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(54) Title: THERAPEUTIC EPITOPES AND USES THEREOF

(57) **Abstract:** The invention herein disclosed is related to epitopes useful in methods of diagnosing, treating, and preventing coeliac disease. Therapeutic compositions which comprise at least one epitope are provided.

THERAPEUTIC EPITOPES AND USES THEREOF

The invention relates to epitopes useful in the diagnosis and therapy of coeliac disease, including diagnostics, therapeutics, kits, and methods of using the foregoing.

An immune reaction to gliadin (a component of gluten) in the diet causes coeliac disease. It is known that immune responses in the intestinal tissue preferentially respond to gliadin which has been modified by an intestinal transglutaminase. Coeliac disease is diagnosed by detection of anti-endomysial antibodies, but this requires confirmation by the finding of a lymphocytic inflammation in intestinal biopsies. The taking of such a biopsy is inconvenient for the patient.

Investigators have previously assumed that only intestinal T cell responses provide an accurate indication of the immune response against gliadins. Therefore they have concentrated on the investigation of T cell responses in intestinal tissue[1]. Gliadin epitopes which require transglutaminase modification (before they are recognised by the immune system) are known[2].

The inventors have found the immunodominant T cell A-gliadin epitope recognised by the immune system in coeliac disease, and have shown that this is recognised by T cells in the peripheral blood of individuals with coeliac disease (see WO 01/25793). Such T cells were found to be present at high enough frequencies to be detectable without restimulation (i.e. a 'fresh response' detection system could be used). The epitope was identified using a non-T cell cloning based method which provided a more accurate reflection of the epitopes being recognised. The immunodominant epitope requires transglutaminase modification (causing substitution of a particular glutamine to glutamate) before immune system recognition.

Based on this work the inventors have developed a test which can be used to diagnose coeliac disease at an early stage. The test may be carried out on a sample from peripheral blood and therefore an intestinal biopsy is not required. The test is more sensitive than the antibody tests which are currently being used.

The invention thus provides a method of diagnosing coeliac disease, or susceptibility to coeliac disease, in an individual comprising:

(a) contacting a sample from the host with an agent selected from (i) the epitope comprising sequence which is: SEQ ID NO:1 (PQPELPY)or SEQ ID NO:2 (QLQPFPQPELPYPQPQS), or an equivalent sequence from a naturally occurring homologue of the gliadin represented by SEQ ID NO:3, (ii) an epitope comprising

5   sequence comprising: SEQ ID NO:1, or an equivalent sequence from a naturally occurring homologue of the gliadin represented by SEQ ID NO:3 (shown in Table 1), which epitope is an isolated oligopeptide derived from a gliadin protein, (iii) an analogue of (i) or (ii) which is capable of being recognised by a T cell receptor that recognises (i) or (ii), which in the case of a peptide analogue is not more than 50

10   amino acids in length, or (iv) a product comprising two or more agents as defined in (i), (ii) or (iii), and (b) determining *in vitro* whether T cells in the sample recognise the agent, recognition by the T cells indicating that the individual has, or is susceptible to, coeliac disease.

Through comprehensive mapping of wheat gliadin T cell epitopes (see

15   Example 13), the inventors have also found epitopes bioactive in coeliac disease in HLA-DQ2+ patients in other wheat gliadins, having similar core sequences (e.g., SEQ ID NOS:18-22) and similar full length sequences (e.g., SEQ ID NOS:31-36), as well as in rye secalins and barley hordeins (e.g., SEQ ID NOS:39-41); see also Tables 20 and 21. Additionally, several epitopes bioactive in coeliac disease in

20   HLA-DQ8+ patients have been identified (e.g., SEQ ID NOS:42-44, 46). This comprehensive mapping thus provides the dominant epitopes recognized by T cells in coeliac patients. Thus, the above-described method and other methods of the invention described herein may be performed using any of these additional identified epitopes, and analogues and equivalents thereof; (i) and (ii) herein include these

25   additional epitopes. That is, the agents of the invention also include these novel epitopes.

The invention also provides use of the agent for the preparation of a diagnostic means for use in a method of diagnosing coeliac disease, or susceptibility to coeliac disease, in an individual, said method comprising determining whether T

30   cells of the individual recognise the agent, recognition by the T cells indicating that the individual has, or is susceptible to, coeliac disease.

The finding of an immunodominant epitope which is modified by transglutaminase (as well as the additional other epitopes defined herein) also allows diagnosis of coeliac disease based on determining whether other types of immune response to this epitope are present. Thus the invention also provides a method of

5   diagnosing coeliac disease, or susceptibility to coeliac disease, in an individual comprising determining the presence of an antibody that binds to the epitope in a sample from the individual, the presence of the antibody indicating that the individual has, or is susceptible to, coeliac disease.

The invention additionally provides the agent, optionally in association with a

10   carrier, for use in a method of treating or preventing coeliac disease by tolerising T cells which recognise the agent. Also provided is an antagonist of a T cell which has a T cell receptor that recognises (i) or (ii), optionally in association with a carrier, for use in a method of treating or preventing coeliac disease by antagonising such T cells. Additionally provided is the agent or an analogue that binds an antibody (that

15   binds the agent) for use in a method of treating or preventing coeliac disease in an individual by tolerising the individual to prevent the production of such an antibody.

The invention provides a method of determining whether a composition is capable of causing coeliac disease comprising determining whether a protein capable of being modified by a transglutaminase to an oligopeptide sequence as defined

20   above is present in the composition, the presence of the protein indicating that the composition is capable of causing coeliac disease.

The invention also provides a mutant gliadin protein whose wild-type sequence can be modified by a transglutaminase to a sequence that comprises an epitope comprising sequence as defined above, but which mutant gliadin protein has

25   been modified in such a way that it does not contain sequence which can be modified by a transglutaminase to a sequence that comprises such an epitope comprising sequence; or a fragment of such a mutant gliadin protein which is at least 15 amino acids long and which comprises sequence which has been modified in said way.

The invention also provides a protein that comprises a sequence which is able

30   to bind to a T cell receptor, which T cell receptor recognises the agent, and which sequence is able to cause antagonism of a T cell that carries such a T cell receptor.

Additionally the invention provides a food that comprises the proteins defined above.

SUMMARY OF THE INVENTION

Herein disclosed are methods of preventing or treating coeliac disease comprising administering to an individual at least one agent selected from: a) a peptide comprising at least one epitope comprising a sequence selected from the group consisting of SEQ ID NOs:18-22, 31-36, 39-44, and 46, and equivalents thereof; and b) an analogue of a) which is capable of being recognised by a T cell receptor that recognises the peptide of a) and which is not more than 50 amino acids in length; and c) optionally, in addition to the agent selected from a) and b), a peptide comprising at least one epitope comprising a sequence selected from SEQ ID NO:1 and SEQ ID NO:2. In some embodiments, the agent is HLA-DQ2-restricted, HLA-DQ8-restricted or one agent is HLA-DQ2-restricted and a second agent is HLA-DQ8-restricted. In some embodiments, the agent comprises a wheat epitope, a rye epitope, a barley epitope or any combination thereof either as a single agent or as multiple agents.

According to an embodiment of the invention, there is provided a method of preventing or treating coeliac disease comprising administering to an individual at least one agent selected from:

(a)   a peptide comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said peptide does not comprise transglutaminase-deamidated sequence PQLPY (SEQ ID NO:12); and

(b)   a peptide analogue of (a) which is capable of being recognised by a T cell receptor that recognises the epitope of (a) and which is not more than 50 amino acids in length; and

optionally, in addition to the agent selected from (a) and (b), administering to said individual a peptide comprising at least one epitope comprising a sequence selected from SEQ ID NO:1 and SEQ ID NO:2.

According to another embodiment of the invention, there is provided the use of an agent for the preparation of a medicament for treating or preventing coeliac disease, wherein the agent comprises:

(a)   a peptide comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said peptide does not comprise transglutaminase-deamidated sequence PQLPY (SEQ ID NO:12); and

(b)   a peptide analogue of (a) which is capable of being recognised by a T cell receptor that recognises the epitope of (a) and which is not more than 50 amino acids in length; and

(c)   optionally, in addition to the agent selected from (a) and (b), a peptide comprising at least one epitope comprising a sequence selected from SEQ ID NO:1 and SEQ ID NO:2.

The present invention also provides methods of preventing or treating coeliac disease comprising administering to an individual a pharmaceutical composition comprising an agent above and pharmaceutically acceptable carrier or diluent.

The present invention also provides methods of preventing or treating coeliac disease comprising administering to an individual a pharmaceutical composition comprising an antagonist of a T cell which has a T cell receptor as defined above, and a pharmaceutically acceptable carrier or diluent.

The present invention also provides methods of preventing or treating coeliac disease comprising administering to an individual a composition for tolerising an individual to a gliadin protein to suppress the production of a T cell or antibody response to an agent as defined above, which composition comprises an agent as defined above.

Also herein disclosed is a method of preventing or treating coeliac disease by 1) diagnosing coeliac disease in an individual by either: a) contacting a sample from the host with at least one agent selected from: i) a peptide comprising at least one epitope comprising a sequence selected from the group consisting of: SEQ ID NOS:18-22, 31-36, 39-44, and 46, and equivalents thereof; and ii) an analogue of i) which is capable of being recognised by a T cell receptor that recognises i) and which is not more than 50 amino acids in length; and iii) optionally, in addition to the agent selected from i) and ii), a peptide comprising at least one epitope comprising a sequence selected from SEQ ID NOS:1 and 2 ; and determining *in vitro* whether T cells in the sample recognise the agent; recognition by the T cells indicating that the individual has, or is susceptible to, coeliac disease; or b) administering an agent as defined above and determining *in vivo* whether T cells in the individual recognise the agent, recognition of the agent indicating that the individual has or is susceptible to coeliac disease; and 2) administering to an individual diagnosed as having, or being susceptible to, coeliac disease a therapeutic agent for preventing or treating coeliac disease.

According to another embodiment of the invention, there is provided a method of preventing or treating coeliac disease comprising:

diagnosing coeliac disease in an individual by either:

a) contacting a sample from the host with at least one agent selected from:

i) a peptide comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said peptide does not comprise transglutaminase-deamidated sequence PQLPY (SEQ ID NO:12), and with the proviso that said peptide does not comprise transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ; and

ii)   a peptide analogue of i) which is capable of being recognised by a T cell receptor that recognises the epitope of i) and which is not more than 50 amino acids in length; and

iii)   optionally, in addition to the agent selected from i) and ii), a peptide comprising at least one epitope comprising a sequence selected from SEQ ID NOS: 1 and 2; and

determining *in vitro* whether T cells in the sample recognise the agent; recognition by the T cells indicating that the individual has, or is susceptible to, coeliac disease; or

b)   administering an agent as defined in claim 1 and determining *in vivo* whether T cells in the individual recognise the agent, recognition of the agent indicating that the individual has or is susceptible to coeliac disease; and

administering to an individual diagnosed as having, or being susceptible to, coeliac disease a therapeutic agent for preventing or treating coeliac disease.

Also herein disclosed is an agent as defined above, optionally in association with a carrier, for use in a method of treating or preventing coeliac disease by tolerising T cells which recognise the agent.

Also herein disclosed is an antagonist of a T cell which has a T cell receptor as defined above, optionally in association with a carrier, for use in a method of treating or preventing coeliac disease by antagonising such T cells.

Also herein disclosed is a protein that comprises a sequence which is able to bind to a T cell receptor, which T cell receptor recognises an agent as defined above, and which sequence is able to cause antagonism of a T cell that carries such a T cell receptor.

Thus, according to another embodiment of the invention, there is provided an isolated protein that comprises a sequence which is able to bind to a T cell receptor, which T cell receptor recognises an agent comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said epitope does not comprise transglutaminase-deamidated sequence PQLPY (SEQ ID NO:12), and with the proviso that said epitope does not comprise transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ; and

which sequence is able to cause antagonism of a T cell that carries such a T cell receptor.

According to another embodiment of the invention, there is provided an agent comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said epitope does not comprise transglutaminase-deamidated sequence PQLPY (SEQ ID NO:12), and with the proviso

that said epitope does not comprise transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ,

5   PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ

or an antagonist of a T cell which has a T cell receptor that recognises said epitope, and which is not more than 50 amino acids in length.

The present invention also provides a pharmaceutical composition comprising an agent or antagonist as defined above and, a pharmaceutically acceptable carrier or diluent.

10   Also herein disclosed is a composition for tolerising an individual to a gliadin protein to suppress the production of a T cell or antibody response to an agent as defined above, which composition comprises an agent as defined above.

Thus, according to another embodiment of the invention, there is provided a composition for tolerising an individual to a gliadin protein to suppress the production of

15   a T cell or antibody response to an agent as defined above, which composition comprises an agent as defined above, with the proviso that said agent does not comprise an epitope comprising transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ,

20   QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ.

Also herein disclosed are compositions for antagonising a T cell response to an agent as defined above, which compositions comprise an antagonist as defined above.

Thus, according to another embodiment of the invention, there is provided a

25   composition for antagonising a T cell response to an agent as defined above, which composition comprises an antagonist of a T cell which has a T cell receptor that recognises said epitope, and which is not more than 50 amino acids in length, with the proviso that said epitope does not comprise transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ,

30   PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ.

Also herein disclosed is a mutant gliadin protein whose wild-type sequence can be modified by a transglutaminase to a sequence which is an agent as defined above, which

35   mutant gliadin protein comprises a mutation which prevents its modification by a transglutaminase to a sequence which is an agent as defined above; or a fragment of such a mutant gliadin protein which is at least 15 amino acids long and which comprises the mutation.

Thus, according to another embodiment of the invention, there is provided a mutant gliadin protein whose wild-type sequence can be modified by a transglutaminase to a sequence which is an agent as defined in claim 1, which wild-type sequence comprises an epitope comprising the amino acid sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the

5   proviso that said epitope does not comprise the amino acid sequence PQLPY (SEQ ID NO:12), and with the proviso that said epitope does not comprise the amino acid sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ,

10   PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ, which mutant gliadin protein comprises a mutation which prevents its modification by a transglutaminase to a sequence which is an agent as defined above; or a fragment of such a mutant gliadin protein which is at least 15 amino acids long and which comprises the mutation.

15   The present invention also provides a polynucleotide that comprises a coding sequence that encodes a protein or fragment as defined above.

The present invention also provides a cell comprising a polynucleotide as defined above or which has been transformed with such a polynucleotide.

The present invention also provides a transgenic mammal that expresses a T cell

20   receptor as defined above.

Also herein disclosed is a method of diagnosing coeliac disease, or susceptibility to coeliac disease, in an individual comprising: a) contacting a sample from the host with at least one agent selected from i) a peptide comprising at least one epitope comprising a sequence selected from the group consisting of: SEQ ID NOS:18-22, 31-36, 39-44, and

25   46, and equivalents thereof; and ii) an analogue of i) which is capable of being recognised by a T cell receptor that recognises i) and which is not more than 50 amino acids in length; and iii) optionally, in addition to the agent selected from i) and ii), a peptide comprising at least one epitope comprising a sequence selected from SEQ ID NOS:1 and 2 ; and b) determining *in vitro* whether T cells in the sample recognise the agent;

30   recognition by the T cells indicating that the individual has, or is susceptible to, coeliac disease.

Thus, according to another embodiment of the invention, there is provided a method of diagnosing coeliac disease, or susceptibility to coeliac disease, in an individual comprising:

35   (a)   contacting a sample from the host with at least one agent selected from

           (i)   a peptide comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said peptide does not comprise the amino acid sequence

PQLPY (SEQ ID NO:12), and with the proviso that said epitope does not comprise transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ; and

(ii)	a peptide analogue of (i) which is capable of being recognised by a T cell receptor that recognises the epitope of (i) and which is not more than 50 amino acids in length; and

(iii)	optionally, in addition to the agent selected from (i) and (ii), a peptide comprising at least one epitope comprising a sequence selected from SEQ ID NOS: 1 and 2; and

(b)	determining *in vitro* whether T cells in the sample recognise the agent; recognition by the T cells indicating that the individual has, or is susceptible to, coeliac disease.

According to another embodiment of the invention, there is provided the use of an agent as defined above for the preparation of a diagnostic means for use in a method of diagnosing coeliac disease, or susceptibility to coeliac disease, in an individual, said method comprising determining whether T cells of the individual recognise the agent, recognition by the T cells indicating that the individual has, or is susceptible to, coeliac disease.

According to another embodiment of the invention, there is provided a method of diagnosing coeliac disease, or susceptibility to coeliac disease, in an individual comprising determining the presence of an antibody that binds to an epitope comprising sequence as defined above in a sample from the individual, the presence of the antibody indicating that the individual has, or is susceptible to, coeliac disease.

According to another embodiment of the invention, there is provided a method of diagnosing coeliac disease, or susceptibility to coeliac disease in an individual comprising administering an agent as defined above and determining *in vivo* whether T cells in the individual recognise the agent, recognition of the agent indicating that the individual has or is susceptible to coeliac disease.

The present invention also provides a method of determining whether a composition is capable of causing coeliac disease comprising determining whether a protein capable of being modified by a transglutaminase to an oligopeptide sequence as defined above is present in the composition, the presence of the protein indicating that the composition is capable of causing coeliac disease.

The present invention also provides a method for identifying an analogue as defined above comprising determining whether a candidate substance is recognised by a T cell

receptor that recognises an epitope comprising sequence as defined above, recognition of the substance indicating that the substance is an analogue.

The present invention also provides a method of identifying an antagonist of a T cell, which T cell recognises an agent as defined above, comprising contacting a candidate substance with the T cell and detecting whether the substance causes a decrease in the ability of the T cell to undergo an antigen specific response, the detecting of any such decrease in said ability indicating that the substance is an antagonist.

The present invention also provides kits for carrying out any of the diagnostic methods or uses described above comprising an agent as defined above and a means to detect the recognition of the peptide by the T cell.

The present invention also provides the use of an agent or antagonist as defined above or a wild type sequence as defined above to produce an antibody specific to the agent, antagonist or wild type sequence.

The present invention also provides the use of a mutation in an epitope of a gliadin protein, which epitope is as defined above, to decrease the ability of the gliadin protein to cause coeliac disease.

The present invention also provides methods of identifying a product which is therapeutic for coeliac disease comprising administering a candidate substance to a transgenic mammal as defined above which has, or which is susceptible to, coeliac disease and determining whether substance prevents or treats coeliac disease in the mammal, the prevention or treatment of coeliac disease indicating that the substance is a therapeutic product.

The present invention also provides a process for the production of a protein encoded by a coding sequence as defined above which process comprises: a) cultivating a cell described above under conditions that allow the expression of the protein; and optionally b) recovering the expressed protein.

Also herein disclosed is a method of obtaining a transgenic plant cell comprising transforming a plant cell with a vector as described above to give a transgenic plant cell.

Also herein disclosed is a method of obtaining a first-generation transgenic plant comprising regenerating a transgenic plant cell transformed with a vector as described above to give a transgenic plant.

Also herein disclosed is a method of obtaining a transgenic plant seed comprising obtaining a transgenic seed from a transgenic plant obtainable as described above.

Also herein disclosed is a method of obtaining a transgenic progeny plant comprising obtaining a second-generation transgenic progeny plant from a first-generation transgenic plant obtainable by a method as described above, and optionally obtaining transgenic plants of one or more further generations from the second-generation progeny plant thus obtained.

Also herein disclosed is a transgenic plant cell, plant, plant seed or progeny plant obtainable by any of the methods described above.

Thus, the present invention also provides a transgenic plant cell, plant seed, progeny plant, plant part or plant product obtained from a plant as defined above.

5   The present invention also provides a transgenic plant or plant seed comprising plant cells as described above.

Also herein disclosed is a transgenic plant cell callus comprising a plant cell as described above obtainable from a transgenic plant cell, first-generation plant, plant seed or progeny as defined above.

10   Also herein disclosed is a method of obtaining a crop product comprising harvesting a crop product from a plant according to any method described above and optionally further processing the harvested product.

Thus, according to other embodiments of the invention, there are provided plant products and crop products obtained from or harvested from plants or plant seeds as

15   defined above, such as grain, optionally further processed into flour or another grain product.

The present invention also provides food that comprises a protein as defined above.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is illustrated by the accompanying drawings in which:

20   Figure 1 shows freshly isolated PBMC (peripheral blood mononuclear cell) IFNγ ELISPOT responses (vertical axis shows spot forming cells per 10^6 PBMC) to transglutaminase (tTG)-treated and untreated peptide pool 3 (each peptide 10μLg/ml) including five overlapping 15mers spanning A-gliadin 51-85 (see Table 1) and a-chymotrypsin-digested gliadin (40μg/ml) in coeliac disease Subject 1, initially in

25   remission following a gluten free diet then challenged with 200g bread daily for three days from day 1 (a). PBMC IFNγ ELISPOT responses by Subject 2 to tTG-treated A-gliadin peptide pools 1-10 spanning the complete A-gliadin protein during ten day bread challenge (b). The horizontal axis shows days after commencing bread.

Figure 2 shows PBMC IFNγ ELISPOT responses to tTG-treated peptide pool 3

30   (spanning A-gliadin 51-85) in 7 individual coeliac disease subjects (vertical axis shows spot forming cells per 10^6 PBMC), initially in remission on gluten free diet, challenged with bread for three days (days 1 to 3). The horizontal axis shows days after commencing bread. (a). PBMC IFNγ ELISPOT responses to tTG-treated overlapping 15mer peptides included in pool 3; bars represent the mean (±SEM) response to individual peptides

35   (10μg/ml) in 6 Coeliac disease subjects on day 6 or 7(b). (In individual subjects, ELISPOT responses to peptides were calculated as a % of response elicited by peptide 12 - as shown by the vertical axis.)

Figure 3 shows PBMC IFNγ ELISPOT responses to tTG-treated truncations of A-gliadin 56-75 (0.1 μM). Bars represent the mean (± SEM) in 5 Coeliac disease subjects. (In individual subjects, responses were calculated as the % of the maximal response elicited by any of the peptides tested.)

5   Figure 4 shows how the minimal structure of the dominant A-gliadin epitope was mapped using tTG-treated 7-17mer A-gliadin peptides (0.1 μM) including the sequence, PQPQLPY (SEQ ID NO:4) (A-gliadin 62-68) (a), and the same peptides without tTG treatment but with the substitution Q→E65 (b). Each line represents PBMC IFNγ ELISPOT responses in each of three Coeliac disease subjects on day 6

10   or 7 after bread was ingested on days 1-3. (In individual subjects, ELISPOT responses were calculated as a % of the response elicited by the 17mer, A-gliadin 57-73.)

Figure 5 shows the amino acids that were deamidated by tTG. A-gliadin 56-75 LQLQPFPQPQLPYPQPQSFP (SEQ ID NO:5) (0.1 μM) was incubated with tTG

15   (50 μg/ml) at 37°C for 2 hours. A single product was identified and purified by reverse phase HPLC. Amino acid analysis allowed % deamidation (Q→E) of each Gln residue in A-gliadin 56-75 attributable to tTG to be calculated (vertical axis).

Figure 6 shows the effect of substituting Q→E in A-gliadin 57-73 at other positions in addition to Q65 using the 17mers: ELQPFPQPELPYPQPQS (SEQ ID

20   NO:6) (E57,65), QLQPFPQPELPYPQPES (SEQ ID NO:7) (E65,72), ELQPFPQPELPYPQPES (SEQ ID NO:8) (E57, 65, 72), and QLQPFPQPELPYPQPQS (SEQ ID NO:2) (E65) in three Coeliac disease subjects on day 6 or 7 after bread was ingested on days 1-3. Vertical axis shows % of the E65 response.

25   Figure 7 shows that tTG treated A-gliadin 56-75 (0.1 μM) elicited IFN-g ELISPOT responses in (a) CD4 and CD8 magnetic bead depleted PBMC. (Bars represent CD4 depleted PBMC responses as a % of CD8 depleted PBMC responses; spot forming cells per million CD8 depleted PBMC were: Subject 4: 29, and Subject 6: 535). (b) PBMC IFNγ ELISPOT responses (spot forming cells/million PBMC)

30   after incubation with monoclonal antibodies to HLA-DR (L243), -DQ (L2) and -DP (B7.21) (10 μg/ml) 1h prior to tTG-treated 56-75 (0.1 μM) in two coeliac disease subjects homozygous for HLA-DQ a1*0501, b1*0201.

Figure 8 shows the effect of substituting Glu at position 65 for other amino acids in the immunodominant epitope. The vertical axis shows the % response in the 3 subjects in relation to the immunodominant epitope.

Figure 9 shows the immunoreactivity of naturally occurring gliadin peptides (measuring responses from 3 subjects) which contain the sequence PQLPY (SEQ ID NO:12) with (shaded) and without (clear) transglutaminase treatment.

Figure 10 shows CD8, CD4, β_7, and α^E -specific immunomagnetic bead depletion of peripheral blood mononuclear cells from two coeliac subjects 6 days after commencing gluten challenge followed by interferon gamma ELISpot. A-gliadin 57-73 QE65 (25mcg/ml), tTG-treated chymotrypsin-digested gliadin (100 mcg/ml) or PPD (10 mcg/ml) were used as antigen.

Figure 11 shows the optimal T cell epitope length.

Figure 12 shows a comparison of A-gliadin 57-73 QE65 with other peptides in a dose response study.

Figure 13 shows a comparison of gliadin and A-gliadin 57-73 QE65 specific responses.

Figure 14 shows the bioactivity of gliadin polymorphisms in coeliac subjects.

Figures 15 and 16 show the defining of the core epitope sequence.

Figures 17 to 27 show the agonist activity of A-gliadin 57-73 QE65 variants.

Figure 28 shows responses in different patient groups.

Figure 29 shows bioactivity of prolamin homologues of A-gliadin 57-73.

Figure 30 shows, for healthy HLA-DQ2 subjects, the change in IFN-gamma ELISpot responses to tTG-deamidated gliadin peptide pools.

Figure 31 shows, for coeliac HLA-DQ2 subjects, the change in IFN-gamma ELISpot responses to tTG-deamidated gliadin peptide pools.

Figure 32 shows individual peptide contributions to "summed" gliadin peptide response.

Figure 33 shows, for coeliac HLA-DQ2/8 subject C08, gluten challenge induced IFNγ ELISpot responses to tTG-deamidated gliadin peptide pools.

Figure 34 shows, for coeliac HLA-DQ2/8 subject C07, gluten challenge induced IFNγ ELISpot responses to tTG-deamidated gliadin peptide pools.

11

Figure 35 shows, for coeliac HLA-DQ8/7 subject C12, gluten challenge induced IFNγ ELISpot responses to tTG-deamidated gliadin peptide pools.

Figure 36 shows, for coeliac HLA-DQ6/8 subject C11, gluten challenge induced IFNγ ELISpot responses to tTG-deamidated gliadin peptide pools.

Detailed Description of the Invention

The term "coeliac disease" encompasses a spectrum of conditions caused by varying degrees of gluten sensitivity, including a severe form characterised by a flat small intestinal mucosa (hyperplastic villous atrophy) and other forms characterised by milder symptoms.

The individual mentioned above (in the context of diagnosis or therapy) is human. They may have coeliac disease (symptomatic or asymptomatic) or be suspected of having it. They may be on a gluten free diet. They may be in an acute phase response (for example they may have coeliac disease, but have only ingested gluten in the last 24 hours before which they had been on a gluten free diet for 14 to 28 days).

The individual may be susceptible to coeliac disease, such as a genetic susceptibility (determined for example by the individual having relatives with coeliac disease or possessing genes which cause predisposition to coeliac disease).

The agent

The agent is typically a peptide, for example of length 7 to 50 amino acids, such as 10 to 40, or 15 to 30 amino acids in length.

SEQ ID NO:1 is PQPELPY. SEQ ID NO:2 is QLQPFPQPELPYPQPQS. SEQ ID NO:3 is shown in Table 1 and is the sequence of a whole A-gliadin. The glutamate at position 4 of SEQ ID NO:1 (equivalent to position 9 of SEQ ID NO:2) is generated by transglutaminase treatment of A-gliadin.

The agent may be the peptide represented by SEQ ID NO:1 or 2 or an epitope comprising sequence that comprises SEQ ID NO:1 which is an isolated oligopeptide derived from a gliadin protein; or an equivalent of these sequences from a naturally occurring gliadin protein which is a homologue of SEQ ID NO:3. Thus the epitope may be a derivative of the protein represented by SEQ ID NO:3. Such a derivative is

typically a fragment of the gliadin, or a mutated derivative of the whole protein or fragment. Therefore the epitope of the invention does not include this naturally occurring whole gliadin protein, and does not include other whole naturally occurring gliadins.

5   The epitope may thus be a fragment of A-gliadin (e.g. SEQ ID NO:3), which comprises the sequence of SEQ ID NO:1, obtainable by treating (fully or partially) with transglutaminase, i.e. with 1, 2, 3 or more glutamines substituted to glutamates (including the substitution within SEQ ID NO:1).

Such fragments may be or may include the sequences represented by

10   positions 55 to 70, 58 to 73, 61 to 77 of SEQ ID NO:3 shown in Table 1. Typically such fragments will be recognised by T cells to at least the same extent that the peptides represented by SEQ ID NO:1 or 2 are recognised in any of the assays described herein using samples from coeliac disease patients.

Additionally, the agent may be the peptide represented by any of SEQ ID

15   NOS:18-22, 31-36, 39-44, and 46 or a protein comprising a sequence corresponding to any of SEQ ID NOS:18-22, 31-36, 39-44, and 46 (such as fragments of a gliadin comprising any of SEQ ID NOS:18-22, 31-36, 39-44, and 46, for example after the gliadin has been treated with transglutaminase). Bioactive fragments of such sequences are also agents of the invention. Sequences equivalent to any of SEQ ID

20   NOS:18-22, 31-36, 39-44, and 46 or analogues of these sequences are also agents of the invention.

In the case where the epitope comprises a sequence equivalent to the above epitopes (including fragments) from another gliadin protein (e.g. any of the gliadin proteins mentioned herein or any gliadins which cause coeliac disease), such

25   equivalent sequences will correspond to a fragment of a gliadin protein typically treated (partially or fully) with transglutaminase. Such equivalent peptides can be determined by aligning the sequences of other gliadin proteins with the gliadin from which the original epitope derives, such as with SEQ ID NO:3 (for example using any of the programs mentioned herein). Transglutaminase is commercially available

30   (e.g. Sigma T-5398). Table 4 provides a few examples of suitable equivalent sequences.

13

The agent which is an analogue is capable of being recognised by a TCR which recognises (i) or (ii). Therefore generally when the analogue is added to T cells in the presence of (i) or (ii), typically also in the presence of an antigen presenting cell (APC) (such as any of the APCs mentioned herein), the analogue inhibits the recognition of (i) or (ii), i.e. the analogue is able to compete with (i) or (ii) in such a system.

The analogue may be one which is capable of binding the TCR which recognises (i) or (ii). Such binding can be tested by standard techniques. Such TCRs can be isolated from T cells which have been shown to recognise (i) or (ii) (e.g. using the method of the invention). Demonstration of the binding of the analogue to the TCRs can then shown by determining whether the TCRs inhibit the binding of the analogue to a substance that binds the analogue, e.g. an antibody to the analogue. Typically the analogue is bound to a class II MHC molecule (e.g. HLA-DQ2) in such an inhibition of binding assay.

Typically the analogue inhibits the binding of (i) or (ii) to a TCR. In this case the amount of (i) or (ii) which can bind the TCR in the presence of the analogue is decreased. This is because the analogue is able to bind the TCR and therefore competes with (i) or (ii) for binding to the TCR.

T cells for use in the above binding experiments can be isolated from patients with coeliac disease, for example with the aid of the method of the invention.

Other binding characteristics of the analogue may also be the same as (i) or (ii), and thus typically the analogue binds to the same MHC class II molecule to which the peptide binds (HLA-DQ2 or -DQ8). The analogue typically binds to antibodies specific for (i) or (ii), and thus inhibits binding of (i) or (ii) to such antibodies.

The analogue is typically a peptide. It may have homology with (i) or (ii), typically at least 70% homology, preferably at least 80, 90%, 95%, 97% or 99% homology with (i) or (ii), for example over a region of at least 15 more (such as the entire length of the analogue and/or (i) or (ii), or across the region which contacts the TCR or binds the MHC molecule) contiguous amino acids. Methods of measuring protein homology are well known in the art and it will be understood by those of skill

14

in the art that in the present context, homology is calculated on the basis of amino acid identity (sometimes referred to as "hard homology").

For example the UWGCG Package provides the BESTFIT program which can be used to calculate homology (for example used on its default settings) (Devereux *et al* (1984) *Nucleic Acids Research* **12**, p387-395). The PILEUP and BLAST algorithms can be used to calculate homology or line up sequences (typically on their default settings), for example as described in Altschul S. F. (1993) J Mol Evol 36:290-300; Altschul, S, F *et al* (1990) J Mol Biol 215:403-10.

Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information on the world wide web through the internet at, for example, "www.ncbi.nlm.nih.gov/". This algorithm involves first identifying high scoring sequence pair (HSPs) by identifying short words of length W in the query sequence that either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighbourhood word score threshold (Altschul *et al*, supra). These initial neighbourhood word hits act as seeds for initiating searches to find HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extensions for the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a word length (W) of 11, the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1992) *Proc. Natl. Acad. Sci.* USA 89: 10915-10919) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

The BLAST algorithm performs a statistical analysis of the similarity between two sequences; see e.g., Karlin and Altschul (1993) *Proc. Natl. Acad. Sci.* USA 90: 5873-5787. One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences

would occur by chance. For example, a sequence is considered similar to another sequence if the smallest sum probability in comparison of the first sequence to the second sequence is less than about 1, preferably less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

The homologous peptide analogues typically differ from (i) or (ii) by 1, 2, 3, 4, 5, 6, 7, 8 or more mutations (which may be substitutions, deletions or insertions). These mutations may be measured across any of the regions mentioned above in relation to calculating homology. The substitutions are preferably 'conservative'. These are defined according to the following Table. Amino acids in the same block in the second column and preferably in the same line in the third column may be substituted for each other:

ALIPHATIC	Non-polar	G A P
		I L V
	Polar – uncharged	C S T M
		N Q
	Polar – charged	D E
		K R
AROMATIC		H F W Y

Typically the amino acids in the analogue at the equivalent positions to amino acids in (i) or (ii) that contribute to binding the MHC molecule or are responsible for the recognition by the TCR, are the same or are conserved.

Typically the analogue peptide comprises one or more modifications, which may be natural post-translation modifications or artificial modifications. The modification may provide a chemical moiety (typically by substitution of a hydrogen, e.g. of a C-H bond), such as an amino, acetyl, hydroxy or halogen (e.g. fluorine) group or carbohydrate group. Typically the modification is present on the N or C terminus.

The analogue may comprise one or more non-natural amino acids, for example amino acids with a side chain different from natural amino acids.

16

Generally, the non-natural amino acid will have an N terminus and/or a C terminus. The non-natural amino acid may be an L- or a D- amino acid.

The analogue typically has a shape, size, flexibility or electronic configuration that is substantially similar to (i) or (ii). It is typically a derivative of (i) or (ii). In one embodiment the analogue is a fusion protein comprising the sequence of SEQ ID NO:1 or 2, or any of the other peptides mentioned herein; and non-gliadin sequence.

In one embodiment the analogue is or mimics (i) or (ii) bound to a MHC class II molecule. 2, 3, 4 or more of such complexes may be associated or bound to each other, for example using a biotin/streptavidin based system, in which typically 2, 3 or 4 biotin labelled MHC molecules bind to a streptavidin moiety. This analogue typically inhibits the binding of the (i) or (ii)/MHC Class II complex to a TCR or antibody which is specific for the complex.

The analogue is typically an antibody or a fragment of an antibody, such as a Fab or (Fab)₂ fragment. The analogue may be immobilised on a solid support, particularly an analogue that mimics peptide bound to a MHC molecule.

The analogue is typically designed by computational means and then synthesised using methods known in the art. Alternatively the analogue can be selected from a library of compounds. The library may be a combinatorial library or a display library, such as a phage display library. The library of compounds may be expressed in the display library in the form of being bound to a MHC class II molecule, such as HLA-DQ2 or -DQ8. Analogues are generally selected from the library based on their ability to mimic the binding characteristics (i) or (ii). Thus they may be selected based on ability to bind a TCR or antibody which recognises (i) or (ii).

Typically analogues will be recognised by T cells to at least the same extent as any of the agents (i) or (ii), for example at least to the same extent as the equivalent epitope and preferably to the same extent as the peptide represented by SEQ ID NO:2, is recognised in any of the assays described herein, typically using T cells from coeliac disease patients. Analogues may be recognised to these extents *in vivo* and thus may be able to induce coeliac disease symptoms to at least the same

17

extent as any of the agents mentioned herein (e.g. in a human patient or animal model).

Analogues may be identified in a method comprising determining whether a candidate substance is recognised by a T cell receptor that recognises an epitope of the invention, recognition of the substance indicating that the substance is an analogue. Such TCRs may be any of the TCRs mentioned herein, and may be present on T cells. Any suitable assay mentioned herein can be used to identify the analogue. In one embodiment this method is carried out *in vivo*. As mentioned above preferred analogues are recognised to at least the same extent as the peptide SEQ ID NO:2, and so the method may be used to identify analogues which are recognised to this extent.

In one embodiment the method comprises determining whether a candidate substance is able to inhibit the recognition of an epitope of the invention, inhibition of recognition indicating that the substance is an analogue.

The agent may be a product comprising at least 2, 5, 10 or 20 agents as defined by (i), (ii) or (iii). Typically the composition comprises epitopes of the invention (or equivalent analogues) from different gliadins, such as any of the species or variety of or types of gliadin mentioned herein. Preferred compositions comprise at least one epitope of the invention, or equivalent analogue, from all of the gliadins present in any of the species or variety mentioned herein, or from 2, 3, 4 or more of the species mentioned herein (such as from the panel of species consisting of wheat, rye, barley, oats and triticale). Thus, the agent may be monovalent or multivalent.

Diagnosis

As mentioned above the method of diagnosis of the invention may be based on the detection of T cells that bind the agent or on the detection of antibodies that recognise the agent.

The T cells that recognise the agent in the method (which includes the use mentioned above) are generally T cells that have been pre-sensitised *in vivo* to gliadin. As mentioned above such antigen-experienced T cells have been found to be present in the peripheral blood.

18

In the method the T cells can be contacted with the agent *in vitro* or *in vivo*, and determining whether the T cells recognise the agent can be performed *in vitro* or *in vivo*. Thus the invention provides the agent for use in a method of diagnosis practiced on the human body. Different agents are provided for simultaneous,

5   separate or sequential use in such a method.

The *in vitro* method is typically carried out in aqueous solution into which the agent is added. The solution will also comprise the T cells (and in certain embodiments the APCs discussed below). The term 'contacting' as used herein includes adding the particular substance to the solution.

10   Determination of whether the T cells recognise the agent is generally accomplished by detecting a change in the state of the T cells in the presence of the agent or determining whether the T cells bind the agent. The change in state is generally caused by antigen specific functional activity of the T cell after the TCR binds the agent. The change of state may be measured inside (e.g. change in

15   intracellular expression of proteins) or outside (e.g. detection of secreted substances) the T cells.

The change in state of the T cell may be the start of or increase in secretion of a substance from the T cell, such as a cytokine, especially IFN-γ, IL-2 or TNF-α. Determination of IFN-γ secretion is particularly preferred. The substance can

20   typically be detected by allowing it to bind to a specific binding agent and then measuring the presence of the specific binding agent/substance complex. The specific binding agent is typically an antibody, such as polyclonal or monoclonal antibodies. Antibodies to cytokines are commercially available, or can be made using standard techniques.

25   Typically the specific binding agent is immobilised on a solid support. After the substance is allowed to bind the solid support can optionally be washed to remove material which is not specifically bound to the agent. The agent/substance complex may be detected by using a second binding agent that will bind the complex. Typically the second agent binds the substance at a site which is different

30   from the site which binds the first agent. The second agent is preferably an antibody and is labelled directly or indirectly by a detectable label.

19

Thus the second agent may be detected by a third agent that is typically labelled directly or indirectly by a detectable label. For example the second agent may comprise a biotin moiety, allowing detection by a third agent which comprises a streptavidin moiety and typically alkaline phosphatase as a detectable label.

In one embodiment the detection system which is used is the *ex-vivo* ELISPOT assay described in WO 98/23960. In that assay IFN-γ secreted from the T cell is bound by a first IFN-γ specific antibody that is immobilised on a solid support. The bound IFN-γ is then detected using a second IFN-γ specific antibody which is labelled with a detectable label. Such a labelled antibody can be obtained from MABTECH (Stockholm, Sweden). Other detectable labels which can be used are discussed below.

The change in state of the T cell that can be measured may be the increase in the uptake of substances by the T cell, such as the uptake of thymidine. The change in state may be an increase in the size of the T cells, or proliferation of the T cells, or a change in cell surface markers on the T cell.

In one embodiment the change of state is detected by measuring the change in the intracellular expression of proteins, for example the increase in intracellular expression of any of the cytokines mentioned above. Such intracellular changes may be detected by contacting the inside of the T cell with a moiety that binds the expressed proteins in a specific manner and which allows sorting of the T cells by flow cytometry.

In one embodiment when binding the TCR the agent is bound to an MHC class II molecule (typically HLA-DQ2 or -DQ8), which is typically present on the surface of an antigen presenting cell (APC). However as mentioned herein other agents can bind a TCR without the need to also bind an MHC molecule.

Generally the T cells which are contacted in the method are taken from the individual in a blood sample, although other types of samples which contain T cells can be used. The sample may be added directly to the assay or may be processed first. Typically the processing may comprise diluting of the sample, for example with water or buffer. Typically the sample is diluted from 1.5 to 100 fold, for example 2 to 50 or 5 to 10 fold.

The processing may comprise separation of components of the sample.
Typically mononuclear cells (MCs) are separated from the samples. The MCs will
comprise the T cells and APCs. Thus in the method the APCs present in the
separated MCs can present the peptide to the T cells. In another embodiment only T
cells, such as only CD4 T cells, can be purified from the sample. PBMCs, MCs and
T cells can be separated from the sample using techniques known in the art, such as
those described in Lalvani *et al* (1997) *J. Exp. Med.* **186**, p859-865.

In one embodiment, the T cells used in the assay are in the form of
unprocessed or diluted samples, or are freshly isolated T cells (such as in the form of
freshly isolated MCs or PBMCs) which are used directly *ex vivo*, i.e. they are not
cultured before being used in the method. Thus the T cells have not been
restimulated in an antigen specific manner *in vitro*. However the T cells can be
cultured before use, for example in the presence of one or more of the agents, and
generally also exogenous growth promoting cytokines. During culturing the agent(s)
are typically present on the surface of APCs, such as the APC used in the method.
Pre-culturing of the T cells may lead to an increase in the sensitivity of the method.
Thus the T cells can be converted into cell lines, such as short term cell lines (for
example as described in Ota *et al* (1990) *Nature* **346**, p183-187).

The APC that is typically present in the method may be from the same
individual as the T cell or from a different host. The APC may be a naturally
occurring APC or an artificial APC. The APC is a cell that is capable of presenting
the peptide to a T cell. It is typically a B cell, dendritic cell or macrophage. It is
typically separated from the same sample as the T cell and is typically co-purified
with the T cell. Thus the APC may be present in MCs or PBMCs. The APC is
typically a freshly isolated *ex vivo* cell or a cultured cell. It may be in the form of a
cell line, such as a short term or immortalised cell line. The APC may express empty
MHC class II molecules on its surface.

In the method one or more (different) agents may be used. Typically the T
cells derived from the sample can be placed into an assay with all the agents which it
is intended to test or the T cells can be divided and placed into separate assays each
of which contain one or more of the agents.

21

The invention also provides the agents such as two or more of any of the agents mentioned herein (e.g. the combinations of agents which are present in the composition agent discussed above) for simultaneous separate or sequential use (eg. for *in vivo* use).

5   In one embodiment agent *per se* is added directly to an assay comprising T cells and APCs. As discussed above the T cells and APCs in such an assay could be in the form of MCs. When agents that can be recognised by the T cell without the need for presentation by APCs are used then APCs are not required. Analogues which mimic the original (i) or (ii) bound to a MHC molecule are an example of such

10   an agent.

        In one embodiment the agent is provided to the APC in the absence of the T cell. The APC is then provided to the T cell, typically after being allowed to present the agent on its surface. The peptide may have been taken up inside the APC and presented, or simply be taken up onto the surface without entering inside the APC.

15   The duration for which the agent is contacted with the T cells will vary depending on the method used for determining recognition of the peptide. Typically 10^5 to 10^7, preferably 5×10^5 to 10^6 PBMCs are added to each assay. In the case where agent is added directly to the assay its concentration is from 10^{-1} to 10^3µg/ml, preferably 0.5 to 50µg/ml or 1 to 10µg/ml.

20   Typically the length of time for which the T cells are incubated with the agent is from 4 to 24 hours, preferably 6 to 16 hours. When using *ex vivo* PBMCs it has been found that 0.3×10^6 PBMCs can be incubated in 10µg/ml of peptide for 12 hours at 37°C.

        The determination of the recognition of the agent by the T cells may be done

25   by measuring the binding of the agent to the T cells (this can be carried out using any suitable binding assay format discussed herein). Typically T cells which bind the agent can be sorted based on this binding, for example using a FACS machine. The presence of T cells that recognise the agent will be deemed to occur if the frequency of cells sorted using the agent is above a "control" value. The frequency of antigen-

30   experienced T cells is generally 1 in 10^6 to 1 in 10^3, and therefore whether or not the sorted cells are antigen-experienced T cells can be determined.

22

The determination of the recognition of the agent by the T cells may be measured *in vivo*. Typically the agent is administered to the host and then a response which indicates recognition of the agent may be measured. The agent is typically administered intradermally or epidermally. The agent is typically administered by

5 contacting with the outside of the skin, and may be retained at the site with the aid of a plaster or dressing. Alternatively the agent may be administered by needle, such as by injection, but can also be administered by other methods such as ballistics (e.g. the ballistics techniques which have been used to deliver nucleic acids). EP-A-0693119 describes techniques that can typically be used to administer the agent.

10 Typically from 0.001 to 1000 µg, for example from 0.01 to 100 µg or 0.1 to 10 µg of agent is administered.

In one embodiment a product can be administered which is capable of providing the agent *in vivo*. Thus a polynucleotide capable of expressing the agent can be administered, typically in any of the ways described above for the

15 administration of the agent. The polynucleotide typically has any of the characteristics of the polynucleotide provided by the invention which is discussed below. The agent is expressed from the polynucleotide *in vivo*. Typically from 0.001 to 1000 µg, for example from 0.01 to 100 µg or 0.1 to 10 µg of polynucleotide is administered.

20 Recognition of the agent administered to the skin is typically indicated by the occurrence of inflammation (e.g. induration, erythema or oedema) at the site of administration. This is generally measured by visual examination of the site.

The method of diagnosis based on the detection of an antibody that binds the agent is typically carried out by contacting a sample from the individual (such as any

25 of the samples mentioned here, optionally processed in any manner mentioned herein) with the agent and determining whether an antibody in the sample binds the agent, such a binding indicating that the individual has, or is susceptible to coeliac disease. Any suitable format of binding assay may be used, such as any such format mentioned herein.

30

Therapy

The identification of the immunodominant epitope and other epitopes described herein allows therapeutic products to be made which target the T cells which recognise this epitope (such T cells being ones which participate in the immune response against gliadin). These findings also allow the prevention or

5   treatment of coeliac disease by suppressing (by tolerisation) an antibody or T cell response to the epitope(s).

Certain agents of the invention bind the TCR that recognises the epitope of the invention (as measured using any of the binding assays discussed above) and cause tolerisation of the T cell that carries the TCR. Such agents, optionally in

10   association with a carrier, can therefore be used to prevent or treat coeliac disease.

Generally tolerisation can be caused by the same peptides which can (after being recognised by the TCR) cause antigen specific functional activity of the T cell (such as any such activity mentioned herein, e.g. secretion of cytokines). Such agents cause tolerisation when they are presented to the immune system in a

15   'tolerising' context.

Tolerisation leads to a decrease in the recognition of a T cell or antibody epitope by the immune system. In the case of a T cell epitope this can be caused by the deletion or anergising of T cells that recognise the epitope. Thus T cell activity (for example as measured in suitable assays mentioned herein) in response to the

20   epitope is decreased. Tolerisation of an antibody response means that a decreased amount of specific antibody to the epitope is produced when the epitope is administered.

Methods of presenting antigens to the immune system in such a context are known and are described for example in Yoshida et al. Clin. Immunol.

25   Immunopathol. 82, 207-215 (1997), Thurau et al. Clin. Exp. Immunol. 109, 370-6 (1997), and Weiner et al. Res. Immunol. 148, 528-33 (1997). In particular certain routes of administration can cause tolerisation, such as oral, nasal or intraperitoneal. Tolerisation may also be accomplished via dendritic cells and tetramers presenting peptide. Particular products which cause tolerisation may be administered (e.g. in a

30   composition that also comprises the agent) to the individual. Such products include cytokines, such as cytokines that favour a Th2 response (e.g. IL-4, TGF-β or IL-10). Products or agent may be administered at a dose that causes tolerisation.

24

The invention provides a protein that comprises a sequence able to act as an antagonist of the T cell (which T cell recognises the agent). Such proteins and such antagonists can also be used to prevent or treat coeliac disease. The antagonist will cause a decrease in the T cell response. In one embodiment, the antagonist binds the

5   TCR of the T cell (generally in the form of a complex with HLA-DQ2 or -DQ8) but instead of causing normal functional activation causing an abnormal signal to be passed through the TCR intracellular signalling cascade, which causes the T cell to have decreased function activity (e.g. in response to recognition of an epitope, typically as measured by any suitable assay mentioned herein).

10   In one embodiment the antagonist competes with epitope to bind a component of MHC processing and presentation pathway, such as an MHC molecule (typically HLA-DQ2 or -DQ8). Thus the antagonist may bind HLA-DQ2 or -DQ8 (and thus be a peptide presented by this MHC molecule), such as peptide TP (Table 10) or a homologue thereof.

15   Methods of causing antagonism are known in the art. In one embodiment the antagonist is a homologue of the epitopes mentioned above and may have any of the sequence, binding or other properties of the agent (particularly analogues). The antagonists typically differ from any of the above epitopes (which are capable of causing a normal antigen specific function in the T cell) by 1, 2, 3, 4 or more

20   mutations (each of which may be a substitution, insertion or deletion). Such antagonists are termed "altered peptide ligands" or "APL" in the art. The mutations are typically at the amino acid positions that contact the TCR.

The antagonist may differ from the epitope by a substitution within the sequence that is equivalent to the sequence represented by amino acids 65 to 67 of A-

25   gliadin (such antagonists are shown in Table 9). Thus preferably the antagonist has a substitution at the equivalent of position 64, 65 or 67. Preferably the substitution is 64W, 67W, 67M or 65T.

Since the T cell immune response to the epitope of the invention in an individual is polyclonal, more than one antagonist may need to be administered to

30   cause antagonism of T cells of the response which have different TCRs. Therefore the antagonists may be administered in a composition which comprises at least 2, 4, 6 or more different antagonists, which each antagonise different T cells.

The invention also provides a method of identifying an antagonist of a T cell (which recognises the agent), comprising contacting a candidate substance with the T cell and detecting whether the substance causes a decrease in the ability of the T cell to undergo an antigen specific response (e.g. using any suitable assay mentioned

5   herein), the detecting of any such decrease in said ability indicating that the substance is an antagonist.

In one embodiment, the antagonists (including combinations of antagonists to a particular epitope) or tolerising (T cell and antibody tolerising) agents are present in a composition comprising at least 2, 4, 6 or more antagonists or agents which

10 antagonise or tolerise to different epitopes of the invention, for example to the combinations of epitopes discussed above in relation to the agents which are a product comprising more than one substance.

Testing whether a composition is capable of causing coeliac disease

15   As mentioned above the invention provides a method of determining whether a composition is capable of causing coeliac disease comprising detecting the presence of a protein sequence which is capable of being modified by a transglutaminase to as sequence comprising the agent or epitope of the invention (such transglutaminase activity may be a human intestinal transglutaminase activity).

20 Typically this is performed by using a binding assay in which a moiety which binds to the sequence in a specific manner is contacted with the composition and the formation of sequence/moiety complex is detected and used to ascertain the presence of the agent. Such a moiety may be any suitable substance (or type of substance) mentioned herein, and is typically a specific antibody. Any suitable format of

25 binding assay can be used (such as those mentioned herein).

In one embodiment, the composition is contacted with at least 2, 5, 10 or more antibodies which are specific for epitopes of the invention from different gliadins, for example a panel of antibodies capable of recognising the combinations of epitopes discussed above in relation to agents of the invention which are a product

30 comprising more than one substance.

The composition typically comprises material from a plant that expresses a gliadin which is capable of causing coeliac disease (for example any of the gliadins

26

or plants mentioned herein). Such material may be a plant part, such as a harvested
product (e.g. seed). The material may be processed products of the plant material
(e.g. any such product mentioned herein), such as a flour or food that comprises the
gliadin. The processing of food material and testing in suitable binding assays is
routine, for example as mentioned in Kricka LJ, J. Biolumin. Chemilumin. 13, 189-
93 (1998).

Binding assays

The determination of binding between any two substances mentioned herein
may be done by measuring a characteristic of either or both substances that changes
upon binding, such as a spectroscopic change.

The binding assay format may be a 'band shift' system. This involves
determining whether the presence of one substance (such as a candidate substance)
advances or retards the progress of the other substance during gel electrophoresis.

The format may be a competitive binding method which determines whether
the one substance is able to inhibit the binding of the other substance to an agent
which is known to bind the other substance, such as a specific antibody.

Mutant gliadin proteins

The invention provides a gliadin protein in which an epitope sequence of the
invention, or sequence which can be modified by a transglutaminase to provide such
a sequence has been mutated so that it no longer causes, or is recognised by, a T cell
response that recognises the epitope. In this context the term recognition refers to the
TCR binding the epitope in such a way that normal (not antagonistic) antigen-
specific functional activity of the T cell occurs.

Methods of identifying equivalent epitopes in other gliadins are discussed
above. The wild type of the mutated gliadin is one which causes coeliac disease.
Such a gliadin may have homology with SEQ ID NO:3, for example to the degree
mentioned above (in relation to the analogue) across all of SEQ ID NO:3 or across
15, 30, 60, 100 or 200 contiguous amino acids of SEQ ID NO:3. Likewise, for other
non-A-gliadins, homology will be present between the mutant and the native form of
that gliadin. The sequences of other natural gliadin proteins are known in the art.

The mutated gliadin will not cause coeliac disease or will cause decreased
symptoms of coeliac disease. Typically the mutation decreases the ability of the
epitope to induce a T cell response. The mutated epitope may have a decreased
binding to HLA-DQ2 or -DQ8, a decreased ability to be presented by an APC or a

5   decreased ability to bind to or to be recognised (i.e. cause antigen-specific functional
activity) by T cells that recognise the agent. The mutated gliadin or epitope will
therefore show no or reduced recognition in any of the assays mentioned herein in
relation to the diagnostic aspects of the invention.

The mutation may be one or more deletions, additions or substitutions of

10   length 1 to 3, 4 to 6, 6 to 10, 11 to 15 or more in the epitope, for example across
sequence SEQ ID NO:2 or across any of SEQ ID NOS: 18-22, 31-36, 39-44, and 46;
or across equivalents thereof. Preferably the mutant gliadin has at least one mutation
in the sequence SEQ ID NO:1. A preferred mutation is at position 65 in A-gliadin
(or in an equivalent position in other gliadins). Typically the naturally occurring

15   glutamine at this position is substituted to any of the amino acids shown in Table 3,
preferably to histidine, tyrosine, tryptophan, lysine, proline, or arginine.

The invention thus also provides use of a mutation (such any of the mutations
in any of the sequences discussed herein) in an epitope of a gliadin protein, which
epitope is an epitope of the invention, to decrease the ability of the gliadin protein to

20   cause coeliac disease.

In one embodiment the mutated sequence is able to act as an antagonist.
Thus the invention provides a protein that comprises a sequence which is able to bind
to a T cell receptor, which T cell receptor recognises an agent of the invention, and
which sequence is able to cause antagonism of a T cell that carries such a T cell

25   receptor.

The invention also provides proteins which are fragments of the above mutant
gliadin proteins, which are at least 15 amino acids long (e.g. at least 30, 60, 100, 150,
200, or 250 amino acids long) and which comprise the mutations discussed above
which decrease the ability of the gliadin to be recognised. Any of the mutant

30   proteins (including fragments) mentioned herein may also be present in the form of
fusion proteins, for example with other gliadins or with non-gliadin proteins.

28

The equivalent wild type protein to the mutated gliadin protein is typically from a graminaceous monocotyledon, such as a plant of genus Triticum, e.g. wheat, rye, barley, oats or triticale. The protein is typically an α, $\alpha\beta$, β, γ or ω gliadin. The gliadin may be an A-gliadin.

Kits

The invention also provides a kit for carrying out the method comprising one or more agents and optionally a means to detect the recognition of the agent by the T cell. Typically the different agents are provided for simultaneous, separate or sequential use. Typically the means to detect recognition allows or aids detection based on the techniques discussed above.

Thus the means may allow detection of a substance secreted by the T cells after recognition. The kit may thus additionally include a specific binding moiety for the substance, such as an antibody. The moiety is typically specific for IFN-γ. The moiety is typically immobilised on a solid support. This means that after binding the moiety the substance will remain in the vicinity of the T cell which secreted it. Thus "spots" of substance/moiety complex are formed on the support, each spot representing a T cell which is secreting the substance. Quantifying the spots, and typically comparing against a control, allows determination of recognition of the agent.

The kit may also comprise a means to detect the substance/moiety complex. A detectable change may occur in the moiety itself after binding the substance, such as a colour change. Alternatively a second moiety directly or indirectly labelled for detection may be allowed to bind the substance/moiety complex to allow the determination of the spots. As discussed above the second moiety may be specific for the substance, but binds a different site on the substance than the first moiety.

The immobilised support may be a plate with wells, such as a microtitre plate. Each assay can therefore be carried out in a separate well in the plate.

The kit may additionally comprise medium for the T cells, detection moieties or washing buffers to be used in the detection steps. The kit may additionally comprise reagents suitable for the separation from the sample, such as the separation of PBMCs or T cells from the sample. The kit may be designed to allow detection of

the T cells directly in the sample without requiring any separation of the components of the sample.

The kit may comprise an instrument which allows administration of the agent, such as intradermal or epidermal administration. Typically such an instrument comprises plaster, dressing or one or more needles. The instrument may allow ballistic delivery of the agent. The agent in the kit may be in the form of a pharmaceutical composition.

The kit may also comprise controls, such as positive or negative controls. The positive control may allow the detection system to be tested. Thus the positive control typically mimics recognition of the agent in any of the above methods. Typically in the kits designed to determine recognition *in vitro* the positive control is a cytokine. In the kit designed to detect *in vivo* recognition of the agent the positive control may be antigen to which most individuals should response.

The kit may also comprise a means to take a sample containing T cells from the host, such as a blood sample. The kit may comprise a means to separate mononuclear cells or T cells from a sample from the host.

