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(54) **Title:** ANTIGEN BINDING PROTEINS WHICH BIND TO THE pMHC HLA-DQ2.5:DQ2.5 PRESENTING A GLIADIN PEPTIDE

(57) **Abstract:** The present invention relates generally to the field of antigen binding proteins such as antibodies, in particular those which bind to HLA-DQ2.5:DQ2.5- glia-α1a, or which bind to HLA-DQ2.5:DQ2.5-glia-α2. The invention further relates to compositions and immunoconjugates comprising such antibodies and to methods of producing such antibodies. The invention also relates to methods and uses which employ such antibodies, for example in the treatment of celiac disease.

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Antigen binding proteins which bind to the pMHC HLA-DQ2.5:DQ2.5 presenting a gliadin peptide

The present invention relates generally to the field of antigen binding proteins, in particular to antibodies which bind to, or bind specifically to, the pMHC (peptide-Major Histocompatibility Complex) HLA-DQ2.5:DQ2.5 presenting a gliadin peptide. More particularly, the invention relates to antigen binding proteins (e.g. antibodies) which bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α1a, or which bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α2. The invention further relates to compositions and immunoconjugates comprising such antibodies and to methods of producing such antibodies. The invention also relates to methods and uses which employ such antibodies, for example in the treatment of celiac disease.

Celiac disease (CD) is an autoimmune-like, chronic T cell-mediated inflammatory disorder of the small intestine caused by dietary gluten proteins from wheat, barley and rye. The disease has a strong HLA association with about 90% of the patients expressing HLA-DQ2.5 (*DQA1*05-DQB1*02*), and most of the remaining HLA-DQ8 (*DQA1*03-DQB1*03:02*) or HLA-DQ2.2 (*DQA1*02:01-DQB1*02*). Gluten proteins are resistant to proteolysis due to high proline content, and as a result, long immunogenic peptide fragments remain in the intestine. The T-cell response to wheat gluten is dominated by reactivity to two epitopes of α-gliadin, DQ2.5-glia-α1a (PFPQPELPY) and DQ2.5-glia-α2 (PQPELPYPQ), which can be found within a proteolysis resistant α-gliadin 33mer peptide, as well as to two epitopes of ω-gliadin, DQ2.5-glia-ω1 (PFPQPEQPF) and DQ2.5-glia-ω2 (PQPEQPFPW). Importantly, the immunogenicity of gluten peptides depends on post-translational modification by the enzyme transglutaminase 2 (TG2), which by deamidation converts certain glutamine residues to glutamate. The introduction of negatively charged anchor residues makes the peptides better suited for HLA-DQ2.5 binding and increase the pMHC (peptide-major histocompatability complex) stability.

Activation of $CD4^+$ T cells by antigen presentation both in the mesenteric lymph nodes and in gut-associated lymphoid tissue is thought to be an initial event in induction of CD pathogenesis. Studies on the characteristics of antigen presenting cells (APC) in the healthy duodenum have identified classical macrophages ($CD163^+$) and DCs ($CD11c^+$) as the main populations, with minor populations of cells with an intermediate DC phenotype ($CD11c^+$ $CD163^+$). The

same cell subpopulations are found in active celiac lesions, but with altered density and somewhat altered phenotypes. Although not commonly regarded as APCs, plasma cells (PCs) secreting antibodies against gluten and TG2 are increased in density in the lamina propria of CD patients. It is not clear how these different cell populations contribute to the disease development. In contrast, only scarce populations of B cells can be found.

Although the T-cell receptor (TCR) is the endogenous binding partner for pMHC, the use of recombinant TCRs for the purpose of detecting peptide presentation is challenging. TCRs have low affinity for pMHC, in the 1-100μM range, and soluble TCRs are intrinsically unstable and production is demanding. Therefore, monoclonal antibodies (mAbs) with TCR-like specificity are attractive alternatives and generation of mAbs against pMHC has been reported using both hybridoma technology and phage display.

What are needed in the art are new, preferably improved, agents, such as antibodies, that can be used as reagents for the investigation of particular gliadin peptides presented by MHC class II molecules, for example in the context of celiac disease. Such antibodies may also be used in the treatment, prophylaxis and diagnosis of celiac disease.

The present inventors have identified antigen binding proteins, specifically antibodies, which bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α1a, or which bind specifically to HLA-DQ2.5:DQ2.5-glia-α2. The antibodies generated by the inventors have advantageous properties which make them ideal agents for the above-mentioned uses.

In one aspect, the invention provides an antigen binding protein which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5 presenting a gliadin peptide, said antigen binding protein comprising at least one light chain variable domain and at least one heavy chain variable domain, each domain comprising three complementarity determining regions (CDRs), wherein

(a) said antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:5, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:5;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:6, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:6;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:417;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:8 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:8;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:9 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:9; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:415; or wherein

(b) said antigen binding protein binds to, or specifically binds, to HLA-DQ2.5:DQ2.5-glia-α2 and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:425;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:427;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:429;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:419;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:421; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:423.

In certain embodiments,

(a) said antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:5, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:5;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:6, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:6;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:418;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:8 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:8;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:9 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:9; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:416 or SEQ ID NO:520; or

(b) said antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:426;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:428;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:430;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:420;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:422; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:424.

In some embodiments, said antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:5, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:5;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:6, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:6;
a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:417;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:8 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:8;
a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:9 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:9; and
a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:415.

In some embodiments, said antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:5, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:5;
a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:6, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:6;
a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:418;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:8 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:8;
a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:9 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:9; and
a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:416 or SEQ ID NO:520.

In some embodiments, said antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:425;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:427;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:429;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:419;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:421; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:423.

In some embodiments, said antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:426;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:428;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:430;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:420;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:422; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:424.

In other embodiments of the present invention, the antigen binding protein comprises a light chain variable domain that comprises

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:435;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:437; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:439.

In other embodiments of the present invention, the antigen binding protein comprises a light chain variable domain that comprises

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:436;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:438; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:440 or SEQ ID NO:521.

In other embodiments of the present invention, the antigen binding protein comprises a heavy chain variable domain that comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:441 (preferably SEQ ID NO:442) or SEQ ID NO:522 (preferably SEQ ID NO: 523);

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:42 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:42, or SEQ ID NO:168 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:168; and

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:443.

In some such embodiments, an antigen binding protein comprising a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:42 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:42 binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a. In other such embodiments, an antigen binding protein comprising a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:168 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:168 binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2.

In other embodiments of the present invention, the antigen binding protein comprises a light chain variable domain that comprises

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:435, preferably SEQ ID NO:436;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:437, preferably SEQ ID NO:438;

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:439, preferably SEQ ID NO:440 or SEQ ID NO:521; and

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:441 (preferably SEQ ID NO:442) or SEQ ID NO: 522 (preferably SEQ ID NO: 523);

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:42 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:42, or SEQ ID NO:168 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:168; and

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:443.

In other embodiments, said antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:41, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:41;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:42, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:42;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:431, preferably SEQ ID NO:432;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:44 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:44;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:45 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:45; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:46.

In one aspect (and in certain embodiments), the invention provides an antigen binding protein which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5

presenting a gliadin peptide, said antigen binding protein comprising at least one light chain variable domain and at least one heavy chain variable domain, each domain comprising three complementarity determining regions (CDRs), wherein

said antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:518, preferably 519;
a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:6, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:6;
a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:417, preferably SEQ ID NO:418;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:8 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:8;
a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:9 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:9; and
a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:415, preferably SEQ ID NO:416 or SEQ ID NO:520, more preferably SEQ ID NO:521.

Other features and properties of other aspects and embodiments of the invention apply, *mutatis mutandis*, to this aspect of the invention.

In some embodiments, said antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:433, preferably 434;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:168 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:168;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:169 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:169;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:170 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:170;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:171 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:171; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:172 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:172.

In some embodiments, said antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:495;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:168 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:168;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:169 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:169;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:170 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:170;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:171 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:171; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:172 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:172.

In a preferred aspect, and in preferred embodiments, the antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and comprises at least one light chain variable domain having a VL CDR1, VL CDR2 and VL CDR3 amino acid sequence as set forth in any one of Tables A-I or Table AA herein and/or (preferably “and”) at least one heavy chain variable domain having a VH CDR1, VH

CDR2 and VH CDR3 amino acid sequence as set forth in any one of Tables A-I or Table AA herein. Tables A-I herein set forth sequences of the R2A1-8E, R3A2-9F, R4A1-3A (also referred to as 107), 107-4.5D, 107-4.6D, 107-4.6C, 107-4.7C, 107-5.6A and 107-15.6A antibodies. Table AA herein sets forth sequences of the RF117 antibody. Thus, preferred antigen binding proteins are those comprising (or based on) these antibody sequences.

In one aspect, and in certain embodiments, the antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and comprises at least one light chain variable domain having a VL CDR1, VL CDR2 and VL CDR3 amino acid sequence as set forth in any one of Tables D-I or Table AA herein and/or (preferably "and") at least one heavy chain variable domain having a VH CDR1, VH CDR2 and VH CDR3 amino acid sequence as set forth in any one of Tables D-I or Table AA herein. Tables D-I herein set forth sequences of the 107-4.5D, 107-4.6D, 107-4.6C, 107-4.7C, 107-5.6A and 107-15.6A antibodies. Table AA herein sets forth sequences of the RF117 antibody. Thus, preferred antigen binding proteins are those comprising (or based on) these antibody sequences.

In a one aspect, and in certain embodiments, the antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and comprises at least one light chain variable domain having a VL CDR1, VL CDR2 and VL CDR3 amino acid sequence as set forth in any one of Tables J-W herein and/or (preferably "and") at least one heavy chain variable domain having a VH CDR1, VH CDR2 and VH CDR3 amino acid sequence as set forth in any one of Tables J-W herein. Tables J-W herein set forth sequences of the 206, 217, 218, 220, 221, 223, 226, 228, 206-2.B11, 206-3.D8, 206-3.C7, 206-3.C11, 206-3.F6 and 206-12.F6 antibodies. Thus, preferred antigen binding proteins are those comprising (or based on) these antibody sequences.

In a one aspect, and in certain embodiments, the antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and has at least one light chain variable domain comprising a VL CDR1, VL CDR2 and VL CDR3 amino acid sequence as set forth in any one of Tables R-W herein and/or (preferably "and") at least one heavy chain variable domain having a VH CDR1, VH CDR2 and VH CDR3 amino acid sequence as set forth in any one of Tables R-W herein. Tables R-W herein set forth sequences of the 206-2.B11, 206-3.D8, 206-3.C7, 206-3.C11, 206-3.F6 and 206-12.F6 antibodies. Thus, preferred antigen binding proteins are those comprising (or based on) these antibody sequences.

In some embodiments, a preferred antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprises (or is based on) the antibody sequences (e.g. three VH CDR sequences and three VL CDR sequences) of the 107-4.7C antibody described herein (see Table G).

In some embodiments, a preferred antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprises (or is based on) the antibody sequences (e.g. three VH CDR sequences and three VL CDR sequences) of the 206-2.B11 antibody described herein (see Table R).

In some embodiments, a preferred antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprises (or is based on) the antibody sequences (e.g. three VH CDR sequences and three VL CDR sequences) of the 206-3.C11 antibody described herein (see Table U).

In some embodiments, the antigen binding protein of the invention is not the R2A1-8E, R3A2-9F or R4A1-3A (also referred to as 107) antibody, e.g. as defined by their light chain variable region and heavy chain variable region sequences herein (see Tables A-C). In some embodiments, the antigen binding protein of the invention is not the 206, 217, 218, 220, 221, 223, 226, 228 antibody e.g. as defined by their light chain variable region and heavy chain variable region sequences herein (see Tables J-Q).

In some embodiments, HLA-DQ2.5:DQ2.5-glia-α1a antigen binding proteins of the invention have a T (threonine) residue at position 5 and/or position 6 of the VH CDR3, and/or a VL FR1 (VL framework 1) sequence other than SEQ ID NO:15.

In some embodiments, HLA-DQ2.5:DQ2.5-glia-α2 antigen binding proteins of the invention do not have an S (serine) residue at position 5 and an S residue at position 6 of the VH CDR1.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:8 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:9 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:10 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:5 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:6 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:7 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and that comprises:

a VL domain that comprises a VL CDR1 of SEQ ID NO:8, a VL CDR2 of SEQ ID NO:9, and a VL CDR3 of SEQ ID NO:10, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:5, a VH CDR2 of SEQ ID NO:6, and a VH CDR3 of SEQ ID NO:7.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:3 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:4,or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:3 and a VL domain that comprises the amino acid sequence of SEQ ID NO:4.

In some embodiments an antibody in IgG format is preferred. A preferred embodiment of the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:444 or a sequence substantially homologous thereto and/or a light chain that comprises the amino acid sequence of SEQ ID NO:445 or a sequence substantially homologous thereto. In another preferred embodiment the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a which has a heavy chain that comprises the amino acid

sequence of SEQ ID NO:446 or a sequence substantially homologous thereto and/or a light chain that comprises the amino acid sequence of SEQ ID NO:447 or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

In a preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:444 and a light chain that comprises the amino acid sequence of SEQ ID NO:445.

In another preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:446 and a light chain that comprises the amino acid sequence of SEQ ID NO:447.

The section immediately above relates to the R2A1-8E antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:26 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:27 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:28 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:23 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:24 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:25 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and that comprises:

a VL domain that comprises a VL CDR1 of SEQ ID NO:26, a VL CDR2 of SEQ ID NO:27, and a VL CDR3 of SEQ ID NO:28, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:23, a VH CDR2 of SEQ ID NO:24, and a VH CDR3 of SEQ ID NO:25.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:21 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:22,or a sequence substantially homologous thereto. A preferred “sequence substantially homologous thereto” is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:21 and a VL domain that comprises the amino acid sequence of SEQ ID NO:22.

In some embodiments an antibody in IgG format is preferred. A preferred embodiment of the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:448 or a sequence substantially homologous thereto and/or a light chain that comprises the amino acid sequence of SEQ ID NO:449 or a sequence substantially homologous thereto. In another preferred embodiment the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:450 or a sequence substantially homologous thereto and/or a light chain that comprises the amino acid sequence of SEQ ID NO:451 or a sequence substantially homologous thereto. A preferred “sequence substantially homologous thereto” is a sequence having at least 80% sequence identity thereto.

In a preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:448 and a light chain that comprises the amino acid sequence of SEQ ID NO:449.

In another preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:450 and a light chain that comprises the amino acid sequence of SEQ ID NO:451.

The section immediately above relates to the R3A2-9F antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:44 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:45 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:46 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:41 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:42 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:43 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and that comprises:

a VL domain that comprises a VL CDR1 of SEQ ID NO:44, a VL CDR2 of SEQ ID NO:45, and a VL CDR3 of SEQ ID NO:46, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:41, a VH CDR2 of SEQ ID NO:42, and a VH CDR3 of SEQ ID NO:43.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:9 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:40,or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:39 and a VL domain that comprises the amino acid sequence of SEQ ID NO:40.

In some embodiments an antibody in IgG format is preferred. A preferred embodiment of the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:452 or a sequence substantially homologous thereto and/or a light chain that comprises the amino acid sequence of SEQ ID NO:453 or a sequence substantially homologous thereto. In another preferred embodiment the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:454 or a sequence substantially homologous thereto and/or a light chain that comprises the amino acid sequence of SEQ ID NO:455 or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

In a preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:452 and a light chain that comprises the amino acid sequence of SEQ ID NO:453.

In another preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:454 and a light chain that comprises the amino acid sequence of SEQ ID NO:455.

The section immediately above relates to the R4A1-3A (107) antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:62 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:63 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:64 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:59 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:60 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:61 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and that comprises:

a VL domain that comprises a VL CDR1 of SEQ ID NO:62, a VL CDR2 of SEQ ID NO:63, and a VL CDR3 of SEQ ID NO:64, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:59, a VH CDR2 of SEQ ID NO:60, and a VH CDR3 of SEQ ID NO:61.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:57 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:58,or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:57 and a VL domain that comprises the amino acid sequence of SEQ ID NO:58.

The section immediately above relates to the 107-4.5D antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:80 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:81 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:82 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:77 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:78 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:79 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and that comprises:

a VL domain that comprises a VL CDR1 of SEQ ID NO:80, a VL CDR2 of SEQ ID NO:81, and a VL CDR3 of SEQ ID NO:82, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:77, a VH CDR2 of SEQ ID NO:78, and a VH CDR3 of SEQ ID NO:79.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:75 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:76,or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:75 and a VL domain that comprises the amino acid sequence of SEQ ID NO:76.

The section immediately above relates to the 107-4.6D antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein

comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:98 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:99 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:100 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:95 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:96 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:97 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and that comprises:

a VL domain that comprises a VL CDR1 of SEQ ID NO:98, a VL CDR2 of SEQ ID NO:99, and a VL CDR3 of SEQ ID NO:100, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:95, a VH CDR2 of SEQ ID NO:96, and a VH CDR3 of SEQ ID NO:97.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:93 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:94,or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a, comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:93 and a VL domain that comprises the amino acid sequence of SEQ ID NO:94.

The section immediately above relates to the 107-4.6C antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:116 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:117 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:118 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:113 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:114 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:115 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and that comprises:

a VL domain that comprises a VL CDR1 of SEQ ID NO:116, a VL CDR2 of SEQ ID NO:117, and a VL CDR3 of SEQ ID NO:118, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:113, a VH CDR2 of SEQ ID NO:114, and a VH CDR3 of SEQ ID NO:115.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:111 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:112,or a sequence substantially homologous

thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:111 and a VL domain that comprises the amino acid sequence of SEQ ID NO:112.

The section immediately above relates to the 107-4.7C antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:134 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:135 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:136 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:131 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:132 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:133 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and that comprises:

a VL domain that comprises a VL CDR1 of SEQ ID NO:134, a VL CDR2 of SEQ ID NO:135, and a VL CDR3 of SEQ ID NO:136, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:131, a VH CDR2 of SEQ ID NO:132, and a VH CDR3 of SEQ ID NO:133.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:129 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:130,or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:129 and a VL domain that comprises the amino acid sequence of SEQ ID NO:130.

The section immediately above relates to the 107-5.6A antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:152 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:153 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:154 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:149 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:150 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:151 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and that comprises:

a VL domain that comprises a VL CDR1 of SEQ ID NO:152, a VL CDR2 of SEQ ID NO:153, and a VL CDR3 of SEQ ID NO:154, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:149, a VH CDR2 of SEQ ID NO:150, and a VH CDR3 of SEQ ID NO:151.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:147 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:148,or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:147 and a VL domain that comprises the amino acid sequence of SEQ ID NO:148.

The section immediately above relates to the 107-15.6A antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:503 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:504 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:505 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:500 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:501 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:502 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and that comprises:

a VL domain that comprises a VL CDR1 of SEQ ID NO:503, a VL CDR2 of SEQ ID NO:504, and a VL CDR3 of SEQ ID NO:505, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:500, a VH CDR2 of SEQ ID NO:501, and a VH CDR3 of SEQ ID NO:502.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:498 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:499,or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:498 and a VL domain that comprises the amino acid sequence of SEQ ID NO:499.

In some embodiments an antibody in IgG format is preferred. A preferred embodiment of the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:514 or a sequence substantially homologous thereto and/or a light chain that comprises the amino acid sequence of SEQ ID NO:515 or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

In a preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:514 and a light chain that comprises the amino acid sequence of SEQ ID NO:515.

The section immediately above relates to the RF117 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:170 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:171 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:172 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:167 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:168 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:169 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises: a VL domain that comprises a VL CDR1 of SEQ ID NO:170, a VL CDR2 of SEQ ID NO:172, and a VL CDR3 of SEQ ID NO:173, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:167, a VH CDR2 of SEQ ID NO:168, and a VH CDR3 of SEQ ID NO:169.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:165 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:166, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that

comprises the amino acid sequence of SEQ ID NO:165 and a VL domain that comprises the amino acid sequence of SEQ ID NO:166.

In some embodiments an antibody in IgG format is preferred. A preferred embodiment of the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:456 or a sequence substantially homologous thereto and/or a light chain that comprises the amino acid sequence of SEQ ID NO:457 or a sequence substantially homologous thereto. In another preferred embodiment the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:458 or a sequence substantially homologous thereto and/or a light chain that comprises the amino acid sequence of SEQ ID NO:459 or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

In a preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:456 and a light chain that comprises the amino acid sequence of SEQ ID NO:457.

In another preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:458 and a light chain that comprises the amino acid sequence of SEQ ID NO:459.

The section immediately above relates to the 206 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:188 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:189 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:190 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:185 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:186 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:187 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises: a VL domain that comprises a VL CDR1 of SEQ ID NO:188, a VL CDR2 of SEQ ID NO:189, and a VL CDR3 of SEQ ID NO:190, and a VH domain that comprises a VH CDR1 of SEQ ID NO:185, a VH CDR2 of SEQ ID NO:186, and a VH CDR3 of SEQ ID NO:187.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:183 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:184, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:183 and a VL domain that comprises the amino acid sequence of SEQ ID NO:184.

The section immediately above relates to the 217 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:206 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:207 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:208 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:203 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:204 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:205 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises: a VL domain that comprises a VL CDR1 of SEQ ID NO:206, a VL CDR2 of SEQ ID NO:207, and a VL CDR3 of SEQ ID NO:208, and
a VH domain that comprises a VH CDR1 of SEQ ID NO:203, a VH CDR2 of SEQ ID NO:204, and a VH CDR3 of SEQ ID NO:205.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:201 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:202, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:201 and a VL domain that comprises the amino acid sequence of SEQ ID NO:202.

The section immediately above relates to the 218 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:224 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:225 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:226 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:221 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:222 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:223 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises:
a VL domain that comprises a VL CDR1 of SEQ ID NO:224, a VL CDR2 of SEQ ID NO:225, and a VL CDR3 of SEQ ID NO:226, and
a VH domain that comprises a VH CDR1 of SEQ ID NO:221, a VH CDR2 of SEQ ID NO:222, and a VH CDR3 of SEQ ID NO:223.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:219 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:220, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:219 and a VL domain that comprises the amino acid sequence of SEQ ID NO:220.

In some embodiments an antibody in IgG format is preferred. A preferred embodiment of the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:460 or a sequence substantially homologous thereto

and/or a light chain that comprises the amino acid sequence of SEQ ID NO:461 or a sequence substantially homologous thereto. In another preferred embodiment the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:462 or a sequence substantially homologous thereto and/or a light chain that comprises the amino acid sequence of SEQ ID NO:463 or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

In a preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:460 and a light chain that comprises the amino acid sequence of SEQ ID NO:461.

In another preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:462 and a light chain that comprises the amino acid sequence of SEQ ID NO:463.

The section immediately above relates to the 220 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:242 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:243 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:244 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:239 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:240 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:241 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises:
a VL domain that comprises a VL CDR1 of SEQ ID NO:242, a VL CDR2 of SEQ ID NO:243, and a VL CDR3 of SEQ ID NO:244, and
a VH domain that comprises a VH CDR1 of SEQ ID NO:239, a VH CDR2 of SEQ ID NO:240, and a VH CDR3 of SEQ ID NO:241.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:237 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:238, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:237 and a VL domain that comprises the amino acid sequence of SEQ ID NO:238.

The section immediately above relates to the 221 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:260 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:261 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:262 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:257 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:258 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:259 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises: a VL domain that comprises a VL CDR1 of SEQ ID NO:260, a VL CDR2 of SEQ ID NO:261, and a VL CDR3 of SEQ ID NO:262, and a VH domain that comprises a VH CDR1 of SEQ ID NO:257, a VH CDR2 of SEQ ID NO:258, and a VH CDR3 of SEQ ID NO:259.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:255 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:256, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:255 and a VL domain that comprises the amino acid sequence of SEQ ID NO:256.

The section immediately above relates to the 223 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:278 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:279 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:280 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:275 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:276 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:277 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises: a VL domain that comprises a VL CDR1 of SEQ ID NO:278, a VL CDR2 of SEQ ID NO:279, and a VL CDR3 of SEQ ID NO:280, and
a VH domain that comprises a VH CDR1 of SEQ ID NO:275, a VH CDR2 of SEQ ID NO:276, and a VH CDR3 of SEQ ID NO:277.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:273 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:274, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that specifically binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:273 and a VL domain that comprises the amino acid sequence of SEQ ID NO:274.

The section immediately above relates to the 226 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:296 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:297 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:298 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:293 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:294 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:295 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises:
a VL domain that comprises a VL CDR1 of SEQ ID NO:296, a VL CDR2 of SEQ ID NO:297, and a VL CDR3 of SEQ ID NO:298, and
a VH domain that comprises a VH CDR1 of SEQ ID NO:293, a VH CDR2 of SEQ ID NO:294, and a VH CDR3 of SEQ ID NO:295.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:291 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:292, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:291 and a VL domain that comprises the amino acid sequence of SEQ ID NO:292.

In some embodiments an antibody in IgG format is preferred. A preferred embodiment of the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:464 or a sequence substantially homologous thereto

and/or a light chain that comprises the amino acid sequence of SEQ ID NO:465 or a sequence substantially homologous thereto. In another preferred embodiment the invention provides an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, which has a heavy chain that comprises the amino acid sequence of SEQ ID NO:466 or a sequence substantially homologous thereto and/or a light chain that comprises the amino acid sequence of SEQ ID NO:467 or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

In a preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:464 and a light chain that comprises the amino acid sequence of SEQ ID NO:465.

In another preferred embodiment, an antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO:466 and a light chain that comprises the amino acid sequence of SEQ ID NO:467.

The section immediately above relates to the 228 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:314 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:315 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:316 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:311 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:312 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:313 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises:
a VL domain that comprises a VL CDR1 of SEQ ID NO:314, a VL CDR2 of SEQ ID NO:315, and a VL CDR3 of SEQ ID NO:316, and
a VH domain that comprises a VH CDR1 of SEQ ID NO:311, a VH CDR2 of SEQ ID NO:312, and a VH CDR3 of SEQ ID NO:313.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:309 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:310, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:309 and a VL domain that comprises the amino acid sequence of SEQ ID NO:310.

The section immediately above relates to the 206-2.B11 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:332 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:333 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:334 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:329 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:330 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:331 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises: a VL domain that comprises a VL CDR1 of SEQ ID NO:332, a VL CDR2 of SEQ ID NO:333, and a VL CDR3 of SEQ ID NO:334, and a VH domain that comprises a VH CDR1 of SEQ ID NO:329, a VH CDR2 of SEQ ID NO:330, and a VH CDR3 of SEQ ID NO:331.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:327 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:328, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:327 and a VL domain that comprises the amino acid sequence of SEQ ID NO:328.

The section immediately above relates to the 206-3.D8 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:350 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:351 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:352 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:347 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:348 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:349 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises: a VL domain that comprises a VL CDR1 of SEQ ID NO:350, a VL CDR2 of SEQ ID NO:351, and a VL CDR3 of SEQ ID NO:352, and

a VH domain that comprises a VH CDR1 of SEQ ID NO:347, a VH CDR2 of SEQ ID NO:348, and a VH CDR3 of SEQ ID NO:349.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:345 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:346, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:345 and a VL domain that comprises the amino acid sequence of SEQ ID NO:346.

The section immediately above relates to the 206-3.C7 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:368 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:369 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:370 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:365 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:366 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:367 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises:
a VL domain that comprises a VL CDR1 of SEQ ID NO:368, a VL CDR2 of SEQ ID NO:369, and a VL CDR3 of SEQ ID NO:370, and
a VH domain that comprises a VH CDR1 of SEQ ID NO:365, a VH CDR2 of SEQ ID NO:366, and a VH CDR3 of SEQ ID NO:367.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:363 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:364, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:363 and a VL domain that comprises the amino acid sequence of SEQ ID NO:364.

The section immediately above relates to the 206-3.C11 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or

specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:386 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:387 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:388 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:383 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:384 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:385 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises: a VL domain that comprises a VL CDR1 of SEQ ID NO:386, a VL CDR2 of SEQ ID NO:387, and a VL CDR3 of SEQ ID NO:388, and
a VH domain that comprises a VH CDR1 of SEQ ID NO:383, a VH CDR2 of SEQ ID NO:384, and a VH CDR3 of SEQ ID NO:385.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:381 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:382, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:381 and a VL domain that comprises the amino acid sequence of SEQ ID NO:382.

The section immediately above relates to the 206-3.F6 antibody.

In one aspect of, and in certain embodiments of, the present invention there is provided an antigen binding protein (e.g. an antibody) which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:404 or a sequence substantially homologous thereto,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:405 or a sequence substantially homologous thereto, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:406 or a sequence substantially homologous thereto; and/or (preferably "and")

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:401 or a sequence substantially homologous thereto,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:402 or a sequence substantially homologous thereto, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:403 or a sequence substantially homologous thereto.

A preferred "sequence substantially homologous thereto" is a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to the stated CDR sequence.

In a preferred embodiment, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and that comprises:
a VL domain that comprises a VL CDR1 of SEQ ID NO:404, a VL CDR2 of SEQ ID NO:405, and a VL CDR3 of SEQ ID NO:406, and
a VH domain that comprises a VH CDR1 of SEQ ID NO:401, a VH CDR2 of SEQ ID NO:402, and a VH CDR3 of SEQ ID NO:403.

Certain preferred embodiments of the invention provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:399 or a sequence substantially homologous thereto and/or a VL domain that comprises the amino acid sequence of SEQ ID NO:400, or a sequence substantially homologous thereto. A preferred "sequence substantially homologous thereto" is a sequence having at least 80% sequence identity thereto.

Further preferred embodiments provide an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a VH domain that comprises the amino acid sequence of SEQ ID NO:399 and a VL domain that comprises the amino acid sequence of SEQ ID NO:400.

The section immediately above relates to the 206-12.F6 antibody.

In some preferred embodiments of the present invention, the antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and comprises a VL CDR1 that has a H at position 1 and/or an S at position 4. In some embodiments, the antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a and has a VL CDR3 that has a P at position 7.

In some preferred embodiments of the present invention, the antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and comprises a VL CDR1 that has a Q at position 1 and/or an S position 4. In some embodiments, the antigen binding protein binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 and has a VL CDR3 that has a P at position 7.

In one aspect, the present invention provides an antigen binding protein which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5 presenting a peptide (e.g. a gliadin peptide (or gliadin derived peptide) or a celiac disease associated peptide or a gluten-derived peptide), said antigen binding protein comprising at least one light chain variable domain and at least one heavy chain variable domain, each domain comprising three complementarity determining regions (CDRs), wherein said antigen binding protein (e.g. antibody) comprises CDRs and/or variable domains as defined elsewhere herein. Other features and properties of other aspects and embodiments of the invention apply, *mutatis mutandis*, to this aspect of the invention.

In another aspect, the present invention provides an antigen binding protein (e.g. an antibody), said antigen binding protein comprising at least one light chain variable domain and at least one heavy chain variable domain, each domain comprising three complementarity determining regions (CDRs), wherein said antigen binding protein (e.g. antibody) comprises CDRs and/or variable domains as defined elsewhere herein. Other features and properties of other aspects and embodiments of the invention apply, *mutatis mutandis*, to this aspect of the invention.

In one aspect, and in certain embodiments, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-

glia- α1a or an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein binding of the antigen binding protein to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 is characterized by a recognition motif (or "footprint" or "codon") which comprises the amino acids at positions corresponding to N92, S93, Y94, D28 and S30 of the light chain variable region of SEQ ID NO:40 or SEQ ID NO:166.

The light chain variable region residues mentioned above, N92, S93, Y94, D28 and S30, correspond to IMGT (ImMunoGeneTics (www.imgt.org)) light chain variable region residue numbers (or residue positions) N108, S114, Y115, D28, S36 in relation to antibody 107 and N108, S109, Y114, D28, S36 in relation to antibody 206.

In one aspect, and in certain embodiments, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a or an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein binding of the antigen binding protein to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 is characterized by a recognition motif (or "footprint" or "codon") which comprises the amino acids at positions corresponding to N92, S93, Y94, D28 and S30 of the light chain variable region of SEQ ID NO:40 or SEQ ID NO:166, and the amino acids at positions corresponding to a Y60, Q64, D66 and R70 of the MHC beta chain of SEQ ID NO:494 (the beta chain of the HLA-DQ2.5), and the amino acids at positions corresponding to H68 S72 and R76 of the MHC alpha chain of SEQ ID NO:493 (the alpha chain of the HLA-DQ2.5).

In one aspect, and in certain embodiments, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a or an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein binding of the antigen binding protein to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 is characterized by a recognition motif (or "footprint" or "codon") which comprises the amino acids at positions N92, S93, Y94, D28 and S30 of said light chain variable region.

In one aspect, and in certain embodiments, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a or an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein binding of the antigen binding protein to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 is characterized by a recognition motif (or "footprint" or "codon") which comprises the amino acids at positions N92, S93, Y94, D28 and S30 of said light chain variable region, and the amino acids at positions Y60, Q64, D66 and R70 of the MHC beta chain of SEQ ID NO:494 (the beta chain of the HLA-DQ2.5), and the amino acids at positions H68 S72 and R76 of the MHC alpha chain of SEQ ID NO:493 (the alpha chain of the HLA-DQ2.5).

