175 the erythrocyte binding antigen 175 molecule preferably residues 20 - 1435 or residues 1062 - 1103 or multiples thereof or part of thereof joined C or N terminally to the cytokine receptor of claims 2,3,4,5,6,7,8,9,10,11,12,13.

16) The hybrid fusion peptide according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13 where

the malaria parasite derived peptide component is all or part of the plasmodium vivax Duffy receptor molecule specially residues 23 - 1051 joined by peptide bonds to the cytokine receptor, or via chemical cross links, joined C or N terminally to the cytokine receptor of claims 2,3,4,5,6,7,8,9,10,11,12,13.

17) The hybrid fusion peptide according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13 where the malaria parasite derived peptide component is all or part of the Pf200 or PMMSA malaria parasite molecule or part of thereof joined C or N terminally to the cytokine receptor of claims 2,3,4,5,6,7,8,9,10,11,12,13.

18) The hybrid fusion peptide according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13 where the malaria parasite derived peptide component is all or part of the plasmodium knowlesi Duffy receptor molecule part of thereof joined C or N terminally to the cytokine receptor of claims 2,3,4,5,6,7,8,9,10,11,12,13.

19) A hybrid fusion peptide according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18 where a peptide sequence is interposed between the malaria parasite peptide and the cytokine receptor and where the interposed peptide is all or part of an immunoglobulin Fc molecule.

20) Protein genes encoding fusion peptides according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19.

21) The fusion peptides according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 for use as medicine to treat and alleviate HIV 1 or HIV 2 or cerebral malaria or endotoxic shock or graft verus host disease or inflammatory disease.

22) The use of the fusion peptides according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 to obtain a medicine for intended therapeutic use in the treatment of HIV 1, HIV 2, hepatitis B, pulmonary fibrosis, cerebral malaria, graft is host disease, endotoxic shock, autoimmune disease, inflammatory disease.

23) The fusion peptides according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 where the malaria parasite component is replaced all or in part by an anti-ideotype antibody or part thereof.

24) The fusion peptides according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18 where the cytokine receptor is replaced by an FAB fragment or anti-ideotype.

20) The use of fusion peptides according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 to obtain a medicine for intended therapeutic use as a testing kit to determine plasma levels of free plasma cytokines.

21) The fusion peptides according to claims 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18 and 19 where the malaria parasite component is replaced by a malaria parasite peptide derived from Plasmodium Berghei; Plasmodium Chabandi; Plasmodium Yoelei Yoelei; Plasmodium Cyanomogli; Plasmodium Gallinaceum.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 94/01900

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/62 C07K14/445 C07K14/715

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,93 18160 (PRENDERGAST, K.R.; GB) 16 September 1993 cited in the application see the whole document	1,20-23
P,X	WO,A,93 19777 (IMMUNEX CORPORATION,US) 14 October 1993 see page 24, line 28 - page 25, line 2; claims 1-22	1
A	EP,A,0 499 834 (BEHRINGWERKE, AG; DE) 26 August 1992 see the whole document	1-26

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 1995	01.02.95

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/GB 94/01900

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9318160	16-09-93	EP-A-	0630407	28-12-94
		GB-A-	2268494	12-01-94
WO-A-9319777	14-10-93	AU-B-	3970293	08-11-93
		CA-A-	2133326	14-10-93
EP-A-0499834	26-08-92	DE-A-	4105348	03-09-92
		AU-A-	1108192	27-08-92
		CA-A-	2061575	22-08-92
		JP-A-	6141868	24-05-94