Polynucleotides, cells, transgenic mammals and antibodies

The invention also provides a polynucleotide which is capable of expression to provide the agent or mutant gliadin proteins. Typically the polynucleotide is DNA or RNA, and is single or double stranded. The polynucleotide will preferably comprise at least 50 bases or base pairs, for example 50 to 100, 100 to 500, 500 to 1000 or 1000 to 2000 or more bases or base pairs. The polynucleotide therefore comprises a sequence which encodes the sequence of SEQ ID NO: 1 or 2 or any of the other agents mentioned herein. To the 5' and 3' of this coding sequence the polynucleotide of the invention has sequence or codons which are different from the sequence or codons 5' and 3' to these sequences in the corresponding gliadin gene.

5' and/or 3' to the sequence encoding the peptide the polynucleotide has coding or non-coding sequence. Sequence 5' and/or 3' to the coding sequence may comprise sequences which aid expression, such as transcription and/or translation, of the sequence encoding the agent. The polynucleotide may be capable of expressing the agent prokaryotic or eukaryotic cell. In one embodiment the polynucleotide is

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capable of expressing the agent in a mammalian cell, such as a human, primate or rodent (e.g. mouse or rat) cell.

A polynucleotide of the invention may hybridise selectively to a polynucleotide that encodes SEQ ID NO:3 at a level significantly above background. Selective hybridisation is typically achieved using conditions of medium to high stringency (for example 0.03M sodium chloride and 0.03M sodium citrate at from about 50°C to about 60°C). However, such hybridisation may be carried out under any suitable conditions known in the art (see Sambrook *et al* (1989), Molecular Cloning: A Laboratory Manual). For example, if high stringency is required, suitable conditions include 0.2 x SSC at 60°C. If lower stringency is required, suitable conditions include 2 x SSC at 60°C.

Agents or proteins of the invention may be encoded by the polynucleotides described herein.

The polynucleotide may form or be incorporated into a replicable vector. Such a vector is able to replicate in a suitable cell. The vector may be an expression vector. In such a vector the polynucleotide of the invention is operably linked to a control sequence which is capable of providing for the expression of the polynucleotide. The vector may contain a selectable marker, such as the ampicillin resistance gene.

The polynucleotide or vector may be present in a cell. Such a cell may have been transformed by the polynucleotide or vector. The cell may express the agent. The cell will be chosen to be compatible with the said vector and may for example be a prokaryotic (bacterial), yeast, insect or mammalian cell. The polynucleotide or vector may be introduced into host cells using conventional techniques including calcium phosphate precipitation, DEAE-dextran transfection, or electroporation.

The invention provides processes for the production of the proteins of the invention by recombinant means. This may comprise (a) cultivating a transformed cell as defined above under conditions that allow the expression of the protein; and preferably (b) recovering the expressed polypeptide. Optionally, the polypeptide may be isolated and/or purified, by techniques known in the art.

The invention also provides TCRs which recognise (or bind) the agent, or fragments thereof which are capable of such recognition (or binding). These can be

31

present in the any form mentioned herein (e.g. purity) discussed herein in relation to the protein of the invention. The invention also provides T cells which express such TCRs which can be present in any form (e.g. purity) discussed herein for the cells of the invention.

The invention also provides monoclonal or polyclonal antibodies which specifically recognise the agents (such as any of the epitopes of the invention) and which recognise the mutant gliadin proteins (and typically which do not recognise the equivalent wild-type gliadins) of the invention, and methods of making such antibodies. Antibodies of the invention bind specifically to these substances of the invention.

For the purposes of this invention, the term "antibody" includes antibody fragments such as Fv, F(ab) and F(ab)$_2$ fragments, as well as single-chain antibodies.

A method for producing a polyclonal antibody comprises immunising a suitable host animal, for example an experimental animal, with the immunogen and isolating immunoglobulins from the serum. The animal may therefore be inoculated with the immunogen, blood subsequently removed from the animal and the IgG fraction purified. A method for producing a monoclonal antibody comprises immortalising cells which produce the desired antibody. Hybridoma cells may be produced by fusing spleen cells from an inoculated experimental animal with tumour cells (Kohler and Milstein (1975) *Nature* **256**, 495-497).

An immortalized cell producing the desired antibody may be selected by a conventional procedure. The hybridomas may be grown in culture or injected intraperitoneally for formation of ascites fluid or into the blood stream of an allogenic host or immunocompromised host. Human antibody may be prepared by *in vitro* immunisation of human lymphocytes, followed by transformation of the lymphocytes with Epstein-Barr virus.

For the production of both monoclonal and polyclonal antibodies, the experimental animal is suitably a goat, rabbit, rat or mouse. If desired, the immunogen may be administered as a conjugate in which the immunogen is coupled, for example via a side chain of one of the amino acid residues, to a suitable carrier. The carrier molecule is typically a physiologically acceptable carrier. The antibody obtained may be isolated and, if desired, purified.

The polynucleotide, agent, protein or antibody of the invention, may carry a detectable label. Detectable labels which allow detection of the secreted substance by visual inspection, optionally with the aid of an optical magnifying means, are preferred. Such a system is typically based on an enzyme label which causes colour

5   change in a substrate, for example alkaline phosphatase causing a colour change in a substrate. Such substrates are commercially available, e.g. from BioRad. Other suitable labels include other enzymes such as peroxidase, or protein labels, such as biotin; or radioisotopes, such as ^{32}P or ^{35}S. The above labels may be detected using known techniques.

10   Polynucleotides, agents, proteins, antibodies or cells of the invention may be in substantially purified form. They may be in substantially isolated form, in which case they will generally comprise at least 80% e.g. at least 90, 95, 97 or 99% of the polynucleotide, peptide, antibody, cells or dry mass in the preparation. The polynucleotide, agent, protein or antibody is typically substantially free of other

15   cellular components. The polynucleotide, agent, protein or antibody may be used in such a substantially isolated, purified or free form in the method or be present in such forms in the kit.

The invention also provides a transgenic non-human mammal which expresses a TCR of the invention. This may be any of the mammals discussed herein

20   (e.g. in relation to the production of the antibody). Preferably the mammal has, or is susceptible, to coeliac disease. The mammal may also express HLA-DQ2 or -DQ8 or HLA-DR3-DQ2 and/or may be given a diet comprising a gliadin which cause coeliac disease (e.g. any of the gliadin proteins mentioned herein). Thus the mammal may act as an animal model for coeliac disease.

25   The invention also provides a method of identifying a product which is therapeutic for coeliac disease comprising administering a candidate substance to a mammal of the invention which has, or which is susceptible to, coeliac disease and determining whether substance prevents or treats coeliac disease in the mammal, the prevention or treatment of coeliac disease indicating that the substance is a

30   therapeutic product. Such a product may be used to treat or prevent coeliac disease.

The invention provides therapeutic (including prophylactic) agents or diagnostic substances (the agents, proteins and polynucleotides of the invention).

33

These substances are formulated for clinical administration by mixing them with a pharmaceutically acceptable carrier or diluent. For example they can be formulated for topical, parenteral, intravenous, intramuscular, subcutaneous, intraocular, intradermal, epidermal or transdermal administration. The substances may be mixed with any vehicle which is pharmaceutically acceptable and appropriate for the desired route of administration. The pharmaceutically carrier or diluent for injection may be, for example, a sterile or isotonic solution such as Water for Injection or physiological saline, or a carrier particle for ballistic delivery.

The dose of the substances may be adjusted according to various parameters, especially according to the agent used; the age, weight and condition of the patient to be treated; the mode of administration used; the severity of the condition to be treated; and the required clinical regimen. As a guide, the amount of substance administered by injection is suitably from 0.01 mg/kg to 30 mg/kg, preferably from 0.1 mg/kg to 10 mg/kg.

The routes of administration and dosages described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and dosage for any particular patient and condition.

The substances of the invention may thus be used in a method of treatment of the human or animal body, or in a diagnostic method practised on the human body. In particular they may be used in a method of treating or preventing coeliac disease. The invention also provide the agents for use in a method of manufacture of a medicament for treating or preventing coeliac disease. Thus the invention provides a method of preventing or treating coeliac disease comprising administering to a human in need thereof a substance of the invention (typically a non-toxic effective amount thereof).

The agent of the invention can be made using standard synthetic chemistry techniques, such as by use of an automated synthesizer. The agent may be made from a longer polypeptide e.g. a fusion protein, which polypeptide typically comprises the sequence of the peptide. The peptide may be derived from the polypeptide by for example hydrolysing the polypeptide, such as using a protease; or by physically breaking the polypeptide. The polynucleotide of the invention can be made using standard techniques, such as by using a synthesiser.

34

Plant cells and plants that express mutant gliadin proteins or express proteins comprising sequences which can act as antagonists

The cell of the invention may be a plant cell, such as a cell of a graminaceous

5 monocotyledonous species. The species may be one whose wild-type form expresses gliadins, such as any of the gliadin proteins mentioned herein (including gliadins with any degree of homology to SEQ ID NO:3 mentioned herein). Such a gliadin may cause coeliac disease in humans. The cell may be of wheat, maize, oats, rye, rice, barley, triticale, sorghum, or sugar cane. Typically the cell is of the Triticum

10 genus, such as aestivum, spelta, polonicum or monococcum.

The plant cell of the invention is typically one which does not express a wild-type gliadin (such as any of the gliadins mentioned herein which may cause coeliac disease), or one which does not express a gliadin comprising a sequence that can be recognised by a T cell that recognises the agent. Thus if the wild-type plant cell did

15 express such a gliadin then it may be engineered to prevent or reduce the expression of such a gliadin or to change the amino acid sequence of the gliadin so that it no longer causes coeliac disease (typically by no longer expressing the epitope of the invention).

This can be done for example by introducing mutations into 1, 2, 3 or more or

20 all of such gliadin genes in the cell, for example into coding or non-coding (e.g. promoter regions). Such mutations can be any of the type or length of mutations discussed herein (e.g., in relation to homologous proteins). The mutations can be introduced in a directed manner (e.g., using site directed mutagenesis or homologous recombination techniques) or in a random manner (e.g. using a mutagen, and then

25 typically selecting for mutagenised cells which no longer express the gliadin (or a gliadin sequence which causes coeliac disease)).

In the case of plants or plant cells that express a protein that comprises a sequence able to act as an antagonist such a plant or plant cell may express a wild-type gliadin protein (e.g. one which causes coeliac disease). Preferably though the

30 presence of the antagonist sequence will cause reduced coeliac disease symptoms (such as no symptoms) in an individual who ingests a food comprising protein from the plant or plant cell.

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The polynucleotide which is present in (or which was transformed into) the plant cell will generally comprise promoter capable of expressing the mutant gliadin protein the plant cell. Depending on the pattern of expression desired, the promoter may be constitutive, tissue- or stage-specific; and/or inducible. For example, strong

5 constitutive expression in plants can be obtained with the CAMV 35S, Rubisco ssu, or histone promoters. Also, tissue-specific or stage-specific promoters may be used to target expression of protein of the invention to particular tissues in a transgenic plant or to particular stages in its development. Thus, for example seed-specific, root-specific, leaf-specific, flower-specific etc promoters may be used. Seed-specific

10 promoters include those described by Dalta *et al* (Biotechnology Ann. Rev. (1997), 3, pp.269-296). Particular examples of seed-specific promoters are napin promoters (EP-A-0 255, 378), phaseolin promoters, glutenine promoters, helianthenine promoters (WO92/17580), albumin promoters (WO98/45460), oleosin promoters (WO98/45461) and ATS1 and ATS3 promoters (PCT/US98/06798).

15 The cell may be in any form. For example, it may be an isolated cell, e.g. a protoplast, or it may be part of a plant tissue, e.g. a callus, or a tissue excised from a plant, or it may be part of a whole plant. The cell may be of any type (e.g. of any type of plant part). For example, an undifferentiated cell, such as a callus cell; or a differentiated cell, such as a cell of a type found in embryos, pollen, roots, shoots or

20 leaves. Plant parts include roots; shoots; leaves; and parts involved in reproduction, such as pollen, ova, stamens, anthers, petals, sepals and other flower parts.

The invention provides a method of obtaining a transgenic plant cell comprising transforming a plant cell with a polynucleotide or vector of the invention to give a transgenic plant cell. Any suitable transformation method may be used (in

25 the case of wheat the techniques disclosed in Vasil V et al, Biotechnology 10, 667-674 (1992) may be used). Preferred transformation techniques include electroporation of plant protoplasts and particle bombardment. Transformation may thus give rise to a chimeric tissue or plant in which some cells are transgenic and some are not.

30 The cell of the invention or thus obtained cell may be regenerated into a transgenic plant by techniques known in the art. These may involve the use of plant growth substances such as auxins, giberellins and/or cytokinins to stimulate the

36

growth and/or division of the transgenic cell. Similarly, techniques such as somatic

embryogenesis and meristem culture may be used. Regeneration techniques are well

known in the art and examples can be found in, e.g. US 4,459,355, US 4,536,475, US

5,464,763, US 5, 177,010, US 5, 187,073, EP 267,159, EP 604, 662, EP 672, 752,

5   US 4,945,050, US 5,036,006, US 5,100,792, US 5,371,014, US 5,478,744, US

5,179,022, US 5,565,346, US 5,484,956, US 5,508,468, US 5,538,877, US

5,554,798, US 5,489,520, US 5,510,318, US 5,204,253, US 5,405,765, EP 442,174,

EP 486,233, EP 486,234, EP 539,563, EP 674,725, WO91/02071 and WO 95/06128.

In many such techniques, one step is the formation of a callus, i.e. a plant

10   tissue comprising expanding and/or dividing cells. Such calli are a further aspect of

the invention as are other types of plant cell cultures and plant parts. Thus, for

example, the invention provides transgenic plant tissues and parts, including

embryos, meristems, seeds, shoots, roots, stems, leaves and flower parts. These may

be chimeric in the sense that some of their cells are cells of the invention and some

15   are not. Transgenic plant parts and tissues, plants and seeds of the invention may be

of any of the plant species mentioned herein.

Regeneration procedures will typically involve the selection of transformed

cells by means of marker genes.

The regeneration step gives rise to a first generation transgenic plant. The

20   invention also provides methods of obtaining transgenic plants of further generations

from this first generation plant. These are known as progeny transgenic plants.

Progeny plants of second, third, fourth, fifth, sixth and further generations may be

obtained from the first generation transgenic plant by any means known in the art.

Thus, the invention provides a method of obtaining a transgenic progeny

25   plant comprising obtaining a second-generation transgenic progeny plant from a

first-generation transgenic plant of the invention, and optionally obtaining transgenic

plants of one or more further generations from the second-generation progeny plant

thus obtained.

Progeny plants may be produced from their predecessors of earlier

30   generations by any known technique. In particular, progeny plants may be produced

by:

obtaining a transgenic seed from a transgenic plant of the invention belonging to a previous generation, then obtaining a transgenic progeny plant of the invention belonging to a new generation by growing up the transgenic seed; and/or

propagating clonally a transgenic plant of the invention belonging to a

5   previous generation to give a transgenic progeny plant of the invention belonging to a new generation; and/or

crossing a first-generation transgenic plant of the invention belonging to a previous generation with another compatible plant to give a transgenic progeny plant of the invention belonging to a new generation; and optionally

10   obtaining transgenic progeny plants of one or more further generations from the progeny plant thus obtained.

These techniques may be used in any combination. For example, clonal propagation and sexual propagation may be used at different points in a process that gives rise to a transgenic plant suitable for cultivation. In particular, repetitive back-

15   crossing with a plant taxon with agronomically desirable characteristics may be undertaken. Further steps of removing cells from a plant and regenerating new plants therefrom may also be carried out.

Also, further desirable characteristics may be introduced by transforming the cells, plant tissues, plants or seeds, at any suitable stage in the above process, to

20   introduce desirable coding sequences other than the polynucleotides of the invention. This may be carried out by the techniques described herein for the introduction of polynucleotides of the invention.

For example, further transgenes may be selected from those coding for other herbicide resistance traits, e.g. tolerance to: Glyphosate (e.g. using an EPSP synthase

25   gene (e.g. EP-A-0 293,358) or a glyphosate oxidoreductase (WO 92/000377) gene); or tolerance to fosametin; a dihalobenzonitrile; glufosinate, e.g. using a phosphinothrycin acetyl transferase (PAT) or glutamine synthase gene (cf. EP-A-0 242,236); asulam, e.g. using a dihydropteroate synthase gene (EP-A-0 369,367); or a sulphonylurea, e.g. using an ALS gene); diphenyl ethers such as acifluorfen or

30   oxyfluorfen, e.g. using a protoporphyrogen oxidase gene); an oxadiazole such as oxadiazon; a cyclic imide such as chlorophthalim; a phenyl pyrazole such as TNP, or a phenopylate or carbamate analogue thereof.

38

Similarly, genes for beneficial properties other than herbicide tolerance may be introduced. For example, genes for insect resistance may be introduced, notably genes encoding *Bacillus thuringiensis* (*Bt*) toxins. Likewise, genes for disease resistance may be introduced, e.g. as in WO91/02701 or WO95/06128.

5 Typically, a protein of the invention is expressed in a plant of the invention. Depending on the promoter used, this expression may be constitutive or inducible. Similarly, it may be tissue- or stage-specific, i.e. directed towards a particular plant tissue (such as any of the tissues mentioned herein) or stage in plant development.

The invention also provides methods of obtaining crop products by 10 harvesting, and optionally processing further, transgenic plants of the invention. By crop product is meant any useful product obtainable from a crop plant.

Products that contain mutant gliadin proteins or proteins that comprise
15 **sequence capable of acting as an antagonist**

The invention provides a product that comprises the mutant gliadin proteins or protein that comprises sequence capable of acting as an antagonist. This is typically derived from or comprise plant parts from plants mentioned herein which express such proteins. Such a product may be obtainable directly by harvesting or 20 indirectly, by harvesting and further processing the plant of the invention. Directly obtainable products include grains. Alternatively, such a product may be obtainable indirectly, by harvesting and further processing. Examples of products obtainable by further processing are flour or distilled alcoholic beverages; food products made from directly obtained or further processed material, e.g. baked products (e.g. bread) 25 made from flour. Typically such food products, which are ingestible and digestible (i.e. non-toxic and of nutrient value) by human individuals.

In the case of food products that comprise the protein which comprises an antagonist sequence the food product may also comprise wild-type gliadin, but preferably the antagonist is able to cause a reduction (e.g. completely) in the coeliac 30 disease symptoms after such food is ingested.

The invention is illustrated by the following nonlimiting Examples:

Example 1

We carried out epitope mapping in Coeliac disease by using a set of 51 synthetic 15-mer peptides that span the complete sequence of a fully characterized a-gliadin, "A-gliadin" (see Table 1). A-Gliadin peptides were also individually treated with tTG to generate products that might mimic those produced in vivo[3]. We also

5   sought to study Coeliac disease patients at the point of initiation of disease relapse to avoid the possibility that epitope "spreading" or "exhaustion" may have occurred, as described in experimental infectious and autoimmune diseases.

Clinical and A-gliadin specific T-cell responses with 3 and 10 day bread challenge

10   In a pilot study, two subjects with Coeliac disease in remission, defined by absence of serum anti-endomysial antibody (EMA), on a gluten free diet were fed four slices of standard gluten-containing white bread daily in addition to their usual gluten free diet. Subject 1 ceased bread because of abdominal pain, mouth ulcers and mild diarrhoea after three days, but Subject 2 continued for 10 days with only

15   mild nausea at one week. The EMA became positive in Subject 2 one week after the bread challenge, indicating the bread used had caused a relapse of Coeliac disease. But in Subject 1, EMA remained negative up to two months after bread challenge. In both subjects, symptoms that appeared with bread challenge resolved within two days after returning to gluten free diet.

20   PBMC responses in IFNγ ELISPOT assays to A-gliadin peptides were not found before or during bread challenge. But from the day after bread withdrawal (Day 4) in Subject 1 a single pool of 5 overlapping peptides spanning A-gliadin 51-85 (Pool 3) treated with tTG showed potent IFNγ responses (see Figure 1a). In Subject 1, the PBMC IFNγ response to A-gliadin peptide remained targeted to Pool 3

25   alone and was maximal on Day 8. The dynamics and magnitude of the response to Pool 3 was similar to that elicited by α-chymotrypsin digested gliadin. PBMC IFNγ responses to tTG-treated Pool 3 were consistently 5 to 12-fold greater than Pool 3 not treated with tTG, and responses to α-chymotrypsin digested gliadin were 3 to 10-fold greater if treated with tTG. In Subject 2, Pool 3 treated with tTG was also the only

30   immunogenic set of A-gliadin peptides on Day 8, but this response was weaker than Subject 1, was not seen on Day 4 and by Day 11 the response to Pool 3 had diminished and other tTG-treated pools of A-gliadin peptides elicited stronger IFNα

responses (see Figure 1b).

The pilot study indicated that the initial T cell response in these Coeliac disease subjects was against a single tTG-treated A-gliadin pool of five peptides and was readily measured in peripheral blood. But if antigen exposure is continued for ten days instead of three, T cell responses to other A-gliadin peptides appear, consistent with epitope spreading.

Coeliac disease-specific IFN-g induction by tTG-treated A-gliadin peptides

In five out of six further Coeliac disease subjects on gluten free diet (see Table 1), bread challenge for three days identified tTG-treated peptides in Pool 3, and in particular, peptides corresponding to 56-70 (12) and 60-75 (13) as the sole A-gliadin components eliciting IFNγ from PBMC (see Figure 2). IL-10 ELISPOT assays run in parallel to IFNγ ELISPOT showed no IL-10 response to tTG-treated peptides 12 or 13. In one subject, there were no IFNγ responses to any A-gliadin peptide or α-chymotrypsin digested gliadin before, during or up to four days after bread challenge. In none of these Coeliac disease subjects did EMA status change from baseline when measured for up to two months after bread challenge.

PBMC from four healthy, EMA-negative subjects with the HLA-DQ alleles α1*0501, β1*0201 (ages 28-52, 2 females) who had been challenged for three days with bread after following a gluten free diet for one month, showed no IFNγ responses above the negative control to any of the A-gliadin peptides with or without tTG treatment. Thus, induction of IFNγ in PBMC to tTG-treated Pool 3 and A-gliadin peptides 56-70 (12) and 60-75 (13) were Coeliac disease specific (7/8 vs. 0/4, $p < 0.01$ by Chi-squared analysis).

Fine mapping of the minimal A-gliadin T cell epitope

tTG-treated peptides representing truncations of A-gliadin 56-75 revealed that the same core peptide sequence QPQLP (SEQ ID NO:9) was essential for antigenicity in all of the five Coeliac disease subjects assessed (see Figure 3). PBMC IFNγ responses to tTG-treated peptides spanning this core sequence beginning with the 7-mer PQPQLPY (SEQ ID NO:4) and increasing in length, indicated that the tTG-treated 17-mer QLQPFPQPQLPYPQPQS (SEQ ID NO:10) (A-gliadin 57-73)

41

possessed optimal activity in the IFNγ ELISPOT (see Figure 4).

Deamidation of Q65 by tTG generates the immunodominant T cell epitope in A-gliadin

5   HPLC analysis demonstrated that tTG treatment of A-gliadin 56-75 generated

a single product that eluted marginally later than the parent peptide. Amino acid

sequencing indicated that out of the six glutamine (Q) residues contained in A-

gliadin 56-75, Q65 was preferentially deamidated by tTG (see Figure 5). Bioactivity

of peptides corresponding to serial expansions from the core A-gliadin 62-68

10   sequence in which glutamate (E) replaced Q65, was equivalent to the same peptides

with Q65 after tTG-treatment (see Figure 4a). Replacement of Q57 and Q72 by E

together or alone, with E65 did not enhance antigenicity of the 17-mer in the three

Coeliac disease subjects studied (see Figure 6). Q57 and Q72 were investigated

because glutamine residues followed by proline in gliadin peptides are not

15   deamidated by tTG in vitro (W. Vader et al, Proceedings 8th International

Symposium Coeliac Disease). Therefore, the immunodominant T cell epitope was

defined as QLQPFPQPELPYPQPQS (SEQ ID NO:2).

Immunodominant T cell epitope response is DQ2-restricted and CD4 dependent

20   In two Coeliac disease subjects homozygous for HLA-DQ α1*0501,

β1*0201, anti-DQ monoclonal antibody blocked the ELISPOT IFNγ response to

tTG-treated A-gliadin 56-75, but anti-DP and -DR antibody did not (see Figure 7).

Anti-CD4 and anti-CD8 magnetic bead depletion of PBMC from two Coeliac disease

subjects indicated the IFNγ response to tTG-treated A-gliadin 56-75 is CD4 T cell-

25   mediated.

Discussion

In this study we describe a rather simple dietary antigen challenge using

standard white bread to elicit a transient population of CD4 T cells in peripheral

30   blood of Coeliac disease subjects responsive to a tTG-treated A-gliadin 17-mer with

the sequence: QLQPFPQPELPYPQPQS (SEQ ID NO:2) (residues 57-73). The

immune response to A-gliadin 56-75 (Q→E65) is restricted to the Coeliac disease-

42

associated HLA allele, DQ α1*0501, β1*0201. Tissue transglutaminase action in vitro selectively deamidates Q65. Elicited peripheral blood IFNg responses to synthetic A-gliadin peptides with the substitution Q→E65 is equivalent to tTG-treated Q65 A-gliadin peptides; both stimulate up to 10-fold more T cells in the IFNg ELISPOT than unmodified Q65 A-gliadin peptides.

We have deliberately defined this Coeliac disease-specific T cell epitope using in vivo antigen challenge and short-term ex vivo immune assays to avoid the possibility of methodological artifacts that may occur with the use of T cell clones in epitope mapping. Our findings indicate that peripheral blood T cell responses to ingestion of gluten are rapid but short-lived and can be utilized for epitope mapping. In vivo antigen challenge has also shown there is a temporal hierarchy of immune responses to A-gliadin peptides; A-gliadin 57-73 modified by tTG not only elicits the strongest IFNg response in PBMC but it is also the first IFNg response to appear.

Because we have assessed only peptides spanning A-gliadin, there may be other epitopes in other gliadins of equal or greater importance in the pathogenesis of Coeliac disease. Indeed, the peptide sequence at the core of the epitope in A-gliadin that we have identified PQPQLPY (SEQ ID NO:4) is shared by several other gliadins (SwissProt and Trembl accession numbers: P02863, Q41528, Q41531, Q41533, Q9ZP09, P04722, P04724, P18573). However, A-gliadin peptides that have previously been shown to possess bioactivity in biopsy challenge and in vivo studies (for example: 31-43, 44-55, and 206-217)[4,5] did not elicit IFNg responses in PBMC following three day bread challenge in Coeliac disease subjects. These peptides may be "secondary" T cell epitopes that arise with spreading of the immune response.

Example 2

The effect on T cell recognition of substitutions in the immunodominant epitope

The effect of substituting the glutamate at position 65 in the 57-73 A-gliadin epitope was determined by measuring peripheral blood responses against the substituted epitopes in an IFNγ ELISPOT assay using synthetic peptides (at 50 μg/ml). The responses were measured in 3 Coeliac disease subjects 6 days after commencing gluten challenge (4 slices bread daily for 3 days). Results are shown in table 3 and Figure 8. As can be seen substitution of the glutamate to histidine,

43

tyrosine, tryptophan, lysine, proline or arginine stimulated a response whose magnitude was less than 10% of the magnitude of the response to the immunodominant epitope. Thus mutation of A-gliadin at this position could be used to produce a mutant gliadin with reduce or absent immunoreactivity.

5

Example 3
Testing the immunoreactivity of equivalent peptides from other naturally occurring gliadins

The immunoreactivity of equivalent peptides form other naturally occurring
10   wheat gliadins was assessed using synthetic peptides corresponding to the naturally occurring sequences which were then treated with transglutaminase. These peptides were tested in an ELISPOT in the same manner and with PBMCs from the same subjects as described in Example 2. At least five of the peptides show immunoreactivity comparable to the A-gliadin 57-73 E65 peptide (after
15   transglutaminase treatment) indicating that other gliadin proteins in wheat are also likely to induce this Coeliac disease-specific immune response (Table 4 and Figure 9).

Methods
20   *Subjects:* Patients used in the study attended a Coeliac Clinic in Oxford, United Kingdom. Coeliac disease was diagnosed on the basis of typical small intestinal histology, and normalization of symptoms and small intestinal histology with gluten free diet.

25   *Tissue typing:* Tissue typing was performed using DNA extracted from EDTA-anticoagulated peripheral blood. HLA-DQA and DQB genotyping was performed by PCR using sequence-specific primer mixes[6-8].

Anti-endomysial antibody assay: EMA were detected by indirect
30   immunofluorescence using patient serum diluted 1:5 with monkey oesophagus, followed by FITC-conjugated goat anti-human IgA. IgA was quantitated prior to EMA, none of the subjects were IgA deficient.

44

Antigen Challenge: Coeliac disease subjects following a gluten free diet, consumed 4 slices of gluten-containing bread (50g/slice, Sainsbury's "standard white sandwich bread") daily for 3 or 10 days. EMA was assessed the week before and up to two months after commencing the bread challenge. Healthy subjects who had followed a gluten free diet for four weeks, consumed their usual diet including four slices of gluten-containing bread for three days, then returned to gluten free diet for a further six days.

IFNγ and IL-10 ELISPOT: PBMC were prepared from 50-100 ml of venous blood by Ficoll-Hypaque density centrifugation. After three washes, PBMC were resuspended in complete RPMI containing 10% heat inactivated human AB serum. ELISPOT assays for single cell secretion of IFNγ and IL-10 were performed using commercial kits (Mabtech; Stockholm, Sweden) with 96-well plates (MAIP-S-45; Millipore, Bedford, MA) according to the manufacturers instructions (as described elsewhere[9]) with $2-5 \times 10^5$ (IFNγ) or $0.4-1 \times 10^5$ (IL-10) PBMC in each well. Peptides were assessed in duplicate wells, and Mycobacterium tuberculosis purified protein derivative (PPD RT49) (Serum Institute; Copenhagen, Denmark) (20 μg/ml) was included as a positive control in all assays.

Peptides: Synthetic peptides were purchased from Research Genetics (Huntsville, Alabama) Mass-spectroscopy and HPLC verified peptides' authenticity and >70% purity. Digestion of gliadin (Sigma; G-3375) (100 mg/ml) with α-chymotrypsin (Sigma; C-3142) 200:1 (w/w) was performed at room temperature in 0.1 M NH_4HCO_3 with 2M urea and was halted after 24 h by heating to 98°C for 10 minutes. After centrifugation (13,000g, 10 minutes), the gliadin digest supernatant was filter-sterilized (0.2 mm). Digestion of gliadin was verified by SDS-PAGE and protein concentration assessed. α-Chymotrypsin-digested gliadin (640 μg/ml) and synthetic gliadin peptides (15-mers: 160 μg/ml, other peptides: 0.1 mM) were individually treated with tTG (Sigma; T-5398) (50 μg/ml) in PBS + $CaCl_2$ 1 mM for 2 h at 37°C. Peptides and peptide pools were aliquotted into sterile 96-well plates and stored frozen at -20°C until use.

Amino acid sequencing of peptides: Reverse phase HPLC was used to purify the peptide resulting from tTG treatment of A-gliadin 56-75. A single product was identified and subjected to amino acid sequencing (automated sequencer Model

5   494A, Applied Biosystems, Foster City, California). The sequence of unmodified G56-75 was confirmed as: LQLQPFPQPQLPYPQPQSFP (SEQ ID NO:5), and tTG treated G56-75 was identified as: LQLQPFPQPELPYPQPQSFP (SEQ ID NO:11). Deamidation of glutamyl residues was defined as the amount (pmol) of glutamate recovered expressed as a percent of the combined amount of glutamine and

10   glutamate recovered in cycles 2, 4, 8, 10, 15 and 17 of the amino acid sequencing. Deamidation attributable to tTG was defined as (% deamidation of glutamine in the tTG treated peptide - % deamidation in the untreated peptide) / (100 - % deamidation in the untreated peptide).

CD4/CD8 and HLA Class II Restriction: Anti-CD4 or anti-CD8 coated magnetic

15   beads (Dynal, Oslo, Norway) were washed four times with RPMI then incubated with PBMC in complete RPMI containing 10% heat inactivated human AB serum (5×10^6 cells/ml) for 30 minutes on ice. Beads were removed using a magnet and cells remaining counted. In vivo HLA-class II restriction of the immune response to tTG-treated A-gliadin 56-75 was established by incubating PBMC (5×10^6 cells/ml)

20   with anti-HLA-DR (L243), -DQ (L2), and -DP (B7.21) monoclonal antibodies (10 µg/ml) at room temperature for one hour prior to the addition of peptide.

Example 4

Mucosal integrin expression by gliadin -specific peripheral blood lymphocytes

25   Interaction between endothelial and lymphocyte adressins facilitates homing of organ-specific lymphocytes. Many adressins are known. The heterodimer $\alpha_4\beta_7$ is specific for lamina propria gut and other mucosal lymphocytes, and $\alpha^E\beta_7$ is specific and intra-epithelial lymphocytes in the gut and skin. Approximately 30% of peripheral blood CD4 T cells express $\alpha_4\beta_7$ and are presumed to be in transit to a

30   mucosal site, while 5% of peripheral blood T cells express $\alpha^E\beta_7$. Immunomagnetic beads coated with antibody specific for α^E or β_7 deplete PBMC of cells expressing $\alpha^E\beta_7$ or $\alpha^E\beta_7$ and $\alpha_4\beta_7$, respectively. In combination with ELISpot assay,

46

immunomagnetic bead depletion allows determination of gliadin-specific T cell
addressin expression that may identify these cells as homing to a mucosal surface.
Interestingly, gluten challenge in vivo is associated with rapid influx of CD4 T cells
to the small intestinal lamina propria (not intra-epithelial sites), where over 90%
lymphocytes express $\alpha_4\beta_7$.

Immunomagnetic beads were prepared and used to deplete PBMC from
coeliac subjects on day 6 or 7 after commencing 3 day gluten challenge. FACS
analysis demonstrated α^E beads depleted approximately 50% of positive CD4 T
cells, while β_7 beads depleted all β_7 positive CD4 T cells. Depletion of PBMC using
CD4- or β_7-beads, but not CD8- or α^E-beads, abolished responses in the interferon
gamma ELISpot. tTG gliadin and PPD responses were abolished by CD4 depletion,
but consistently affected by integrin-specific bead depletion.

Thus A-gliadin 57-73 QE65-specific T cells induced after gluten challenge in
coeliac disease express the integrin, $\alpha_4\beta_7$, present on lamina propria CD4 T cells in
the small intestine.

Example 5

Optimal T cell Epitope Length

Previous data testing peptides from 7 to 17 amino acids in length spanning
the
core of the dominant T cell epitope in A-gliadin indicated that the 17mer, A-gliadin
57-73 QE65 (SEQ ID NO:2) induced maximal responses in the interferon gamma
Elispot using peripheral blood mononuclear cells (PBMC) from coeliac volunteers 6
days after commencing a 3-day gluten challenge.

Peptides representing expansions form the core sequence of the dominant T
cell epitope in A-gliadin were assessed in the IFN gamma ELISPOT using peripheral
blood mononuclear cells (PBMC) from coeliac volunteers in 6 days after
commencing a 3-day gluten challenge (n=4). Peptide 13: A-gliadin 59-71 QE65
(13mer), peptide 15: 58-72 QE65 (15mer), ..., peptide 27: 52-78 SE65 (27mer).

As shown in Figure 11 expansion of the A-gliadin 57-73 QE65 sequence does
not substantially enhance response in the IFNgamma Elispot. Subsequent Examples

47

characterise the agonist and antagonist activity of A-gliadin 57-73 QE65 using 17mer
peptides.

Example 6

5   *Comparison of A-gliadin 57-73 QE65 with other DQ2-restricted T cell epitopes in*
    coeliac disease

      Dose response studies were performed using peptides corresponding to
unmodified and transglutaminase-treated peptides corresponding to T cell epitopes of
gluten-specific T cell clones and lines from intestinal biopsies of coeliac subjects.

10 Responses to peptides were expressed as percent of response to A-gliadin 57-73
QE65. All subjects were HLA-DQ2+ (none were DQ8+).

      The studies indicate that A-gliadin 57-73 QE65 is the most potent gliadin
peptide for induction of interferon gamma in the ELISpot assay using coeliac PBMC
after gluten challenge (see Figure 12a-h, and Tables 5 and 6). The second and third

15 epitopes are suboptimal fragments of larger peptides i.e. A-gliadin 57-73 QE65 and
GDA4_WHEAT P04724-84-100 QE92. The epitope is only modestly bioactive
(approximately 1/20th as active as A-gliadin 57-73 QE65 after blank is subtracted).

      A-gliadin 57-73 QE65 is more potent than other known T cell epitopes in
coeliac disease. There are 16 polymorphisms of A-gliadin 57-73 (including the

20 sequence PQLPY (SEQ ID NO:12)) amongst sequenced gliadin genes, their
bioactivity is assessed next.

Example 7

Comparison of gliadin- and A-gliadin 57-73 QE65-specific responses in peripheral

25 *blood*

      The relative contribution of the dominant epitope, A-gliadin 57-73 QE65, to
the total T cell response to gliadin in coeliac disease is a critical issue. Pepsin-
trypsin and chymotrypsin-digested gliadin have been traditionally used as antigen for
development of T cell lines and clones in coeliac disease. However, it is possible

30 that these proteases may cleave through certain peptide epitopes. Indeed,
chymotrypsin digestion of recombinant α9-gliadin generates the peptide
QLQPFPQPELPY (SEQ ID NO:13), that is a truncation of the optimal epitope

48

sequence QLQPFPQPELPYPQPQS (SEQ ID NO:2) (see above).
Transglutaminase-treatment substantially increases the potency of chymotrypsin-
digested gliadin in proliferation assays of gliadin-specific T cell clones and lines.
Hence, transglutaminase-treated chymotrypsin-digested gliadin (tTG gliadin) may

5   not be an ideal antigen, but responses against this mixture may approximate the
"total" number of peripheral blood lymphocyte specific for gliadin. Comparison of
responses against A-gliadin 57-73 QE65 and tTG gliadin in the ELISpot assay gives
an indication of the contribution of this dominant epitope to the overall immune
response to gliadin in coeliac disease, and also be a measure of epitope spreading.

10 PBMC collected on day 6 or 7 after commencing gluten challenge in 4
coeliac subjects were assessed in dose response studies using chymotrypsin-digested
gliadin +/- tTG treatment and compared with ELISpot responses to an optimal
concentration of A-gliadin 57-73 QE65 (25mcg/ml). TTG treatment of gliadin
enhanced PBMC responses in the ELISpot approximately 10-fold (tTG was

15 comparable to blank when assessed alone) (see Figure 13a-c). In the four coeliac
subjects studied, A-gliadin 57-73 QE65 (25 mcg/ml) elicited responses between 14
and 115% those of tTG gliadin (500 mcg/ml), and the greater the response to A-
gliadin 57-73 QE65 the greater proportion it represented of the tTG gliadin response.

Relatively limited data suggest that A-gliadin 57-73 QE65 responses are

20 comparable to tTG gliadin in some subjects. Epitope spreading associated with more
evolved anti-gliadin T cell responses may account for the smaller contribution of A-
gliadin 57-73 QE65 to "total" gliadin responses in peripheral blood in some
individuals. Epitope spreading may be maintained in individuals with less strictly
gluten free diets.

25

Example 8
*Definition of gliadin peptides bioactive in coeliac disease: polymorphisms of A-
gliadin 57-73*

Overlapping 15mer peptides spanning the complete sequence of A-gliadin

30 were assessed in order to identify the immunodominant sequence in coeliac disease.
A-gliadin was the first fully sequenced alpha gliadin protein and gene, but is one of
approximately 30-50 related alpha gliadin proteins in wheat. Twenty five distinct

49

alpha-gliadin genes have been identified by searching protein data bases, Swiss-Prot

and TREMBL describing a further 8 alpha-gliadins. Contained within these 25

alpha-gliadins, there are 16 distinct polymorphisms of the sequence corresponding to

A-gliadin 57-73 (see Table 7).

5   Synthetic peptides corresponding to these 16 polymorphisms, in an

unmodified form, after treatment with transglutaminase in vitro, as well as with

glutamate substituted at position 10 (equivalent to QE65 in A-gliadin 57-73) were

assessed using PBMC from coeliac subjects, normally following a gluten free diet,

day 6 or 7 after gluten challenge in interferon gamma ELISpot assays. Glutamate-

10   substituted peptides were compared at three concentrations (2.5, 25 and 250

mcg/ml), unmodified peptide and transglutaminase-treated peptides were assessed at

25 mcg/ml only. Bioactivity was expressed as % of response associated with A-

gliadin 57-73 QE65 25 mcg/ml in individual subjects (n=4). (See Fig 14).

          Bioactivity of "wild-type" peptides was substantially increased (>5-fold) by

15   treatment with transglutaminase. Transglutaminase treatment of wild-type peptides

resulted in bioactivity similar to that of the same peptides substituted with glutamate

at position 10. Bioactivities of five glutamate-substituted peptides (B, C, K, L, M),

were >70% that of A-gliadin 57-73 QE65 (A), but none was significantly more

bioactive than A-gliadin 57-73 QE65. PBMC responses to glutamate-substituted

20   peptides at concentrations of 2.5 and 250 mcg/ml were comparable to those at 25

mcg/ml. Six glutamate-substituted gliadin peptides (H, I, J, N, O, P) were <15% as

bioactive as A-gliadin 57-73 QE65. Other peptides were intermediate in bioactivity.

          At least six gliadin-derived peptides are equivalent in potency to A-gliadin

57-73 QE65 after modification by transglutaminase. Relatively non-bioactive

25   polymorphisms of A-gliadin 57-73 also exist. These data indicate that

transglutaminase modification of peptides from several gliadins of *Triticum*

aestivum, T. uartu and *T. spelta* may be capable of generating the immunodominant

T cell epitope in coeliac disease.

          Genetic modification of wheat to generate non-coeliac-toxic wheat may likely

30   require removal or modification of multiple gliadin genes. Generation of wheat

containing gliadins or other proteins or peptides incorporating sequences defining

altered peptide ligand antagonists of A-gliadin 57-73 is an alternative strategy to

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generate genetically modified wheat that is therapeutic rather than "non-toxic" in coeliac disease.

Example 9

Definition of Core Epitope Sequence:

Comparison of peptides corresponding to truncations of A-gliadin 56-75 from the N- and C-terminal indicated that the core sequence of the T cell epitope is PELPY (A-gliadin 64-68). Attempts to define non-agonists and antagonists will focus on variants of A-gliadin that are substituted at residues that substantially contribute to its bioactivity.

Peptides corresponding to A-gliadin 57-73 QE65 with alanine (Figure 15) or lysine (Figure 16) substituted for residues 57 to 73 were compared in the IFN gamma ELISPOT using peripheral blood mononuclear cells (PBMC) from coeliac volunteers 6 days after commencing a 3-day gluten challenge (n=8). (BL is blank, E is A-gliadin 57-73 QE65: QLQPFPQPELPYPQPQS (SEQ ID NO:2)).

It was found that residues corresponding to A-gliadin 60-70 QE65 (PFPQPELPYPQ (SEQ ID NO:14)) contribute substantially to the bioactivity in A-gliadin 57-73 QE65. Variants of A-gliadin 57-73 QE65 substituted at positions 60-70 are assessed in a 2-step procedure. Initially, A-gliadin 57-73 QE65 substituted at positions 60-70 using 10 different amino acids with contrasting properties are assessed. A second group of A-gliadin 57-73 QE65 variants (substituted with all other naturally occurring amino acids except cysteine at positions that prove are sensitive to modification) are assessed in a second round.

Example 10

Agonist activity of substituted variants of A-gliadin 57-73 QE65

A-gliadin 60-70 QE65 is the core sequence of the dominant T cell epitope in A-gliadin. Antagonist and non-agonist peptide variants of this epitope are most likely generated by modification of this core sequence. Initially, A-gliadin 57-73 QE65 substituted at positions 60-70 using 10 different amino acids with contrasting properties will be assessed in the IFNgamma ELISPOT using PBMC from coeliac subjects 6 days after starting 3 day gluten challenge. A second group of A-gliadin

57-73 QE65 variants (substituted with all other naturally occurring amino acids except cysteine) at positions 61-70 were also assessed. Both groups of peptides (all at 50 mcg/ml, in duplicate) were assessed using PBMC from 8 subjects and compared to the unmodified peptide (20 replicates per assay). Previous studies

5   indicate that the optimal concentration for A-gliadin 57-73 QE65 in this assay is between 10 and 100 mcg/ml.

Results are expressed as mean response in spot forming cells (95% confidence interval) as % A-G 57-73 QE65 mean response in each individual. Unpaired t-tests will be used to compare ELISPOT responses of modified peptides

10   with A-G 57-73 QE65. Super-agonists were defined as having a greater response than A-G 57-73 QE65 at a level of significance of $p<0.01$; partial agonists as having a response less than A-G 57-73 QE65 at a level of significance of $p<0.01$, and non-agonists as being not significantly different ($p>0.01$) from blank (buffer without peptide). Peptides with agonist activity 30% or less that of A-gliadin 57-73 QE65

15   were considered "suitable" partial or non-agonists to assess for antagonistic activity (see Table 8 and Figures 17-27).

The IFNgamma ELISPOT response of PBMC to A-gliadin 57-73 QE65 is highly specific at a molecular level. Proline at position 64 (P64), glutamate at 65 (E65) and leucine at position 66 (L66), and to a lesser extent Q63, P67, Y68 and P69

20   are particularly sensitive to modification. The substitutions Y61 and Y70 both generate super-agonists with 30% greater bioactivity than the parent peptide, probably by enhancing binding to HLA-DQ2 since the motif for this HLA molecule indicates a preference for bulky hydrophobic resides at positions 1 and 9. Eighteen non-agonist peptides were identified. Bioactivities of the variants (50 mcg/ml): P65,

25   K64, K65 and Y65 (bioactivity 7-8%) were comparable to blank (7%). In total, 57 mutated variants of A-gliadin 57-73 QE65 were 30% or less bioactive than A-gliadin 57-73 QE65.

The molecular specificity of the peripheral blood lymphocyte (PBL) T cell response to the dominant epitope, A-gliadin 57-73 QE65, is consistently reproducible

30   amongst HLA-DQ2+ coeliac subjects, and is highly specific to a restricted number of amino acids in the core 7 amino acids. Certain single-amino acid variants of A-gliadin 57-73 QE65 are consistently non-agonists in all HLA-DQ2+ coeliac subjects.

Example 11

Antagonist activity of substituted variants

The homogeneity of the PBL T cell response to A-gliadin 57-73 QE65 in
HLA-DQ2+ coeliac disease suggests that altered peptide ligands (APL) capable of
antagonism in PBMC ex vivo may exist, even though the PBL T cell response is
likely to be poly- or oligo-clonal. APL antagonists are generally weak agonists.
Fifty-seven single amino acid-substituted variants of A-gliadin 57-73 QE65 with
agonist activity 30% or less have been identified and are suitable candidates as APL
antagonists. In addition, certain weakly bioactive naturally occurring polymorphisms
of A-gliadin 57-73 QE65 have also been identified (see below) and may be
"naturally occurring" APL antagonists. It has also been suggested that competition
for binding MHC may also antagonise antigen-specific T cell immune. Hence, non-
gliadin peptides that do not induce IFNgamma responses in coeliac PBMC after
gluten challenge but are known to bind to HLA-DQ2 may be capable of reducing T
cell responses elicited by A-gliadin 57-73 QE65. Two peptides that bind avidly to
HLA-DQ2 are HLA class 1 α 46-60 (HLA 1a) (PRAPWIEQEGPEYW (SEQ ID
NO:15)) and thyroid peroxidase (tp) 632-645Y (IDVWLGGLLAENFLPY (SEQ ID
NO:16)).

Simultaneous addition of peptide (50µg/ml) or buffer and A-gliadin 57-73
QE65 (10µg/ml) in IFNgamma ELISPOT using PBMC from coeliac volunteers 6
days after commencing 3 day gluten challenge (n=5). Results were expressed as
response with peptide plus A-G 57-73 QE65 (mean of duplicates) as % response with
buffer plus A-G 57-73 QE65 (mean of 20 replicates). (See Table 9).

Four single amino acid-substituted variants of A-gliadin 57-73 QE65 reduce
the interferon gamma PBMC ELISPOT response to A-gliadin 57-73 QE65 (p<0.01)
by between 25% and 28%, 13 other peptide variants reduce the ELISPOT response
by between 18% and 24% (p<0.06). The HLA-DQ2 binder, thyroid peroxidase (tp)
632-645Y reduces PBMC interferon gamma responses to A-gliadin 57-73 QE65 by
31% (p<0.0001) but the other HLA-DQ2 binder, HLA class 1 α 46-60, does not alter
responses (see Tables 9 and 10). The peptide corresponding to a transglutaminase-
modified polymorphism of A-gliadin 57-73, SwissProt accession no.: P04725 82-98

QE90 (PQPQPFPPELPYPQPQS (SEQ ID NO:17)) reduces responses to A-gliadin
57-73 QE65 by 19% (p<0.009) (see Table 11).

Interferon gamma responses of PBMC to A-gliadin 57-73 QE65 in ELISPOT
assays are reduced by co-administration of certain single-amino acid A-gliadin 57-73
QE65 variants, a polymorphism of A-gliadin 57-73 QE65, and an unrelated peptide
known to bind HLA-DQ2 in five-fold excess. These finding suggest that altered
peptide ligand antagonists of A-gliadin 57-73 QE65 exist. Not only putative APL
antagonists but also certain peptides that bind HLA-DQ2 effectively reduce PBL T
cell responses to A-gliadin 57-73 QE65.

These findings support two strategies to interrupt the T cell response to the
dominant A-gliadin epitope in HLA-DQ2+ coeliac disease.

1. Optimisation of APL antagonists by substituting amino acids at more than
   one position (64-67) for use as "traditional" peptide pharmaceuticals or for
   specific genetic modification of gliadin genes in wheat.

2. Use of high affinity HLA-DQ2 binding peptides to competitively inhibit
   presentation of A-gliadin 57-73 QE65 in association with HLA-DQ2.

These two approaches may be mutually compatible. Super-agonists were
generated by replacing F61 and Q70 with tyrosine residues. It is likely these super-
agonists resulted from improved binding to HLA-DQ2 rather than enhanced contact
with the T cell receptor. By combining these modifications with other substitutions
that generate modestly effective APL antagonists might substantially enhance the
inhibitory effect of substituted A-gliadin 57-73 QE65 variants.

Example 12

*Development of interferon gamma ELISpot using PBMC and A-gliadin 57-73 QE65
and P04724 84-100 QE92 as a diagnostic for coeliac disease: Definition of immune-
responsiveness in newly diagnosed coeliac disease*

Induction of responsiveness to the dominant A-gliadin T cell epitope in
PBMC measured in the interferon gamma ELISpot follows gluten challenge in
almost all DQ2+ coeliac subjects following a long term strict gluten free diet (GFD)
but not in healthy DQ2+ subjects after 4 weeks following a strict GFD. A-gliadin

54

57-73 QE65 responses are not measurable in PBMC of coeliac subjects before gluten challenge and pilot data have suggested these responses could not be measured in PBMC of untreated coeliacs. These data suggest that in coeliac disease immune-responsiveness to A-gliadin 57-73 QE65 is restored following antigen exclusion (GFD). If a diagnostic test is to be developed using the ELISpot assay and PBMC, it is desirable to define the duration of GFD required before gluten challenge is capable of inducing responses to A-gliadin 57-73 QE65 and other immunoreactive gliadin peptides in blood.

Newly diagnosed DQ2+ coeliac subjects were recruited from the gastroenterology outpatient service. PBMC were prepared and tested in interferon gamma ELISpot assays before subjects commenced GFD, and at one or two weeks after commencing GFD. In addition, gluten challenge (3 days consuming 4 slices standard white bread, 200g/day) was performed at one or two weeks after starting GFD. PBMC were prepared and assayed on day six are after commencing gluten challenge. A-gliadin 57-73 QE65 (A), P04724 84-100 QE92 (B) (alone and combined) and A-gliadin 57-73 QP65 (P65) (non-bioactive variant, see above) (all 25 mcg/ml) were assessed.

All but one newly diagnosed coeliac patient was DQ2+ (one was DQ8+) (n=11). PBMC from newly diagnosed coeliacs that were untreated, or after 1 or 2 weeks following GFD did not show responses to A-gliadin 57-73 QE65 and P04724 84-100 QE92 (alone or combined) that were not significantly different from blank or A-gliadin 57-73 QP65 (n=9) (see Figure 28). Gluten challenge in coeliacs who had followed GFD for only one week did not substantially enhance responses to A-gliadin 57-73 QE65 or P04724 84-100 QE92 (alone or combined). But gluten challenge 2 weeks after commencing GFD did induce responses to A-gliadin 57-73 QE65 and P04724 84-100 QE92 (alone or combined) that were significantly greater than the non-bioactive variant A-gliadin 57-73 QP65 and blank. Although these responses after gluten challenge at 2 weeks were substantial they appear to be less than in subjects >2 months after commencing GFD. Responses to A-gliadin 57-73 QE65 alone were equivalent or greater than responses to P04724 84-100 QE92 alone or when mixed with A-gliadin 57-73 QE65. None of the subjects experienced troubling symptoms with gluten challenge.

Immune responsiveness (as measured in PBMC after gluten challenge) to A-gliadin is partially restored 2 weeks after commencing GFD, implying that "immune unresponsiveness" to this dominant T cell epitope prevails in untreated coeliac disease and for at least one week after starting GFD. The optimal timing of a

5   diagnostic test for coeliac disease using gluten challenge and measurement of responses to A-gliadin 57-73 QE65 in the ELISpot assay is at least 2 weeks after commencing a GFD.

Interferon gamma-secreting T cells specific to A-gliadin 57-73 QE65 cannot be measured in the peripheral blood in untreated coeliacs, and can only be induced

10 by gluten challenge after at least 2 weeks GFD (antigen exclusion). Therefore, timing of a diagnostic test using this methodology is crucial and further studies are needed for its optimization. These finding are consistent with functional anergy of T cells specific for the dominant epitope, A-gliadin 57-73 QE65, reversed by antigen exclusion (GFD). This phenomenon has not been previously demonstrated in a

15 human disease, and supports the possibility that T cell anergy may be inducible with peptide therapy in coeliac disease.

Example 13

Comprehensive Mapping of Wheat Gliadin T Cell Epitopes

20 Antigen challenge induces antigen-specific T cells in peripheral blood. In coeliac disease, gluten is the antigen that maintains this immune-mediated disease. Gluten challenge in coeliac disease being treated with a gluten free diet leads to the appearance of gluten-specific T cells in peripheral blood, so enabling determination of the molecular specificity of gluten T cell epitopes. As described above, we have

25 identified a single dominant T cell epitope in a model gluten protein, A-gliadin (57-73 deamidated at Q65). In this Example, gluten challenge in coeliac patients was used to test all potential 12 amino acid sequences in every known wheat gliadin protein derived from 111 entries in Genbank. In total, 652 20mer peptides were tested in HLA-DQ2 and HLA-DQ8 associated coeliac disease. Seven of the 9

30 coeliac subjects with the classical HLA-DQ2 complex (HLA-DQA1*05, HLA-DQB1*02) present in over 90% of coeliacs had an inducible A-gliadin 57-73 QE65- and gliadin-specific T cell response in peripheral blood. A-gliadin 57-73 was the

56

only significant α-gliadin T cell epitope, as well as the most potent gliadin T cell epitope, in HLA-DQ2-associated coeliac disease. In addition, there were as many as 5 families of structurally related peptides that were between 10 and 70% as potent as A-gliadin 57-73 in the interferon-γ ELISpot assay. These new T cell epitopes were

5   derived from γ- and ω-gliadins and included common sequences that were structurally very similar, but not identical to the core sequence of A-gliadin 57-73 (core sequence: FPQPQLPYP (SEQ ID NO:18)), for example: FPQPQQPFP (SEQ ID NO:19) and PQQPQQPFP (SEQ ID NO:20). Although no homologues of A-gliadin 57-73 have been found in rye or barley, the other two cereals toxic in coeliac

10   disease, the newly defined T cell epitopes in γ- and ω-gliadins have exact matches in rye and barley storage proteins (secalins and hordeins, respectively).

Coeliac disease not associated with HLA-DQ2 is almost always associated with HLA-DQ8. None of the seven HLA-DQ8+ coeliac subjects had inducible A-gliadin 57-73-specific T cell responses following gluten challenge, unless they also

15   possessed the complete HLA-DQ2 complex. Two of 4 HLA-DQ8+ coeliac subjects who did not possess the complete HLA-DQ2 complex, had inducible gliadin peptide-specific T cell responses following gluten challenge. In one HLA-DQ8 subject, a novel dominant T cell epitope was identified with the core sequence LQPQNPSQQQPQ (SEQ ID NO:21). The transglutaminase-deamidated version of

20   this peptide was more potent than the non-deamidated peptide. Previous studies suggest that the transglutaminase-deamidated peptide would have the sequence LQPENPSQEQPE (SEQ ID NO:22); but further studies are required to confirm this sequence. Amongst the healthy HLA-DQ2 (10) and HLA-DQ8 (1) subjects who followed a gluten free diet for a month, gliadin peptide-specific T cell responses

25   were uncommon, seldom changed with gluten challenge, and were never potent T cell epitopes revealed with gluten challenge in coeliac subjects. In conclusion, there are unlikely to be more than six important T cell epitopes in HLA-DQ2-associated coeliac disease, of which A-gliadin 57-73 is the most potent. HLA-DQ2- and HLA-DQ8-associated coeliac disease do not share the same T cell specificity.

30   We have shown that short-term gluten challenge of individuals with coeliac disease following a gluten free diet induces gliadin-specific T cells in peripheral blood. The frequency of these T cells is maximal in peripheral blood on day 6 and

57

then rapidly wanes over the following week. Peripheral blood gliadin-specific T cells express the integrin α4β7 that is associated with homing to the gut lamina propria. We exploited this human antigen-challenge design to map T cell epitopes relevant to coeliac disease in the archetypal gluten α-gliadin protein, A-gliadin.

5   Using 15mer peptides overlapping by 10 amino acids with and without deamidation by transglutaminase (tTG), we demonstrated that T cells induced in peripheral blood initially target only one A-gliadin peptide, residues 57-73 in which glutamine at position 65 is deamidated. The epitope is HLA-DQ2-restricted, consistent with the intimate association of coeliac disease with HLA-DQ2.

10   Coeliac disease is reactivated by wheat, rye and barley exposure. The α/β-gliadin fraction of wheat gluten is consistently toxic in coeliac disease, and most studies have focused on these proteins. The gene cluster coding for α/β-gliadins is located on wheat chromosome 6C. There are no homologues of α/β-gliadins in rye or barley. However, all three of the wheat gliadin subtypes (α/β, γ, and ω) are toxic

15   in coeliac disease. The γ- and ω-gliadin genes are located on chromosome 1A in wheat, and are homologous to the secalins and hordeins in rye and barley.

There are now genes identified for 61 α-gliadins in wheat (Triticum aestivum). The α-gliadin sequences are closely homologous, but the dominant epitope in A-gliadin derives from the most polymorphic region in the α-gliadin

20   sequence. Anderson et al (1997) have estimated that there are a total of about 150 distinct α-gliadin genes in T. aestivum, but many are psuedogenes. Hence, it is unlikely that T-cell epitopes relevant to coeliac disease are not included within known α-gliadin sequences.

Our work has identified a group of deamidated α-gliadin peptides almost

25   identical to A-gliadin 57-73 as potent T cell epitopes specific to coeliac disease. Over 90% of coeliac patients are HLA-DQ2+, and so far, we have only assessed HLA-DQ2+ coeliac subjects after gluten challenge. However, coeliac patients who do not express HLA-DQ2 nearly all carry HLA-DQ8. Hence, it is critical to know whether A-gliadin 57-73 and its homologues in other wheat, rye and barley gluten

30   proteins are the only T-cell epitopes recognized by T cells induced by gluten challenge in both HLA-DQ2+ and HLA-DQ8+ coeliac disease. If this were the case, design of peptide therapeutics for coeliac disease might only require one peptide.