In some embodiments, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a or an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 wherein binding of the antigen binding protein to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 is characterized by a recognition motif as described above, has three VL CDRs and/or three VH CDRs, or a light chain variable domain and/or a heavy chain variable domain, or a light chain and/or a heavy chain as described elsewhere herein. Thus, other features and properties of other aspects and embodiments of the invention apply, *mutatis mutandis*, to these aspects of the invention.

A "recognition motif" (or "footprint" or "codon" or "binding motif") may be defined as a group of amino acids that contribute to (or participate in), or a group of amino acids that are predicted to contribute to (or predicted to participate in), the binding (or interaction) between the antigen binding protein and the target antigen (in this case the pMHCs HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2). A person skilled in the art will be familiar with suitable methods and techniques for identifying or predicting recognition motifs and any suitable method may be used. For example, the recognition motif may be as determined or predicted using antibody modeling or antibody docking methods (e.g. antibody modeling or antibody docking software). The RosettaAntibody and/or SnugDock applications (software) may be used for such methods in order to generate models of the docked complexes of an antigen binding protein (e.g. antibody) and its pMHC target, for example as described in Example 4 herein. In some embodiments, antibody

modeling (or antibody docking) may be done using the crystal structure of the binary complex of HLA-DQ2.5:DQ2.5-glia-α1a (PDB ID 1S9V [C.-Y. Kim, 2004]) or the crystal structure of HLA-DQ2.5:DQ2.5-glia-α2 (PDB ID 4OZF [Petersen et al., 2014]) as docking partners, e.g. as described in Example 4 herein. In some embodiments, the recognition motif is as determined by crystallographic methods (e.g. the crystal structure of the antigen binding protein: HLA-DQ2.5:DQ2.5-glia-α1a complex or antigen binding protein: HLA-DQ2.5:DQ2.5-glia-α2 complex.

In one aspect, the invention provides an antigen binding protein that binds to HLA-DQ2.5 presenting a gliadin peptide, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, said light chain variable region comprising

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:435;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:437; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:439.

In one aspect, the invention provides an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a or to HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, said light chain variable region comprising

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:435;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:437; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:439.

In some embodiments, the antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a or an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprising a light chain variable region as defined in the paragraph immediately above, comprises three VL CDRs and/or three VH CDRs, or a light chain variable domain and/or a heavy chain

variable domain, or a light chain and/or a heavy chain as described elsewhere herein. Thus, other features and properties of other aspects and embodiments of the invention apply, *mutatis mutandis*, to these aspects of the invention.

For example, in preferred embodiments, the antigen binding protein comprises a light chain variable domain that comprises

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:436;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:438; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:440 or SEQ ID NO:521.

In preferred embodiments, the antigen binding protein comprises a heavy chain variable domain that comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:441 (preferably SEQ ID NO:442) or SEQ ID NO:522 (preferably SEQ ID NO:523);

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:42 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:42, or SEQ ID NO:168 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:168; and

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:443.

Antigen binding proteins are described herein as comprising certain elements or regions (e.g. CDRs) “comprising” or “that comprise” the stated amino acid sequences. In some embodiments, antigen binding proteins of the invention are those comprising elements or regions (e.g. CDRs) “consisting of” or “that consist of” the stated amino acid sequences.

In preferred embodiments of the present invention, an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprises a heavy chain variable region that is an IGHV6 (or IGHV6-1) heavy chain variable

region. IGHV6-1 stands for immunoglobulin heavy variable 6-1. Thus, in some embodiments, an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprises a heavy chain variable region that is characterised by IGHV6 (or IGHV6-1) gene usage. Put another way, in some embodiments an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a comprises a heavy chain variable region that is characterised by an IGHV6 (or IGHV6-1) heavy chain gene segment. Characteristics of IGHV6 (or IGHV6-1) are known to a person skilled in the art (for example from IMGT®, the international ImMunoGeneTics information system®, http://www.imgt.org).

In preferred embodiments of the present invention, an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprises a heavy chain variable region that is an IGHV1 (or IGHV1-69) heavy chain variable region. IGHV1-69 stands for immunoglobulin heavy variable 1-69. Thus, in some embodiments, an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprises a heavy chain variable region that is characterised by IGHV1 (or IGHV1-69) gene usage. Put another way, in some embodiments an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprises a heavy chain variable region that is characterised by an IGHV1 (or IGHV1-69) heavy chain gene segment. Characteristics of IGHV1 (or IGHV1-69) are known to a person skilled in the art (for example from IMGT®, the international ImMunoGeneTics information system®, http://www.imgt.org).

In preferred embodiments of the present invention, an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a or an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprises a light chain variable region that is an IGKV1 light chain variable region. IGKV1 stands for immunoglobulin kappa variable 1. Thus, in some embodiments, an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a or an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprises a light chain variable region that is characterised by IGKV1 gene usage. Put another way, in some embodiments an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a or an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 comprises a light chain variable region that is characterised by an IGKV1 light chain gene segment. Characteristics of IGKV1 are known to a person skilled in the art (for example from IMGT®, the international ImMunoGeneTics information system®, http://www.imgt.org).

In preferred embodiments of the present invention, the IGKV1 mentioned above in connection with an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a is IGKV1-9.

In preferred embodiments of the present invention, the IGKV1 mentioned above in connection with an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 is IGKV1-12.

Further details and options in connection with IGHV for IGKV gene usage are set forth in the sequence Tables herein and any of these may be used in accordance with the present invention Details and options in connection with IGHD (immunoglobulin heavy diversity), IGHJ (immunoglobulin heavy joining), IGKD (immunoglobulin kappa diversity) and IGKJ (immunoglobulin kappa joining) usage are also set forth in the sequence Tables herein. In some embodiments, antigen binding proteins of the invention may be characterised by the presence (or usage) of any one or more of the IGHV, IGKV, IGHD, IGKD, IGHJ or IGKJ mentioned in the sequence Tables herein (or combinations thereof, e.g. the specific combinations mentioned in the sequence Tables).

The term "substantially homologous" as used herein in connection with an amino acid or nucleic acid sequence includes sequences having at least 65%, 70% or 75%, preferably at least 80%, and even more preferably at least 85%, 90%, 95%, 96%, 97%, 98% or 99%, sequence identity to the amino acid or nucleic acid sequence disclosed. Substantially homologous sequences of the invention thus include single or multiple base or amino acid alterations (additions, substitutions, insertions or deletions) to the sequences of the invention. At the amino acid level preferred substantially homologous sequences contain up to 5, e.g. only 1, 2, 3, 4 or 5, preferably 1, 2 or 3, more preferably 1 or 2, altered amino acids, in one or more of the framework regions and/or one or more of the CDRs making up the sequences of the invention. Said alterations can be with conservative or non-conservative amino acids. Preferably said alterations are conservative amino acid substitutions.

In certain embodiments, if a given starting sequence is relatively short (e.g. five amino acids in length or three amino acids in length), then fewer amino acid substitutions may be present in sequences substantially homologous thereto as compared with the number of amino acid substitutions that might optionally be made in a sequence substantially homologous to a longer starting sequence. For example, in certain preferred embodiments the VL CDR2 sequence of antigen binding proteins of the invention is three amino acids in length. A sequence substantially homologous to a starting VH CDR2 sequence in accordance with the

present invention, e.g. a starting VH CDR2 sequence which in some embodiments may be three amino acid residues in length, preferably has 1 or 2 (more preferably 1) altered amino acids in comparison with the starting sequence. Accordingly, in some embodiments the number of altered amino acids in substantially homologous sequences (e.g. in substantially homologous CDR sequences) can be tailored to the length of a given starting CDR sequence. For example, different numbers of altered amino acids can be present depending on the length of a given starting CDR sequence such as to achieve a particular % sequence identity in the CDRs, for example a sequence identity of at least 60%, 70%, 80%, or at least, 90%.

Routine methods in the art such as alanine scanning mutagenesis and/or analysis of crystal structure of the antigen-antibody complex can be used in order to determine which amino acid residues of the CDRs do not contribute or do not contribute significantly to antigen binding and therefore are good candidates for alteration or substitution in the embodiments of the invention involving substantially homologous sequences.

The term "substantially homologous" also includes modifications or chemical equivalents of the amino acid and nucleotide sequences of the present invention that perform substantially the same function as the proteins or nucleic acid molecules of the invention in substantially the same way. For example, any substantially homologous antigen binding protein (e.g. antibody) should retain the ability to bind to the antigen (pMHC antigen) as described herein. Preferably, any substantially homologous antigen binding protein (e.g. antibody) should retain one or more (or all) of the functional capabilities of the starting antigen binding protein (e.g. antibody).

Preferably, any substantially homologous antigen binding protein (e.g antibody) should retain the ability to bind to, or specifically bind to, the same epitope of the antigen as recognized by the antigen binding protein (e.g. antibody) in question, for example, the same epitope recognized by the CDR domains of the invention or the VH and VL domains of the invention as described herein. Thus, preferably, any substantially homologous antigen binding protein (e.g. antibody) should retain the ability to compete with one or more of the various antigen binding proteins of the invention for binding to the relevant antigen. Binding to the same epitope/antigen can be readily tested by methods well known and described in the art, e.g. using binding assays, e.g. a competition assay. Retention of other functional properties can also readily be tested by methods well known and described in the art or herein.

Thus, a person skilled in the art will appreciate that binding assays can be used to test whether "substantially homologous" antigen binding proteins (e.g. antibodies) have the same binding specificities as the antigen binding proteins of the invention, for example, binding assays such as competition assays or ELISA assays, e.g. as described elsewhere herein. Surface Plasmon Resonance (e.g. BIAcore) assays could also readily be used to establish whether "substantially homologous" antigen binding proteins can bind to the relevant antigen. The skilled person will be aware of other suitable methods and variations.

As outlined below, a competition binding assay can be used to test whether "substantially homologous" antibodies retain the ability to bind to, or specifically bind to, substantially the same epitope of the relevant antigen as recognized by the antigen binding proteins of the invention (e.g. the 107 antibody or the 206 antibody), or have the ability to compete with one or more of the various antigen binding proteins of the invention. The method described below is only one example of a suitable competition assay. The skilled person will be aware of other suitable methods and variations.

An exemplary competition assay involves assessing the binding of various effective concentrations of an antigen binding protein of the invention to the relevant antigen in the presence of varying concentrations of a test antigen binding protein (e.g. a substantially homologous antigen binding protein e.g. antibody). The amount of inhibition of binding induced by the test antigen binding protein can then be assessed. A test antigen binding protein that shows increased competition with an antigen binding protein of the invention at increasing concentrations (i.e. increasing concentrations of the test antigen binding protein result in a corresponding reduction in the amount of antigen binding protein of the invention binding to the relevant antigen) is evidence of binding to substantially the same epitope. Preferably, the test antigen binding protein significantly reduces the amount of antigen binding protein of the invention that binds to the relevant antigen. Preferably, the test antigen binding protein reduces the amount of antigen binding protein of the invention that binds to the relevant antigen by at least about 95%. ELISA and flow cytometry assays may be used for assessing inhibition of binding in such a competition assay but other suitable techniques would be well known to a person skilled in the art.

In some embodiments, “substantially homologous” antigen binding proteins which retain the ability to bind to, or specifically bind to, substantially the same (or the same) epitope of the relevant antigen as recognized by antigen binding proteins

of the invention (e.g. the 107 or 206 antibodies) or which have the ability to compete with one or more of the various antigen binding proteins of the invention (e.g. the 107 or 2016 antibodies) are preferred.

The term "competing antigen binding protein", as used herein, refers to antigen binding proteins that bind to about, substantially or essentially the same, or even the same, epitope as a "reference antigen binding protein". Competing antigen binding proteins are thus able to effectively compete with a reference antibody for binding to the relevant antigen. Preferably, the competing antigen binding protein can bind to the same epitope as the reference antigen binding protein. Alternatively viewed, the competing antigen binding protein preferably has the same epitope specificity as the reference antigen binding protein.

"Reference antigen binding proteins" as used herein are antigen binding proteins which can bind to the relevant antigen in accordance with the invention. Preferably, reference antigen binding proteins have a VH and a VL domain as defined herein. For example, a reference antigen binding protein which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a may comprise a VL domain an a VH domain of the 107 antibody (i.e. comprise a VL domain of SEQ ID NO:40 and a VH domain of SEQ ID NO:39), and a reference antigen binding protein which binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 may comprise a VL domain an a VH domain of the 206 antibody (i.e. comprise a VL domain of SEQ ID NO:166 and a VH domain of SEQ ID NO:165) . Thus a preferred reference antigen binding protein may be the 107 antibody or the 206 antibody as defined herein.

The identification of one or more competing antigen binding proteins (e.g. antibodies) is a straightforward technical matter now that reference antibodies such as the 107 antibody and the 206 antibody have been provided. As the identification of competing antigen binding proteins (e.g. antibodies) is determined in comparison to a reference antigen binding protein (e.g. antibody), it will be understood that actually determining the epitope to which either or both antigen binding proteins bind is not in any way required in order to identify a competing antigen binding protein. However, epitope mapping can be performed using standard techniques, if desired.

Substantially homologous sequences of proteins of the invention include, without limitation, conservative amino acid substitutions, or for example alterations that do not affect the VH, VL or CDR domains of the antibodies, e.g. antibodies where tag sequences, toxins or other components are added that do not contribute to the binding of antigen, or alterations to convert one type or format of antibody molecule or fragment to another type or format of antibody molecule or fragment

(e.g. conversion from Fab to scFv or whole antibody or vice versa), or the conversion of an antibody molecule to a particular class or subclass of antibody molecule (e.g. the conversion of an antibody molecule to IgG or a subclass thereof, e.g. IgG_2).

A "conservative amino acid substitution", as used herein, is one in which the amino acid residue is replaced with another amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (e.g. lysine, arginine, histidine), acidic side chains (e.g. aspartic acid, glutamic acid), uncharged polar side chains (e.g. glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g. glycine, cysteine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g. threonine, valine, isoleucine) and aromatic side chains (e.g. tyrosine, phenylalanine, tryptophan, histidine).

Homology may be assessed by any convenient method. However, for determining the degree of homology between sequences, computer programs that make multiple alignments of sequences are useful, for instance Clustal W (Thompson, Higgins, Gibson, *Nucleic Acids Res.*, 22:4673-4680, 1994). If desired, the Clustal W algorithm can be used together with BLOSUM 62 scoring matrix (Henikoff and Henikoff, *Proc. Natl. Acad. Sci. USA*, 89:10915–10919, 1992) and a gap opening penalty of 10 and gap extension penalty of 0.1, so that the highest order match is obtained between two sequences wherein at least 50% of the total length of one of the sequences is involved in the alignment. Other methods that may be used to align sequences are the alignment method of Needleman and Wunsch (Needleman and Wunsch, *J. Mol. Biol.*, 48:443, 1970) as revised by Smith and Waterman (Smith and Waterman, *Adv. Appl. Math.*, 2:482, 1981) so that the highest order match is obtained between the two sequences and the number of identical amino acids is determined between the two sequences. Other methods to calculate the percentage identity between two amino acid sequences are generally art recognized and include, for example, those described by Carillo and Lipton (Carillo and Lipton, *SIAM J. Applied Math.*, 48:1073, 1988) and those described in Computational Molecular Biology, Lesk, e.d. Oxford University Press, New York, 1988, Biocomputing: Informatics and Genomics Projects.

Generally, computer programs will be employed for such calculations. Programs that compare and align pairs of sequences, like ALIGN (Myers and Miller, *CABIOS*, 4:11-17, 1988), FASTA (Pearson and Lipman, *Proc. Natl. Acad. Sci. USA*, 85:2444-2448, 1988; Pearson, *Methods in Enzymology*, 183:63-98, 1990) and

gapped BLAST (Altschul *et al.*, *Nucleic Acids Res.*, 25:3389-3402, 1997), BLASTP, BLASTN, or GCG (Devereux, Haeberli, Smithies, *Nucleic Acids Res.*, 12:387, 1984) are also useful for this purpose. Furthermore, the Dali server at the European Bioinformatics institute offers structure-based alignments of protein sequences (Holm, *Trends in Biochemical Sciences*, 20:478-480, 1995; Holm, *J. Mol. Biol.*, 233:123-38, 1993; Holm, *Nucleic Acid Res.*, 26:316-9, 1998).

By way of providing a reference point, sequences according to the present invention having 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% homology, sequence identity *etc.* may be determined using the ALIGN program with default parameters (for instance available on Internet at the GENESTREAM network server, IGH, Montpellier, France).

As described above, the present invention provides antigen binding proteins (e.g. antibodies) that bind to, or specifically bind to, HLA-DQ2.5:DQ2.5-glia-α1a and antigen binding proteins (e.g. antibodies) that bind to, or specifically bind to, HLA-DQ2.5:DQ2.5-glia-α2.

HLA-DQ2.5 (encoded by *DQA1*05* and *DQB1*02*) is specific type of MHC Class 2 molecule that has a strong association with celiac disease.

HLA-DQ2.5 comprises a α-chain (typically having an α_1 domain and an α_2 domain and typically encoded by *DQA1*05*) and a β-chain (typically having a β_1 domain and a β_2 domain and typically encoded by *DQB1*02*). Amino acid sequences of the α- and β- chains of HLA-DQ2.5 are set forth herein (the α-chain sequence is set forth in SEQ ID NO:493; the β- chain sequence is set forth in SEQ ID NO:494).

HLA-DQ2.5 can present gliadin epitopes, for example epitopes of α-gliadin, for example DQ2.5-glia-α1a and DQ2.5-glia-α2. The amino acid sequence of the deamidated DQ2.5-glia-α1a epitope is set forth in SEQ ID NO:472. The amino acid sequence of the deamidated DQ2.5-glia-α2 epitope is set forth in SEQ ID NO:473. These deamidated forms of the DQ2.5-glia-α1a and DQ2.5-glia-α2 epitopes may be considered to be celiac disease-associated forms of DQ2.5-glia-α1a and DQ2.5-glia-α2 epitopes. These epitopes of α-gliadin are typically present on a proteolysis resistant α-gliadin 33-mer peptide (SEQ ID NO:476). However, for the avoidance of doubt, and as is evident from elsewhere herein, antigen binding proteins (e.g. antibodies) of the invention can bind to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 when the DQ2.5-glia-α1a or DQ2.5-glia-α2 epitope is not comprised within (i.e. is not in the context of) the proteolysis resistant α-gliadin 33-mer peptide. Although the α-gliadin 33-mer peptide can associate with (or bind to)

HLA-DQ2.5, the binding groove (or binding pocket) of the HLA-DQ2.5 molecule (i.e. the MHC molecule) can only present, or accommodate, a single 9-mer epitope (e.g. the DQ2.5-glia-α1a epitope or the DQ2.5-glia-α2 epitope) at a given time. Which epitope is presented by HLA-DQ2.5 is determined by the "register" (or position) in which the 33-mer is bound to (associated with) the HLA-DQ2.5. HLA-DQ2.5 may also present, or accommodate, epitopes of other gliadins, for example ω-gliadin (e.g. DQ2.5-glia-ω1 (SEQ ID NO:477) or DQ2.5-glia-ω2 (SEQ ID NO:478)).

The non- disease associated form of the DQ2.5-glia-α1a epitope (or "native" form or non-deamidated form is set forth in SEQ ID NO:491). The non- disease associated form of the DQ2.5-glia-α2 epitope (or "native" form or non-deamidated form) is set forth in SEQ ID NO:492.

At its broadest "DQ2.5-glia-α1a" includes the disease associated form of the epitope (deamidated form) of SEQ ID NO:472 and the non-disease associated form of the epitope (non-deamidated form or native form) of SEQ ID NO:491.

At its broadest "DQ2.5-glia-α2" includes the disease associated form of the epitope (deamidated form) of SEQ ID NO:473 and the non-disease associated form of the epitope (non-deamidated form or native form) of SEQ ID NO:492.

The non-disease associated forms of the epitopes may also be present on a proteolysis resistant α-gliadin 33-mer peptide.

In some embodiments, an antigen binding protein which binds to, or binds specifically to, HLA-DQ2.5:DQ2.5-glia-α1a does not bind to (or cross-react with), or does not significantly bind to (or cross-react with), a HLA-DQ2.5:DQ2.5-glia-α1a complex in which the DQ2.5-glia-α1a epitope sequence has a Q residue instead of an E residue at position 6 of the 9-mer. Thus, in some embodiments, an antigen binding protein which binds to, or binds specifically to, HLA-DQ2.5:DQ2.5-glia-α1a does not bind to (or cross-react with), or does not significantly bind to (or cross-react with), a HLA-DQ2.5 complex presenting a DQ2.5-glia-α1a epitope of SEQ ID NO:491. Thus, in some embodiments, an antigen binding protein which binds to, or binds specifically to, HLA-DQ2.5:DQ2.5-glia-α1a does not bind to (or cross-react with), or does not significantly bind to (or cross-react with), a HLA-DQ2.5 complex presenting a native or non-deamidated form of DQ2.5-glia-α1a. Without wishing to be bound by theory, the DQ2.5-glia-α1a epitope of SEQ ID NO:472 (PFPQPELPY) represents a deamidated form of the DQ2.5-glia-α1a epitope and may be considered to be a celiac disease-associated form of the epitope. In some embodiments, an antigen binding protein that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a is specific for the disease associated form (or version) of the DQ2.5-glia-α1a epitope (SEQ ID NO:472), which may be advantageous (e.g. in

celiac disease therapy). Put another way, in some embodiments the DQ2.5-glia-α1a epitope is as set forth in SEQ ID NO:472.

In some embodiments, an antigen binding protein that binds to, or binds specifically to, HLA-DQ2.5:DQ2.5-glia-α2 may bind to HLA-DQ2.5:DQ2.5-glia-α2 in which the DQ2.5-glia-α2 epitope is as set forth in SEQ ID NO:473 (PQPELPYPQ) and/or a DQ2.5-glia-α2 epitope which has a Q residue instead of an E residue at position 4 of the 9-mer. Thus, in some embodiments an antigen binding protein that binds to, or binds specifically to, HLA-DQ2.5:DQ2.5-glia-α2 may bind to HLA-DQ2.5:DQ2.5-glia-α2 in which the DQ2.5-glia-α2 epitope is as set forth SEQ ID NO:473 (PQPELPYPQ) and/or as set forth in SEQ ID NO:492. In other embodiments, an antigen binding protein that binds to, or binds specifically to, HLA-DQ2.5:DQ2.5-glia-α2 may bind to HLA-DQ2.5:DQ2.5-glia-α2 in which the DQ2.5-glia-α2 epitope is as set forth SEQ ID NO:473 (PQPELPYPQ) but not bind (or cross-react), or not significantly bind (or significantly) cross-react, with non-deamidated the DQ2.5-glia-α2 epitope as set forth in SEQ ID NO:492.

HLA-DQ2.5:DQ2.5-glia-α1a means a HLA-DQ2.5 molecule that is presenting (or “loaded” with) a DQ2.5-glia-α1a epitope. Put another way, HLA-DQ2.5:DQ2.5-glia-α1a means a HLA-DQ2.5-peptide complex (pMHC) in which the DQ2.5-glia-α1a epitope is presented in the antigen binding groove (or accommodated in the antigen binding groove).

HLA-DQ2.5:DQ2.5-glia-α2 means a HLA-DQ2.5 molecule that is presenting (or “loaded” with) a DQ2.5-glia-α2 epitope. Put another way, HLA-DQ2.5:DQ2.5-glia-α2 means a HLA-DQ2.5-peptide complex (pMHC) in which the DQ2.5-glia-α2 epitope is presented in the antigen binding groove (or accommodated in the antigen binding groove).

In some embodiments, the invention provides antigen binding proteins (e.g. antibodies) that bind to, or specifically bind to, HLA-DQ2.5:DQ2.5-glia-α1a. As used herein, the term "that specifically binds to HLA-DQ2.5:DQ2.5-glia-α1a" in the context of antigen binding proteins means those antigen binding proteins that are capable of binding to HLA-DQ2.5:DQ2.5-glia-α1a and which do not cross-react (or do not bind) or do not significantly cross-react (or do not significantly bind) HLA-DQ2.5:DQ2.5-glia-α2. In some embodiments, an antigen binding protein which “binds specifically to HLA-DQ2.5:DQ2.5-glia-α1a” in accordance with the present invention also does not cross-react with other HLA-DQ2.5:DQ2.5-glia complexes (antigens) or non-HLA-DQ2.5:DQ2.5-glia complexes (antigens).

In some embodiments, antigen binding proteins (e.g. antibodies) “bind to” HLA-DQ2.5:DQ2.5-glia-α1a but do not “specifically bind to” HLA-DQ2.5:DQ2.5-glia-α1a. The term “bind to” is broader than the term “specifically bind to”. In this regard, in some embodiments, antigen binding proteins (e.g. antibodies) that bind to HLA-DQ2.5:DQ2.5-glia-α1a may have a degree of promiscuity (or cross-reactivity) in relation to the HLA-DQ2.5:epitope bound, for example they may in some embodiments cross-react (or bind) with other peptides, for example other peptides presented by HLA-DQ2.5 (e.g. other celiac disease associated peptides, or other gliadin or gliadin-derived peptides, or variants of gliadin derived peptides, or other gluten-derived peptides). Typically and preferably, antigen binding proteins (e.g. antibodies) that bind to HLA-DQ2.5:DQ2.5-glia-α1a do not cross-react (or do not bind) or do not significantly cross-react (or do not significantly bind) with DQ2.5:DQ2.5-glia-α2.

The specific HLA-DQ2.5:DQ2.5-glia-α1a antibodies exemplified herein (e.g. the 107 antibody) are examples of antigen binding proteins that bind to, or specifically bind to, HLA-DQ2.5:DQ2.5-glia-α1a.

In some embodiments, the invention provides antigen binding proteins (e.g. antibodies) that bind to, specifically bind to, HLA-DQ2.5:DQ2.5-glia-α2. As used herein, the term "that specifically binds to HLA-DQ2.5:DQ2.5-glia-α2" in the context of antigen binding proteins means those antigen binding proteins that are capable of binding to HLA-DQ2.5:DQ2.5-glia-α2 and which do not cross-react (or do not bind) or do not significantly cross-react (or do not significantly bind) HLA-DQ2.5:DQ2.5-glia-α1a. In some embodiments, an antigen binding protein which “binds specifically to HLA-DQ2.5:DQ2.5-glia-α2” in accordance with the present invention also does not cross-react with other HLA-DQ2.5:DQ2.5-glia complexes (antigens) or non-HLA-DQ2.5:DQ2.5-glia complexes (antigens).

In some embodiments, antigen binding proteins (e.g. antibodies) “bind to” HLA-DQ2.5:DQ2.5-glia-α2 but do not “specifically bind to” HLA-DQ2.5:DQ2.5-glia-α2. The term “bind to” is broader than the term “specifically bind to”. In this regard, in some embodiments, antigen binding proteins (e.g. antibodies) that bind to HLA-DQ2.5:DQ2.5-glia-α2 may have a degree of promiscuity (or cross-reactivity) in relation to the HLA-DQ2.5:epitope bound, for example they may in some embodiments cross-react (or bind) with other peptides, for example other peptides presented by HLA-DQ2.5 (e.g. other celiac disease associated peptides, or other gliadin peptides or gliadin-derived peptides, or variants of gliadin derived peptides, or other gluten-derived peptides). Typically and preferably, antigen binding proteins (e.g. antibodies) that bind to HLA-DQ2.5:DQ2.5-glia-α2 do not cross-react (or do not

bind) or do not significantly cross-react (or do not significantly bind) with DQ2.5:DQ2.5-glia-α1a.

The specific HLA-DQ2.5:DQ2.5-glia-α2 antibodies exemplified herein (e.g. the 206 antibody) are examples of antigen binding proteins that bind to, or specifically bind to, HLA-DQ2.5:DQ2.5-glia-α2.

The skilled person is familiar with methods and techniques that can be used for assessing whether or not a given antigen binding protein can bind to, or specifically bind to, HLA-DQ2.5:DQ2.5-glia-α1a, or can bind to, or specifically bind to, HLA-DQ2.5:DQ2.5-glia-α2 and any appropriate method or technique can be used, for example an ELISA assay or a surface plasmon resonance assay. Exemplary and preferred methods are described in the Example section herein.

In some embodiments, the HLA-DQ2.5:DQ2.5-glia-α1a is a recombinant soluble molecule in which a glia-α1a epitope (or peptide), for example in the context of SEQ ID NO:474, is covalently attached to the HLA-DQ2.5 (MHC) molecule. Such recombinant soluble molecules may be made by any appropriate means, for example as described in Example 1 herein (and by Fallang *et al.*, 2008 and Quartsen *et al.*, 2001).

In some embodiments, the HLA-DQ2.5:DQ2.5-glia-α2 is a recombinant soluble molecule in which a glia-α2 epitope (or peptide), for example in the context of SEQ ID NO:475, is covalently attached to the HLA-DQ2.5 (MHC) molecule. Such recombinant soluble molecules may be made by any appropriate means, for example as described in Example 1 herein (and by Fallang *et al*. 2008 and Quartsen *et al*. 2001).

In some embodiments, the HLA-DQ2.5:DQ2.5-glia-α1a is on cells (e.g. $DQ2.5^+$ dendritic cells) that have been loaded with a soluble DQ-2.5-glia-α1a epitope (or peptide), for example in the context of SEQ ID NO:474, e.g. by contacting the cells with a soluble DQ-2.5-glia-α1a epitope (or peptide), for example in the context of SEQ ID NO:474, e.g. as described in the Example section herein. Thus, in some embodiments, the HLA-DQ2.5:DQ2.5-glia-α1a does not have a DQ-2.5-glia-α1a epitope (or peptide) covalently attached to the HLA-DQ2.5 molecule.

In some embodiments, the HLA-DQ2.5:DQ2.5-glia-α2 is on cells (e.g. $DQ2.5^+$ dendritic cells) that have been loaded with a soluble DQ-2.5-glia-α2 epitope (or peptide), for example in the context of SEQ ID NO:475, e.g. by contacting the cells with a soluble DQ-2.5-glia-α2 epitope (or peptide), for example in the context of SEQ ID NO:475, e.g. analogously to as described in the Example section herein in relation to HLA-DQ2.5:DQ2.5-glia-α1a. Thus, in some embodiments, the HLA-

DQ2.5:DQ2.5-glia-α2 does not have a DQ-2.5-glia-α2 epitope (or peptide) covalently attached to the HLA-DQ2.5 molecule.

In some embodiments, the antigen binding proteins of the invention bind to their antigen (HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2) with a binding affinity (K_D) of 10μM or less (e.g. 0.1nM to 10μM), preferably 5μM or less, or 4μM or less, or 3μM or less, or 2μM or less, or 1μM or less.

In some embodiments, the antigen binding proteins of the invention bind to their antigen (HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2) with a binding affinity (K_D) of 500nM or less (e.g. 0.1nM to 500nM), or 400nM or less, or 300nM or less, or 200nM or less, more preferably 100nM or less.

In preferred embodiments, the antigen binding proteins of the invention bind to their antigen (HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2) with a binding affinity (K_D) of 100nM or less (e.g. 0.1nM to 100nM), preferably 90nM or less, 80nM or less, 70nM or less, 60nM or less, 50nM or less, 40nM or less, 30nM or less, 20nM or less (e.g. 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4.5, 4, 3.5, 3, 2.5, 2, 1.5 or 1nM, or less), or 10nM or less (e.g. 9, 8, 7, 6, 5, 4.5, 4, 3.5, 3, 2.5, 2, 1.5 or 1nM, or less).

In some embodiments, the antigen binding proteins of the invention bind to their antigen (HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2) with a binding affinity (K_D) of 1nM or less (e.g. 1pM to 1nM, or 10pM to 1nM, or 20pM to 1nM, or 50pM to 1nM, or 100pM to 1nM, or 1pM to 500pM, or 10pM to 500pM, or 20pM to 500pM, or 50pM to 500pM, or 100pM to 500pM, or 1pM to 100pM, or 10pM to 100pM, or 20pM to 100pM, or 50pM to 100pM), preferably 900pM or less, 800pM or less, 700pM or less, 600pM or less, 500pM or less, 400pM or less, 300pM or less, 200pM or less (e.g. 200, 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 45, 40, 35, 30, 25, 20, 15 or 10pM, or less), or 100pM or less (e.g. 90, 80, 70, 60, 50, 45, 40, 35, 30, 25, 20, 15 or 1pM, or less).

In certain preferred embodiments, the HLA-DQ2.5:DQ2.5-glia-α1a antigen binding proteins of the invention bind to their antigen (HLA-DQ2.5:DQ2.5-glia-α1a) with a binding affinity (K_D) that is less than 74nM, preferably 70nM or less, or 60nM or less, or 50nM or less, or 40nM or less, or 30nM or less, or 20nM or less, or 10nM or less, or 5nM or less, or 2nM or less, or 1nM or less).

In certain preferred embodiments, the HLA-DQ2.5:DQ2.5-glia-α2 antigen binding proteins of the invention bind to their antigen (HLA-DQ2.5:DQ2.5-glia-α2) with a binding affinity (K_D) that is less than 20nM, preferably 15nM or less, or 10nM or less, or 5nM or less, or 2nM or less, or 1nM or less.

Preferably, the above-mentioned affinities and affinity range values apply when the antigen binding protein is an antibody or antigen binding fragment thereof. Particularly preferably the above-mentioned affinities and affinity range values apply when the antigen binding protein is a scFv (i.e. an antibody in the scFv format or in the Fab format).