58

Homologues of A-gliadin 57-73 as T-cell epitopes

Initial searches of SwissProt and Trembl gene databases for cereal genes coding for the core sequence of A-gliadin 57-73 (PQLPY <SEQ ID NO:12>) only revealed α/β-gliadins. However, our fine-mapping studies of the A-gliadin 57-73 QE65 epitope revealed a limited number of permissive point substitutions in the core region (PQLP) (note Q65 is actually deamidated in the epitope). Hence, we extended our search to genes in SwissProt or Trembl databases encoding for peptides with the sequence XXXXXXXPQ[ILMP][PST]XXXXXX (SEQ ID NO:23). Homologues were identified amongst γ-gliadins, glutenins, hordeins and secalins (see Table 12). A further homologue was identified in ω-gliadin by visual search of the three ω-gliadin entries in Genbank.

These homologues of A-gliadin 57-73 were assessed after deamidation by tTG (or synthesis of the glutamate(QE)-substituted variant in four close homologues) using the IFNγ ELISpot assay with peripheral blood mononuclear cells after gluten challenge in coeliac subjects. The ω-gliadin sequence (AAG17702 141-157) was the only bioactive peptide, approximately half as potent as A-gliadin 57-73 (see Table 12, and Figure 29). Hence, searches for homologues of the dominant A-gliadin epitope failed to account for the toxicity of γ-gliadin, secalins, and hordeins.

Methods

Design of a set of peptides spanning all possible wheat gliadin T-cell epitopes

In order to identify all possible T cell epitopes coded by the known wheat (Triticum aestivum) gliadin genes or gene fragments (61 α/β-, 47 γ-, and 3 ω-gliadin entries in Genbank), gene-derived protein sequences were aligned using the CustalW software (MegAlign) and arranged into phylogenetic groupings (see Table 22). Many entries represented truncations of longer sequences, and many gene segments were identical except for the length of polyglutamine repeats or rare substitutions. Hence, it was possible to rationalize all potential unique 12 amino acid sequences encoded by known wheat genes to be included in a set of 652 20mer peptides. (Signal peptide sequences were not included). Peptide sequences are listed in Table 23.

Comprehensive epitope mapping

59

Healthy controls (HLA-DQ2+ n=10, and HLA-DQ8+ n=1) who had followed a gluten free diet for 4 weeks, and coeliac subjects (six HLA-DQ2, four complex heterozygotes HLA-DQ2/8, and three HLA-DQ8/X) (see Table 13) following long-term gluten free diet were studied before and on day 6 and 7 after 3-day gluten

5   challenge (four 50g slices of standard white bread – Sainsbury's sandwich bread, each day). Peripheral blood (a total of 300ml over seven days) was collected and peripheral blood mononuclear cells (PBMC) were separated by Lymphoprep density gradient. PBMC were incubated with pools of 6 or 8 20mer peptides, or single peptides with or without deamidation by tTG in overnight interferon gamma (IFNγ)

10   ELISpot assays.

Peptides were synthesized in batches of 96 as Pepsets (Mimotopes Inc., Melbourne Australia). Approximately 0.6 micromole of each of 652 20mers was provided. Two marker 20mer peptides were included in each set of 96 (VLQQHNIAHGSSQVLQESTY – peptide 161 (SEQ ID NO:24), and

15   IKDFHVYFRESRDALWKGPG (SEQ ID NO:25)) and were characterized by reverse phase-HPLC and amino acid sequence analysis. Average purities of these marker peptides were 50% and 19%, respectively. Peptides were initially dissolved in acetonitrile (10%) and Hepes 100mM to 10mg/ml.

The final concentration of individual peptides in pools (or alone) incubated

20   with PBMC for the IFNγ ELISpot assays was 20 μg/ml. Five-times concentrated solutions of peptides and pools in PBS with calcium chloride 1mM were aliquotted and stored in 96-well plates according to the template later used in ELISpot assays. Deamidated peptides and pools of peptides were prepared by incubation with guinea pig tissue tTG (Sigma T5398) in the ratio 100:32 μg/ml for two hours at 37°C.

25   Peptides solutions were stored at –20°C and freshly thawed prior to use.

Gliadin (Sigma G3375) (100 mg/ml) in endotoxin-free water and 2M urea was boiled for 10 minutes, cooled to room temperature and incubated with filter (0.2 μm)-sterilised pepsin (Sigma P6887) (2 mg/ml) in HCl 0.02M or chymotrypsin (C3142) (4mg/ml) in ammonium bicarbonate (0.2M). After incubation for 4 hours,

30   pepsin-digested gliadin was neutralized with sodium hydroxide, and then both pepsin- and chymotrypsin-digested gliadin were boiled for 15 minutes. Identical incubations with protease in which gliadin was omitted were also performed.

60

Samples were centrifuged at 15 000g, then protein concentrations were estimated in supernatants by the BCA method (Pierce, USA). Before final use in IFNγ ELISpot assays, aliquots of gliadin-protease were incubated with tTG in the ratio 2500:64 μg/ml.

5   IFNγ ELISpot assays (Mabtech, Sweden) were performed in 96-well plates (MAIP S-45, Millipore) in which each well contained 25μl of peptide solution and 100μl of PBMC (2-8x10^5/well) in RPMI containing 10% heat inactivated human AB serum. Deamidated peptide pools were assessed in one 96-well ELISpot plate, and peptides pools without deamidation in a second plate (with an identical layout) on
10   both day 0 and day 6. All wells in the plate containing deamidated peptides included tTG (64 μg/ml). In each ELISpot plate there were 83 wells with peptide pools (one unique pool in each well), and a series of wells for "control" peptides (peptides all >90% purity, characterized by MS and HPLC, Research Genetics): P04722 77-93 (QLQPFPQPQLPYPQPQP (SEQ ID NO:26)), P04722 77-93 QE85 (in duplicate)
15   (QLQPFPQPELPYPQPQP (SEQ ID NO:27)), P02863 77-93 (QLQPFPQPQLPYSQPQP (SEQ ID NO:28)), P02863 77-93 QE85 (QLQPFPQPELPYSQPQP (SEQ ID NO:29)), and chymotrypsin-digested gliadin (500 μg/ml), pepsin-digested gliadin (500 μg/ml), chymotrypsin (20 μg/ml) alone, pepsin (10 μg/ml) alone, and blank (PBS+/-tTG) (in triplicate).
20   After development and drying, IFNγ ELISpot plates were assessed using the MAIP automated ELISpot plate counter. In HLA-DQ2 healthy and coeliac subjects, induction of spot forming cells (sfc) by peptide pools in the IFNγ ELISpot assay was tested using a one-tailed Wilcoxon Matched-Pairs Signed-Ranks test (using SPSS software) applied to spot forming cells (sfc) per million PBMC minus blank on day 6
25   versus day 0 ("net response"). Significant induction of an IFNγ response to peptide pools in PBMC by *in vivo* gluten challenge was defined as a median "net response" of at least 10 sfc/million PBMC and $p < 0.05$ level of significance. Significant response to a particular pool of peptides on day 6 was followed by assessment of individual peptides within each pool using PBMC drawn the same day or on day 7.
30   For IFNγ ELISpot assays of individual peptides, bioactivity was expressed as a percent of response to P04722 77-93 QE85 assessed in the same ELISpot plate. Median response to blank (PBS alone) was 0.2 (range 0-5) sfc per well, and the

61

positive control (P04722 77-93 QE85) 76.5 (range: 25-282) sfc per well using a median of 0.36 million (range: 0.3-0.72) PBMC. Hence, median response to blank expressed as a percentage of P04722 77-93 QE65 was 0.2% (range: 0-6.7). Individual peptides with mean bioactivity greater than10% that of P04722 QE85

5   were analyzed for common structural motifs.

Results

Healthy HLA-DQ2 subjects

None of the healthy HLA-DQ2+ subjects following a gluten free diet for a month had IFNγ ELISpot responses to homologues of A-gliadin 57-73 before or after

10   gluten challenge. However, in 9/10 healthy subjects, gluten challenge was associated with a significant increase in IFNγ responses to both peptic- and chymotryptic-digests of gliadin, from a median of 0-4 sfc/million on day 0 to a median of 16-29 sfc/million (see Table 14). Gliadin responses in healthy subjects were unaffected by deamidation (see Table 15). Amongst healthy subjects, there was no consistent

15   induction of IFNγ responses to specific gliadin peptide pools with gluten challenge (see Figure 30, and Table 16). IFNγ ELISpot responses were occasionally found, but these were weak, and not altered by deamidation. Many of the strongest responses to pools were also present on day 0 (see Table 17, subjects H2, H8 and H9). Four healthy subjects did show definite responses to pool 50,and the two with strongest

20   responses on day 6 also had responses on day 0. In both subjects, the post-challenge responses to pool 50 responses were due to peptide 390 (QQTYPQRPQQPFPQTQQPQQ (SEQ ID NO:30)).

HLA-DQ2 coeliac subjects

Following gluten challenge in HLA-DQ2+ coeliac subjects, median IFNγ

25   ELISpot responses to P04722 77-93 E85 rose from a median of 0 to 133 sfc/million (see Table 4). One of the six coeliac subjects (C06) did not respond to P04722 77-93 QE85 (2 sfc/million) and had only weak responses to gliadin peptide pools (maximum: Pool 50+tTG 27 sfc/million). Consistent with earlier work, bioactivity of wild-type P04722 increased 6.5 times with deamidation by tTG (see Table 15).

30   Interferon-gamma responses to gliadin-digests were present at baseline, but were substantially increased by gluten challenge from a median of 20 up to 92 sfc/million for chymotryptic-gliadin, and from 44 up to 176 sfc/million for peptide-gliadin.

62

Deamidation of gliadin increased bioactivity by a median of 3.2 times for
chymotryptic-gliadin and 1.9 times for peptic-gliadin (see Table 15). (Note that the
acidity required for digestion by pepsin is likely to result in partial deamidation of
gliadin.)

5   In contrast to healthy subjects, gluten challenge induced IFNγ ELISpot
responses to 22 of the 83 tTG-treated pools including peptides from α-, γ- and ω-
gliadins (see Figure 31, and Table 17). Bioactivity of pools was highly consistent
between subjects (see Table 18). IFNγ ELISpot responses elicited by peptide pools
were almost always increased by deamidation (see Table 17). But enhancement of
10   bioactivity of pools by deamidation was not as marked as for P04722 77-73 Q85,
even for pools including homologues of A-gliadin 57-73. This suggests that Pepset
peptides were partially deamidated during synthesis or in preparation, for example
the Pepset peptides are delivered as salts of trifluoracetic acid (TFA) after
lyophilisation from a TFA solution.

15   One hundred and seventy individual tTG-deamidated peptides from 21 of the
most bioactive pools were separately assessed. Seventy-two deamidated peptides
were greater than 10% as bioactive as P04722 77-93 QE85 at an equivalent
concentration (20 μg/ml) (see Table 19). The five most potent peptides (85-94%
bioactivity of P04722 QE85) were previously identified α-gliadin homologues A-
20   gliadin 57-73. Fifty of the bioactive peptides were not homologues of A-gliadin 57-
73, but could be divided into six families of structurally related sequences (see Table
20). The most bioactive sequence of each of the peptide families were:
PQQPQQP<u>QQPFPQPQQPFP</u>W (SEQ ID NO:31) (peptide 626, median 72%
bioactivity of P04722 QE85), QQP<u>QQPFPQPQQPQLPFP</u>QQ (SEQ ID NO:32)
25   (343, 34%), QA<u>FPQPQQTFPHQPQQQ</u>FPQ (SEQ ID NO:33) (355, 27%),
TQQP<u>QQPFPQQPQQPFP</u>QTQ (SEQ ID NO:34) (396, 23%),
<u>PIQPQQPFPQQPQQPQQPFP</u> (SEQ ID NO:35) (625, 22%),
PQQSFS<u>YQQQPFPQQPYP</u>QQ (SEQ ID NO:36) (618, 18%) (core sequences are
underlined). All of these sequences include glutamine residues predicted to be
30   susceptible to deamidation by transglutaminase (e.g. QXP, QXPF (SEQ ID NO:37),
QXX[FY] (SEQ ID NO:38)) (see Vader et al 2002). Some bioactive peptides
contain two core sequences from different families.

63

Consistent with the possibility that different T-cell populations respond to peptides with distinct core sequences, bioactivity of peptides from different families appear to be additive. For example, median bioactivity of tTG-treated Pool 81 was 141% of P04722 QE85, while bioactivity of individual peptides was in rank order:

5   Peptide 631 (homologue of A-gliadin 57-73) 61%, 636 (homologue of 626) 51%, and 635 19%, 629 16%, and 634 13% (all homologues of 396).

Although likely to be an oversimplification, the contribution of each "peptide family" to the summed IFNγ ELISpot response to gliadin peptides was compared in the HLA-DQ2+ coeliac subjects (see Figure 32). Accordingly, the contribution of

10   P04722 77-73 E85 to the summed response to gliadin peptides is between 1/5 and 2/3.

Using the peptide homology search programme, WWW PepPepSearch, which can be accessed through the world wide web of the internet at, for example, "cbrg.inf.ethz.ch/subsection3_1_5.html.", and by direct comparison with Genbank

15   sequences for rye secalins, exact matches were found for the core sequences QQPFPQPQQPFP (SEQ ID NO:39) in barley hordeins (HOR8) and rye secalins (A23277, CAA26449, AAG35598), QQPFPQQPQQPFP (SEQ ID NO:40) in barley hordeins (HOG1 and HOR8), and for PIQPQQPFPQQP (SEQ ID NO:41) also in barley hordeins (HOR8).

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HLA-DQ8-associated coeliac disease

Seven HLA-DQ8+ coeliac subjects were studied before and after gluten challenge. Five of these HLA-DQ8+ (HLA-DQA0*0301-3, HLA-DQB0*0302) subjects also carried one or both of the coeliac disease-associated HLA-DQ2

25   complex (DQA0*05, DQB0*02). Two of the three subjects with both coeliac-associated HLA-DQ complexes had potent responses to gliadin peptide pools (and individual peptides including P04722 77-93 E85) that were qualitatively and quantitatively identical to HLA-DQ2 coeliac subjects (see Figures 33 and 34, and Table 18). Deamidated peptide pool 74 was bioactive in both HLA-DQ2/8 subjects,

30   but only in one of the 6 HLA-DQ2/X subjects. Pretreatment of pool 74 with tTG enhances bioactivity between 3.8 and 22-times, and bioactivity of tTG-treated pool 74 in the three responders is equivalent to between 78% and 350% the bioactivity of

64

P04722 77-93 E85. Currently, it is not known which peptides are bioactive in Pool 74 in subject C02, C07, and C08.

Two of the four HLA-DQ8 coeliac subjects that lacked both or one of the HLA-DQ2 alleles associated with coeliac disease showed very weak IFNγ ELISpot responses to gliadin peptide pools, but the other two did respond to both protease-digested gliadin and specific peptide pools. Subject C12 (HLA-DQ7/8) responded vigorously to deamidated Pools 1-3 (see Figure 35). Assessment of individual peptides in these pools identified a series of closely related bioactive peptides including the core sequence LQPQNPSQQQPQ (SEQ ID NO:42) (see Table 20). Previous work (by us) has demonstrated that three glutamine residues in this sequence are susceptible to tTG-mediated deamidation (underlined). Homology searches using WWW PepPepSearch have identified close matches to LQPQNPSQQQPQ (SEQ ID NO:43) only in wheat α-gliadins.

The fourth HLA-DQ8 subject (C11) had inducible IFNγ ELISpot responses to tTG-treated Pool 33 (see Figure 36). Pools 32 and 33 include polymorphisms of a previously defined HLA-DQ8 restricted gliadin epitope (QQYPSGQGSFQPSQQNPQ (SEQ ID NO:44)) active after deamidation by tTG (underlined Gln are deamidated and convey bioactivity) (van der Wal et al 1998). Currently, it is not known which peptides are bioactive in Pool 33 in subject C11.

Comprehensive T cell epitope mapping in HLA-DQ2-associated coeliac disease using in vivo gluten challenge and a set of 652 peptides spanning all known 12 amino acid sequences in wheat gliadin has thus identified at least 72 peptides at 10% as bioactive as the known α-gliadin epitope, A-gliadin 57-73 E65. However, these bioactive peptides can be reduced to a set of perhaps as few as 5 distinct but closely related families of peptides. Almost all these peptides are rich in proline, glutamine, phenylalanine, and/or tyrosine and include the sequence PQ(QL)P(FY)P (SEQ ID NO:45). This sequence facilitates deamidation of Q in position 2 by tTG. By analogy with deamidation of A-gliadin 57-68 (Arentz-Hansen 2000), the enhanced bioactivity of these peptides generally found with deamidation by tTG may be due to increased affinity of binding for HLA-DQ2.

Cross-reactivity amongst T cells in vivo recognizing more than one of these bioactive gliadin peptides is possible. However, if each set of related peptides does

65

activate a distinct T cell population in vivo, the epitope corresponding to A-gliadin 57-73 E65 is the most potent and is generally recognized by at least 40% of the peripheral blood T cells that secrete IFNγ in response to gliadin after gluten challenge.

5.   No gliadin-peptide specific responses were found in HLA-DQ2/8 coeliac disease that differed qualitatively from those in HLA-DQ2/X-associated coeliac disease. However, peripheral blood T cells in HLA-DQ8+ coeliac subjects without both HLA-DQ2 alleles did not recognize A-gliadin 57-73 E65 homologues. Two different epitopes were dominant in two HLA-DQ8+ coeliacs. The dominant epitope

10   in one of these HLA-DQ8+ individuals has not been identified previously (LQPQNPSQQQPQ (SEQ ID NO:46)).

Given the teaching herein, design of an immunotherapy for coeliac disease utilizing all the commonly recognised T cell epitopes is practical and may include fewer than six distinct peptides. Epitopes in wheat γ- and ω-gliadins are also present

15   in barley hordeins and rye secalins.

Example 14

Several ELISpot assays were performed as previously described and yielded the following results and/or conclusions:

20   *Examination of multiple α-gliadin polymorphisms with PQLPY*

Potent agonists of A-gliadin 57-73QE (G01) include QLQPFPQPELPYPQPQS (G01), PQL-Y---------------------P (G10), and PQPQPFL------------------ (G12). Less potent include ---------------------L------P (G04), ----------R------------------P (G05), and ---------------------S------P (G06). Less potent yet

25   include --------L------------S------P (G07), --------S------------S------P (G08), -----------

--------S--S------P (G09), and PQPQPFP------------------ (G13). Dashes indicate identity with the G01 sequence in the particular position.

Gluten challenge induces A-gliadin 57-73 QE65 T cells only after two weeks of

30   *gluten-free diet in newly diagnosed coeliac disease*

Additional analyses indicated that tTG-deamidated gliadin responses change after two weeks of gluten-free diet in newly diagnosed coeliac disease. Other

analyses indicated that deamidated gliadin-specific T cells are CD4$^+$α$_4$β$_7$$^+$ HLA-DQ2 restricted.

Optimal epitope (clones versus gluten challenge)

A "dominant" epitope is defined by γIFN ELISpot after gluten challenge. QLQPFPQPELPYPQPQS (100% ELISpot response). Epitopes defined by intestinal T cell clones: QLQPFPQPELPY (27%), PQPELPYPQPELPY (52%), and QQLPQPEQPQQSFPEQERPF (9%).

Dominance among individual peptide responses

Dominance depends on wheat or rye. For wheat, dominant peptides include peptide numbers 89, 90 and 91 (referring to sequence numbers in Table 23). For rye, dominant peptides include peptide numbers 368, 369, 370, 371, and 372 (referring to sequence numbers in Table 23). Some peptides, including 635 and 636 (referring to sequence numbers in Table 23) showed activity in both rye and wheat.

In vivo gluten challenge allows T cell epitope hierarchy to be defined for coeliac disease

The epitope hierarchy is consistent among HLA-DQ2$^+$ coeliacs but different for HLA-DQ8$^+$ coeliacs. The hierarchy depends on what cereal is consumed. Deamidation generates almost all gliadin epitopes. HLA-DQ2, DQ8, and DR4 present deamidated peptides. HLA-DQ2/8-associated coeliac disease preferentially present DQ2-associated gliadin epitopes. Gliadin epitopes are sufficiently restricted to justify development of epitope-based therapeutics.

Other analyses indicated the following: HLA-DR3-DQ2 (85-95%) and HLA-DR4-DQ8 (5-15%).

Other analyses indicated the following:

HLA-DQ	HLA-DQA1 allele	HLA-DQB1 allele	Duodenal histology	Gluten free	EMA on gluten (on GFD)

C01	2,6	102/6, 501	201, 602	SVA	1 yr	+(-)
C02	2,2	501	201	SVA	1 yr	+(-)
C03	2,5	101/4/5, 501	201, 501	PVA	1 yr	+(-)
C04	2,5	101/4/5, 501	201, 501	SVA	7 yr	+(-)
C05	2,2	201, 501	201, 202	SVA	4 mo	+(ND)
C06	2,2	201, 501	201, 202	SVA	2 yr	+(-)
C07	2,8	301-3, 501	201, 302	SVA	1 yr	+(-)
C08	2,8	301-3, 501	201,302/8	SVA	11 yr	ND (-)
C09	2,8	301-3, 501	201, 302	SVA	29 yr	+(-)
C10	2,8	201, 301-3	202, 302	IEL	1 yr	+(-)
C11	6,8	102/6, 301-3	602/15, 302/8	IEL	9 mo	- (ND)
C12	8,7	301-3, 505	302, 301/9-10	SVA	2 yr	- (-)
C13	8,8	301	302	SVA	1 yr	+ (+)

Another analysis was carried out to determine the bioactivity of individual tTG-deamidated peptides in pools 1-3 in subject C12. The results are as follows (sequence numbers refer to the peptides listed in Table 23): Sequence 8 (100%), Sequence 5 (85%), Sequence 6 (82%), Sequence 3 (77%), Sequence 1 (67%), Sequence 2 (59%), Sequence 9 (49%), Sequence 7 (49%), Sequence 10 (33%), Sequence 4 (15%), Sequence 12 (8%), Sequence 11 (0%), Sequence 23 (26%), Sequence 14 (18%), Sequence 15 (18%), Sequence 17 (18%), Sequence 16 (13%), Sequence 14 (8%), Sequence 22 (5%), Sequence 18 (3%), Sequence 19 (3%), Sequence 20 (0%), Sequence 21 (0%). The predicted deamidated sequence is LQPENPSQEQPE.

Individual ELISpot responses by PBMC (Spot forming cells determined by ELISpot Reader)

Peptide (see Table 23)	C01	C02	C03	C04	C05
65	16	2	1	2	3
66	32	6	13	0	6
67	16	3	4	0	4
68	25	8	4	2	2

68

69	4	0	0	0	0
70	2	1	0	0	0
71	1	1	0	0	1
72	0	0	0	0	0
73	95	21	42	31	31
74	122	15	29	21	28
75	5	1	2	2	5
76	108	13	28	16	22
77	3	0	1	0	1
78	21	2	3	5	3
79	20	0	2	0	2
80	5	2	0	0	3
81	4	1	2	3	1
82	3	3	5	2	2
83	14	2	0	0	1
84	3	0	0	0	0
85	14	1	2	1	2
86	11	0	2	0	2

Cross-reactivity

To deal with data from 652 peptides in 29 subjects, or to determine when a particular response is a true positive peptide-specific T-cell response, or to determine when a response to a peptide is due to cross-reactivity with another structurally related peptide, expression of a particular peptide response can be as a percentage of a "dominant" peptide response. Alternately, the expression can be a "relatedness" as correlation coefficients between peptide responses, or via bioinformatics.

Additional epitopes

A representative result is as follows:

Combination of peptides with P04722E (all 20mcg/ml) (n=4)

                     Alone   P04722E+

Pep 626	60	135
P04722E	100	110
HLAa	0	85

(expressed as percent P04722E)

626+tT: PQQPQQPQQPFPQPQQPFPW

P04724E: QLQPFPQPELPYPQPQL

TTG-deamidation of peptide 626 (n=12)

No tTG = 100%

TTG   = 170%

Substitution at particular positions

Substitution of Peptide 626   PQQP[Q1]QP[Q2]QPFPQP[Q3]QPFPW(n=12)

	Glu	Arg
Q1	95	90
Q2	145	80
Q3	155	10

(expressed as percent wild-type peptide)

Bioactivity of tTG-treated 15mers spanning Peptide 626/627 (PQQPQQPQQPFPQPQQPFPWQP) (n=8)

P1-15	5
P2-16	4
P3-17	3
P4-18	38
P5-19	65
P6-20	95
P7-21	65
P8-22	90

(expressed as percent of maximal 15mer response)

70

Multiple epitopes:

        P04724E: QLQPFPQPQLPYPQPQL

        626+tTG: PQQPQQPQQPFPQPQQPFPW

        Minimal epitope: QPQQPFPQPQQPFPW

Immunomagnetic depletion of PBMC by beads coated with anti-CD4 and by anti-integrin β_7 depleted IFNγ ELISpot responses, while immunomagnetic depletion of PBMC by beads coated with anti-CD8 or anti-alphaE integrin. Thus, the PBMC secreting IFNγ are CD4+ and $\alpha_4\beta_7$+, associated with homing to the lamina propria in the gut.

Blocked by anti-DQ antibody but not by anti-DR antibody in heterozygotes and homozygotes for HLA-DQ2. This may imply multiple epitopes within one sequence.

T cell epitopes in coeliac disease

Other investigators have characterized certain intestinal T cell clone epitopes. See, e.g., Vader et al., Gastroenterology 2002, 122:1729-37; Arentz-Hansen et al., Gastroenterology 2002, 123:803-809. These are examples of epitopes whose relevance is at best unclear because of the in vitro techniques used to clone T cells.

Intestinal versus peripheral blood clones

Intestinal: 1) intestinal biopsies, 2) T cell clones raised against peptic-tryptic digest of gluten, 3) all HLA-DQ2 restricted, 4) clones respond to gliadin deamidated by transglutaminase.

Peripheral blood: 1) T cell clones raised against gluten are HLA-DR, DQ and DP restricted. Result: Intestinal T cell clones can be exclusively used to map coeliac disease associated epitopes

GDA_9Wheat 307 aa Definition Alpha/Beta-Gliadin MM1 Precursor (Prolamin) Accession P18573 -- Genbank (which is incorporated herein by reference in its entirety)

Intestinal T cell clone epitopes

71

A definition of intestinal T cell clone epitopes can be found in, for example, Arentz-Hansen et al., J Exp Med. 2000, 191:603-12. Also disclosed therein are gliadin epitopes for intestinal T cell clones. Deamidated QLQPFPQPQLPY is an epitope, with a deamidated sequence of QLQPFPQPELPY. There is an HLA-DQ2

5   restriction. A homology search shows other bioactive rAlpha-gliadins include PQPQLPY singly or duplicated. A majority of T cell clones respond to either/or

DQ2-αI: QLQPFPQPELPY   DQ2-αII: PQPELPYPQPELPY

Dominant gliadin T cell epitopes

10 All deamidated by transglutaminase.

Peripheral blood day 6 after gluten challenge: A-gliadin 57-73:

QLQPFPQPELPYPQPQS

Intestinal T cell clones: DQ2-αI: QLQPFPQPELPY DQ2-αII: PQPELPYPQPELPY

15 *Intestinal T-cell Clone Epitope Mapping*

α-Gliadins	A1	PFPQPQLPY
	A2	PQPQLPYPQ
	A3	PYPQPQLPY
	Glia-20	PQQPYPQPQPQ
Γ-Gliadins	G1	PQQSFPQQQ
	G2	IIPQQPAQ
	G3	FPQQPQQPYPQQP
	G4	FSQPQQQFPQPQ
	G5	LQPQQPFPQQPQQPYPQQPQ
	Glu-21	QSEQSQQPFPQQF
	Glu-5	Q(IL)PQQPQQF
Glutenin	Glt-156	PFSQQQQSPF
	Glt-17	PFSQQQQQ

30

72

Gluten exposure and induction of IFNγ-secreting A-Gliadin 57-73QE65-specific T cells in peripheral blood

Untreated coeliac disease, followed by gluten free diet for 1, 2, or 8 weeks, followed by gluten exposure (3 days bread 200g/day), followed by gluten free diet

Result 1: Duration of gluten free diet and IFNγ ELISpot responses on day 0 and day 6 of gluten challenge: A-gliadin 57-73 QE65 (results expressed as IFNγ specific spots/million PPBMC)

Day 0: none (5), 1 week (1), 2 weeks (2), 8 weeks (1)

Day 6: none (0), 1 week (4), 2 weeks (28), 8 weeks (48)

Result 2: Duration of gluten free diet and IFNγ ELISpot responses on day 0 and day 6 of gluten challenge: tTG-gliadin (results expressed as IFNγ specific spots/million PPBMC)

Day 0: none (45), 1 week (62), 2 weeks (5), 8 weeks (5)

Day 6: none (0), 1 week (67), 2 weeks (40), 8 weeks (60)

Result 3: Duration of gluten free diet and IFNγ ELISpot responses on day 0 and day 6 of gluten challenge: A-gliadin 57-73 P65 (results expressed as IFNγ specific spots/million PPBMC)

Day 0: none (1), 1 week (2), 2 weeks (1), 8 weeks (1)

Day 6: none (0), 1 week (0), 2 weeks (0), 8 weeks (0)

Result 4: Duration of gluten free diet and IFNγ ELISpot responses on day 0 and day 6 of gluten challenge: PPD (results expressed as IFNγ specific spots/million PPBMC)

Day 0: none (90), 1 week (88), 2 weeks (210), 8 weeks (150)

Day 6: none (0), 1 week (100), 2 weeks (210), 8 weeks (100)

Result 5: Duration of gluten free diet and IFNγ ELISpot responses on day 0 and day 6 of gluten challenge: tTG (results expressed as IFNγ specific spots/million PPBMC)

Day 0: none (5), 1 week (4), 2 weeks (3), 8 weeks (2)

Day 6: none (0), 1 week (4), 2 weeks (1), 8 weeks (2)

Gluten challenge in HLA-DQ2 coeliac disease on long term gluten

73

Characterization of anti-gliadin T cell response was carried out in peripheral blood on day 6-8 after 3-day gluten challenge.

Result 1: PBMC Day 6 Long-term gluten free diet (preincubation with anti-HLA-DR and -DQ antibody) (expressed as % inhibition)

DR-: tTG-gliadin 100 mcg/ml (105), A-gliadin 57-73 QE65 50 mcg/ml (90), PPD 5 mcg/ml (30)

DQ-: tTG-gliadin 100 mcg/ml (5), A-gliadin 57-73 QE65 50 mcg/ml (22), PPD 5 mcg/ml (78).

Result 2: PBMC Day 6 Long-term gluten free diet (expressed as % CD8-depleted PBMC response)

B7 depletion: tTG-gliadin n=6 (7), A-gliadin 57-73 n=9 (6), PPD n=8 (62)

AE depletion: tTG-gliadin n=6 (120), A-gliadin 57-73 n=9 (80), PPD n=8 (110).

CD4 depletion: tTG-gliadin n=6 (10), A-gliadin 57-73 n=9 (9), PPD n=8 (10).

Therapeutic peptides include, but are not limited to

QLQPFPQPQLPYPQPQS (AG01)

QLQPFPQPQLPYPQPQP (AG02)

QLQPFPQPQLPYPQPQL (AG03)

QLQPFPQPQLPYLQPQP (AG04)

QLQPFPRPQLPYPQPQP (AG05)

QLQPFPQPQLPYSQPQP (AG06)

QLQPFLQPQLPYSQPQP (AG07)

QLQPFSQPQLPYSQPQP (AG08)

QLQPFPQPQLSYSQPQP (AG09)

PQLPYPQPQLPYPQPQP (AG10)

PQLPYPQPQLPYPQPQL (AG11)

PQPQPFLPQLPYPQPQS (AG12)

PQPQPFPPQLPYPQPQS (AG13)

PQPQPFPPQLPYPQYQP (AG14)

PQPQPFPPQLPYPQPPP (AG015)

74

Briefly after oral antigen challenge, specificities of peripheral blood T cells reflect those of intestinal T cell clones. In peripheral blood, epitopes of intestinal T cell clones are sub-optimal compared to A-gliadin 57-73 QE65, which is an optimal α-gliadin epitope.

Example 15

ELISpot assays were also carried out for mapping purposes as follows.

Fine-mapping the dominant DQ=8 associated epitope

Sequence / sfc	tTG-treated sequence / sfc
VPQLQPQNPSQQQPQEQV / 76	RWPVPQLQPQNPSQQ / 60
	WPVPQLQPQNPSQQQ / 90
VPQLQPENPSQQQPQEQV / 3	PVPQLQPQNPSQQQP / 130
VPQLQPRNPSQQQPQEQV / 76	VPQLQPQNPSQQQPQ / 140
	PQLQPQNPSQQQPQE / 59
VPQLQPQNPSQEQPQEQV / 100	QLQPQNPSQQQPQEQ / 95
VPQLQPQNPSQRQPQEQV / 1	LQPQNPSQQQPQEQV / 30
	QPQNPSQQQPQEQVP / 4
VPQLQPQNPSQQQPEEQV / 71	
VPQLQPQNPSQQQPREQV / 27	DQ8 Gliadin Epitope
	GDA09 202Q / 6
VPQLQPQNPSQEQPEEQV / 81	GDA09 202E / 83
VPQLQPENPSQQQPEEQV / 2	GDA09 202Q+tTG / 17
VPQLQPENPSQEQPQEQV / 6	BI + tTG / 0
VPQLQPENPSQEQPEEQV / 5	BI / 0

Fine-mapping dominant epitope (2)

Pool 33 (deamidated) / sfc

A2b3 301 qqyp sgqg ffqp sqqn pqaq / 2

A2b5 301 qqyp sgqg ffqp fqqn pqaq / 1

A3a1 301 qqyp sgqg ffqp sqqn pqaq / 0

A3b1 301 qqyp ssqv sfqp sqln pqaq / 0

A3b2 301 qqyp ssqg sfqp sqqn pqaq / 2

A4a 301   eqyp sgqv sfqs sqqn pqaq / 28

A1b1 309 sfrp sqqn plaq gsvq pqql / 2

A1a1 309 sfrp sqqn pqaq gsvq pqql / 2

Example 16

Bioactivity of gliadin epitopes in IFNγ-ELISpot (25 mcg/ml, n=6) (expressed as % A-gliadin 57-73 QE65 response)

DQ2-AII: wild type (WT) (4), WT + tTG (52), Glu-substituted (52)

DQ2-AI: wild type (WT) (2), WT + tTG (22), Glu-substituted (28)

GDA09: wild type (WT) (1), WT + tTG (7), Glu-substituted (8)

A-G31-49: wild type (WT) (2), WT + tTG (3), Glu-substituted (0)

Dose response of A-Gliadin 57-73 QE65 (G01E) (n=8) (expressed as %G01E maximal response)

0.025 mcg/ml (1), 0.05 mcg/ml (8), 0.1 mcg/ml (10), 0.25 mcg/ml (22), 0.5 mcg/ml (38), 1 mcg/ml (43), 2.5 mcg/ml (52), 5 mcg/ml (70), 10 mcg/ml (81), 25 mcg/ml (95), 50 mcg/ml (90), 100 mcg/ml (85).

IFNγ ELISpot response to gliadin epitopes alone or mixed with A-gliadin 57-75 (G01E) (all 50 mcg/ml, tTG-gliadin 100 mcg/ml, PPD 5 mcg/ml; n=9) (expressed as % G01E response)

Alone: DQ2-A1 (20), DQ2-A2 (55), Omega G1 (50), tTG Gliadin (80), PPD (220), DQ2 binder (0)

G01E+: DQ2-A1 (90), DQ2-A2 (95), Omega G1 (100), tTG Gliadin (120), PPD (280), DQ2 binder (80)

Effect of alanine and lysine substitution of A-gliadin 57-73 QE65 on IFNγ ELISpot responses in individual coeliac subjects (n=8)

Epitope sequence: QLQPFPQPELPYPQPQS

Alanine substitution at positions 57-59 and 72-73 showed little to no decrease in % A-gliadin 57-73 QE65 response. Alanine substitution at positions 60-62 and 68-71 showed moderate decrease in % A-gliadin 57-73 QE65 response.

76

Alanine substitution at positions 63-67 showed most decrease in % A-gliadin 57-73
QE65 response.

Effect of lysine substitution of A-gliadin 57-73 QE65 on IFNγ ELISpot
responses in individual coeliac subjects (n=8);

Epitope sequence: QLQPFPQPELPYPQPQS

Lysine substitution at positions 57-59 and 71-73 showed little to no decrease
in % A-gliadin 57-73 QE65 response. Lysine substitution at positions 60-61 and 69-
70 showed moderate decrease in % A-gliadin 57-73 QE65 response. Lysine
substitution at positions 62-68 showed most decrease in % A-gliadin 57-73 QE65
response.

Example 17

Table 24 shows the results of analyses examining the 652 peptides with
several patients challenged with wheat or rye.

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77

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Each of the PCT publications, U.S. patents, other patents, journal references, and any other publications cited or referred to herein is incorporated herein by reference in their entirety.

78

Table 1. A-Gliadin protein sequence (based on amino acid sequencing)

```
    VRVPVPQLQP QNPSQQQPQE QVPLVQQQQF PGQQQQFPPQ QPYPQPQPFP SQQPYLQLQP FPQPQLPYPQ
5   1          11         21         31         41         51         61
    PQSFPPQQPY PQPQPQYSQP QQPISQQQAQ QQQQQQQQQQ QQQILQQILQ QQLIPCMDVV LQQHNIAHAR
    71         81         91         101        111        121        131
    SQVLQQSTYQ LLQELCCQHL WQIPEQSQCQ AIHNVVHAII LHQQQKQQQQ PSSQVSFQQP LQQYP LGQGS
    141        151        161        171        181        191        201
10  FRPSQQNPQA QGSVQPQQLP QFEEIRNLAL QTLPAMCNVY IAPYCTIAPF GIFGTN
    211        221        231        241        251        261
```

Table 2. Coeliac disease subjects studied

	Age Sex	Gluten free diet	HLA-DQ2	Bread challenge	Symptoms with bread
1	64 f	14 yr	Homozygote	3 days	Abdominal pain, lethargy, mouth ulcers, diarrhoea
2	57 m	1 yr	Heterozygote	10 days	Lethargy, nausea
3	35 f	7 yr	Heterozygote	3 days	Nausea
4	36 m	6 wk	Homozygote	3 days	Abdominal pain, mouth ulcers, diarrhoea
5	26 m	19 yr	Heterozygote	3 days	None
6	58 m	35 yr	Heterozygote	3 days	None
7	55 m	1 yr	Heterozygote	3 days	Diarrhoea
8	48 f	15 yr	Homozygote	3 days	Abdominal pain, diarrhoea

15

Aminoacid at position 65	Range	Mean
Glutamate	(100)	100%
Asparagine	(50-84)	70%
Aspartate	(50-94)	65%
Alanine	(44-76)	64%
Cysteine	(45-83)	62%
Serine	(45-75)	62%
Valine	(24-79)	56%
Threonine	(46-66)	55%
Glycine	(34-47)	40%
Leucine	(8-46)	33%
Glutamine	(16-21)	19%
Isoleucine	(3-25)	14%
Methionine	(3-32)	14%
Phenylalanine	(0-33)	12%
Histidine	(0-13)	8%
Tyrosine	(0-17)	8%
Tryptophan	(0-17)	8%
Lysine	(0-11)	4%
Proline	(0-4)	2%
Arginine	(0-2)	1%

Table 3

pt response G	TG	Peptide sequence	Corresponding residues in gliadin protein sequences (Accession no.)	
13)		QLQPFPQPQLPYPQPQS	57-73	α-Gliadin (T. aestivum) Q41545
	100 (100)	QLQPFPQPELPYPQPQS	57-73	α-Gliadin (T. aestivum) Q41545
7)	53 (44-67)	QLQPFPQPQLPYSQPQP	77-93	α/β-Gliadin precursor (Tricetum. aestivum) P02863
			76-92	α-Gliadin (T. aestivum) Q41528
			77-93	α-Gliadin storage protein (T. aestivum) Q41531
			57-73	α-Gliadin mature peptide (T. aestivum) Q41533
			77-93	α-Gliadin precursor (T. spelta) Q9ZP09
-20)	83 (61-113)	QLQPFPQPQLPYPQPQP	77-93	α/β-Gliadin A-II precursor (T. aestivum) P0472
-33)	83 (74-97)	QLQPFPQPQLPYPQPQL	77-93	α/β-Gliadin A-IV precursor (T. aestivum) P04724
			77-93	α/β-Gliadin MM1 precursor (T. aestivum) P18573
7)	109 (41-152)	PQLPYPQPQLPYPQPQP	84-100	α/β-Gliadin A-IV precursor (T. aestivum) P04724
		PQLPYPQPQLPYPQPQL	84-100	α/β-Gliadin MM1 precursor (T. aestivum) P18573
!)	3 (0-7)	QLQPFLQPQLPYSQPQP	77-93	α/β-Gliadin A-I precursor (T. aestivum) P04721
			77-93	α-Gliadin (T. aestivum) Q41509
))	2 (0-7)	QLQPFSQPQLPYSQPQP	77-93	α-Gliadin storage protein (T. aestivum) Q41530
		PQPQPFPPQLPYPQTQP	77-93	α/β-Gliadin A-III precursor (T. aestivum) P04723
-40)	24 (11-43)	PQPQPFPPQLPYPQPQS	82-98	α/β-Gliadin A-V precursor (T. aestivum) P04725
-30)	19 (11-33)	PQPQPFPPQLPYPQPPP	82-98	α/β-Gliadin clone PW1215 precursor (T. aestivum) P04726
			82-98	α/β-Gliadin (T. urartu) Q41632
-30)	21 (11-33)	PQPQPFLPQLPYPQPQS	79-95	α/β-Gliadin clone PW8142 precursor (T. aestivum) P04726
			79-95	α-Gliadin (T. aestivum) Q41529
			79-95	α/β-Gliadin precursor (T. aestivum) Q41546

Table 4

80

able 5. T cell epitopes described in coeliac disease

urce	Restriction	Frequency	Sequence*
imma -gliadin	DQ2	3/NS (iTCC)	QQLPQPEQPQQSFPEQERPF
pha-gliadin	DQ2	12/17 (iTCL)	QLQPFPQPELPY
pha-gliadin	DQ2	11/17 (iTCL)	PQPELPYPQPELPY
pha-gliadin	DQ2	1/23 (bTCC)	LGQQQPFPPQQPYPQPQPF
pha-gliadin	DQ8	3/NS (iTCC)	QQYPSGEGSFQPSQENPQ
utenin	DQ8	1/1 (iTCC)	GQQGYYPTSPQQSGQ
pha-gliadin	DQ2	11/12 in vivo	QLQPFPQPELPYPQPQS

i not stated in original publication, iTCC intestinal T cell clone, iTCL intestinal polyclonal T cell line, bTCC peripheral blood
:ell clone
.ll peptides are the products of transglutaminase modifying wild type gluten peptides except the fourth and sixth peptides

ible 6. Relative bioactivity of gliadin T cell epitopes in coeliac PBMC after gluten challenge

quence*	ELISpot response as % A-gliadin 57-73 QE65 (all 25mcg/ml)		
	Wild type	Wildtype+tTG	E-substituted
)LPQPEQPQQSFPEQERPF	9 (3)	18 (7)	10 (5)
.QPFPQPELPY	6 (2)	19 (1)	8 (3)
PELPYPQPELPY	13 (6)	53 (8)	48 (9)
)YPSGEGSFQPSQENPQ	10 (3)	9 (3)	14 (8)
QPFPQPELPYPQPQS	18 (7)	87 (7)	100
LPYPQPELPYPQPQP	14 (4)	80 (17)	69 (20)

:quence refers that of transglutaminase (tTG) modified peptide and the T cell epitope. Wild type is the unmodified gliadin
tide. Data from 4 subjects. Blank was 5 (1) %.

81

Table 7. Polymorphisms of A-gliadin 57-73

A. Sequences derived from Nordic autumn wheat strain Mjoelner

Alpha-gliadin protein (single letter code refers to Fig. 14 peptides)	Polymorphism
Q41545 A-gliadin (from sequenced protein) 57-73 (A)	QLQPFPQPQLPYPQPQS
Gli alpha 1,6: (EMBL: AJ133605 & AJ133602 58-74) (J)	QPQPFPPPQLPYPQTQP
Gli alpha 3,4,5: (EMBL: AJ133606, AJ133607, AJ133608 57-73) (I)	QLQPFPQPQLSYSQPQP
Gli alpha 7: (EMBL: AJ133604 57-73) (E)	QLQPFPRPQLPYPQPQP
Gli alpha 8, 9, 11: (EMBL:) (F)	QLQPFPQPQLPYSQPQP
Gli alpha 10: (EMBL: AJ133610 57-73) (D)	QLQPFPQPQLPYLQPQS

B. SWISSPROT and TREMBL scan (10.12.99) for gliadins containing the sequence: XXXXXXXPQLPYXXXXX

Wheat (Triticum aestivum unless stated) gliadin accession number	Polymorphism
Q41545 A-gliadin (from sequenced protein) 57-73 (A)	QLQPFPQPQLPYPQPQS
SWISSPROT:	
GDA0_WHEAT P02863 77-93 (F)	QLQPFPQPQLPYSQPQP
GDA1_WHEAT P04721 77-93 (G)	QLQPFLQPQLPYSQPQP
GDA2_WHEAT P04722 77-93 (B)	QLQPFPQPQLPYPQPQP
GDA3_WHEAT P04723 77-93 (O)	PQPQPFPPQLPYPQTQP
GDA4_WHEAT P04724 77-93 (C)	QLQPFPQPQLPYPQPQL
GDA4_WHEAT P04724 84-100 (K)	PQLPYPQPQLPYPQPQP
GDA5_WHEAT P04725 82-98 (N)	PQPQPFPPQLPYPQPQS
GDA6_WHEAT P04726 82-98 (P)	PQPQPFPPQLPYPQPPP
GDA7_WHEAT P04727 79-95 (M)	PQPQPFLPQLPYPQPQS
GDA9_WHEAT P18573 77-93 (C)	QLQPFPQPQLPYPQPQL
GDA9_WHEAT P18573 84-100 (L)	PQLPYPQPQLPYPQPQL
GDA9_WHEAT P18573 91-107 (K)	PQLPYPQPQLPYPQPQP
TREMBL	
Q41509 ALPHA-GLIADIN 77-93 (G)	QLQPFLQPQLPYSQPQP
Q41528 ALPHA-GLIADIN 76-92 (F)	QLQPFPQPQLPYSQPQP
Q41529 ALPHA-GLIADIN 79-95 (M)	PQPQPFLPQLPYPQPQS
Q41530 ALPHA-GLIADIN 77-93 (H)	QLQPFSQPQLPYSQPQP
Q41531 ALPHA-GLIADIN 77-93 (F)	QLQPFPQPQLPYSQPQP
Q41533 ALPHA-GLIADIN 57-73 (F)	QLQPFPQPQLPYSQPQP
Q41546 ALPHA/BETA-GLIADIN 79-95 (M)	PQPQPFLPQLPYPQPQS
Q41632 ALPHA/BETA-TYPE GLIADIN. Triticum urartu 82-98 (P)	PQPQPFPPQLPYPQPPP
Q9ZP09 ALPHA-GLIADIN Triticum spelta 77-93 (F)	QLQPFPQPQLPYSQPQP

Table 8. Bioactivity of substituted variants of A-gliadin 57-73 QE65 (Subst) compared to unmodified A-gliadin 57-73 QE65 (G) (mean 100%, 95% CI 97-104) and blank (no peptide, bl) (mean 7.1%, 95% CI: 5.7-8.5)

Subst	%	P vs G	Subst	%	P vs G	Subst	%	P vs G	Subst	%	P vs G	P vs bl
Super-agonists			F62	71	0.001	H62	47	<0.0001	N66	24	<0.0001	
Y61	129	<0.0001	V63	70	<0.0001	G69	47	<0.0001	R64	24	<0.0001	
Y70	129	0.0006	S69	70	<0.0001	N63	47	<0.0001	K63	23	<0.0001	
Agonists			H63	70	<0.0001	H68	47	<0.0001	V65	23	<0.0001	
W70	119	0.017	F63	70	0.008	M68	46	<0.0001	H66	23	<0.0001	
K57	118	0.02	P70	69	<0.0001	D68	46	<0.0001	H67	22	<0.0001	
Y59	117	0.04	T62	69	<0.0001	V69	46	<0.0001	L64	22	<0.0001	
A57	116	0.046	L61	69	<0.0001	G63	45	<0.0001	S66	22	<0.0001	
S70	116	0.045	S61	69	<0.0001	V64	45	<0.0001	F67	21	<0.0001	
K58	114	0.08	T61	69	<0.0001	E61	45	<0.0001	W66	21	<0.0001	
W59	110	0.21	T63	69	<0.0001	A69	43	<0.0001	G64	21	<0.0001	
A73	109	0.24	M66	68	<0.0001	R62	42	<0.0001	G65	21	<0.0001	
I59	108	0.37	T69	67	<0.0001	G68	42	<0.0001	D64	21	<0.0001	
G59	108	0.34	K60	66	<0.0001	A64	42	<0.0001	I65	21	<0.0001	
A58	108	0.35	S62	66	<0.0001	C65	42	<0.0001	M64	20	<0.0001	<0.0001
W60	105	0.62	M61	66	<0.0001	N67	41	<0.0001	G67	19	<0.0001	<0.0001
A59	104	0.61	P61	65	<0.0001	W63	41	<0.0001	T65	19	<0.0001	0.003
K72	104	0.65	M62	64	<0.0001	F69	41	<0.0001	A66	19	<0.0001	<0.0001
S59	103	0.76	Q61	64	<0.0001	N68	40	<0.0001	I64	19	<0.0001	0.0003
K73	102	0.8	G61	64	<0.0001	V66	40	<0.0001	R63	19	<0.0001	<0.0001
A70	102	0.81	A63	64	<0.0001	H69	40	<0.0001	W67	19	<0.0001	<0.0001
Y60	101	0.96	L62	60	<0.0001	M69	40	<0.0001	K68	18	<0.0001	<0.0001
A72	100	0.94	I68	60	<0.0001	R69	40	<0.0001	H64	18	<0.0001	<0.0001
S63	98	0.67	S67	59	<0.0001	W69	40	<0.0001	W64	18	<0.0001	0.0001
K59	96	0.46	N61	59	<0.0001	Q69	39	<0.0001	Q65	18	<0.0001	0.0002
I60	96	0.5	I69	59	<0.0001	L67	38	<0.0001	F64	16	<0.0001	0.0008
G70	95	0.41	V61	58	<0.0001	K69	38	<0.0001	L65	16	<0.0001	0.0022
D65	95	0.44	D61	58	<0.0001	K62	38	<0.0001	N64	16	<0.0001	<0.0001
E70	93	0.27	E60	57	<0.0001	E67	37	<0.0001	F65	16	<0.0001	0.12
I63	92	0.19	A61	57	<0.0001	L69	37	<0.0001	Q67	15	<0.0001	0.0012
S60	92	0.23	Q62	56	<0.0001	S64	36	<0.0001	M65	14	<0.0001	0.015
P59	88	0.08	F68	56	<0.0001	G62	36	<0.0001	D66	14	<0.0001	0.013
M63	87	0.03	N65	56	<0.0001	E69	36	<0.0001	R67	14	<0.0001	0.002
K71	85	0.047	A62	56	<0.0001	E68	36	<0.0001	Non-agonists			
V62	84	0.04	A68	53	<0.0001	V67	35	<0.0001	P63	13	<0.0001	0.012
I70	84	0.04	P66	53	<0.0001	D62	35	<0.0001	E64	12	<0.0001	0.053
I61	83	0.01	R61	53	<0.0001	R68	34	<0.0001	W65	11	<0.0001	0.24
V68	82	0.0045	S68	53	<0.0001	Q66	34	<0.0001	Q64	11	<0.0001	0.15
E59	81	0.01	Y63	52	<0.0001	A67	33	<0.0001	G66	11	<0.0001	0.07
Partial agonists			N69	51	<0.0001	N62	32	<0.0001	R65	11	<0.0001	0.26
W61	79	0.002	E63	51	<0.0001	F66	31	<0.0001	Y67	10	<0.0001	0.13
A60	78	0.002	T64	51	<0.0001	E62	31	<0.0001	E66	10	<0.0001	0.17
Y62	78	0.006	T67	51	<0.0001	D69	31	<0.0001	K66	10	<0.0001	0.21
G60	77	0.003	Y69	50	<0.0001	D67	30	<0.0001	R66	10	<0.0001	0.23
A71	77	0.003	D63	50	<0.0001	M67	29	<0.0001	K67	10	<0.0001	0.11
W62	76	0.0009	A65	49	<0.0001	Y66	28	<0.0001	P65	8	<0.0001	0.57
Q60	76	0.001	K61	49	<0.0001	I67	28	<0.0001	K64	8	<0.0001	0.82
L63	74	0.0002	I66	49	<0.0001	H65	26	<0.0001	K65	8	<0.0001	0.63
I62	74	0.0005	T68	48	<0.0001	P68	26	<0.0001	Y65	7	<0.0001	0.9
K70	74	0.001	S65	48	<0.0001	Y64	25	<0.0001				
H61	72	<0.0001	L68	48	<0.0001	EK65	25	<0.0001				
W68	72	<0.0001	Q68	48	<0.0001	T66	25	<0.0001				

Table 9. Antagonism of A-gliadin 57-73 QE65 interferon gamma ELISPOT response by substituted variants of A-gliadin 57-73 QE65 (Subst) (P is significance level in unpaired t-test). Agonist activity (% agonist) of peptides compared to A-gliadin 57-73 QE65 is also shown.

Subst	% Inhibit.	P	% agonist.	Subst	% Inhibit.	P	% agonist.
Antagonists				65R 13	0.18		11
65T	28	0.004	19	65M	13	0.16	14
67M	27	0.0052	29	68P	13	0.16	26
64W	26	0.007	18	63R	13	0.19	19
67W	25	0.0088	19	66G	12	0.19	11
Potential antagonists				65Q	12	0.2	18
67I	24	0.013	10	65Y	12	0.22	7
67Y	24	0.013	21	66S	12	0.22	22
64G	21	0.03	21	67F	11	0.25	21
64D	21	0.029	16	66R	10	0.29	10
65L	20	0.046	26	67K	10	0.29	10
66N	20	0.037	24	64F	10	0.29	16
65H	20	0.038	16	65F	9	0.41	16
64N	19	0.05	16	63P	8	0.42	13
64Y	19	0.06	25	65EK	8	0.39	25
66Y	19	0.048	28	64Q	7	0.49	11
64E	19	0.049	12	64I	5	0.6	21
67A	18	0.058	30	68K	5	0.56	19
67H	18	0.052	22	67Q	5	0.61	18
Non-antagonists				65G 5	0.62		15
65V	17	0.07	23	64M	4	0.7	20
65I	17	0.086	21	66H	4	0.66	23
66T	17	0.069	25	66 E	3	0.76	10
65W	15	0.11	11	66D	1	0.9	14
67R	15	0.13	14	63K	1	0.88	23
65P	15	0.13	8	64H	1	0.93	18
65K	15	0.11	8	66K	0	0.98	10
66W	15	0.12	21	64K	-2	0.88	8
67G	14	0.14	19	64L	-11	0.26	22
66A	14	0.14	19				

Table 10. Inhibition of A-gliadin 57-73 QE65 interferon gamma ELISPOT response by peptides known to bind HLA-DQ2 (P is significance level in unpaired t-test).

Peptide	% Inhibit.	P
TP	31	<0.0001
HLA1a	0	0.95

84

Table 11. Antagonism of A-gliadin 57-73 QE65 interferon gamma ELISpot response by naturally occurring polymorphisms of A-gliadin 57-73 QE65 (P is significance level in unpaired t-test).

A-gliadin 57-73 QE65 polymorphism		% Inhibit.	P
P04725 82-98 QE90	PQPQPFPPELPYPQPQS	19	0.009
Q41509 77-93 QE85	QLQPFLQPELPYSQPQP	11	0.15
Gli α 1,6 58-74 QE66	QPQPFPPPELPYPQTQP	11	0.11
P04723 77-93 QE85	PQPQPFPPELPYPQTQP	10	0.14
Gli α 3-5 57-73 QE65	QLQPFPQPELSYSQPQP	7	0.34
P02863 77-93 QE85	QLQPFPQPELPYSQPQP	6	0.35
Q41509 77-93 QE85	QLQPFLQPELPYSQPQP	6	0.41
P04727 79-95 QE65	PQPQPFLPELPYPQPQS	6	0.39
P04726 82-98 QE90	PQPQPFPPELPYPQPPP	5	0.43

5

Table 12. Prolamin homologues of A-gliadin 57-73 (excluding alpha/beta-gliadins)

Prolamin	Accession number	Sequence	% Bioactivity*
Wheat: α-gliadin	A-gliadin (57-73)	QLQPFPQPQLPYPQPQS	100 (0)
Wheat: ω-gliadin	AAG17702 (141-157)	PQ.............................F......QSE	32 (6.4)
Barley: C-hordein	Q40055 (166-182)	...QPFPL...............F............Q	2.3 (2.0)
Wheat γ-gliadin	P21292 (96-112)	...QTFPQ...............F......QPQ	2.1 (4.2)
Rye: secalin	Q43639 (335-351)	...QPSPQ...............F............Q	1.6 (1.4)
Barley: γ-hordein	P80198 (52-68)	...QPFPQ...............HQHQFP	-1.0 (1.8)
Wheat: LMW glutenin	P16315 (67-83)	LQ...QPIL............FS...Q...Q	-0.9 (1.0)
Wheat: HMW glutenin	P08489 (718-734)	HGYYPTS.........SGQGQRP	6.4 (4.0)
Wheat γ-gliadin	P04730 (120-136)	...QCCQQL......I...QQSRYQ	0.7 (0.9)
Wheat: LMW glutenin	P10386 (183-199)	...QCCQQL......I...QQSRYE	-0.7 (0.5)
Wheat: LMW glutenin	O49958 (214-230)	...QCCRQL......I...EQSRYD	-1.1 (0.3)
Barley: B1-hordein	P06470 (176-192)	...QCCQQL......I...EQFRHE	1.8 (1.4)
Barley: B-hordein	Q40026 (176-192)	...QCCQQL......ISEQFRHE	0.5 (0.9)

*Bioactivity is expressed as 100x(spot forming cells with peptide 25mcg/ml plus tTG 8mcg/ml minus

blank)/(spot forming cells with A-gliadin 57-73 25mcg/ml plus tTG 8mcg/ml minus blank) (mean (SEM), n=5).

Peptides were preincubated with tTG for 2h 37°C. Note, Q is deamidated in A-gliadin 57-73 by tTG.

5

Table 13. Clinical details of coeliac subjects.

	HLA-DQ	HLA-DQA1 alleles	HLA-DQB1 alleles	Duodenal histology	Gluten free	EMA on gluten (on GFD)
C01	2, 6	102/6, 501	201, 602	SVA	1 yr	+ (-)
C02	2, 2	501	201	SVA	1 yr	+ (-)
C03	2, 5	101/4/5, 501	201, 501	PVA	1 yr	+ (-)
C04	2, 5	101/4-5, 501	201, 501	SVA	7 yr	+ (-)
C05	2, 2	201, 501	201, 202	SVA	4 mo	+ (ND)
C06	2, 2	201, 501	201, 202	SVA	2 yr	+ (-)
C07	2, 8	301-3, 501	201, 302	SVA	1 yr	+ (-)
C08	2, 8	301-3, 501	201, 302/8	SVA	11 yr	ND (-)
C09	2, 8	301-3, 501	201, 302	SVA	29 yr	+ (-)
C10	2, 8	201, 301-3	202, 302	IEL	1 yr	+ (-)
C11	6, 8	102/6, 301-3	602/15, 302/8	IEL	9 mo	- (ND)
C12	8, 7	301-3, 505	302, 301/9-10	SVA	2 yr	- (-)
C13	8, 8	301	302	SVA	1 yr	+ (+)

SVA subtotal villous atrophy, PVA partial villous atrophy, IEL increased intra-epithelial atrophy, GFD gluten-free diet, ND not done.

5

Table 14. HLA-DQ2+ Coeliac (C01-6) and healthy control (H01-10) IFNγ

ELISpot responses to control peptides (20 µg/ml) and gliadin (500 µg/ml) before

and after gluten challenge (sfc/million PBMC minus response to PBS alone)

Peptide	Healthy Day 0	Healthy Day 6	Coeliac Day 0	Coeliac Day 6
P04722 77-93	0 (-4 to 17)	0 (-5 to 9)	-2 (-3 to 0)	27 (0-100)*
P04722 77-93 + tTG	0 (-5 to 4)	0 (-9 to 3)	0 (-4 to 11)	141 (8 to 290)**
P04722 77-93 QE85	0 (-5 to 5)	0 (-3 to 4)	0 (-6 to 14)	133 (10 to 297)*
P02863 77-93	0 (-4 to 13)	2 (-3 to 5)	-2 (-3 to 2)	8 (-2 to 42)**
P02863 77-93 + tTG	-1 (-5 to 4)	-1 (-4 to 11)	1 (-4 to 6)	65 (8-164)**
P02863 77-93 QE85	0 (-4 to 13)	0 (-4 to 14)	-1 (-4 to 6)	42 (-2 to 176)*
Gliadin chymotrypsin	2 (-5 to 20)	18 (0 to 185)*	20 (11 to 145)	92 (50 to 154)
Gliadin chymotrypsin + tTG	0 (-1 to 28)	16 (-9 to 171)*	55 (29 to 248)	269 (206 to 384)**
Chymotrypsin	0 (-4 to 5)	1 (-4 to 11)	-2 (-5 to 5)	1 (-4 to 8)
Chymotrypsin + tTG	0 (-5 to 8)	6 (0 to 29)	-2 (-3 to 11)	2 (-3 to 18)*
Gliadin pepsin	4 (-4 to 28)	29 (0 to 189)***	44 (10 to 221)	176 (54 to 265)**
Gliadin pepsin + tTG	2 (-3 to 80)	27 (-4 to 241)***	61 (8 to 172)	280 (207 to 406)**
Pepsin	0 (-4 to 10)	0 (-3 to 12)	0 (-2 to 3)	2 (-2 to 8)
Pepsin + tTG	0 (-3 to 8)	0 (-5 to 9)	1 (-6 to 3)	0 (-3 to 14)
PBS alone	4 (0 to 6)	2 (0 to 6)	4 (1 to 12)	4 (0 to 4)
PBS + tTG	3 (0 to 8)	3 (0 to 11)	4 (2 to 10)	4 (2 to 11)

5   Day 6 vs. Day 0: *P<0.05 **P,0.02, ***P<0.01 by one-tailed Wilcoxon Matched-Pairs Signed-Ranks test

88

Table 15. Effect of deamidation by tTG to gliadin (0.5 mg/ml) and A-gliadin 57-

73 homologues on IFNγ ELISpot responses in HLA-DQ2+ coeliac (C01-6) and

healthy control subjects (H01-10) (median ratio tTG:no tTG pretreatment,

5   range)

Peptide	Healthy Day 6	Coeliac Day 0	Coeliac Day 6
Gliadin chymotrypsin	0.94 (0.4-9.0)	2.1 (0.8-6.8)*	3.2 (1.8 -4.2)**
Gliadin pepsin	1.4 (0.5-1.4)	1.4 (0.8-4.0)*	1.9 (1.1-4.4)**
P04722 77-93 Q85			6.5 (2.3-12)**
P04722 77-93 E85			0.7 (0.6-1.1)
P02863 77-93 Q85			7.5 (3.9-19.9)**
P02863 77-93 E85			1.0 (0.8-1.2)

TTG>no tTG: *P<0.05 **P,0.02, ***P<0.01 by one-tailed Wilcoxon Matched-Pairs Signed-Ranks test

Table 16. Healthy subjects: IFNγ ELISpot Responses (>10 sfc/million PBMC and >4 x buffer only) to tTG-treated gliadin peptide Pools on Day 6 of gluten challenge (sfc/million PBMC) (*italic*: response also present on Day 0):

Group 1 – HLA-DQ2 (DQA1*0501-5, DQB1*0201)

Group 2 – HLA-DQ8 (DQA1*0301, DQB1*0302) and absent or "incomplete" DQ2 (only DQA1*0501-5 or DQB1*0201)

	Group 1										Group 2
Subject	H01	H02	H03	H04	H05	H06	H07	H08	H09	H10	H11
HLA-DQ	2, 6	2, 7	2, 8	2, 5	2, 6	2, 6	2, 6	2, 7	2, 5	2, 5	8, 8
Pool 1	.	.	.	.	.	.	.	.	.	.	.
2	.	.	.	.	.	.	.	.	.	.	.
3	.	.	.	.	.	.	.	.	.	.	.
4	.	.	.	.	.	.	.	.	13	.	.
5	.	17	.	.	.	.	.	.	*24*	.	.
6	.	.	.	.	.	.	.	.	*31*	.	.
7	.	.	.	.	.	.	.	.	.	.	.
8	.	.	.	.	.	.	.	.	.	.	.
9	.	.	.	.	.	.	.	.	.	.	.
10	.	.	.	.	.	.	.	.	.	.	.
11	.	.	.	.	.	.	.	.	.	.	.
12	.	.	.	.	.	.	.	.	.	.	.
13	.	.	.	.	.	.	.	.	.	.	.
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18	.	.	.	.	.	.	20	.	.	.	.
19	.	.	.	.	.	.	.	.	.	.	.
20	.	11	.	.	.	.	.	.	.	.	.
21	.	11	.	.	.	.	.	.	27	.	.
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23	.	*43*	.	.	.	.	.	.	.	.	.
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25	.	11	.	.	.	.	.	.	.	.	.
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30	.	.	.	.	.	.	.	.	23	.	.
31	.	.	.	.	.	.	.	.	.	.	.
32	.	.	.	.	.	.	.	.	.	.	.
33	.	20	.	.	.	.	.	.	.	.	.
34	.	.	.	.	.	.	.	.	.	.	.
35	.	11	.	.	.	.	.	.	.	.	.
36	.	.	.	.	.	.	.	.	.	.	.
37	.	.	.	.	.	.	.	.	*18*	.	.
38	14	.	.	.	.	.	.	.	12	.	.
39	.	.	.	.	.	.	.	.	11	.	.
40	.	14	.	.	.	.	.	.	17	.	.
41	.	.	.	.	.	.	.	.	.	.	.
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43	.	.	.	.	.	.	.	.	11	.		.
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50	.	14	.	.	12	.	.	22	.	14		.
51	.	.	.	.	.	.	.	.	.	.		.
52	.	14	.	.	.	.	.	.	.	.		.
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54	.	.	.	.	.	.	.	12	.	.		.
55	.	.	.	.	.	.	.	.	.	.		.
56	.	.	.	.	.	.	.	.	.	.		.
57	.	23	.	.	.	.	12	.	.	.		.
58	.	14	.	.	.	.	.	.	.	.		.
59	.	.	.	.	.	.	.	.	.	.		.
60	.	.	.	.	.	.	.	.	.	.		.
61	.	23	.	.	.	.	.	11	11	.		.
62	.	.	.	.	.	.	.	.	.	.		.
63	.	.	.	.	.	.	.	.	.	.		.
64	.	20	.	.	.	.	.	.	.	.		.
65	.	.	.	.	.	.	.	.	.	.		.
66	.	14	.	.	.	.	.	.	.	.		.
67	.	11	.	.	.	.	.	.	.	.		.
68	.	20	.	.	.	.	.	20	.	.		.
69	.	20	.	.	.	.	.	.	.	.		.
70	.	.	.	.	.	.	.	.	.	.		.
71	.	.	.	.	.	.	.	.	.	.		16
72	.	11	.	.	.	.	.	.	.	.		.
73	.	14	.	.	.	.	.	.	.	.		.
74	.	.	.	.	.	.	.	.	.	.		.
75	.	.	.	.	.	.	.	.	.	.		.
76	.	14	.	.	.	.	.	.	.	.		.
77	.	.	.	.	.	.	.	.	.	.		.
78	.	11	.	.	.	.	.	.	.	.		.
79	.	11	.	.	19	.	.	.	.	.		.
80	.	.	.	.	.	.	.	.	.	.		.
81	.	.	.	.	.	.	.	.	.	.		.
82	.	.	.	.	.	.	.	.	.	.		.
83	.	.	.	.	.	.	.	.	.	.		.
P04722 77-93	.	.	.	.	.	.	.	.	.	.		.
P04722 77-93 E	.	.	.	.	.	.	.	.	.	.		.
P04722 77-93 E	.	.	.	.	.	.	.	.	.	.		.
P02863 77-93	.	.	.	.	.	.	.	11	.	.		.
P02863 77-93 E	.	.	.	.	.	.	.	.	.	.		.
Gliadin+C	171	40	25	16	10	.	18	14	.	17		90
Chymotrypsin	29	26	18	.	.	.	.	22	.	.		.
Gliadin+Pepsin	241	151	29	24	48	.	16	45	.	19		35
Pepsin												

91

Table 17: tTG-deamidated gliadin peptide pools showing significant increase in

IFN gamma responses between Day 0 and Day 6 of gluten challenge in HLA-

DQ2 coeliac subjects C01-6 (Day 6 –Day 0 response, and ratio of responses to

5   tTG-deamidated pool and same pool without tTG treatment)

Pool	IFNg ELISpot (Median sfc/million)	tTG: no tTG (Median)	Pool	IFNg ELISpot (Median sfc/million)	tTG: no tTG (Median)
9	59***	1.0	49	46***	1.4
10	116**	1.7	50	50***	4.6
11	24***	2.5	51	40***	1.7
12	133***	1.1	52	30***	3.1
13	26**	2.1	53	27**	1.4
42	30**	1.2	76	17***	1.1
43	32***	1.3	79	20***	0.9
44	24***	1.5	80	83***	1
45	10***	1.1	81	141***	1.1
46	12***	2.1	82	22***	1.5
48	17***	1.4	83	16**	1.8

Day 6 vs. Day 0 **$P<0.02$, ***$P<0.01$ by one-tailed Wilcoxon Matched-Pairs Signed-Ranks test

92

Table 18. Coeliac subjects: IFNγ ELISpot Responses >10 sfc/million PBMC and

>4 x buffer only to tTG-treated Pepset Pools on Day 6 of gluten challenge

(sfc/million PBMC) (*italic*: response also present on Day 0):

Group 1 – HLA-DQ2 (DQA1*0501-5, DQB1*0201/2),

Group 2 – HLA-DQ2/8 (DQA1*0501-5, *0301, and DQB1*0201/2, *0302), and

Group 3 – HLA-DQ8 (DQA1*0301, DQB1*0302) and absent or "incomplete"

DQ2 (only DQA1*0501-5 or DQB1*0201/2)

Subject	Group 1:						Group 2:			Group 3			
	C01	C02	C03	C04	C05	C06	C07	C08	C09	C10	C11	C12	C13
HLA-DQ	2, 6	2, 2	2, 5	2, 5	2, 2	2, 2	2, 8	2, 8	2, 8	2, 8	6,8	7, 8	8, 8
Pool 1	.						23					223	
2	.											155	
3	.											41	
4	11									22	.		
5	.									.	.		
6	18			21			20	17		.	.		
7	.							353		.	.		
8	11	64				14	20	480		.	.		13
9	93	127		92	25		32	460		.	.		18
10	175	491	58	200	48		84	*787*		.	.		
11	32	118		33	14		26	27		12	.		
12	204	379	54	225	61		129	587		12	.		
13	93	142		29	18			*60*		.	.		11
14	.	45		21			17			.	.		
15	18	30					38	43		.	.		
16	.							37		.	.		
17	.									.	.		
18	.									.	.		
19	11										.		
20	11	215					51	167		.	.		
21	.								11	.	.		
22	.	21								.	.		
23	.	18		21						12	.		
24	.	15						10		.	.		
25	.	*15*								12	.		
26	.	*18*						13		12	.		
27	.	*15*								.			
28	.									.	.		11
29	.						11			.	.		
30	11						11			.	.		
31	.	70								.	.		
32	.	18					20			.	.		
33	11			10			*14*		*11*	.	40		*11*
34	.								11	.	.		
35	.									.	.		
36	.									.	.		
37	.			23		14				.	.		
38	.	24		19			20			.	.		
39	.	49		15					*11*	.	.		
40	.						14			.	.		

41	.	21								.	.		
42	39	42		44	21		11	63		12	.		
43	50	91	13	75	14		190	113		.	.	21	
44	32	97	17	96	13		87	107		.	.		
45	.	21	10	100	11		38	110		.	.		
46	14	55		102	18		63	163		.	.		
47	14	58		38			223	97		.	.	31	
48	21	106		60	14		144	353		.	.	57	
49	75	170	17	142	30		202	293		.	.	39	
50	57	245	23	140	61	27	248	143		.	.		11
51	68	106	10	127			220	267		.	.	29	
52	43	121		79	13	16	175	180		.	.		
53	36	94		92	29		69	53		.	.		
54	36			35	11		166	27		.	.	19	13
55	.									.	.		
56	29			.	..				11	.	.		
57	.	36					20	13		.	.		
58	.									.	.		
59	.		10					53		.	.		
60	.	18		15			11	53		.	.		
61	.						20			.	.		
62	14	18		13			60			.	.		
63	.		10			14				28	.		
64	.	15								18	.		
65		36		25	23		35	27		.	11		
66				31	11	10	17			.	.		
67	.			17			17			.	.		
68	.		19	127		14				.	.		
69	.	15		10			20	20			.		
70	.	12	31		13	10				.			
71	11	21	13				14	.		.	18		
72	.					16				.	.		
73	.			13		14	11			.	.		
74	.	239				.	254	447		.	.		
75	.									.	.		
76	18	21	19	15						.	.	12	
77	.	88				10		13		.	.		
78	.	18	17	69						.	.		
79	11	85		44	29	12	44	43		.	.		
80	132	133	33	240	39	12	208	467		12	.	70	
81	171	318	113	367	104	12	211	530		.	.	74	
82	18	300	17	125	32	16	241	723		.	.		
83	14	164		31	21		163	277		15	.		
P04722 77-93	211	291	75	281	66		78	740		.	.		
P04722 77-93 E	164	297	108	221	64	10	84	653		.	.		
P04722 77-93 E	161	182	98	256	73	16	63	500		.	.		
P02863 77-93	139	164	35	94	36		29	603		.	.		
P02863 77-93 E	46	176	19	88	41		23	520		.	.		
Gliadin+C	214	273	265	360	384	206	278	543	17		25	527	71
Chymotrypsin						18							
Gliadin+Pepsin	239	315	269	406	207	292	357	557		42	89	335	87
Pepsin	.					14							

Table 19. Deamidated peptides with mean bioactivity > 10% of P04722 E85 (20 µg/ml) in HLA-DQ2 coeliac subjects C01-5

Rank	No.	Sequence	Mean (SEM)	Rank	No.	Sequence	Mean (SEM)
	89	PQLPYPQPQLPYPQPQLPYP	94 (18)	37	413	SKQPQQPFPQPQQPQQSFPQ	18 (4)
*2	91	PQPFPPQLPYPQPQLPYPQP	89 (12)	38	380	QPQQPQQPFPQPQQPQLPFP	18 (6)
*3	74	MQLQPFPQPQLPYPQPQLPY	88 (14)	39	618	PQQSFSYQQQPFFQQPYPQQ	18 (7)
*4	90	PQLPYPQPQLPYPQPQPFRP	87 (16)	*40	78	LQLQPFPRPQLPYPQPQPFR	17 (8)
*5	76	LQLQPFPQPQLPYPQPQPFR	85 (15)	41	390	QQTYPQRPQQPFFQTQQPQQ	17 (9)
6	626	PQQPQQPQQPFPQPQQPFPW	72 (23)	42	348	QQTFPQPQQTFPHQPQQQFP	16 (10)
7	627	QPFPQPQQPFPWQPQQPFPQ	66 (30)	43	409	QPQQPFPQLQQPQQPIPQPQ	16 (2)
*8	631	FPQQPQQPFFQPQLPFPQQS	61 (12)	44	382	QQPFPQQPQQPFFQTQQPQQ	16 (6)
9	636	PQQPQQPFFQPQQPIPVQPQ	51 (10)	45	629	PFFQTQQSFPLQPQQPFPQQ	16 (5)
*10	73	LQLQPFPQPQLPYPQPQLPY	49 (11)	46	643	PLQPQQPFPQQPQQPFFQQP	16 (6)
11	412	SQQPQQPFPQPQQQFPQFQQ	34 (19)	47	389	QQPFFQTQQPQQPFFQQPQQ	16 (6)
12	343	QQPQQPFFQPQQPQLPFPQQ	34 (11)	48	350	QQIFPQPQQTFPHQPQQAFP	15 (8)
*13	68	LQLQPFPQPQLPYLQPQPFR	33 (10)	49	65	PFPSQQPYPQPQPFPQPQPF	15 (5)
*14	66	LQLQPFPQPQLPYSQPQPFR	32 (7)	50	349	QQIFPQPQQTFPHQPQQQFP	15 (9)
*15	96	PQPFPPQLPYPQPQSFPPQQ	28 (6)	51	610	PWQQQPLPPQQSFSQQPPFS	15 (11)
16	393	QLPFPQQPQQPFFQPQQPQQ	27 (8)	*52	81	PQPQPFPQPQLPYPQTQPFPP	15 (5)
17	355	QAFPQPQQTFPHQPQQQFPQ	27 (15)	*53	75	MQLQPFPQPQPFPPQLPYPQ	14 (5)
*18	67	LQLQPFPQPQLPYSQPQQFR	26 (6)	54	368	QQFPQPQQPQQPFFQQPQQQ	14 (7)
19	335	QQQQPFFQPQQPQQPFPQPQ	25 (11)	*55	82	PQPQPFPQPQPFPPQLPYPQ	14 (3)
*20	95	PQPFLPQLPYPQPQSFPPQQ	24 (6)	*56	80	LQLQPFPQPQPFPPQLPYPQ	14 (4)
21	396	TQQPQQPFPQQPQQPFFQTQ	23 (9)	57	624	FTQPQQPTPIQPQQPFPQQP	14 (6)
22	609	SCISGLERPWQQQPLPPQQS	23 (18)	58	407	QPQQPFPQSQQPQQPFFQPQ	14 (5)
23	385	QQPFPQPQQPQLPFPQQPQQ	23 (7)	59	337	QQQPFFQPQQPFCQQPQRTI	13 (4)
24	375	PQQPFFPQPQQPQQPFFQPQQ	23 (10)	60	634	PQQLQQPFPLQPQQPFPQQP	13 (3)
25	406	QPQQPFPQLQQPQQPFFQPQ	22 (8)	61	388	QQPYPQQPQQPFFQTQQPQQ	13 (3)
26	625	PIQPQQPFPQQPQQPQQPFP	22 (9)	62	641	FPELQQPIPQQPQQPFPLQP	13 (7)
27	378	QQPQQPFPQQPQQQFPQPQQ	22 (10)	63	399	QQPFPQTQQPQQPFFQLQQP	13 (5)
28	371	PQQQFQPQQPFFQQPQQTY	22 (10)	64	387	QQTFPQQPQLPFPQQPQQPF	13 (4)
29	642	PQQPQQPFFLQPQQPFPQQP	20 (8)	65	628	PFPWQPQQPFPQTQQSFPLQ	12 (4)
30	635	PLQPQQPFPQQPQQPFFQPQ	19 (5)	*66	88	PQPFPPQLPYSQPQPFRPQQ	12 (3)
*31	93	PQPFPPQLPYPQPQPFRPQQ	19 (5)	67	408	QPQQPFPQSKQPQQPFFQPQ	12 (5)
32	377	PQQQFPQPQQPQQPFFQQPQ	19 (9)	*68	77	LQLQPFPQPQPFPPQLPYPQ	11 (4)
33	411	LQQPQQPFPQPQQQLPQPQQ	19 (4)	69	370	PQQQFLQPQQPFFQQPQQPY	11 (5)
34	415	SQQPQQPFPQPQQPQQSFFQ	18 (5)	*70	79	LQLQPFPQPQPFLPQLPYPQ	11 (5)
*35	94	PQPFPPQLPYPQPQPPFSPQQ	18 (3)	71	379	QQPQQQFFQPQQPQQPFPQP	11 (5)
36	329	PSGQVQWPQQQPFFQPQQPF	18 (4)	72	397	PQQPQQPFPQTQQPQQPFPQ	11 (3)

* Indicates homologue of A-gliadin 57-73 with the core sequence PQLP(Y/F)

Table 20. Peptides >10% as bioactive as P04722 QE65 grouped by structure.

Rank	Peptide no. (Pool) Gliadin-subtype	Sequence	IFNg ELISpot response compared to P04722 77-93 QE85: mean (SEM)
		Group 1: Homologues of A-gliadin 57-73	
	P04722 77-93	QLQPFPQPQLPYPQPQP	
1	89 (12) α	PQL...Y.............................LPYP	94 (18)
2	91 (12) α	PQPFPPQL...Y.........................	89 (12)
3	74 (10) α	M.....................................LPY	88 (14)
4	90 (12) α	PQL...Y.............................PFRP	87 (16)
5	76 (10) α	L.....................................PFR	85 (15)
8	631 (81) ω	FPQQPQ.......................F......QS	61 (12)
10	73 (10) α	L.....................................LPY	49 (11)
13	68 (9) α	L.............................L........PFR	33 (10)
14	66 (9) α	L.............................S........PFR	32 (7)
18	67 (9) α	L.............................S........QFR	26 (6)
20	95 (13) α	PQPFL............................FPPQQ	24 (6)
31	93 (12) α	PQPFP............................PFRPQQ	19 (5)
35	94 (12) α	PQPFP.........................PPFSPQQ	18 (3)
40	78 (10) α	L....................R.........................PFR	17 (8)
52	81 (11) α	PQPQPFP.......................T...PFPP	15 (5)
53	75 (10) α	MQLQPFPQPQPF.......................	14 (5)
55	82 (11) α	PQPQPFPQPQPF.......................	14 (3)
56	80 (10) α	LQLQPFPQPQPF.......................	14 (4)
66	88 (11) α	PQPFP...................S.........PFRPQQ	12 (3)
68	77 (10) α	LQLQPFPQPQPFP....................	11 (4)
70	79 (10) α	LQLQPFPQPQPFL....................	11 (5)
		Group 2: Homologues of peptide 626	
		QQPFPQPQQPFP	
6	626(80) ω	PQQPQQP.............................W	72 (23)
7	627(80) ω	..............................WQPQQPFPQ	66 (30)
9	636(81) ω	PQQP.............................L...VQPQ	51 (10)
11	412(53) γ	SQQP.........................Q........PQQ	34 (19)
33	411(53) γ	LQQP.........................Q........PQQ	19 (4)
36	329(42) γ	PSGQVQWPQ.............................	18 (4)
41	390(50) γ	QQTYPQRP..................T.........QQ	17 (9)
59	337(43) γ	Q...............................CQQPQRTI	13 (4)
61	388(50) γ	QQPYPQQP..................T.........QQ	13 (3)
		Group 3: Homologues of peptide 355	
		FPQPQQTFPHQPQQQFP	
17	355(46) γ	QA...Q	27 (15)
42	348(45) γ	QQT.......................................	16 (10)
48	350(45) γ	QQI.................................A......	15 (8)
50	349(45) γ	QQI.......................................	15 (9)
		Group 4: Homologues of Peptide 396	
		QQPFPQQPQQPFP	
21	396(51) γ	TQQP....................................QTQ	23 (9)
27	378(49) γ	QQP....................................QPQQ	22 (10)
28	371(48) γ	PQQQFIQP.............................TY	22 (10)
29	642(82) ω	PQQP..................L....................QQP	20 (8)
30	635(81) ω	PLQP....................................QPQ	19 (5)
44	382(49) γ	...................................QTQQPQQ	16 (6)
45	629(81) ω	PFPQT......S.....L....................QQ	16 (5)
46	643(82) ω	PLQP....................................QQP	16 (6)
60	634(81) ω	PQQL..................L....................QQP	13 (3)
64	387(50) γ	......T.....................L.........QQPQQPF	13 (4)
62	641(82) ω	FPEL.........I.........................LQP	13 (7)

		Group 5: Homologues of Peptide 343 (overlap Groups 2 and 4)	
		QQPFPQPQQPQLPFPQ	
12	343(44) γ	QQP...Q	34 (11)
16	393(51) γ	QLPFPQQP.................................	27 (8)
19	335(43) γ	QQ.....................................Q..........PQ	25 (11)
23	385(50) γ	....QPQQ	23 (7)
24	375(48) γ	P...Q.........PQQ	23 (10)
25	406(52) γ	QP.................L...........Q...........PQ	22 (8)
32	377(49) γ	P.......Q.....................Q..........QPQ	19 (9)
34	415(53) γ	SQQP...........................QS........	18 (5)
37	413(53) γ	SKQP...........................QS........	18 (4)
38	380(49) γ	QPQQP..................................	18 (6)
43	409(53) γ	QP.................L...........Q...L......PQ	16 (2)
47	389(50) γ	.....................T...........Q..........QPQQ	16 (6)
58	407(52) γ	QP..................S...........Q..........PQ	14 (5)
63	399(51) γ	......................T...........Q..........LQQP	13 (5)
67	408(52) γ	QP.................SK.........Q..........PQ	12 (5)
71	379(49) γ	QQP......Q......................Q..........P	11 (5)
72	397(51) γ	PQQP...................T...........Q........	11 (3)
		Group 6: Peptide 625	
		PIQPQQPFPQQP	
26	625(80) ω	..................................QQPQQPFP	22 (9)
57	624(80) ω	FTQPQQPT................................	14 (6)
65	628(80) ω	PF...W.....................TQQSFPLQ	12 (4)
		Group 7: Peptide 618	
39	618(79) ω	PQQSFSYQQQPFPQQPYPQQ	18 (7)

5

Table 21. Bioactivity of individual tTG-deamidated Pools 1-3 peptides in Subject C12:

No.	Sequence	%	No.	Sequence	%
8	AVRWPVPQLQPQNPSQQQPQ	100	23	LQPQNPSQQQPQEQVPLMQQ	26
		85			18
5	MVRVTVPQ………………………		14	……………………EQVPLVQQ	
		82			18
6	AVRVSVPQ………………………		15	…………………H……EQVPLVQQ	
		77			18
3	MVRVPVPQ…………………H……		17	…………………KQVPLVQQ	
		67			13
1	AVRFPVPQ…………………L……		16	…………D…………EQVPLVQQ	
		59			8
2	MVRVPVPQ………………………		13	…………………EQVPLVQQ	
		49			5
9	AVRVPVPQ……L………………		22	………K……………EQVPLVQQ	
		49			3
7	AVRVPVPQ………………………		18	……L…………………EQVPLVQE	
		33			3
10	MVRVPVPQ……L………………		19	……L…………………EQVPLVQE	
4	MVRVPMPQ…………D…………	15	20	P…………………P………GQVPLVQQ	0
12	AVRVPVPQ………K…………	8	21	P…………………P………RQVPLVQQ	0
11	AVRVPVPQP……………P………	0			

Core sequence of epitope is underlined. Predicted deamidated sequence is: LQPENPSQEQPE

98

Table 22: Phylogenetic groupings of wheat (Triticum aestivum) gliadins

	Alpha/beta-gliadins (n=61)		
A1a1	AAA96525, EEWTA, P02863	A1b13	B22364, P04271
A1a2	CAB76963	A2a1	AAB23109, CAA35238, P18573, S10015
A1a3	AAA96276	A2a2	CAB76964
A1a4	CAA26384, S07923	A2b1	P04724, T06500, AAA348282
A1a5	AAA34280	A2b2	D22364
A1a6	P04728	A2b3	P04722, T06498, AAA34276
A1b1	CAB76962	A2b4	C22364
A1b2	CAB76961	A2b5	CAB76956
A1b3	BAA12318	A3a1	AAA34277, CAA26383, P04726, S07361
A1b4	CAB76960	A3a2	1307187B, A27319, S13333
A1b5	CAB76958	A3b1	AAA96522
A1b6	CAB76959	A3b2i	AAA34279, P04727,
A1b7	CAB76955	A3b2ii	CAA26385, S07924
A1b8	AAA96524	A3b3	A22364, AAA34278, AAB23108, C61218, P04725
A1b9	CAA10257	A4a	P04723, AAA34283, T06504
A1b10	AAA96523, T06282	A4b	E22364
A1b11	AAA17741, S52124	A4c	CAB76957
A1b12	AAA34281	A4d	CAB76954
	Gamma-gliadins (n=47)		Gamma-gliadins
GI1a	P08079, AAA34288, PS0094, CAC11079, AAD30556, CAC11057, CAC11065, CAC11056	GI5a	AAK84774, AAK84772
GI1b	CAC11089, CAC11064, CAC11080, CAC11078, AAD30440	GI5b	AAK84773
GI1c	CAC11087	GI5c	AAK84776
GI1d	CAC11088	GI6a	JA0153, P21292, AAA34272, 1507333A
GI1e	CAC11055	GI6b	AAK84777
GI2a	JS0402, P08453, AAA34289	GI6c	1802407A, AAK84775, AAK84780
GI2b	AAF42989, AAK84779, AAK84779	GI7	AAB31090
GI3a	AAK84778	GIIa	AAA34287, P04730, S07398
GI3b	CAB75404	GIIb	1209306A
GI3c	BAA11251	GIIIa	P04729
GI4	EEWTG, P06659, AAA34274	GIIIb	AAA34286
	Omega-gliadins (n=3)		
O1a	AAG17702		
O1b	P02865		
O1c	A59156		

Table 23. Synthetic peptides spanning all known wheat gliadin 12mers

Protein	Position* Sequence	No.	Protein	Position* Sequence	No.
POOL 1			**POOL 43**		
A1A1	20 AVRF PVPQ LQPQ NPSQ QLPQ	1	GI2A 33	QQQL VPQL QQPL SQQP QQTF	331
A1A2	20 MVRV PVPQ LQPQ NPSQ QQPQ	2	GI3A 33	QQQP FPQP HQPF SQQP QQTF	332
A1B1	20 MVRV PVPQ LQPQ NPSQ QHPQ	3	GI4 33	QQQP FLQP HQPF SQQP QQIF	333
A1B2	20 MVRV PMPQ LQPQ DPSQ QQPQ	4	GI5A 33	QQQQ PFPQ PQQP FSQQ PQQI	334
A1B7	20 MVRV TVPQ LQPQ NPSQ QQPQ	5	GI5B 33	QQQQ PFPQ PQQP QQPF PQPQ	335
A1B8	20 AVRV SVPQ LQPQ NPSQ QQPQ	6	GI5C 33	QQQP FRQP QQPF YQQP QHTF	336
A1B8	20 AVRV PVPQ LQPQ NPSQ QQPQ	7	GI6A 33	QQQP FPQP QQPF CQQP QRTI	337
A1B10	20 AVRW PVPQ LQPQ NPSQ QQPQ	8	GI6C 42	QQQP FPQP QQPF CEQP QRTI	338
POOL 2			**POOL 44**		
A2B3	20 AVRV PVPQ LQLQ NPSQ QQPQ	9	GI1A 42	HQPF SQQP QQTF PQPQ QTFP	339
A2B5	20 MVRV PVPQ LQLQ NPSQ QQPQ	10	GI2A 42	QQPL SQQP QQTF PQPQ QTFP	340
A3A1	20 AVRV PVPQ PQPQ NPSQ PQPQ	11	GI4 42	HQPF SQQP QQIF PQPQ QTFP	341
A3B1	20 AVRV PVPQ LQPK NPSQ QQPQ	12	GI5A 42	QQPF SQQP QQIF PQPQ QTFP	342
A1A1	28 LQPQ NPSQ QLPQ EQVP LVQQ	13	GI5B 42	QQPQ PFPQ PQQP PQLP FPQQ	343
A1A2	28 LQPQ NPSQ QQPQ EQVP LVQQ	14	GI5C 42	QQPF YQQP QHTF PQPQ QTCP	344
A1B1	28 LQPQ NPSQ QHPQ EQVP LVQQ	15	GI6A 42	QQPF CQQP QRTI PQPH QTFH	345
A1B2	28 LQPQ DPSQ QQPQ EQVP LVQQ	16	GI6B 42	QQPF CQQP QQTI PQPH QTFH	346
POOL 3			**POOL 45**		
A2B1	28 LQPQ NPSQ QQPQ KQVP LVQQ	17	GI6C 42	QQPF CEQP QRTI PQPH QTFH	347
A2B3	28 LQLQ NPSQ QQPQ EQVP LVQE	18	GI1A 50	QQTF PQPQ QTFP HQPQ QQFP	348
A2B5	28 LQLQ NPSQ QQPQ EQVP LVQE	19	GI4 50	QQIF PQPQ QTFP HQPQ QQFP	349
A3A1	28 PQPQ NPSQ PQPQ GQVP LVQQ	20	GI5A 50	QQIF PQPQ QTFP HQPQ QAFP	350
A3A2	28 PQPQ NPSQ PQPQ RQVP LVQQ	21	GI6A 50	QRTI PQPH QTFH HQPQ QTFP	351
A3B1	28 LQPK NPSQ QQPQ EQVP LVQQ	22	GI5A 58	QTFP HQPQ QAFP QPQQ TFPH	352
A4A	28 LQPQ NPSQ QQPQ EQVP LMQQ	23	GI6A 58	QTFH HQPQ QTFP QPQQ TYPH	353
A1A1	36 QLPQ EQVP LVQQ QQFL GQQQ	24	GI6C 58	QTFH HQPQ QTFP QPEQ TYPH	354
POOL 4			**POOL 46**		
A1B1	36 QHPQ EQVP LVQQ QQFL GQQQ	25	GI5A 66	QAFP QPQQ TFPH QPQQ QFPQ	355
A1B2	36 QQPQ EQVP LVQQ QQFL GQQQ	26	GI5C 66	QHTF PQPQ QTCP HQPQ QQFP	356
A1B12	36 QQPQ EQVP LVQQ QQFL GQQQ	27	GI6A 66	QTFP QPQQ TYPH QPQQ QFPQ	357
A2A1	36 QQPQ EQVP LVQQ QQFP GQQQ	28	GI6C 66	QTFP QPEQ TYPH QPQQ QFPQ	358
A2B1	36 QQPQ KQVP LVQQ QQFP GQQQ	29	GI1A 73	QTFP HQPQ QQFP QPQQ PQQQ	359
A2B3	36 QQPQ EQVP LVQE QQFQ GQQQ	30	GI2A 73	QTFP HQPQ QQVP QPQQ PQQP	360
A3A1	36 PQPQ GQVP LVQQ QQFP GQQQ	31	GI3A 73	QTFP HQPQ QQFS QPQQ PQQQ	361
A3A2	36 PQPQ RQVP LVQQ QQFP GQQQ	32	GI5C 73	QTCP HQPQ QQFP QPQQ PQQP	362
POOL 5			**POOL 47**		
A4A	36 QQPQ EQVP LMQQ QQQF PGQQ	33	GI6A 73	QTYP HQPQ QQFP QTQQ PQQP	363
A1A1	44 LVQQ QQFL GQQQ PFPP QQPY	34	GI1A 81	QQFP QPQQ PQQQ FLQP QQPF	364
A1B1	44 LVQQ QQFL GQQQ SFPP QQPY	35	GI2A 81	QQVP QPQQ PQQP FLQP QQPF	365
A1B12	44 LVQQ QQFL GQQQ PFPP QQPY	36	GI3A 81	QQFS QPQQ PQQQ FIQP QQPF	366
A2A1	44 LVQQ QQFP GQQQ PFPP QQPY	37	GI4 81	QQFP QPQQ PQQQ FLQP RQPF	367
A2B3	44 LVQE QQFQ GQQQ PFPP QQPY	38	GI5A 81	QQFP QPQQ PQQP FPQQ PQQQ	368
A3A1	44 LVQQ QQFP GQQQ QFPP QQPY	39	GI6A 81	QQFP QTQQ PQQP FPQP QQTF	369
A4A	44 LMQQ QQQF PGQQ EQFP PQQP	40	GI1A 89	PQQQ FLQP QQPF PQQP QQPY	370
POOL 6			**POOL 48**		
A4D	44 LMQQ QQQF PGQQ ERFP PQQP	41	GI3A 89	PQQQ FIQP QQPF PQQP QQTY	371
A1A1	53 GQQQ PFPP QQPY PQPQ PFPS	42	GI3B 89	PQQQ FIQP QQPQ QTYP QRPQ	372
A1A3	53 GQQQ PFPP QQPY PQPQ FPSQ	43	GI4 89	PQQQ FLQP RQPF PQQP QQPY	373
A1B1	53 GQQQ SFPP QQPY PQPQ PFPS	44	GI5A 89	PQQP FPQQ PQQQ FPQP QQPQ	374
A2B1	53 GQQQ PFPP QQPY PQQQ PFPS	45	GI5C 89	PQQP FPQP QQPQ QPFP QPQQ	375
A3A1	53 GQQQ QFPP QQPY PQPQ PFPS	46	GI6A 89	PQQP FPQP QQTF PQQP QLPF	376
A4A	53 GQQE QFPP QQPY PHQQ PFPS	47	**POOL 49**		
A4D	53 GQQE RFPP QQPY PHQQ PFPS	48	GI5A 97	PQQQ FPQP QQPQ QPFP QQPQ	377
POOL 7			GI5A 105	QQPQ PFPQ QQPQ QQFP QPQQ	378
A1A1	61 QQPY PQPQ PFPS QLPY LQLQ	49	GI5A 113	QQPQ QQFP QPQQ PQQP FPQP	379
A1A3	61 QQPY PQPQ FPSQ LPYL QLQP	50	GI5A 121	QPQQ PQQP FPQP QQPQ LPFP	380
A1B1	61 QQPY PQPQ PFPS QQPY LQLQ	51	GI1A 126	QQPF PQQP QQPY PQQP QQPF	381
A2B1	61 QQPY PQQQ PFPS QQPY MQLQ	52	GI2A 126	QQPF PQQP QQPF PQTQ QPQQ	382
A4A	61 QQPY PHQQ PFPS QQPY PQPQ	53	GI3A 126	QQPF PQQP QQTY PQRP QQPF	383
A1A1	69 PFPS QLPY LQLQ PFPQ PQLP	54	GI4 126	RQPF PQQP QQPY PQQP QQPF	384
A1B1	69 PFPS QQPY LQLQ PFPQ PQLP	55	**POOL 50**		
A1B10	69 PFPS QQPY LQLQ PFSQ PQLP	56	GI5A 126	QQPF PQPQ QPQL PFPQ QPQQ	385
POOL 8			GI5C 126	QQPF PQPQ QAQL PFPQ QPQQ	386
A1B11	69 PFPS QQPY LQLQ PFLQ PQLP	57	GI6A 126	QQTF PQQP QLPF PQQP QQPF	387
A1B12	69 PFPS QQPY LQLQ PFLQ PQPF	58	GI1A 134	QQPY PQQP QQPF PQTQ QPQQ	388
A2A1	69 PFPS QQPY LQLQ PFPQ PQLP	59	GI2A 134	QQPF PQTQ QPQQ PFPQ QPQQ	389
A2B1	69 PFPS QQPY MQLQ PFPQ PQLP	60	GI3A 134	QQTY PQRP QQPF PQTQ QPQQ	390
A2B2	69 PFPS QQPY MQLQ PFPQ PQPF	61	GI5A 134	QPQL PFPQ QPQQ QPQQ PFPQ	391

A2B4 69 PFPS QQPY LQLQ PFPQ PQPF
A2B5 69 PFPS QQPY LQLQ PFPR PQLP
A4A 69 PFPS QQPY PQPQ PFPP QLPY
POOL 9
A4B 69 PFPS QQPY PQPQ PFPQ PQPF
A1A1 77 LQLQ PFPQ PQLP YSQP QPFR
A1A4 77 LQLQ PFPQ PQLP YSQP QQFR
A1B1 77 LQLQ PFPQ PQLP YLQP QPFR
A1B4 77 LQLQ PFPQ PQLS YSQP QPFR
A1B10 77 LQLQ PFSQ PQLP YSQP QPFR
A1B11 77 LQLQ PFLQ PQLP YSQP QPFR
A1B12 77 LQLQ PFLQ PQPF PPQL PYSQ
POOL 10
A2A1 77 LQLQ PFPQ PQLP YPQP QLPY
A2B1 77 MQLQ PFPQ PQLP YPQP QLPY
A2B2 77 MQLQ PFPQ PQPF PPQL PYPQ
A2B3 77 LQLQ PFPQ PQLP YPQP QPFR
A2B4 77 LQLQ PFPQ PQPF PPQL PYPQ
A2B5 77 LQLQ PFPR PQLP YPQP QPFR
A3B1 77 LQLQ PFPQ PQPF LPQL PYPQ
A3B3 77 LQLQ PFPQ PQPF PPQL PYPQ
POOL 11
A4A 77 PQPQ PFPP QLPY PQTQ PFPP
A4B 77 PQPQ PFPQ PQPF PPQL PYPQ
A1A1 85 PQLP YSQP QPFR PQQP YPQP
A1A6 85 PQLP YSQP QPFR PQQP YPQP
A1B1 85 PQLP YLQP QPFR PQQP YPQP
A1B4 85 PQLS YSQP QPFR PQQP YPQP
A1B6 85 PQLS YSQP QPFR PQQL YPQP
A1B12 85 PQPF PPQL PYSQ PQPF RPQQ
POOL 12
A2A1 85 PQLP YPQP QLPY PQPQ LPYP
A2B1 85 PQLP YPQP QLPY PQPQ PFRP
A2B2 85 PQPF PPQL PYPQ PQLP YPQP
A2B3 85 PQLP YPQP QPFR PQQP YPQP
A2B4 85 PQPF PPQL PYPQ PQPF RPQQ
A3A1 85 PQPF PPQL PYPQ PPPF SPQQ
POOL 13
A3B1 85 PQPF LPQL PYPQ PQSF PPQQ
A3B3 85 PQPF PPQL PYPQ PQSF PPQQ
A4A 85 QLPY PQTQ PFPP QQPY PQPQ
A4B 85 PQPF PPQL PYPQ TQPF PPQQ
A2A1 106 LPYP QPQP FRPQ QPYP QSQP
A2B1 106 LPYP QPQP FRPQ QPSYP QPQP
A3A1 106 LPYP QPPP FSPQ QPYP QPQP
A3B1 106 LPQL PYPQ PQSF PPQQ PYPQ
POOL 14
A4A 106 PPQL PYPQ TQPF PPQQ PYPQ
A1A1 112 QPFR PQQP YPQP QPQY SQPQ
A1B6 112 QPFR PQQL YPQP QPQY SQPQ
A2A1 112 QPFR PQQP YPQS QPQY SQPQ
A2B1 112 QPFR PQQS YPQP QPQY SQPQ
A3A1 112 PPFS PQQP YPQP QPQY PQPQ
A3B1 112 QSFP PQQP YPQQ RPKY LQPQ
A3B2 112 QSFP PQQP YPQQ RPMY LQPQ
POOL 15
A3B3 112 QSFP PQQP YPQQ QPQY LQPQ
A4A 112 QPFP PQQP YPQP QPQY PQPQ
A1A1 120 YPQP QPQY SQPQ QPIS QQQQ
A1B3 120 YPQP QPQY SQPQ EPIS QQQQ
A2A1 120 YPQS QPQY SQPQ QPIS QQQQ
A3A1 120 YPQP QPQY PQPQ QPIS QQQA
A3B1 120 YPQQ RPKY LQPQ QPIS QQQA
A3B2 120 YPQQ RPMY LQPQ QPIS QQQA
POOL 16
A3B3 120 YPQQ QPQY LQPQ QPIS QQQA
A1A1 128 SQPQ QPIS QQQQ QQQQ QQQQ
A1B3 128 SQPQ EPIS QQQQ QQQQ QQQI
A3A1 128 PQPQ QPIS QQQA QQQQ QQQQ
A1A1 138 QQQQ QQQQ QQQQ QQQQ ILQQ
A1A6 138 QQQQ QQQQ QQQQ QEQQ ILQQ
A1B11 138 QQQQ QQQQ QQQQ QQQQ IIQQ

62	GI5C 134 QAQL PFPQ QPQQ PLPQ PQQP	392
63	POOL 51	
64	GI6A 134 QLPF PQQP QQPF PQPQ QPQQ	393
	GI2A 142 QPQQ PFPQ QPQQ PFPQ TQQP	394
65	GI2A 150 QPQQ PFPQ TQQP QQPF PQQP	395
66	GI2A 158 TQQP QQPF PQQP QQPF PQTQ	396
67	GI2A 166 PQQP QQPF PQTQ QPQQ PFPQ	397
68	GI1A 170 QQPF PQTQ QPQQ LFPQ SQQP	398
69	GI2A 170 QQPF PQTQ QPQQ PFPQ LQQP	399
70	GI3A 170 QQPF PQTQ QPQQ PFPQ SQQP	400
71	POOL 52	
72	GI4 170 QQPF PQTQ QPQQ PFPQ SKQP	401
	GI5A 170 QQPF PQPQ QPQQ PFPQ LQQP	402
73	GI5C 170 QQPL PQPQ QPQQ PFPQ SQQP	403
74	GI6A 170 QQPF PQPQ QPQQ PFPQ SQQP	404
75	GI1A 178 QPQQ LFPQ SQQP QQQF SQPQ	405
76	GI2A 178 QPQQ PFPQ LQQP QQPF PQPQ	406
77	GI3A 178 QPQQ PFPQ SQQP QQPF PQPQ	407
78	GI4 178 QPQQ PFPQ SKQP QQPF PQPQ	408
79	POOL 53	
80	GI5A 178 QPQQ PFPQ LQQP QQPL PQPQ	409
	GI1A 186 SQQP QQQF SQPQ QQFP QPQQ	410
81	GI2A 186 LQQP QQPF PQPQ QQLP QPQQ	411
82	GI3A 186 SQQP QQPF PQPQ QQFP QPQQ	412
83	GI4 186 SKQP QQPF PQPQ QPQQ SFPQ	413
84	GI5A 186 LQQP QQPL PQPQ QPQQ PFPQ	414
85	GI5C 186 SQQP QQPF PQPQ QPQQ SFPQ	415
86	GI1A 194 SQPQ QQFP QPQQ PQQS FPQQ	416
87	POOL 54	
88	GI2A 194 PQPQ QQLP QPQQ PQQS FPQQ	417
	GI3A 194 PQPQ QQFP QPQQ PQQS FPQQ	418
89	GI4 194 PQPQ QPQQ SFPQ QQPS LIQQ	419
90	GI5A 194 PQPQ QPQQ PFPQ QQQP LIQP	420
91	GI5C 194 PQPQ QPQQ SFPQ QQQP LIQP	421
92	GI1A 202 QPQQ PQQS FPQQ QPPF IQPS	422
93	GI2A 202 QPQQ PQQS FPQQ QRPF IQPS	423
94	GI3A 202 QPQQ PQQS FPQQ QPSL IQQS	424
	POOL 55	
95	GI1A 210 FPQQ QPPF IQPS LQQQ VNPC	425
96	GI2A 210 FPQQ QRPF IQPS LQQQ LNPC	426
97	GI3A 210 FPQQ QPSL IQQS LQQQ LNPC	427
98	GI5A 210 FPQQ QQPL IQPY LQQQ MNPC	428
99	GI6A 210 FPQQ QQPA IQSF LQQQ MNPC	429
100	GI1A 218 IQPS LQQQ VNPC KNFL LQQC	430
101	GI2A 218 IQPS LQQQ LNPC KNIL LQQS	431
102	GI3A 218 IQQS LQQQ LNPC KNFL LQQC	432
	POOL 56	
103	GI5A 218 IQPY LQQQ MNPC KNYL LQQC	433
104	GI6A 218 IQSF LQQQ MNPC KNFL LQQC	434
105	GI1A 226 VNPC KNFL LQQC KPVS LVSS	435
106	GI2A 226 LNPC KNIL LQQS KPAS LVSS	436
107	GI3A 226 LNPC KNFL LQQC KPVS LVSS	437
108	GI5A 226 MNPC KNYL LQQC NPVS LVSS	438
109	GI6A 226 MNPC KNFL LQQC NHVS LVSS	439
110	GI1A 234 LQQC KPVS LVSS LWSM IWPQ	440
	POOL 57	
111	GI2A 234 LQQS KPAS LVSS LWSI IWPQ	441
112	GI3A 234 LQQC KPVS LVSS LWSM ILPR	442
113	GI5A 234 LQQC NPVS LVSS LVSM ILPR	443
114	GI6A 234 LQQC NHVS LVSS LVSI ILPR	444
115	GI1A 242 LVSS LWSM IWPQ SDCQ VMRQ	445
116	GI2A 242 LVSS LWSI IWPQ SDCQ VMRQ	446
117	GI3A 242 LVSS LWSM ILPR SDCQ VMRQ	447
118	GI4 242 LVSS LWSI ILPP SDCQ VMRQ	448
	POOL 58	
119	GI5A 242 LVSS LVSM ILPR SDCK VMRQ	449
120	GI5C 242 LVSS LVSM ILPR SDCQ VMQQ	450
121	GI6A 242 LVSS LVSI ILPR SDCQ VMQQ	451
122	GI1A 250 IWPQ SDCQ VMRQ QCCQ QLAQ	452
123	GI3A 250 ILPR SDCQ VMRQ QCCQ QLAQ	453
124	GI4 250 ILPP SDCQ VMRQ QCCQ QLAQ	454
125	GI5A 250 ILPR SDCK VMRQ QCCQ QLAR	455

A2A1 138 QQQQ QQQQ QQKQ QQQQ QQQI
POOL 17
A4B 139 AQQQ QQQQ QQQQ QQQQ TLQQ
A1A1 146 QQQQ QQQQ ILQQ ILQQ QLIP
A1A6 146 QQQQ QEQQ ILQQ ILQQ QLIP
A1B6 146 QQQQ QEQQ ILQQ MLQQ QLIP
A1B10 146 QQQQ QEQQ ILQQ ILQQ QLTP
A1B11 146 QQQQ QQQQ IIQQ ILQQ QLIP
A2A1 146 QQKQ QQQQ QQQI LQQI LQQQ
A3A2 146 QQQQ QQQQ ILPQ ILQQ QLIP
POOL 18
A4A 146 QQQQ QQQQ TLQQ ILQQ QLIP
A1A1 163 ILQQ ILQQ QLIP CMDV VLQQ
A1B6 163 ILQQ MLQQ QLIP CMDV VLQQ
A1B10 163 ILQQ ILQQ QLTP CMDV VLQQ
A2B1 163 ILQQ ILQQ QLIP CRDV VLQQ
A3A2 163 ILPQ ILQQ QLIP CRDV VLQQ
A4A 163 TLQQ ILQQ QLIP CRDV VLQQ
A1A1 171 QLIP CMDV VLQQ HNIA HGRS
POOL 19
A1A3 171 QLIP CMDV VLQQ HNKA HGRS
A1B2 171 QLIP CMDV VLQQ HNLA HGRS
A1B7 171 QLIP CMDV VLQQ HNIV HGRS
A1B10 171 QLTP CMDV VLQQ HNIA RGRS
A1B11 171 QLIP CMDV VLQQ HNIV HGKS
A2A1 171 QLIP CRDV VLQQ HSIA YGSS
A2B1 171 QLIP CRDV VLQQ HSIA HGSS
A2B3 171 QLIP CRDV VLQQ HNIA HGSS
POOL 20
A3A1 171 QLIP CRDV VLQQ HNIA HARS
A3B1 171 QLIP CRDV VLQQ HNIA HASS
A1A1 179 VLQQ HNIA HGRS QVLQ QSTY
A1A3 179 VLQQ HNKA HGRS QVLQ QSTY
A1B2 179 VLQQ HNLA HGRS QVLQ QSTY
A1B7 179 VLQQ HNIV HGRS QVLQ QSTY
A1B10 179 VLQQ HNIA RGRS QVLQ QSTY
A1B11 179 VLQQ HNIV HGKS QVLQ QSTY
POOL 21
A2A1 179 VLQQ HSIA YGSS QVLQ QSTY
A2B1 179 VLQQ HSIA HGSS QVLQ QSTY
A2B3 179 VLQQ HNIA HGSS QVLQ ESTY
A3A1 179 VLQQ HNIA HARS QVLQ QSTY
A3B1 179 VLQQ HNIA HASS QVLQ QSTY
A4A 179 VLQQ HNIA HASS QVLQ QSSY
A1A1 187 HGRS QVLQ QSTY QLLQ ELCC
A1A3 187 HGRS QVLQ QSTY QLLR ELCC
POOL 22
A1B8 187 HGRS QVLQ QSTY QLLR ELCC
A1B11 187 HGKS QVLQ QSTY QLLQ ELCC
A2A1 187 YGSS QVLQ QSTY QLVQ QLCC
A2B1 187 HGSS QVLQ QSTY QLVQ QFCC
A2B3 187 HGSS QVLQ ESTY QLVQ QLCC
A3A1 187 HARS QVLQ QSTY QPLQ QLCC
A3B1 187 HASS QVLQ QSTY QLLQ QLCC
A4A 187 HASS QVLQ QSSY QQLQ QLCC
POOL 23
A1A1 195 QSTY QLLQ ELCC QHLW QIPE
A1A3 195 QSTY QLLR ELCC QHLW QIPE
A1B8 195 QSTY QLLR ELCC QHLW QIPE
A2A1 195 QSTY QLVQ QLCC QQLW QIPE
A2B1 195 QSTY QLVQ QFCC QQLW QIPE
A3A1 195 QSTY QPLQ QLCC QQLW QIPE
A3B1 195 QSTY QLLQ QLCC QQLL QIPE
A4A 195 QSSY QQLQ QLCC QQLF QIPE
POOL 24
A1A1 203 ELCC QHLW QIPE QSQC QAIH
A1B6 203 ELCC QHLW QILE QSQC QAIH
A1B10 203 ELCC QHLW QIPE KLQC QAIH
A2A1 203 QLCC QQLW QIPE QSRC QAIH
A2B1 203 QFCC QQLW QIPE QSRC QAIH
A3B1 203 QLCC QQLL QIPE QSRC QAIH
POOL 25

126 GI5C 250 ILPR SDCQ VMQQ QCCQ QLAQ 456
POOL 59
127 GI1A 258 VMRQ QCCQ QLAQ IPQQ LQCA 457
128 GI5A 258 VMRQ QCCQ QLAR IPQQ LQCA 458
129 GI5C 258 VMQQ QCCQ QLAQ IPRQ LQCA 459
130 GI6A 258 VMQQ QCCQ QLAQ IPQQ LQCA 460
131 GI1A 266 QLAQ IPQQ LQCA AIHT IIHS 461
132 GI1B 266 QLAQ IPQQ LQCA AIHT VIHS 462
133 GI2A 266 QLAQ IPQQ LQCA AIHS VVHS 463
134 GI3A 266 QLAQ IPQQ LQCA AIHS IVHS 464
POOL 60
135 GI5A 266 QLAR IPQQ LQCA AIHG IVHS 465
136 GI5C 266 QLAQ IPRQ LQCA AIHS VVHS 466
137 GI6A 266 QLAQ IPQQ LQCA AIHS VAHS 467
138 GI1A 274 LQCA AIHT IIHS IIMQ QEQQ 468
139 GI1B 274 LQCA AIHT VIHS IIMQ QEQQ 469
140 GI2A 274 LQCA AIHS VVHS IIMQ QQQQ 470
141 **POOL 61**
142 GI3A 274 LQCA AIHS IVHS IIMQ QEQQ 471
    GI4 274 LQCA AIHS VVHS IIMQ QEQQ 472
143 GI5A 274 LQCA AIHG IVHS IIMQ QEQQ 473
144 GI6A 274 LQCA AIHS VAHS IIMQ QEQQ 474
145 GI1A 282 IIHS IIMQ QEQQ EQQQ GMHI 475
146 GI1B 282 VIHS IIMQ QEQQ QGMH ILLP 476
147 GI2A 282 VVHS IIMQ QQQQ QQQQ QGID 477
148 GI3A 282 IVHS IIMQ QEQQ EQRQ GVQI 478
149 **POOL 62**
150 GI4 282 VVHS IIMQ QEQQ EQLQ GVQI 479
    GI5A 282 IVHS IIMQ QEQQ QQQQ QQQQ 480
151 GI5C 282 VVHS IVMQ QEQQ QGIQ ILRP 481
152 GI6A 282 VAHS IIMQ QEQQ QGVP ILRP 482
153 GI1A 290 QEQQ EQQQ GMHI LLPL YQQQ 483
154 GI2A 290 QQQQ QQQQ QGID IFLP LSQH 484
155 GI2B 290 QQQQ QQQQ QGMH IFLP LSQQ 485
156 GI3A 290 QEQQ EQRQ GVQI LVPL SQQQ 486
157 **POOL 63**
158 GI4 290 QEQQ EQLQ GVQI LVPL SQQQ 487
    GI5A 290 QEQQ QQQQ QQQG IQIM 488
159 GI5C 290 QEQQ QGIQ ILRP LFQL VQGQ 489
160 GI6A 290 QEQQ QGVP ILRP LFQL AQGL 490
161 GI5A 298 QQQQ QQQG IQIM RPLF QLVQ 491
162 GI1A 305 GMHI LLPL YQQQ QVGQ GTLV 492
163 GI2A 305 GIDI FLPL SQHE QVGQ GSLV 493
164 GI2B 305 GMHI FLPL SQQQ QVGQ GSLV 494
165 **POOL 64**
166 GI3A 305 GVQI LVPL SQQQ QVGQ GTLV 495
    GI4 305 GVQI LVPL SQQQ QVGQ GILV 496
167 GI5A 305 GIQI MRPL FQLV QGQG IIQP 497
168 GI5C 305 GIQI LRPL FQLV QGQG IIQP 498
169 GI6A 305 GVPI LRPL FQLA QGLG IIQP 499
170 GI1A 313 YQQQ QVGQ GTLV QGQG IIQP 500
171 GI2A 313 SQHE QVGQ GSLV QGQG IIQP 501
172 GI2B 313 SQQQ QVGQ GSLV QGQG IIQP 502
173 **POOL 65**
174 GI3A 313 SQQQ QVGQ GTLV QGQG IIQP 503
    GI4 313 SQQQ QVGQ GILV QGQG IIQP 504
175 GI1A 321 GTLV QGQG IIQP QQPA QLEA 505
176 GI2A 321 GSLV QGQG IIQP QQPA QLEA 506
177 GI5A 321 FQLV QGQG IIQP QQPA QLEV 507
178 GI6A 321 FQLA QGLG IIQP QQPA QLEG 508
179 GI1A 329 IIQP QQPA QLEA IRSL VLQT 509
180 GI3A 329 IIQP QQPA QLEV IRSL VLQT 510
181 **POOL 66**
182 GI3C 329 IIQP QQPA QLEV IRSS VLQT 511
    GI5C 329 IIQP QQPA QYEV IRSL VLRT 512
183 GI6A 329 IIQP QQPA QLEG IRSL VLKT 513
184 GI1A 337 QLEA IRSL VLQT LPTM CNVY 514
185 GI2A 337 QLEA IRSL VLQT LPSM CNVY 515
186 GI3A 337 QLEV IRSL VLQT LATM CNVY 516
187 GI3C 337 QLEV IRSS VLQT LATM CNVY 517
188 GI5A 337 QLEV IRSL VLGT LPTM CNVF 518
    POOL 67