Binding affinities (K_D) may be determined by any appropriate means, an exemplary and preferred method being to use surface plasmon resonance (SPR), e.g. BIAcore, for example as described in the Example section herein. In preferred embodiments, the binding affinities are as determined using SPR (e.g. BIAcore) single-cycle kinetic analysis (single-cycle kinetic method), for example using a protocol as described in Example 1 herein. In some embodiments, binding affinities (e.g. of Fab fragments) may be determined using SPR (e.g. BIAcore) multi-cycle analysis (multi-cycle kinetic method).

In certain preferred embodiments, the HLA-DQ2.5:DQ2.5-glia-α1a antigen binding proteins of the invention (e.g. antibodies) bind to their antigen (HLA-DQ2.5:DQ2.5-glia-α1a) with a binding affinity that is higher (or improved), preferably significantly higher, than the binding affinity for HLA-DQ2.5:DQ2.5-glia-α1a of the specifically described R2A1-8E, R3A2-9F or R4A1-3A (107) antibodies. The R2A1-8E antibody is characterised by a VL domain of SEQ ID NO:4 and a VH domain of SEQ ID NO:3; the R3A2-9F antibody is characterised by a VL domain of SEQ ID NO:22 and a VH domain of SEQ ID NO:21; the R4A1-3A (107) antibody is characterised by a VL domain of SEQ ID NO:40 and a VH domain of SEQ ID NO:39. A higher (or improved) binding affinity is characterised by a K_D (equilibrium dissociation constant) value (e.g. in nM) that is lower.

Thus, in some embodiments, the HLA-DQ2.5:DQ2.5-glia-α1a antigen binding proteins of the invention (e.g. antibodies) have a higher (or improved), preferably significantly higher, affinity for HLA-DQ2.5:DQ2.5-glia-α1a relative to the R2A1-8E, R3A2-9F and R4A1-3A (107) antibodies.

In a particularly preferred embodiment, the HLA-DQ2.5:DQ2.5-glia-α1a antigen binding proteins of the invention (e.g. antibodies) have a higher (or improved), preferably significantly higher, affinity for HLA-DQ2.5:DQ2.5-glia-α1a relative to the R4A1-3A (107) antibody.

A significantly higher affinity may be any meaningfully improved affinity, for example an affinity that is at least 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 20-fold higher, 50-fold higher or 100-fold higher than the binding affinity of the specifically described R2A1-8E, R3A2-9F or R4A1-3A (107) antibodies (preferably the R4A1-3A (107) antibody). In some embodiments, a significantly higher affinity may be

characterised by an affinity value (e.g. K_D in nM) that is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or at least 95% lower than the affinity value of the specifically described R2A1-8E, R3A2-9F or R4A1-3A (107) antibodies (preferably the R4A1-3A (107) antibody).

In certain preferred embodiments, the HLA-DQ2.5:DQ2.5-glia-α2 antigen binding proteins of the invention (e.g. antibodies) bind to their antigen (HLA-DQ2.5:DQ2.5-glia-α2) with a binding affinity that is higher, preferably significantly higher, than the binding affinity for HLA-DQ2.5:DQ2.5-glia-α2 of the specifically described 206, 217, 218, 220, 221, 223, 226 or 228 antibodies. The 206 antibody is characterised by a VL domain of SEQ ID NO:166 and a VH domain of SEQ ID NO:165; the 217 antibody is characterised by a VL domain of SEQ ID NO:184 and a VH domain of SEQ ID NO:183; the 218 antibody is characterised by a VL domain of SEQ ID NO:202 and a VH domain of SEQ ID NO:201; the 220 antibody is characterised by a VL domain of SEQ ID NO:220 and a VH domain of SEQ ID NO:219; the 221 antibody is characterised by a VL domain of SEQ ID NO:238 and a VH domain of SEQ ID NO:237; the 223 antibody is characterised by a VL domain of SEQ ID NO:256 and a VH domain of SEQ ID NO:255; the 226 antibody is characterised by a VL domain of SEQ ID NO:274 and a VH domain of SEQ ID NO:273; the 228 antibody is characterised by a VL domain of SEQ ID NO:292 and a VH domain of SEQ ID NO:291. A higher (or improved) binding affinity is characterised by a K_D (equilibrium dissociation constant) value (e.g. in nM) that is lower.

Thus, in some embodiments, the HLA-DQ2.5:DQ2.5-glia-α2 antigen binding proteins of the invention (e.g. antibodies) have a higher (or improved), preferably significantly higher, affinity for HLA-DQ2.5:DQ2.5-glia-α2 relative to the 206, 217, 218, 220, 221, 223, 226 or 228 antibodies.

In a particularly preferred embodiment, the HLA-DQ2.5:DQ2.5-glia-α2 antigen binding proteins of the invention (e.g. antibodies) have a higher (or improved), preferably significantly higher, affinity for HLA-DQ2.5:DQ2.5-glia-α2 relative to the 206 antibody.

A significantly higher affinity may be any meaningfully improved affinity, for example an affinity that is at least 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 20-fold, 50-fold or 100-fold higher than the binding affinity of the specifically described 206, 217, 218, 220, 221, 223, 226 or 228 antibodies (preferably the 206 antibody). In some embodiments, a significantly higher affinity may be characterised by an affinity value (e.g. K_D in nM) that is at least 10%, at least 20%, at least 30%, at least 40%, at least

50%, at least 60%, at least 70%, at least 80%, at least 90% or at least 95% lower than the affinity value of the specifically described 206, 217, 218, 220, 221, 223, 226 or 228 antibodies (preferably the 206 antibody).

Although a binding affinity value (e.g. K_D in nM) may be determined for an antigen binding protein (e.g. antibody) that may have a higher affinity for the relevant antigen than the specifically described R2A1-8E, R3A2-9F, R4A1-3A (107), 206, 217, 218, 220, 221, 223, 226 or 228 antibodies, it is not necessary to determine such a binding affinity value (e.g. K_D in nM) in order to determine whether or not there is a higher binding affinity. It can be sufficient to simply compare the R2A1-8E, R3A2-9F, R4A1-3A (107), 206, 217, 218, 220, 221, 223, 226 or 228 antibodies with a putative affinity improved (or affinity matured) antibody by any appropriate means (e.g. SPR or ELISA) and to assess whether or not a relative increase (or improvement) in binding affinity is observed (e.g. by inspecting SPR traces/graphs obtained); determining actual affinity (K_D) values is not necessary (although it may be done).

In some embodiments, HLA-DQ2.5:DQ2.5-glia-α1a antigen binding proteins of the invention (e.g. antibodies) have a K_{off} (or "off-rate" or dissociation constant) (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α1a that is ≤0.05, or ≤0.02, or ≤0.01, or ≤$1x10^{-3}$, or ≤$1x10^{-4}$, or ≤$1x10^{-5}$, or ≤$1x10^{-6}$, or ≤$1x10^{-7}$ (s^{-1}). In some embodiments, antigen binding proteins of the invention have a K_{off} (or "off-rate") (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α1a that is between about 0.05 and $1x10^{-7}$).

In some embodiments, HLA-DQ2.5:DQ2.5-glia-α1a antigen binding proteins of the invention (e.g. antibodies) have a K_{off} (or "off-rate" or dissociation constant) (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α1a that is lower (preferably significantly lower, e.g. statistically significantly lower such as with a probability value of ≤0.05) than the K_{off} (or "off-rate") (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α1a of the antibody 107 of the invention (e.g. when antibodies are in the Fab format). In some embodiments, antigen binding proteins (e.g. antibodies) of the present invention have a K_{off} (or "off-rate") (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α1a that is at least 50%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95% lower than the K_{off} (or "off-rate") (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α1a of the 107 antibody of the invention (e.g. when antibodies are in the Fab format).

In some embodiments, HLA-DQ2.5:DQ2.5-glia-α2 antigen binding proteins of the invention (e.g. antibodies) have a K_{off} (or "off-rate" or dissociation constant) (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α2 that is ≤0.5, ≤0.4 ≤0.3, ≤0.2, ≤0.1, ≤0.05, or ≤0.02, or ≤0.01, or ≤$1x10^{-3}$, or ≤$1x10^{-4}$, or ≤$1x10^{-5}$, or ≤$1x10^{-6}$, or ≤$1x10^{-7}$ (s^{-1}). In some

embodiments, antigen binding proteins of the invention have a K_{off} (or "off-rate") (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α2 that is between about 0.5 and $1x10^{-7}$).

In some embodiments, HLA-DQ2.5:DQ2.5-glia-α2 antigen binding proteins of the invention (e.g. antibodies) have a K_{off} (or "off-rate" or dissociation constant) (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α2 that is lower (preferably significantly lower, e.g. statistically significantly lower such as with a probability value of ≤0.05) than the K_{off} (or "off-rate") (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α2 of the antibody 206 of the invention (e.g. when antibodies are in the Fab format). In some embodiments, antibodies of the present invention have a K_{off} (or "off-rate") (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α2 that is at least 50%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95% lower than the K_{off} (or "off-rate") (s^{-1}) for HLA-DQ2.5:DQ2.5-glia-α2 of the 206 antibody of the invention (e.g. when antibodies are in the Fab format).

The K_{off} (or "off-rate") may be determined by any suitable method and the skilled person is familiar with these. For example, K_{off} (or "off-rate") can be determined in a Surface Plasmon Resonance assay (e.g. BIAcore assay), e.g. as described in the Example section herein. In preferred embodiments, the above discussion of "off-rates" applies when the antigen binding protein is in the Fab format.

As described above, certain preferred antibodies of the invention have a lower (or slower) "off-rate" (K_{off} or dissociation constant) than antibodies 107 or 206). Differing off-rates can lead to differences in pharmacokinetics. Without wishing to be bound by theory, antibodies with lower off-rates may be particularly beneficial as they may sit more tightly on the target antigen and thus may be more effective, e.g. at inhibiting T-cell activation.

Typically, antigen binding proteins (e.g. antibodies) of the invention do not bind (or do not significantly bind) to the soluble form of the respective gluten-derived peptide. Thus, typically, HLA-DQ2.5:DQ2.5-glia-α1a antigen binding proteins do not significantly bind (or do not bind) to a soluble DQ2.5-glia-α1a epitope. Typically, HLA-DQ2.5:DQ2.5-glia-α2 antigen binding proteins do not significantly bind (or do not bind) to a soluble DQ2.5-glia-α2 epitope. Thus, typically, antigen binding proteins (e.g. antibodies) of the invention do not bind (or do not significantly bind) to the respective gluten-derived peptide unless the peptide is presented by a HLA-DQ2.5 complex. Determination of whether or not a given antigen binding protein can significantly bind to the soluble form of DQ2.5-glia-α1a or DQ2.5-glia-α2 can be done by any appropriate means, e.g. a competition assay such as a competition ELISA assay, e.g. as described in the Example section herein.

Thus, HLA-DQ2.5:DQ2.5-glia-α1a antigen binding proteins of the invention typically bind to, or specifically bind to, the DQ2.5-glia-α1a epitope (or peptide), solely (or strictly) in the context of the MHC, i.e. HLA-DQ2.5. This may be assessed by any appropriate means, for example by a competition ELISA, for example as set forth in the Example section herein.

HLA-DQ2.5:DQ2.5-glia-α2 antigen binding proteins of the invention typically bind to, or specifically bind to, the DQ2.5-glia-α2 epitope (or peptide), solely (or strictly) in the context of the MHC, i.e. HLA-DQ2.5. This may be assessed by any appropriate means, for example by a competition ELISA, for example a competition ELISA modified from the Example section herein.

In accordance with the present invention, HLA-DQ2.5:DQ2.5-glia-α1a antigen binding proteins do not specifically bind to the HLA-DQ2.5 molecule itself (i.e. the MHC molecule itself), e.g. in the absence of a presented DQ2.5-glia-α1a epitope. In accordance with the present invention, HLA-DQ2.5:DQ2.5-glia-α2 antigen binding proteins do not specifically bind to the HLA-DQ2.5 molecule itself (i.e. the MHC molecule itself), e.g. in the absence of a presented DQ2.5-glia-α2 epitope. Put another way, antigen binding proteins of the present invention do not bind to an “unloaded” HLA-DQ2.5 molecule.

As discussed above, in some embodiments, an antigen binding protein which “binds specifically to HLA-DQ2.5:DQ2.5-glia-α1a” in accordance with the present invention does not bind (or cross-react), or does not significantly bind or (significantly cross-react) to other HLA-DQ2.5:DQ2.5-glia complexes (antigens). Thus, in some embodiments, antigen binding proteins which bind specifically to HLA-DQ2.5:DQ2.5-glia-α1a do not bind (or cross-react), or do not significantly bind (or significantly cross-react) to HLA-DQ2.5:DQ2.5-glia-γ1, HLA-DQ2.5:DQ2.5-glia-γ2, HLA-DQ2.5:DQ2.5-glia-γ3, HLA-DQ2.5:DQ2.5-glia-γ4c, HLA-DQ2.5:DQ2.5-glia-ω1, HLA-DQ2.5:DQ2.5-glia-ω2 or HLA-DQ2.5:DQ2.5-glia-α2. In some embodiments, antigen binding proteins which bind specifically to HLA-DQ2.5:DQ2.5-glia-α1a do not bind (or cross-react), or do not significantly bind (or significantly cross-react) to HLA-DQ2.5:CLIP2. In some embodiments, antigen binding proteins which bind specifically to HLA-DQ2.5:DQ2.5-glia-α1a do not bind (or cross-react), or do not significantly bind (or significantly cross-react) to HLA-DQ2.5:DQ2.5-hor3. Whether or not a given antigen binding protein cross-reacts with these other HLA-DQ2.5:DQ2.5-glia complexes (antigens) or HLA-DQ2.5-CLIP2 or HLA-DQ2.5:DQ2.5-hor-3 can be assessed by any appropriate means, for example using an ELISA assay as described in the Example section herein.

In some embodiments, an antigen binding protein which "binds to HLA-DQ2.5:DQ2.5-glia-α1a" in accordance with the present invention also does not bind (or does not significantly bind) to one or more (or all) of HLA-DQ2.5:DQ2.5-glia-γ1, HLA-DQ2.5:DQ2.5-glia-γ2, HLA-DQ2.5:DQ2.5-glia-γ3, HLA-DQ2.5:DQ2.5-glia-γ4c, HLA-DQ2.5:DQ2.5-glia-ω1, HLA-DQ2.5:DQ2.5-glia-ω2, HLA-DQ2.5:DQ2.5-glia-α2, HLA-DQ2.5:CLIP2 or HLA-DQ2.5:DQ2.5-hor-3.

As discussed above, in some embodiments, an antigen binding protein which "binds specifically to HLA-DQ2.5:DQ2.5-glia-α2" in accordance with the present invention does not bind (or cross-react), or does not significantly bind or (significantly cross-react) to other HLA-DQ2.5:DQ2.5-glia complexes (antigens). In some embodiments, antigen binding proteins which bind specifically to HLA-DQ2.5:DQ2.5-glia-α2 do not bind (or cross-react), or do not significantly bind (or significantly cross-react) to HLA-DQ2.5:DQ2.5-glia-γ1, HLA-DQ2.5:DQ2.5-glia-γ2, HLA-DQ2.5:DQ2.5-glia-γ3, HLA-DQ2.5:DQ2.5-glia-γ4c, HLA-DQ2.5:DQ2.5-glia-ω1, HLA-DQ2.5:DQ2.5-glia-ω2 or HLA-DQ2.5:DQ2.5-glia-α1a. In some embodiments, antigen binding proteins which bind specifically to HLA-DQ2.5:DQ2.5-glia-α2 do not bind (or cross-react), or do not significantly bind (or significantly cross-react) to HLA-DQ2.5:CLIP2 or HLA-DQ2.5:DQ2.5-hor-3. Whether or not a given antigen binding protein cross-reacts with these other HLA-DQ2.5:DQ2.5-glia complexes (antigens) or HLA-DQ2.5-CLIP2 or HLA-DQ2.5:DQ2.5-hor-3 can be assessed by any appropriate means, for example using an ELISA assay as described in the Example section herein.

In some embodiments, an antigen binding protein which "binds to HLA-DQ2.5:DQ2.5-glia-α2" in accordance with the present invention also does not bind (or does not significantly bind) to one or more (or all) of HLA-DQ2.5:DQ2.5-glia-γ1, HLA-DQ2.5:DQ2.5-glia-γ2, HLA-DQ2.5:DQ2.5-glia-γ3, HLA-DQ2.5:DQ2.5-glia-γ4c, HLA-DQ2.5:DQ2.5-glia-ω1, HLA-DQ2.5:DQ2.5-glia-ω2, HLA-DQ2.5:DQ2.5-glia-α1a, HLA-DQ2.5:CLIP2 or HLA-DQ2.5:DQ2.5-hor-3.

In some embodiments, an antigen binding protein which binds to, or binds specifically to, HLA-DQ2.5:DQ2.5-glia-α1a or which binds to, or binds specifically to, HLA-DQ2.5:DQ2.5-glia-α2 binds to the respective HLA-DQ2.5:DQ2.5-glia peptide complex when said complex is present on (or in) cells (or is expressed on or in cells, or has been transduced into cells), e.g. murine A20 B cells. In some embodiments, the cells have been transduced with HLA-DQ2.5 covalently linked to a DQ2.5-glia-α1a epitope (or peptide) or a DQ2.5-glia-α2 epitope (or peptide), e.g. as described in the Example section herein. Binding to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 on or in cells (e.g. murine A20 B cells) can be assessed by

any appropriate means, e.g. by flow cytometry, for example as described in the Example section herein.

In some embodiments, antigen binding proteins that bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α1a are capable of binding to HLA-DQ2.5$^+$ cells that are loaded with soluble DQ2.5-glia-α1a peptide. In some such embodiments the cells are HLA-DQ2.5$^+$ dendritic cells (DCs), for example HLA-DQ2.5$^+$ dendritic cells derived from a donor (e.g. a human donor). In some embodiments, the cells are HLA-DQ2.5$^+$ monocyte-derived dendritic cells derived (or obtained) via *in vitro* differentiation of PBMCs (peripheral blood mononuclear cells) from a HLA-DQ2.5$^+$ donor. Methods of *in vitro* differentiation of PBMCs to DCs are known in the art and an exemplary and preferred method is set out in the Example section herein. HLA-DQ2.5$^+$ dendritic cells may be loaded with a soluble DQ2.5-glia-α1a peptide by any appropriate means, for example by supplementation of the culture media with a HLADQ2.5-glia-α1a peptide (e.g. SEQ ID NO:474), for example with 40μM peptide, during the DC maturation process. An exemplary and preferred method is set out in the Example section. Assessment of whether a given antigen binding protein is capable of binding to HLA-DQ2.5$^+$ cells (e.g. HLA-DQ2.5$^+$ dendritic cells) that are loaded with soluble DQ2.5-glia-α1a peptide may be done by any appropriate method, but flow cytometry is typically preferred, e.g. as described in the Example section.

In some embodiments, antigen binding proteins that bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α2 are capable of binding to HLA-DQ2.5$^+$ cells that are loaded with soluble DQ2.5-glia-α2 peptide. In some such embodiments the cells are HLA-DQ2.5$^+$ dendritic cells (DCs), for example as described above. HLA-DQ2.5$^+$ dendritic cells may be loaded with a soluble DQ2.5-glia-α2 peptide by any appropriate means, for example by supplementation of the culture media with a HLADQ2.5-glia-α2 peptide (e.g. SEQ ID NO:475), for example with 40μM peptide, during the DC maturation process. An exemplary and preferred method is set out in the Example section. Assessment of whether a given antigen binding protein is capable of binding to HLA-DQ2.5$^+$ cells (e.g. HLA-DQ2.5$^+$ dendritic cells) that are loaded with soluble DQ2.5-glia-α2 peptide may be done by any appropriate method, but flow cytometry is typically preferred, e.g. as described in the Example section.

In some embodiments, antigen binding proteins that bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α1a are capable of binding to HLA-DQ2.5:DQ2.5-glia-α1a on cells (e.g. single-cell suspensions) isolated from intestinal (e.g. duodenal) biopsies from HLA-DQ2.5$^+$ individuals (human subjects, e.g. with a

Marsh score of 3A, 3B or 3C) that have fed on gluten-containing food and thereby have generated a DQ2.5-glia-α1a epitope (native or deamidated). Such individuals may be confirmed or non-confirmed celiacs, treated or non-treated (or inadequately treated in the sense that they have trace presentation of the pMHC). In some embodiments, the individual is an untreated celiac disease subject (a subject not on a gluten-free diet). In some such embodiments, the cells are B cells ($CD19^+$ $CD38^-$) or plasma cells, PCs ($CD27^+$ $CD38^+$). Isolation of cells from intestinal (e.g. duodenal) biopsies may be done by any suitable method. An exemplary method is described in the example section herein. Assessment of whether a given antibody is capable of binding to HLA-DQ2.5:DQ2.5-glia-α1a on such cells from intestinal biopsies may be done by any appropriate method, but flow cytometry is typically preferred, e.g. as described in the Example section.

Small intestinal plasma cells can be separated into three major subsets based on CD45 expression; $CD19^+CD45^+$, $CD19^-CD45^+$and $CD19^-CD45^-$. In some embodiments, antigen binding proteins that bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α1a are capable of binding to plasma cells in each of these cell populations.

In some embodiments, antigen binding proteins that bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α2 are capable of binding to HLA-DQ2.5:DQ2.5-glia-α2 on cells (e.g. single-cell suspensions) isolated from intestinal (e.g. duodenal) biopsies from HLA-$DQ2.5^+$ individuals (human subjects, e.g. with a Marsh score of 3A, 3B or 3C) that have fed on gluten-containing food and thereby have generated an DQ2.5-glia-α2 epitope (native or deamidated). Such individuals may be confirmed or non-confirmed celiacs, treated or non-treated (or inadequately treated in the sense that they have trace presentation of the pMHC). In some embodiments, the individual is an untreated celiac disease subject (a subject not on a gluten-free diet). In some such embodiments, the cells are B cells ($CD19^+$ $CD38^-$) or plasma cells, PCs ($CD27^+$ $CD38^+$). Assessment of whether a given antibody is capable of binding to HLA-DQ2.5:DQ2.5-glia-α2 on such cells from intestinal biopsies may be done by any appropriate method, but flow cytometry is typically preferred, e.g. as described in the Example section.

Small intestinal plasma cells can be separated into three major subsets based on CD45 expression; $CD19^+CD45^+$, $CD19^-CD45^+$and $CD19^-CD45^-$. In some embodiments, antigen binding proteins that bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α2 are capable of binding to plasma cells in each of these cell populations.

The "Marsh" scoring system is a classification system used in the art to rate (or score) damage to the small intestine. Scores of 0 to 4 may be given, with higher scores representing increased damage.

In some embodiments, antigen binding proteins (e.g. antibodies) that bind to HLA-DQ2.5:DQ2.5-glia-α1a or that bind to HLA-DQ2.5:DQ2.5-glia-α2 are capable of inhibiting T-cell activation (e.g. T-cell activation by antigen presenting cells having HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2, as the case may be). In some embodiments, antigen binding proteins (e.g. antibodies) that bind to HLA-DQ2.5:DQ2.5-glia-α1a or that bind to HLA-DQ2.5:DQ2.5-glia-α2 are capable of inhibiting T-cell activation *in vitro*. This may be assessed by any suitable methods and the skilled person will be familiar with such methods.

In some embodiments, antigen binding proteins (e.g. antibodies) that bind to HLA-DQ2.5:DQ2.5-glia-α1a or that bind to HLA-DQ2.5:DQ2.5-glia-α2 are capable of inhibiting T-cell activation by at least 10%, preferably at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or even 100%. In preferred embodiments, 0% inhibition (or conversely 100% activation) is the degree of inhibition in the absence of an antigen binding protein (e.g. antibody). Thus, relative inhibitory capacity (or activity) of an antigen binding protein (e.g. antibody) may be determined by normalizing to the T-cell activation in the absence of antigen binding protein (e.g. antibody), which may be set as 100% activation.

In some embodiments, inhibition of T-cell activation by an antigen binding protein (e.g. antibody) that binds to HLA-DQ2.5:DQ2.5-glia-α1a is as assessed *in vitro* by:

- Contacting (e.g. overnight) $DQ2.5^+$ antigen presenting cells (APCs), e.g. Raji B-cells, with a DQ2.5-glia-α1a peptide (e.g. loading with soluble DQ2.5-glia-α1a peptide) and typically washing away the unloaded (free) peptide;
- Contacting said (peptide-loaded) cells with the antigen binding protein (e.g. antibody) that binds to HLA-DQ2.5:DQ2.5-glia-α1a (e.g. 1μM final concentration of antigen binding protein);
- Contacting (e.g. overnight at e.g. 37°C) a T-cell clone (e.g. SKW3 cells) expressing a T-cell receptor (TCR) that is specific for DQ2.5:DQ2.5-glia-α1a (suitable Examples of TCRs are provided in Example 9 herein) with the peptide loaded cells that have been contacted with the antigen binding protein (e.g. antibody);

- Determining or measuring T-cell activation, e.g. based on an increase or upregulation of CD69, e.g. as assessed by flow cytometry.

A particularly preferred method for assessing (or determining or measuring) T-cell activation (and the inhibition of T-cell activation by an antigen binding protein (e.g. antibody) that binds to HLA-DQ2.5:DQ2.5-glia-α1a) is provided in Example 9 herein.

In some embodiments, inhibition of T-cell activation by an antigen binding protein (e.g. antibody) that binds to HLA-DQ2.5:DQ2.5-glia-α2 is as assessed *in vitro* by:

- Contacting (e.g. overnight) $DQ2.5^+$ antigen presenting cells (APCs), e.g. Raji B-cells, with a DQ2.5-glia-α2 peptide (e.g. loading with soluble DQ2.5-glia-α2 peptide) and typically washing away the unloaded (free) peptide;
- Contacting said (peptide-loaded) cells with the antigen binding protein (e.g. antibody) that binds to HLA-DQ2.5:DQ2.5-glia-α2 (e.g. 1μM final concentration of antigen binding protein);
- Contacting (e.g. overnight at e.g. 37°C) a T-cell clone expressing a T-cell receptor (TCR) that is specific for DQ2.5:DQ2.5-glia-α2 (suitable Examples are provided in Example 9 herein) with the peptide loaded cells that have been contacted with the antigen binding protein (e.g. antibody);
- Determining or measuring T-cell activation, e.g. based on an increase or upregulation of CD69, e.g. as assessed by flow cytometry.

A particularly preferred method for assessing (or determining or measuring) T-cell activation (and the inhibition of T-cell activation by an antigen binding protein (e.g. antibody) that binds to HLA-DQ2.5:DQ2.5-glia-α2) is provided in Example 9 herein.

In some embodiments, antigen binding proteins that bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α1a are capable of inhibiting and/or killing cells (e.g. antigen presenting cells such as B cells or plasma cells, for example as defined elsewhere herein) that express or present HLA-DQ2.5:DQ2.5-glia-α1a. Thus, in some embodiments, antigen binding proteins that bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α1a have inhibitory or cytotoxic activity.

In some embodiments, antigen binding proteins that bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α2 are capable of inhibiting and/or killing cells (e.g. antigen presenting cells such as B cells or plasma cells, for example as defined elsewhere herein) that express or present HLA-DQ2.5:DQ2.5-glia-α2. Thus, in some embodiments, antigen binding proteins that bind to, or bind specifically to, HLA-DQ2.5:DQ2.5-glia-α2 have inhibitory or cytotoxic activity.

Described herein are antigen binding proteins of the invention that bind specifically to HLA-DQ2.5:DQ2.5-glia-α1a or bind specifically to HLA-DQ2.5:DQ2.5-glia-α2. However, in an alternative aspect, also disclosed and provided herein are antigen binding proteins that do not have the same epitope specificity. Thus, although antigen binding proteins that bind specifically to HLA-DQ2.5:DQ2.5-glia-α1a or that bind specifically to HLA-DQ2.5:DQ2.5-glia-α2 are in certain circumstances preferred, in an alternative aspect, the invention provides certain antigen binding proteins that show a degree of promiscuity (or cross-reactivity) in relation to the HLA-DQ2.5:DQ2.5-glia epitopes bound. As described above, in some embodiments, antigen binding proteins that bind to HLA-DQ2.5:DQ2.5-glia-α1a may additionally bind to other peptides, for example other peptides presented by HLA-DQ2.5 (e.g. other celiac disease associated peptides, or other gliadin peptides or gliadin-derived peptides, or variants of gliadin derived peptides, or other gluten-derived peptides). As described above, in some embodiments, antigen binding proteins that bind to HLA-DQ2.5:DQ2.5-glia-α2 may additionally bind to other peptides, for example other peptides presented by HLA-DQ2.5 (e.g. other celiac disease associated peptides, or other gliadin peptides or gliadin-derived peptides, or variants of gliadin derived peptides, or other gluten-derived peptides). For example, certain antibodies may bind to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 and additionally bind to one or more of HLA-DQ2.5:DQ2.5-glia-γ1, HLA-DQ2.5:DQ2.5-glia-γ2, HLA-DQ2.5:DQ2.5-glia-γ3, HLA-DQ2.5:DQ2.5-glia-γ4c, HLA-DQ2.5:DQ2.5-glia-ω1 or HLA-DQ2.5:DQ2.5-glia-ω2. Certain antibodies may bind to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 and additionally bind to HLA-DQ2.5:CLIP2 or HLA-DQ2.5:DQ2.5-hor-3. Certain antibodies may bind to HLA-DQ2.5:DQ2.5-glia-α1a and to HLA-DQ2.5:DQ2.5-glia-α2. However, typically and preferably, antigen binding proteins (e.g. antibodies) that bind to HLA-DQ2.5:DQ2.5-glia-α1a do not bind to (or do not significantly bind to) HLA-DQ2.5:DQ2.5-glia-α2. Typically and preferably, antigen binding proteins (e.g. antibodies) that bind to HLA-DQ2.5:DQ2.5-glia-α2 do not bind to (or do not significantly bind to) HLA-DQ2.5:DQ2.5-glia-α1a.

Thus, in one alternative aspect, the present invention provides an antigen binding protein which binds to HLA-DQ2.5:DQ2.5 presenting a peptide (e.g. a celiac disease associated peptide, such as a gliadin peptide or a gliadin derived peptide or a gluten-derived peptide), said antigen binding protein comprising at least one light chain variable domain and at least one heavy chain variable domain, each domain comprising three complementarity determining regions (CDRs), wherein

(a) said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α1a and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:5, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:5;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:6, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:6;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:417;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:8 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:8;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:9 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:9; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:415; or wherein

(b) said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α2 and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:425;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:427;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:429;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:419;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:421; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:423.

All of the discussion elsewhere herein in relation to, for example, sequences and aspects and preferred embodiments, may be applied, *mutatis mutandis*, to aspects of the invention in which antibodies which bind to HLA-DQ2.5:DQ2.5-glia-α1a or to HLA-DQ2.5:DQ2.5-glia-α2 may exhibit binding to other epitopes (i.e. exhibit epitope cross-reactivity).

In another alternative aspect, also disclosed and provided herein are antigen binding proteins that bind to HLA-DQ2.5:DQ2.5-glia-α1a or to HLA-DQ2.5:DQ2.5-glia-α2 and do not significantly bind to (or do not significantly cross-react with) HLA-DQ2.5 complexes without a gliadin peptide presented. All of the discussion elsewhere herein in relation to, for example, sequences and aspects and preferred embodiments, may be applied, *mutatis mutandis*, to this aspect of the invention.

In another alternative aspect, also disclosed and provided herein are antigen binding proteins that bind to HLA-DQ2.5:DQ2.5-glia-α1a or to HLA-DQ2.5:DQ2.5-glia-α2 and do not significantly bind to (or do not significantly cross-react with) gliadin peptides unless they are presented by HLA-DQ2.5 complexes. All of the discussion elsewhere herein in relation to, for example, sequences and aspects and preferred embodiments, may be applied, *mutatis mutandis*, to this aspect of the invention.

An antigen binding protein according to any aspect of the present invention and disclosure may be defined as a binding protein comprising an antigen-binding domain obtained or derived from an antibody, or based on an antigen binding domain of an antibody. Thus, for example, light and heavy chain variable regions as described herein are those obtained or derived from an antibody, or based on an antigen binding domain of an antibody. For the avoidance of doubt, in accordance with the present invention the antigen binding domain is not from a T-cell receptor (TCR). Thus, for the avoidance of doubt, antigen binding proteins in accordance with the present invention do not include TCRs.

Preferably, the protein having an antigen binding domain is an antibody or an antigen binding fragment thereof.

The terms "antibody" and "immunoglobulin", as used herein, refer broadly to any immunological binding agent that comprises an antigen binding domain (e.g. a

human antigen binding domain), including polyclonal and monoclonal antibodies. Depending on the type of constant domain in the heavy chains, whole antibodies are assigned to one of five major classes: IgA, IgD, IgE, IgG, and IgM and the antibodies of the invention may be in any one of these classes. Several of these are further divided into subclasses or isotypes, such as IgG1, IgG2, IgG3, IgG4, and the like. The heavy-chain constant domains that correspond to the difference classes of immunoglobulins are termed α, δ, ε, γ and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

Generally, where whole antibodies rather than antigen binding regions are used in the invention, IgG (e.g. IgG_1 or IgG_{2b} such as human IgG_1 or mouse IgG_{2b}) and/or IgM are preferred because they are the most common antibodies in the physiological situation and because they are most easily made in a laboratory setting.