A3B3 203 GLCC QQLL QIPE QSQC QAIH
A4A 203 QLCC QQLF QIPE QSRC QAIH
A1A1 211 QIPE QSQC QAIH NVVH AIIL
A1B3 211 QIPE QSQC QAIQ NVVH AIIL
A1B6 211 QILE QSQC QAIH NVVH AIIL
A1B9 211 QIPE QSQC QAIH KVVH AIIL
A1B10 211 QIPE KLQC QAIH NVVH AIIL
A2A1 211 QIPE QSRC QAIH NVVH AIIL
POOL 26
A3B3 211 QIPE QSQC QAIH NVAH AIIM
A4A 211 QIPE QSRC QAIH NVVH AIIL
A1A1 219 QAIH NVVH AIIL HQQQ KQQQ
A1A6 219 QAIH NVVH AIIL HQQQ QKQQ
A1B3 219 QAIQ NVVH AIIL HQQQ KQQQ
A1B9 219 QAIH KVVH AIIL HQQQ KQQQ
A1B13 219 QAIH NVVH AIIL HQQQ QQQQ
A2B3 219 QAIH NVVH AIIL HQQH HHHQ
POOL 27
A3A1 219 QAIH NVVH AIIL HQQQ RQQQ
A3B1 219 QAIH NVVH AIIM HQQE QQQQ
A3B3 219 QAIH NVAH AIIM HQQQ QQQQ
A4A 219 QAIH NVVH AIIL HHHQ QQQQ
A1A1 227 AIIL HQQQ KQQQ QPSS QVSF
A1A6 227 AIIL HQQQ QKQQ QQPS SQFS
A1B2 227 AIIL HQQQ KQQQ QLSS QVSF
A1B10 227 AIIL HQQQ KQQQ PSSQ VSFQ
POOL 28
A1B13 227 AIIL HQQQ QQQQ EQKQ QLQQ
A2A1 227 AIIL HQQQ QQQQ QQQQ QPLS
A2B3 227 AIIL HQQH HHHQ QQQQ QQQQ
A2B4 227 AIIL HQQH HHHQ EQKQ QLQQ
A3A1 227 AIIL HQQQ RQQQ PSSQ VSLQ
A3B1 227 AIIM HQQE QQQQ LQQQ QQQQ
A3B3 227 AIIM HQQQ QQQQ EQKQ QLQQ
A4A 227 AIIL HHHQ QQQQ QPSS QVSY
POOL 29
A1A1 235 KQQQ QPSS QVSF QQPL QQYP
A1A6 235 KQQQ QPSS QFSF QQPL QQYP
A1B2 235 KQQQ QLSS QVSF QQPQ QQYP
A1B10 235 KQQQ PSSQ VSFQ QPQQ QYPL
A1B13 235 QQQQ EQKQ QLQQ QQQQ QQQL
A2B4 235 HHHQ EQKQ QLQQ QQQQ QQQL
A3A1 235 RQQQ PSSQ VSLQ QPQQ QYPS
A3B1 235 QQQQ LQQQ QQQQ LQQQ QQQQ
POOL 30
A4A 235 QQQQ QPSS QVSY QQPQ EQYP
A1B13 243 QLQQ QQQQ QQQL QQQQ QKQQ
A1B13 251 QQQL QQQQ QQQQ QKQQ QQPS SQVS
A2A1 260 QQQQ QQQQ QPLS QVSF QQPQ
A2B1 260 QQQQ QQQQ QPLS QVCF QQSQ
A2B3 260 HHHQ QQQQ QQQQ QPLS QVSF
A3B1 260 QQQQ QQQQ QPSS QVSF QQPQ
A2A1 289 QPLS QVSF QQPQ QQYP SGQG
POOL 31
A2B1 289 QPLS QVCF QQSQ QQYP SGQG
A3B1 289 QPSS QVSF QQPQ QQYP SSQV
A1A1 293 QVSF QQPL QQYP LGQG SFRP
A1A6 293 QFSF QQPL QQYP LGQG SFRP
A1B2 293 QVSF QQPQ QQYP LGQG SFRP
A2A1 293 QVSF QQPQ QQYP SGQG SFQP
A2B1 293 QVCF QQSQ QQYP SGQG SFQP
A2B3 293 QVSF QQPQ QQYP SGQG FFQP
POOL 32
A2B5 293 QVSF QQPQ QQYP SGQG FFQP
A3A1 293 QVSL QQPQ QQYP SGQG FFQP
A3B1 293 QVSF QQPQ QQYP SSQV SFQP
A3B2 293 QVSF QQPQ QQYP SSQG SFQP
A4A 293 QVSY QQPQ EQYP SGQV SFQS
A1A1 301 QQYP LGQG SFRP SQQN PQAQ
A1B2 301 QQYP LGQG SFRP SQQN SQAQ
A2A1 301 QQYP SGQG SFQP SQQN PQAQ
POOL 33

189	GI5C 337 QYEV IRSL VLRT LPNM CNVY	519
190	GI6A 337 QLEG IRSL VLKT LPTM CNVY	520
191	GI1A 345 VLQT LPTM CNVY VPPE CSII	521
192	GI2A 345 VLQT LPSM CNVY VPPE CSIM	522
193	GI3A 345 VLQT LATM CNVY VPPY CSTI	523
194	GI5A 345 VLGT LPTM CNVF VPPE CSTT	524
195	GI5C 345 VLRT LPNM CNVY VRPD CSTI	525
196	GI6A 345 VLKT LPTM CNVY VPPD CSTI	526
	POOL 68	
197	GI1A 353 CNVY VPPE CSII KAPF SSVV	527
198	GI2A 353 CNVY VPPE CSIM RAPF ASIV	528
199	GI3A 353 CNVY VPPY CSTI RAPF ASIV	529
200	GI5A 353 CNVF VPPE CSTT KAPF ASIV	530
201	GI5C 353 CNVY VRPD CSTI NAPF ASIV	531
202	GI6A 353 CNVY VPPD CSTI NVPY ANID	532
203	GI1A 361 CSII KAPF SSVV AGIG GQ	533
204	GI2A 361 CSIM RAPF ASIV AGIG GQ	534
	POOL 69	
205	GI3A 361 CSTI RAPF ASIV AGIG GQYR	535
206	GI4 361 CSTI RAPF ASIV ASIG GQ	536
207	GI5A 361 CSTT KAPF ASIV ADIG GQ	537
208	GI5C 361 CSTI NAPF ASIV AGIS GQ	538
209	GI6A 361 CSTI NVPY ANID AGIG GQ	539
210	GII 1 PQQP FPLQ PQQS FLWQ SQQP	540
211	GII 9 PQQS FLWQ SQQP FLQQ PQQP	541
212	GII 17 SQQP FLQQ PQQP SPQP QQVV	542
	POOL 70	
213	GII 25 PQQP SPQP QQVV QIIS PATP	543
214	GII 33 QQVV QIIS PATP TTIP SAGK	544
215	GII 41 PATP TTIP SAGK PTSA PFPQ	545
216	GII 49 SAGK PTSA PFPQ QQQQ HQQL	546
217	GII 57 PFPQ QQQQ HQQL AQQQ IPVV	547
218	GII 65 HQQL AQQQ IPVV QPSI LQQL	548
219	GII 73 IPVV QPSI LQQL NPCK VFLQ	549
220	GII 81 LQQL NPCK VFLQ QQCS PVAM	550
	POOL 71	
221	GII 89 VFLQ QQCS PVAM PQRL ARSQ	551
222	GII 97 PVAM PQRL ARSQ MLQQ SSCH	552
223	GII 105 ARSQ MLQQ SSCH VMQQ QCCQ	553
224	GII 113 SSCH VMQQ QCCQ QLPQ IPQQ	554
225	GII 121 QCCQ QLPQ IPQQ SRYQ AIRA	555
226	GII 127B PQIP QQSR YEAI RAII YSII	556
227	GII 129 IPQQ SRYQ AIRA IIYS IILQ	557
228	GII 137 AIRA IIYS IILQ EQQQ VQGS	558
	POOL 72	
229	GII 145 IILQ EQQQ VQGS IQSQ QQQP	559
230	GII 153 VQGS IQSQ QQQP QQLG QCVS	560
231	GII 161 QQQP QQLG QCVS QPQQ QSQQ	561
232	GII 169 QCVS QPQQ QSQQ QLGQ QPQQ	562
233	GII 177 QSQQ QLGQ QPQQ QQLA QGTF	563
234	GII 185 QPQQ QQLA QGTF LQPH QIAQ	564
235	**POOL 73**	
236	GII 193 QGTF LQPH QIAQ LEVM TSIA	565
	GII 201 QIAQ LEVM TSIA LRIL PTMC	566
237	GII 209 TSIA LRIL PTMC SVNV PLYR	567
238	GII 217 PTMC SVNV PLYR TTTS VPFG	568
239	GII 225 PLYR TTTS VPFG VGTG VGAY	569
240	GIII 1A 1 TITR TFPI PTIS SNNN HHFR	570
241	GIII 1A 9 PTIS SNNN HHFR SNSN HHFH	571
242	GIII 1A 17 HHFR SNSN HHFH SNNN QFYR	572
243	**POOL 74**	
244	GIII 1A 25 HHFH SNNN QFYR NNNS PGHN	573
	GIII 1A 33 QFYR NNNS PGHN NPLN NNNS	574
245	GIII 1A 41 PGHN NPLN NNNS PNNN SPSN	575
246	GIII 1A 49 NNNS PNNN SPSN HHNN SPNN	576
247	GIII 1A 57 SPSN HHNN SPNN NFQY HTHP	577
248	GIII 1A 65 SPNN NFQY HTHP SNHK NLPH	578
249	GIII 1A 73 HTHP SNHK NLPH TNNI QQQQ	579
250	GIII 1A 81 NLPH TNNI QQQQ PPFS QQQQ	580
251	**POOL 75**	
252	GIII 1A 89 QQQQ PPFS QQQQ PPFS QQQQ	581
	GIII 1A 97 QQQQ PPFS QQQQ PVLP QQSP	582

A2B3 301 QQYP SGQG FFQP SQQN PQAQ
A2B5 301 QQYP SGQG FFQP FQQN PQAQ
A3A1 301 QQYP SGQG FFQP SQQN PQAQ
A3B1 301 QQYP SSQV SFQP SQLN PQAQ
A3B2 301 QQYP SSQG SFQP SQQN PQAQ
A4A 301 EQYP SGQV SFQS SQQN PQAQ
A1B1 309 SFRP SQQN PLAQ GSVQ PQQL
A1A1 309 SFRP SQQN PQAQ GSVQ PQQL
POOL 34
A1A3 309 SFRP SQQN PQTQ GSVQ PQQL
A1B2 309 SFRP SQQN SQAQ GSVQ PQQL
A1B3 309 SFRP SQQN PQDQ GSVQ PQQL
A1B4 309 SFRP SQQN PRAQ GSVQ PQQL
A2A1 309 SFQP SQQN PQAQ GSVQ PQQL
A2B3 309 FFQP SQQN PQAQ GSFQ PQQL
A2B5 309 FFQP FQQN PQAQ GSFQ PQQL
A3A1 309 FFQP SQQN PQAQ GSFQ PQQL
Pool 35
A3B1 309 SFQP SQLN PQAQ GSVQ PQQL
A3B1 309 SFQP SQLN PQAQ GSVQ PQQL
A3B2 309 SFQP SQQN PQAQ GSVQ PQQL
A4A 309 SFQS SQQN PQAQ GSVQ PQQL
A1A1 317 PQAQ GSVQ PQQL PQFE EIRN
A1A3 317 PQTQ GSVQ PQQL PQFE EIRN
A1A6 317 PQAQ GSVQ PQQL PQFE IRNL
A1B1 317 PLAQ GSVQ PQQL PQFE EIRN
POOL 36
A1B3 317 PQDQ GSVQ PQQL PQFE EIRN
A1B4 317 PRAQ GSVQ PQQL PQFE EIRN
A2B3 317 PQAQ GSFQ PQQL PQFE EIRN
A2B5 317 PQAQ GSFQ PQQL PQFE AIRN
A3B1 317 PQAQ GSVQ PQQL PQFA EIRN
A4A 317 PQAQ GSVQ PQQL PQFQ EIRN
Pool 37
A1A1 325 PQQL PQFE EIRN LALQ TLPA
A1A6 325 PQQL PQFE IRNL ALQT LPAM
A1B12 325 PQQL PQFE EIRN LARK
A2A1 325 PQQL PQFE EIRN LALE TLPA
A2B5 325 PQQL PQFE AIRN LALQ TLPA
A3B1 325 PQQL PQFA EIRN LALQ TLPA
A4A 325 PQQL PQFQ EIRN LALQ TLPA
A1A1 333 EIRN LALQ TLPA MCNV YIPP
POOL 38
A1A3 333 EIRN LALQ TLPS MCNV YIPP
A2A1 333 EIRN LALE TLPA MCNV YIPP
A3A1 333 EIRN LALQ TLPR MCNV YIPP
A1A1 341 TLPA MCNV YIPP YCTI APFG
A1A3 341 TLPS MCNV YIPP YCTI APFG
A1B1 341 TLPA MCNV YIPP YCTI VPFG
A1B4 341 TLPA MCNV YIPP YCAM APFG
A1B9 341 TLPA MCNV YIPP YCTI TPFG
Pool 39
A2A1 341 TLPA MCNV YIPP YCTI APVG
A2B2 341 TLPA MCNV YIPP YCST TIAP
A3A1 341 TLPR MCNV YIPP YCST TIAP
A3A2 341 TLPR MCNV YIPP YCST TTAP
A3B1 341 TLPA MCNV YIPP HCST TIAP
A1A1 349 YIPP YCTI APFG IFGT NYR
A1B1 349 YIPP YCTI VPFG IFGT NYR
A1B4 349 YIPP YCAM APFG IFGT NYR
Pool 40
A1B5 349 YIPP YCTM APFG IFGT NYR
A1B9 349 YIPP YCTI TPFG IFGT N
A2A1 349 YIPP YCTI APVG IFGT NYR
A2B2 349 YIPP YCST TIAP VGIF GTN
A3A2 349 YIPP YCST TTAP FGIF GTN
A3B1 349 YIPP HCST TIAP FGIF GTN
A3B3 349 YIPP HCST TIAP FGIS GTN
A4D 350 IPPY CSTT IAPF GIFG TNYR
Pool 41
GI1A 17 GTAN MQVD PSSQ VQWP QQQP
GI2A 17 GTAN IQVD PSGQ VQWL QQQL

253 GIII 1A 105 QQQQ PVLP QQSP FSQQ QQLV   583
254 GIII 1A 113 QQSP FSQQ QQLV LPPQ QQQQ   584
255 GIII 1A 121 QQLV LPPQ QQQQ QLVQ QQIP   585
256 GIII 1A 129 QQQQ QLVQ QQIP IVQP SVLQ   586
257 GIII 1A 137 QQIP IVQP SVLQ QLNP CKVF   587
258 GIII 1A 145 SVLQ QLNP CKVF LQQQ CSPV   588
259 POOL 76
260 GIII 1A 153 CKVF LQQQ CSPV AMPQ RLAR   589
    GIII 1A 161 CSPV AMPQ RLAR SQMW QQSS   590
261 GIII 1A 169 RLAR SQMW QQSS CHVM QQQC   591
262 GIII 1A 177 QQSS CHVM QQQC CQQL QQIP   592
263 GIII 1A 185 QQQC CQQL QQIP EQSR YEAI   593
264 GIII 1A 193 QQIP EQSR YEAI RAII YSII   594
265 GIII 1A 201 YEAI RAII YSII LQEQ QQGF   595
266 GIII 1A 209 YSII LQEQ QQGF VQPQ QQQP   596
267 POOL 77
268 GIII 1A 217 QQGF VQPQ QQQP QQSG QGVS   597
    GIII 1A 225 QQQP QQSG QGVS QSQQ QSQQ   598
269 GIII 1A 233 QGVS QSQQ QSQQ QLGQ CSFQ   599
270 GIII 1A 241 QSQQ QLGQ CSFQ QPQQ QLGQ   600
271 GIII 1A 249 CSFQ QPQQ QLGQ QPQQ QQQQ   601
272 GIII 1A 257 QLGQ QPQQ QQQQ QVLQ GTFL   602
273 GIII 1A 263 QQQQ QVLQ GTFL QPHQ IAHL   603
274 GIII 1A 271 GTFL QPHQ IAHL EAVT SIAL   604
275 POOL 78
276 GIII 1A 279 IAHL EAVT SIAL RTLP TMCS   605
    GIII 1A 287 SIAL RTLP TMCS VNVP LYSA   606
277 GIII 1A 295 TMCS VNVP LYSA TTSV PFGV   607
278 GIII 1A 303 LYSA TTSV PFGV GTGV GAY   608
279 GIII 1B 26 SCIS GLER PWQQ QPLP QQQS   609
280 GIII 1B 34 PWQQ QPLP QQQS FSQQ PPFS   610
281 GIII 1B 42 PQQS FSQQ PPFS QQQQ QPLP   611
282 GIII 1B 50 PPFS QQQQ QPLP QQPS FSQQ   612
Pool 79
283 GIII 1B 58 QPLP QQPS FSQQ QPPF SQQQ   613
284 GIII 1B 66 FSQQ QPPF SQQQ PILS QQPP   614
285 GIII 1B 74 SQQQ PILS QQPP FSQQ QQPV   615
286 O 1A 17 ATAA RELN PSNK ELQS PQQS   616
287 O 1A 25 PSNK ELQS PQQS FSYQ QQPF   617
288 O 1A 33 PQQS FSYQ QQPF PQQP YPQQ   618
289 O 1A 41 QQPF PQQP YPQQ PYPS QQPY   619
290 O 1A 49 YPQQ PYPS QQPY PSQQ PFPT   620
POOL 80
291 O 1A 57 QQPY PSQQ PFPT PQQQ FPEQ   621
292 O 1A 65 PFPT PQQQ FPEQ SQQP FTQP   622
293 O 1A 73 FPEQ SQQP FTQP QQPT PIQP   623
294 O 1A 81 FTQP QQPT PIQP QQPF PQQP   624
295 O 1A 89 PIQP QQPF PQQP QQPQ QPFP   625
296 O 1A 97 PQQP QQPQ QPFP QPQQ PFPW   626
297 O 1A 105 QPFP QPQQ PFPW QPQQ PFPQ   627
298 O 1A 113 PFPW QPQQ PFPQ TQQS FPLQ   628
POOL 81
299 O 1A 121 PFPQ TQQS FPLQ PQQP FPQQ   629
300 O 1A 129 FPLQ PQQP FPQQ PQQP FPQP   630
301 O 1A 137 FPQQ PQQP FPQP QLPF PQQS   631
302 O 1A 145 FPQP QLPF PQQS EQII PQQL   632
303 O 1A 153 PQQS EQII PQQL QQPF PLQP   633
304 O 1A 161 PQQL QQPF PLQP QQPF PQQP   634
305 O 1A 169 PLQP QQPF PQQP QQPF PQPQ   635
306 O 1A 177 PQQP QQPF PQPQ QPIP VQPQ   636
Pool 82
307 O 1A 185 PQPQ QPIP VQPQ QSFP QQSQ   637
308 O 1A 193 VQPQ QSFP QQSQ QSQQ PFAQ   638
309 O 1A 201 QQSQ QSQQ PFAQ PQQL FPEL   639
310 O 1A 209 PFAQ PQQL FPEL QQPI PQQP   640
311 O 1A 217 FPEL QQPI PQQP QQPF PLQP   641
312 O 1A 225 PQQP QQPF PLQP QQPF PQQP   642
313 O 1A 233 PLQP QQPF PQQP QQPF PQQP   643
314 O 1A 241 PQQP QQPF PQQP QQSF PQQP   644
POOL 83
315 O 1A 249 PQQP QQSF PQQP QQPY PQQQ   645
316 O 1A 257 PQQP QQPY PQQQ PYGS SLTS   646

104

GI3A 17 ATAN MQVD PSGQ VPWP QQQP	317	O 1A 265 PQQQ PYGS SLTS IGGQ	647
GI3B 19 MN IQVD PSGQ VPWP QQQP FP	318	O 1B 1 ARQL NPSD QELQ SPQQ LYPQ	648
GI4 17 ATAN MQAD PSGQ VQWP QQQP	319	O 1B 9 QELQ SPQQ LYPQ QPYP QQPY	649
GI5A 17 TTAN IQVD PSGQ VQWP QQQQ	320	O 1C 1 SRLL SPRG KELH TPQE QFPQ	650
GI5C 17 ATAN MQVD PSGQ VQWP QQQP	321	O 1C 9 KELH TPQE QFPQ QQQF PQPQ	651
GI7 20 QIVF PSGQ VQWP QQQQ PFP	322	O 1C 17 QFPQ QQQF PQPQ QFPQ	652
Pool 42			
GI1A 25 PSSQ VQWP QQQP VPQP HQPF	323		
GI2A 25 PSGQ VQWL QQQL VPQL QQPL	324		
GI3A 25 PSGQ VPWP QQQP FPQP HQPF	325		
GI4 25 PSGQ VQWP QQQP FLQP HQPF	326		
GI5A 25 PSGQ VQWP QQQQ PFPQ PQQP	327		
GI5C 25 PSGQ VQWP QQQP FRQP QQPF	328		
GI6A 25 PSGQ VQWP QQQP FPQP QQPF	329		
GI1A 33 QQQP VPQP HQPF SQQP QQTF	330		

*Position of N-terminal residue in α-, γ1-, γ2-, γ3-, or ω consensus sequence

Table 24. 652 synthetic peptides and ELISpot analysis with patients and gluten challenge

COELIAC SUBJECT	C14	C15	C16	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	C27	C28
HLA-DQ	22	22	22	22	22	22	2X	2X	2X	2X	28	28	2X	2X	2X
ANTIGEN CHALLENGE	WHEAT												RYE		
DURATION OF CHALLENGE (DAYS)	3	3	6	3	6	3	3	3	3	0.5	3	1	3	3	3
DOMINANT PEPTIDE ELISPOT SFC	203	46	96	195	114	136	29	57	129	259	50	18	163	52	229
BLANK ELISPOT SFC	1	2	4	0.5	3	1	1	4	3	2	1	2	1	2	6

Peptide	Sequence	C14	C15	C16	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	C27	C28
1	AVRFPVPQLQPQNPSQQLPQ															
2	MVRVPVPQLQPQNPSQQQPQ															
3	MVRVPVPQLQPQNPSQQHPQ															
4	MVRVPMPQLQPQDPSQQQPQ															
5	MVRVTVPQLQPQNPSQQQPQ															
6	AVRVSVPQLQPQNPSQQQPQ															
7	AVRFPVPQLQPQNPSQQQPQ															
8	AVRWPVPQLQPQNPSQQQPQ															
9	AVRVPVPQLQLQNPSQQQPQ															
10	MVRVPVPQLQLQNPSQQQPQ															
11	AVRVPVPQPQPQNPSQPQPQ															
12	AVRVPVPQLQPKNPSQQQPQ															
13	LQPQNPSQQLPQEQVPLVQQ															
14	LQPQNPSQQQPQEQVPLVQQ															
15	LQPQNPSQQHPQEQVPLVQQ															
16	LQPQDPSQQQPQEQVPLVQQ															
17	LQPQNPSQQQPQKQVPLVQQ															
18	LQLQNPSQQQPQEQVPLVQE															
19	LQLQNPSQQQPQEQVPLVQE															
20	PQPQNPSQPQPQGQVPLVQQ															
21	PQPQNPSQPQPQRQVPLVQQ															
22	LQPKNPSQQQPQEQVPLVQQ													■			
23	LQPQNPSQQQPQEQVPLMQQ															
24	QLPQEQVPLVQQQQFLGQQQ															
25	QHPQEQVPLVQQQQFLGQQQ															
26	QQPQEQVPLVQQQQFLGQQQ															
27	QQPQEQVPLVQQQQFLGQQQ															
28	QQPQEQVPLVQQQQFPGQQQ															
29	QQPQKQVPLVQQQQFPGQQQ															
30	QQPQEQVPLVQEQQFQGQQQ															
31	PQPQGQVPLVQQQQFPGQQQ															
32	PQPQRQVPLVQQQQFPGQQQ															
33	QQPQEQVPLMQQQQQFPGQQ															
34	LVQQQQFLGQQQPFPPQQPY															
35	LVQQQQFLGQQQSFPPQQPY															
36	LVQQQQFLGQQQPFPPQQPY															
37	LVQQQQFPGQQQQFPPQQPY															
38	LVQEQQFQGQQQPFPPQQPY															
39	LVQQQQFPGQQQQFPPQQPY															
40	LMQQQQQFPGQQEQFPPQQP															
41	LMQQQQQFPGQQERFPPQQP													■			
42	GQQQPFPPQQPYPQPQPFPS															
43	GQQQPFPPQQPYPQPQFPSQ															

#	Sequence
44	GQQQSFPPQQPYPQPQPFPS
45	GQQQPFPPQQPYPQQQPFPS
46	GQQQQFPPQQPYPQPQPFPS
47	GQQEQFPPQQPYPHQQPFPS
48	GQQERFPPQQPYPHQQPFPS
49	QQPYPQPQPFPSQLPYLQLQ
50	QQPYPQPQFPSQLPYLQLQP
51	QQPYPQPQPFPSQQPYLQLQ
52	QQPYPQQQPFPSQQPYMQLQ
53	QQPYPHQQPFPSQQPYPQPQ
54	PFPSQLPYLQLQPFPQPQLP
55	PFPSQQPYLQLQPFPQPQLP
56	PFPSQQPYLQLQPFSQPQLP
57	PFPSQQPYLQLQPFLQPQLP
58	PFPSQQPYLQLQPFLQPQPF
59	PFPSQQPYLQLQPFPQPQLP
60	PFPSQQPYMQLQPFPQPQLP
61	PFPSQQPYMQLQPFPQPQPF
62	PFPSQQPYLQLQPFPQPQPF
63	PFPSQQPYLQLQPFPRPQLP
64	PFPSQQPYPQPQPFPPQLPY
65	PFPSQQPYPQPQPFPQPQPF
66	LQLQPFPQPQLPYSQPQPFR
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549	IPVVQPSILQQLNPCKVFLQ																
550	LQQLNPCKVFLQQQCSPVAM																
551	VFLQQQCSPVAMPQRLARSQ																
552	PVAMPQRLARSQMLQQSSCH																
553	ARSQMLQQSSCHVMQQQCCQ																
554	SSCHVMQQQCCQQLPQIPQQ																
555	QCCQQLPQIPQQSRYQAIRA																
556	PQIPQQSRYEAIRAIIYSII																
557	IPQQSRYQAIRAIIYSIILQ																
558	AIRAIIYSIILQEQQQVQGS																
559	IILQEQQQVQGSIQSQQQQP																
560	VQGSIQSQQQQPQQLGQCVS																
561	QQQPQQLGQCVSQPQQQSQQ																
562	QCVSQPQQQSQQQLGQQPQQ																
563	QSQQQLGQQPQQQQLAQGTF																
564	QPQQQLAQGTFLQPHQIAQ																
565	QGTFLQPHQIAQLEVMTSIA																
566	QIAQLEVMTSIALRILPTMC																
567	TSIALRILPTMCSVNVPLYR																
568	PTMCSVNVPLYRTTTSVPFG																
569	PLYRTTTSVPFGVGTGVGAY																
570	TITRTFPIPTISSNNNHHFR																
571	PTISSNNNHHFRSNSNHHFH																
572	HHFRSNSNHHFHSNNNQFYR																
573	HHFHSNNNQFYRNNNSPGHN																
574	QFYRNNNSPGHNNPLNNNNS																
575	PGHNNPLNNNNSPNNNSPSN																
576	NNNSPNNNSPSNHHNNSPNN																
577	SPSNHHNNSPNNNFQYHTHP																
578	SPNNNFQYHTHPSNHKNLPH																
579	HTHPSNHKNLPHTNNIQQQQ																
580	NLPHTNNIQQQQPPFSQQQQ																
581	QQQQPPFSQQQQPPFSQQQQ																
582	QQQQPPFSQQQQPVLPQQSP																
583	QQQQPVLPQQSPFSQQQQLV																
584	QQSPFSQQQQLVLPPQQQQQ																
585	QQLVLPPQQQQQQLVQQQIP																
586	QQQQQLVQQQIPIVQPSVLQ																
587	QQIPIVQPSVLQQLNPCKVF																
588	SVLQQLNPCKVFLQQQCSPV																
589	CKVFLQQQCSPVAMPQRLAR				■					■						■	
590	CSPVAMPQRLARSQMWQQSS																
591	RLARSQMWQQSSCHVMQQQC																
592	QQSSCHVMQQQCCQQLQQIP																
593	QQQCCQQLQQIPEQSRYEAI																

	Sequence
594	QQIPEQSRYEAIRAIIYSII
595	YEAIRAIIYSIILQEQQQGF
596	YSIILQEQQQGFVQPQQQQP
597	QQGFVQPQQQQPQQSGQGVS
598	QQQPQQSGQGVSQSQQQSQQ
599	QGVSQSQQQSQQQLGQCSFQ
600	QSQQQLGQCSFQQPQQQLGQ
601	CSFQQPQQQLGQQPQQQQQQ
602	QLGQQPQQQQQQVLQGTFL
603	QQQQQVLQGTFLQPHQIAHL
604	GTFLQPHQIAHLEAVTSIAL
605	IAHLEAVTSIALRTLPTMCS
606	SIALRTLPTMCSVNVPLYSA
607	TMCSVNVPLYSATTSVPFGV
608	LYSATTSVPFGVGTGVGAY
609	SCISGLERPWQQQPLPPQQS
610	PWQQQPLPPQQSFSQQPPFS
611	PQQSFSQQPPFSQQQQQPLP
612	PPFSQQQQQPLPQQPSFSQQ
613	QPLPQQPSFSQQQPPFSQQQ
614	FSQQQPPFSQQQPILSQQPP
615	SQQQPILSQQPPFSQQQQPV
616	ATAARELNPSNKELQSPQQS
617	PSNKELQSPQQSFSYQQQPF
618	PQQSFSYQQQPFPQQPYPQQ
619	QQPFPQQPYPQQPYPSQQPY
620	YPQQPYPSQQPYPSQQPFPT
621	QQPYPSQQPFPTPQQQFPEQ
622	PFPTPQQQFPEQSQQPFTQP
623	FPEQSQQPFTQPQQPTPIQP
624	FTQPQQPTPIQPQQPFPQQP
625	PIQPQQPFPQQPQQPQQPFP
626	PQQPQQPQQPFPQPQQPFPW
627	QPFPQPQQPFPWQPQQPFPQ
628	PFPWQPQQPFPQTQQSFPLQ
629	PFPQTQQSFPLQPQQPFPQQ
630	FPLQPQQPFPQQPQQPFPQP
631	FPQQPQQPFPQPQLPFPQQS
632	FPQPQLPFPQQSEQIIPQQL
633	PQQSEQIIPQQLQQPFPLQP
634	PQQLQQPFPLQPQQPFPQQP
635	PLQPQQPFPQQPQQPFPQPQ
636	PQQPQQPFPQPQQPIPVQPQ
637	PQPQQPIPVQPQQSFPQQSQ
638	VQPQQSFPQQSQQSQQPFAQ
639	QQSQQSQQPFAQPQQLFPEL
640	PFAQPQQLFPELQQPIPQQP
641	FPELQQPIPQQPQQPFPLQP
642	PQQPQQPFPLQPQQPFPQQP
643	PLQPQQPFPQQPQQPFPQQP
644	PQQPQQPFPQQPQQSFPQQP
645	PQQPQQSFPQQPQQPYPQQQ
646	PQQPQQPYPQQQPYGSSLTS
647	PQQQPYGSSLTSIGGQ
648	ARQLNPSDQELQSPQQLYPQ

117

649	QELQSPQQLYPQQFYPQQPY																		
650	SRLLSPRGKELHTPQEQFPQ																		
651	KELHTPQEQFPQQQQFPQPQ																		
652	QFPQQQQFPQPQQFPQ																		

70.1 to 100
40.1 to 70
25.1 to 40
10.1 to 25
5.1 to 10
<5

>3 x B1

The claims defining the invention are as follows:

1.   A method of preventing or treating coeliac disease comprising administering to an individual at least one agent selected from:

(a)   a peptide comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said peptide does not comprise transglutaminase-deamidated sequence PQLPY (SEQ ID NO:12); and

(b)   a peptide analogue of (a) which is capable of being recognised by a T cell receptor that recognises the epitope of (a) and which is not more than 50 amino acids in length; and

optionally, in addition to the agent selected from (a) and (b), administering to said individual a peptide comprising at least one epitope comprising a sequence selected from SEQ ID NO:1 and SEQ ID NO:2.

2.   A method of claim 1 wherein the peptide of (a) comprises at least one epitope comprising a sequence selected from transglutaminase-deamidated

PQQPQQPQQPFPQPQQPFPW SEQ ID NO: 732,

QPFPQPQQPFPWPQQPFPQ SEQ ID NO: 733,

PQQPQQPFPQPQQPIPVQPQ SEQ ID NO: 742,

SQQPQQPFPQPQQQFPQPQQ SEQ ID NO: 518,

LQQPQQPFPQPQQQLPQPQQ SEQ ID NO: 517,

PSGQVQWPQQQPFPQPQQPF SEQ ID NO: 435,

QQTYPQRPQQPFPQTQQPQQ SEQ ID NO: 496,

QQQPFPQPQQPFCQQPQRTI SEQ ID NO: 443,

QQPYPQQPQQPFPQTQQPQQ SEQ ID NO: 494,

QAFPQPQQTFPHQPQQQFPQ SEQ ID NO: 461,

QQTFPQPQQTFPHQPQQQFP SEQ ID NO: 454,

QQIFPQPQQTFPHQPQQAFP SEQ ID NO: 456, or

QQIFPQPQQTFPHQPQQQFP SEQ ID NO: 455.

3.   A method of claim 1 wherein the agent is HLA-DQ2-restricted or HLA-DQ8-restricted.

4.   A method of claim 1 wherein one agent is HLA-DQ2-restricted and a second agent is HLA-DQ8-restricted.

5.   A method of any one of claims 1 to 4 wherein one or more agents are administered to said individual and said one or more agents are selected from an agent comprising a wheat epitope, an agent comprising a rye epitope, an agent comprising a barley epitope, or any combination thereof.

6.   A method of any one of claims 1 to 4 wherein a single agent comprises a wheat epitope, a barley epitope, and a rye epitope.

7. A method of preventing or treating coeliac disease comprising administering to an individual a pharmaceutical composition comprising an agent as defined in claim 1 or claim 2 and a pharmaceutically acceptable carrier or diluent.

8. A method of preventing or treating coeliac disease comprising administering to an individual a pharmaceutical composition comprising an antagonist of a T cell which has a T cell receptor as defined in claim 1, and a pharmaceutically acceptable carrier or diluent.

9. A method of preventing or treating coeliac disease comprising administering to an individual a composition for tolerising an individual to a gliadin protein to suppress the production of a T cell or antibody response to an agent as defined in claim 1, which composition comprises an agent as defined in claim 1.

10. A method of preventing or treating coeliac disease comprising:

diagnosing coeliac disease in an individual by either:

 a) contacting a sample from the host with at least one agent selected from:

  i) a peptide comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said peptide does not comprise transglutaminase-deamidated sequence PQLPY (SEQ ID NO:12), and with the proviso that said peptide does not comprise transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ; and

  ii) a peptide analogue of i) which is capable of being recognised by a T cell receptor that recognises the epitope of i) and which is not more than 50 amino acids in length; and

  iii) optionally, in addition to the agent selected from i) and ii), a peptide comprising at least one epitope comprising a sequence selected from SEQ ID NOS: 1 and 2; and

determining *in vitro* whether T cells in the sample recognise the agent; recognition by the T cells indicating that the individual has, or is susceptible to, coeliac disease; or

 b) administering an agent as defined in claim 1 and determining *in vivo* whether T cells in the individual recognise the agent, recognition of the agent indicating that the individual has or is susceptible to coeliac disease; and

administering to an individual diagnosed as having, or being susceptible to, coeliac disease a therapeutic agent for preventing or treating coeliac disease.

11. A method of claim 10 wherein the peptide of (a) comprises at least one epitope comprising a sequence selected from transglutaminase-deamidated

  PQQPQQPQQPFPQPQQPFPW SEQ ID NO: 732,

QPFPQPQQPFPWQPQQPFPQ SEQ ID NO: 733,

PQQPQQPFPQPQQPIPVQPQ SEQ ID NO: 742,

SQQPQQPFPQPQQQFPQPQQ SEQ ID NO: 518,

LQQPQQPFPQPQQQLPQPQQ SEQ ID NO: 517,

PSGQVQWPQQQPFPQPQQPF SEQ ID NO: 435,

QQTYPQRPQQPFPQTQQPQQ SEQ ID NO: 496,

QQQPFPQPQQPFCQQPQRTI SEQ ID NO: 443,

QQPYPQQPQQPFPQTQQPQQ SEQ ID NO: 494,

QAFPQPQQTFPHQPQQQFPQ SEQ ID NO: 461,

QQTFPQPQQTFPHQPQQQFP SEQ ID NO: 454,

QQIFPQPQQTFPHQPQQAFP SEQ ID NO: 456, or

QQIFPQPQQTFPHQPQQQFP SEQ ID NO: 455.

12.   Use of an agent for the preparation of a medicament for treating or preventing coeliac disease, wherein the agent comprises:

(a)   a peptide comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said peptide does not comprise transglutaminase-deamidated sequence PQLPY (SEQ ID NO:12); and

(b)   a peptide analogue of (a) which is capable of being recognised by a T cell receptor that recognises the epitope of (a) and which is not more than 50 amino acids in length; and

(c)   optionally, in addition to the agent selected from (a) and (b), a peptide comprising at least one epitope comprising a sequence selected from SEQ ID NO:1 and SEQ ID NO:2.

13.   A use of claim 12 wherein the peptide of (a) comprises at least one epitope comprising a sequence selected from transglutaminase-deamidated

PQQPQQPQQPFPQPQQPFPW SEQ ID NO: 732,

QPFPQPQQPFPWQPQQPFPQ SEQ ID NO: 733,

PQQPQQPFPQPQQPIPVQPQ SEQ ID NO: 742,

SQQPQQPFPQPQQQFPQPQQ SEQ ID NO: 518,

LQQPQQPFPQPQQQLPQPQQ SEQ ID NO: 517,

PSGQVQWPQQQPFPQPQQPF SEQ ID NO: 435,

QQTYPQRPQQPFPQTQQPQQ SEQ ID NO: 496,

QQQPFPQPQQPFCQQPQRTI SEQ ID NO: 443,

QQPYPQQPQQPFPQTQQPQQ SEQ ID NO: 494,

QAFPQPQQTFPHQPQQQFPQ SEQ ID NO: 461,

QQTFPQPQQTFPHQPQQQFP SEQ ID NO: 454,

QQIFPQPQQTFPHQPQQAFP SEQ ID NO: 456, or

QQIFPQPQQTFPHQPQQQFP SEQ ID NO: 455.

14.   A use of claim 12 wherein the agent is HLA-DQ2-restricted or HLA-DQ8-restricted.

15.   A use of claim 12 wherein one agent is HLA-DQ2-restricted and a second agent is HLA-DQ8-restricted.

16.   A use of any one of claims 12 to 15 wherein one or more agents are used for the manufacture of said medicament and said one or more agents are selected from an agent comprising a wheat epitope, an agent comprising a rye epitope, an agent comprising a barley epitope or any combination thereof.

17.   A use of any one of claims 12 to 15 wherein a single agent comprises a wheat epitope, a barley epitope, and a rye epitope.

18.   A use of any one of claims 12 to 17 wherein the agent is present within a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent.

19.   A use of any one of claims 12 to 17 wherein the agent is present within a pharmaceutical composition comprising an antagonist of a T cell which has a T cell receptor as defined in claim 12, and a pharmaceutically acceptable carrier or diluent.

20.   A use of any one of claims 12 to 19 wherein the agent is present within a composition for tolerising an individual to a gliadin protein to suppress the production of a T cell or antibody response to an agent as defined in claim 1.

21.   An isolated protein that comprises a sequence which is able to bind to a T cell receptor, which T cell receptor recognises an agent comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said epitope does not comprise transglutaminase-deamidated sequence PQLPY (SEQ ID NO:12), and with the proviso that said epitope does not comprise transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ; and

which sequence is able to cause antagonism of a T cell that carries such a T cell receptor.

22.   An agent comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said epitope does not comprise transglutaminase-deamidated sequence PQLPY (SEQ ID NO:12), and with the proviso that said epitope does not comprise transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ

or an antagonist of a T cell which has a T cell receptor that recognises said epitope, and which is not more than 50 amino acids in length.

23. A pharmaceutical composition comprising an agent as defined in claim 1 or an antagonist of a T cell which has a T cell receptor that recognises said epitope, and which is not more than 50 amino acids in length and a pharmaceutically acceptable carrier or diluent.

24. A composition for tolerising an individual to a gliadin protein to suppress the production of a T cell or antibody response to an agent as defined in claim 1, which composition comprises an agent as defined in claim 1, with the proviso that said agent does not comprise an epitope comprising transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ.

25. A composition for antagonising a T cell response to an agent as defined in claim 1, which composition comprises an antagonist of a T cell which has a T cell receptor that recognises said epitope, and which is not more than 50 amino acids in length, with the proviso that said epitope does not comprise transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ.

26. A mutant gliadin protein whose wild-type sequence can be modified by a transglutaminase to a sequence which is an agent as defined in claim 1, which wild-type sequence comprises an epitope comprising the amino acid sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said epitope does not comprise the amino acid sequence PQLPY (SEQ ID NO:12), and with the proviso that said epitope does not comprise the amino acid sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ, which mutant gliadin protein comprises a mutation which prevents its modification by a transglutaminase to a sequence which is an agent as defined in claim 1; or a fragment of such a mutant gliadin protein which is at least 15 amino acids long and which comprises the mutation.

27. A polynucleotide that comprises a coding sequence that encodes a protein or fragment as defined in claim 21 or claim 26.

28. A cell comprising a polynucleotide as defined in claim 27 or which has been transformed with such a polynucleotide.

29.   A transgenic mammal that expresses a T cell receptor as defined in claim 1.

30.   A method of diagnosing coeliac disease, or susceptibility to coeliac disease, in an individual comprising:

(a)   contacting a sample from the host with at least one agent selected from

(i)   a peptide comprising at least one epitope comprising transglutaminase-deamidated sequence PQ(QL)P(FY)P (SEQ ID NO:45) with the proviso that said peptide does not comprise the amino acid sequence PQLPY (SEQ ID NO:12), and with the proviso that said epitope does not comprise transglutaminase-deamidated sequence QQPFPQQPQQPYPQ, QQPYPQQPQQPFPQ, QQPFPQQPQQPFPQ, PFPQTQQPQQPFPQ, PFPQLQQPQQPFPQ, RQPFPQQPQQPYPQ, QFPQTQQPQQPFPQ, QQTFPQQPQLPFPQ, QLPFPQQPQQPFPQ, PFPQPQQPQQPFPQ, PFPQSQQPQQPFPQ, or QQTYPQRPQQPFPQ; and

(ii)   a peptide analogue of (i) which is capable of being recognised by a T cell receptor that recognises the epitope of (i) and which is not more than 50 amino acids in length; and

(iii)   optionally, in addition to the agent selected from (i) and (ii), a peptide comprising at least one epitope comprising a sequence selected from SEQ ID NOS: 1 and 2; and

(b)   determining *in vitro* whether T cells in the sample recognise the agent; recognition by the T cells indicating that the individual has, or is susceptible to, coeliac disease.

31.   A method of claim 30 wherein the peptide of (a) comprises at least one epitope comprising a sequence selected from transglutaminase-deamidated

PQQPQQPQQPFPQPQQPFPW   SEQ ID NO: 732,
QPFPQPQQPFPWQPQQPFPQ   SEQ ID NO: 733,
PQQPQQPFPQPQQPIPVQPQ   SEQ ID NO: 742,
SQQPQQPFPQPQQQFPQPQQ   SEQ ID NO: 518,
LQQPQQPFPQPQQQLPQPQQ   SEQ ID NO: 517,
PSGQVQWPQQQPFPQPQQPF   SEQ ID NO: 435,
QQTYPQRPQQPFPQTQQPQQ   SEQ ID NO: 496,
QQQPFPQPQQPFCQQPQRTI   SEQ ID NO: 443,
QQPYPQQPQQPFPQTQQPQQ   SEQ ID NO: 494,
QAFPQPQQTFPHQPQQQFPQ   SEQ ID NO: 461,
QQTFPQPQQTFPHQPQQQFP   SEQ ID NO: 454,
QQIFPQPQQTFPHQPQQAFP   SEQ ID NO: 456, or
QQIFPQPQQTFPHQPQQQFP   SEQ ID NO: 455.

32.   Use of an agent as defined in claim 30 or claim 31 for the preparation of a diagnostic means for use in a method of diagnosing coeliac disease, or susceptibility to coeliac disease, in an individual, said method comprising determining whether T cells of the individual recognise the agent, recognition by the T cells indicating that the individual has, or is susceptible to, coeliac disease.

33.   A method according to claim 30 or claim 31, or a use according to claim 32, wherein the agent is an analogue (iii) which comprises (i) or (ii) bound to (a) an HLA molecule, or (b) a fragment of an HLA molecule capable of binding (i) or (ii).

34.   A method or use according to claim 33 wherein the HLA molecule or fragment is in a complex comprising four HLA molecules or fragments of HLA molecules.

35.   Use according to any one of claims 32, 33 or 34 wherein the method comprises administering the agent to the skin of an individual and detecting the presence of inflammation at the site of administration, the detection of inflammation indicating that the T cells of the individual recognise the agent.

36.   A method according to any one of claims 30, 31, 33 or 34 wherein the sample is a blood sample.

37.   A method according to any one of claims 30, 31, 33, 34 or 36 wherein the T cells are not restimulated in antigen specific manner *in vitro* before the said determining.

38.   A method for identifying an analogue as defined in any one of claims 30, 33 or 34 comprising determining whether a candidate substance is recognised by a T cell receptor that recognises an epitope comprising sequence as defined in claim 30, recognition of the substance indicating that the substance is an analogue.

39.   A method of diagnosing coeliac disease, or susceptibility to coeliac disease, in an individual comprising determining the presence of an antibody that binds to an epitope comprising sequence as defined in claim 30 in a sample from the individual, the presence of the antibody indicating that the individual has, or is susceptible to, coeliac disease.

40.   A method of determining whether a composition is capable of causing coeliac disease comprising determining whether a protein capable of being modified by a transglutaminase to an oligopeptide sequence as defined in claim 30 is present in the composition, the presence of the protein indicating that the composition is capable of causing coeliac disease.

41.   A method according to claim 40 wherein the said determining is done by contacting the composition with an antibody specific for the sequence which is capable of being modified to the oligopeptide sequence, binding of the antibody to a protein in the composition indicating the composition is capable of causing coeliac disease.

42.   A method of identifying an antagonist of a T cell, which T cell recognises an agent as defined in claim 30, comprising contacting a candidate substance with the T cell and detecting whether the substance causes a decrease in the ability of the T cell to undergo an antigen specific response, the detecting of any such decrease in said ability indicating that the substance is an antagonist.

43.   A kit for carrying out a method according to any one of claims 30, 31, 33, 34, 36 or 37, or a use according to any one of claims 32 to 35 comprising an agent as defined in any one of claims 30, 31, 33 or 34 and a means to detect the recognition of the peptide by the T cell.

44.   Use of an agent or antagonist as defined in claim 42 or a wild type sequence as defined in claim 26 to produce an antibody specific to the agent, antagonist or wild type sequence.

45.   Use of a mutation in an epitope of a gliadin protein, which epitope is as defined in claim 30, to decrease the ability of the gliadin protein to cause coeliac disease.

46.   Method of identifying a product which is therapeutic for coeliac disease comprising administering a candidate substance to a transgenic mammal as defined in claim 29 which has, or which is susceptible to, coeliac disease and determining whether the substance prevents or treats coeliac disease in the mammal, the prevention or treatment of coeliac disease indicating that the substance is a therapeutic product.

47.   A method of diagnosing coeliac disease, or susceptibility to coeliac disease in an individual comprising administering an agent as defined in claim 30 and determining *in vivo* whether T cells in the individual recognise the agent, recognition of the agent indicating that the individual has or is susceptible to coeliac disease.

48.   A cell according to claim 28 which is a cell of a graminaceous monocotyledonous species.

49.   A cell according to claim 48 which is a cell of wheat, maize, oats, rye, rice, barley, triticale, sorghum, or sugar cane.

50.   A process for the production of a protein encoded by a coding sequence as defined in claim 27 which process comprises:

(a)   cultivating a cell according to any one of claims 28, 48 or 49 under conditions that allow the expression of the protein; and optionally

(b)   recovering the expressed protein.

51.   A transgenic plant or plant seed comprising plant cells according to claim 48 or claim 49.

52.   A transgenic plant regenerated from a cell according to claim 48 or claim 49.

53.   A transgenic plant cell, plant seed, progeny plant, plant part or plant product obtained from a plant according to claim 51 or claim 52.

54.   A plant product according to claim 53 which is grain, optionally further processed into flour or another grain product.

55.   A crop product harvested from a plant or plant seed as defined in claim 51.

56.   A food that comprises a protein as defined in claim 21 or claim 26.

57.   A food according to claim 56 in which a protein as defined in claim 21 or claim 26 is used instead of wild-type gliadin.

Dated 19 November, 2009
Isis Innovation Limited

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

Fig.1a.

Peptide pool 3
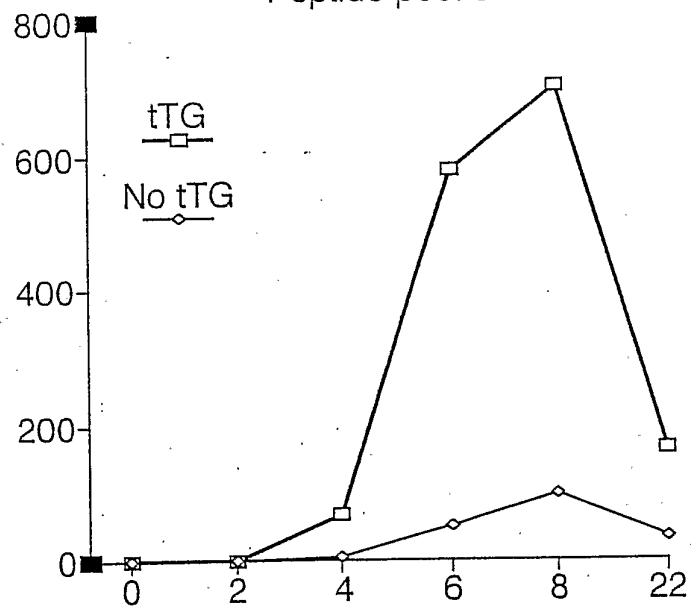
Gliadin digest
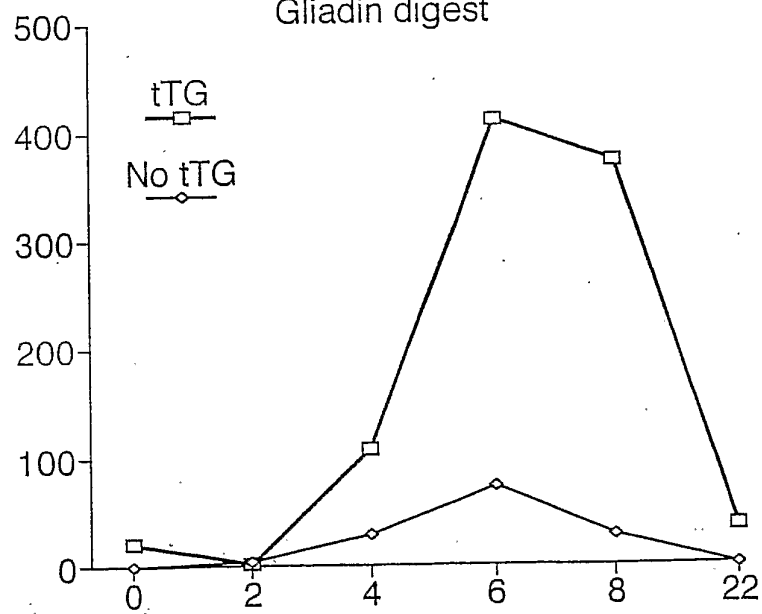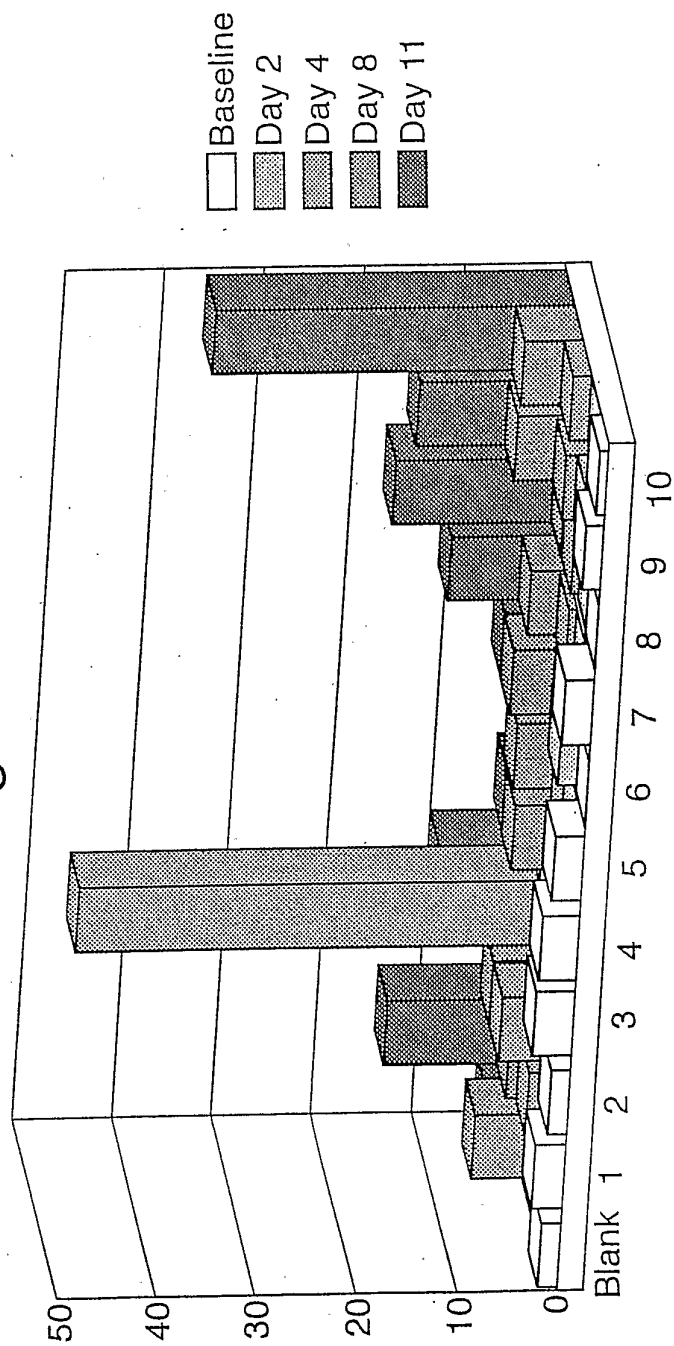
Fig.1b.

Fig.2a.

Fig.2b.

Fig.3.

Fig.4a.

Fig.4b.

Fig.5.

Fig.6.

Fig.7a.

CD4 depletion

Fig.7b.

HLA-Class II restriction

Fig.8.

Fig.9.
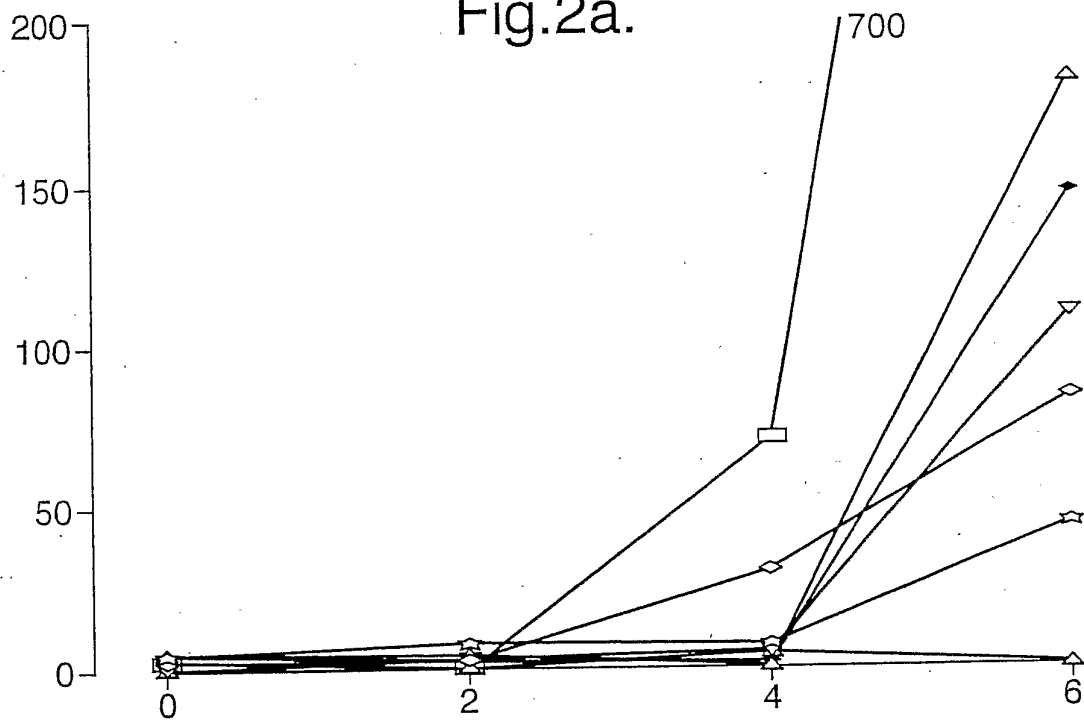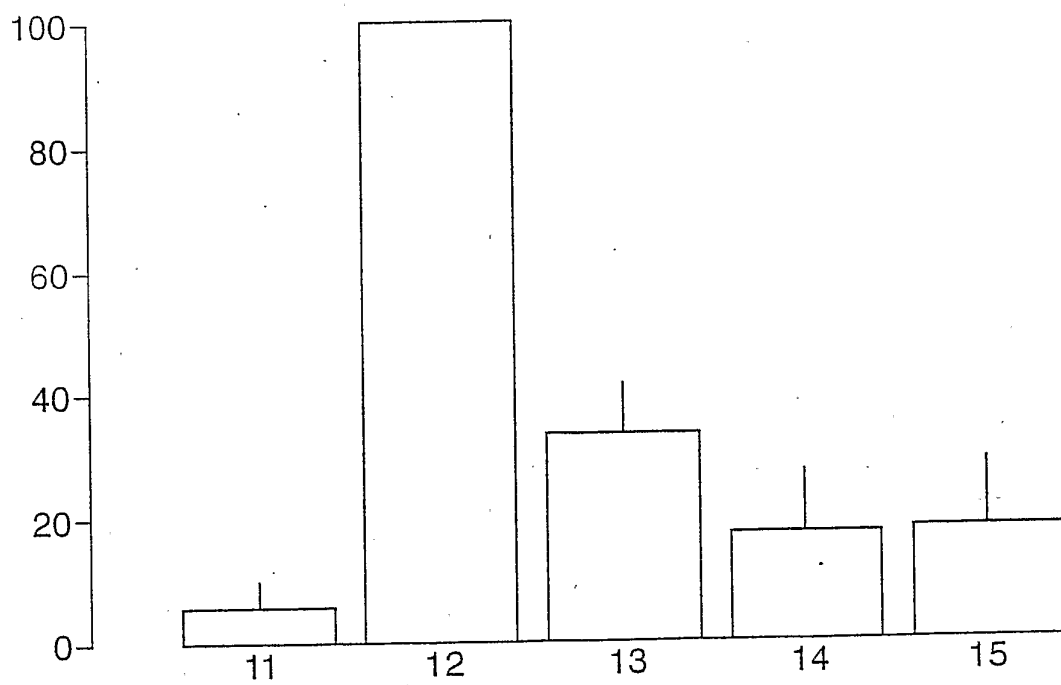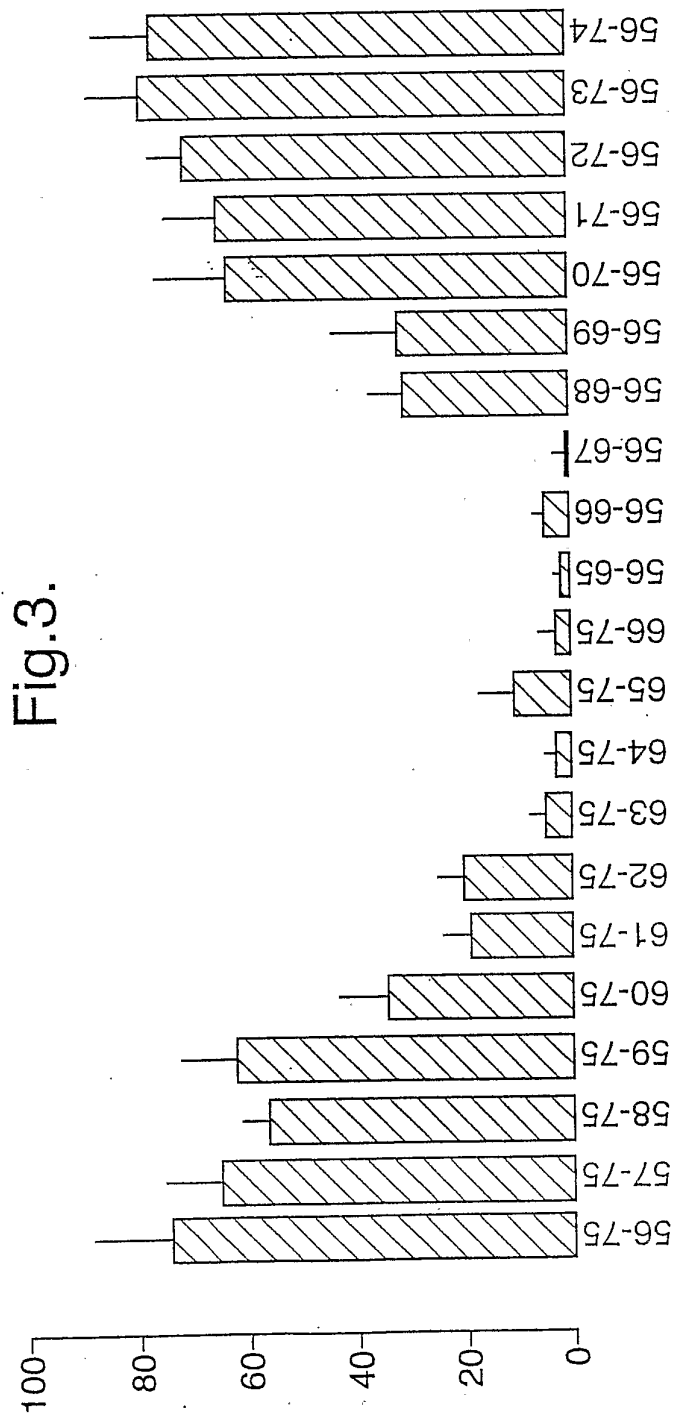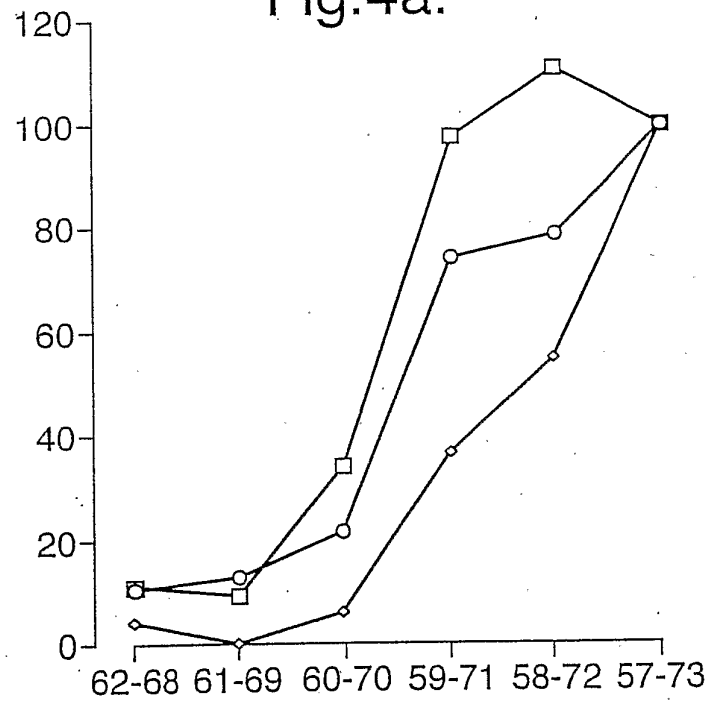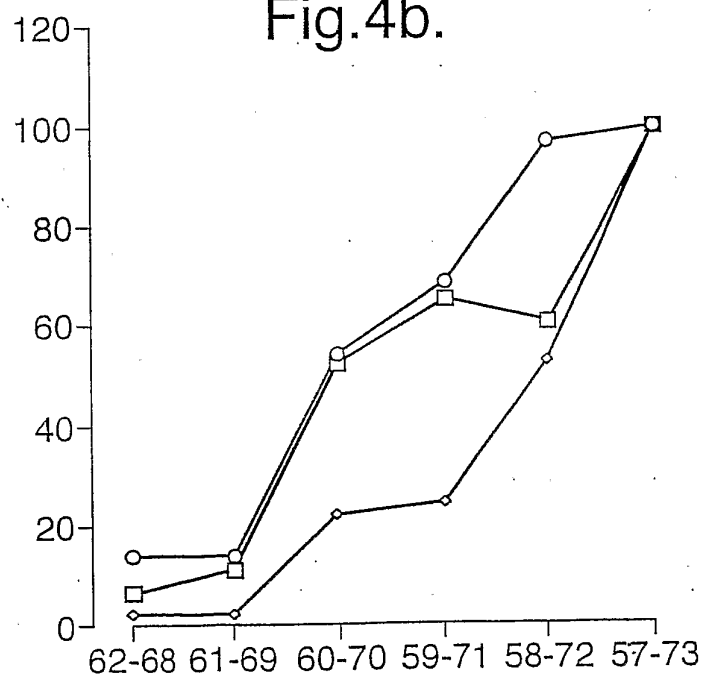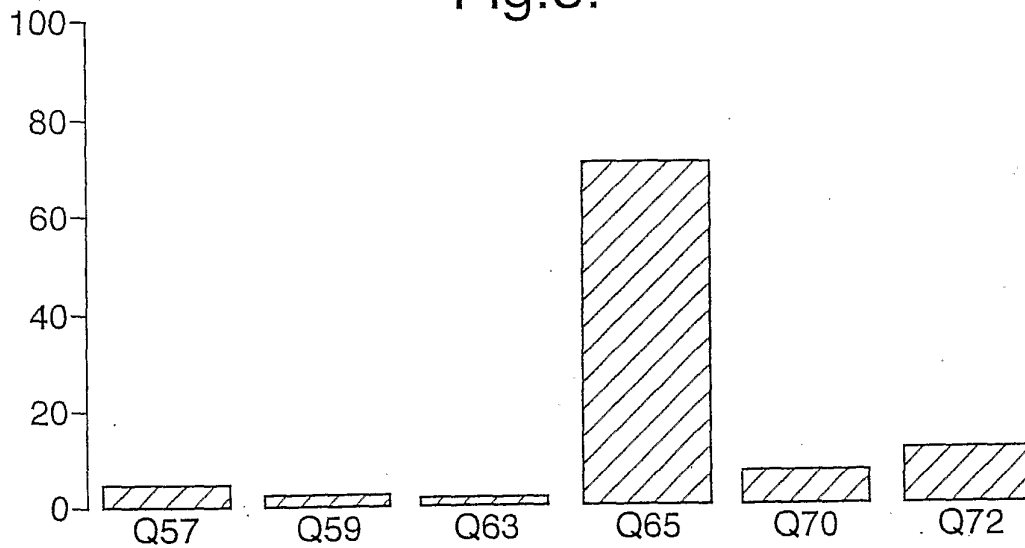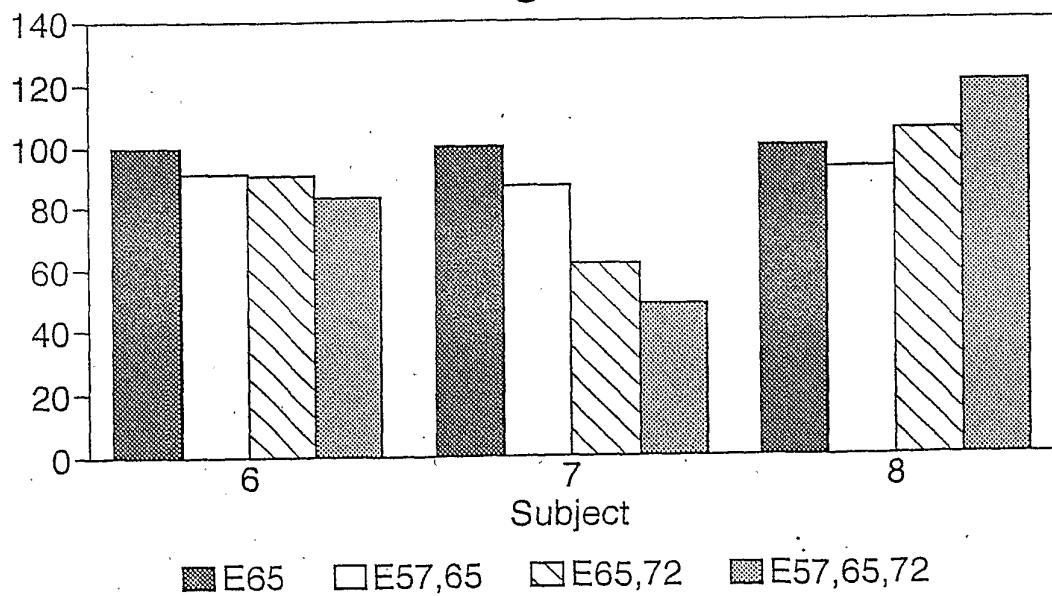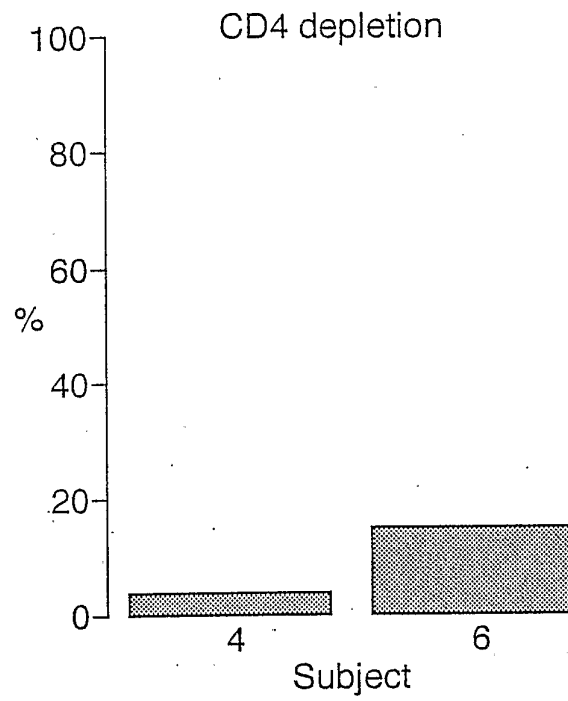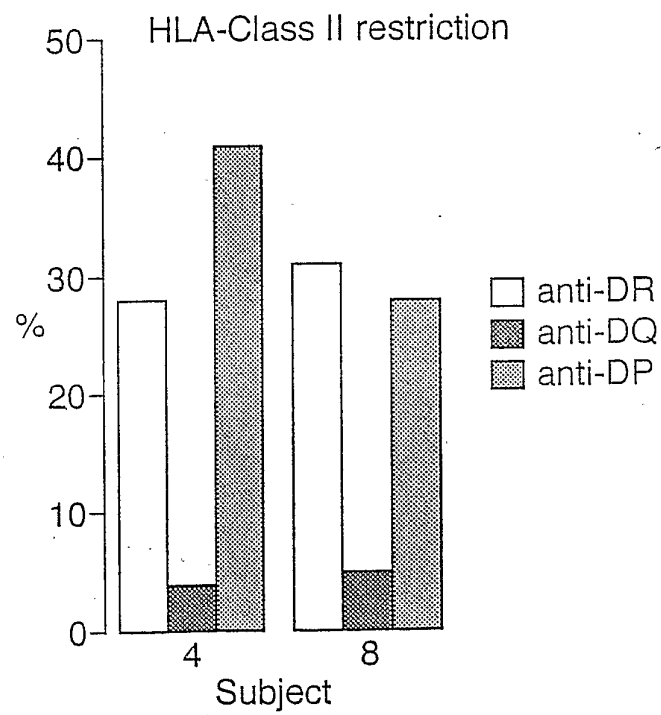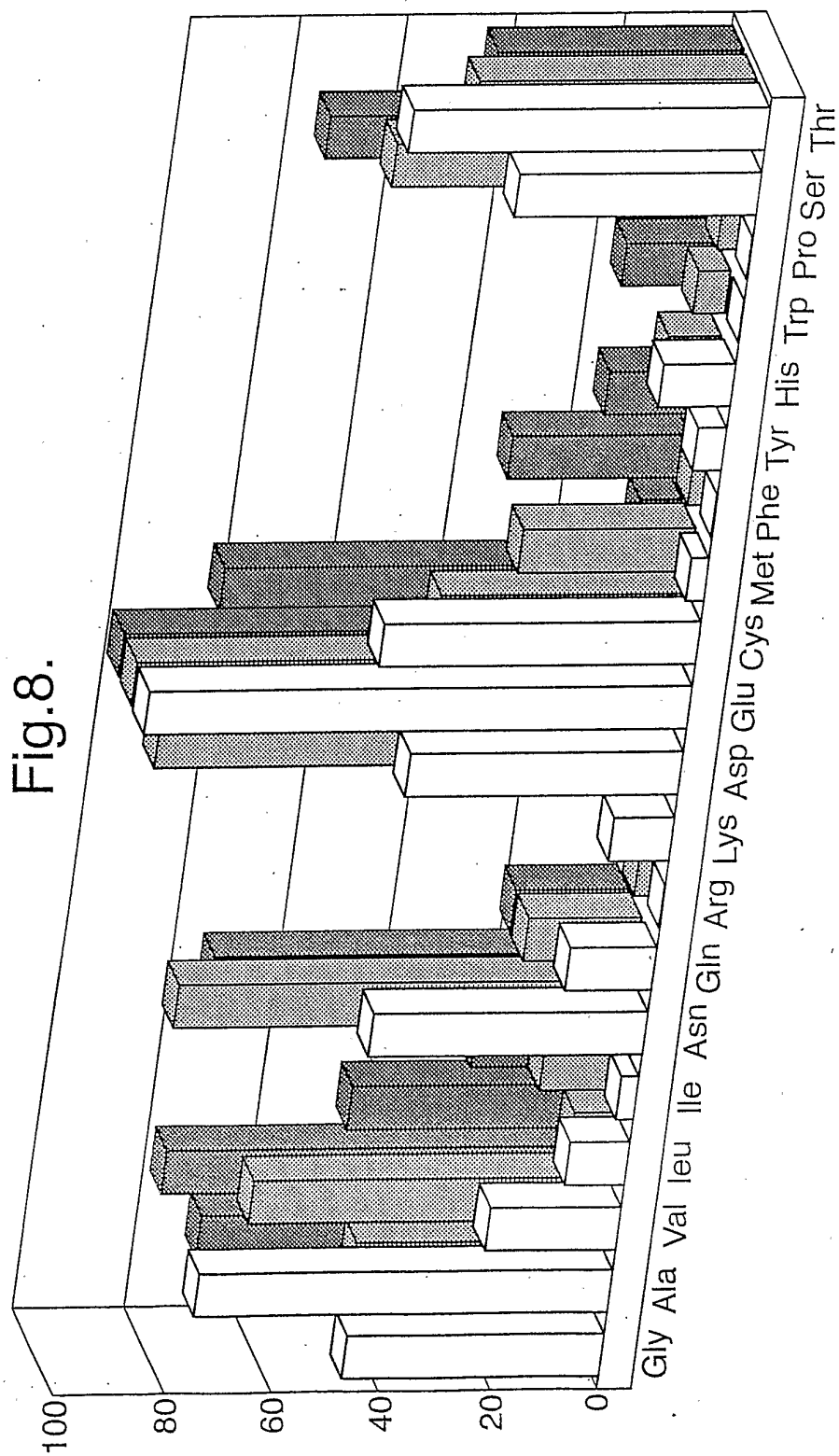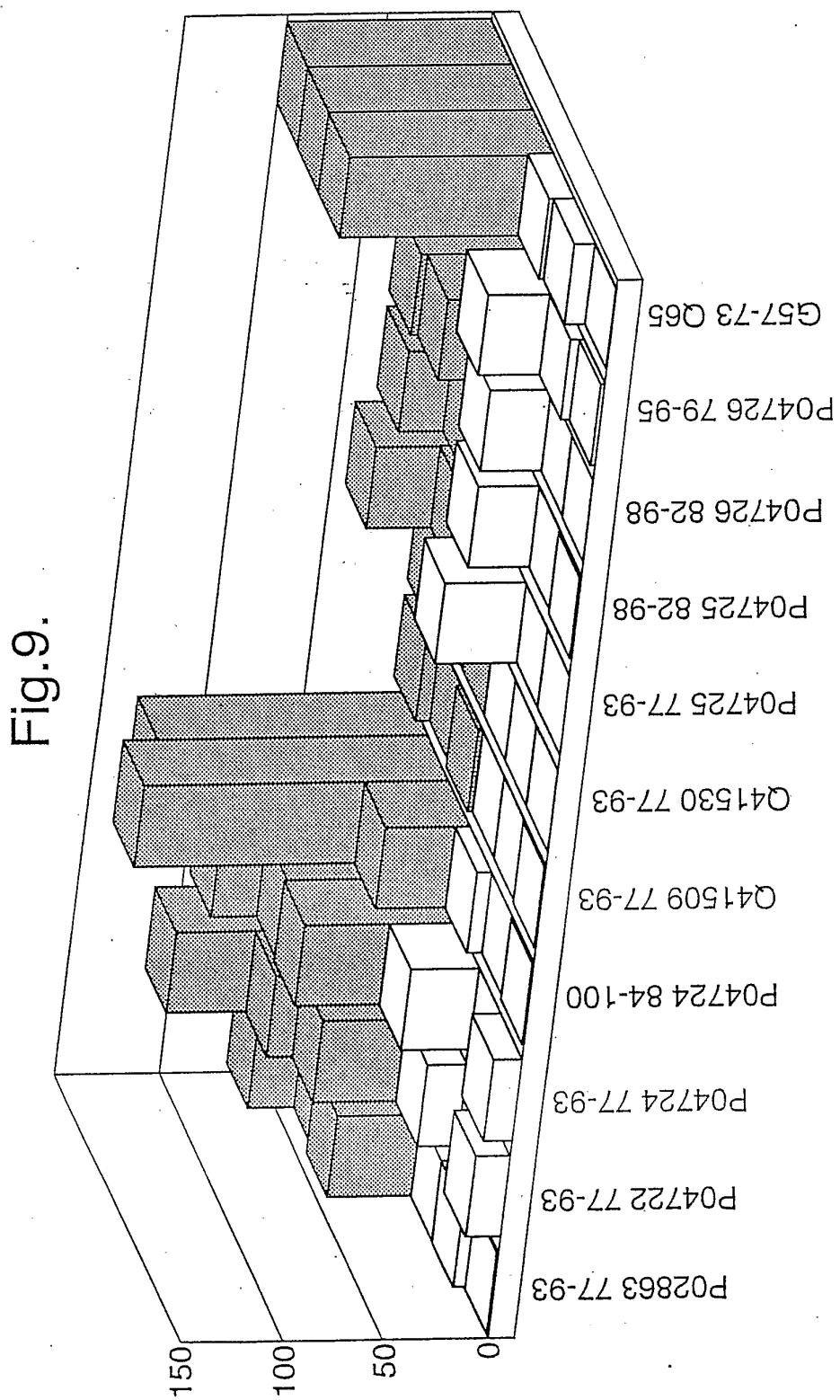
Fig.10.
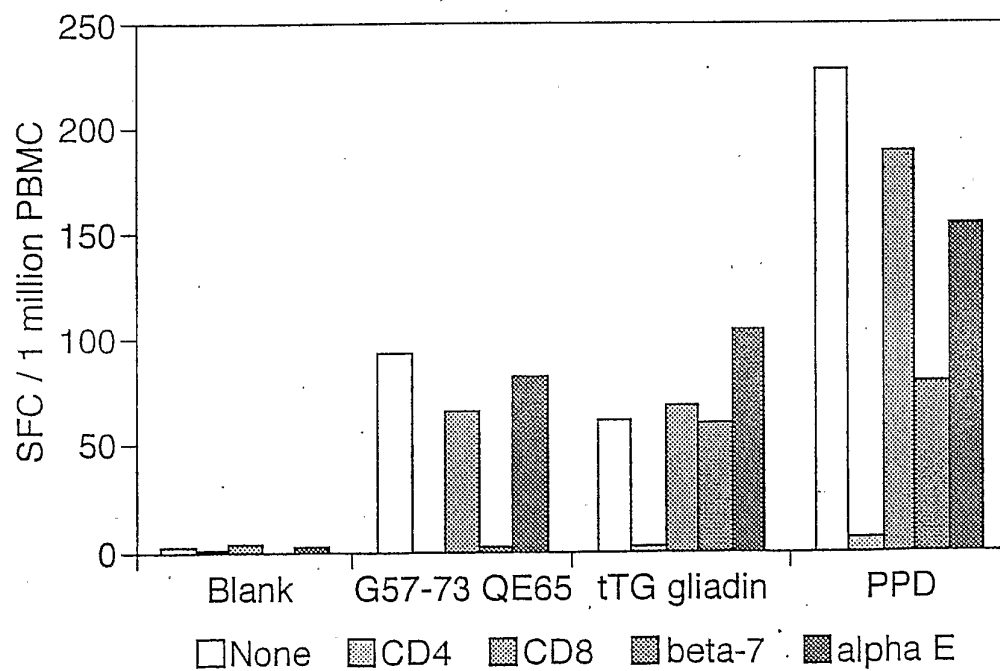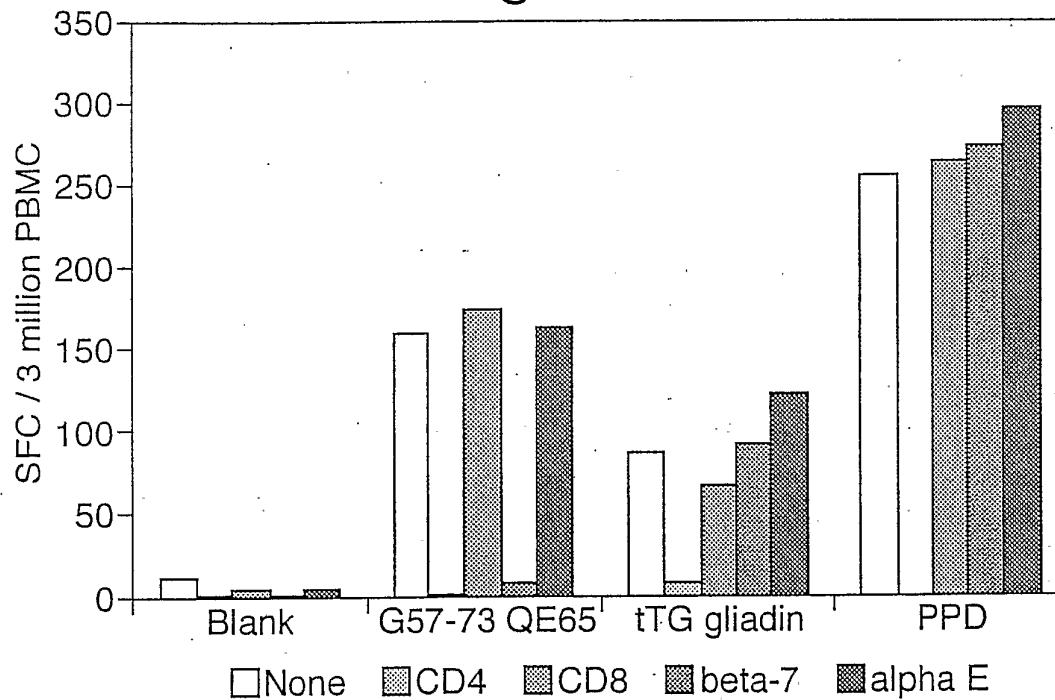
Fig.11.

Peptide length and bioactivity: Means (n=4)
A-gliadin 57-73 QE65 (17aa)=100%
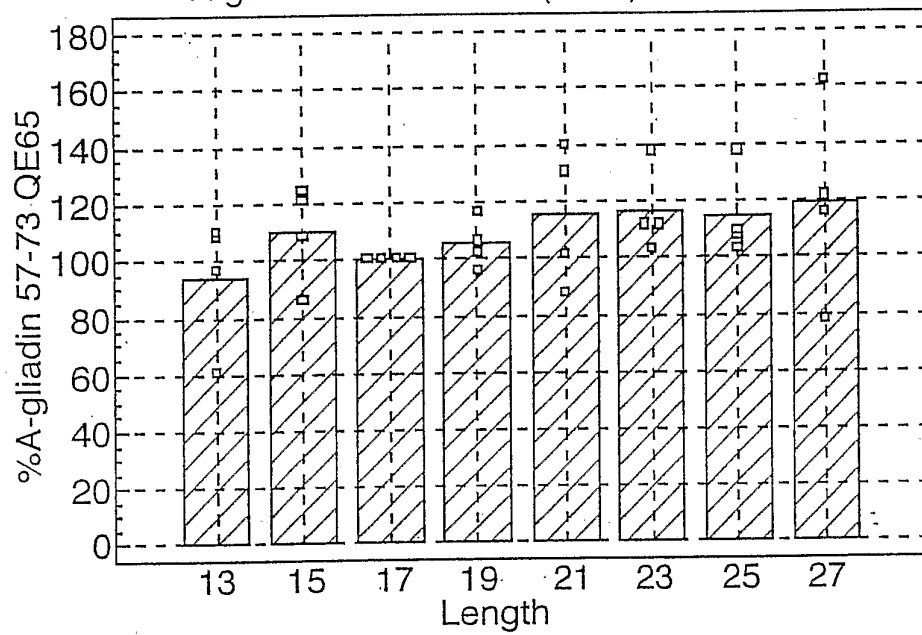
Fig.12a.

Dose response to A-gliadin 57-73 QE65:
QLQPFPQPELPYPQPQS.

A-gliadin 57-73 QE65 (mean+SEM,n=4)
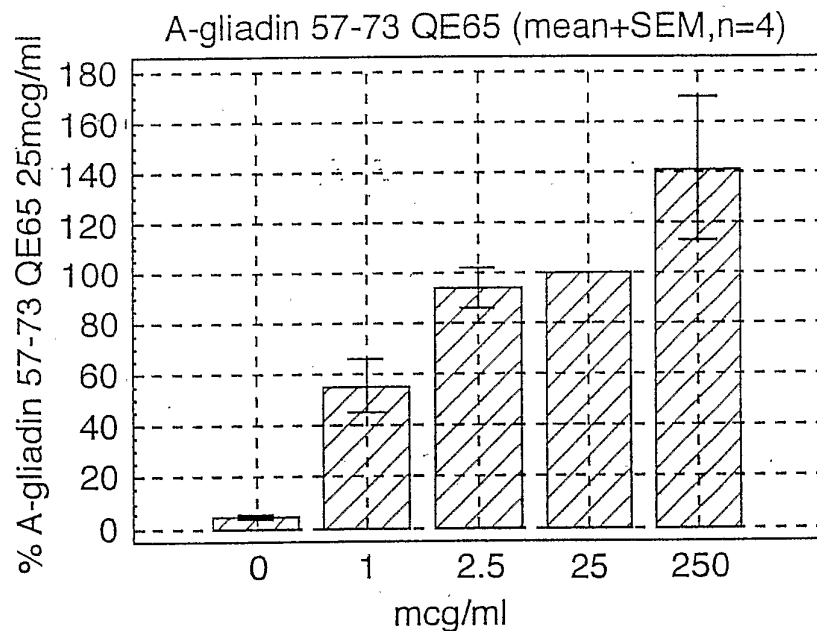
Fig.12b.

Dose response to GDA4_WHEAT P04724 84-100 QE92:
PQLPYPQPELPYPQPQP.

GDA4 84-100 QE92 (sequence K) (mean+SEM,n=4)
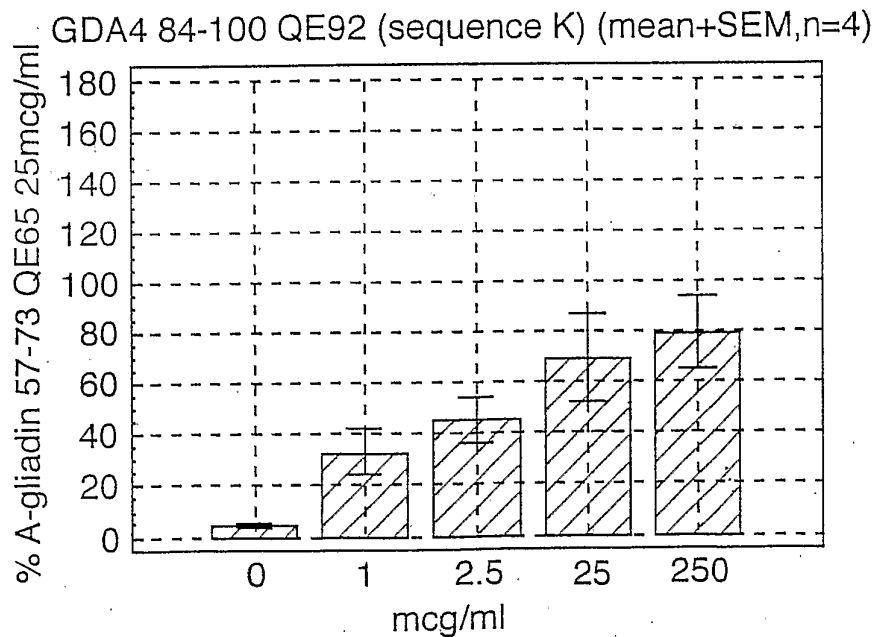
Fig.12c.

Dose response to A-gliadin 57-73:
QLQPFPQPQLPYPQPQS (2.5, 25 & 250 mcg/ml),
and A-gliadin 57-73 (25 mcg/ml) + tTG treatment.

A-gliadin 57-73 (mean+SEM,n=4)
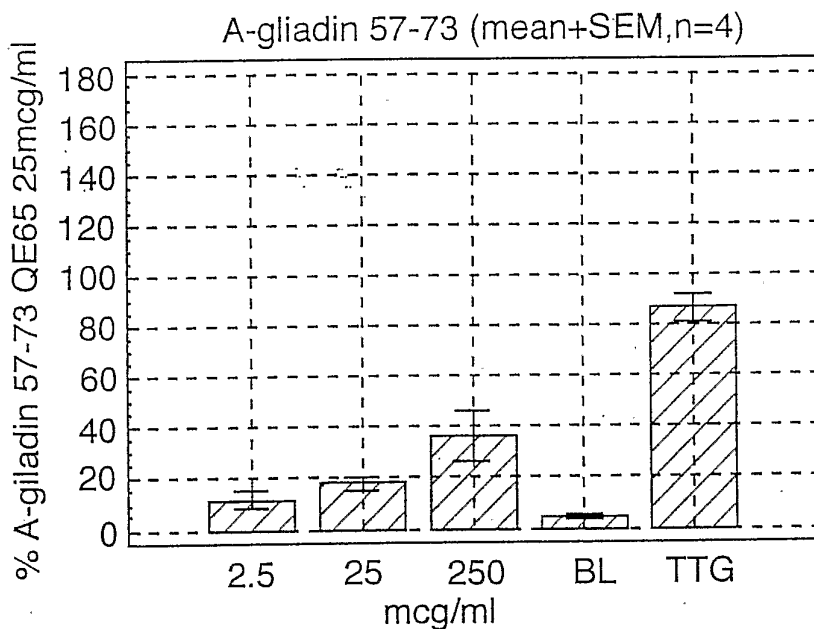
Fig.12d.

Dose response to GDA4_WHEAT P04724 84-100:
PQLPYPQPQLPYPQPQP (2.5, 25 & 250 mcg/ml),
and P04724 84-100 (25 mcg/ml) + tTG treatment.

GDA4 84-100 Q92 (mean+SEM,n=4)
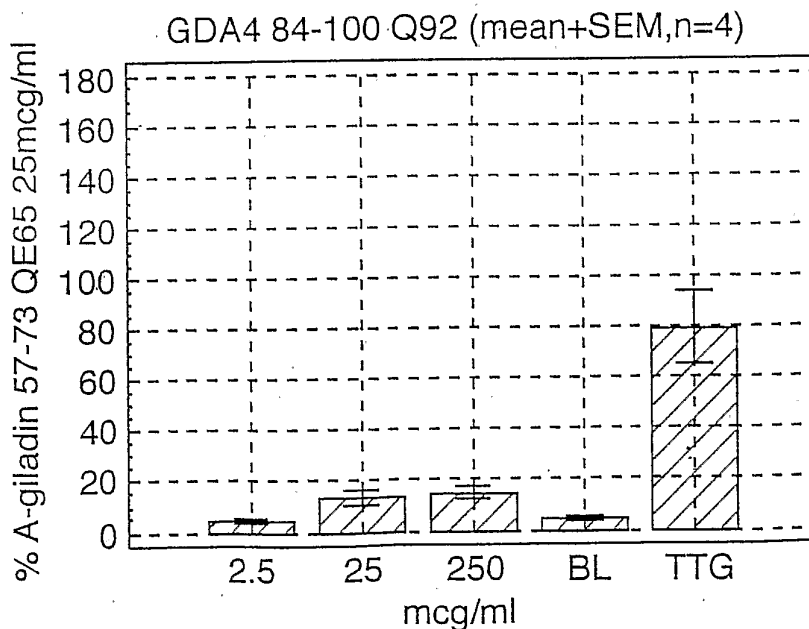
Fig.12e.

Dose response to the DQ2-restricted α gliadin T
cell epitope A-gliadin 57-68 QE65:
QLQPFPQPELPY (E65) (2.5, 25 & 250 mcg/ml),
and A-gliadin 57-68: QLQPFPQPQLPY (Q65)
(25 mcg/ml) +/- tTG treatment.

A9 57-68 (mean+SEM,n=4)
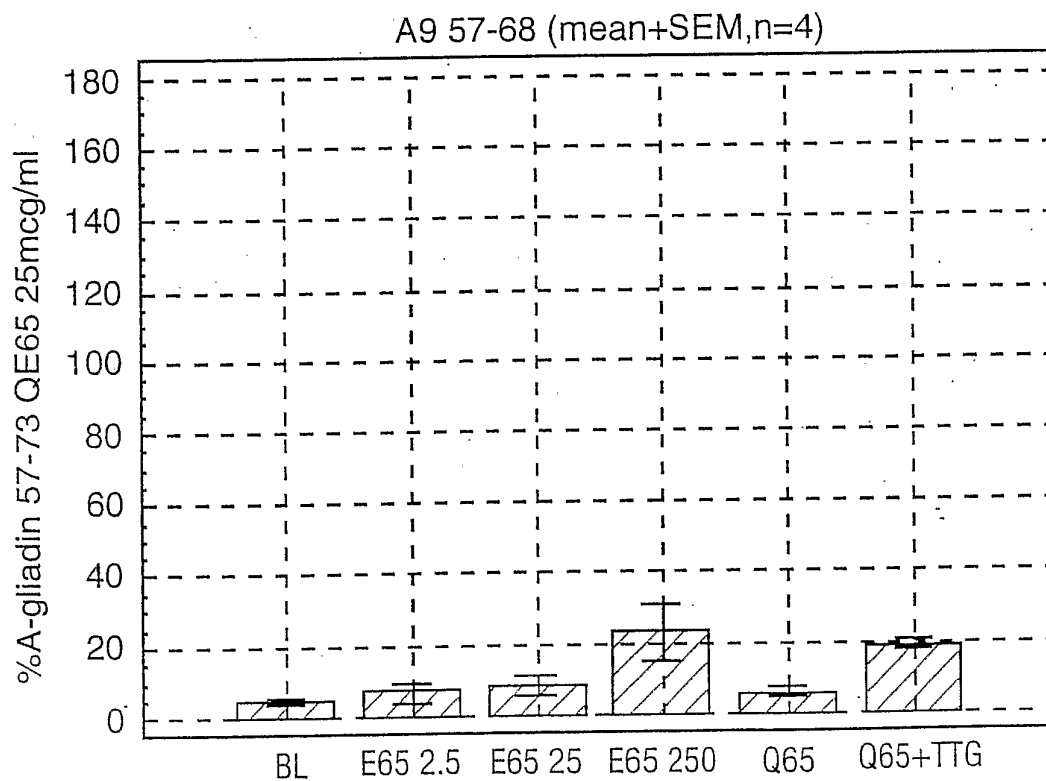
Fig.12f.

Dose response to the DQ2-restricted α gliadin T
cell epitope α–2 62-75 QE65 & QE72:
PQPELPYPQPELPY (E65) (2.5, 25 & 250
mcg/ml), and α–2 62-75: PQPQLPYPQPQLPY
(Q65) (25 mcg/ml) +/- tTG treatment.

A2 62-75 (mean+SEM,n=4)
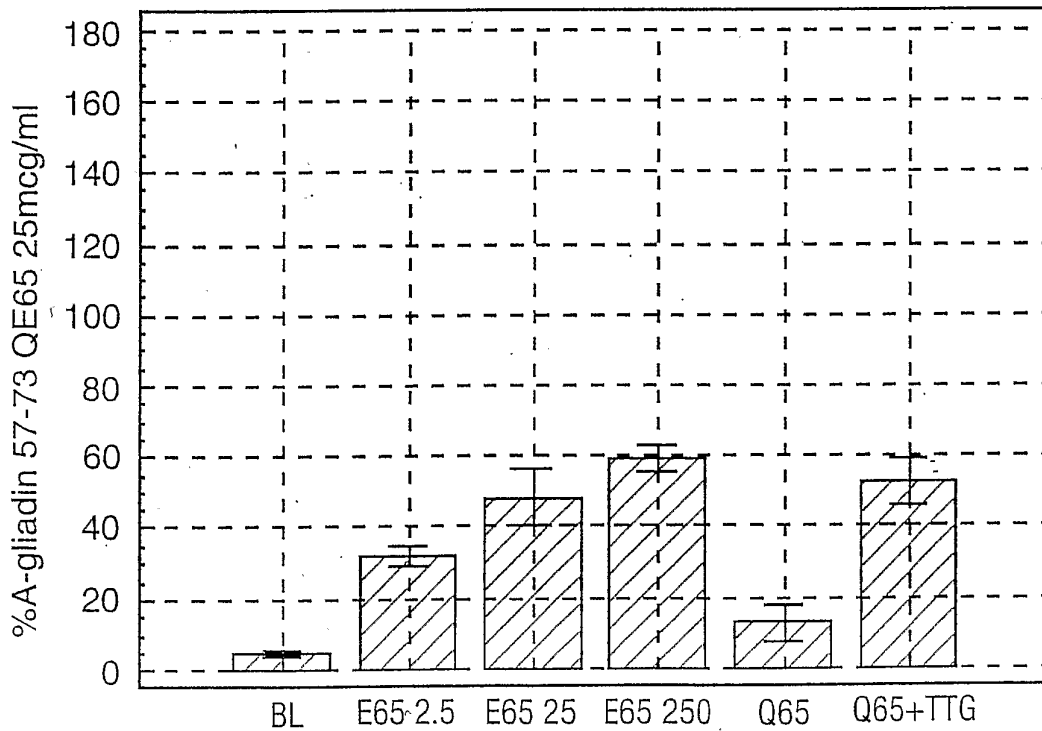
Fig.12g.

Dose response to the DQ8-restricted α gliadin T cell epitope GDA9 202-219: QE208 & 216: QQYPSGEGSFQPSQENPQ (E) (25 & 250 mcg/ml), and to GDA9 202-219 QQYPSGQGSFQPSQQNPQ (Q) (25 mcg/ml) +/- tTG treatment.

GDA09 202-219 (mean+SEM,n=4)
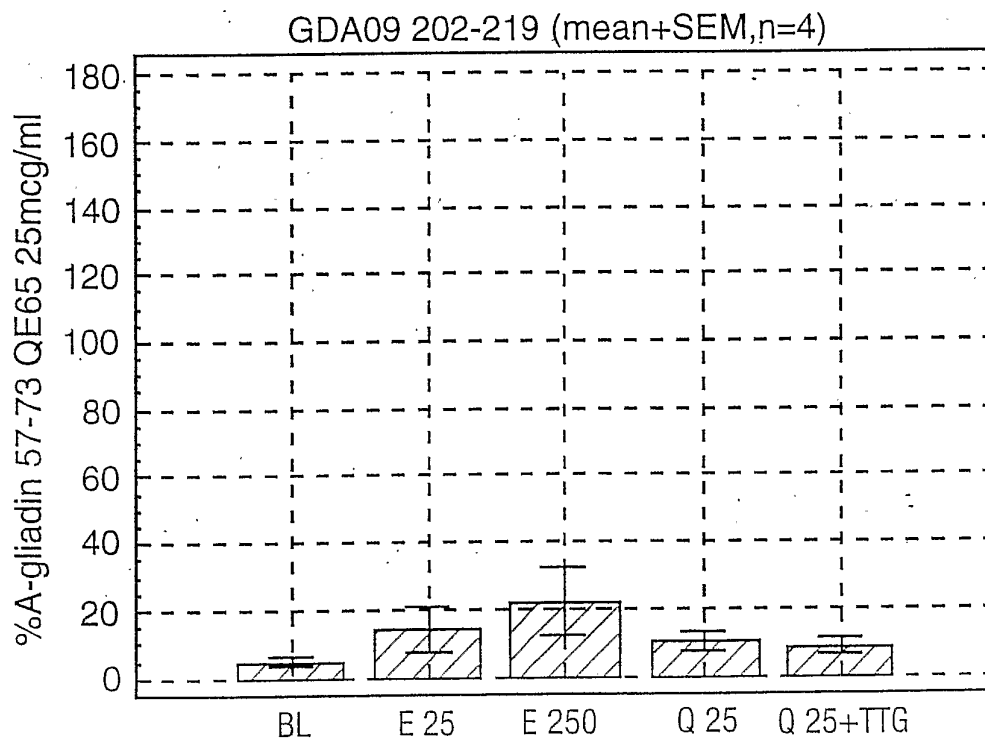
Fig.12h.

Dose response to the DQ2-restricted γ gliadin T
cell epitope GDB2 134-153 QE140, 148,150:
QQLPQPEQPQQSFPEQERPF (E) (25 & 250
mcg/ml), and to GDB2 134-153:
QQLPQPQQPQQSFPQQQRPF (Q) (25 mcg/ml) +/- tTG treatment.

GDB2 134-153 (mean+SEM,n=4)
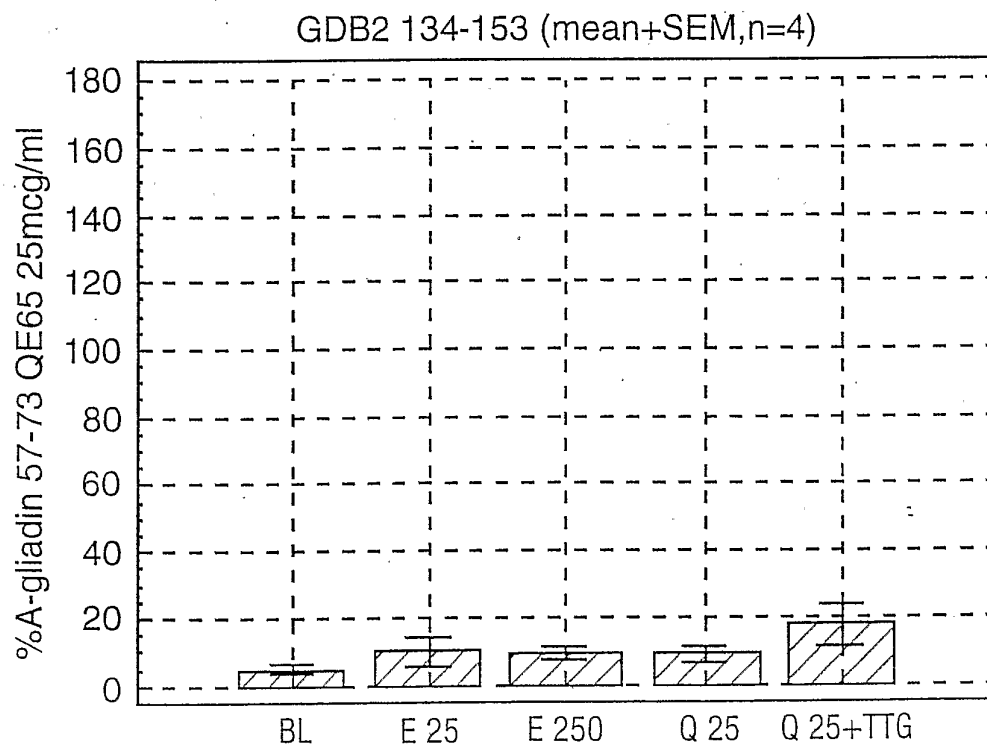
Fig.13a.

Dose response to gliadin digest by
chymotrysin.

Gliadin digest (mean+SEM, n=4)
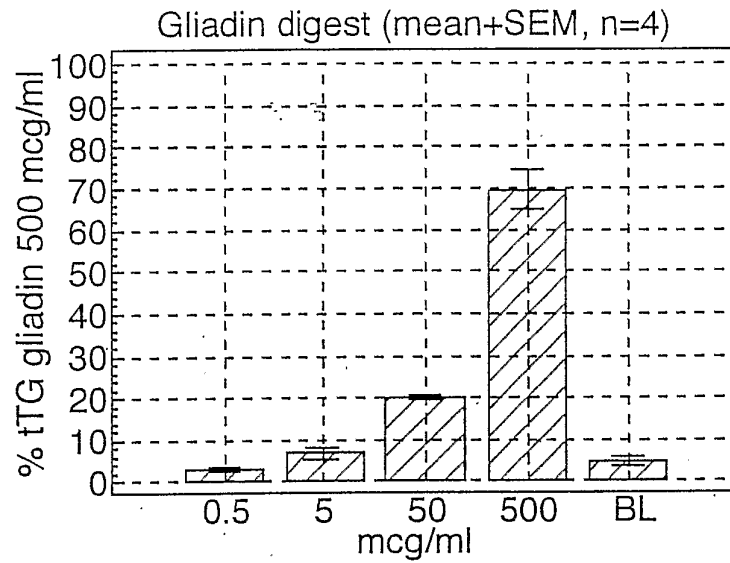
Fig.13b.

Dose response to gliadin digested by
chymotrysin then treated with tTG.

tTG-treated gliadin digest (mean+SEM, n=4)
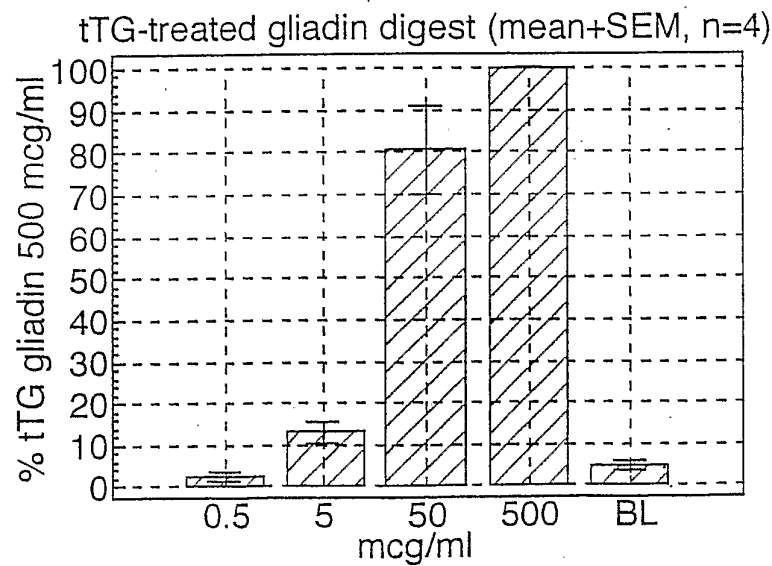
Fig.13c.

Total ELISpot responses to A-gliadin 57-73 QE65
(25mcg/ml) versus A-gliadin 57-73 QE65 responses
as percent of tTG gliadin (500mcg/ml) responses.

Responses to dominant epitope and complete antigen
(A-gliadin 57-73 QE65 and tTG-treated gliadin)
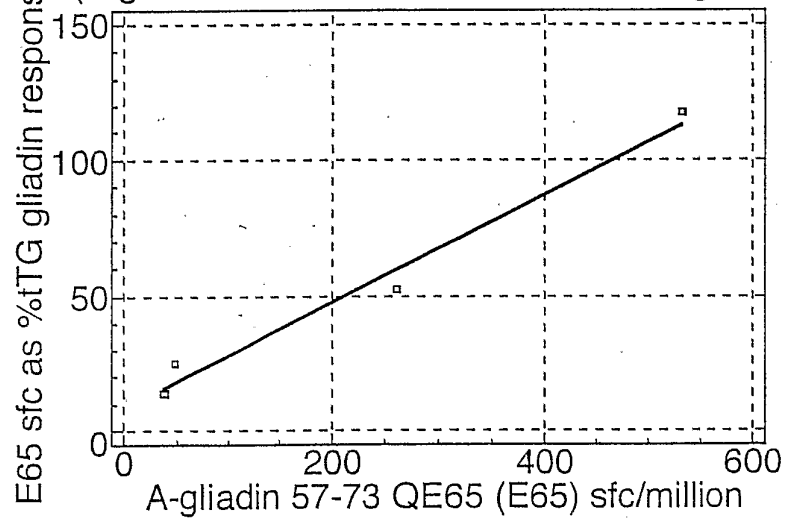
(Fig.14.)

Bioactivity of gliadin polymorphisms of A-gliadin 57-73
(A) in coeliac subjects 6/7 days after gluten challenge
(Gamma-Interferon Elispot) (n=4).

Fig.14a.

A QLQPFPQPQLPYPQPQS
B QLQPFPQPQLPYPQPQP
C QLQPFPQPQLPYPQPQL
D QLQPFPQPQLPYLQPQS
E QLQPFPRPQLPYPQPQP
F QLQPFPQPQLPYSQPQP
G QLQPFLQPQLPYSQPQP
H QLQPFSQPQLPYSQPQP

I QLQPFPQPQLSYSQPQP
J QPQPFPPPQLPYPQTQP
K PQLPYPQPQLPYPQPQP
L PQLPYPQPQLPYPQPQL
M PQPQPFLPQLPYPQPQS
N PQPQPFPPQLPYPQPQS
O PQPQPFPPQLPYPQTQP
P PQPQPFPPQLPYPQPPP

Fig.14b.

tTG treated: Means (error bars: 1 SEM)

A	QLQPFPQPQLPYPQPQS
B	QLQPFPQPQLPYPQPQP
C	QLQPFPQPQLPYPQPQL
D	QLQPFPQPQLPYLQPQS
E	QLQPFPRPQLPYPQPQP
F	QLQPFPQPQLPYSQPQP
G	QLQPFLQPQLPYSQPQP
H	QLQPFSQPQLPYSQPQP

I	QLQPFPQPQLSYSQPQP
J	QPQPFPPPQLPYPQTQP
K	PQLPYPQPQLPYPQPQP
L	PQLPYPQPQLPYPQPQL
M	PQPQPFLPQLPYPQPQS
N	PQPQPFPPQLPYPQPQS
O	PQPQPFPPQLPYPQTQP
P	PQPQPFPPQLPYPQPPP

Fig.14c.

QE65 substituted (25 mcg/ml): Means (error bars: 1 SEM)
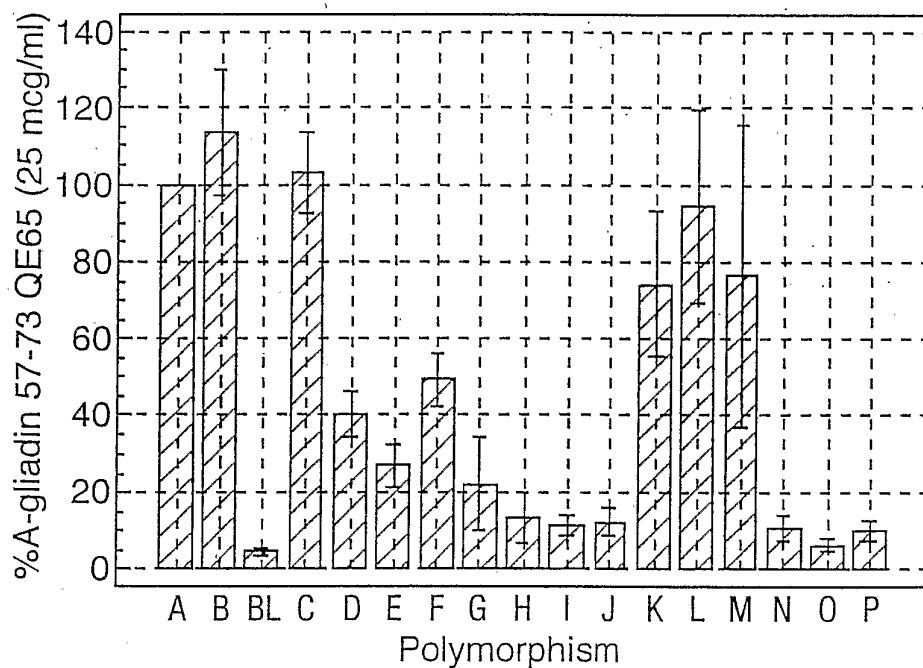
A QLQPFPQPQLPYPQPQS	I QLQPFPQPQLSYSQPQP
B QLQPFPQPQLPYPQPQP	J QPQPFPPPQLPYPQTQP
C QLQPFPQPQLPYPQPQL	K PQLPYPQPQLPYPQPQP
D QLQPFPQPQLPYLQPQS	L PQLPYPQPQLPYPQPQL
E QLQPFPRPQLPYPQPQP	M PQPQPFLPQLPYPQPQS
F QLQPFPQPQLPYSQPQP	N PQPQPFPPQLPYPQPQS
G QLQPFLQPQLPYSQPQP	O PQPQPFPPQLPYPQTQP
H QLQPFSQPQLPYSQPQP	P PQPQPFPPQLPYPQPPP

Fig.14d.

QE65-substituted (2.5 mcg/ml): Means (error bars: 1 SEM)
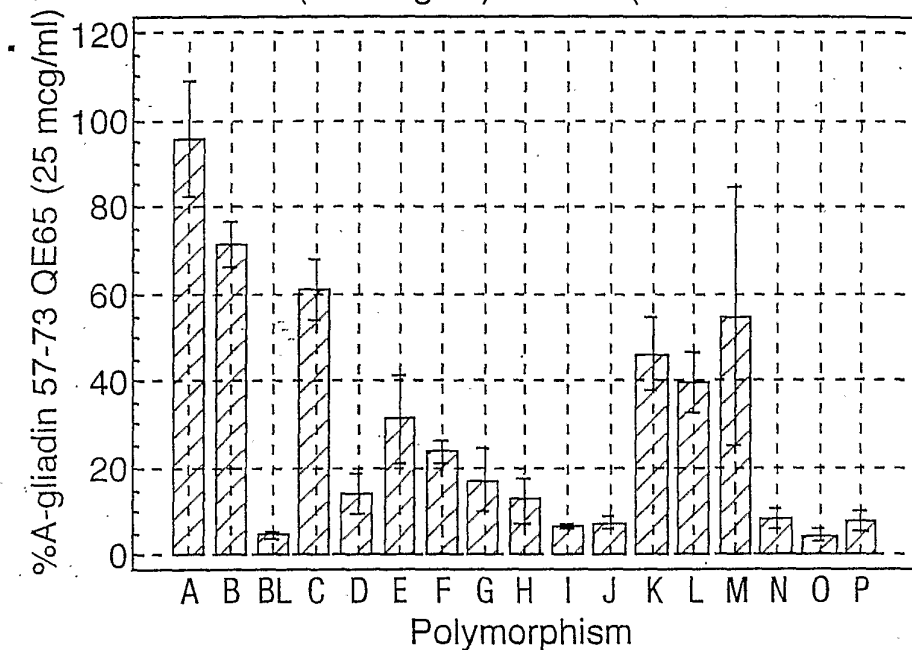
Fig.14e.