The "light chains" of mammalian antibodies are assigned to one of two clearly distinct types: kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains and some amino acids in the framework regions of their variable domains. In some embodiments, kappa (κ) light chains are preferred.

As will be understood by those in the art, the immunological binding reagents encompassed by the term "antibody" includes or extends to all antibodies and antigen binding fragments thereof, including whole antibodies, dimeric, trimeric and multimeric antibodies; bispecific antibodies; chimeric antibodies; recombinant and engineered antibodies, and fragments thereof.

The term "antibody" is thus used to refer to any antibody-like molecule that has an antigen binding region, and this term includes antibody fragments that comprise an antigen binding domain such as Fab', Fab, $F(ab')_2$, single domain antibodies (DABs), TandAbs dimer, Fv, scFv (single chain Fv), dsFv, ds-scFv, Fd, linear antibodies, minibodies, diabodies, bispecific antibody fragments, bibody, tribody (scFv-Fab fusions, bispecific or trispecific, respectively); sc-diabody; kappa(lamda) bodies (scFv-CL fusions); BiTE (Bispecific T-cell Engager, scFv-scFv tandems to attract T cells); DVD-Ig (dual variable domain antibody, bispecific format); SIP (small immunoprotein, a kind of minibody); SMIP ("small modular immunopharmaceutical" scFv-Fc dimer; DART (ds-stabilized diabody "Dual Affinity ReTargeting"); small antibody mimetics.

The techniques for preparing and using various antibody-based constructs and fragments are well known in the art. Diabodies, in particular, are further described in EP 404 097 and WO 93/11161; whereas linear antibodies are further described in the art.

Antibodies of the present invention are typically and preferably human antibodies (e.g. fully human antibodies).

However, antibodies may also be of other types e.g. murine antibodies or humanized antibodies. “Humanized” versions of antibodies are based on substantially non-human variable region domains, e.g. mouse variable region domains, and typically certain amino acids have been changed to better correspond with the amino acids typically present in human antibodies. Methods for generating humanized antibodies are well known in the art. For example, humanized antibodies can be accomplished by inserting the appropriate CDRs (e.g. murine CDRs) into a human antibody "scaffold".

In preferred embodiments the antibodies of the invention are human antibodies, more preferably fully human antibodies. In this regard, human antibodies generally have at least two potential advantages for use in human therapy. First, the human immune system should not recognize the antibody as foreign. Second, the half-life in the human circulation will be similar to naturally occurring human antibodies, allowing smaller and less frequent doses to be given.

However, although human antibodies are generally recognized to display these advantages, it is known that the development of human antibodies that have high enough affinities and appropriate functional properties to make them candidates for successful human therapy is by no means straightforward.

The term "human" as used herein in connection with antibody molecules and binding proteins first refers to antibodies and binding proteins having variable regions (*e.g.,* V_H, V_L, CDR or FR regions) and, optionally, constant antibody regions, isolated or derived from a human repertoire or derived from or corresponding to sequences found in humans or a human repertoire, *e.g.,* in the human germline or somatic cells.

The "human" antibodies and binding proteins of the invention further include amino acid residues not encoded by human sequences, e.g., mutations introduced by random or site directed mutations *in vitro*, for example mutations introduced by *in vitro* cloning or PCR, for example in an affinity maturation method. Particular examples of such mutations are mutations that involve conservative substitutions or other mutations in a small number of residues of the antibody or binding protein, e.g., in up to 5, 4, 3, 2 or 1 of the residues of the antibody or binding protein,

preferably e.g., in up to 5, 4, 3, 2 or 1 of the residues making up one or more of the CDRs of the antibody or binding protein. Certain examples of such "human" antibodies include antibodies and variable regions that have been subjected to standard modification techniques to reduce the amount of potentially immunogenic sites.

Thus, the "human" antibodies of the invention include sequences derived from and related to sequences found in humans, but which may not naturally exist within the human antibody germline repertoire *in vivo*. In addition, the human antibodies and binding proteins of the present invention include proteins comprising human consensus sequences identified from human sequences, or sequences substantially homologous to human sequences.

In addition, the human antibodies and binding proteins of the present invention are not limited to combinations of V_H, V_L, CDR or FR regions that are themselves found in combination in human antibody molecules. Thus, the human antibodies and binding proteins of the invention can include or correspond to combinations of such regions that do not necessarily exist naturally in humans (e.g. are not naturally occurring antibodies).

In preferred embodiments, the human antibodies will be fully human antibodies. "Fully human" antibodies, as used herein, are antibodies comprising "human" variable region domains and/or CDRs, as defined above, without substantial non-human antibody sequences or without any non-human antibody sequences. For example, antibodies comprising human variable region domains and/or CDRs "without substantial non-human antibody sequences" are antibodies, domains and/or CDRs in which only up to 5, 4, 3, 2 or 1 amino acids are amino acids that are not encoded by human antibody sequences. Thus, "fully human" antibodies are distinguished from "humanized" antibodies, which are based on substantially non-human variable region domains, *e.g.*, mouse variable region domains, in which certain amino acids have been changed to better correspond with the amino acids typically present in human antibodies.

The "fully human" antibodies of the invention may be human variable region domains and/or CDRs without any other substantial antibody sequences, such as being single chain antibodies. Alternatively, the "fully human" antibodies of the invention may be human variable region domains and/or CDRs integral with or operatively attached to one or more human antibody constant regions. Certain preferred fully human antibodies are IgG antibodies with the full complement of IgG constant regions.

In other embodiments, "human" antibodies of the invention will be part-human chimeric antibodies. "Part-human chimeric" antibodies, as used herein, are antibodies comprising "human" variable region domains and/or CDRs operatively attached to, or grafted onto, a constant region of a non-human species, such as rat or mouse. Such part-human chimeric antibodies may be used, for example, in pre-clinical studies, wherein the constant region will preferably be of the same species of animal used in the pre-clinical testing. These part-human chimeric antibodies may also be used, for example, in *ex vivo* diagnostics, wherein the constant region of the non-human species may provide additional options for antibody detection.

Antibodies of the present invention may also be CDR grafted antibodies. Such antibodies are antibodies comprising the CDR sequences (e.g. 3 VH CDRs and/or 3 VL CDRs) of an antibody of the invention grafted into a framework region that is different from the framework region with which the CDRs are associated in the VL and/or VH domains described herein.

The term "heavy chain complementarity determining region" ("heavy chain CDR") as used herein refers to regions of hypervariability within the heavy chain variable region (V_H domain) of an antibody molecule. The heavy chain variable region has three CDRs termed heavy chain CDR1, heavy chain CDR2 and heavy chain CDR3 from the amino terminus to carboxy terminus. The heavy chain variable region also has four framework regions (FR1, FR2, FR3 and FR4 from the amino terminus to carboxy terminus). These framework regions separate the CDRs. Preferred heavy chain variable region framework sequences are set forth in the sequence tables herein. Thus, the invention provides antigen binding proteins (e.g. antibodies) which comprise a heavy chain variable region comprising three CDRs that are separated by (or flanked by) framework FR regions.

The term "heavy chain variable region" (V_H domain) as used herein refers to the variable region of a heavy chain of an antibody molecule.

The term "light chain complementarity determining region" ("light chain CDR") as used herein refers to regions of hypervariability within the light chain variable region (V_L domain) of an antibody molecule. Light chain variable regions have three CDRs termed light chain CDR1, light chain CDR2 and light chain CDR3 from the amino terminus to the carboxy terminus. The light chain variable region also has four framework regions (FR1, FR2, FR3 and FR4 from the amino terminus to carboxy terminus). These framework regions separate the CDRs. Preferred light chain variable region framework sequences are set forth in the sequence tables herein. Thus, the invention provides antigen binding proteins (e.g. antibodies) which

comprise a light chain variable region comprising three CDRs that are separated by (or flanked by) framework FR regions.

The term "light chain variable region" (V_L domain) as used herein refers to the variable region of a light chain of an antibody molecule.

Antibodies can be fragmented using conventional techniques. For example, $F(ab')_2$ fragments can be generated by treating the antibody with pepsin. The resulting $F(ab')_2$ fragment can be treated to reduce disulfide bridges to produce Fab' fragments. Papain digestion can lead to the formation of Fab fragments. Fab, Fab' and $F(ab')_2$, scFv, Fv, dsFv, Fd, dAbs, TandAbs, ds-scFv, dimers, minibodies, diabodies, bispecific antibody fragments and other fragments can also be synthesized by recombinant techniques or can be chemically synthesized. Techniques for producing antibody fragments are well known and described in the art.

In certain embodiments, the antibody or antibody fragment of the present invention comprises all or a portion of a heavy chain constant region, such as an IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgE, IgM or IgD constant region. Preferably, the heavy chain constant region is an IgG heavy chain constant region, e.g. an IgG_1 or an IgG_{2b} heavy chain constant region, or a portion thereof. Furthermore, the antibody or antibody fragment can comprise all or a portion of a kappa light chain constant region or a lambda light chain constant region, or a portion thereof. All or part of such constant regions may be produced naturally or may be wholly or partially synthetic. Appropriate sequences for such constant regions are well known and documented in the art. When a full complement of constant regions from the heavy and light chains are included in the antibodies of the invention, such antibodies are typically referred to herein as "full length" antibodies or "whole" antibodies. In some embodiments, IgG_1 antibodies are preferred (e.g. human IgG_1 antibodies). In some embodiments, IgG_{2b} antibodies are preferred (e.g. mouse IgG_{2b} antibodies).

The antibodies or antibody fragments can be produced naturally or can be wholly or partially synthetically produced. Thus the antibody may be from any appropriate source, for example recombinant sources and/or produced in transgenic animals or transgenic plants, or in eggs using the IgY technology. Thus, the antibody molecules can be produced *in vitro* or *in vivo*.

Preferably, the antibody or antibody fragment comprises an antibody light chain variable region (V_L) that comprises three CDR domains and an antibody

heavy chain variable region (V_H) that comprises three CDR domains. Said VL and VH generally form the antigen binding site.

An "Fv" fragment is the minimum antibody fragment that contains a complete antigen-recognition and binding site. This region has a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. It is in this configuration that the three hypervariable regions (CDRs) of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six hypervariable regions (CDRs) confer antigen-binding specificity to the antibody.

However, it is well documented in the art that the presence of three CDRs from the light chain variable domain and three CDRs from the heavy chain variable domain of an antibody is not always necessary for antigen binding. Thus, constructs smaller than the above classical antibody fragment are known to be effective.

For example, camelid antibodies have an extensive antigen binding repertoire but are devoid of light chains. Also, results with single domain antibodies comprising VH domains alone or VL domains alone show that these domains can bind to antigen with acceptably high affinities. Thus, three CDRs can effectively bind antigen.

The term "fragment" as used herein refers to fragments of biological relevance, e.g. fragments that contribute to antigen binding, e.g. form part of the antigen binding site, and/or contribute to the functional properties of the antibodies of the invention. Certain preferred fragments comprise a heavy chain variable region (V_H domain) and a light chain variable region (V_L domain) of the antibodies of the invention.

Thus, although antibodies of the invention comprise six CDR regions (three from a light chain and three from a heavy chain), antibodies can have fewer than six CDR regions (e.g. 3 CDR regions). Antibodies can have CDRs from only the heavy chain or light chain.

Preferred light chain CDR regions for use in conjunction with the specified heavy chain CDR regions are described elsewhere herein. However, other light chain variable regions that comprise three CDRs for use in conjunction with the heavy chain variable regions of the invention are also contemplated. Appropriate light chain variable regions which can be used in combination with the heavy chain variable regions of the invention and which give rise to an antibody which binds HLA-DQ2.5:DQ2.5-gliadin peptides in accordance with the invention can be readily identified by a person skilled in the art.

For example, a heavy chain variable region of the invention can be combined with a single light chain variable region or a repertoire of light chain variable regions and the resulting antibodies tested for binding to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2.

If desired, similar methods could be used to identify alternative heavy chain variable regions for use in combination with preferred light chain variable regions of the invention.

A yet further aspect of the invention provides an antibody, preferably an isolated antibody, more preferably a human (or fully human) antibody, which binds to or specifically recognizes HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 and which has the ability to compete with (i.e. bind to the same or substantially the same epitope as) one or more of the specific antibodies of the invention described herein, or the ability to compete with an antibody comprising the same CDRs as one or more of the specific antibodies described herein for binding to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2. Other features and properties of other aspects of the invention apply, *mutatis mutandis*, to this aspect of the invention.

Binding to the same epitope/antigen can be readily tested by methods well known and described in the art, e.g. using binding assays such as a competitive inhibition assay. Thus, a person skilled in the art will appreciate that binding assays can be used to identify other antibodies and antibody fragments with the same binding specificities as the antibodies and antibody fragments of the invention. Suitable binding assays are discussed elsewhere herein.

Preferably, the above described abilities and properties are observed at a measurable or significant level and more preferably at a statistically significant level, when compared to appropriate control levels. More preferably, one or more of the above described abilities and properties are observed at a level which is measurably better, or more preferably significantly better, when compared to the abilities observed for reference antigen binding proteins (e.g. one or more of the R2A1-8E, R3A2-9F, R4A1-3A (also referred to as 107), 206, 217, 218, 220, 221, 223, 226 or 228 antibodies).

In any statistical analysis referred to herein, preferably the statistically significant difference over a relevant control or other comparative entity or measurement has a probability value of < 0.1, preferably < 0.05. Appropriate methods of determining statistical significance are well known and documented in the art and any of these may be used.

In other preferred embodiments, second generation antigen binding proteins (e.g. antibodies) are provided that have enhanced or superior properties in comparison to an original HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 antigen binding protein (e.g. antibody) of the invention.

Comparisons to identify effective second generation antigen binding proteins (e.g. antibodies) are readily conducted and quantified, e.g. using one or more of the various assays described in detail herein or in the art. Second generation antibodies that have an enhanced biological property or activity of at least about 2-fold, 5-fold, 10-fold, 20-fold, and preferably, at least about 50-fold, in comparison to the specific HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 antigen binding proteins (e.g. antibodies) of the present invention, are encompassed by the present invention.

Other constructs, conjugates and molecules (e.g. soluble binding molecules) containing an antigen binding domain (or antigen binding region), e.g. an antibody-derived antigen bind region or domain are encompassed by the present invention. In such constructs, conjugates (e.g. targeting conjugates) and molecules, the VL CDRs and VH CDRs may be on the same chain (same polypeptide) or be on separate chains (separate polypeptides). In such constructs, conjugates and molecules, the VL domain and VH domain may be on the same chain (same polypeptide) or may be on separate chains (separate polypeptides). When the VL CDRs and VH CDRs (or VL domain and VH domain) are on separate chains (separate polypeptides), the separate chains may be linked by any convenient means and the skilled person is familiar with different possibilities for such linking (e.g. covalent linkages e.g. via the introduction of cysteine residues into a constant region to enable disulphide bonding, i.e. linkage via a disulphide bond).

In some embodiments the invention provides CARs (chimeric antigen receptors) or CAR (chimeric antigen receptor) T cells. Thus, in one embodiment the invention provides CARs or CAR T cells comprising (or based on) an antibody of the invention. A protein comprising an antigen binding domain of the present invention may be coupled to (e.g. fused with) transmembrane domain or a intracellular domain of a CAR.

A CAR is a chimeric antigen receptor. As is known to the skilled person, a CAR commonly comprises a single-chain Fv domain (scFv) derived from an antibody fused to a signalling tail which, upon antigen binding, transduces a signal across a cell membrane to activate the effector functions of an immune effector cell, e.g. a T-cell or an NK cell. CARs may be used to redirect immune effector cells to a

target of interest in immunotherapy. CARs, and their therapeutic uses, are described in Maude *et al.* (Blood, Volume 125(26), 4017-4023, 2015). CAR immunotherapy has proven successful in a number of trials, but is limited by the breadth of available targets.

CARs are discussed in WO 2017/118745 (which is incorporated herein by reference), including suitable transmembrane domains and intracellular signalling domains which may be included in CARs. The transmembrane domain may be based on or derived from the transmembrane domain of any transmembrane protein. Typically it may be, or may be derived from, a transmembrane domain from CD8α, CD28, CD4, CD3ζ, CD45, CD9, CD16, CD22, CD33, CD64, CD80, CD86, CD134, CD137, or CD154, preferably from a human said protein. In one embodiment, the transmembrane domain may be, or may be derived from, a transmembrane domain from CD8α, CD28, CD4, or CD3ζ, preferably from human CD28, CD4, or CD3ζ. In another embodiment the transmembrane domain may be synthetic in which case it would comprise predominantly hydrophobic residues such as leucine and valine. The transmembrane domain may be the transmembrane domain of the human TCR α-chain constant region or a human TCR β-chain constant region.

The term "intracellular signalling domain" refers herein to the part of the CAR signalling tail that participates in transducing the message of effective CAR binding to a target antigen-MHC complex into the interior of an immune effector cell expressing the CAR, to elicit effector cell function, e.g. activation, cytokine production, proliferation and/or cytotoxic activity, including the release of cytotoxic factors to the CAR-bound target cell, or other cellular responses elicited with antigen binding to the extracellular CAR domain. The term "effector function" refers to a specialised function of the cell. Effector function of a T-cell, for example, may be cytolytic activity or helper activity including the secretion of a cytokine. Thus, the term "intracellular signalling domain" refers to a protein domain which transduces the effector function signal and directs the cell to perform a specialised function. While an entire natural intracellular signalling domain can be employed, in many cases it is not necessary to use an entire domain as found in nature. To the extent that a truncated portion of an intracellular signalling domain is used, such a truncated portion may be used in place of the entire domain as long as it transduces the effector function signal. The term intracellular signalling domain is meant to include any truncated portion of an intracellular signalling domain sufficient to transduce effector function signal. The intracellular signalling domain is also known

as the, "signal transduction domain," and is typically derived from portions of the human CD3ζ or FcRy chains.

Additionally, to allow or to augment full activation of the immune effector cell the CAR may be provided with a secondary, or co-stimulatory domain. Thus, the intracellular signalling domain may initiate antigen-dependent primary activation (i.e. may be a primary cytoplasmic signalling sequence) and the co-stimulatory domain may act in an antigen-independent manner to provide a secondary or co-stimulatory signal (secondary cytoplasmic signalling sequence(s)). Primary cytoplasmic signalling sequences may regulate primary activation, including in an inhibitory way. Primary cytoplasmic signalling sequences that act in a co-stimulatory manner may contain signalling motifs which are known as immunoreceptor tyrosine-based activation motifs or ITAMs.

The term "co-stimulatory signalling domain" or "co-stimulatory domain", refers to the portion of the CAR comprising the intracellular domain of a co-stimulatory molecule. Co-stimulatory molecules are cell surface molecules other than antigen receptors or Fc receptors that provide a second signal required for efficient activation and function of an immune effector cell (e.g. a T-cell) upon binding to antigen. Examples of such co-stimulatory molecules include CD27, CD28, 4- IBB (CD137), OX40 (CD134), CD30, CD40, PD-1, ICOS (CD278), LFA-1 , CD2, CD7, LIGHT, NKD2C, B7-H2 and a ligand that specifically binds CD83, more particularly the intracellular domains of such molecules. Preferably the molecules are human. Accordingly, while exemplary or preferred co-stimulatory domains are derived from 4-1BB, CD28 or OX40 (CD134), other co-stimulatory domains are contemplated for use with the CARs described herein. The co-stimulatory domains may be used singly or in combination (i.e. one or more co-stimulatory domains may be included). The inclusion of one or more co-stimulatory signalling domains may enhance the efficacy and expansion of immune effector cells expressing the CARs.

In some embodiments, an antigen binding protein of the present invention comprises two variable domains, i.e. a variable domain comprising three VH CDRs and a variable domain comprising three VL CDRs, each fused to a constant region (typically to the N-terminus of the constant region), wherein the two constant regions are linked (e.g. via a covalent linkage, such a disulphide bond), and optionally a targeting moiety is attached to one (or both) of the constant regions (e.g. at the C-terminus of the constant domain).

In some embodiments, an antigen binding protein of the present invention comprises two variable domains, i.e. a variable domain comprising three VH CDRs

and a variable domain comprising three VL CDRs (typically fused together), one constant region that is fused to (typically the C-terminus of) one of the variable domains (e.g. a heavy chain or a light chain constant region), one transmembrane domain and one intracellular signalling domain (typically the transmembrane domain being fused to (e.g. the C-terminus of) the constant domain and the intracellular signalling domain being fused to (e.g. the C-terminus of) the transmembrane domain).

In some embodiments, an antigen binding protein of the present invention comprises two variable domains, i.e. a variable domain comprising three VH CDRs and a variable domain comprising three VL CDRs, each fused to a constant region (typically to the N-terminus of the constant region), wherein the two constant regions are linked (e.g. via a covalent linkage, such as a disulphide bond), and one of the constant regions has fused thereto (typically at the C-terminus of said constant region) a transmembrane domain and the transmembrane domain has fused thereto (typically at the C-terminus of said transmembrane domain) an intracellular signalling domain.

In some embodiments, an antigen binding protein of the present invention comprises two variable domains, i.e. a variable domain comprising three VH CDRs and a variable domain comprising three VL CDRs, each fused to a constant region (typically to the N-terminus of the constant region), wherein the two constant regions are linked (e.g. via a covalent linkage, such a disulphide bond), and one (or both) of the constant regions is linked (or connected) to a lipid (e.g. a membrane anchoring lipid) which can target micelles (e.g. micelles comprising or containing a drug). Typically, the lipid is connected to (or linked to or attached to) the C-terminus of the constant region.

In some embodiments, an antigen binding protein of the present invention comprises two Fv domains, which may be fused together (e.g. at their respective C-terminuses) and each Fv domain may have a linkage (e.g. a covalent linkage, such as a disulphide bond) linking the two chains of the Fv domain.

In one aspect, the present invention provides a bispecific antigen binding protein (e.g. an antibody or antigen binding fragment thereof), wherein said bispecific antigen binding protein comprises at least one heavy chain variable region and at least one light chain variable region of an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a as defined elsewhere herein and at least one heavy chain variable region and at least one light chain variable region

of an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 as defined elsewhere herein.

In some embodiments, the antigen binding protein of the invention is a BiTe molecule (Bispecific T-cell engager). The BiTe format (BiTe molecule) is known to a person skilled in the art. In brief, two scFv molecules, targeting (or binding) different antigens, are operatively coupled (attached) through a linker (typically a genetically encoded synthetic linker) which brings (or places) both scFvs (or scFv units) into a single open reading frame (ORF). In certain embodiments, one scFv (or scFv unit) of a BiTe binds (or targets) HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 in accordance with the present invention and the other scFv (or scFv unit) targets CD3.

In some embodiments, the present invention provides a bispecific antigen binding protein (e.g. an antibody or antigen binding fragment thereof), wherein said bispecific antigen binding protein comprises at least one heavy chain variable region and at least one light chain variable region of an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α1a as defined elsewhere herein or at least one heavy chain variable region and at least one light chain variable region of an antibody that binds to, or specifically binds to, HLA-DQ2.5:DQ2.5-glia-α2 as defined elsewhere herein, and at least one heavy chain variable region and at least one light chain variable region of an antibody that binds to CD3.

The antibody, binding protein and nucleic acid molecules of the invention are generally "isolated" or "purified" molecules insofar as they are distinguished from any such components that may be present *in situ* within a human or animal body or a tissue sample derived from a human or animal body. The sequences may, however, correspond to or be substantially homologous to sequences as found in a human or animal body. Thus, the term "isolated" or "purified" as used herein in reference to nucleic acid molecules or sequences and proteins or polypeptides, e.g. antibodies, refers to such molecules when isolated from, purified from, or substantially free of their natural environment, e.g. isolated from or purified from the human or animal body (if indeed they occur naturally), or refers to such molecules when produced by a technical process, i.e. includes recombinant and synthetically produced molecules.

Thus, when used in connection with a protein or polypeptide molecule such as light chain CDRs 1, 2 and 3, heavy chain CDRs 1, 2 and 3, light chain variable regions, heavy chain variable regions, and binding proteins or antibodies of the invention, including full length antibodies, the term "isolated" or "purified" typically

refers to a protein substantially free of cellular material or other proteins from the source from which it is derived. In some embodiments, particularly where the protein is to be administered to humans or animals, such isolated or purified proteins are substantially free of culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized.

Nucleic acid molecules comprising nucleotide sequences that encode the antigen binding proteins (e.g. antibodies) of the present invention as defined herein or parts or fragments thereof, or nucleic acid molecules substantially homologous thereto, form yet further aspects of the invention. Preferred nucleic acid molecules are those encoding a VH region of an antibody of the present invention. Other preferred nucleic acid molecules are those encoding a VL region of an antibody of the present invention. Other preferred nucleic acid molecules are those encoding a VH region of an antibody of the present invention and a VL region of an antibody of the present invention.

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:4 (such as SEQ ID NO:2) and/or a VH region of SEQ ID NO:3 (such as SEQ ID NO:1).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:22 (such as SEQ ID NO:20) and/or a VH region of SEQ ID NO:21 (such as SEQ ID NO:19).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:40 (such as SEQ ID NO:38) and/or a VH region of SEQ ID NO:39 (such as SEQ ID NO:37).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:58 (such as SEQ ID NO:56) and/or a VH region of SEQ ID NO:57 (such as SEQ ID NO:55).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:76 (such as SEQ ID NO:74) and/or a VH region of SEQ ID NO:75 (such as SEQ ID NO:73).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:94 (such as SEQ ID NO:92) and/or a VH region of SEQ ID NO:93 (such as SEQ ID NO:91).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:112 (such as SEQ ID NO:110) and/or a VH region of SEQ ID NO:111 (such as SEQ ID NO:109).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:130 (such as SEQ ID NO:128) and/or a VH region of SEQ ID NO:129 (such as SEQ ID NO:127).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:148 (such as SEQ ID NO:146) and/or a VH region of SEQ ID NO:147 (such as SEQ ID NO:145).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:166 (such as SEQ ID NO:164) and/or a VH region of SEQ ID NO:165 (such as SEQ ID NO:163).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:184 (such as SEQ ID NO:182) and/or a VH region of SEQ ID NO:183 (such as SEQ ID NO:181).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:202 (such as SEQ ID NO:200) and/or a VH region of SEQ ID NO:201 (such as SEQ ID NO:199).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:220 (such as SEQ ID NO:218) and/or a VH region of SEQ ID NO:219 (such as SEQ ID NO:217).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:238 (such as SEQ ID NO:236) and/or a VH region of SEQ ID NO:237 (such as SEQ ID NO:235).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:256 (such as SEQ ID NO:254) and/or a VH region of SEQ ID NO:255 (such as SEQ ID NO:253).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:274 (such as SEQ ID NO:272) and/or a VH region of SEQ ID NO:273 (such as SEQ ID NO:271).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:292 (such as SEQ ID NO:290) and/or a VH region of SEQ ID NO:291 (such as SEQ ID NO:289).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:310 (such as SEQ ID NO:308) and/or a VH region of SEQ ID NO:309 (such as SEQ ID NO:307).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:328 (such as SEQ ID NO:326) and/or a VH region of SEQ ID NO:327 (such as SEQ ID NO:325).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:346 (such as SEQ ID NO:344) and/or a VH region of SEQ ID NO:345 (such as SEQ ID NO:343).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:364 (such as SEQ ID NO:362) and/or a VH region of SEQ ID NO:363 (such as SEQ ID NO:361).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:382 (such as SEQ ID NO:380) and/or a VH region of SEQ ID NO:381 (such as SEQ ID NO:379).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:400 (such as SEQ ID NO:398) and/or a VH region of SEQ ID NO:399 (such as SEQ ID NO:397).

In some embodiments, preferred nucleic acid molecules are those encoding a VL region of SEQ ID NO:499 (such as SEQ ID NO:497) and/or a VH region of SEQ ID NO:498 (such as SEQ ID NO:496).

In some embodiments, nucleic acid molecules are those encoding the IgG heavy and/or light chain sequences defined herein, or sequences substantially homologous thereto.

In some embodiments nucleic acid molecules are those having a nucleic acid sequence that is substantially homologous to the specific nucleic acid sequences defined herein, for example having at least 80% sequence identity to specific nucleic acid sequences defined herein.

The term "nucleic acid sequence" or "nucleic acid molecule" as used herein refers to a sequence of nucleoside or nucleotide monomers composed of naturally occurring bases, sugars and intersugar (backbone) linkages. The term also includes modified or substituted sequences comprising non-naturally occurring monomers or portions thereof. The nucleic acid sequences of the present invention may be deoxyribonucleic acid sequences (DNA) or ribonucleic acid sequences (RNA) and may include naturally occurring bases including adenine, guanine, cytosine, thymidine and uracil. The sequences may also contain modified bases. Examples of such modified bases include aza and deaza adenine, guanine, cytosine, thymidine and uracil; and xanthine and hypoxanthine. The nucleic acid molecules may be double stranded or single stranded. The nucleic acid molecules may be wholly or partially synthetic or recombinant.

A person skilled in the art will appreciate that the proteins and polypeptides of the invention, such as the light and heavy CDRs, the light and heavy chain variable regions, antibodies, antibody fragments, and immunoconjugates, may be

prepared in any of several ways well known and described in the art, but are most preferably prepared using recombinant methods.

Nucleic acid fragments encoding the light and heavy chain variable regions of the antibodies of the invention can be derived or produced by any appropriate method, e.g. by cloning or synthesis.

Once nucleic acid fragments encoding the light and heavy chain variable regions of the antibodies of the invention have been obtained, these fragments can be further manipulated by standard recombinant DNA techniques, for example to convert the variable region fragments into full length antibody molecules with appropriate constant region domains, or into particular formats of antibody fragment discussed elsewhere herein, e.g. Fab fragments, scFv fragments, etc. Typically, or as part of this further manipulation procedure, the nucleic acid fragments encoding the antibody molecules of the invention are generally incorporated into one or more appropriate expression vectors in order to facilitate production of the antibodies of the invention.

Possible expression vectors include but are not limited to cosmids, plasmids, or modified viruses (e.g. replication defective retroviruses, adenoviruses and adeno-associated viruses), so long as the vector is compatible with the host cell used. The expression vectors are "suitable for transformation of a host cell", which means that the expression vectors contain a nucleic acid molecule of the invention and regulatory sequences selected on the basis of the host cells to be used for expression, which are operatively linked to the nucleic acid molecule. Operatively linked is intended to mean that the nucleic acid is linked to regulatory sequences in a manner that allows expression of the nucleic acid.

The invention therefore contemplates a recombinant expression vector containing a nucleic acid molecule of the invention, or a fragment thereof, and the necessary regulatory sequences for the transcription and translation of the protein sequence encoded by the nucleic acid molecule of the invention.

Suitable regulatory sequences may be derived from a variety of sources, including bacterial, fungal, viral, mammalian, or insect genes and are well known in the art. Selection of appropriate regulatory sequences is dependent on the host cell chosen as discussed below, and may be readily accomplished by one of ordinary skill in the art. Examples of such regulatory sequences include: a transcriptional promoter and enhancer or RNA polymerase binding sequence, a ribosomal binding sequence, including a translation initiation signal. Additionally, depending on the host cell chosen and the vector employed, other sequences, such as an origin of

replication, additional DNA restriction sites, enhancers, and sequences conferring inducibility of transcription may be incorporated into the expression vector.

The recombinant expression vectors of the invention may also contain a selectable marker gene that facilitates the selection of host cells transformed or transfected with a recombinant molecule of the invention.

The recombinant expression vectors may also contain genes that encode a fusion moiety that provides increased expression of the recombinant protein; increased solubility of the recombinant protein; and aid in the purification of the target recombinant protein by acting as a ligand in affinity purification (for example appropriate "tags" to enable purification and/or identification may be present, *e.g.,* His tags or myc tags).

Recombinant expression vectors can be introduced into host cells to produce a transformed host cell. The terms "transformed with", "transfected with", "transformation" and "transfection" are intended to encompass introduction of nucleic acid (*e.g.,* a vector) into a cell by one of many possible techniques known in the art. Suitable methods for transforming and transfecting host cells can be found in Sambrook *et al.*, 1989 (Sambrook, Fritsch and Maniatis, *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Press, Cold Spring Harbor, NY, 1989) and other laboratory textbooks.

Suitable host cells include a wide variety of eukaryotic host cells and prokaryotic cells. For example, the proteins of the invention may be expressed in yeast cells or mammalian cells. In addition, the proteins of the invention may be expressed in prokaryotic cells, such as *Escherichia coli*.

Given the teachings provided herein, promoters, terminators, and methods for introducing expression vectors of an appropriate type into plant, avian, and insect cells may also be readily accomplished.

Alternatively, the proteins of the invention may also be expressed in non-human transgenic animals such as, rats, rabbits, sheep and pigs.

The proteins of the invention may also be prepared by chemical synthesis using techniques well known in the chemistry of proteins such as solid phase synthesis.

N-terminal or C-terminal fusion proteins comprising the antibodies and proteins of the invention conjugated to other molecules, such as proteins, may be prepared by fusing through recombinant techniques. The resultant fusion proteins contain an antibody or protein of the invention fused to the selected protein or marker protein, or tag protein as described herein. The antibodies and proteins of

the invention may also be conjugated to other proteins by known techniques. For example, the proteins may be coupled using heterobifunctional thiol-containing linkers as described in WO 90/10457, N-succinimidyl-3-(2-pyridyldithio-proprionate) or N-succinimidyl-5 thioacetate.

A yet further aspect provides an expression construct or expression vector comprising one or more of the nucleic acid fragments or segments or molecules of the invention. Preferably the expression constructs or vectors are recombinant. Preferably said constructs or vectors further comprise the necessary regulatory sequences for the transcription and translation of the protein sequence encoded by the nucleic acid molecule of the invention.

A yet further aspect provides a host cell or virus comprising one or more expression constructs or expression vectors of the invention. Also provided are host cells or viruses comprising one or more of the nucleic acid molecules of the invention. A host cell (e.g. a mammalian host cell) or virus expressing an antibody of the invention forms a yet further aspect.

A yet further aspect of the invention provides a method of producing (or manufacturing) a protein (e.g. antibody) of the present invention comprising a step of culturing the host cells of the invention. Preferred methods comprise the steps of (i) culturing a host cell comprising one or more of the recombinant expression vectors or one or more of the nucleic acid sequences of the invention under conditions suitable for the expression of the encoded antibody or protein; and optionally (ii) isolating or obtaining the antibody or protein from the host cell or from the growth medium/supernatant. Such methods of production (or manufacture) may also comprise a step of purification of the antibody or protein product and/or formulating the antibody or product into a composition including at least one additional component, such as a pharmaceutically acceptable carrier or excipient.

In embodiments when the protein (e.g. antibody) of the invention is made up of more than one polypeptide chain (e.g. certain fragments such as Fab fragments or whole antibodies), then all the polypeptides are preferably expressed in the host cell, either from the same or a different expression vector, so that the complete proteins, e.g. antibody proteins of the invention, can assemble in the host cell and be isolated or purified therefrom.

In another aspect, the invention provides a method of binding HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2, comprising contacting a composition comprising HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 with an antigen binding protein of the invention, or an immunoconjugate thereof.

In yet another aspect, the invention provides a method of detecting HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2, comprising contacting a composition suspected of containing HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 with an antigen binding protein of the invention, or an immunoconjugate thereof, under conditions effective to allow the formation of HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2/antibody complexes and detecting the complexes so formed.

In another aspect, and in some embodiments, the invention provides a method of detecting HLA-DQ2.5:DQ2.5 presenting a celiac disease associated peptide, or another gliadin peptide or gliadin-derived peptide, or variant of a gliadin derived peptide, or another gluten-derived peptide, comprising contacting a composition suspected of containing such a pMHC with an antigen binding protein of the invention, or an immunoconjugate thereof, under conditions effective to allow the formation of pMHC /antibody complexes and detecting the complexes so formed.

The antibodies of the invention may also be used to produce further antigen binding proteins, e.g. antibodies, that bind to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2. Such uses involve for example the addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a parent antibody to form a new antibody, wherein said parent antibody is one of the antibodies of the invention as defined elsewhere herein, and testing the resulting new antibody to identify antibodies that bind to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 in accordance with the invention. Such methods can be used to form multiple new antibodies that can all be tested for their ability to bind HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2. Preferably said addition, deletion, substitution or insertion of one or more amino acids takes place in one or more of the CDR domains.

Such modification or mutation to a parent antibody can be carried out in any appropriate manner using techniques well known and documented in the art, for example by carrying out methods of random or directed mutagenesis. If directed mutagenesis is to be used then one strategy to identify appropriate residues for mutagenesis utilizes the resolution of the crystal structure of the binding protein-antigen complex, *e.g.,* the Ab-Ag complex, or homology/docking modelling of the binding protein-antigen complex to identify the key residues involved in the antigen binding. Alanine scanning mutagenesis is also a routine method which can be used to identify the key residues involved in the antigen binding. Subsequently, those

residues can be mutated to enhance the interaction. Alternatively, one or more amino acid residues can simply be targeted for directed mutagenesis and the effect on binding to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 assessed.

Random mutagenesis can be carried out in any appropriate way, *e.g.,* by error-prone PCR, chain shuffling or mutator E. coli strains.

Thus, one or more of the V_H domains of the invention can be combined with a single V_L domain or a repertoire of V_L domains from any appropriate source and the resulting new antigen binding proteins (e.g. antibodies) tested to identify antibodies which bind to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2. Conversely, one or more of the V_L domains of the invention can be combined with a single V_H domain or repertoire of V_H domains from any appropriate source and the resulting new antigen binding proteins (e.g. antibodies) tested to identify antibodies that bind to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2.

Similarly, one or more, or preferably all three CDRs of the V_H and/or V_L domains of the invention can be grafted into a single V_H and/or V_L domain or a repertoire of V_H and/or V_L domains, as appropriate, and the resulting new antigen binding proteins (e.g. antibodies) tested to identify antibodies that bind to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2.

Methods of carrying out the above described manipulation of amino acids and protein domains are well known to a person skilled in the art. For example, said manipulations could conveniently be carried out by genetic engineering at the nucleic acid level wherein nucleic acid molecules encoding appropriate binding proteins and domains thereof are modified such that the amino acid sequence of the resulting expressed protein is in turn modified in the appropriate way.

The new antibodies produced by these methods will preferably have improved functional properties, e.g. a higher or enhanced affinity (or at least an equivalent affinity) for HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 as the parent antibodies, and can be treated and used in the same way as the antibodies of the invention as described elsewhere herein (*e.g.,* for therapy, diagnosis, in compositions etc.). Alternatively, or additionally, the new antibodies will have one or more other improved functional properties as described elsewhere herein.

New antibodies produced, obtained or obtainable by these methods form a yet further aspect of the invention.

Testing the ability of one or more antigen binding proteins (e.g. antibodies) to bind to HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 can be carried

out by any appropriate method, which are well known and described in the art. Suitable methods are also described in the Examples section.

The invention also provides a range of conjugated antigen binding proteins (e.g. antibodies) and fragments thereof in which the antigen binding protein is operatively attached to at least one other therapeutic or diagnostic agent. The term "immunoconjugate" is broadly used to define the operative association of the antigen binding protein (e.g. antibody) with another effective agent (e.g. therapeutic agent) and is not intended to refer solely to any type of operative association, and is particularly not limited to chemical "conjugation". Recombinant fusion proteins are particularly contemplated. So long as the delivery or targeting agent is able to bind to the target and the therapeutic or diagnostic agent is sufficiently functional upon delivery, the mode of attachment will be suitable.

The therapeutic agent may be a drug molecule, e.g. a toxin to kill a target cell. A suitable toxin is a toxin which, alone, is unable to enter, kill or otherwise disrupt a human cell but, when taken up by a human cell via the immunoconjugate, is able to exert its toxic effects. Such a toxin will thus only be taken up by, and exert its target effects on, a cell bound by the immunoconjugate, into which the immunoconjugate is taken up. The toxin may be any known appropriate cytotoxic species, i.e. it may be any suitable cytotoxin. By “cytotoxin” as used herein is meant any toxin which inhibits the growth and/or viability of a cell. Growth includes the division of a target cell (i.e. a cell into which it enters). The toxin may thus be any toxin which reduces or has a negative impact on the viability or survival of a cell and in particular includes any toxin which induces death of a target cell, e.g. the toxin may induce apoptosis or necrosis of a target cell.

Such a toxin may be a peptide toxin lacking a targeting domain. For instance, it may be a peptide toxin which natively lacks a targeting domain, or it may be a peptide toxin modified relative to its native form to remove its targeting domain. Examples of such toxins include saporin and gelonin, which are ribosome-inactivating proteins (RIPs) of the same family as e.g. ricin, but which are unable to cross the plasma membrane of a cell. Similarly, the enzymatic domains (i.e. catalytic domains) of a cytotoxin of a pathogen may be used, such as the enzymatic domain of a bacterial cytotoxin, e.g. the enzymatic domain of diphtheria toxin, *Pseudomonas* exotoxin A or a Clostridial cytotoxin, e.g. TcsL of *Clostridium sordellii*.

The immunoconjugate may be encoded as a fusion protein, with the toxin linked for example to a single chain antigen binding protein construct, or to one of the chains of antigen binding protein with 2 or more chains, at the N or C terminus. Alternatively, the toxin may be conjugated to the antigen binding protein using any

suitable method known in the art. For instance, the antigen binding protein may be biotinylated and conjugated to streptavidin-conjugated toxin (or *vice versa*). Other suitable methods are known to those skilled in the art.

The therapeutic agent may be any other useful therapeutic agent, for instance any other agent capable of killing or abrogating a cell, e.g. a radioisotope.

A diagnostic agent is an agent useful for diagnostic purposes. Such an agent may in particular be a tracer or a label, i.e. an agent which can be detected in order to follow its passage through a human body. A tracer or label may in particular be detected by a scan, e.g. a PET scan or a CT scan. Many tracers and labels are known in the art, including radiolabels. Any suitable tracer or label may be used according to the present disclosure, including the common radioisotopes ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{99}Tc and ^{123}I and ^{125}I. A diagnostic agent may be conjugated to an antigen binding protein using any suitable labelling group, such as are known in the art. For instance, the antigen binding protein may be radiolabelled using radiolabelled biotin.

The antigen binding protein may be conjugated to a carrier comprising or containing a therapeutic or diagnostic agent. Pharmaceutical carriers are known in the art. Examples of suitable carriers include in particular micelles and liposomes. As is known to the skilled person, a micelle is an aggregate of surfactants (e.g. fatty acids) in an aqueous liquid, in which the hydrophilic head groups of the surfactants form the surface of the aggregate and the hydrophobic tail groups the core. A liposome is a spherical vesicle formed from a lipid bilayer surrounding an aqueous core. The therapeutic or diagnostic agent may be located within the core of a micelle or liposome.

Liposomes and micelles may be synthesised using any method known in the art. Suitable methods for liposome synthesis and drug loading are described in e.g. Akbarzadeh *et al.*, Nanoscale Res Lett 8(1): 102, 2013. Liposomes and micelles may be conjugated to antigen binding proteins using methods known in the art, e.g. the methods taught in Reulen *et al.*, Bioconjug Chem 18(2): 590-596, 2007; or Kung & Redemann, Biochim Biophys Acta 862(2): 435-439, 1986.

An immunoconjugate comprising a therapeutic agent, or a carrier comprising a therapeutic agent, may be used in therapy. An immunoconjugate comprising a diagnostic agent, or a carrier comprising a diagnostic agent, may be used in *in vivo* diagnostic methods.

In some embodiments, antigen binding proteins (e.g. antibodies) of the invention are used (e.g. used therapeutically) in their "naked" unconjugated form.

Compositions comprising at least a first antigen binding protein (e.g. antibody) of the invention or an immunoconjugate thereof constitute a further aspect

of the present invention. Formulations (compositions) comprising one or more antigen binding protein (e.g. antibody) of the invention in admixture with a suitable diluent, carrier or excipient constitute a preferred embodiment of the present invention. Such formulations may be for pharmaceutical use and thus compositions of the invention are preferably pharmaceutically acceptable. Suitable diluents, excipients and carriers are known to the skilled man.

The compositions according to the invention may be presented, for example, in a form suitable for oral, nasal, parenteral, intravenal, topical or rectal administration. In a preferred embodiment, compositions according to the invention are presented in a form suitable for intravenal administration. In some embodiments, compositions according to the invention are presented in a form suitable for intraperitoneal (i.p.) administration. In some embodiments, compositions according to the invention are presented in a form suitable for injection.

The active compounds defined herein may be presented in the conventional pharmacological forms of administration, such as tablets, coated tablets, nasal sprays, solutions, emulsions, liposomes, powders, capsules or sustained release forms. Conventional pharmaceutical excipients as well as the usual methods of production may be employed for the preparation of these forms.

Injection solutions may, for example, be produced in the conventional manner, such as by the addition of preservation agents, such as p-hydroxybenzoates, or stabilizers, such as EDTA. The solutions may then be filled into injection vials or ampoules.

Nasal sprays may be formulated similarly in aqueous solution and packed into spray containers, either with an aerosol propellant or provided with means for manual compression.

The pharmaceutical compositions (formulations) of the present invention are preferably administered parenterally. Intravenous administration is preferred. In some embodiments, administration is intraperitoneal (i.p.) administration. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe. Alternatively, parenteral administration can be performed by means of an infusion pump. A further option is a composition which may be a powder or a liquid for the administration of the antigen binding protein (e.g. antibody) in the form of a nasal or pulmonal spray. As a still further option, the antigen binding proteins of the invention can also be administered

transdermally, e.g. from a patch, optionally an iontophoretic patch, or transmucosally, e.g. bucally.

Suitable dosage units can be determined by a person skilled in the art.

The pharmaceutical compositions may additionally comprise further active ingredients (e.g. as described elsewhere herein) in the context of co-administration regimens or combined regimens.

A further aspect of the present invention provides the antigen binding proteins (e.g. antibodies) defined herein for use in therapy.

By “therapy” as used herein is meant the treatment of any medical condition. Such treatment may be prophylactic (i.e. preventative), curative (or treatment intended to be curative), or palliative (i.e. treatment designed merely to limit, relieve or improve the symptoms of a condition).

Preferably, antigen binding proteins (e.g. antibodies) defined herein are for use in the treatment of celiac disease. Thus, in one aspect, the present invention provides the antibodies defined herein for use in the treatment of celiac disease.

In another aspect, the present invention provides immunoconjugates of the invention for use in therapy, in particular for use in the treatment of celiac disease.

In another aspect, the present invention provides antigen binding proteins, or immunoconjugates thereof, for use in inhibiting and/or killing cells (e.g. antigen presenting cells such as B cells or plasma cells, for example as defined elsewhere herein) that express or present HLA-DQ2.5:DQ2.5-glia-α1a and/or HLA-DQ2.5:DQ2.5-glia-α2.

The *in vivo* methods and uses as described herein are generally carried out in a human.

Thus, the term "animal" or "patient" as used herein typically means human.

Alternatively viewed, the present invention provides a method of treating celiac disease which method comprises administering to a patient in need thereof a therapeutically effective amount of an antigen binding protein (e.g. antibody) of the invention as defined herein. Embodiments of the therapeutic uses of the invention described herein apply, *mutatis mutandis*, to this aspect of the invention.

In another aspect, the present invention provides a method of inhibiting and/or killing cells (e.g. antigen presenting cells such as B cells or plasma cells, for example as defined elsewhere herein) that express or present HLA-DQ2.5:DQ2.5-glia-α1a and/or HLA-DQ2.5:DQ2.5-glia-α2, which method comprises administering

to a patient (e.g. a celiac disease patient) in need thereof a therapeutically effective amount of an antigen binding protein (e.g. antibody) of the invention as defined herein.

By “therapeutically effective amount” is meant an amount sufficient to show benefit to the condition of the subject. Whether an amount is sufficient to show benefit to the condition of the subject may be determined by the subject him/herself or a physician.

Further alternatively viewed, the present invention provides the use of an antigen binding protein (e.g. antibody) of the invention as defined herein in the manufacture of a medicament for use in therapy. Preferred therapy is the treatment of celiac disease. Embodiments of the therapeutic uses of the invention described herein apply, *mutatis mutandis*, to this aspect of the invention.

Further alternatively viewed, the present invention provides the use of an antigen binding protein (e.g. antibody) of the invention as defined herein for the treatment of celiac disease. Embodiments of the therapeutic uses of the invention described herein apply, *mutatis mutandis*, to this aspect of the invention.

The antigen binding proteins (e.g. antibodies) and compositions and methods and uses of the present invention may be used in combination with other therapeutics and diagnostics. In terms of biological agents, preferably diagnostic or therapeutic agents, for use "in combination" with an antibody in accordance with the present invention, the term "in combination" is succinctly used to cover a range of embodiments. The "in combination" terminology, unless otherwise specifically stated or made clear from the scientific terminology, thus applies to various formats of combined compositions, pharmaceuticals, cocktails, kits, methods, and first and second medical uses.

The "combined" embodiments of the invention thus include, for example, where an antigen binding protein (e.g. antibody) of the invention is a naked antigen binding protein and is used in combination with an agent or therapeutic agent that is not operatively attached thereto. In other "combined" embodiments of the invention, an antigen binding protein (e.g. antibody) of the invention is an immunoconjugate wherein the antigen binding protein is itself operatively associated or combined with the agent or therapeutic agent. The operative attachment includes all forms of direct and indirect attachment as described herein and known in the art.

The "combined" uses, particularly in terms of an antigen binding protein (e.g. antibody) of the invention in combination with therapeutic agents, also include combined compositions, pharmaceuticals, cocktails, kits, methods, and first and

second medical uses wherein the therapeutic agent is in the form of a prodrug. In such embodiments, the activating component able to convert the prodrug to the functional form of the drug may again be operatively associated with the antigen binding protein (e.g. antibodies) of the present invention.

In certain embodiments, the therapeutic compositions, combinations, pharmaceuticals, cocktails, kits, methods, and first and second medical uses will be "prodrug combinations". As will be understood by those of ordinary skill in the art, the term "prodrug combination", unless otherwise stated, means that the antigen binding protein (e.g. antibody) of the invention is operatively attached to a component capable of converting the prodrug to the active drug, not that the antigen binding protein (e.g. antibody) is attached to the prodrug itself. However, there is no requirement that the prodrug embodiments of the invention need to be used as prodrug combinations. Accordingly, prodrugs may be used in any manner that they are used in the art.

Thus, where combined compositions, pharmaceuticals, cocktails, kits, methods, and first and second medical uses are described, preferably in terms of diagnostic agents, and more preferably therapeutic agents, the combinations include antigen binding protein (e.g. antibody) that are “naked” (e.g. “naked” antibodies) and immunoconjugates, and wherein practice of the *in vivo* embodiments of the invention involves the prior, simultaneous or subsequent administration of the naked antigen binding protein or immunoconjugate and the biological, diagnostic or therapeutic agent; so long as, in some conjugated or unconjugated form, the overall provision of some form of the antigen binding protein (e.g. antibody) and some form of the biological, diagnostic or therapeutic agent is achieved.

The invention therefore provides compositions, pharmaceutical compositions, therapeutic kits and medicinal cocktails comprising, optionally in at least a first composition or container, a biologically effective amount of at least a first antigen binding protein (e.g. antibody) of the invention, or an antigen-binding fragment or immunoconjugate of such protein; and a biologically effective amount of at least a second biological agent, component or system.

The "at least a second biological agent, component or system" will often be a therapeutic or diagnostic agent, component or system, but it need not be. For example, the at least a second biological agent, component or system may comprise components for modification of the antigen binding protein (e.g. antibody) and/or for attaching other agents to the antigen binding protein. Certain preferred second biological agents, components or systems are prodrugs or components for

making and using prodrugs, including components for making the prodrug itself and components for adapting the antigen binding proteins (e.g. antibodies) of the invention to function in such prodrug or ADEPT embodiments.

Where therapeutic or diagnostic agents are included as the at least a second biological agent, component or system, such therapeutics and/or diagnostics will typically be those for use in connection with the treatment or diagnosis of disease, preferably celiac disease.

Thus, in certain embodiments "at least a second therapeutic agent" will be included in the therapeutic kit or cocktail. The term is chosen in reference to the antigen binding protein (e.g. antibody) of the invention being the first therapeutic agent.

In terms of compositions, kits and/or medicaments of the invention, the combined effective amounts of the therapeutic agents may be comprised within a single container or container means, or comprised within distinct containers or container means. The cocktails will generally be admixed together for combined use. Agents formulated for intravenous administration will often be preferred. Imaging components may also be included. The kits may also comprise instructions for using the at least a first antigen binding protein (e.g. antibody) and the one or more other biological agents included.

Speaking generally, the at least a second therapeutic agent may be administered to the animal or patient substantially simultaneously with an antigen binding protein (e.g. antibody) of the invention; such as from a single pharmaceutical composition or from two pharmaceutical compositions administered closely together.

Alternatively, the at least a second therapeutic agent may be administered to the animal or patient at a time sequential to the administration of the antigen binding protein (e.g. antibody) of the invention. "At a time sequential", as used herein, means "staggered", such that the at least a second therapeutic agent is administered to the animal or patient at a time distinct to the administration of the antigen binding protein (e.g. antibody) of the invention. Generally, the two agents are administered at times effectively spaced apart to allow the two agents to exert their respective therapeutic effects, i.e., they are administered at "biologically effective time intervals". The at least a second therapeutic agent may be administered to the animal or patient at a biologically effective time prior to the antigen binding protein (e.g. antibody) of the invention, or at a biologically effective time subsequent to that therapeutic.

Yet further aspects are methods of diagnosis or imaging of a subject comprising the administration of an appropriate amount of an antibody or other protein of the invention as defined herein to the subject and detecting the presence and/or amount and/or the location of the antibody or other protein of the invention in the subject.

A preferred disease to be imaged or diagnosed in accordance with the present invention is celiac disease.

In one embodiment, the invention provides a method of diagnosing celiac disease in a mammal comprising the step of:

(a) contacting a test sample taken from said mammal with one or more of the antigen binding proteins (e.g. antibodies) of the invention.

In a further embodiment, the invention provides a method of diagnosing celiac disease in a mammal comprising the steps of:

(a) contacting a test sample taken from said mammal with one or more of the antigen binding proteins (e.g. antibodies) of the invention;

(b) measuring the presence and/or amount and/or location of antigen binding protein (e.g. antibody)-antigen complex in the test sample; and, optionally

(c) comparing the presence and/or amount of antigen binding protein (e.g. antibody)-antigen complex in the test sample to a control.

In the above methods, said contacting step is carried out under conditions that permit the formation of an antigen binding protein (e.g. antibody)-antigen complex. Appropriate conditions can readily be determined by a person skilled in the art.

In the above methods any appropriate test sample may be used, for example a blood sample, biopsy cells, tissues or organs suspected of being affected by celiac disease (e.g. small intestine) or histological sections.

In certain of the above methods, the presence of any amount of antigen binding protein (e.g. antibody)-antigen complex in the test sample would be indicative of the presence of celiac disease. Preferably, for a positive diagnosis to be made, the amount of antigen binding protein (e.g. antibody)-antigen complex in the test sample is greater than, preferably significantly greater than, the amount found in an appropriate control sample. More preferably, the significantly greater levels are statistically significant, preferably with a probability value of <0.05.

Appropriate methods of determining statistical significance are well known and documented in the art and any of these may be used.

Appropriate control samples could be readily chosen by a person skilled in the art, for example, in the case of diagnosis of celiac disease, an appropriate control would be a sample from a subject that did not have celiac disease. Appropriate control "values" could also be readily determined without running a control "sample" in every test, e.g. by reference to the range for normal subjects known in the art.

For use in the diagnostic or imaging applications, the antigen binding proteins (e.g. antibodies) of the invention may be labeled with a detectable marker such as a radio-opaque or radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{123}I, ^{125}I, ^{131}I; a radioactive emitter (e.g. α, β or γ emitters); a fluorescent (fluorophore) or chemiluminescent (chromophore) compound, such as fluorescein isothiocyanate, rhodamine or luciferin; an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase; an imaging agent; or a metal ion; or a chemical moiety such as biotin which may be detected by binding to a specific cognate detectable moiety, e.g. labelled avidin/streptavidin. Methods of attaching a label to a binding protein, such as an antibody or antibody fragment, are known in the art. Such detectable markers allow the presence, amount or location of binding protein-antigen complexes in the test sample to be examined.

Preferred detectable markers for *in vivo* use include an X-ray detectable compound, such as bismuth (III), gold (III), lanthanum (III) or lead (II); a radioactive ion, such as copper^{67}, gallium^{67}, gallium^{68}, indium^{111}, indium^{113}, iodine^{123}, iodine^{125}, iodine^{131}, mercury^{197}, mercury^{203}, rhenium^{186}, rhenium^{188}, rubidium^{97}, rubidium^{103}, technetium^{99m} or yttrium^{90}; a nuclear magnetic spin-resonance isotope, such as cobalt (II), copper (II), chromium (III), dysprosium (III), erbium (III), gadolinium (III), holmium (III), iron (II), iron (III), manganese (II), neodymium (III), nickel (II), samarium (III), terbium (III), vanadium (II) or ytterbium (III); or rhodamine or fluorescein.

The invention also includes diagnostic or imaging agents comprising the antigen binding proteins (e.g. antibodies) of the invention attached to a label that produces a detectable signal, directly or indirectly. Appropriate labels are described elsewhere herein.

In one embodiment the method of diagnosing celiac disease is an *in vitro* method.

In one embodiment the method of diagnosing celiac disease is an *in vivo* method.

Alternatively viewed, the present invention provides a method for screening for celiac disease in a subject.

In some embodiments, antigen binding proteins (e.g. antibodies) of the present invention can be used as companion diagnostics.

In one embodiment (e.g. of methods of diagnosing), the subject (e.g. a human) is a subject at risk of developing celiac disease or at risk of the occurrence of celiac disease, e.g. a healthy subject or a subject not displaying any symptoms of celiac disease or any other appropriate "at risk" subject. In another embodiment the subject is a subject having, or suspected of having (or developing), or potentially having (or developing) celiac disease.

In some aspects, a method of the invention may further comprise an initial step of selecting a subject (e.g. a human subject) at risk of developing celiac disease, or at risk of the occurrence of celiac disease, or suspected of having (or developing) celiac disease, or potentially having (or developing) celiac disease. Subjects may be selected on the basis that, for example, the subject (or sample, e.g. tissue biopsy, from the subject) is positive for one or more celiac disease markers or risk factors.

In some aspects, diagnostic methods of the invention are provided which further comprise a step of treating celiac disease by therapy, e.g. using an antigen binding protein (e.g. antibody) of the present invention. For example, if the result of a method of the invention is indicative of celiac disease in the subject (e.g. a positive diagnosis of celiac disease is made), then an additional step of treating the celiac disease by therapy or surgery can be performed.

The invention further includes kits comprising one or more of the antigen binding proteins (e.g. antibodies), immunoconjugates or compositions of the invention or one or more of the nucleic acid molecules encoding the antibodies of the invention, or one or more recombinant expression vectors comprising the nucleic acid sequences of the invention, or one or more host cells or viruses comprising the recombinant expression vectors or nucleic acid sequences of the invention. Preferably, said kits are for use in the methods and uses as described herein, e.g. the therapeutic, diagnostic or imaging methods as described herein, or are for use in the *in vitro* assays or methods as described herein. The antigen binding protein (e.g. antibody) in such kits may be a conjugate as described

elsewhere herein, e.g. may be conjugated to a detectable moiety or may be an immunoconjugate. Preferably said kits comprise instructions for use of the kit components. Preferably said kits are for diagnosing or treating celiac disease, and optionally comprise instructions for use of the kit components to diagnose or treat this disease.

The antigen binding proteins (e.g. antibodies) of the invention as defined herein may also be used as molecular tools for *in vitro* or *in vivo* applications and assays. As the antigen binding proteins (e.g. antibodies) have an antigen binding site, these can function as members of specific binding pairs and these molecules can be used in any assay where the particular binding pair member is required.

Thus, yet further aspects of the invention provide a reagent that comprises an antigen binding protein (e.g. antibody) of the invention as defined herein and the use of such antigen binding proteins as molecular tools, for example in *in vitro* or *in vivo* assays.

TABLES OF NUCLEOTIDE AND AMINO ACID SEQUENCES DISCLOSED HEREIN AND THEIR SEQUENCE IDENTIFIERS (SEQ ID NOs)

All nucleotide sequences are recited herein 5' to 3' in line with convention in this technical field.

Tables A, B, C, D, E, F, G, H, I and AA contain sequences of antibodies that bind to, or specifically bind to, HLA-DQ2.5:DQ2.5-glia-α1a. Tables A-I herein set forth sequences of the R2A1-8E, R3A2-9F, R4A1-3A (also referred to as 107), 107-4.5D, 107-4.6D, 107-4.6C, 107-4.7C, 107-5.6A and 107-15.6A antibodies. Table AA herein sets forth sequences of the RF117 antibody.

Tables J, K, L, M, N, O, P, Q, R, S, T, U, V and W contain sequences of antibodies that bind to, or specifically bind to, HLA-DQ2.5:DQ2.5-glia-α2. Tables J-W herein set forth sequences of the 206, 217, 218, 220, 221, 223, 226, 228, 206-2.B11, 206-3.D8, 206-3.C7, 206-3.C11, 206-3.F6 and 206-12.F6 antibodies.

Table A		
SEQ ID NO:	**Description**	**Sequence**
R2A1-8E		

Table A		
SEQ ID NO:	**Description**	**Sequence**
1	VH domain (nt)	IGHV6-1*01/ IGHJ6*02/IGHD6-19*01 CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGG TGAAGCCCTCGCAGACCCTCTCACTCACCTGTGCC ATCTCCGGGGACAGTGTCTCTAGCAACAGTGCTG CTTGGAACTGGATCAGGCAGTCCCCATCGAGAGG CCTTGAGTGGCTGGGAAGGACATACTACAGGTCC AAGTGGTATAATGATTATGCAGTATCTGTGAAAAGT CGAATAACCATCAACCCAGACACATCCAAGAACCA GTTCTCCCTGCAGCTGAACTCTGTGACTCCCGAGG ACACGGCTGTGTATTACTGTGCAAGAGATAGCAGC AGTGGCTGGCATCCTTACGGTATGGACGTCTGGG GCCAAGGGACCACGGTCACCGTCTCCTCA
2	VL domain (nt)	IGKV1-9*01/IGKJ4*01 GACATCCAGGTGACCCAGTCTC CATCCTTCCTGTCTGCATCTGTAGGAGACAGAGTC ACCATCACTTGCCGGGCCAGTCACGACATTAGCA GTTATTTAGCCTGGTATCAACACAAACCAGGGAAA GCCCCCAAACTCCTGATCCATGCTGCATCCATTTT GCAAAGTGGGGTCCCATCAAGGTTCAGCGGAAGT GGATCTGGGACAGAATTCACTCTCACAATCAGCAG CCTGCAGCCTGAAGATTTTGCAACGTACTACTGTC AACAGCTTAATAGTTACCCTCTGCTCACTTTCGGC GGAGGGACCAAAGTGGATATCAAA
3	VH domain (aa)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAA WNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVK SRITINPDTSKNQFSLQLNSVTPEDTAVYYCARDSS SGWHPYGMDVWGQGTTVTVSS
4	VL domain (aa)	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWY QHKPGKAPKLLIHAASILQSGVPSRFSGSGSGTEFT LTISSLQPEDFATYYCQQLNSYPLLTFGGGTKVDIK
5	Heavy CDR1	GDSVSSNSAA
6	Heavy CDR2	TYYRSKWYN
7	Heavy CDR3	ARDSSSGWHPYGMDV
8	Light CDR1	HDISSY
9	Light CDR2	AAS

Table A		
SEQ ID NO:	**Description**	**Sequence**
10	Light CDR3	QQLNSYPLLT
11	Heavy FR1	QVQLQQSGPGLVKPSQTLSLTCAIS
12	Heavy FR2	WNWIRQSPSRGLEWLGR
13	Heavy FR3	DYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYC
14	Heavy FR4	WGQGTTVTVSS
15	Light FR1	DIQVTQSPSFLSASVGDRVTITCRAS
16	Light FR2	LAWYQHKPGKAPKLLIH
17	Light FR3	ILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC
18	Light FR4	FGGGTKVDIK
444	Heavy chain (aa) (variable + constant domain). mIgG$_{2b}$	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARDSSSGWHPYGMDVWGQGTT VTVSSAKTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYFPESV TVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQ TVTCSVAHPASSTTVDKKLEPSGPISTINPCPPCKECHKCPAP NLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVSEDDPDVQ ISWFVNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWM SGKEFKCKVNNKDLPSPIERTISKIKGLVRAPQVYILPPPAEQL SRKDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLD SDGSYFIYSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTI SRSPGK
445	Light chain (aa) (variable + constant domain). mIgG$_{2b}$	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPGK APKLLIHAASILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATY YCQQLNSYPLLTFGGGTKVDIKRADAAPTVSIFPPSSEQLTSG GASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDS KDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNR NEC
446	Heavy chain (aa) (variable + constant	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARDSSSGWHPYGMDVWGQGTT

Table A		
SEQ ID NO:	**Description**	**Sequence**
	domain). hIgG$_1$	VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK
447	Light chain (aa) (variable + constant domain). hIgG$_1$	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPGK APKLLIHAASILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATY YCQQLNSYPLLTFGGGTKVDIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC

Table B		
SEQ ID NO:	**Description**	**Sequence**
R3A2-9F		
19	VH domain (nt)	IGHV6-1*01/ IGHJ6*02/IGHD6-19*01 CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGG TGAAGCCCTCGCAGACCCTCTCACTCACCTGTGCC ATCTCCGGGGACAGTGTCTCTAGCAACAGTGCTG CTTGGAACTGGATCAGGCAGTCCCCATCGAGAGG CCTTGAGTGGCTGGGAAGGACATACTACAGGTCC AAGTGGTATAATGATTATGCAGTATCTGTGAAAAGT CGAATAACCATCAACCCAGACACATCCAAGAACCA GTTCTCCCTGCAGCTGAACTCTGTGACTCCCGAGG ACACGGCTGTGTATTACTGTGCAAGAGATAGCAGC AGTGGCTGGCATCCTTACGGTATGGACGTCTGGG GCCAAGGGACCACGGTCACCGTCTCCTCA