QE65-substituted (250 mcg/ml): Means (error bars: 1 SEM)
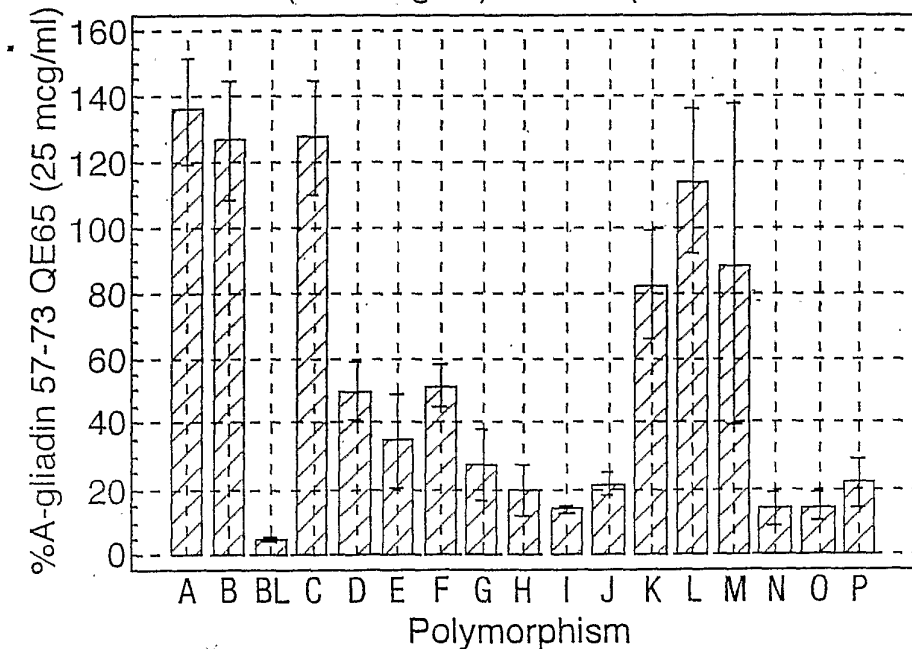
A	QLQPFPQPQLPYPQPQS	
B	QLQPFPQPQLPYPQPQP	
C	QLQPFPQPQLPYPQPQL	
D	QLQPFPQPQLPYLQPQS	
E	QLQPFPRPQLPYPQPQP	
F	QLQPFPQPQLPYSQPQP	
G	QLQPFLQPQLPYSQPQP	
H	QLQPFSQPQLPYSQPQP	
I	QLQPFPQPQLSYSQPQP	
J	QPQPFPPPQLPYPQTQP	
K	PQLPYPQPQLPYPQPQP	
L	PQLPYPQPQLPYPQPQL	
M	PQPQPFLPQLPYPQPQS	
N	PQPQPFPPQLPYPQPQS	
O	PQPQPFPPQLPYPQTQP	
P	PQPQPFPPQLPYPQPPP	

Fig.15.

Alanine scan: Means (error bars: 95% CI for mean)

Alanine at position
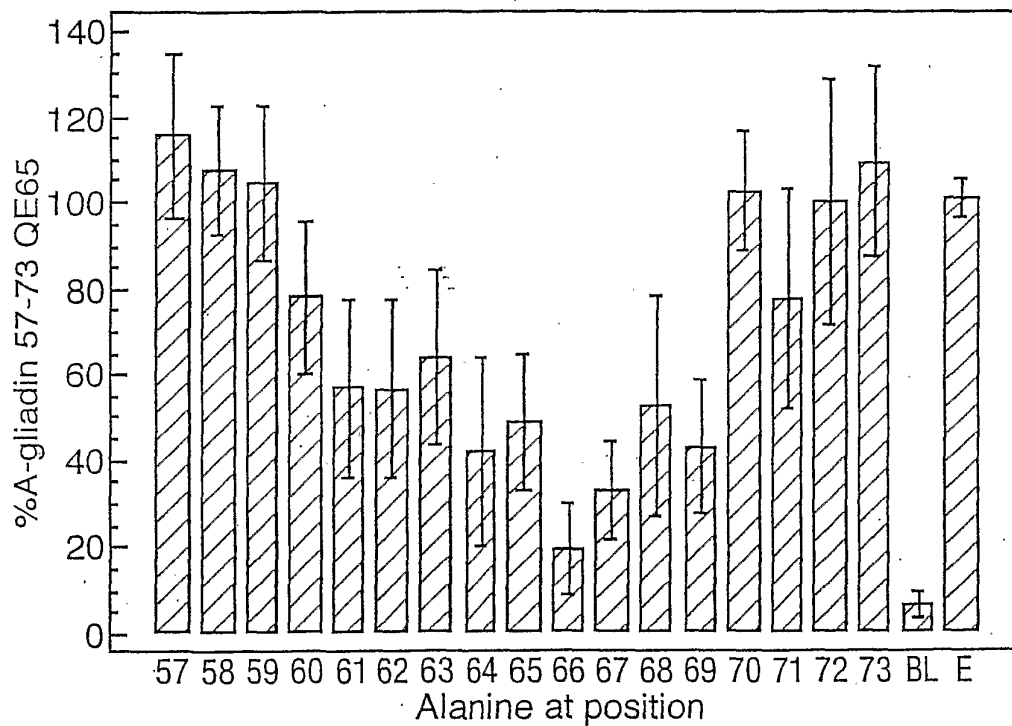
Fig.16.

Lysine scan: Means (error bars: 95% CI for mean)
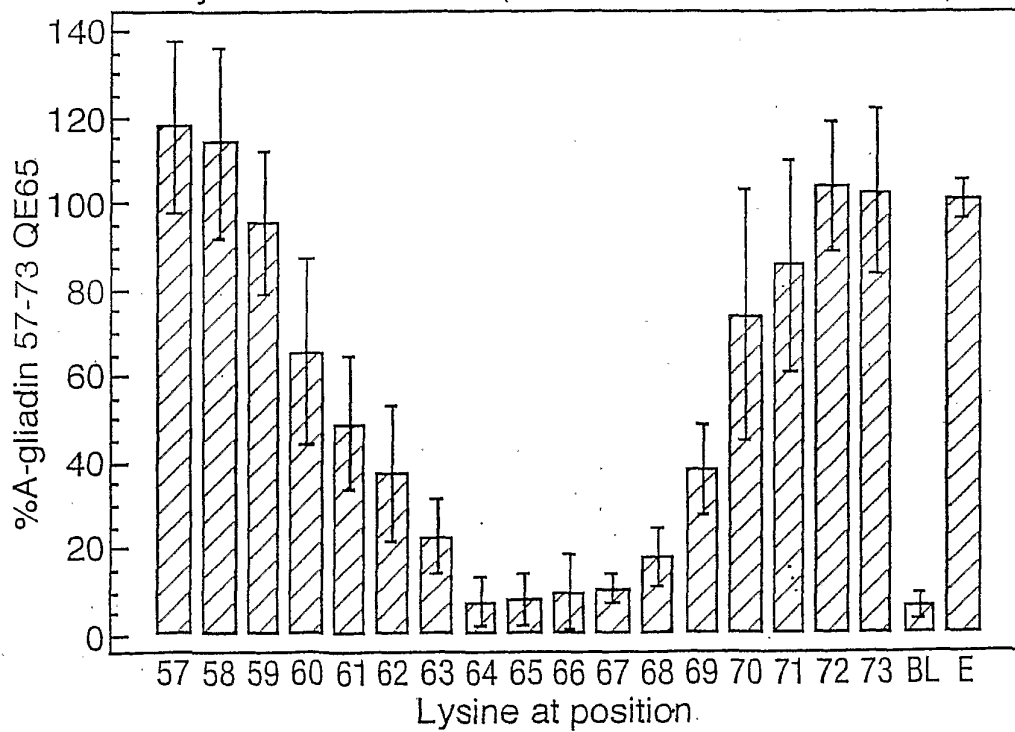
Lysine at position

Fig.17.

Agonist activity of A-gliadin 57-73 QE65 variants according
to position substituted (Mean of 8 coeliac subjects' PBMC
responses in interferon gamma ELISPOT after gluten challenge)
QLQ<u>PFPQPELPYPQP</u>QS
60..................70

P60: Means (error bars: 95% CI for mean)
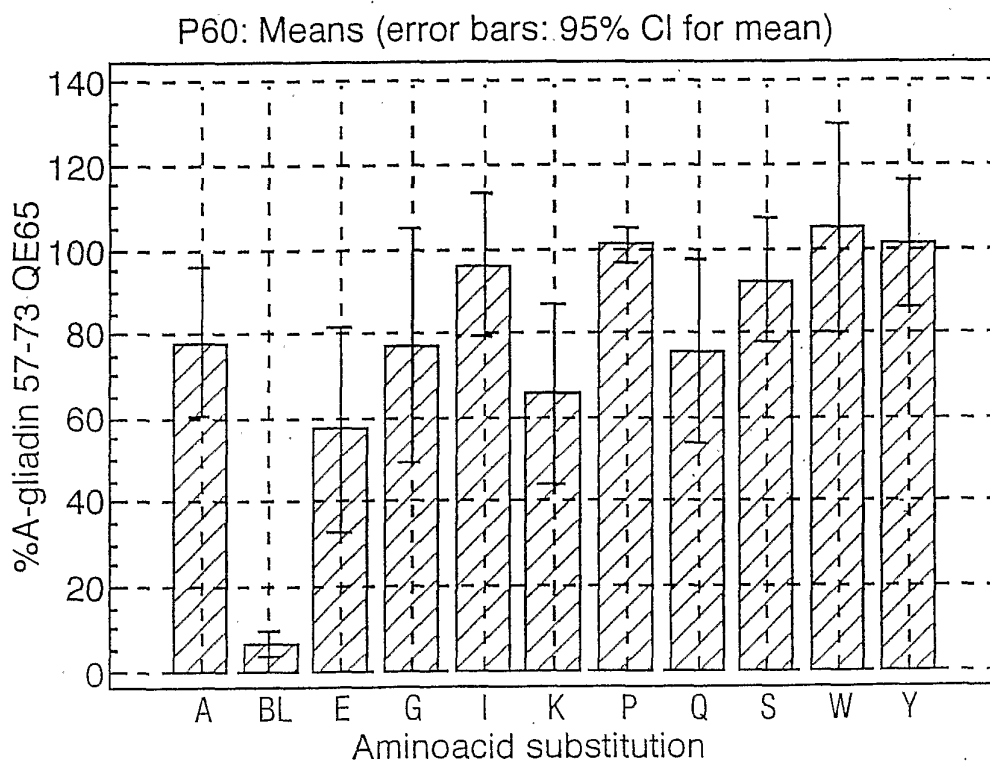
Fig.18.

Agonist activity of A-gliadin 57-73 QE65 variants according
to position substituted (Mean of 8 coeliac subjects' PBMC
responses in interferon gamma ELISPOT after gluten challenge)
QLQP<u>FPQPELPYPQ</u>PQS
60...................70

F61: Means (error bars: 95% CI for mean)
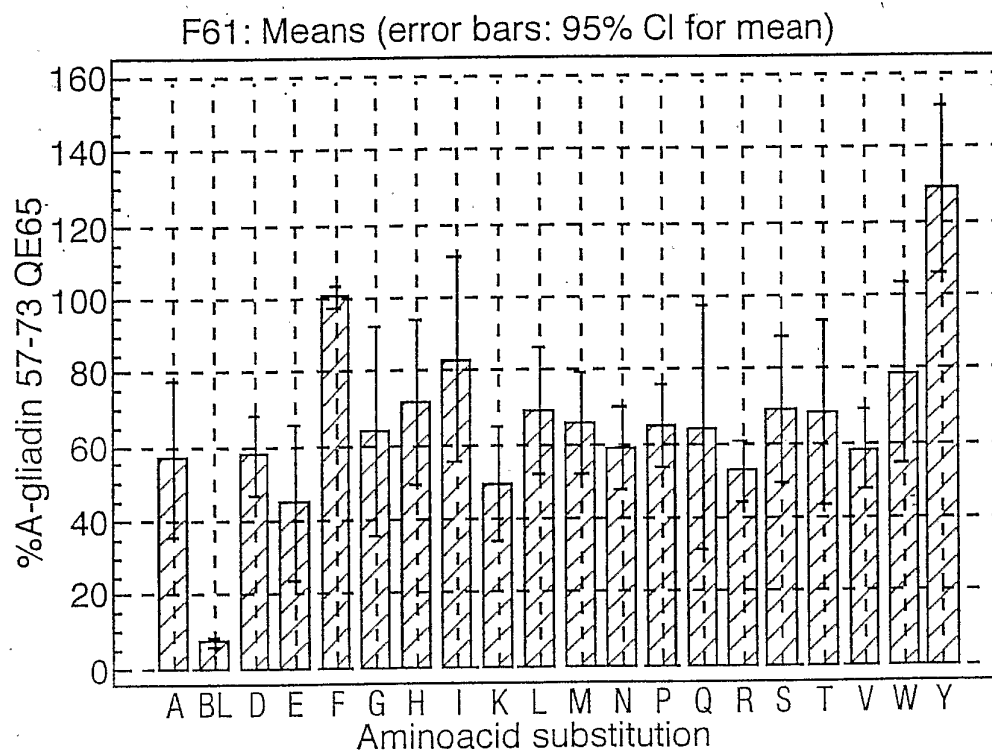
Fig.19.

Agonist activity of A-gliadin 57-73 QE65 variants according
to position substituted (Mean of 8 coeliac subjects' PBMC
responses in interferon gamma ELISPOT after gluten challenge)
QLQPFPQPELPYPQPQS
60..................70

P62 Means (error bars: 95% CI for mean)
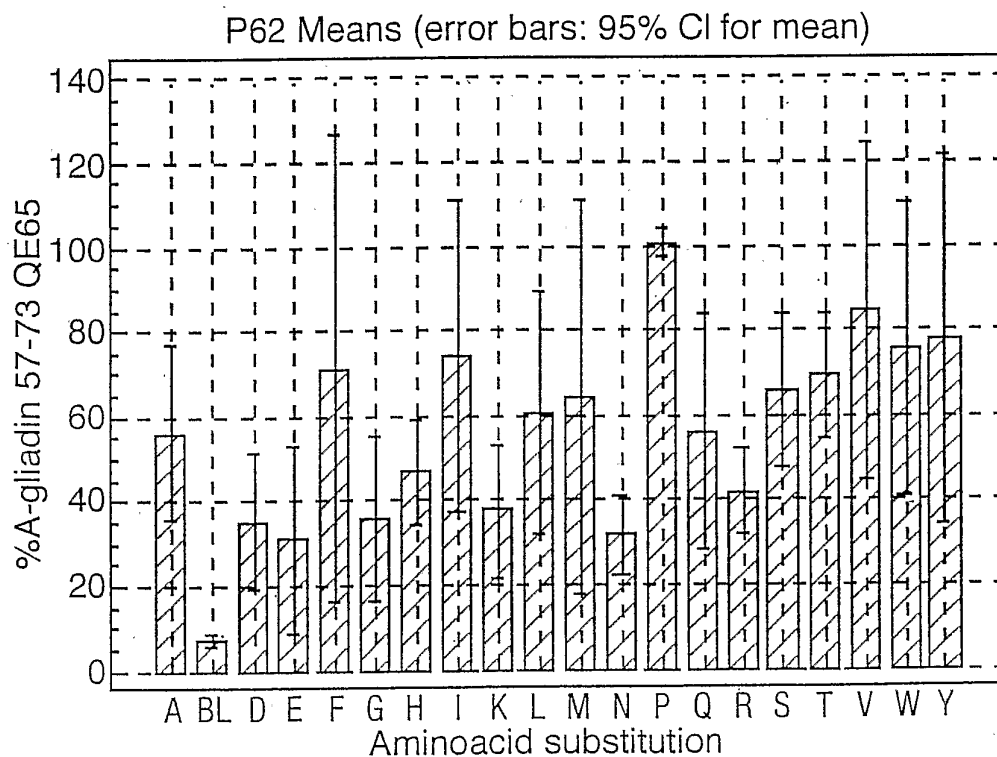
Fig.20.

Agonist activity of A-gliadin 57-73 QE65 variants according
to position substituted (Mean of 8 coeliac subjects' PBMC
responses in interferon gamma ELISPOT after gluten challenge)
QLQPFPQPELPYPQPQS
60...................70

Q63 Means (error bars: 95% CI for mean)

Fig.21.

Agonist activity of A-gliadin 57-73 QE65 variants according
to position substituted (Mean of 8 coeliac subjects' PBMC
responses in interferon gamma ELISPOT after gluten challenge)
QLQPFPQPELPYPQPQS
60...................70

P64 Means (error bars: 95% CI for mean)

Fig.22.

Agonist activity of A-gliadin 57-73 QE65 variants according
to position substituted (Mean of 8 coeliac subjects' PBMC
responses in interferon gamma ELISPOT after gluten challenge)
QLQPFPQPELPYPQPQS
60................70

E65 Means (error bars: 95% CI for mean)
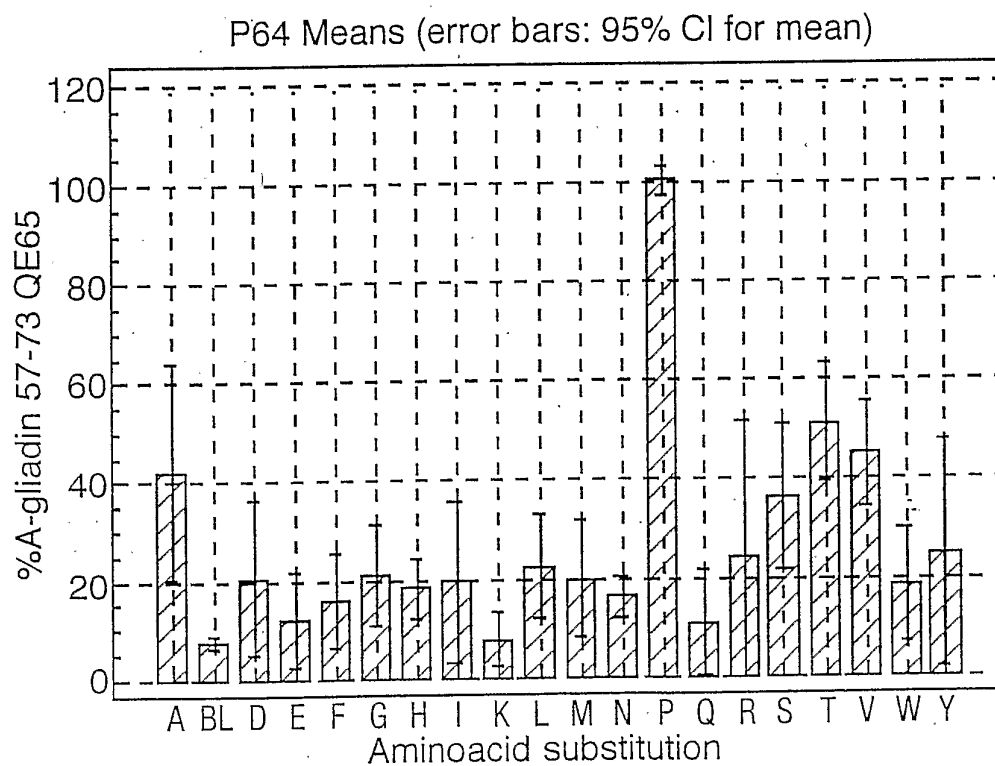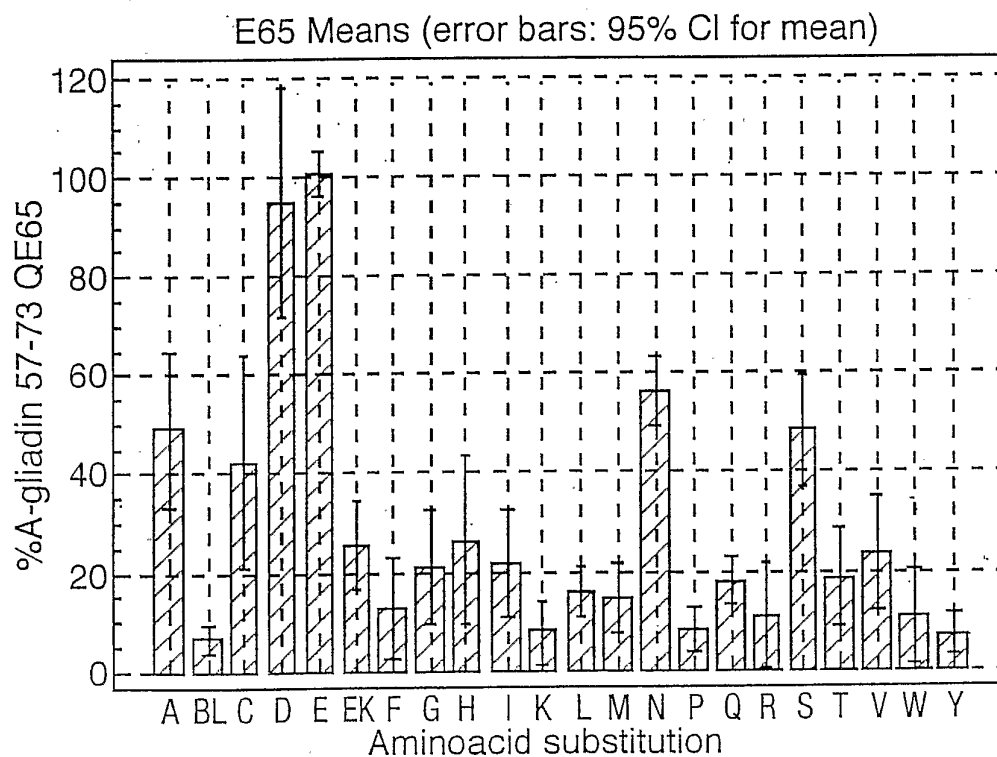
Fig.23.

Agonist activity of A-gliadin 57-73 QE65 variants according
to position substituted (Mean of 8 coeliac subjects' PBMC
responses in interferon gamma ELISPOT after gluten challenge)
QLQP<u>FPQPELPYPQP</u>QS
60.................70

L66 Means (error bars: 95% CI for mean)
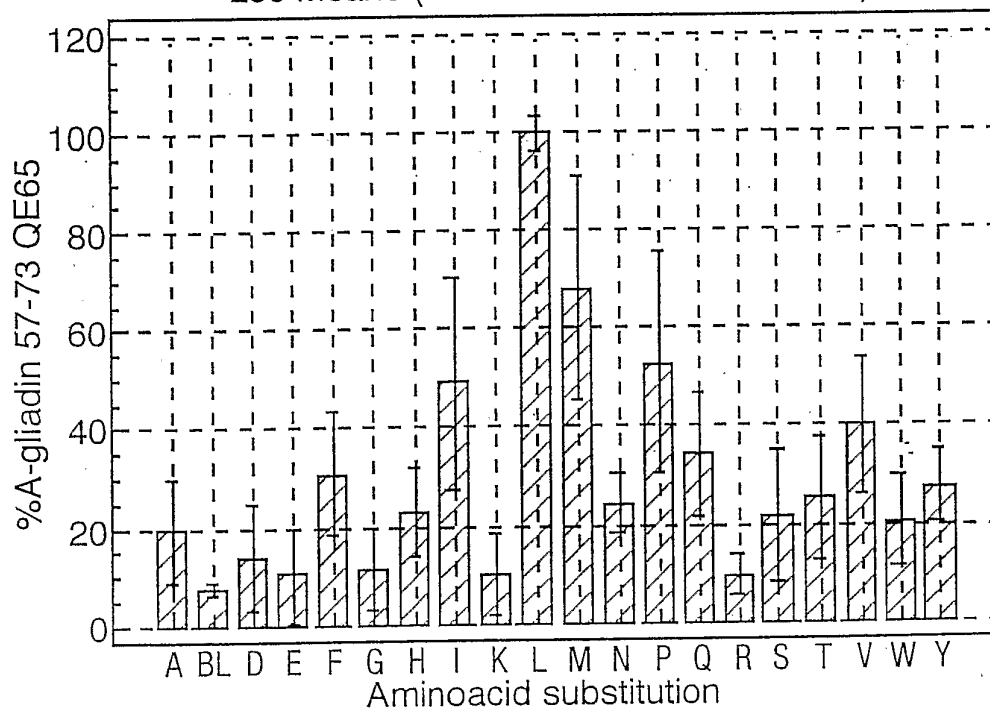
Fig.24.

Agonist activity of A-gliadin 57-73 QE65 variants according
to position substituted (Mean of 8 coeliac subjects' PBMC
responses in interferon gamma ELISPOT after gluten challenge)
QLQ<u>PFPQPELPYPQ</u>PQS
60.................70

P67 Means (error bars: 95% CI for mean)

Fig.25.

Agonist activity of A-gliadin 57-73 QE65 variants according
to position substituted (Mean of 8 coeliac subjects' PBMC
responses in interferon gamma ELISPOT after gluten challenge)
QLQPFPQPELPYPQPQS
60..................70

Y68 Means (error bars: 95% CI for mean)

Fig.26.

Agonist activity of A-gliadin 57-73 QE65 variants according
to position substituted (Mean of 8 coeliac subjects' PBMC
responses in interferon gamma ELISPOT after gluten challenge)
QLQ<u>PFPQPELPYPQPQS</u>
60...................70

P69 Means (error bars: 95% CI for mean)

Fig.27.

Agonist activity of A-gliadin 57-73 QE65 variants according
to position substituted (Mean of 8 coeliac subjects' PBMC
responses in interferon gamma ELISPOT after gluten challenge)
QLQPFPQPELPYPQPQS
60................70

Q70 Means (error bars: 95% CI for mean)

(Fig.28.)

Interferon gamma ELISpot responses in newly diagnosed
and treated coeliac subjects, before and after gluten challenge.

Fig.28a.   Untreated, newly diagnosed coeliacs(Mean+SEM,n=9)

Fig.28b.

One week GFD (Mean+SEM,n=4)

Fig.28c.

Day 6 gluten challenge after 1wk GFD (Mean+SEM,n+4)

Fig.28d.

Two weeks GFD (Means+SEM,n=3)

Fig.28e.

Day 6 gluten challenge after 2 wk GFD (Means+SEM,n=3)

Fig.28f.

2 months GFD (Mean+SEM,n=3)

Fig.28g.

Day 6 gluten challenge after 2 mo GFD (Mean+SEM,n=3)
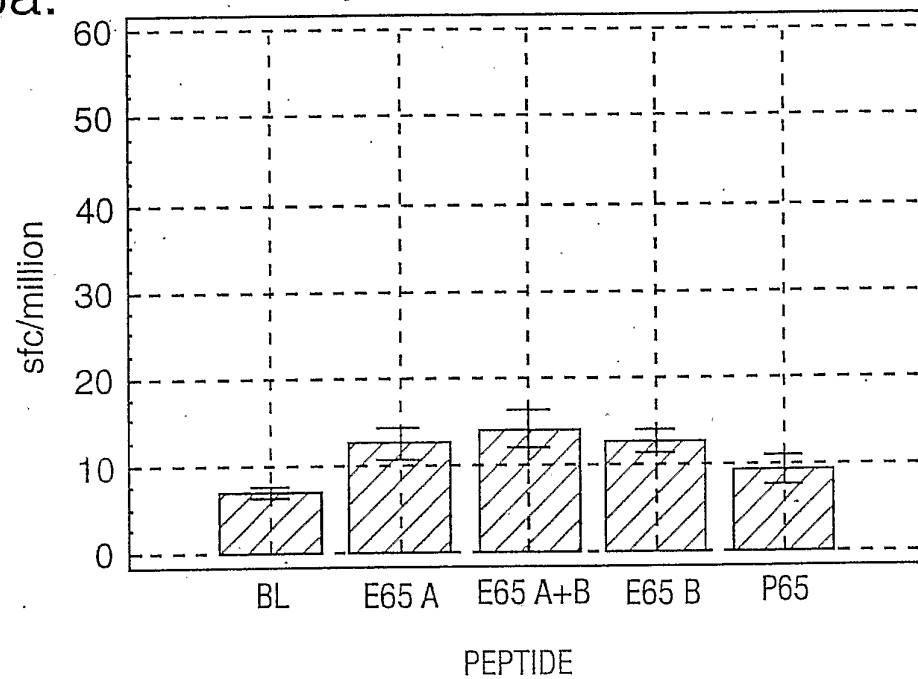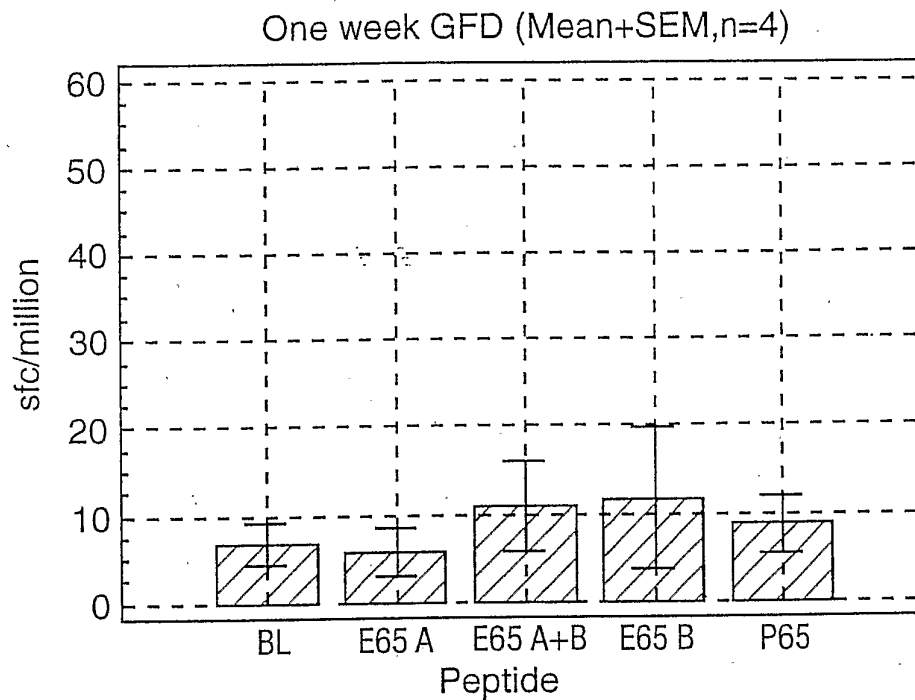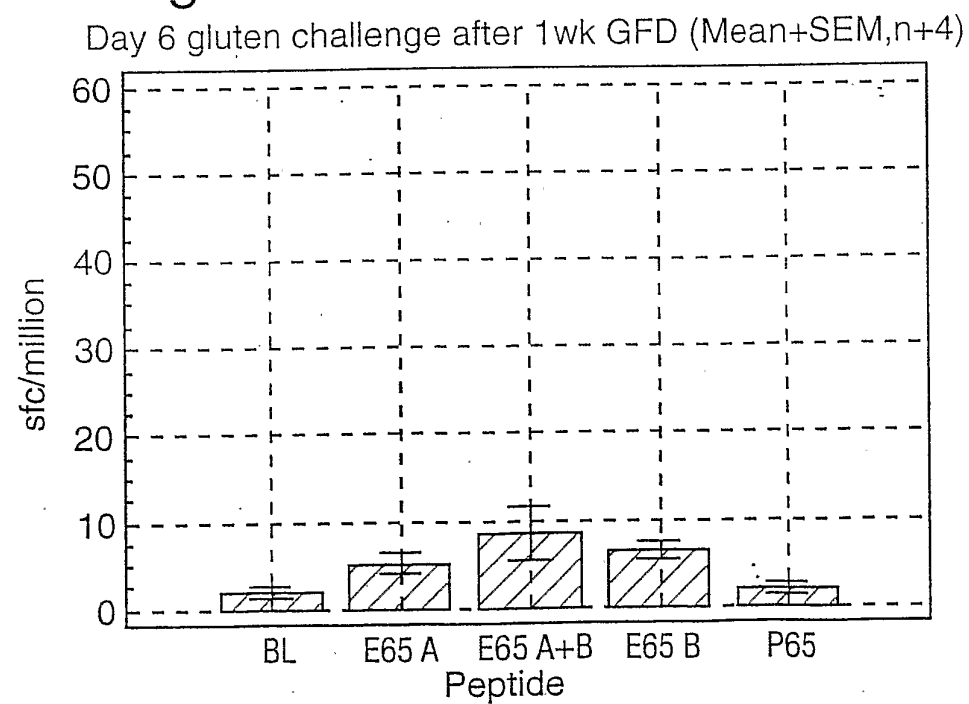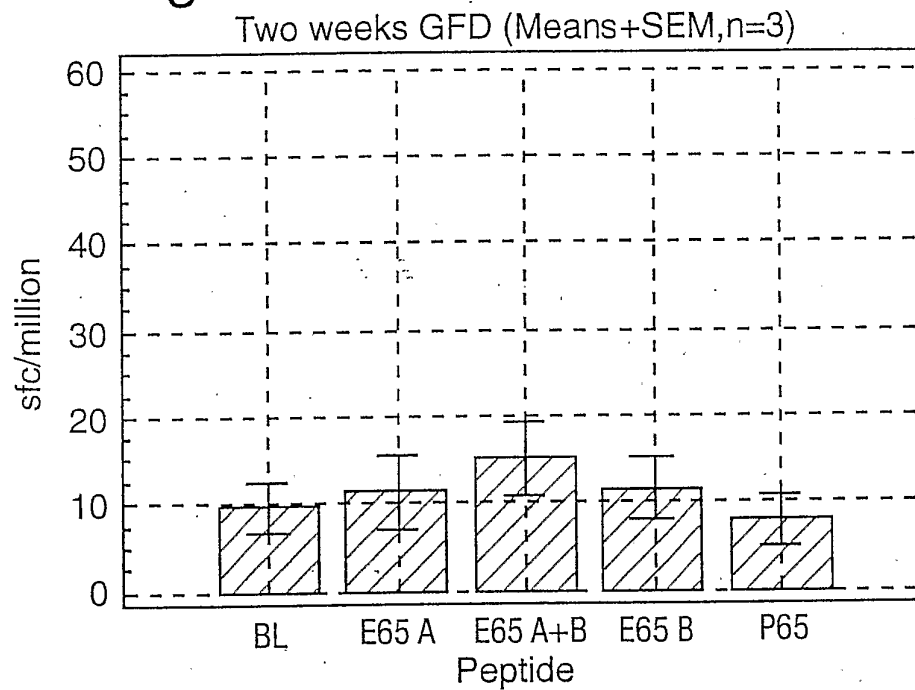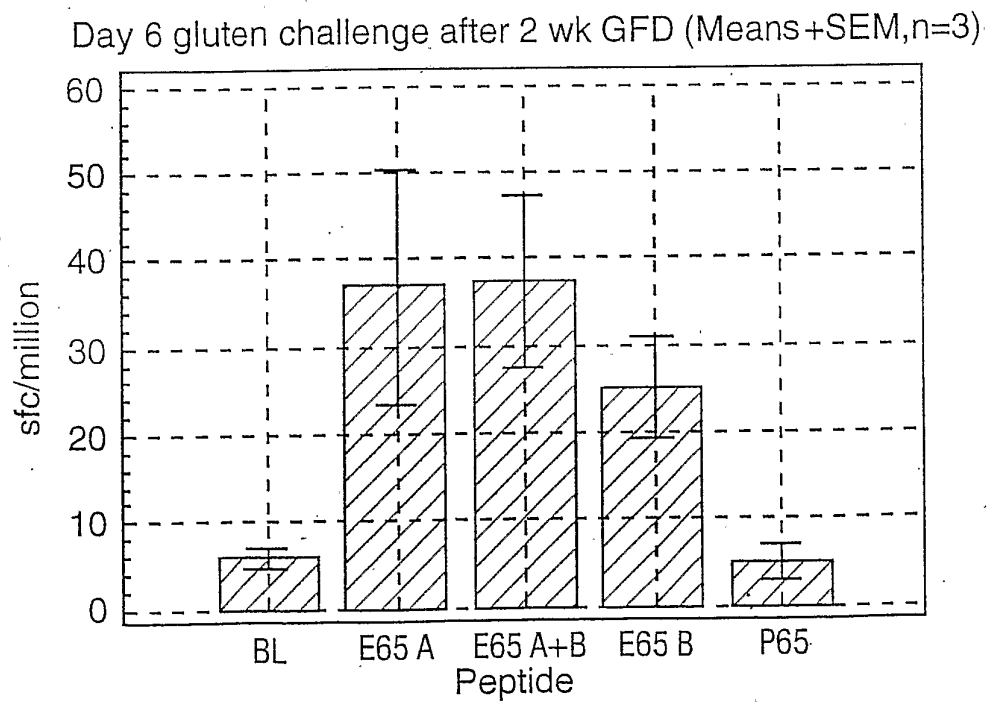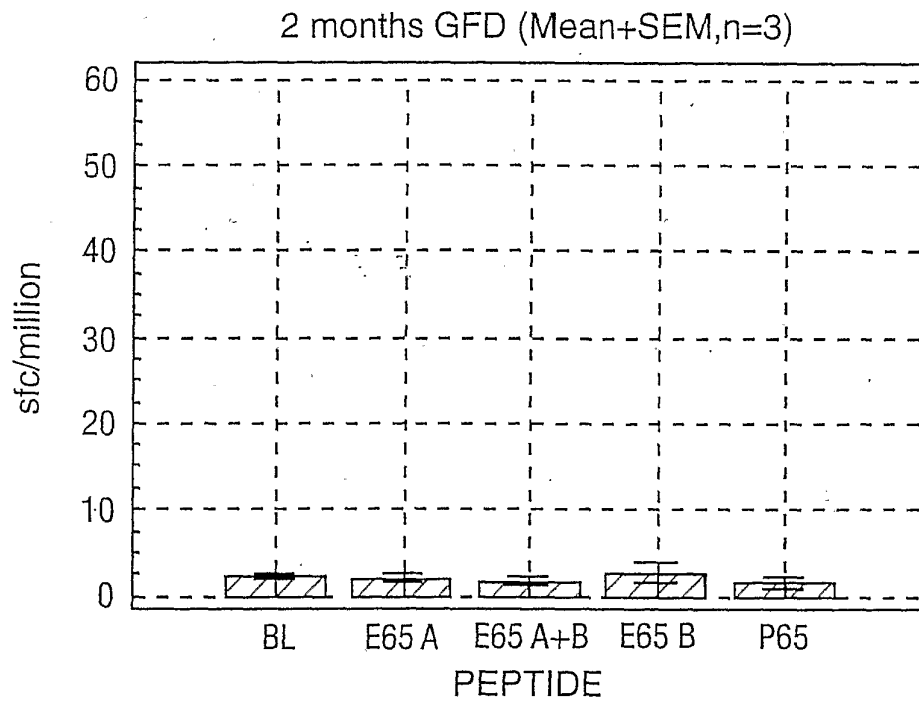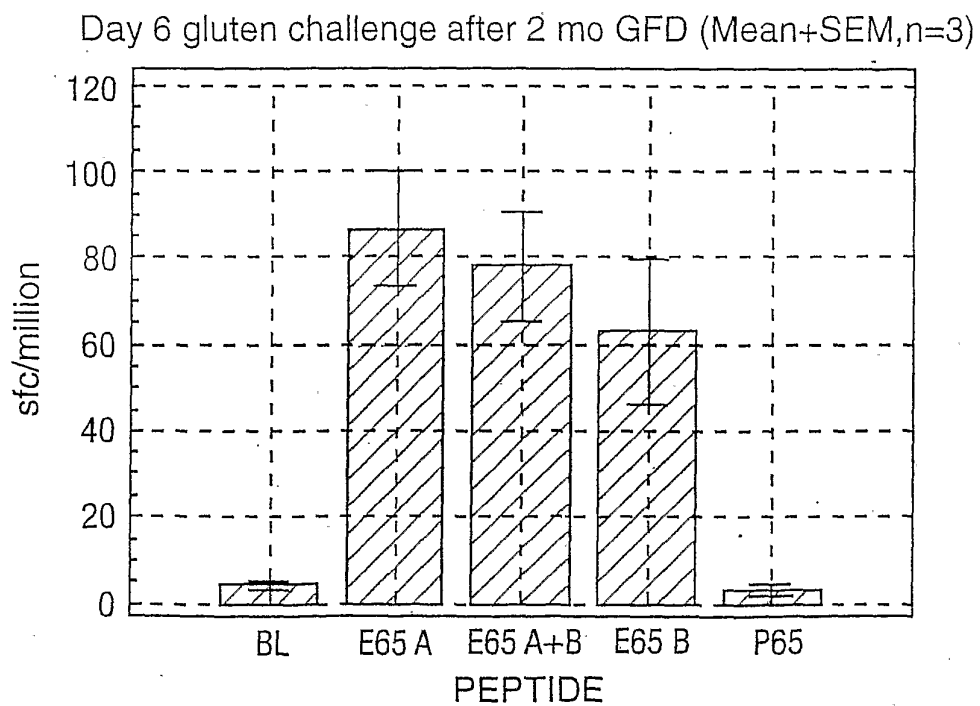
Figure 29. Bioactivity of prolamin homologues of A-gliadin 57-73 (IFNg-ELISpot, mean+SEM, n=6)
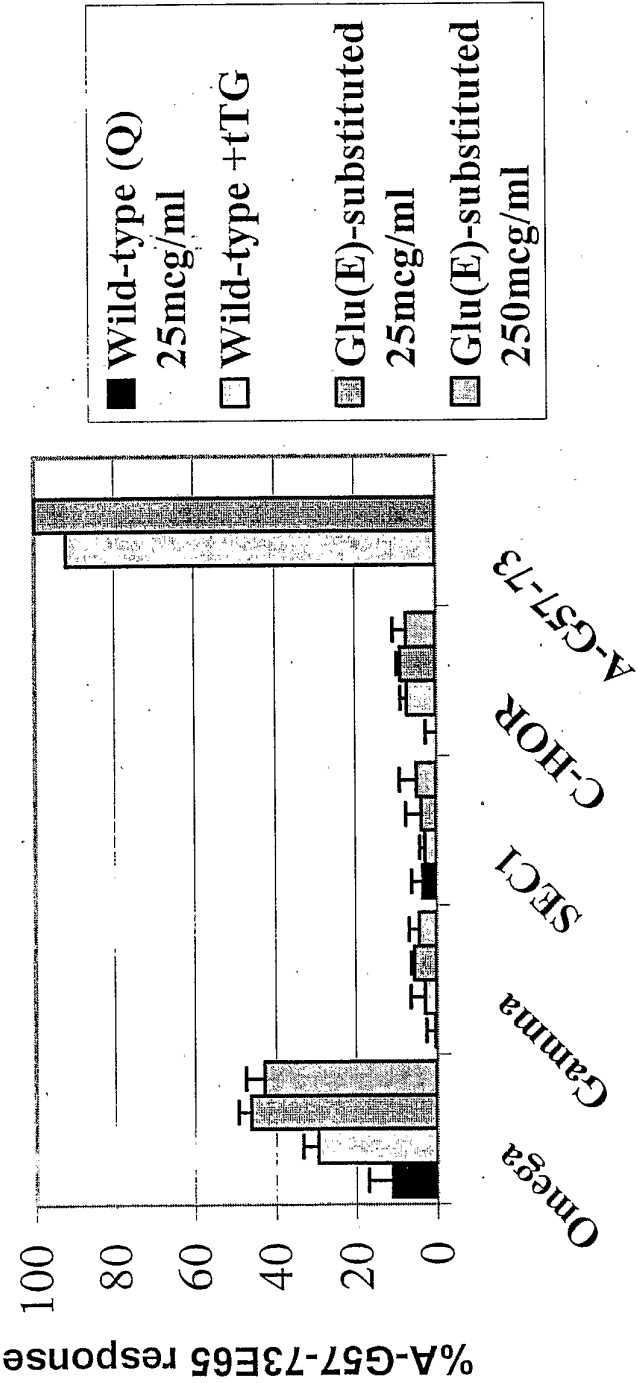
Omega: AAG17702 (141-157), Gamma: :P21292 (96-112), SEC1: Q43639 (335-351), C-HOR: Q40055 (166-182). E-substituted peptides were synthesized with E for Q at position 9.

Figure 30. Healthy HLA-DQ2 Subjects: Change in IFNgamma ELISpot Responses to tTG-deamidated Gliadin Peptide Pools (median change Day 6 vs Day 0, n=10)
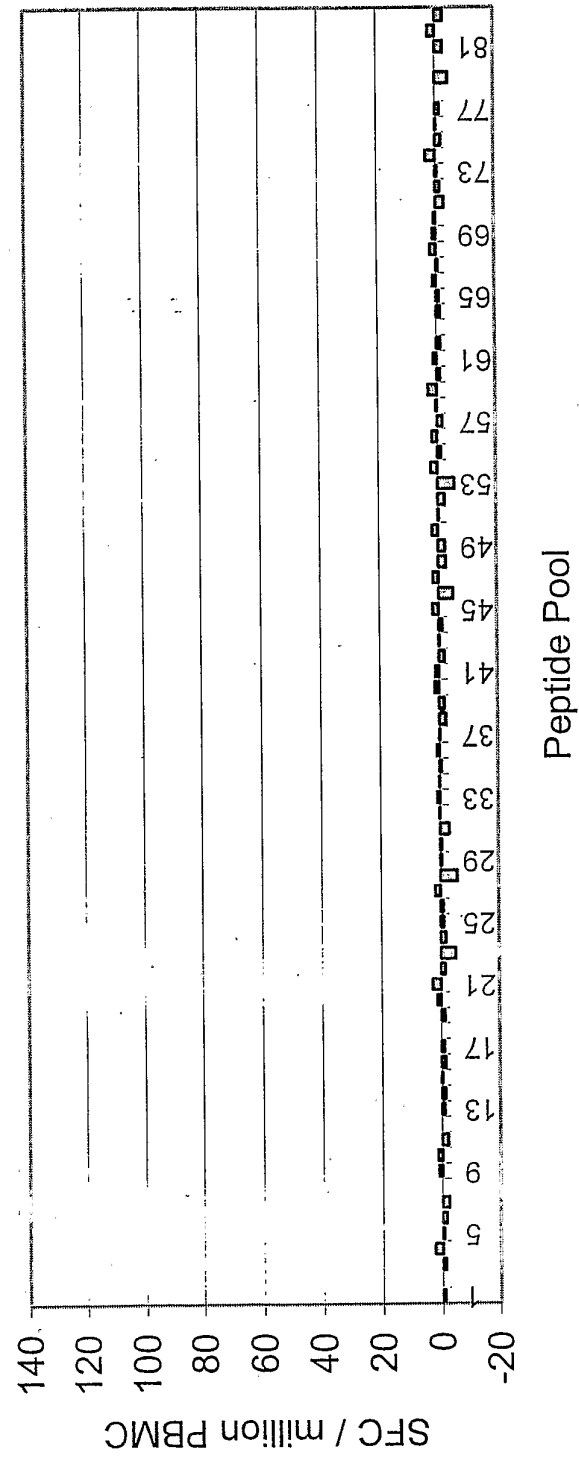
Figure 31. Coeliac HLA-DQ2 Subjects: Change in IFNgamma ELISpot Responses to tTG-deamidated Gliadin Peptide Pools (median change Day 6 vs Day 0, n=6)
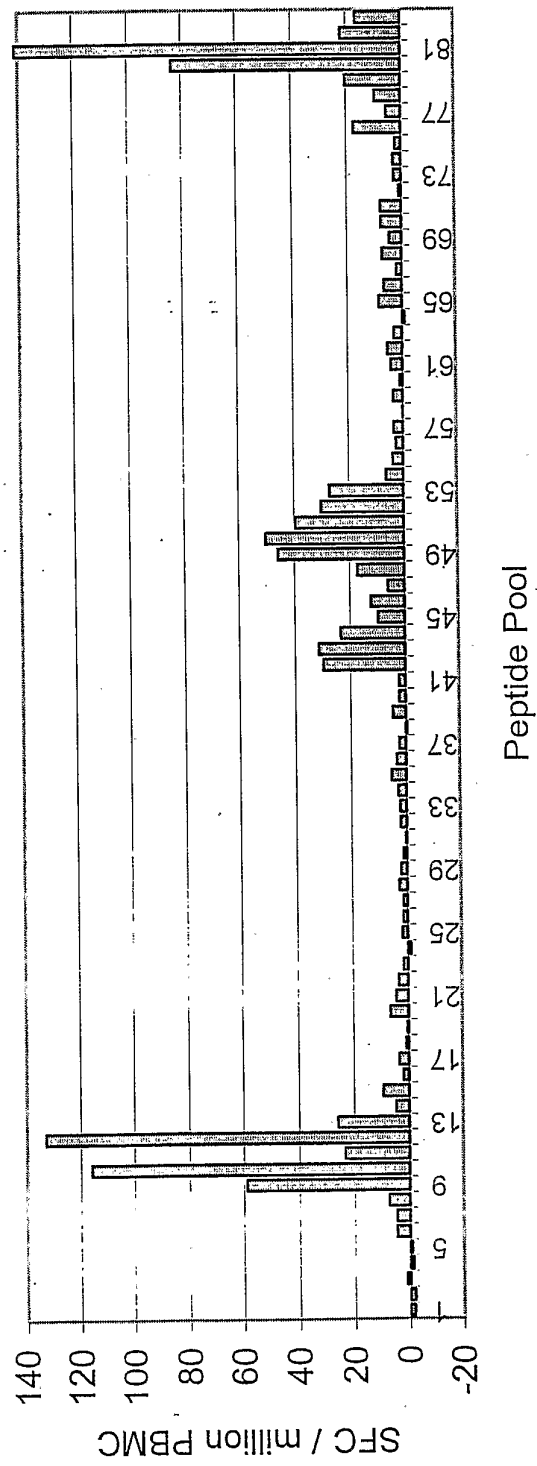
Figure 32. Individual Peptide Contributions to "Summed" Gliadin Peptide Response
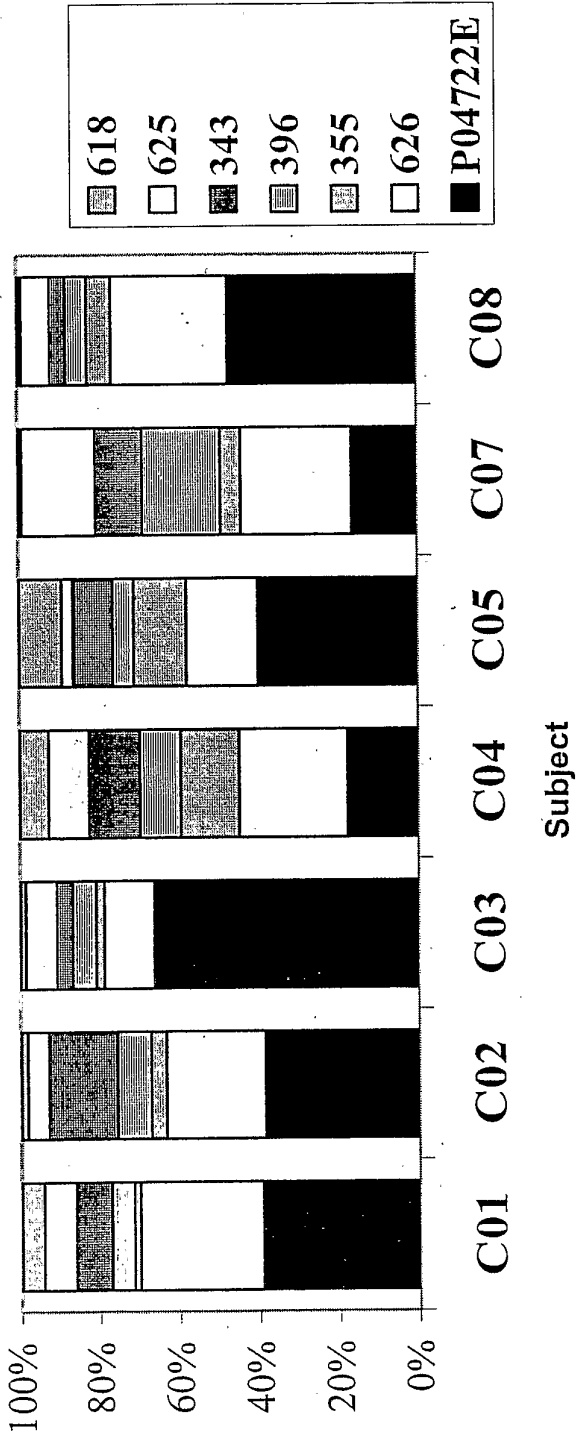
Figure 33. Coeliac HLA-DQ2/8 Subject C08: Gluten challenge induced IFNgamma ELISpot Responses to tTG-deamidated Gliadin Peptide Pools
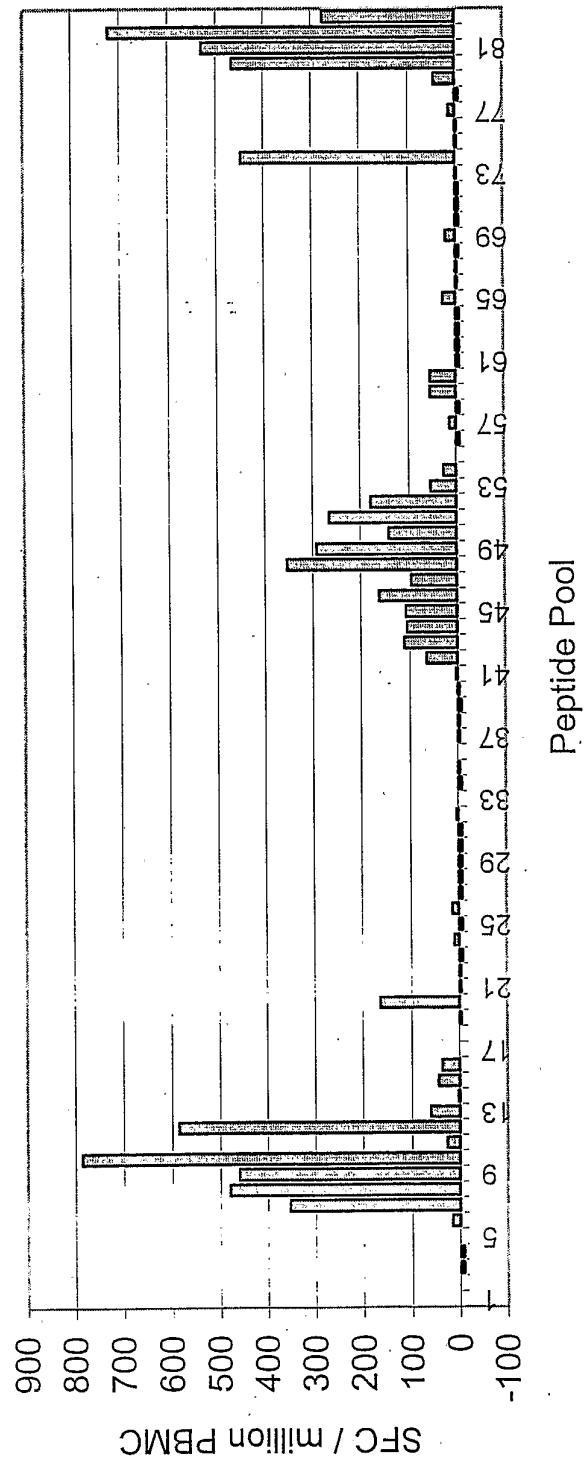
Figure 34. Coeliac HLA-DQ2/8 Subject C07: Change in IFNgamma ELISpot Responses to tTG-deamidated Gliadin Peptide Pools
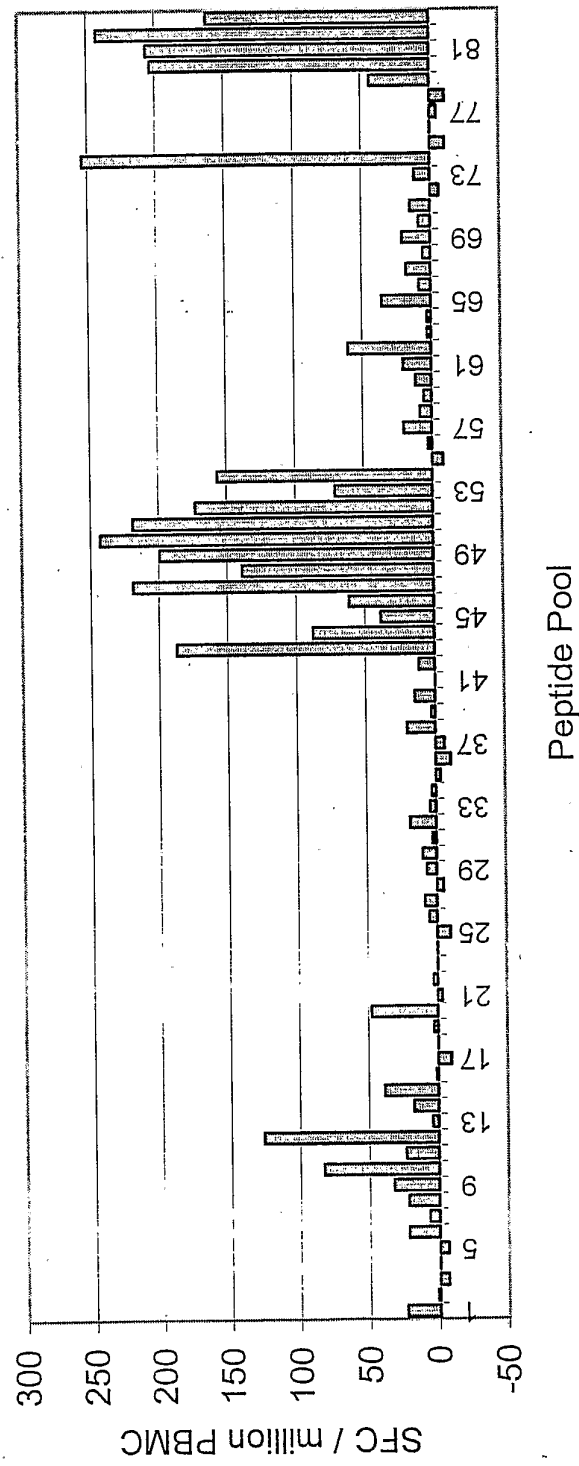
Figure 35. Coeliac HLA-DQ8/7 Subject C12: Gluten challenge induced IFNgamma ELISpot Responses to tTG-deamidated Gliadin Peptide Pools
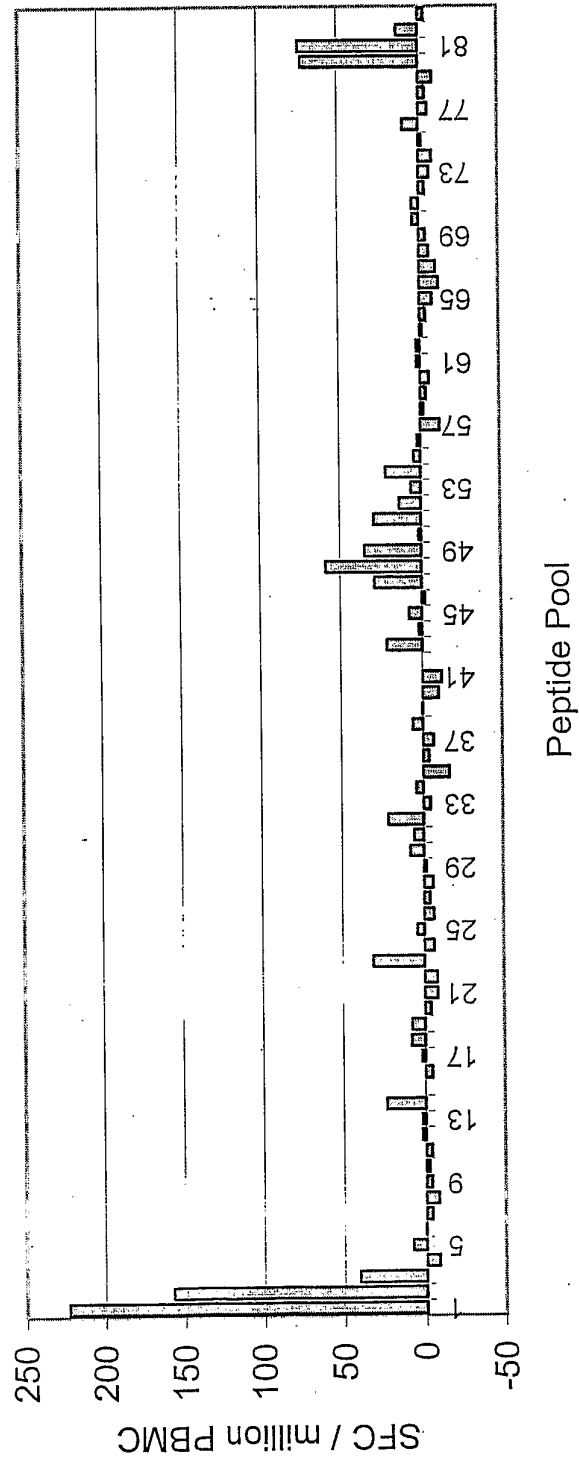
Figure 36. Coeliac HLA-DQ6/8 Subject C11: Change in IFNgamma ELISpot Responses to tTG-deamidated Gliadin Peptide Pools
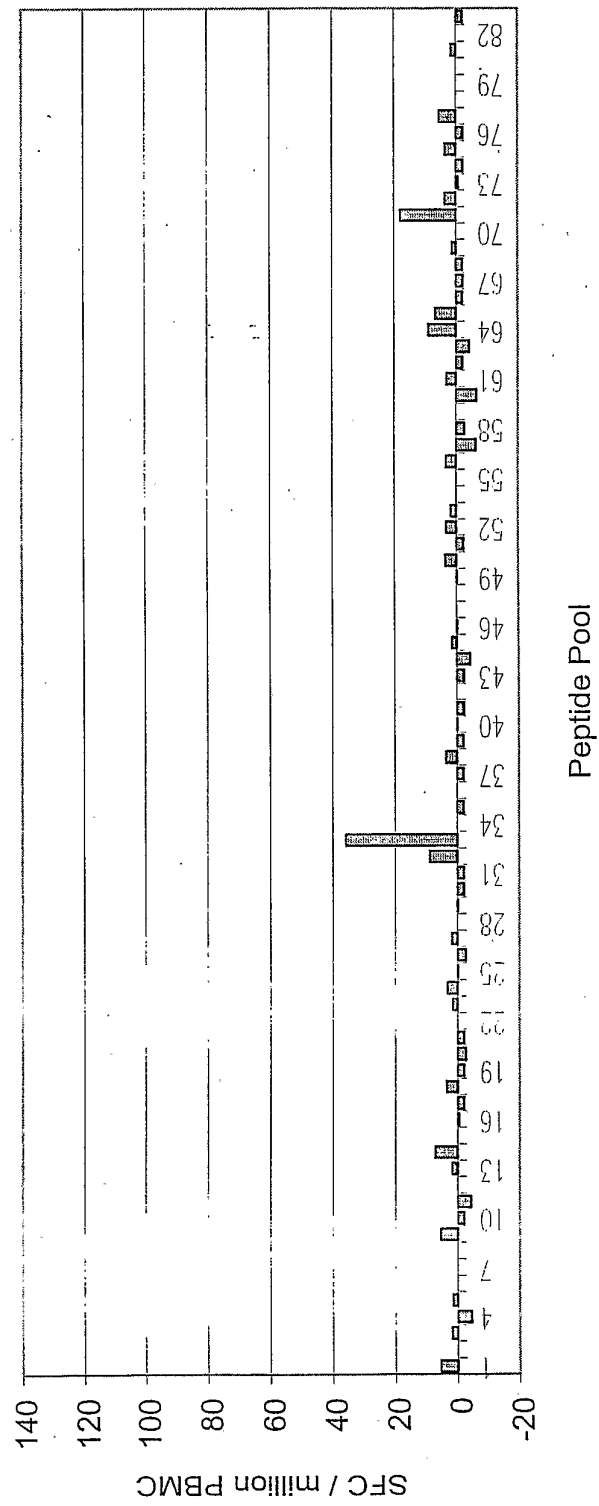
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<110>   ISIS INNOVATION LIMITED
          ANDERSON, Robert Paul
          HILL, Adrian Vivian Sinton
          JEWELL, Derek Parry