Table B		
SEQ ID NO:	**Description**	**Sequence**
20	VL domain (nt)	IGKV1-9*01/IGKJ5*01 GACATCCAGGTGACCCAGTCTCCATCCTTCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCC GGGCCAGTCACGACATTAGCAGTTATTTAGCCTGG TATCAACACAAACCAGGGAAAGCCCCCAAACTCCT GATCCATGCTGCATCCATTTTGCAAAGTGGGGTCC CATCAAGGTTCAGCGGAAGTGGATCTGGGACAGA ATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACGTACTACTGTCAAGATCTCAATAGTT ATCCTCTCTTCGGCCAAGGGACACGACTGGAGATT AAA
21	VH domain (aa)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAA WNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVK SRITINPDTSKNQFSLQLNSVTPEDTAVYYCARDSS SGWHPYGMDVWGQGTTVTVSS
22	VL domain (aa)	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQ HKPGKAPKLLIHAASILQSGVPSRFSGSGSGTEFTLTI SSLQPEDFATYYCQDLNSYPLFGQGTRLEIK
23	Heavy CDR1	GDSVSSNSAA
24	Heavy CDR2	TYYRSKWYN
25	Heavy CDR3	ARDSSSGWHPYGMDV
26	Light CDR1	HDISSY
27	Light CDR2	AAS
28	Light CDR3	QDLNSYPL
29	Heavy FR1	QVQLQQSGPGLVKPSQTLSLTCAIS
30	Heavy FR2	WNWIRQSPSRGLEWLGR
31	Heavy FR3	DYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYC
32	Heavy FR4	WGQGTTVTVSS
33	Light FR1	DIQVTQSPSFLSASVGDRVTITCRAS

Table B		
SEQ ID NO:	**Description**	**Sequence**
34	Light FR2	LAWYQHKPGKAPKLLIH
35	Light FR3	ILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC
36	Light FR4	FGQGTRLEIK
448	Heavy chain (aa) (variable +constant domain). mIgG$_{2b}$	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARDSSSGWHPYGMDVWGQGTT VTVSSAKTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYFPESV TVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQ TVTCSVAHPASSTTVDKKLEPSGPISTINPCPPCKECHKCPAP NLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVSEDDPDVQ ISWFVNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWM SGKEFKCKVNNKDLPSPIERTISKIKGLVRAPQVYILPPPAEQL SRKDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLD SDGSYFIYSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTI SRSPGK
449	Light chain (aa) (variable +constant domain). mIgG$_{2b}$	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPGK APKLLIHAASILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATY YCQDLNSYPLFGQGTRLEIKRADAAPTVSIFPPSSEQLTSGG ASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRN EC
450	Heavy chain (aa) (variable + constant domain). hIgG$_1$	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARDSSSGWHPYGMDVWGQGTT VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK
451	Light chain (aa) (variable + constant	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPGK APKLLIHAASILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATY

Table B		
SEQ ID NO:	**Description**	**Sequence**
	domain). hIgG$_1$	YCQDLNSYPLFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C

Table C		
SEQ ID NO:	**Description**	**Sequence**
R4A1-3A (107)		
37	VH domain (nt)	IGHV6-1*01/ IGHJ6*02/IGHD6-19*01 CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGG TGAAGCCCTCGCAGACCCTCTCACTCACCTGTGCC ATCTCCGGGGACAGTGTCTCTAGCAACAGTGCTG CTTGGAACTGGATCAGGCAGTCCCCATCGAGAGG CCTTGAGTGGCTGGGAAGGACATACTACAGGTCC AAGTGGTATAATGATTATGCAGTATCTGTGAAAAGT CGAATAACCATCAACCCAGACACATCCAAGAACCA GTTCTCCCTGCAGCTGAACTCTGTGACTCCCGAGG ACACGGCTGTGTATTACTGTGCAAGAGATAGCAGC AGTGGCTGGCATCCTTACGGTATGGACGTCTGGG GCCAAGGGACCACGGTCACCGTCTCCTCA
38	VL domain (nt)	IGKV1-9*01/IGKJ5*01 GACATCCAGGTGACCCAGTCTCCATCCTTCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCC GGGCCAGTCACGACATTAGCAGTTATTTAGCCTGG TATCAACACAAACCATGGAAAGCCCCCAAACTCCT GATCCATGCTGCATCCATTTTGCAAAGTGGGGTCC CATCAAGGTTCAGCGGAAGTGGATCTGGGACAGA ATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACGTACTACTGTCAAGATCTCAATAGTT ATCCTCTCTTCGGCCAAGGGACACGACTGGAGATT AAA
39	VH domain (aa)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAA WNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVK SRITINPDTSKNQFSLQLNSVTPEDTAVYYCARDSS SGWHPYGMDVWGQGTTVTVSS

Table C		
SEQ ID NO:	**Description**	**Sequence**
40	VL domain (aa)	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQ HKPWKAPKLLIHAASILQSGVPSRFSGSGSGTEFTLTI SSLQPEDFATYYCQDLNSYPLFGQGTRLEIK
41	Heavy CDR1	GDSVSSNSAA
42	Heavy CDR2	TYYRSKWYN
43	Heavy CDR3	ARDSSSGWHPYGMDV
44	Light CDR1	HDISSY
45	Light CDR2	AAS
46	Light CDR3	QDLNSYPL
47	Heavy FR1	QVQLQQSGPGLVKPSQTLSLTCAIS
48	Heavy FR2	WNWIRQSPSRGLEWLGR
49	Heavy FR3	DYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYC
50	Heavy FR4	WGQGTTVTVSS
51	Light FR1	DIQVTQSPSFLSASVGDRVTITCRAS
52	Light FR2	LAWYQHKPWKAPKLLIH
53	Light FR3	ILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC
54	Light FR4	FGQGTRLEIK
452	Heavy chain (aa) (variable +constant domain). mIgG$_{2b}$	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARDSSSGWHPYGMDVWGQGTT VTVSSAKTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYFPESV TVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQ TVTCSVAHPASSTTVDKKLEPSGPISTINPCPPCKECHKCPAP NLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVSEDDPDVQ ISWFVNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWM SGKEFKCKVNNKDLPSPIERTISKIKGLVRAPQVYILPPPAEQL SRKDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLD

Table C		
SEQ ID NO:	**Description**	**Sequence**
		SDGSYFIYSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSPGK
453	Light chain (aa) (variable +constant domain). mIgG$_{2b}$	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPWKAPKLLIHAASILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQDLNSYPLFGQGTRLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC
454	Heavy chain (aa) (variable + constant domain). hIgG$_1$	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARDSSSGWHPYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
455	Light chain (aa) (variable + constant domain). hIgG$_1$	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPWKAPKLLIHAASILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQDLNSYPLFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Table D		
SEQ ID NO:	**Description**	**Sequence**
107-4.5D		

Table D		
SEQ ID NO:	**Description**	**Sequence**
55	VH domain (nt)	IGHV6-1*01 IGHJ6*02 IGHD6-19*01 CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAA GCCCTCGCAGACCCTCTCACTCACCTGTGCCATCTCCGGG GACAGTGTCTCTAGCAACAGTGCTGCTTGGAACTGGATC AGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAG GACATACTACAGGTCCAAGTGGTATAATGATTATGCAGT ATCTGTGAAAAGTCGAATAACCATCAACCCAGACACATCC AAGAACCAGTTCTCCCTGCAGCTGAACTCTGTGACTCCCG AGGACACGGCTGTGTATTACTGTGCAAGAGATTCTACTA CTGGGTGGAATGCTTACGGTATGGACGTCTGGGGCCAAG GGACCACGGTCACCGTCTCCTCA
56	VL domain (nt)	IGKV1-9*01 IGKJ5*01 GACATCCAGGTGACCCAGTCTCCATCCTTCCTGTCTGCAT CTGTAGGAGACAGAGTCACCATCACTTGCCGGGCCAGTC ACGACATTAGCAGTTATTTAGCCTGGTATCAACACAAACC GTGGAAAGCCCCCAAACTCCTGATCCATGCTGCATCCATT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGAAGTGGA TCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGC CTGAAGATTTTGCAACGTACTACTGTCAAGATCTCAATAG TTATCCTCTCTTCGGCCAAGGGACACGACTGGAGATTAAA
57	VH domain (aa)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARDSTTGWNAYGMDVWGQGTT VTVSS
58	VL domain (aa)	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPW KAPKLLIHAASILQSGVPSRFSGSGSGTEFTLTISSLQPEDFAT YYCQDLNSYPLFGQGTRLEIK
59	Heavy CDR1	GDSVSSNSAA
60	Heavy CDR2	TYYRSKWYN
61	Heavy CDR3	ARDSTTGWNAYGMDV
62	Light CDR1	HDISSY
63	Light CDR2	AAS
64	Light CDR3	QDLNSYPL

Table D		
SEQ ID NO:	**Description**	**Sequence**
65	Heavy FR1	QVQLQQSGPGLVKPSQTLSLTCAIS
66	Heavy FR2	WNWIRQSPSRGLEWLGR
67	Heavy FR3	DYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYC
68	Heavy FR4	WGQGTTVTVSS
69	Light FR1	DIQVTQSPSFLSASVGDRVTITCRAS
70	Light FR2	LAWYQHKPWKAPKLLIH
71	Light FR3	ILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC
72	Light FR4	FGQGTRLEIK

Table E		
SEQ ID NO:	**Description**	**Sequence**
107-4.6D		
73	VH domain (nt)	IGHV6-1*01 IGHJ6*02 IGHD6-19*01 CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAA GCCCTCGCAGACCCTCTCACTCACCTGTGCCATCTCCGGG GACAGTGTCTCTAGCAACAGTGCTGCTTGGAACTGGATC AGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAG GACATACTACAGGTCCAAGTGGTATAATGATTATGCAGT ATCTGTGAAAAGTCGAATAACCATCAACCCAGACACATCC AAGAACCAGTTCTCCCTGCAGCTGAACTCTGTGACTCCCG AGGACACGGCTGTGTATTACTGTGCAAGAGATTCTACGA GTGGGTGGCATCCTTACGGTATGGACGTCTGGGGCCAAG GGACCACGGTCACCGTCTCCTCA
74	VL domain (nt)	IGKV1-9*01 IGKJ5*01

Table E		
SEQ ID NO:	**Description**	**Sequence**
		GACATCCAGGTGACCCAGTCTCCATCCTTCCTGTCTGCAT CTGTAGGAGACAGAGTCACCATCACTTGCCGGGCCAGTC ACGACATTAGCAGTTATTTAGCCTGGTATCAACACAAACC GTGGAAAGCCCCCAAACTCCTGATCCATGCTGCATCCATT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGAAGTGGA TCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGC CTGAAGATTTTGCAACGTACTACTGTCAAGATCTCAATAG TTATCCTCTCTTCGGCCAAGGGACACGACTGGAGATTAAA
75	VH domain (aa)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARDSTSGWHPYGMDVWGQGTT VTVSS
76	VL domain (aa)	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPW KAPKLLIHAASILQSGVPSRFSGSGSGTEFTLTISSLQPEDFAT YYCQDLNSYPLFGQGTRLEIK
77	Heavy CDR1	GDSVSSNSAA
78	Heavy CDR2	TYYRSKWYN
79	Heavy CDR3	ARDSTSGWHPYGMDV
80	Light CDR1	HDISSY
81	Light CDR2	AAS
82	Light CDR3	QDLNSYPL
83	Heavy FR1	QVQLQQSGPGLVKPSQTLSLTCAIS
84	Heavy FR2	WNWIRQSPSRGLEWLGR
85	Heavy FR3	DYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYC
86	Heavy FR4	WGQGTTVTVSS
87	Light FR1	DIQVTQSPSFLSASVGDRVTITCRAS
88	Light FR2	LAWYQHKPWKAPKLLIH

Table E		
SEQ ID NO:	**Description**	**Sequence**
89	Light FR3	ILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC
90	Light FR4	FGQGTRLEIK

Table F		
SEQ ID NO:	**Description**	**Sequence**
107-4.6C		
91	VH domain (nt)	IGHV6-1*01 IGHJ6*02 IGHD6-19*01 CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAA GCCCTCGCAGACCCTCTCACTCACCTGTGCCATCTCCGGG GACAGTGTCTCTAGCAACAGTGCTGCTTGGAACTGGATC AGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAG GACATACTACAGGTCCAAGTGGTATAATGATTATGCAGT ATCTGTGAAAAGTCGAATAACCATCAACCCAGACACATCC AAGAACCAGTTCTCCCTGCAGCTGAACTCTGTGACTCCCG AGGACACGGCTGTGTATTACTGTGCAAGAGATTCGACTA CGGGGTGGGGTGCGTACGGTATGGACGTCTGGGGCCAA GGGACCACGGTCACCGTCTCCTCA
92	VL domain (nt)	IGKV1-9*01 IGKJ5*01 GACATCCAGGTGACCCAGTCTCCATCCTTCCTGTCTGCAT CTGTAGGAGACAGAGTCACCATCACTTGCCGGGCCAGTC ACGACATTAGCAGTTATTTAGCCTGGTATCAACACAAACC GTGGAAAGCCCCCAAACTCCTGATCCATGCTGCATCCATT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGAAGTGGA TCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGC CTGAAGATTTTGCAACGTACTACTGTCAAGATCTCAATAG TTATCCTCTCTTCGGCCAAGGGACACGACTGGAGATTAAA
93	VH domain (aa)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ

Table F		
SEQ ID NO:	**Description**	**Sequence**
		FSLQLNSVTPEDTAVYYCARDSTTGWGAYGMDVWGQGTTVTVSS
94	VL domain (aa)	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPWKAPKLLIHAASILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQDLNSYPLFGQGTRLEIK
95	Heavy CDR1	GDSVSSNSAA
96	Heavy CDR2	TYYRSKWYN
97	Heavy CDR3	ARDSTTGWGAYGMDV
98	Light CDR1	HDISSY
99	Light CDR2	AAS
100	Light CDR3	QDLNSYPL
101	Heavy FR1	QVQLQQSGPGLVKPSQTLSLTCAIS
102	Heavy FR2	WNWIRQSPSRGLEWLGR
103	Heavy FR3	DYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYC
104	Heavy FR4	WGQGTTVTVSS
105	Light FR1	DIQVTQSPSFLSASVGDRVTITCRAS
106	Light FR2	LAWYQHKPWKAPKLLIH
107	Light FR3	ILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC
108	Light FR4	FGQGTRLEIK

Table G		
SEQ ID NO:	**Description**	**Sequence**
107-4.7C		
109	VH domain (nt)	IGHV6-1*01 IGHJ6*02 IGHD6-19*01 CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAA GCCCTCGCAGACCCTCTCACTCACCTGTGCCATCTCCGGG GACAGTGTCTCTAGCAACAGTGCTGCTTGGAACTGGATC AGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAG GACATACTACAGGTCCAAGTGGTATAATGATTATGCAGT ATCTGTGAAAAGTCGAATAACCATCAACCCAGACACATCC AAGAACCAGTTCTCCCTGCAGCTGAACTCTGTGACTCCCG AGGACACGGCTGTGTATTACTGTGCAAGAGATAGGACTA CTGGGTGGCATCCGTACGGTATGGACGTCTGGGGCCAAG GGACCACGGTCACCGTCTCCTCA
110	VL domain (nt)	IGKV1-9*01 IGKJ5*01 GACATCCAGGTGACCCAGTCTCCATCCTTCCTGTCTGCAT CTGTAGGAGACAGAGTCACCATCACTTGCCGGGCCAGTC ACGACATTAGCAGTTATTTAGCCTGGTATCAACACAAACC GTGGAAAGCCCCCAAACTCCTGATCCATGCTGCATCCATT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGAAGTGGA TCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGC CTGAAGATTTTGCAACGTACTACTGTCAAGATCTCAATAG TTATCCTCTCTTCGGCCAAGGGACACGACTGGAGATTAAA
111	VH domain (aa)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARDRTTGWHPYGMDVWGQGTT VTVSS
112	VL domain (aa)	DIQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPW KAPKLLIHAASILQSGVPSRFSGSGSGTEFTLTISSLQPEDFAT YYCQDLNSYPLFGQGTRLEIK
113	Heavy CDR1	GDSVSSNSAA
114	Heavy CDR2	TYYRSKWYN
115	Heavy CDR3	ARDRTTGWHPYGMDV
116	Light CDR1	HDISSY

Table G		
SEQ ID NO:	**Description**	**Sequence**
117	Light CDR2	AAS
118	Light CDR3	QDLNSYPL
119	Heavy FR1	QVQLQQSGPGLVKPSQTLSLTCAIS
120	Heavy FR2	WNWIRQSPSRGLEWLGR
121	Heavy FR3	DYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYC
122	Heavy FR4	WGQGTTVTVSS
123	Light FR1	DIQVTQSPSFLSASVGDRVTITCRAS
124	Light FR2	LAWYQHKPWKAPKLLIH
125	Light FR3	ILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC
126	Light FR4	FGQGTRLEIK

Table H		
SEQ ID NO:	**Description**	**Sequence**
107-5.6A		
127	VH domain (nt)	IGHV6-1*01 IGHJ6*02 IGHD6-19*01 CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAA GCCCTCGCAGACCCTCTCACTCACCTGTGCCATCTCCGGG GACAGTGTCTCTAGCAGCAGTGCTGCTTGGAACTGGATC AGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAG GACATACTACAGGTCCAAGTGGTATAATGATTATGCAGT ATCTGTGAAAAGTCGAATAACCATCAACCCAGACACATCC AAGAACCAGTTCTCCCTGCAGCTGAACTCTGTGACTCCCG AGGACACGGCTGTGTATTACTGTGCAAGAGATAGCAGCA GTGGCTGGCATCCTTACGGTATGGACGTCTGGGGCCAAG

Table H		
SEQ ID NO:	**Description**	**Sequence**
		GGACCACGGTCACCGTCTCCTCA
128	VL domain (nt)	IGKV1-9*01 IGKJ5*01 GACGTCCAGGTGACCCAGTCTCCATCCTTCCTGTCTGCAT CTGTAGGAGACAGAGTCACCATCACTTGCCGGGCCAGTC ACGACATTAGCAGTTATTTAGCCTGGTATCAACACAAACC GTGGAAAGCCCCCAAACTCCTGATCCATGCTGCATCCGTT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGAAGTGGA TCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGC CTGAAGATTTTGCAACGTACTACTGTCAAAATCTCAATAG TTATCCTCTCTTCGGCCAAGGGACACGACTGGAGATTAAA
129	VH domain (aa)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSSSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARDSSSGWHPYGMDVWGQGTT VTVSS
130	VL domain (aa)	DVQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPW KAPKLLIHAASVLQSGVPSRFSGSGSGTEFTLTISSLQPEDFAT YYCQNLNSYPLFGQGTRLEIK
131	Heavy CDR1	GDSVSSSSAA
132	Heavy CDR2	TYYRSKWYN
133	Heavy CDR3	ARDSSSGWHPYGMDV
134	Light CDR1	HDISSY
135	Light CDR2	AAS
136	Light CDR3	QNLNSYPL
137	Heavy FR1	QVQLQQSGPGLVKPSQTLSLTCAIS
138	Heavy FR2	WNWIRQSPSRGLEWLGR
139	Heavy FR3	DYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYC
140	Heavy FR4	WGQGTTVTVSS
141	Light FR1	DVQVTQSPSFLSASVGDRVTITCRAS

Table H		
SEQ ID NO:	**Description**	**Sequence**
142	Light FR2	LAWYQHKPWKAPKLLIH
143	Light FR3	VLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC
144	Light FR4	FGQGTRLEIK

Table I		
SEQ ID NO:	**Description**	**Sequence**
107-15.6A		
145	VH domain (nt)	IGHV6-1*01 IGHJ6*02 IGHD6-19*01 CAGGTACAGCTGCAGCAGTCAGGTCCAGAACTGGTGAA GCCCTCGCAGACCCTCTCACTCACCTGTGCCATCTCCGGG GACAGTGTCTCTAGCAACAGTGCTGCTTGGAACTGGATC AGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAG GACATACTACAGGTCCAAGTGGTATAATGATTATGCAGT ATCTGTGAAAAGTCGAATAACCATCAACCCAGACACATCC AAGAACCAGTTCTCCCTGCAGCTGAACTCTGTGACTCCCG AGGACACGGCTGTGTATTACTGTGCAAGAGATAGCAGCA GTGGCTGGCATCCTTACGGTATGGACGTCTGGGGCCAAG GGACCACGGTCACCGTCTCCTCA
146	VL domain (nt)	IGKV1-9*01 IGKJ5*01 GACATCCGGGTGACCCAGTCTCCATCCTTCCTGTCTGCAT CTGTAGGAGACAGAGTCACCATCACTTGCCGGACCAGTC ACGACATTAGCAGTTATTTAGCCTGGTATCAACACAAACC GTGGAAAGCCCCCAAACTCCTGATCCATGCTGCATCCATT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGAAGTGGA TCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGC CTGAAGATTTTGCAACGTACTACTGTCAAGATCTCAATAG TTATCCTCTCTTCGGCCAAGGGACACGACTGGAGATTAAA
147	VH domain (aa)	QVQLQQSGPELVKPSQTLSLTCAISGDSVSSNSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ

Table I		
SEQ ID NO:	**Description**	**Sequence**
		FSLQLNSVTPEDTAVYYCARDSSSGWHPYGMDVWGQGTTVTVSS
148	VL domain (aa)	DIRVTQSPSFLSASVGDRVTITCRTSHDISSYLAWYQHKPWKAPKLLIHAASILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQDLNSYPLFGQGTRLEIK
149	Heavy CDR1	GDSVSSNSAA
150	Heavy CDR2	TYYRSKWYN
151	Heavy CDR3	ARDSSSGWHPYGMDV
152	Light CDR1	HDISSY
153	Light CDR2	AAS
154	Light CDR3	QDLNSYPL
155	Heavy FR1	QVQLQQSGPELVKPSQTLSLTCAIS
156	Heavy FR2	WNWIRQSPSRGLEWLGR
157	Heavy FR3	DYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYC
158	Heavy FR4	WGQGTTVTVSS
159	Light FR1	DIRVTQSPSFLSASVGDRVTITCRTS
160	Light FR2	LAWYQHKPWKAPKLLIH
161	Light FR3	ILQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC
162	Light FR4	FGQGTRLEIK

Table J		
SEQ ID NO:	**Description**	**Sequence**
206		
163	VH domain (nt)	IGHV1-69*12 IGHJ6*02 IGHD2-8*01 CAGGTCCAGCTTGTGCAGTCTGGGGCTGAGGTGAAGAA GCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG AGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACA GGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCA TCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCA GGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCAC AGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACAC GGCCGTGTATTACTGTGCGAGAGACGTACAGAGGATGG GGATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTC TCCTCA
164	VL domain (nt)	IGKV1-12*01 or IGKV1-12*02 or IGKV1D-12*02 IGKJ4*01 GACATCCAGATGACCCAGTCTCCTTCTTCCGTCTCTACATC TGTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCA GGATATTAGTAACTGGTTAGCCTGGTATCAGCAGAAACC AGGAAAAGCCCCTAAGCTCCTGATCTATGATTCATCCACT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGA TCTGGGACAGATTTCACTCTCACCATCAGCACCCTGCAGC CTGAGGATTTTGCAACTTATTACTGTCAACAGTTTAATAG TTATCCCCTCACTTTCGGCGGAGGGACCAAAGTGGATATC AAA
165	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCARDVQRMGMDVWGQGTTVTVSS
166	VL domain (aa)	DIQMTQSPSSVSTSVGDRVTITCRASQDISNWLAWYQQKP GKAPKLLIYDSSTLQSGVPSRFSGSGSGTDFTLTISTLQPEDFA TYYCQQFNSYPLTFGGGTKVDIK
167	Heavy CDR1	GGTFSSYA
168	Heavy CDR2	IIPIFGTA
169	Heavy CDR3	ARDVQRMGMDV

Table J		
SEQ ID NO:	**Description**	**Sequence**
170	Light CDR1	QDISNW
171	Light CDR2	DSS
172	Light CDR3	QQFNSYPLT
173	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
174	Heavy FR2	ISWVRQAPGQGLEWMGG
175	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
176	Heavy FR4	WGQGTTVTVSS
177	Light FR1	DIQMTQSPSSVSTSVGDRVTITCRAS
178	Light FR2	LAWYQQKPGKAPKLLIY
179	Light FR3	TLQSGVPSRFSGSGSGTDFTLTISTLQPEDFATYYC
180	Light FR4	FGGGTKVDIK
456	Heavy chain (aa) (variable + constant domain). mIgG$_{2b}$	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCARDVQRMGMDVWGQGTTVTVSSAKT TPPSVYPLAPGCGDTTGSSVTLGCLVKGYFPESVTVTWNSG SLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAH PASSTTVDKKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSV FIFPPNIKDVLMISLTPKVTCVVVDVSEDDPDVQISWFVNNV EVHTAQTQTHREDYASTIRVVSTLPIQHQDWMSGKEFKCK VNNKDLPSPIERTISKIKGLVRAPQVYILPPPAEQLSRKDVSLT CLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYFIY SKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSPGK
457	Light chain (aa) (variable + constant domain).	DIQMTQSPSSVSTSVGDRVTITCRASQDISNWLAWYQQKP GKAPKLLIYDSSTLQSGVPSRFSGSGSGTDFTLTISTLQPEDFA TYYCQQFNSYPLTFGGGTKVDIKRADAAPTVSIFPPSSEQLTS

Table J		
SEQ ID NO:	**Description**	**Sequence**
	mIgG$_{2b}$	GGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQ DSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSF NRNEC
458	Heavy chain (aa) (variable + constant domain). hIgG$_1$	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCARDVQRMGMDVWGQGTTVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
459	Light chain (aa) (variable + constant domain). hIgG$_1$	DIQMTQSPSSVSTSVGDRVTITCRASQDISNWLAWYQQKP GKAPKLLIYDSSTLQSGVPSRFSGSGSGTDFTLTISTLQPEDFA TYYCQQFNSYPLTFGGGTKVDIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC

Table K		
SEQ ID NO:	**Description**	**Sequence**
217		

Table K		
SEQ ID NO:	**Description**	**Sequence**
181	VH domain (nt)	IGHV1-69*12 IGHJ4*02 IGHD2-8*01 CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAA GCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG AGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACA GGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCA TCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCA GGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCAC AGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACAC GGCCGTGTATTACTGTGCGAGAGGGGCTATTGGCGTATT CTCGGGCTACTTTGACTACTGGGGCCAGGGAACCCTGGT CACCGTCTCCTCA
182	VL domain (nt)	IGKV4-1*01 IGKJ4*0 GATATTGTGCTGACGCAGACTCCAGACTCCCTGGCTGTGT CTCCGGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCC AGAGTGTTTTATACAGCTCCAACAATAAGAACTACTTAGC TTGGTACCAGCAGAAACCAGGACAGCCTCCTAAGCTGCT CATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGA CCGATTCAGTGGCAGCGGGTCTGGGACAGATtTCACTCTC ACCATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTGTAT TACTGTCAGCAATATTATGATACCCCTCTCACTTTCGGCG GAGGGACCAAGGTGGAGATCAAA
183	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCARGAIGVFSGYFDYWGQGTLVTVSS
184	VL domain (aa)	DIVLTQTPDSLAVSPGERATINCKSSQSVLYSSNNKNYLAWY QQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSL QAEDVAVYYCQQYYDTPLTFGGGTKVEIK
185	Heavy CDR1	GGTFSSYA
186	Heavy CDR2	IIPIFGTA
187	Heavy CDR3	ARGAIGVFSGYFDY
188	Light CDR1	QSVLYSSNNKN
189	Light CDR2	WAS
190	Light CDR3	QQYYDTPLT

Table K		
SEQ ID NO:	**Description**	**Sequence**
191	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
192	Heavy FR2	ISWVRQAPGQGLEWMGG
193	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
194	Heavy FR4	WGQGTLVTVSS
195	Light FR1	DIVLTQTPDSLAVSPGERATINCKSS
196	Light FR2	LAWYQQKPGQPPKLLIY
197	Light FR3	TRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC
198	Light FR4	FGGGTKVEIK

Table L		
SEQ ID NO:	**Description**	**Sequence**
218		
199	VH domain (nt)	IGHV1-69*01 or IGHV1-69D*01 IGHJ4*02 IGHD3-22*01 CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAA GCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG AGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACA GGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCA TCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCA GGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCAC AGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACAC GGCCGTGTATTACTGTGCGAGAGGGTATTACTATGATAG CAGTGCCCTGGACTACTGGGGCCAGGGAACCCTGGTCAC CGTCTCCTCA

Table L		
SEQ ID NO:	**Description**	**Sequence**
200	VL domain (nt)	IGKV2-40*02 IGKJ4*01 or IGKJ4*02 CAGTCTGCTCTGATTCAGCCTGCCTCCGTGTCTGGGTCTC CTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCA GTGACGTTGGTGGTTATGGCTATGTCTCCTGGTACCAACA CCACCCAGGCAAAGCCCCCAAACTCATCATTTATGATGTC TCCAATCGGCCCTCAGGGGTTTCTGATCGCTTCTCTGGCT CCAAGTCTGCCAACACGGCCTCcCTGACCATCTCTGGGCT CCAGACTGAGGACGAGGCTGATTATTACTGCAGCTCATA TACAAGCAGCGGCACTGTGCTCTTCGGCGGAGGGACCAA GCTCACCGTCCTA
201	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCARGYYYDSSALDYWGQGTLVTVSS
202	VL domain (aa)	QSALIQPASVSGSPGQSITISCTGTSSDVGGYGYVSWYQHH PGKAPKLIIYDVSNRPSGVSDRFSGSKSANTASLTISGLQTED EADYYCSSYTSSGTVLFGGGTKLTVL
203	Heavy CDR1	GGTFSSYA
204	Heavy CDR2	IIPIFGTA
205	Heavy CDR3	ARGYYYDSSALDY
206	Light CDR1	GTSSDVGGYG
207	Light CDR2	DVS
208	Light CDR3	SSYTSSGTVL
209	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
210	Heavy FR2	ISWVRQAPGQGLEWMGG
211	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
212	Heavy FR4	WGQGTLVTVSS
213	Light FR1	QSALIQPASVSGSPGQSITISCT
214	Light FR2	VSWYQHHPGKAPKLIIY

Table L		
SEQ ID NO:	**Description**	**Sequence**
215	Light FR3	NRPSGVSDRFSGSKSANTASLTISGLQTEDEADYYC
216	Light FR4	FGGGTKLTVL

Table M		
SEQ ID NO:	**Description**	**Sequence**
220		
217	VH domain (nt)	IGHV1-69*01 or IGHV1-69D*01 IGHJ4*02 IGHD2-15*01 CAGGTGCAGctgGTGGAATCTGGGGCTGAGGTGAAGAAG CCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGA GGCACCTTCAGCAGCTATGCTATCAGCTGGgtGCGACAGG CCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATC CCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGG GCAGAGCCACGATTACCGCGGACGAATCCACGAGCACAG CCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGG CCGTGTATTACTGTGCGAGAGGCCGAAATACCTATTGTA GTGGTGGTAGCTGCTACTCCCCGCACTTTGACTACTGGG GCCAGGGAACCCTGGTCACCGTCTCCTCA
218	VL domain (nt)	IGKV1-33*01 or IGKV1D-33*01 IGKJ4*01 GACATCCAGGTGACCCAGTCTCCATCCTCCCTGTCTGCAT CTGTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTC AGGACATTAGCAACTATTTAAATTGGTATCAGCAGAAACC AGGGAAAGCCCCTAAGCTCCTGATCTACGATGCATCCAA TTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGG ATCTGGGACAGATTTTACTTTCACCATCAGCAGCCTGCAG CCTGAAGATATTGCAACATATTACTGTCAACAGTATGATA ATCTCCCAACTTTCGGCGGAGGGACCAAGGTGGAGATCA AA
219	VH domain (aa)	QVQLVESGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRATITADESTSTAYME

Table M		
SEQ ID NO:	**Description**	**Sequence**
		LSSLRSEDTAVYYCARGRNTYCSGGSCYSPHFDYWGQGTLV TVSS
220	VL domain (aa)	DIQVTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIAT YYCQQYDNLPTFGGGTKVEIK
221	Heavy CDR1	GGTFSSYA
222	Heavy CDR2	IIPIFGTA
223	Heavy CDR3	ARGRNTYCSGGSCYSPHFDY
224	Light CDR1	QDISNY
225	Light CDR2	DAS
226	Light CDR3	QQYDNLPT
227	Heavy FR1	QVQLVESGAEVKKPGSSVKVSCKAS
228	Heavy FR2	ISWVRQAPGQGLEWMGG
229	Heavy FR3	NYAQKFQGRATITADESTSTAYMELSSLRSEDTAVYYC
230	Heavy FR4	WGQGTLVTVSS
231	Light FR1	DIQVTQSPSSLSASVGDRVTITCQAS
232	Light FR2	LNWYQQKPGKAPKLLIY
233	Light FR3	NLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYYC
234	Light FR4	FGGGTKVEIK
460	Heavy chain (aa) (variable + constant domain). $mIgG_{2b}$	QVQLVESGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRATITADESTSTAYME LSSLRSEDTAVYYCARGRNTYCSGGSCYSPHFDYWGQGTLV TVSSAKTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYFPESVT VTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQT

Table M

SEQ ID NO:	Description	Sequence
		VTCSVAHPASSTTVDKKLEPSGPISTINPCPPCKECHKCPAPN LEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVSEDDPDVQIS WFVNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWMS GKEFKCKVNNKDLPSPIERTISKIKGLVRAPQVYILPPPAEQLS RKDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDS DGSYFIYSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTIS RSPGK
461	Light chain (aa) (variable + constant domain). $mIgG_{2b}$	DIQVTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIAT YYCQQYDNLPTFGGGTKVEIKRADAAPTVSIFPPSSEQLTSG GASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDS KDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNR NEC
462	Heavy chain (aa) (variable + constant domain). $hIgG_1$	QVQLVESGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRATITADESTSTAYME LSSLRSEDTAVYYCARGRNTYCSGGSCYSPHFDYWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK
463	Light chain (aa) (variable + constant domain). $hIgG_1$	DIQVTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIAT YYCQQYDNLPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR

Table M		
SEQ ID NO:	**Description**	**Sequence**
		GEC

Table N		
SEQ ID NO:	**Description**	**Sequence**
221		
235	VH domain (nt)	IGHV1-69*01 or IGHV1-69D*01 IGHJ4*02 IGHD6-19*01 CAGgtGCAGCTGGTGGAATCTGGGGCTGAGGTGAAGAAGCCTG GGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTT CAGCAGCTATGCTATCAGCTGGGTGCGACAGGCCCCTGGACAA GGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAG CAAACTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGC GGACGAATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTG AGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGAGTG CCGTCCGGGTATAGCAGTGGCTGGTTTTACTACTTTGACTACTG GGGCCAGGGAACCCTGGTCACCGTCTCCTCA
236	VL domain (nt)	IGKV3-15*01 IGKJ1*01 GAAATTGTGATGACACAGTCTCCATCCTCCCTGTCTGCATCTGT AGGAGACAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTT AACACCAACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTC CCAGGCTCCTCATCTATGGTGCATCTACCAGGGCCACTGGTAGC CCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGAGTTCACTC TCACCATCAGCAGCCTGCAGCCTGGTGATTTTGCAACTTATTAC TGCCAACAGTATGATAATTATCCCCTGACGTTCGGCCAAGGGA CCAAGGTGGAAATCAAA
237	VH domain (aa)	QVQLVESGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGL EWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDT AVYYCARGVPSGYSSGWFYYFDYWGQGTLVTVSS
238	VL domain (aa)	EIVMTQSPSSLSASVGDRATLSCRASQSVNTNLAWYQQKPGQAP RLLIYGASTRATGSPARFSGSGSGTEFTLTISSLQPGDFATYYCQQY DNYPLTFGQGTKVEIK
239	Heavy CDR1	GGTFSSYA

Table N		
SEQ ID NO:	**Description**	**Sequence**
240	Heavy CDR2	IIPIFGTA
241	Heavy CDR3	ARGVPSGYSSGWFYYFDY
242	Light CDR1	QSVNTN
243	Light CDR2	GAS
244	Light CDR3	QQYDNYPLT
245	Heavy FR1	QVQLVESGAEVKKPGSSVKVSCKAS
246	Heavy FR2	ISWVRQAPGQGLEWMGG
247	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
248	Heavy FR4	WGQGTLVTVSS
249	Light FR1	EIVMTQSPSSLSASVGDRATLSCRAS
250	Light FR2	LAWYQQKPGQAPRLLIY
251	Light FR3	TRATGSPARFSGSGSGTEFTLTISSLQPGDFATYYC
252	Light FR4	FGQGTKVEIK

Table O		
SEQ ID NO:	**Description**	**Sequence**
223		
253	VH domain (nt)	IGHV1-69*1 IGHJ6*02 IGHD2-15*01

Table O		
SEQ ID NO:	**Description**	**Sequence**
		CAGGTCCAGCTGgtACAGTCTGGGGCTGAGGTGAAGAAG CCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGA GGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAG GCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCAT CCCTATCTTTGGTACAGTAAACTACGCACAGAAGTTCCAG GGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACA GCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACG GCCGTGTATTACTGTGCGAGAGTCGCGGTTATTCCCCCG GACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACC ACGGTCACCGTCTCCTCA
254	VL domain (nt)	IGKV3-15*01 IGKJ3*01 GAAACGACACTCACGCAGTCTCCAGCCACCCTGTCTGTGT CTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTC AGAGTGTTAGCAGCAACTTAGCCTGGTACCAGCAGAGAC CTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAC CAGGGCCGCTGGTATCCCAGTCAGGTTCAGTGGCAGTGG GTCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCA GTCTGAAGATTTTGCAGTTTATTACTGTCAGCACTATGAT AACTGGCCTCCGCGATTCACTTTCGGCCCTGGGACCAAA GTGGATATTAAA
255	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTVNYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCARVAVIPPDYYYGMDVWGQGTTVTVSS
256	VL domain (aa)	ETTLTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQRPG QAPRLLIYGASTRAAGIPVRFSGSGSGTEFTLTISSLQSEDFAV YYCQHYDNWPPRFTFGPGTKVDIK
257	Heavy CDR1	GGTFSSYA
258	Heavy CDR2	IIPIFGTV
259	Heavy CDR3	ARVAVIPPDYYYGMDV
260	Light CDR1	QSVSSN
261	Light CDR2	GAS
262	Light CDR3	QHYDNWPPRFT
263	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
264	Heavy FR2	ISWVRQAPGQGLEWMGG

Table O		
SEQ ID NO:	**Description**	**Sequence**
265	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
266	Heavy FR4	WGQGTTVTVSS
267	Light FR1	ETTLTQSPATLSVSPGERATLSCRAS
268	Light FR2	LAWYQQRPGQAPRLLIY
269	Light FR3	TRAAGIPVRFSGSGSGTEFTLTISSLQSEDFAVYYC
270	Light FR4	FGPGTKVDIK

Table P		
SEQ ID NO:	**Description**	**Sequence**
226		
271	VH domain (nt)	IGHV1-69*12 IGHJ1*01 IGHD3-10*01 CAGGTCCAGctgGTGCAGTCTGGGGCTGAGGTGAAGAAG CCTGGGTCCTCGGTGAAGGTCTCATGCAAGGCTTCTGGA GGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAG GCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCAT CCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAG GGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACA GCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACG GCCGTGTATTACTGTGCGAGGGGAGCCGGCCCGTTATGG TTCAGGGAGTTAGTGTACTTCCAGCACTGGGGCCAGGGA ACCCTGGTCACCGTCTCCTCA
272	VL domain (nt)	IGKV3-15*01 IGKJ3*0 GAAATTGTGATGACGCAGTCTCCAGCCACTCTGTCTGTGT CTCCAGGGGAGAGGGCCACCCTCTCCTGCAGGGTCAGTC AGAATATAATAAAAAACTTAGCCTGGTACCAACAGAAAC CTGGCCAGGCTCCCAGGCTCCTCATTTATGATGCCTCCAC CAGGGCCACTGGTATCCCAGCCAGGTTCACTGGCAGTGG GTCTGGGACAGAGTTCACTCTCACCATCGACGACCTGCA

Table P		
SEQ ID NO:	**Description**	**Sequence**
		GTCTGAAGATTCTGCAGTTTATTTCTGTCAGCAGTACAATTGGTGGCCTCGTTTCGGCCCTGGGACCAAAGTGGATATCAAA
273	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGAGPLWFRELVYFQHWGQGTLVTVSS
274	VL domain (aa)	EIVMTQSPATLSVSPGERATLSCRVSQNIIKNLAWYQQKPGQAPRLLIYDASTRATGIPARFTGSGSGTEFTLTIDDLQSEDSAVYFCQQYNWWPRFGPGTKVDIK
275	Heavy CDR1	GGTFSSYA
276	Heavy CDR2	IIPIFGTA
277	Heavy CDR3	ARGAGPLWFRELVYFQH
278	Light CDR1	QNIIKN
279	Light CDR2	DAS
280	Light CDR3	QQYNWWPR
281	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
282	Heavy FR2	ISWVRQAPGQGLEWMGG
283	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
284	Heavy FR4	WGQGTLVTVSS
285	Light FR1	EIVMTQSPATLSVSPGERATLSCRVS
286	Light FR2	LAWYQQKPGQAPRLLIY
287	Light FR3	TRATGIPARFTGSGSGTEFTLTIDDLQSEDSAVYFC
288	Light FR4	FGPGTKVDIK

Table Q		
SEQ ID NO:	**Description**	**Sequence**
228		
289	VH domain (nt)	IGHV1-69*01 or IGHV1-69D*01 IGHJ6*02 IGHD3-3*01 CAGGTGCAGCTGGTGCAATCTGGGGCTGAGGTGAAGAA GCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG AGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACA GGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCA TCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCA GGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCAC AGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACAC GGCCGTGTATTACTGTGCGAGAGGCCAGGTTTTGATCTG GACGTACTACTACGGTATGGACGTCTGGGGCCAAGGGAC CACGGTCACCGTCTCCTCA
290	VL domain (nt)	IGKV1-33*01 or IGKV1D-33*01 IGKJ4*01 GACATCCGGTTGACCCAGTCTCCATCCTCCCTGTCTGCAT CTGTAGGAGATAGAGTCACCATCACTTGCCAGGCGAGTC AGGACATTAGCAACTATTTAAATTGGTATCAGCAGAAACC AGGGAAAGCCCCTAAGCTCCTGATCTACGATGCATCCAA TTTAGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGG ATCTGGGACAGATTTTACTTTCATCATCAGCAGCCTGCAG CCTGAAGATATTGCAACATATTACTGTCAACAGTATGATA ATCTCCCGCTCACTTTCGGTGGAGGGACCAAGCTGGAGA TCAAA
291	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCARGQVLIWTYYYGMDVWGQGTTVTVS S
292	VL domain (aa)	DIRLTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFIISSLQPEDIAT YYCQQYDNLPLTFGGGTKLEIK
293	Heavy CDR1	GGTFSSYA
294	Heavy CDR2	IIPIFGTA
295	Heavy CDR3	ARGQVLIWTYYYGMDV
296	Light CDR1	QDISNY

Table Q		
SEQ ID NO:	**Description**	**Sequence**
297	Light CDR2	DAS
298	Light CDR3	QQYDNLPLT
299	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
300	Heavy FR2	ISWVRQAPGQGLEWMGG
301	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
302	Heavy FR4	WGQGTTVTVSS
303	Light FR1	DIRLTQSPSSLSASVGDRVTITCQAS
304	Light FR2	LNWYQQKPGKAPKLLIY
305	Light FR3	NLETGVPSRFSGSGSGTDFTFIISSLQPEDIATYYC
306	Light FR4	FGGGTKLEIK
464	Heavy chain (aa) (variable + constant domain). mIgG$_{2b}$	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCARGQVLIWTYYYGMDVWGQGTTVTVS SAKTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYFPESVTVTW NSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCS VAHPASSTTVDKKLEPSGPISTINPCPPCKECHKCPAPNLEG GPSVFIFPPNIKDVLMISLTPKVTCVVVDVSEDDPDVQISWF VNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWMSGKE FKCKVNNKDLPSPIERTISKIKGLVRAPQVYILPPPAEQLSRKD VSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGS YFIYSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSP GK
465	Light chain (aa)	DIRLTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG

Table Q		
SEQ ID NO:	**Description**	**Sequence**
	(variable + constant domain). mIgG$_{2b}$	KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFIISSLQPEDIAT YYCQQYDNLPLTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSG GASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDS KDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNR NEC
466	Heavy chain (aa) (variable + constant domain). hIgG$_1$	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP GQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCARGQVLIWTYYYGMDVWGQGTTVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
467	Light chain (aa) (variable + constant domain). hIgG$_1$	DIRLTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFIISSLQPEDIAT YYCQQYDNLPLTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC

Table R		
SEQ ID NO:	**Description**	**Sequence**
206-2.B11		

Table R		
SEQ ID NO:	**Description**	**Sequence**
307	VH domain (nt)	IGHV1-69*12 IGHJ6*02 IGHD2-8*01 CAGGTCCAGCTTGTGCAGTCTGGGGCTGAGGTGAAGAA GCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG AGGCACCTCTACGGGTTTTATTGGTGCTATCAGCTGGGTG CGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGG GATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAG TTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACG AGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAG GACACGGCCGTGTATTACTGTGCGAGAGACGTACAGAG GATGGGGATGGACGTCTGGGGCCAAGGGACCACGGTCA CCGTCTCCTCA
308	VL domain (nt)	IGKV1-12*01 OR IGKV1-12*02 OR IGKV1D-12*02 IGKJ4*01 GACATCCAGATGACCCAGTCTCCTTCTTCCGTCTCTACATC TGTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCA GGATATTAGTAACTGGTTAGCCTGGTATCAGCAGAAACC AGGAAAAGCCCCTAAGCTCCTGATCTATGATTCATCCACT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGA TCTGGGACAGATTTCACTCTCACCATCAGCACCCTGCAGC CTGAGGATTTTGCAACTTATTACTGTCAACAGTTTAATAG TTATCCCCTCACTTTCGGCGGAGGGACCAAAGTGGATATC AAA
309	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTSTGFIGAISWVRQ APGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAY MELSSLRSEDTAVYYCARDVQRMGMDVWGQGTTVTVSS
310	VL domain (aa)	DIQMTQSPSSVSTSVGDRVTITCRASQDISNWLAWYQQKP GKAPKLLIYDSSTLQSGVPSRFSGSGSGTDFTLTISTLQPEDFA TYYCQQFNSYPLTFGGGTKVDIK
311	Heavy CDR1	GGTSTGFIGA
312	Heavy CDR2	IIPIFGTA
313	Heavy CDR3	ARDVQRMGMDV
314	Light CDR1	QDISNW
315	Light CDR2	DSS
316	Light CDR3	QQFNSYPLT

Table R		
SEQ ID NO:	**Description**	**Sequence**
317	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
318	Heavy FR2	ISWVRQAPGQGLEWMGG
319	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
320	Heavy FR4	WGQGTTVTVSS
321	Light FR1	DIQMTQSPSSVSTSVGDRVTITCRAS
322	Light FR2	LAWYQQKPGKAPKLLIY
323	Light FR3	TLQSGVPSRFSGSGSGTDFTLTISTLQPEDFATYYC
324	Light FR4	FGGGTKVDIK

Table S		
SEQ ID NO:	**Description**	**Sequence**
206-3.D8		
325	VH domain (nt)	IGHV1-69*12 IGHJ6*02 IGHD2-8*01 CAGGTCCAGCTTGTGCAGTCTGGGGCTGAGGTGAAGAA GCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG AGGCACCTTTCAGTCTTATTATGGGGCTATCAGCTGGGTG CGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGG GATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAG TTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACG AGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAG GACACGGCCGTGTATTACTGTGCGAGAGACGTACAGAG GATGGGGATGGACGTCTGGGGCCAAGGGACCACGGTCA CCGTCTCCTCA
326	VL domain (nt)	IGKV1-12*01 OR IGKV1-12*02 OR IGKV1D-12*02 IGKJ4*01 GACATCCAGATGACCCAGTCTCCTTCTTCCGTCTCTACATC TGTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCA

Table S		
SEQ ID NO:	**Description**	**Sequence**
		GGATATTAGTAACTGGTTAGCCTGGTATCAGCAGAAACC AGGAAAAGCCCCTAAGCTCCTGATCTATGATTCATCCACT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGA TCTGGGACAGATTTCACTCTCACCATCAGCACCCTGCAGC CTGAGGATTTTGCAACTTATTACTGTCAACAGTTTAATAG TTATCCCCTCACTTTCGGCGGAGGGACCAAAGTGGATATC AAA
327	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFQSYYGAISWVR QAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTA YMELSSLRSEDTAVYYCARDVQRMGMDVWGQGTTVTVSS
328	VL domain (aa)	DIQMTQSPSSVSTSVGDRVTITCRASQDISNWLAWYQQKP GKAPKLLIYDSSTLQSGVPSRFSGSGSGTDFTLTISTLQPEDFA TYYCQQFNSYPLTFGGGTKVDIK
329	Heavy CDR1	GGTFQSYYGA
330	Heavy CDR2	IIPIFGTA
331	Heavy CDR3	ARDVQRMGMDV
332	Light CDR1	QDISNW
333	Light CDR2	DSS
334	Light CDR3	QQFNSYPLT
335	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
336	Heavy FR2	ISWVRQAPGQGLEWMGG
337	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
338	Heavy FR4	WGQGTTVTVSS
339	Light FR1	DIQMTQSPSSVSTSVGDRVTITCRAS
340	Light FR2	LAWYQQKPGKAPKLLIY
341	Light FR3	TLQSGVPSRFSGSGSGTDFTLTISTLQPEDFATYYC
342	Light FR4	FGGGTKVDIK

Table T		
SEQ ID NO:	**Description**	**Sequence**
206-3.C7		
343	VH domain (nt)	IGHV1-69*12 IGHJ6*02 IGHD2-8*01 CAGGTCCAGCTTGTGCAGTCTGGGGCTGAGGTGAAGAA GCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG AGGCACCAATTTGATGGGGTATTATGGTGCTATCAGCTG GGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGG GAGGGATCATCCCTATCTTTGGTACAGCAAACTACGCACA GAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATC CACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATC TGAGGACACGGCCGTGTATTACTGTGCGAGAGACGTACA GAGGATGGGGATGGACGTCTGGGGCCAAGGGACCACG GTCACCGTCTCCTCA
344	VL domain (nt)	IGKV1-12*01 OR IGKV1-12*02 OR IGKV1D-12*02 IGKJ4*01 GACATCCAGATGACCCAGTCTCCTTCTTCCGTCTCTACATC TGTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCA GGATATTAGTAACTGGTTAGCCTGGTATCAGCAGAAACC AGGAAAAGCCCCTAAGCTCCTGATCTATGATTCATCCACT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGA TCTGGGACAGATTTCACTCTCACCATCAGCACCCTGCAGC CTGAGGATTTTGCAACTTATTACTGTCAACAGTTTAATAG TTATCCCCTCACTTTCGGCGGAGGGACCAAAGTGGATATC AAA
345	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTNLMGYYGAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTST AYMELSSLRSEDTAVYYCARDVQRMGMDVWGQGTTVTV SS
346	VL domain (aa)	DIQMTQSPSSVSTSVGDRVTITCRASQDISNWLAWYQQKP GKAPKLLIYDSSTLQSGVPSRFSGSGSGTDFTLTISTLQPEDFA TYYCQQFNSYPLTFGGGTKVDIK
347	Heavy CDR1	GGTNLMGYYGA
348	Heavy CDR2	IIPIFGTA
349	Heavy CDR3	ARDVQRMGMDV
350	Light CDR1	QDISNW

Table T		
SEQ ID NO:	**Description**	**Sequence**
351	Light CDR2	DSS
352	Light CDR3	QQFNSYPLT
353	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
354	Heavy FR2	ISWVRQAPGQGLEWMGG
355	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
356	Heavy FR4	WGQGTTVTVSS
357	Light FR1	DIQMTQSPSSVSTSVGDRVTITCRAS
358	Light FR2	LAWYQQKPGKAPKLLIY
359	Light FR3	TLQSGVPSRFSGSGSGTDFTLTISTLQPEDFATYYC
360	Light FR4	FGGGTKVDIK

Table U		
SEQ ID NO:	**Description**	**Sequence**
206-3.C11		
361	VH domain (nt)	IGHV1-69*12 IGHJ6*02 IGHD2-8*01 CAGGTCCAGCTTGTGCAGTCTGGGGCTGAGGTGAAGAA GCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG AGGCACCGTTAGGTCTAGGGTTCATGCTATCAGCTGGGT GCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAG GGATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAA GTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCAC GAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGA GGACACGGCCGTGTATTACTGTGCGAGAGACGTACAGA GGATGGGGATGGACGTCTGGGGCCAAGGGACCACGGTC

Table U		
SEQ ID NO:	**Description**	**Sequence**
		ACCGTCTCCTCA
362	VL domain (nt)	IGKV1-12*01 OR IGKV1-12*02 OR IGKV1D-12*02 IGKJ4*01 GACATCCAGATGACCCAGTCTCCTTCTTCCGTCTCTACATC TGTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCA GGATATTAGTAACTGGTTAGCCTGGTATCAGCAGAAACC AGGAAAAGCCCCTAAGCTCCTGATCTATGATTCATCCACT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGA TCTGGGACAGATTTCACTCTCACCATCAGCACCCTGCAGC CTGAGGATTTTGCAACTTATTACTGTCAACAGTTTAATAG TTATCCCCTCACTTTCGGCGGAGGGACCAAAGTGGATATC AAA
363	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTVRSRVHAISWVR QAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTA YMELSSLRSEDTAVYYCARDVQRMGMDVWGQGTTVTVSS
364	VL domain (aa)	DIQMTQSPSSVSTSVGDRVTITCRASQDISNWLAWYQQKP GKAPKLLIYDSSTLQSGVPSRFSGSGSGTDFTLTISTLQPEDFA TYYCQQFNSYPLTFGGGTKVDIK
365	Heavy CDR1	GGTVRSRVHA
366	Heavy CDR2	IIPIFGTA
367	Heavy CDR3	ARDVQRMGMDV
368	Light CDR1	QDISNW
369	Light CDR2	DSS
370	Light CDR3	QQFNSYPLT
371	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
372	Heavy FR2	ISWVRQAPGQGLEWMGG
373	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
374	Heavy FR4	WGQGTTVTVSS
375	Light FR1	DIQMTQSPSSVSTSVGDRVTITCRAS
376	Light FR2	LAWYQQKPGKAPKLLIY

Table U		
SEQ ID NO:	**Description**	**Sequence**
377	Light FR3	TLQSGVPSRFSGSGSGTDFTLTISTLQPEDFATYYC
378	Light FR4	FGGGTKVDIK

Table V		
SEQ ID NO:	**Description**	**Sequence**
206-3.F6		
379	VH domain (nt)	IGHV1-69*12 IGHJ6*02 IGHD2-8*01 CAGGTCCAGCTTGTGCAGTCTGGGGCTGAGGTGAAGAA GCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG AGGCACCGGGTCGGAGTTTATGGGTGCTATCAGCTGGGT GCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAG GGATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAA GTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCAC GAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGA GGACACGGCCGTGTATTACTGTGCGAGAGACGTACAGA GGATGGGGATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCCTCA
380	VL domain (nt)	IGKV1-12*01 OR IGKV1-12*02 OR IGKV1D-12*02 IGKJ4*01 GACATCCAGATGACCCAGTCTCCTTCTTCCGTCTCTACATC TGTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCA GGATATTAGTAACTGGTTAGCCTGGTATCAGCAGAAACC AGGAAAAGCCCCTAAGCTCCTGATCTATGATTCATCCACT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGA TCTGGGACAGATTTCACTCTCACCATCAGCACCCTGCAGC CTGAGGATTTTGCAACTTATTACTGTCAACAGTTTAATAG TTATCCCCTCACTTTCGGCGGAGGGACCAAAGTGGATATC AAA
381	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTGSEFMGAISWVR QAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTA YMELSSLRSEDTAVYYCARDVQRMGMDVWGQGTTVTVSS

Table V		
SEQ ID NO:	**Description**	**Sequence**
382	VL domain (aa)	DIQMTQSPSSVSTSVGDRVTITCRASQDISNWLAWYQQKP GKAPKLLIYDSSTLQSGVPSRFSGSGSGTDFTLTISTLQPEDFA TYYCQQFNSYPLTFGGGTKVDIK
383	Heavy CDR1	GGTGSEFMGA
384	Heavy CDR2	IIPIFGTA
385	Heavy CDR3	ARDVQRMGMDV
386	Light CDR1	QDISNW
387	Light CDR2	DSS
388	Light CDR3	QQFNSYPLT
389	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
390	Heavy FR2	ISWVRQAPGQGLEWMGG
391	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
392	Heavy FR4	WGQGTTVTVSS
393	Light FR1	DIQMTQSPSSVSTSVGDRVTITCRAS
394	Light FR2	LAWYQQKPGKAPKLLIY
395	Light FR3	TLQSGVPSRFSGSGSGTDFTLTISTLQPEDFATYYC
396	Light FR4	FGGGTKVDIK

Table W		
SEQ ID NO:	**Description**	**Sequence**
206-12.F6		

Table W		
SEQ ID NO:	**Description**	**Sequence**
397	VH domain (nt)	IGHV1-69*12 IGHJ6*02 IGHD2-8*01 CAGGTCCAGCTTGTGCAGTCTGGGGCTGAGGTGAAGAA GCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG AGGCACCTATAATCCGGGTGTGTCTGCTATCAGCTGGGT GCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAG GGATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAA GTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCAC GAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGA GGACACGGCCGTGTATTACTGTGCGAGAGACGTACAGA GGATGGGGATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCCTCA
398	VL domain (nt)	IGKV1-12*01 OR IGKV1-12*02 OR IGKV1D-12*02 IGKJ4*01 GACATCCAGATGACCCAGTCTCCTTCTTCCGTCTCTACATC TGTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCA GGATATTAGTAACTGGTTAGCCTGGTATCAGCAGAAACC AGGAAAAGCCCCTAAGCTCCTGATCTATGATTCATCCACT TTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGA TCTGGGACAGATTTCACTCTCACCATCAGCACCCTGCAGC CTGAGGATTTTGCAACTTATTACTGTCAACAGTTTAATAG TTATCCCCTCACTTTCGGCGGAGGGACCAAAGTGGATATC AAA
399	VH domain (aa)	QVQLVQSGAEVKKPGSSVKVSCKASGGTYNPGVSAISWVR QAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTA YMELSSLRSEDTAVYYCARDVQRMGMDVWGQGTTVTVSS
400	VL domain (aa)	DIQMTQSPSSVSTSVGDRVTITCRASQDISNWLAWYQQKP GKAPKLLIYDSSTLQSGVPSRFSGSGSGTDFTLTISTLQPEDFA TYYCQQFNSYPLTFGGGTKVDIK
401	Heavy CDR1	GGTYNPGVSA
402	Heavy CDR2	IIPIFGTA
403	Heavy CDR3	ARDVQRMGMDV
404	Light CDR1	QDISNW
405	Light CDR2	DSS
406	Light CDR3	QQFNSYPLT

Table W		
SEQ ID NO:	**Description**	**Sequence**
407	Heavy FR1	QVQLVQSGAEVKKPGSSVKVSCKAS
408	Heavy FR2	ISWVRQAPGQGLEWMGG
409	Heavy FR3	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC
410	Heavy FR4	WGQGTTVTVSS
411	Light FR1	DIQMTQSPSSVSTSVGDRVTITCRAS
412	Light FR2	LAWYQQKPGKAPKLLIY
413	Light FR3	TLQSGVPSRFSGSGSGTDFTLTISTLQPEDFATYYC
414	Light FR4	FGGGTKVDIK

Table X presents certain consensus amino acid sequences.

Table X		
SEQ ID NO:	**Description**	**Sequence**
415	VL CDR3 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α1a antigen binding proteins described herein (in Tables A-I and AA)	$QX_2LNSYPLX_9X_{10}$ wherein X_2 can be any amino acid; X_9 can be any amino acid or no amino acid; and X_{10} can be any amino acid or no amino acid.
416	VL CDR3 consensus sequence relating to certain of the specifically described HLA-DQ2.5-gliadin-α1a antigen binding proteins described herein (in Tables A-G and I)	$QX_2LNSYPLX_9X_{10}$ wherein X_2 is Q or D; X_9 is no amino acid or L; and X_{10} is no amino acid or T.

417	VH CDR3 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α1a antigen binding proteins described herein (Tables A-I and AA)	$ARDX_4X_5X_6GWX_9X_{10}YGMDV$ wherein X_4 can be any amino acid; X_5 can be any amino acid; X_6 can be any amino acid; X_9 can be any amino acid; and X_{10} can be any amino acid;
418	VH CDR3 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α1a antigen binding proteins described herein (Tables A-I and AA)	$ARDX_4X_5X_6GWX_9X_{10}YGMDV$ wherein X_4 is S or R; X_5 is S or T ; X_6 is S or T; X_9 is H or N or G; X_{10} is P or A;
419	VL CDR1 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins described herein (Tables J-W)	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ wherein X_1 is Q or G; X_2 is D or S or T or N; X_3 is I or V or S; X_4 is S or L or N or I; X_5 is N or S or Y or D or T or K; X_6 is W or N or S or V or Y; X_7 is no amino acid or any amino acid; X_8 is no amino acid or any amino acid; X_9 is no amino acid or any amino acid; X_{10} is no amino acid or any amino acid; X_{11} is no amino acid or any amino acid; X_{12} is no amino acid or any amino acid.
420	VL CDR1 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins described herein (Tables J-W)	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ wherein X_1 is Q or G X_2 is D or S or T or N X_3 is I or V or S X_4 is S or L or N or I

		X_5 is N or S or Y or D or T or K X_6 is W or N or S or V or Y X_7 is no amino acid or S or G; X_8 is no amino acid or N or G; X_9 is no amino acid or N or Y; X_{10} is no amino acid or K or G. X_{11} is no amino acid or N or Y; $X_{12\ is}$ no amino acid or Y.
421	VL CDR2 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins described herein (Tables J-W)	X_1X_2S wherein X_1 can be any amino acid; X_2 can be any amino acid.
422	VL CDR2 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins described herein (Tables J-W)	X_1X_2S wherein X_1 is D or G or W; X_2 is S or A or V.
423	VL CDR3 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins described herein (Tables J-W)	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}$ wherein X_1 is Q or S X_2 is Q or S or H X_3 is F or Y X_4 is N or Y or D or T X_5 is S or N or D or W X_6 is Y or W or T or S or L X_7 is P or G X_8 is L or T or P or R X_9 is no amino acid or any amino acid X_{10} is no amino acid or any amino acid X_{11} is no amino acid or any amino acid
424	VL CDR3 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins described herein (Tables J-W)	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}$ wherein X_1 is Q or S X_2 is Q or S or H X_3 is F or Y X_4 is N or Y or D or T X_5 is S or N or D or W X_6 is Y or W or T or S or L X_7 is P or G

		X_8 is L or T or P or R X_9 is no amino acid or T or V or R X_{10} is no amino acid or L or F X_{11} is no amino acid or T
425	VH CDR1 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins described herein (Tables J-W)	$GGTX_4X_5X_6X_7X_8X_9X_{10}X_{11}$ wherein X_4 is F or S or N or V or G or Y X_5 is S or T or Q or L or R or N X_6 is S or G or M or E or P X_7 is Y or F or G or R X_8 is A or G or I or Y or V or M X_9 is no amino acid or any amino acid X_{10} is no amino acid or any amino acid X_{11} is no amino acid or any amino acid
426	VH CDR1 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins described herein (Tables J-W)	$GGTX_4X_5X_6X_7X_8X_9X_{10}X_{11}$ wherein X_4 is F or S or N or V or G or Y X_5 is S or T or Q or L or R or N X_6 is S or G or M or E or P X_7 is Y or F or G or R X_8 is A or G or I or Y or V or M X_9 is no amino acid or G or Y or H or S X_{10} is no amino acid or A or G X_{11} is no amino acid or A
427	VH CDR2 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins described herein (Tables J-W)	$IIPIFGTX_8$ wherein X_8 can be any amino acid
428	VH CDR2 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins described herein (Tables J-W)	$IIPIFGTX_8$ wherein X_8 is A or V
429	VH CDR3 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins	$ARX_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}$ wherein X_3 is D or V or G

	described herein (Tables J-W)	X_4 is V or A or Y or R or Q X_5 is Q or I or Y or N or P or V or G X_6 is R or G or Y or T or S or I or P or L X_7 is M or G or V or D or Y or P or L or I X_8 is G or F or S or C or Y or P or W X_9 is M or F or S or D or T X_{10} is D or G or A or S or Y or R X_{11} is V or Y or L or G or E X_{12} is no amino acid or any amino acid X_{13} is no amino acid or any amino acid X_{14} is no amino acid or any amino acid X_{15} is no amino acid or any amino acid X_{16} is no amino acid or any amino acid X_{17} is no amino acid or any amino acid X_{18} is no amino acid or any amino acid X_{19} is no amino acid or any amino acid X_{20} is no amino acid or any amino acid
430	VH CDR3 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α2 antigen binding proteins described herein (Tables J-W)	$ARX_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}$ wherein X_3 is D or V or G X_4 is V or A or Y or R or Q X_5 is Q or I or Y or N or P or V or G X_6 is R or G or Y or T or S or I or P or L X_7 is M or G or V or D or Y or P or L or I X_8 is G or F or S or C or Y or P or W X_9 is M or F or S or D or T X_{10} is D or G or A or S or Y or R X_{11} is V or Y or L or G or E X_{12} is no amino acid or F or D or S or W or Y or L X_{13} is no amino acid or D or Y or C or F or G or V X_{14} is no amino acid or Y or M X_{15} is no amino acid or S or Y or D or F X_{16} is no amino acid or P or F or V or Q X_{17} is no amino acid or H or D X_{18} is no amino acid or F or Y X_{19} is no amino acid or D X_{20} is no amino acid or Y
431	VH CDR3 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein and the specifically described affinity matured variants thereof described herein (Tables C-I and AA)	$ARDX_4X_5X_6GWX_9X_{10}YGMDV$ wherein X_4 can be any amino acid; X_5 can be any amino acid; X_6 can be any amino acid; X_9 can be any amino acid; X_{10} can be any amino acid.