<120>   THERAPEUTIC EPITOPES AND USES THEREOF

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Gln Pro Gln Glu Gln Val Pro Leu Val Gln Gln Gln Gln Phe Pro Gly
                20   25   30

Gln Gln Gln Gln Phe Pro Pro Gln Gln Pro Tyr Pro Gln Pro Gln Pro
                35   40   45

Phe Pro Ser Gln Gln Pro Tyr Leu Gln Leu Gln Pro Phe Pro Gln Pro
        50   55   60

Gln Leu Pro Tyr Pro Gln Pro Gln Ser Phe Pro Pro Gln Gln Pro Tyr
65   70   75   80

Page 1

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Pro Gln Pro Gln Pro Gln Tyr Ser Gln Pro Gln Gln Pro Ile Ser Gln
                85                  90                  95
Gln Gln Ala Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln
            100                 105                 110
Gln Ile Leu Gln Gln Ile Leu Gln Gln Gln Leu Ile Pro Cys Met Asp
        115                 120                 125
Val Val Leu Gln Gln His Asn Ile Ala His Ala Arg Ser Gln Val Leu
    130                 135                 140
Gln Gln Ser Thr Tyr Gln Leu Leu Gln Glu Leu Cys Cys Gln His Leu
145                 150                 155                 160
Trp Gln Ile Pro Glu Gln Ser Gln Cys Gln Ala Ile His Asn Val Val
                165                 170                 175
His Ala Ile Ile Leu His Gln Gln Gln Lys Gln Gln Gln Gln Pro Ser
            180                 185                 190
Ser Gln Val Ser Phe Gln Gln Pro Leu Gln Gln Tyr Pro Leu Gly Gln
            195                 200                 205
Gly Ser Phe Arg Pro Ser Gln Gln Asn Pro Gln Ala Gln Gly Ser Val
    210                 215                 220
Gln Pro Gln Gln Leu Pro Gln Phe Glu Glu Ile Arg Asn Leu Ala Leu
225                 230                 235                 240
Gln Thr Leu Pro Ala Met Cys Asn Val Tyr Ile Ala Pro Tyr Cys Thr
                245                 250                 255
Ile Ala Pro Phe Gly Ile Phe Gly Thr Asn
                260                 265
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Pro Gln Pro Gln Leu Pro Tyr
1               5
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1               5                   10                  15
Gln Ser Phe Pro
            20
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<223>   peptide

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Glu Leu Gln Pro Phe Pro Gln Pro Glu Leu Pro Tyr Pro Gln Pro Gln
1   5   10   15

Ser

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1   5   10   15

Ser

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Glu Leu Gln Pro Phe Pro Gln Pro Glu Leu Pro Tyr Pro Gln Pro Glu
1   5 '   10   15

Ser

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Gln Pro Gln Leu Pro
1   5

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Gln Leu Gln Pro Phe Pro Gln Pro Gln Leu Pro Tyr Pro Gln Pro Gln
1   5   10   15

Ser

<210>   11
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Page 3

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1                   5                   10                  15

Gln Ser Phe Pro
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Pro Gln Leu Pro Tyr
1                   5


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Gln Leu Gln Pro Phe Pro Gln Pro Glu Leu Pro Tyr
1                   5                   10


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1                   5                   10


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Pro Arg Ala Pro Trp Ile Glu Gln Glu Gly Pro Glu Tyr Trp
1                   5                   10


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Ile Asp Val Trp Leu Gly Gly Leu Leu Ala Glu Asn Phe Leu Pro Tyr
1   5   10   15

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Pro Gln Pro Gln Pro Phe Pro Pro Glu Leu Pro Tyr Pro Gln Pro Gln
1   5   10   15

Ser

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Phe Pro Gln Pro Gln Leu Pro Tyr Pro
1   5

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1   5

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1   5

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Leu Gln Pro Gln Asn Pro Ser Gln Gln Gln Pro Gln
1   5   10

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Page 5

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Leu Gln Pro Glu Asn Pro Ser Gln Glu Gln Pro Glu
1                   5                   10

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<223>    Xaa is Pro, Ser or Thr


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1                   5                   10                  15

Xaa


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1                   5                   10                  15

Glu Ser Thr Tyr
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<400>    25
Ile Lys Asp Phe His Val Tyr Phe Arg Glu Ser Arg Asp Ala Leu Trp
1                   5                   10                  15

Lys Gly Pro Gly
                20
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Gln Leu Gln Pro Phe Pro Gln Pro Gln Leu Pro Tyr Pro Gln Pro Gln
1                5                   10                  15

Pro


<210>    27
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Gln Leu Gln Pro Phe Pro Gln Pro Glu Leu Pro Tyr Pro Gln Pro Gln
1                5                   10                  15

Pro


<210>    28
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<400>    28
Gln Leu Gln Pro Phe Pro Gln Pro Gln Leu Pro Tyr Ser Gln Pro Gln
1                5                   10                  15

Pro


<210>    29
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Gln Leu Gln Pro Phe Pro Gln Pro Glu Leu Pro Tyr Ser Gln Pro Gln
1                5                   10                  15

Pro


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<400>    30
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Gln Gln Thr Tyr Pro Gln Arg Pro Gln Gln Pro Phe Pro Gln Thr Gln
1   5   10   15

Gln Pro Gln Gln
            20

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Pro Gln Gln Pro Gln Gln Pro Gln Gln Pro Phe Pro Gln Pro Gln Gln
1   5   10   15

Pro Phe Pro Trp
            20

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Gln Gln Pro Gln Gln Pro Phe Pro Gln Pro Gln Gln Pro Gln Leu Pro
1   5   10   15

Phe Pro Gln Gln
            20

<210>   33
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<400>   33
Gln Ala Phe Pro Gln Pro Gln Gln Thr Phe Pro His Gln Pro Gln Gln
1   5   10   15

Gln Phe Pro Gln
            20

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Thr Gln Gln Pro Gln Gln Pro Phe Pro Gln Gln Pro Gln Gln Pro Phe
1   5   10   15

Pro Gln Thr Gln
            20

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1   5   10   15

Gln Pro Phe Pro
            20

<210>   36
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<400>   36
Pro Gln Gln Ser Phe Ser Tyr Gln Gln Gln Pro Phe Pro Gln Gln Pro
1   5   10   15

Tyr Pro Gln Gln
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Gln Xaa Pro Phe
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Gln Gln Pro Phe Pro Gln Pro Gln Gln Pro Phe Pro
1   5   10

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1   5   10

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Pro Ile Gln Pro Gln Gln Pro Phe Pro Gln Gln Pro
1   5   10

<210>   42
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Leu Gln Pro Gln Asn Pro Ser Gln Gln Gln Pro Gln
1   5   10

<210>   43
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<212>   PRT
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Leu Gln Pro Gln Asn Pro Ser Gln Gln Gln Pro Gln
1   5   10

<210>   44
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Gln Gln Tyr Pro Ser Gly Gln Gly Ser Phe Gln Pro Ser Gln Gln Asn
1   5   10   15

Pro Gln

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<400>    45
Pro Gln Xaa Pro Xaa Pro
1                   5


<210>    46
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Leu Gln Pro Gln Asn Pro Ser Gln Gln Gln Pro Gln
1               5               10


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<212>    PRT
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Pro Gln Pro Glu Leu Pro Tyr Pro Gln Pro Glu Leu Pro Tyr
1               5               10


<210>    48
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Gln Gln Leu Pro Gln Pro Glu Gln Pro Gln Gln Ser Phe Pro Glu Gln
1               5               10              15

Glu Arg Pro Phe
            20


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Gln Leu Gln Pro Phe Pro Gln Pro Glu Leu Pro Tyr Pro Gln Pro Gln
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Leu

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1   5   10   15

Pro Phe Pro Trp Gln Pro
                  20

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1   5   10   15

Leu

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1   5   10   15

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Gln Leu Gln Pro Phe Pro Gln Pro Gln Leu Pro Tyr
1   5   10

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Pro Phe Pro Gln Pro Gln Leu Pro Tyr

<210> 55
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Pro Gln Pro Gln Leu Pro Tyr Pro Gln
1   5

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Pro Tyr Pro Gln Pro Gln Leu Pro Tyr
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1   5   10

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1   5

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Ile Ile Pro Gln Gln Pro Ala Gln
1   5

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1   5   10

<210>   61
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1   5   10

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1   5   10   15

Gln Gln Pro Gln
                20

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1   5

<210>   65
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<400>   65

Page 14

Pro Phe Ser Gln Gln Gln Gln Ser Pro Phe
1   5   10

<210>   66
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<400>   66
Pro Phe Ser Gln Gln Gln Gln Gln
1   5

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1   5   10   15

Pro

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1   5   10   15

Pro

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1   5   10   15

Pro

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1   5   10   15

Pro

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1   5   10   15

Pro

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1   5   10   15

Pro

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1   5   10   15

Leu

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1   5   10   15

Ser

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1   5   10   15

Ser

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1   5   10   15

Pro

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1   5   10   15

Pro

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1   5   10   15

Gln Val

<210>   79
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1   5   10   15

Gln Val

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1   5   10   15

Gln Val

<210>   81
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Val Pro Gln Leu Gln Pro Gln Asn Pro Ser Gln Glu Gln Pro Gln Glu
1   5   10   15

Gln Val

<210>   82
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Val Pro Gln Leu Gln Pro Gln Asn Pro Ser Gln Arg Gln Pro Gln Glu
1   5   10   15

Gln Val

<210>   83
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<400>   83
Val Pro Gln Leu Gln Pro Gln Asn Pro Ser Gln Gln Gln Pro Glu Glu
1   5   10   15

Gln Val

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1   5   10   15

Gln Val

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1   5   10   15

Gln Val

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1   5   10   15

Gln Val

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1   5   10   15

Gln Val

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1   5   10   15

Gln Val

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Arg Trp Pro Val Pro Gln Leu Gln Pro Gln Asn Pro Ser Gln Gln
1                5                  10                  15


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1                5                  10                  15


<210>    91
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<400>    91
Pro Val Pro Gln Leu Gln Pro Gln Asn Pro Ser Gln Gln Gln Pro
1                5                  10                  15


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Pro Gln Leu Gln Pro Gln Asn Pro Ser Gln Gln Gln Pro Gln Glu
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Leu Gln Pro Gln Asn Pro Ser Gln Gln Gln Pro Gln Glu Gln Val
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Pro Gln Pro Gln Pro Phe Pro Pro Gln Leu Pro Tyr Pro Gln Thr Gln
1               5                   10                  15

Pro
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Leu Gly Gln Gln Gln Pro Phe Pro Pro Gln Gln Pro Tyr Pro Gln Pro
1               5                   10                  15

Gln Pro Phe
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Gln Gln Tyr Pro Ser Gly Glu Gly Ser Phe Gln Pro Ser Gln Glu Asn
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Pro Gln

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1   5   10   15

Pro

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Pro Gln Pro Gln Leu Pro Tyr Pro Gln Pro Gln Leu Pro Tyr
1   5   10

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1   5   10   15

Gln Arg Pro Phe
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Gln Leu Gln Pro Phe Pro Gln Pro Gln Leu Pro Tyr Leu Gln Pro Gln
1   5   10   15

Ser

<210> 105
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Gln Pro Gln Pro Phe Pro Pro Pro Gln Leu Pro Tyr Pro Gln Thr Gln
1   5   10   15

Pro

<210> 106
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1   5   10   15

Ser

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Ala Val Arg Phe Pro Val Pro Gln Leu Gln Pro Gln Asn Pro Ser Gln
1   5   10   15

Gln Leu Pro Gln
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<400> 108
Met Val Arg Val Pro Val Pro Gln Leu Gln Pro Gln Asn Pro Ser Gln
1   5   10   15

Gln Gln Pro Gln
            20

<210> 109
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Met Val Arg Val Pro Val Pro Gln Leu Gln Pro Gln Asn Pro Ser Gln
1                5                   10                  15

Gln His Pro Gln
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Gln Gln Pro Gln
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1                5                   10                  15

Gln Gln Pro Gln
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1                5                   10                  15

Gln Gln Pro Gln
            20


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Ala Val Arg Val Pro Val Pro Gln Leu Gln Pro Gln Asn Pro Ser Gln
1                5                   10                  15

Gln Gln Pro Gln
            20
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Gln Gln Pro Gln
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1               5               10              15

Gln Gln Pro Gln
            20

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1               5               10              15

Gln Gln Pro Gln
            20

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1               5               10              15

Pro Gln Pro Gln
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<400>    118
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Ala Val Arg Val Pro Val Pro Gln Leu Gln Pro Lys Asn Pro Ser Gln
1   5   10   15

Gln Gln Pro Gln
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1   5   10   15

Leu Val Gln Gln
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1   5   10   15

Leu Val Gln Gln
            20

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1   5   10   15

Leu Val Gln Gln
            20

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<400>   122
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1   5   10   15

Leu Val Gln Gln
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1   5   10   15

Leu Val Gln Gln
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1   5   10   15

Leu Val Gln Glu
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1   5   10   15

Leu Val Gln Glu
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1   5   10   15

Leu Val Gln Gln
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1   5   10   15

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Leu Val Gln Gln
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<400>    128
Leu Gln Pro Lys Asn Pro Ser Gln Gln Gln Pro Gln Glu Gln Val Pro
1                5                   10                  15

Leu Val Gln Gln
                20


<210>    129
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<220>
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<400>    129
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1                5                   10                  15

Leu Met Gln Gln
                20


<210>    130
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<400>    130
Gln Leu Pro Gln Glu Gln Val Pro Leu Val Gln Gln Gln Gln Phe Leu
1                5                   10                  15

Gly Gln Gln Gln
                20


<210>    131
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<220>
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<400>    131
Gln His Pro Gln Glu Gln Val Pro Leu Val Gln Gln Gln Gln Phe Leu
1                5                   10                  15

Gly Gln Gln Gln
                20


<210>    132
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<220>
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<223>   peptide

<400>   132
Gln Gln Pro Gln Glu Gln Val Pro Leu Val Gln Gln Gln Gln Phe Leu
1   5   10   15

Gly Gln Gln Gln
            20

<210>   133
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<220>
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<400>   133
Gln Gln Pro Gln Glu Gln Val Pro Leu Val Gln Gln Gln Gln Phe Leu
1   5   10   15

Gly Gln Gln Gln
            20

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<220>
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<400>   134
Gln Gln Pro Gln Glu Gln Val Pro Leu Val Gln Gln Gln Gln Phe Pro
1   5   10   15

Gly Gln Gln Gln
            20

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1   5   10   15

Gly Gln Gln Gln
            20

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<220>
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<400>   136
Gln Gln Pro Gln Glu Gln Val Pro Leu Val Gln Glu Gln Gln Phe Gln
1   5   10   15

Gly Gln Gln Gln
            20

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<210> 137
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<212> PRT
<213> Artificial Sequence

<220>
<223> peptide

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Pro Gln Pro Gln Gly Gln Val Pro Leu Val Gln Gln Gln Gln Phe Pro
1   5   10   15

Gly Gln Gln Gln
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<212> PRT
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Pro Gln Pro Gln Arg Gln Val Pro Leu Val Gln Gln Gln Gln Phe Pro
1   5   10   15

Gly Gln Gln Gln
            20

<210> 139
<211> 20
<212> PRT
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<220>
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<400> 139
Gln Gln Pro Gln Glu Gln Val Pro Leu Met Gln Gln Gln Gln Gln Phe
1   5   10   15

Pro Gly Gln Gln
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<210> 140
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<212> PRT
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1   5   10   15

Gln Gln Pro Tyr
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<210> 141
<211> 20
<212> PRT
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<220>
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<400> 141

Leu Val Gln Gln Gln Gln Phe Leu Gly Gln Gln Gln Ser Phe Pro Pro
1   5   10   15

Gln Gln Pro Tyr
            20

<210>   142
<211>   20
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<220>
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<400>   142
Leu Val Gln Gln Gln Gln Phe Leu Gly Gln Gln Gln Pro Phe Pro Pro
1   5   10   15

Gln Gln Pro Tyr
            20

<210>   143
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<220>
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<400>   143
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1   5   10   15

Gln Gln Pro Tyr
            20

<210>   144
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<400>   144
Leu Val Gln Glu Gln Gln Phe Gln Gly Gln Gln Gln Pro Phe Pro Pro
1   5   10   15

Gln Gln Pro Tyr
            20

<210>   145
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<400>   145
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1   5   10   15

Gln Gln Pro Tyr
            20

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<400>   146
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1   5   10   15

Pro Gln Gln Pro
            20

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<400>   147
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1   5   10   15

Pro Gln Gln Pro
            20

<210>   148
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<220>
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1   5   10   15

Pro Phe Pro Ser
            20

<210>   149
<211>   20
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1   5   10   15

Phe Pro Ser Gln
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<210>   150
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1   5   10   15

Pro Phe Pro Ser
            20

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1   5   10   15

Pro Phe Pro Ser
            20

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1   5   10   15

Pro Phe Pro Ser
            20

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<220>
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1   5   10   15

Pro Phe Pro Ser
            20

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1   5   10   15

Pro Phe Pro Ser
            20

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1   5   10   15

Leu Gln Leu Gln
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Gln Gln Pro Tyr Pro Gln Pro Gln Phe Pro Ser Gln Leu Pro Tyr Leu
1   5   10   15

Gln Leu Gln Pro
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1   5   10   15

Leu Gln Leu Gln
            20

<210>   158
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<220>
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<400>   158
Gln Gln Pro Tyr Pro Gln Gln Gln Pro Phe Pro Ser Gln Gln Pro Tyr
1   5   10   15

Met Gln Leu Gln
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<210>   159
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<212>   PRT
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<220>
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1   5   10   15

Pro Gln Pro Gln
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Pro Gln Leu Pro
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<400> 161
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1   5   10   15

Pro Gln Leu Pro
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<400> 162
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1   5   10   15

Pro Gln Leu Pro
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<400> 163
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1   5   10   15

Pro Gln Leu Pro
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<400> 164

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1   5   10   15

Pro Gln Pro Phe
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<400>   165
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1   5   10   15

Pro Gln Leu Pro
            20

<210>   166
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<220>
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<400>   166
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1   5   10   15

Pro Gln Leu Pro
            20

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<213>   Artificial Sequence

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<400>   167
Pro Phe Pro Ser Gln Gln Pro Tyr Met Gln Leu Gln Pro Phe Pro Gln
1   5   10   15

Pro Gln Pro Phe
            20

<210>   168
<211>   20
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<220>
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<400>   168
Pro Phe Pro Ser Gln Gln Pro Tyr Leu Gln Leu Gln Pro Phe Pro Gln
1   5   10   15

Pro Gln Pro Phe
            20

<210>   169
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<400>   169
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1   5   10   15

Pro Gln Leu Pro
            20

<210>   170
<211>   20
<212>   PRT
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1   5   10   15

Gln Leu Pro Tyr
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1   5   10   15

Pro Gln Pro Phe
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<400>   172
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1   5   10   15

Gln Pro Phe Arg
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<400>   173
Leu Gln Leu Gln Pro Phe Pro Gln Pro Gln Leu Pro Tyr Ser Gln Pro
1   5   10   15

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Gln Gln Phe Arg
                20

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<400>     174
Leu Gln Leu Gln Pro Phe Pro Gln Pro Gln Leu Pro Tyr Leu Gln Pro
1               5                   10                  15

Gln Pro Phe Arg
                20

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<400>     175
Leu Gln Leu Gln Pro Phe Pro Gln Pro Gln Leu Ser Tyr Ser Gln Pro
1               5                   10                  15

Gln Pro Phe Arg
                20

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<400>     176
Leu Gln Leu Gln Pro Phe Ser Gln Pro Gln Leu Pro Tyr Ser Gln Pro
1               5                   10                  15

Gln Pro Phe Arg
                20

<210>     177
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Pro Tyr Ser Gln
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Gln Leu Pro Tyr
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Pro Tyr Pro Gln
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Gln Pro Phe Arg
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Pro Tyr Pro Gln
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Gln Pro Phe Arg
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Pro Tyr Pro Gln
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Pro Tyr Pro Gln
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Pro Tyr Pro Gln
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Tyr Pro Gln Pro
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Tyr Pro Gln Pro
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Tyr Pro Gln Pro
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Pro Pro Gln Gln
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Gln Pro Gln Pro
            20

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1               5                   10                  15

Gln Pro Gln Pro
            20

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Pro Tyr Pro Gln
            20

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Pro Tyr Pro Gln
            20

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Page 45

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1               5               10              15

Ser Gln Pro Gln
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Ser Gln Pro Gln
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1               5               10              15

Ser Gln Pro Gln
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1               5               10              15

Ser Gln Pro Gln
            20
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Pro Gln Pro Gln
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1   5   10   15

Leu Gln Pro Gln
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Pro Gln Pro Gln
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Gln Gln Gln Gln
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1   5   10   15

Gln Gln Gln Gln
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1   5   10   15

Gln Gln Gln Gln
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1   5   10   15

Gln Gln Gln Ala
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1   5   10   15

Gln Gln Gln Ala
            20

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<223>   peptide

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1   5   10   15

Gln Gln Gln Ala
            20

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1   5   10   15

Gln Gln Gln Ala
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1   5   10   15

Gln Gln Gln Gln
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1   5   10   15

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1   5   10   15

Gln Gln Gln Gln
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1               5                   10                  15

Ile Leu Gln Gln
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1               5                   10                  15

Ile Leu Gln Gln
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1               5                   10                  15

Ile Ile Gln Gln
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1               5                   10                  15

Gln Gln Gln Ile
             20

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Ala Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln
1   5   10   15

Thr Leu Gln Gln
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1   5   10   15

Gln Leu Ile Pro
            20

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1   5   10   15

Gln Leu Ile Pro
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1   5   10   15

Gln Leu Ile Pro
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1   5   10   15

Gln Leu Thr Pro
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Page 51

<213>   Artificial Sequence

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1   5   10   15

Gln Leu Ile Pro
            20

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1   5   10   15

Leu Gln Gln Gln
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1   5   10   15

Gln Leu Ile Pro
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1   5   10   15

Gln Leu Ile Pro
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Val Leu Gln Gln
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1   5   10   15

Val Leu Gln Gln
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1   5   10   15

Val Leu Gln Gln
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1   5   10   15

Val Leu Gln Gln
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1   5   10   15

Val Leu Gln Gln
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1   5   10   15

Val Leu Gln Gln
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1   5   10   15

His Gly Arg Ser
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Gln Leu Ile Pro Cys Met Asp Val Val Leu Gln Gln His Asn Lys Ala
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His Gly Arg Ser
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1   5   10   15

His Gly Arg Ser
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His Gly Arg Ser
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Arg Gly Arg Ser
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His Gly Lys Ser
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Tyr Gly Ser Ser
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His Gly Ser Ser
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1   5   10   15

His Gly Ser Ser
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1   5   10   15

His Ala Arg Ser
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<400>   258
Gln Leu Ile Pro Cys Arg Asp Val Val Leu Gln Gln His Asn Ile Ala
1   5   10   15

His Ala Ser Ser
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Gln Ser Thr Tyr
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Gln Ser Thr Tyr
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Gln Ser Thr Tyr
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Gln Ser Thr Tyr
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Gln Ser Thr Tyr
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Gln Ser Thr Tyr
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Glu Ser Thr Tyr
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Gln Ser Thr Tyr
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Gln Ser Thr Tyr
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Gln Ser Ser Tyr
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Glu Leu Cys Cys
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Glu Leu Cys Cys
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Glu Leu Cys Cys
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Glu Leu Cys Cys
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Gln Leu Cys Cys
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Page 60

His Ala Ser Ser Gln Val Leu Gln Gln Ser Thr Tyr Gln Leu Leu Gln
1   5   10   15

Gln Leu Cys Cys
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Gln Ile Pro Glu
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1   5   10   15

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1   5   10   15

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Gln Ile Pro Glu
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Gln Ala Ile His
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1   5   10   15

Gln Ala Ile His
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Gln Ala Ile His
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Gln Ala Ile His
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Gln Ala Ile His
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Gln Ala Ile His
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1   5   10   15

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Ala Ile Ile Leu
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Ala Ile Ile Leu
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Ala Ile Ile Leu
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Ala Ile Ile Leu
            20

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Page 65

Gln Ile Pro Glu Gln Ser Arg Cys Gln Ala Ile His Asn Val Val His
1   5   10   15

Ala Ile Ile Leu
              20

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Ala Ile Ile Met
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1   5   10   15

Ala Ile Ile Leu
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Lys Gln Gln Gln
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1   5   10   15

Gln Lys Gln Gln
              20

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Gln Ala Ile Gln Asn Val Val His Ala Ile Ile Leu His Gln Gln Gln
1   5   10   15

Lys Gln Gln Gln
            20

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1   5   10   15

Lys Gln Gln Gln
            20

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1   5   10   15

Gln Gln Gln Gln
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His His His Gln
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Arg Gln Gln Gln
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Gln Gln Gln Gln
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1   5   10   15

Gln Gln Gln Gln
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Gln Gln Gln Gln
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Gln Val Ser Phe
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Ser Gln Phe Ser
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Gln Val Ser Phe
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1   5   10   15

Val Ser Phe Gln
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Gln Pro Leu Ser
            20

Page 69

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Ala Ile Ile Leu His Gln Gln His His His His Gln Gln Gln Gln Gln
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Gln Gln Gln Gln
            20

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Val Ser Leu Gln
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Gln Val Ser Tyr
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Gln Gln Tyr Pro
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1   5   10   15

Gln Gln Tyr Pro
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1   5   10   15

Gln Gln Tyr Pro
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1   5   10   15

Gln Tyr Pro Leu
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1   5   10   15

Gln Gln Gln Leu
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1   5   10   15

Gln Gln Gln Leu
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Gln Tyr Pro Ser
            20

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1   5   10   15

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Gln Gln Gln Gln
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1                5                   10                  15
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Glu Gln Tyr Pro
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1                5                   10                  15
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Gln Lys Gln Gln
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1                5                   10                  15
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Ser Gln Val Ser
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Gln Gln Pro Gln
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Gln Gln Ser Gln
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Gln Val Ser Phe
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1   5   10   15

Gln Gln Pro Gln
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Ser Gly Gln Gly
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Ser Ser Gln Val
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Ser Phe Arg Pro
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Ser Phe Arg Pro
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Phe Phe Gln Pro
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Phe Phe Gln Pro
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Pro Gln Ala Gln
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1   5   10   15

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Pro Gln Ala Gln
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Pro Gln Ala Gln
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Pro Gln Ala Gln
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Pro Gln Gln Leu
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Pro Gln Gln Leu
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1   5   10   15

Pro Gln Gln Leu
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Pro Gln Gln Leu
            20

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Pro Gln Gln Leu
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Ser Phe Arg Pro Ser Gln Gln Asn Pro Arg Ala Gln Gly Ser Val Gln
1   5   10   15

Pro Gln Gln Leu
            20

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<400>   371

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Ser Phe Gln Pro Ser Gln Gln Asn Pro Gln Ala Gln Gly Ser Val Gln
1               5                   10              15
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Pro Gln Gln Leu
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1               5                   10              15
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Pro Gln Gln Leu
            20
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1               5                   10              15
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Pro Gln Gln Leu
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1               5                   10              15
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Pro Gln Gln Leu
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Pro Gln Gln Leu
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1   5   10   15

Pro Gln Gln Leu
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Pro Gln Gln Leu
            20

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1   5   10   15

Pro Gln Gln Leu
            20

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Pro Gln Ala Gln Gly Ser Val Gln Pro Gln Gln Leu Pro Gln Phe Glu
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Glu Ile Arg Asn
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Pro Gln Thr Gln Gly Ser Val Gln Pro Gln Gln Leu Pro Gln Phe Glu
1   5   10   15

Page 82

Glu Ile Arg Asn
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<400>   381
Pro Gln Ala Gln Gly Ser Val Gln Pro Gln Gln Leu Pro Gln Phe Glu
1   5   10   15

Ile Arg Asn Leu
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1   5   10   15

Glu Ile Arg Asn
                20

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Glu Ile Arg Asn
                20

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Glu Ile Arg Asn
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Glu Ile Arg Asn
            20

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1   5   10   15

Ala Ile Arg Asn
            20

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1   5   10   15

Glu Ile Arg Asn
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Pro Gln Ala Gln Gly Ser Val Gln Pro Gln Gln Leu Pro Gln Phe Gln
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Glu Ile Arg Asn
            20

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Pro Gln Gln Leu Pro Gln Phe Glu Glu Ile Arg Asn Leu Ala Leu Gln
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Thr Leu Pro Ala
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Leu Pro Ala Met
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1                5                   10                  15


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Pro Gln Gln Leu Pro Gln Phe Glu Glu Ile Arg Asn Leu Ala Leu Glu
1                5                   10                  15

Thr Leu Pro Ala
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Pro Gln Gln Leu Pro Gln Phe Glu Ala Ile Arg Asn Leu Ala Leu Gln
1                5                   10                  15

Thr Leu Pro Ala
            20

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Pro Gln Gln Leu Pro Gln Phe Ala Glu Ile Arg Asn Leu Ala Leu Gln
1                5                   10                  15
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Thr Leu Pro Ala
            20

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Pro Gln Gln Leu Pro Gln Phe Gln Glu Ile Arg Asn Leu Ala Leu Gln
1   5   10   15

Thr Leu Pro Ala
            20

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Glu Ile Arg Asn Leu Ala Leu Gln Thr Leu Pro Ala Met Cys Asn Val
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Tyr Ile Pro Pro
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<400>   397
Glu Ile Arg Asn Leu Ala Leu Gln Thr Leu Pro Ser Met Cys Asn Val
1   5   10   15

Tyr Ile Pro Pro
            20

<210>   398
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Glu Ile Arg Asn Leu Ala Leu Glu Thr Leu Pro Ala Met Cys Asn Val
1   5   10   15

Tyr Ile Pro Pro
            20

<210>   399
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Glu Ile Arg Asn Leu Ala Leu Gln Thr Leu Pro Arg Met Cys Asn Val
1               5                   10                  15

Tyr Ile Pro Pro
            20


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1               5                   10                  15

Ala Pro Phe Gly
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1               5                   10                  15

Ala Pro Phe Gly
            20


<210>    402
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1               5                   10                  15

Val Pro Phe Gly
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<210>    403
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1               5                   10                  15

Ala Pro Phe Gly
            20
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<210>   404
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Thr Leu Pro Ala Met Cys Asn Val Tyr Ile Pro Pro Tyr Cys Thr Ile
1   5   10   15

Thr Pro Phe Gly
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1   5   10   15

Ala Pro Val Gly
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1   5   10   15

Thr Ile Ala Pro
            20

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<400>   407
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1   5   10   15

Thr Ile Ala Pro
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<210>   408
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<400>   408
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1   5   10   15

Thr Thr Ala Pro
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<210>   409
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<400>   409
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1   5   10   15

Thr Ile Ala Pro
            20

<210>   410
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<400>   410
Tyr Ile Pro Pro Tyr Cys Thr Ile Ala Pro Phe Gly Ile Phe Gly Thr
1   5   10   15

Asn Tyr Arg

<210>   411
<211>   19
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<400>   411
Tyr Ile Pro Pro Tyr Cys Thr Ile Val Pro Phe Gly Ile Phe Gly Thr
1   5   10   15

Asn Tyr Arg

<210>   412
<211>   19
<212>   PRT
<213>   Artificial Sequence

<220>
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<400>   412
Tyr Ile Pro Pro Tyr Cys Ala Met Ala Pro Phe Gly Ile Phe Gly Thr
1   5   10   15

Asn Tyr Arg

<210>   413
<211>   19

Page 89

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<212>    PRT
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<220>
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<400>    413
Tyr Ile Pro Pro Tyr Cys Thr Met Ala Pro Phe Gly Ile Phe Gly Thr
1                5                   10                  15

Asn Tyr Arg


<210>    414
<211>    17
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<213>    Artificial Sequence

<220>
<223>    peptide

<400>    414
Tyr Ile Pro Pro Tyr Cys Thr Ile Thr Pro Phe Gly Ile Phe Gly Thr
1                5                   10                  15

Asn


<210>    415
<211>    19
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<220>
<223>    peptide

<400>    415
Tyr Ile Pro Pro Tyr Cys Thr Ile Ala Pro Val Gly Ile Phe Gly Thr
1                5                   10                  15

Asn Tyr Arg


<210>    416
<211>    19
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<220>
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<400>    416
Tyr Ile Pro Pro Tyr Cys Ser Thr Thr Ile Ala Pro Val Gly Ile Phe
1                5                   10                  15

Gly Thr Asn


<210>    417
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<220>
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<400>    417
Tyr Ile Pro Pro Tyr Cys Ser Thr Thr Thr Ala Pro Phe Gly Ile Phe
1                5                   10                  15
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Gly Thr Asn

<210>   418
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<400>   418
Tyr Ile Pro Pro His Cys Ser Thr Thr Ile Ala Pro Phe Gly Ile Phe
1   5   10   15

Gly Thr Asn

<210>   419
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<220>
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<400>   419
Tyr Ile Pro Pro His Cys Ser Thr Thr Ile Ala Pro Phe Gly Ile Ser
1   5   10   15

Gly Thr Asn

<210>   420
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<220>
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<400>   420
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1   5   10   15

Thr Asn Tyr Arg
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<400>   421
Gly Thr Ala Asn Met Gln Val Asp Pro Ser Ser Gln Val Gln Trp Pro
1   5   10   15

Gln Gln Gln Pro
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<210>   422
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<213>   Artificial Sequence

Page 91

<220>
<223>   peptide

<400>   422
Gly Thr Ala Asn Ile Gln Val Asp Pro Ser Gly Gln Val Gln Trp Leu
1   5   10   15

Gln Gln Gln Leu
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<210>   423
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<213>   Artificial Sequence

<220>
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<400>   423
Ala Thr Ala Asn Met Gln Val Asp Pro Ser Gly Gln Val Pro Trp Pro
1   5   10   15

Gln Gln Gln Pro
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<210>   424
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<220>
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Met Asn Ile Gln Val Asp Pro Ser Gly Gln Val Pro Trp Pro Gln Gln
1   5   10   15

Gln Pro Phe Pro
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<210>   425
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<213>   Artificial Sequence

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Ala Thr Ala Asn Met Gln Ala Asp Pro Ser Gly Gln Val Gln Trp Pro
1   5   10   15

Gln Gln Gln Pro
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<210>   426
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1   5   10   15

Gln Gln Gln Gln
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Pro Phe Pro


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Page 94

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Gln Gln Thr Phe
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Gln Gln Thr Phe
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Gln Thr Phe Pro
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1   5   10   15

Gln Thr Phe Pro
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1   5   10   15

Gln Thr Phe Pro
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Gln Thr Phe Pro
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Phe Pro Gln Gln
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Gln Thr Phe His
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1               5                   10                  15

Gln Thr Phe His
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Gln Thr Phe His
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Gln Gln Phe Pro
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Gln Thr Phe Pro
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Thr Phe Pro His
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Page 99

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Thr Tyr Pro His
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Thr Tyr Pro His
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1                   5                   10                  15

Gln Phe Pro Gln
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Gln Gln Phe Pro
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Gln Phe Pro Gln
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Pro Gln Gln Gln
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Pro Gln Gln Gln
            20


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1   5   10   15

Pro Gln Gln Pro
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1   5   10   15

Pro Gln Gln Pro
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1   5   10   15

Gln Gln Pro Phe
            20

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Gln Gln Pro Phe
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1               5                   10                  15

Arg Gln Pro Phe
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Pro Gln Gln Gln
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1               5                   10                  15

Gln Gln Thr Phe
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1               5                   10                  15

Gln Gln Pro Tyr
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1   5   10   15

Gln Gln Thr Tyr
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Gln Arg Pro Gln
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1   5   10   15

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1   5   10   15

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1   5   10   15

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1   5   10   15

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1   5   10   15

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1   5   10   15

Gln Pro Gln Gln
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Phe Pro Gln Pro
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1   5   10   15

Page 105

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Leu Pro Phe Pro
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1               5                   10                  15

Gln Gln Pro Phe
            20


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1               5                   10                  15

Gln Pro Gln Gln
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Gln Gln Pro Phe
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1               5                   10                  15

Gln Gln Pro Phe
            20


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Page 106

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1   5   10   15

Gln Pro Gln Gln
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1   5   10   15

Gln Pro Gln Gln
            20

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1   5   10   15

Gln Gln Pro Phe
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1   5   10   15

Gln Pro Gln Gln
            20

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1   5   10   15

Gln Pro Gln Gln
            20

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1                 5                   10                  15

Gln Pro Gln Gln
            20


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1                 5                   10                  15

Pro Phe Pro Gln
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1                 5                   10                  15

Pro Gln Gln Pro
            20


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1                 5                   10                  15

Gln Pro Gln Gln
            20


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Thr Gln Gln Pro
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1   5   10   15

Pro Gln Gln Pro
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Pro Gln Thr Gln
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1   5   10   15

Pro Phe Pro Gln
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Ser Gln Gln Pro
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1   5   10   15

Leu Gln Gln Pro
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1   5   10   15

Ser Gln Gln Pro
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1   5   10   15

Ser Lys Gln Pro
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Leu Gln Gln Pro
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Gln Pro Gln Gln
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Page 115

Leu Asn Pro Cys
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Page 118

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Gly Val Gln Ile
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Ile Leu Arg Pro
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Page 127

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Leu Ser Gln Gln
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Ser Gln Gln Gln
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1   5   10   15

Ser Gln Gln Gln
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Ile Gln Ile Met
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Val Gln Gly Gln
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Ala Gln Gly Leu
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Gln Leu Val Gln
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Gly Met His Ile Leu Leu Pro Leu Tyr Gln Gln Gln Gln Val Gly Gln
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Gly Thr Leu Val
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Gly Ser Leu Val
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Gly Ser Leu Val
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1   5   10   15

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Gly Thr Leu Val
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Gly Ile Leu Val
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1                   5                   10                  15

Ile Ile Gln Pro
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1                   5                   10                  15

Ile Ile Gln Pro
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Ile Ile Gln Pro
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Ile Ile Gln Pro
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Ile Ile Gln Pro
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1   5   10   15

Ile Ile Gln Pro
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Gln Leu Glu Ala
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Gln Leu Glu Ala
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1                5                   10                  15

Gln Leu Glu Val
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1                5                   10                  15

Gln Leu Glu Gly
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Val Leu Gln Thr
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1   5   10   15

Val Leu Gln Thr
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Val Leu Gln Thr
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Val Leu Arg Thr
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Val Leu Lys Thr
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Cys Asn Val Tyr
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1   5   10   15

Cys Asn Val Tyr
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1   5   10   15

Cys Asn Val Tyr
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Gln Leu Glu Val Ile Arg Ser Ser Val Leu Gln Thr Leu Ala Thr Met
1   5   10   15

Cys Asn Val Tyr
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Gln Leu Glu Val Ile Arg Ser Leu Val Leu Gly Thr Leu Pro Thr Met
1   5   10   15

Page 135

Cys Asn Val Phe
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<210>   625
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1   5   10   15

Cys Asn Val Tyr
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1   5   10   15

Cys Asn Val Tyr
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Val Leu Gln Thr Leu Pro Thr Met Cys Asn Val Tyr Val Pro Pro Glu
1   5   10   15

Cys Ser Ile Ile
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Val Leu Gln Thr Leu Pro Ser Met Cys Asn Val Tyr Val Pro Pro Glu
1   5   10   15

Cys Ser Ile Met
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Cys Ser Thr Ile
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Cys Ser Thr Thr
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Cys Ser Thr Ile
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1   5   10   15

Cys Ser Thr Ile
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Cys Asn Val Tyr Val Pro Pro Glu Cys Ser Ile Ile Lys Ala Pro Phe
1   5   10   15

Ser Ser Val Val
            20

Page 137

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Ala Ser Ile Val
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Ala Ser Ile Val
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Ala Ser Ile Val
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1                   5                   10                  15

Ala Ser Ile Val
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Ala Asn Ile Asp
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<220>
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<400>   639
Cys Ser Ile Ile Lys Ala Pro Phe Ser Ser Val Val Ala Gly Ile Gly
1   5   10   15

Gly Gln

<210>   640
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Cys Ser Ile Met Arg Ala Pro Phe Ala Ser Ile Val Ala Gly Ile Gly
1   5   10   15

Gly Gln

<210>   641
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1   5   10   15

Gly Gln Tyr Arg
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1   5   10   15

Gly Gln

<210>   643
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Cys Ser Thr Thr Lys Ala Pro Phe Ala Ser Ile Val Ala Asp Ile Gly
1               5                   10                  15

Gly Gln


<210>    644
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Cys Ser Thr Ile Asn Ala Pro Phe Ala Ser Ile Val Ala Gly Ile Ser
1               5                   10                  15

Gly Gln


<210>    645
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<400>    645
Cys Ser Thr Ile Asn Val Pro Tyr Ala Asn Ile Asp Ala Gly Ile Gly
1               5                   10                  15

Gly Gln


<210>    646
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Pro Gln Gln Pro Phe Pro Leu Gln Pro Gln Gln Ser Phe Leu Trp Gln
1               5                   10                  15

Ser Gln Gln Pro
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<220>
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<400>    647
Pro Gln Gln Ser Phe Leu Trp Gln Ser Gln Gln Pro Phe Leu Gln Gln
1               5                   10                  15
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Page 140

Pro Gln Gln Pro
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<210>   648
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<212>   PRT
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<220>
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Ser Gln Gln Pro Phe Leu Gln Gln Pro Gln Gln Pro Ser Pro Gln Pro
1   5   10   15

Gln Gln Val Val
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<210>   649
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Pro Gln Gln Pro Ser Pro Gln Pro Gln Gln Val Val Gln Ile Ile Ser
1   5   10   15

Pro Ala Thr Pro
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<210>   650
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<400>   650
Gln Gln Val Val Gln Ile Ile Ser Pro Ala Thr Pro Thr Thr Ile Pro
1   5   10   15

Ser Ala Gly Lys
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Pro Ala Thr Pro Thr Thr Ile Pro Ser Ala Gly Lys Pro Thr Ser Ala
1   5   10   15

Pro Phe Pro Gln
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<210>   652
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Page 141

<220>
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Ser Ala Gly Lys Pro Thr Ser Ala Pro Phe Pro Gln Gln Gln Gln Gln
1   5   10   15

His Gln Gln Leu
                20

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Pro Phe Pro Gln Gln Gln Gln Gln His Gln Gln Leu Ala Gln Gln Gln
1   5   10   15

Ile Pro Val Val
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1   5   10   15

Leu Gln Gln Leu
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<400>   655
Ile Pro Val Val Gln Pro Ser Ile Leu Gln Gln Leu Asn Pro Cys Lys
1   5   10   15

Val Phe Leu Gln
                20

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<400>   656
Leu Gln Gln Leu Asn Pro Cys Lys Val Phe Leu Gln Gln Gln Cys Ser
1   5   10   15

Pro Val Ala Met
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Page 142

<210> 657
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<220>
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Val Phe Leu Gln Gln Gln Cys Ser Pro Val Ala Met Pro Gln Arg Leu
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Ala Arg Ser Gln
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Pro Val Ala Met Pro Gln Arg Leu Ala Arg Ser Gln Met Leu Gln Gln
1   5   10   15

Ser Ser Cys His
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Ala Arg Ser Gln Met Leu Gln Gln Ser Ser Cys His Val Met Gln Gln
1   5   10   15

Gln Cys Cys Gln
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1   5   10   15

Ile Pro Gln Gln
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Gln Cys Cys Gln Gln Leu Pro Gln Ile Pro Gln Gln Ser Arg Tyr Gln
1   5   10   15

Ala Ile Arg Ala
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<210>   662
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<400>   662
Pro Gln Ile Pro Gln Gln Ser Arg Tyr Glu Ala Ile Arg Ala Ile Ile
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Tyr Ser Ile Ile
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<400>   663
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1   5   10   15

Ile Ile Leu Gln
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<400>   664
Ala Ile Arg Ala Ile Ile Tyr Ser Ile Ile Leu Gln Glu Gln Gln Gln
1   5   10   15

Val Gln Gly Ser
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<210>   665
<211>   20
<212>   PRT
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<400>   665
Ile Ile Leu Gln Glu Gln Gln Gln Val Gln Gly Ser Ile Gln Ser Gln
1   5   10   15

Gln Gln Gln Pro
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<210>   666
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<212>    PRT
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<400>    666
Val Gln Gly Ser Ile Gln Ser Gln Gln Gln Gln Pro Gln Gln Leu Gly
1               5                   10                  15

Gln Cys Val Ser
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<210>    667
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<400>    667
Gln Gln Gln Pro Gln Gln Leu Gly Gln Cys Val Ser Gln Pro Gln Gln
1               5                   10                  15

Gln Ser Gln Gln
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<210>    668
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<400>    668
Gln Cys Val Ser Gln Pro Gln Gln Ser Gln Gln Gln Leu Gly Gln
1               5                   10                  15

Gln Pro Gln Gln
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<210>    669
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<400>    669
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1               5                   10                  15

Gln Gly Thr Phe
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<210>    670
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<400>    670
Gln Pro Gln Gln Gln Gln Leu Ala Gln Gly Thr Phe Leu Gln Pro His
1               5                   10                  15
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Gln Ile Ala Gln
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<210>   671
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<400>   671
Gln Gly Thr Phe Leu Gln Pro His Gln Ile Ala Gln Leu Glu Val Met
1               5                   10                  15

Thr Ser Ile Ala
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<400>   672
Gln Ile Ala Gln Leu Glu Val Met Thr Ser Ile Ala Leu Arg Ile Leu
1               5                   10                  15

Pro Thr Met Cys
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<210>   673
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<220>
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<400>   673
Thr Ser Ile Ala Leu Arg Ile Leu Pro Thr Met Cys Ser Val Asn Val
1               5                   10                  15

Pro Leu Tyr Arg
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<210>   674
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<220>
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<400>   674
Pro Thr Met Cys Ser Val Asn Val Pro Leu Tyr Arg Thr Thr Thr Ser
1               5                   10                  15

Val Pro Phe Gly
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<220>
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Pro Leu Tyr Arg Thr Thr Thr Ser Val Pro Phe Gly Val Gly Thr Gly
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Val Gly Ala Tyr
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<210>   676
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<220>
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<400>   676
Thr Ile Thr Arg Thr Phe Pro Ile Pro Thr Ile Ser Ser Asn Asn Asn
1   5   10   15

His His Phe Arg
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<210>   677
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<400>   677
Pro Thr Ile Ser Ser Asn Asn Asn His His Phe Arg Ser Asn Ser Asn
1   5   10   15

His His Phe His
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Gln Phe Tyr Arg
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Pro Gly His Asn
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Asn Asn Asn Ser
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Ser Pro Ser Asn
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Ser Pro Asn Asn
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His Thr His Pro
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Asn Leu Pro His
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Gln Gln Gln Gln
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1   5   10   15

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1   5   10   15

Gln Gln Gln Gln
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Gln Gln Ser Pro
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Page 149

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Gln Gln Leu Val
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Gln Gln Gln Gln
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Gln Gln Ile Pro
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Ser Val Leu Gln
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Page 150

Cys Lys Val Phe
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Ser Val Leu Gln Gln Leu Asn Pro Cys Lys Val Phe Leu Gln Gln Gln
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Cys Ser Pro Val
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Arg Leu Ala Arg
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Gln Gln Ser Ser
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1   5   10   15

Gln Gln Gln Cys
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Gln Gln Ser Ser Cys His Val Met Gln Gln Gln Cys Cys Gln Gln Leu
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Gln Gln Ile Pro
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1               5               10                  15

Tyr Glu Ala Ile
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Tyr Ser Ile Ile
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<210>    701
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<400>    701
Tyr Glu Ala Ile Arg Ala Ile Ile Tyr Ser Ile Ile Leu Gln Glu Gln
1               5               10                  15

Gln Gln Gly Phe
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Tyr Ser Ile Ile Leu Gln Glu Gln Gln Gly Phe Val Gln Pro Gln
1               5               10                  15

Gln Gln Gln Pro
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<210>   703
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Gln Gly Val Ser
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<210>   704
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1               5                   10                  15

Gln Ser Gln Gln
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<210>   705
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1               5                   10                  15

Cys Ser Phe Gln
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<210>   706
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Gln Ser Gln Gln Gln Leu Gly Gln Cys Ser Phe Gln Gln Pro Gln Gln
1               5                   10                  15

Gln Leu Gly Gln
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1   5   10   15

Gln Gln Gln Gln
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Gln Leu Gly Gln Gln Pro Gln Gln Gln Gln Gln Gln Val Leu Gln
1   5   10   15

Gly Thr Phe Leu
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Gln Gln Gln Gln Gln Val Leu Gln Gly Thr Phe Leu Gln Pro His Gln
1   5   10   15

Ile Ala His Leu
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Gly Thr Phe Leu Gln Pro His Gln Ile Ala His Leu Glu Ala Val Thr
1   5   10   15

Ser Ile Ala Leu
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Ile Ala His Leu Glu Ala Val Thr Ser Ile Ala Leu Arg Thr Leu Pro
1   5   10   15

Thr Met Cys Ser
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<210>   712
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Ser Ile Ala Leu Arg Thr Leu Pro Thr Met Cys Ser Val Asn Val Pro
1               5                   10                  15

Leu Tyr Ser Ala
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Thr Met Cys Ser Val Asn Val Pro Leu Tyr Ser Ala Thr Thr Ser Val
1               5                   10                  15

Pro Phe Gly Val
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Leu Tyr Ser Ala Thr Thr Ser Val Pro Phe Gly Val Gly Thr Gly Val
1               5                   10                  15

Gly Ala Tyr


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Pro Gln Gln Ser
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<210>    716
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<220>
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Pro Trp Gln Gln Gln Pro Leu Pro Pro Gln Gln Ser Phe Ser Gln Gln
1               5                   10                  15
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Page 155

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Pro Pro Phe Ser
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<210>    717
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<400>    717
Pro Gln Gln Ser Phe Ser Gln Gln Pro Pro Phe Ser Gln Gln Gln Gln
1                5                   10                  15

Gln Pro Leu Pro
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Pro Pro Phe Ser Gln Gln Gln Gln Gln Pro Leu Pro Gln Gln Pro Ser
1                5                   10                  15

Phe Ser Gln Gln
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1                5                   10                  15

Ser Gln Gln Gln
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1                5                   10                  15

Gln Gln Pro Pro
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<210>    721
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Page 156

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1   5   10   15

Gln Gln Pro Val
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1   5   10   15

Pro Gln Gln Ser
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Pro Ser Asn Lys Glu Leu Gln Ser Pro Gln Gln Ser Phe Ser Tyr Gln
1   5   10   15

Gln Gln Pro Phe
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Pro Gln Gln Ser Phe Ser Tyr Gln Gln Gln Pro Phe Pro Gln Gln Pro
1   5   10   15

Tyr Pro Gln Gln
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<210>   725
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Gln Gln Pro Phe Pro Gln Gln Pro Tyr Pro Gln Gln Pro Tyr Pro Ser
1   5   10   15

Gln Gln Pro Tyr
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Tyr Pro Gln Gln Pro Tyr Pro Ser Gln Gln Pro Tyr Pro Ser Gln Gln
1   5   10   15

Pro Phe Pro Thr
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Gln Gln Pro Tyr Pro Ser Gln Gln Pro Phe Pro Thr Pro Gln Gln Gln
1   5   10   15

Phe Pro Glu Gln
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1   5   10   15

Phe Thr Gln Pro
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<210> 729
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Phe Pro Glu Gln Ser Gln Gln Pro Phe Thr Gln Pro Gln Gln Pro Thr
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Pro Ile Gln Pro
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1               5                   10                  15

Pro Gln Gln Pro
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Pro Ile Gln Pro Gln Gln Pro Phe Pro Gln Gln Pro Gln Gln Pro Gln
1               5                   10                  15

Gln Pro Phe Pro
            20


<210>    732
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1               5                   10                  15

Pro Phe Pro Trp
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1               5                   10                  15

Pro Phe Pro Gln
            20


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1               5                   10                  15

Phe Pro Leu Gln
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<210>    735
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Page 159

<212> PRT
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1   5   10   15

Phe Pro Gln Gln
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1   5   10   15

Phe Pro Gln Pro
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1   5   10   15

Pro Gln Gln Ser
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1   5   10   15

Pro Gln Gln Leu
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Pro Gln Gln Ser Glu Gln Ile Ile Pro Gln Gln Leu Gln Gln Pro Phe
1   5   10   15

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Pro Leu Gln Pro
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1               5               10              15

Pro Gln Gln Pro
            20


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1               5               10              15

Pro Gln Pro Gln
            20


<210>    742
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1               5               10              15

Val Gln Pro Gln
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<400>    743
Pro Gln Pro Gln Gln Pro Ile Pro Val Gln Pro Gln Gln Ser Phe Pro
1               5               10              15

Gln Gln Ser Gln
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1               5               10              15

Pro Phe Ala Gln
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Gln Gln Ser Gln Gln Ser Gln Gln Pro Phe Ala Gln Pro Gln Gln Leu
1               5               10              15

Phe Pro Glu Leu
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Pro Phe Ala Gln Pro Gln Gln Leu Phe Pro Glu Leu Gln Gln Pro Ile
1               5               10              15

Pro Gln Gln Pro
            20


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Phe Pro Glu Leu Gln Gln Pro Ile Pro Gln Gln Pro Gln Gln Pro Phe
1               5               10              15

Pro Leu Gln Pro
            20


<210>    748
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<400>    748
Pro Gln Gln Pro Gln Gln Pro Phe Pro Leu Gln Pro Gln Gln Pro Phe
1               5               10              15

Pro Gln Gln Pro
            20
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Page 162

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<210>    749
<211>    20
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<400>    749
Pro Leu Gln Pro Gln Gln Pro Phe Pro Gln Gln Pro Gln Gln Pro Phe
1                   5                   10                  15

Pro Gln Gln Pro
            20


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<400>    750
Pro Gln Gln Pro Gln Gln Pro Phe Pro Gln Gln Pro Gln Gln Ser Phe
1                   5                   10                  15

Pro Gln Gln Pro
            20


<210>    751
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<220>
<223>    peptide

<400>    751
Pro Gln Gln Pro Gln Gln Ser Phe Pro Gln Gln Pro Gln Gln Pro Tyr
1                   5                   10                  15

Pro Gln Gln Gln
            20


<210>    752
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<220>
<223>    peptide

<400>    752
Pro Gln Gln Pro Gln Gln Pro Tyr Pro Gln Gln Gln Pro Tyr Gly Ser
1                   5                   10                  15

Ser Leu Thr Ser
            20


<210>    753
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<212>    PRT
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<220>
<223>    peptide
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Page 163

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<400>    753
Pro Gln Gln Gln Pro Tyr Gly Ser Ser Leu Thr Ser Ile Gly Gly Gln
1               5                   10                  15


<210>    754
<211>    20
<212>    PRT
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<400>    754
Ala Arg Gln Leu Asn Pro Ser Asp Gln Glu Leu Gln Ser Pro Gln Gln
1               5                   10                  15

Leu Tyr Pro Gln
            20

<210>    755
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<400>    755
Gln Glu Leu Gln Ser Pro Gln Gln Leu Tyr Pro Gln Gln Pro Tyr Pro
1               5                   10                  15

Gln Gln Pro Tyr
            20

<210>    756
<211>    20
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<400>    756
Ser Arg Leu Leu Ser Pro Arg Gly Lys Glu Leu His Thr Pro Gln Glu
1               5                   10                  15

Gln Phe Pro Gln
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<210>    757
<211>    20
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<213>    Artificial Sequence

<220>
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<400>    757
Lys Glu Leu His Thr Pro Gln Glu Gln Phe Pro Gln Gln Gln Gln Phe
1               5                   10                  15

Pro Gln Pro Gln
            20

<210>    758
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<220>
<223>   peptide

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1   5   10   15