432	VH CDR3 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein and the specifically described affinity matured variants thereof described herein (Tables C-I and AA)	$ARDX_4X_5X_6GWX_9X_{10}YGMDV$ wherein X_4 is S or R ; X_5 is S or T; X_6 is S or T; X_9 is H or N or G; X_{10} is P or A;
433	VH CDR1 consensus sequence relating to the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and the specifically described affinity matured variants thereof described herein (Tables J and R-W)	$GGTX_4X_5X_6X_7X_8X_9X_{10}X_{11}$ wherein X_4 can be any amino acid; X_5 can be any amino acid; X_6 can be any amino acid; X_7 can be any amino acid; X_8 can be any amino acid X_9 can be no amino acid or any amino acid; X_{10} can be no amino acid or any amino acid; X_{11} can be no amino acid or any amino acid.
434	VH CDR1 consensus sequence relating to the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and the specifically described affinity matured variants thereof described herein (Tables J and R-W)	$GGTX_4X_5X_6X_7X_8X_9X_{10}X_{11}$ wherein X_4 is F or S or N or V or G or Y; X_5 is S or T or Q or L or R or N; X_6 is S or G or M or E or P; X_7 is Y or F or R or G; X_8 is A or I or Y or V or M; X_9 is no amino acid or G or Y or H or S; X_{10} is no amino acid or A or G; X_{11} is no amino acid or A.
435	VL CDR1 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and the specifically described affinity matured variants thereof described herein (Tables C-J and R to W and AA)	$X_1DISX_5X_6$ wherein X_1 can be any amino acid; X_5 can be any amino acid; X_6 can be any amino acid.
436	VL CDR1 consensus sequence relating to the	$X_1DISX_5X_6$

	HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and the specifically described affinity matured variants thereof described herein (Tables C-J and R to W and AA)	wherein X_1 is H or Q; X_5 id S or N; X_6 is Y or W.
437	VL CDR2 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and the specifically described affinity matured variants thereof described herein (Tables C-J and R to W and AA)	X_1X_2S wherein X_1 can be any amino acid; X_2 can be any amino acid.
438	VL CDR2 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and the specifically described affinity matured variants thereof described herein (Tables C-J and R to W and AA)	X_1X_2S wherein X_1 is A or D; X_2 is A or S.
439	VL CDR3 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and the specifically described affinity matured variants thereof described herein (Tables C-J and R to W and AA)	$QX_2X_3NSYPLX_9$ wherein X_2 can be any amino acid; X_3 can be any amino acid; X_9 can be no amino acid or any amino acid.
440	VL CDR3 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and certain of the specifically	$QX_2X_3NSYPLX_9$ wherein X_2 is D or Q; X_3 is L or F; and X_9 is no amino acid or T.

	described affinity matured variants thereof described herein (Tables C-G, I, J and R to W)	
441	VH CDR1 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and certain of the specifically described affinity matured variants thereof described herein (Tables C-G, I, J and R to W).	$GX_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}$ wherein X_2 is G or D X_3 is S or T X_4 is V or F or S or N of G or Y X_5 is S or T or Q or L or R or N X_6 is S or G or M or E or P X_7 is N or Y or F or G or R X_8 is S or A or I or Y or V or M X_9 is no amino acid or any amino acid X_{10} is no amino acid or any amino acid X_{11} is no amino acid or any amino acid
442	VH CDR1 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and certain of the specifically described affinity matured variants thereof described herein (Tables C-G, I, J and R to W).	$GX_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}$ wherein X_2 is G or D X_3 is S or T X_4 is V or F or S or N of G or Y X_5 is S or T or Q or L or R or N X_6 is S or G or M or E or P X_7 is N or Y or F or G or R X_8 is S or A or I or Y or V or M X_9 is no amino acid or A or G or Y or H or S X_{10} is no amino acid or A or G X_{11} is no amino acid or A
443	VH CDR3 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and the specifically described affinity matured variants thereof described herein (Tables C-J and R to W and AA).	$ARDX_nGMDV$ X can be any amino acid and n is 4, 5, 6, 7 or 8.
495	VH CDR1 consensus sequence relating to the HLA-DQ2.5-gliadin-α2 specifically described affinity matured antibodies described herein (Tables R-W).	$GGTX_4X_5X_6X_7X_8X_9X_{10}X_{11}$ wherein X_4 is F or S or N or V or G or Y; X_5 is S or T or Q or L or R or N;

		X_6 is S or G or M or E or P; X_7 is Y or F or R or G; X_8 is I or Y or V or M; X_9 is be no amino acid or G or Y or H or S; X_{10} is be no amino acid or A or G; X_{11} is be no amino acid or A.
518	VH CDR1 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibodies described herein (Tables A-I and AA).	GDSVSSX$_7$SAA wherein X_7 can be any amino acid
519	VH CDR1 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibodies described herein (Tables A-I and AA).	GDSVSSX$_7$SAA wherein X_7 is N or S
520	VL CDR3 consensus sequence relating to all the specifically described HLA-DQ2.5-gliadin-α1a antigen binding proteins described herein (Tables A-I and AA)	QX$_2$LNSYPLX$_9$X$_{10}$ wherein X_2 is Q or D or N; X_9 is no amino acid or L; and X_{10} is no amino acid or T.
521	VL CDR3 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and the specifically described affinity matured variants thereof described herein (Tables C-J and R to W and AA)	QX$_2$X$_3$NSYPLX$_9$ wherein X_2 is D or Q or N; X_3 is L or F; and X_9 is no amino acid or T.
522	VH CDR1 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and the specifically described affinity matured variants thereof described herein (Tables C-J and R to W	GX$_2$X$_3$X$_4$X$_5$X$_6$X$_7$X$_8$X$_9$X$_{10}$X$_{11}$ wherein X_2 is G or D X_3 is S or T X_4 is V or F or S or N of G or Y X_5 is S or T or Q or L or R or N X_6 is S or G or M or E or P X_7 is N or Y or F or G or R or S X_8 is S or A or I or Y or V or M

	and AA).	X_9 is no amino acid or any amino acid X_{10} is no amino acid or any amino acid X_{11} is no amino acid or any amino acid
523	VH CDR1 consensus sequence relating to the HLA-DQ2.5-gliadin-α1a antibody 107 described herein, the HLA-DQ2.5-gliadin-α2 antibody 206 described herein and the specifically described affinity matured variants thereof described herein (Tables C-J and R to W and AA).	$GX_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}$ wherein X_2 is G or D X_3 is S or T X_4 is V or F or S or N of G or Y X_5 is S or T or Q or L or R or N X_6 is S or G or M or E or P X_7 is N or Y or F or G or R or S X_8 is S or A or I or Y or V or M X_9 is no amino acid or A or G or Y or H or S X_{10} is no amino acid or A or G X_{11} is no amino acid or A

Table AA		
SEQ ID NO:	**Description**	**Sequence**
RF117 (combination mutant derived from 4.7C and 5.6A)		
496	VH domain (nt)	IGHV6-1*01 IGHJ6*02 IGHD6-19*01 CAGGTACAGCTGCAGCAGTCAGGTCCAGGAC TGGTGAAGCCCTCGCAGACCCTCTCACTCAC CTGTGCCATCTCCGGGGACAGTGTCTCTAGC AGCAGTGCTGCTTGGAACTGGATCAGGCAGT CCCCATCGAGAGGCCTTGAGTGGCTGGGAAG GACATACTACAGGTCCAAGTGGTATAATGATT ATGCAGTATCTGTGAAAAGTCGAATAACCATC AACCCAGACACATCCAAGAACCAGTTCTCCCT GCAGCTGAACTCTGTGACTCCCGAGGACACG GCTGTGTATTACTGTGCAAGAGATAGGACTAC TGGGTGGCATCCGTATGGTATGGACGTCTGG GGCCAAGGGACCACGGTCACCGTCTCCTCA
497	VL domain (nt)	IGKV1-9*01 IGKJ5*01 GACGTCCAGGTGACCCAGTCTCCATCCTTCCT GTCTGCATCTGTAGGAGACAGAGTCACCATCA CTTGCCGGGCCAGTCACGACATTAGCAGTTAT

Table AA		
SEQ ID NO:	**Description**	**Sequence**
		TTAGCCTGGTATCAACACAAACCGTGGAAAGC CCCCAAACTCCTGATCCATGCTGCATCCGTTT TGCAAAGTGGGGTCCCATCAAGGTTCAGCGG AAGTGGATCTGGGACAGAATTCACTCTCACAA TCAGCAGCCTGCAGCCTGAAGATTTTGCAAC GTACTACTGTCAAAATCTCAATAGTTATCCTCT CTTCGGCCAAGGGACACGACTGGAGATTAAA
498	VH domain (aa)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSSS AAWNWIRQSPSRGLEWLGRTYYRSKWYNDYA VSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYY CARDRTTGWHPYGMDVWGQGTTVTVSS
499	VL domain (aa)	DVQVTQSPSFLSASVGDRVTITCRASHDISSYLA WYQHKPWKAPKLLIHAASVLQSGVPSRFSGSG SGTEFTLTISSLQPEDFATYYCQNLNSYPLFGQ GTRLEIK
500	Heavy CDR1	GDSVSSSSAA
501	Heavy CDR2	TYYRSKWYN
502	Heavy CDR3	ARDRTTGWHPYGMDV
503	Light CDR1	HDISSY
504	Light CDR2	AAS
505	Light CDR3	QNLNSYPL
506	Heavy FR1	Q V Q L Q Q S G P G L V K P S Q T L S L T C A I S
507	Heavy FR2	W N W I R Q S P S R G L E W L G R
508	Heavy FR3	D Y A V S V K S R I T I N P D T S K N Q F S L Q L N S V T P E D T A V Y Y C
509	Heavy FR4	W G Q G T T V T V S S
510	Light FR1	D V Q V T Q S P S F L S A S V G D R V T I T C R A S
511	Light FR2	L A W Y Q H K P W K A P K L L I H
512	Light FR3	V L Q S G V P S R F S G S G S G T E F T L T I S S L

Table AA		
SEQ ID NO:	**Description**	**Sequence**
		Q P E D F A T Y Y C
513	Light FR4	F G Q G T R L E I K
514	Heavy chain (aa) (variable + constant domain). hIgG1	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSSSAAWNWIR QSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARDRTTGWHPYGMDVWGQGTT VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK
515	Light chain (aa) (variable + constant domain). hIgG$_1$	DVQVTQSPSFLSASVGDRVTITCRASHDISSYLAWYQHKPW KAPKLLIHAASVLQSGVPSRFSGSGSGTEFTLTISSLQPEDFAT YYCQNLNSYPLFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC

EXEMPLARY CONSTANT DOMAIN SEQUENCES

Mouse IgG$_{2b}$ constant domain –heavy chain mouse gamma 2b (SEQ ID NO:468)

AKTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYFPESVTVTWNSGSLSSSVHTFPA LLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHPASSTTVDKKLEPSGPISTINPCPP CKECHKCPAPNLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVSEDDPDVQISWF VNNVEVHTAQTQTHREDYASTIRVVSTLPIQHQDWMSGKEFKCKVNNKDLPSPIE RTISKIKGLVRAPQVYILPPPAEQLSRKDVSLTCLVVGFNPGDISVEWTSNGHTEEN YKDTAPVLDSDGSYFIYSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSPG K

Mouse constant domain –IgG kappa (SEQ ID NO:469)

ADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSW TDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

Human IgG$_1$ constant domain –heavy chain human gamma 1 (SEQ ID NO:470)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP
CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Human constant domain –IgG kappa (SEQ ID NO:471)

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV
TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

OTHER SEQUENCES

DQ2.5-glia-α1a (SEQ ID NO:472)

PFPQPELPY

DQ2.5-glia-α2 (SEQ ID NO:473)

PQPELPYPQ

DQ2.5-glia-α1a plus flanking residues (SEQ ID NO:474)

QLQPFPQPELPY

DQ2.5-glia-α2 plus flanking residues (SEQ ID NO:475)

PQPELPYPQPE

α-gliadin 33-mer peptide (SEQ ID NO:476)

LQLQPFPQPELPYPQPELPYPQPELPYPQPQPF

DQ2.5-glia-ω1 (SEQ ID NO:477)

PFPQPEQPF

DQ2.5-glia-ω2 (SEQ ID NO:478)

PQPEQPFPW

DQ2.5-glia-ω1 plus flanking sequence (SEQ ID NO:479)

QQPFPQPEQPFP

DQ2.5-glia-ω2 plus flanking sequence (SEQ ID NO:480)

FPQPEQPFPWQP

DQ2.5-glia-γ1 (SEQ ID NO:481)

PQQSFPEQE

DQ2.5-glia-γ1 plus flanking sequence (SEQ ID NO:482)

PEQPQQSFPEQERP

DQ2.5-glia-γ2 (SEQ ID NO:483)

IQPEQPAQL

DQ2.5-glia-γ2 plus flanking sequence (SEQ ID NO:484)

QGIIQPEQPAQL

DQ2.5-glia-γ3 (SEQ ID NO:485)

EQPEQPYPQ

DQ2.5-glia-γ3 plus flanking sequence (SEQ ID NO:486)

TEQPEQPYPQP

DQ2.5-glia-γ4c (SEQ ID NO:487)

EQPEQPFPQ

DQ2.5-glia-γ4c plus flanking sequence (SEQ ID NO:488)

TEQPEQPFPQP

CLIP2 (SEQ ID NO:489)

PLLMQALP

CLIP2 plus flanking sequence (SEQ ID NO: 490)

MATPLLMQALPMGAL

DQ2.5-glia-α1a (native form or non-deamidated form - SEQ ID NO:491)

PFPQPQLPY

DQ2.5-glia-α2 (native form or non-deamidated form - SEQ ID NO:492)

PQPQLPYPQ

*Mature α-chain of HLA-DQ2.5 MHC molecule (SEQ ID NO:493) (IMGT – HLA allele name: DQA1*05:01:01:01)*

IVADHVASYGVNLYQSYGPSGQYTHEFDGDEQFYVDLGRKETVWCLPVLRQFRF
DPQFALTNIAVLKHNLNSLIKRSNSTAATNEVPEVTVFSKSPVTLGQPNILICLVDNIF
PPVVNITWLSNGHSVTEGVSETSFLSKSDHSFFKISYLTLLPSAEESYDCKVEHWG
LDKPLLKHWEPEIPAPMSELTETVVCALGLSVGLVGIVVGTVFIIRGLRSVGASRHQ
GPL

*Mature β-chain of HLA-DQ2.5 MHC molecule (SEQ ID NO:494) (IMGT – HLA allele name:DQB1*02:01:01)*

RDSPEDFVYQFKGMCYFTNGTERVRLVSRSIYNREEIVRFDSDVGEFRAVTLLGLP
AAEYWNSQKDILERKRAAVDRVCRHNYQLELRTTLQRRVEPTVTISPSRTEALNH

HNLLVCSVTDFYPAQIKVRWFRNDQEETAGVVSTPLIRNGDWTFQILVMLEMTPQ
RGDVYTCHVEHPSLQSPITVEWRAQSESAQSKMLSGIGGFVLGLIFLGLGLIIHHRS
QKGLLH

The invention will now be further described in the following non-limiting Examples with reference to the following drawings:

Figure 1. Screening of HLA-DQ2.5:DQ2.5-glia-αIa-specific binders and affinity measurements. **(A)** Representative ELISA (n=2) of normalized, rescued phage outputs from R2 and R3 analyzed for binding to HLA-DQ2.5 with either DQ2.5-glia-α1a or CLIP2 peptides. Phage displaying an irrelevant specificity (scFv anti-NIP) was included as control. mAb 2.12.E11 specific for the DQ2.5 β-chain was used to assess capture-level of pMHC. Error bars illustrate mean ± SD of duplicates. **(B)** ScFvs selected in R2, R3, and R4 were batch-cloned into a vector for soluble expression and random clones expressed and analyzed for target reactivity by ELISA. Clones preferentially binding HLA-DQ2.5:DQ2.5-glia-α1a compared to HLA-DQ2.5:CLIP2 were chosen and sequenced. IGHV and IGKV gene segment usage was identified from the IMGT database. The pie charts show the gene segments used by the 11 unique clones. **(C)** The unique clones were expressed and purified and binding affinity to HLA-DQ2.5:DQ2.5-glia-α1a was determined by single cycle kinetics using a 3-fold concentration series ranging from 2μM - 0.025μM scFv. Representative sensograms of clones R2A1-8E, R3A2-9F, and R4A1-3A which bound specifically and are shown as indicated (n=2-3). K_Ds were derived by fitting the data to a 1:1 Langmuir model. Steady state affinity evaluations are shown as inset figures. NA=not available.

Figure 2. The HLA-DQ2.5:DQ2.5-glia-αIa-specific mAbs are highly specific. The three hIgG1 mAbs and isotype control mAb were reformatted to hIgG1, expressed by transient transfection in human 293E cells and purified from supernatants before assessment of specificity. **(A and B)** Competition ELISAs where the mAbs were pre-incubated with titrated amounts of (A) soluble pMHCs, HLA-DQ2.5:DQ2.5-glia-α1a and HLA-DQ2.5:DQ2.5-glia-α2, or the corresponding free peptides, or (B) 33mer α-gliadin before assessment of ability to compete with binding to plate-bound HLA-DQ2.5:DQ2.5-glia-α1a (n=3). **(C)** Eight different HLA-DQ2.5:gluten peptide complexes and HLA-DQ2.5:CLIP2 were used in ELISA for specificity analysis (n=2). mAb 2.12.E11 was included to control pMHC capture levels. In each set of 9 bars,

moving from left to right, bar 1 is HLA-DQ2.5-glia-α1a, bar 2 is CLIP2, bar 3 is HLA-DQ2.5-glia-γ1, bar 4 is HLA-DQ2.5-glia-γ2, bar 5 is HLA-DQ2.5-glia-γ3, bar 6 is HLA-DQ2.5-glia-γ4c, bar 7 is HLA-DQ2.5-glia-ω1, bar 8 is HLA-DQ2.5-glia-ω2, bar 9 is HLA-DQ2.5-glia-α2.

Figure 3. Mapping the fine-specificity and the structural basis for specificity. **(A)** Flow cytometric analysis of A20 B cells expressing HLA-DQ2.5 with covalently coupled DQ2.5-glia-α1a or CLIP2 peptides stained with the hIgG1 mAbs or hIgG1 isotype control mAb. Bound mAbs were detected using a biotinylated secondary anti-human IgG1 followed by streptavidin-RPE (n=2). **(B)** The hIgG1 mAbs were used to stain a panel of either HLA-DQ2.5:peptide or HLA-DQ2.2:peptide expressing A20 B cells and binding was analyzed by flow cytometry. Data are shown as the ratio median fluorescent intensity (MFI) of the hIgG1 mAbs compared to hIgG1 isotype control mAb (n=2). For each set of 3 bars, moving from left to right, bar 1 represents the mAb R2A1-8E, bar 2 represents the MAb R3A2-9F and bar 3 represents the MAb R4A1-3A. **(C)** Peptide alignment of DQ2.5-glia-α1a (forest green) and DQ2.5-glia-ω1 (cyan). Residues differing are underlined in the peptide sequences. Based on the crystal structure of HLA-DQ2.5:DQ2.5-glia-α1a (PDB ID 1S9V) [Kim, C.Y., et al., 2004]. (**D**) Overlay of the top three docking models of the Fvs onto HLA-DQ2.5:DQ2.5-glia-α1a [Kim, C.Y., et al., 2004]. Peptide residues that were mutated in the fine-specificity analysis and the HLA-DQ2.5/HLA-DQ2.2 polymorphisms are illustrated (αY22 and αS72). (**E**) In all three models V_H CDR3 is placed close to p7. (**F**) CDR1 and CDR3 of V_L both contain residues in close proximity to p9 in two of the Fv models. (**G**) In two of the Fv models V_L CDR1 (D28 and S36) is placed in close proximity to αS72, with potential H-bond formation. (**D-G**) Coloring in molecular structures as follows: V_H and V_L, black; MHCα, grey; MHCβ, light orange; DQ2.5-glia-α1a, forest green; CDR1 and CDR2 of V_H, deep purple; CDR3 of V_H, red; CDR1 and CDR2 of V_L, deep teal; CDR3 of V_L, blue; αS72 and αY22, hot pink; p7 and p9, pale green; H-bonds, yellow dashes. (**E-G**) Residues within 5 Å of p7, p9 and αS72, respectively, are shown.

Figure 4. Specific detection of gluten peptide presentation in context of HLA-DQ2.5. (*A*) Monocytes isolated from human PMBCs were *in vitro* differentiated to monocyte-derived DCs, loaded with peptide and stained with hIgG1 mAb R3A2-9F or isotype control mAb before flow cytometric analysis (n=1). (*B*) Single-cell

suspensions of intestinal biopsies obtained from patients undergoing gastroduodenoscopy were stained with a panel of antibodies to phenotypically characterize DQ2.5-glia-α1a presenting cells along with R3A2-9F mIgG2b. Bound R3A2-9F was detected using a FITC-conjugated secondary anti-mouse IgG2b Ab. Samples from three HLA-DQ2.5$^+$ untreated CD (UCD) patients with Marsh 3B/C were run in parallel. The mean percent of mIgG2b mAb R3A2-9F positive cells compared to no primary antibody is shown ± SD. Mφ, macrophages.

Figure 5. PCs and B cells of gut biopsies present the DQ2.5-glia-α1a peptide. Detection of DQ2.5-glia-α1a presentation among PCs and B cells in single-cells suspension prepared from intestinal biopsies from either untreated CD (UCD) or treated CD (TCD) patients or healthy controls. mIgG2b mAb R3A2-9F or R4A1-3A were used for detection and percent positive cells was determined relative to use of secondary antibody alone. (*A*) Representative flow cytometric gating strategy to identify PCs and B cells from single-cell suspensions. (*B*) Percentage of specific HLA-DQ2.5:DQ2.5-glia-α1a detection among CD19$^+$ PCs, CD45$^+$ PCs, CD45$^-$ PCs, and B cells in HLA-DQ2.5$^+$ UCD CD patients (n=18) compared to controls (grouped healthy and non-HLA-DQ2.5$^+$ CD patients, n=15). Two-tailed *P*-values are shown (unpaired t-test). (*C*) Stratification of the control patients among the CD19$^+$ PCs from (A). Ctrl HLA-DQ2.5$^+$ (n=5), Ctrl HLA-DQ2.5$^-$ (n=5), UCD HLA-DQ2.5$^+$ (n=18), TCD HLA-DQ2.5$^+$ (n=3), UCD HLA-DQ8$^+$ (n=1), and UCD HLA-DQ2.2$^+$ (n=1). (*D*) The HLA-DQ2.5$^+$ UCD patients (n=18) were stratified according to Marsh score as indicated. (*B-D*) Non-CD ctrl patients did not have mucosal alterations. Each data point represents an individual subject. Red (i.e. horizontal) bars indicate mean percentage.

Figure 6. DQ2.5-glia-α1a presenting PCs express TG2-specific IgA and MHC class II. (A and B) PC subsets were sorted by flow cytometry from single-cells suspensions from HLA-DQ2.5$^+$ UCD patients (n=3) all with positive serum anti-TG2 IgA titers and with marsh score 3B/C. (**A**) Representative micrographs of sorted PCs subsets as indicated. Two individual cells within each group are shown **(B)** Representative TG2-specific ELISPOT using the sorted PC subsets as indicated. TG2-specific IgA autoantibodies were captured onto TG2-coated plates and detected using AP-conjugated anti-IgA Ab. T cells were used as negative control. (**C**) Percentage MHC class II expression among APC present in single-cell

suspensions from HLA-DQ2.5^{+} UCD patients (n=4). Each data point represents an individual subject; Mo, monocytes; Mφ, macrophages; two-tailed p-values from unpaired t-test; *, P≤0.05; **, P≤0.01; ***, P≤0.001; ****, P≤0.0001; ns, not significant.

Figure 7. Validation of purified scFv clones and SPR binding analysis to control pMHCs. The 11 unique scFv clones were expressed and purified from *E. coli* periplasmic fractions. **(A)** SDS-PAGE gel analysis of the scFv clones which specifically bound DQ2.5:DQ2.5-glia-α1a. Gels were run after purification by IMAC and size exclusion chromatography under non-reducing and reducing conditions. scFv size of approx. 30 KDa is indicated. **(B)** Analytical gel filtration profiles of the candidate scFv clones and HLA-DQ2.5:DQ2.5-glia-α1a as indicated after a freeze/thaw cycle as the samples were subjected to prior to SPR analysis. **(C and D)** Representative SPR sensograms of the candidate scFv clones for binding to (C) HLA-DQ2.5:CLIP2 (n=2) and (D) HLA-DQ2.5:DQ2.5-glia-α2 (n=2). **(E and F)** Overlays of the DQ2.5-glia-α1a peptide with (E) CLIP2 and (F) DQ2.5-glia-α2. Peptide sequences are indicated and the residues differing are underlined. Based on the crystal structures of HLA-DQ2.5:DQ2.5-glia-α1a (PDB: 1S9V) and HLA-DQ2.5:DQ2.5-glia-α2 (PDB: 4OZH) [Kim, C.Y., et al., 2004; Petersen, J., et al., 2014].

Figure 8. Reformatting of candidate clones to hIgG1 and SPR binding analysis. The three specific clones were reformatted to hIgG1, expressed by transient transfection of human 293E cells and purified from supernatants along with isotype control hIgG1 mAb (anti-NIP). **(A)** SDS-PAGE gel of purified hIgG1 mAbs run under non-reducing and reducing conditions. Appropriate bands at approx. 150 KDa for full-length hIgG1 and bands at 50 KDa and 23 KDa (reduced heavy and light chains, respectively) are indicated. **(B)** SPR sensograms of hIgG1 mAbs along with the corresponding scFv fragments were run over HLA-DQ2.5:DQ2.5-glia-α1a to validate gain in functional affinity after reformatting to full-length mAbs.

Figure 9. Fine-specificity assessment. (A) Flow cytometric analysis of A20 B cells transduced to express HLA-DQ2.5 with covalently coupled DQ2.5-glia-α1a or CLIP2 peptides stained with biotinylated mAb 2.12.E11 or isotype control mAb, followed by RPE-conjugated streptavidin (n=2). **(B)** Flow cytometric assessment of the pMHC

expression level of the panel of A20 B cells transduced with either HLA-DQ2.5 or HLA-DQ2.2 with covalently coupled peptide. Q indicated native (glutamine) DQ2.5-glia-α1a epitope. Unless specified, all epitopes are in the deamidated forms. All cells were stained with biotinylated mAb 2.12.E11 followed by streptavidin-RPE (n=2). **(C and D)** Representative SPR sensograms showing binding to (C) HLA-DQ2.5:DQ2.5-glia-ω1 (n=2) and (D) HLA-DQ2.2:DQ2.5-glia-α1a (n=1) after capture of pHLA on sensor chips and injection of scFv clones as indicated. **(E)** SPR binding analysis of the DQ2 conformational-specific mAb SPV-L3 to evaluate the conformational integrity of HLA-DQ2.5:DQ2.5-glia-α1a, HLA-DQ2.5:DQ2.5-glia-ω1, HLA-DQ2.5:DQ2.5-glia-ω2, and HLA-DQ2.2:DQ2.5-glia-α1a as indicated after binding experiments.

Figure 10. Construction of mIgG2b mAbs and flow cytometric analysis of single-cell suspensions from CD patient biopsies. (*A*) SDS-PAGE gels of the mAbs R3A2-9F and R4A1-3A and isotype control mAb after reformatting to mIgG2b and purification from supernatants of transfected HEK293E cells. Full-length mIgG2b of approx. 150 KDa run under non-reducing conditions and separated heavy and light chains at approx. 50 KDa and 23 KDa run under reducing conditions are indicated. (*B*) Representative ELISA showing retained specificity of mIgG2b mAbs R3A2-9F and R4A1-3A after reformatting (n=2). mAb 2.12.E11 was included to control pMHC capture levels. (*C*) The figure is based on Figure 3b showing detection of HLA-DQ2.5:DQ2.5-glia-α1a using mAb R3A2-9F with or without use of FcR block. Single-cell suspensions of intestinal biopsies from 3 patients all being HLA-DQ2.5$^+$ with Marsh 3B/C were run in parallel.

Figure 11. Flow cytometric gating strategy and analysis of PCs and B cells presenting DQ2.5-glia-α1a peptide. Single-cell suspensions were prepared from intestinal biopsies, cells were stained with indicated antibodies and immediately analyzed by flow cytometry. (*A*) Representative gating strategy for detection of gluten peptide presentation is shown. FSC-A, FSC-H and SSC-W were used to gate out doublet cells. (*B*) Stratification of the control patients among the CD45$^+$ PCs, CD45$^-$ PCs and B cells from Figure 4b. Ctrl HLA-DQ2.5$^+$ (n=5), Ctrl HLA-DQ2.5$^-$ (n=5), UCD HLA-DQ2.5$^+$ (n=18), TCD HLA-DQ2.5$^+$ (n=3), UCD HLA-DQ8$^+$ (n=1), and UCD HLA-DQ2.2$^+$ (n=1). mIgG2b mAb R3A2-9F or R4A1-3A were used for detection and percent positive cells was determined relative to use of secondary antibody alone. Each data point represents an individual subject; non-CD ctrl

patients did not have mucosal alterations; red (i.e. horizontal) bars indicate mean percentage.

Figure 12. Gating strategy for detection of MHC class II on APC subsets. Single-cell suspensions prepared from intestinal biopsies were stained with indicated antibodies and immediately analyzed by flow cytometry. Representative gating strategy for detection of MHC class II on PCs, B cells and bulk DCs, monocytes and macrophages are shown. HLA staining (red) is overlaid isotype control staining (black). FSC-A and FSC-H were used to gate out doublet cells.

Figure 13. SPR experiments with candidate scFvs: scFvs were analyzed in SPR using a single cycle kinetics method. They were tested for binding to HLA-DQ2.5:DQ2.5-glia-α2. They were tested for cross-reactivity with HLA-DQ2.5:DQ2.5-glia-α1a and HLA-DQ2.5:DQ2.5-ω2. The scFv concentrations varied for different candidates but were the same for all three antigens.

Figure 14. Different HLA-DQ2.5:gluten peptide complexes and HLA-DQ2.5:CLIP2 were used in ELISA for specificity analysis of HLA-DQ2.5:DQ2.5-glia-α2 antibodies. The peptides are annotated according to Sollid, L.M., *et al.,* (*Immunogenetics*, 2012, 64(6): 455–460) (A). An antibody specific for HLA-DQ2.5:DQ2.5-glia-α1a and an antibody with irrelevant specificity were used as positive and negative controls (B). mAb 2.12.E11 specific for the DQ2 β-chain was included to control pMHC capture levels (C). Error bars illustrate mean ± SD of duplicates. The biotinylated pMHCs captured were: HLA-DQ2.5:DQ2.5-glia-α2 (native (P4Q)), HLA-DQ2.5:DQ2.5-glia-α2 (deamidated P4E), HLA-DQ2.5:DQ2.5-glia-ω2, HLA-DQ2.5:DQ2.5-α1a, HLA-DQ2.5:DQ2.5-hor3, HLA-DQ2.5:DQ2.5-glia-γ2, and HLA-DQ2.5:CLIP2. HSA = human serum albumin; BSA = bovine serum albumin.

Figure 15. ELISA against different pMHC complexes with affinity matured clones (scFv): Binding of the affinity matured antibodies to HLA-DQ2.5:CLIP, HLA-DQ2.5:DQ2.5-glia-α1a, and HLA-DQ2.5:DQ2.5-glia-α2. 2.12.E11 was used to control for functionality of pMHC molecules and similar levels of pMHC immobilization. In each set of 3 bars, moving from left to right, bar 1 represents

HLA-DQ2.5:DQ2.5-glia-α1a, bar 2 represents HLA-DQ2.5:DQ2.5-glia-α2, bar 3 represents HLA-DQ2.5:CLIP.

Figure 16. SPR experiments with affinity matured clones (scFv): Binding kinetics of the affinity matured variants towards the two gliadin complexes (HLA-DQ2.5:DQ2.5-glia-α1a (over a1a) and HLA-DQ2.5:DQ2.5-glia-α2 (over a2)) was analysed in SPR. All curves are normalized to the mother clones. The affinity matured scFv bound their targets and showed different off-rates. All of them showed improved off-rates compared to the mother clone. None of them was cross-reactive to the other α-gliadin complex (only depicted for 12.F6, 3.F6, 15.A6, and 4.7C).

Figure 17. Biophysical characterization of antibodies. A+B: Fab fragments were ranked based on off-rates in SPR, with the clone 4.7C marked with a single asterisk (*) and the clone 3.C11 marked with a double asterisk (**) (A: binding to HLA-DQ2.5:DQ2.5-glia-α1a, B: binding to HLA-DQ2.5:DQ2.5-glia-α2). C+D: Melting temperatures of the mother clones and the affinity matured Fab fragments with the clone 4.7C marked with a single asterisk (*) and the 3.C11 clone marked by a double asterisk (**) (C: HLA-DQ2.5:DQ2.5-glia-α1a, D: HLA-DQ2.5:DQ2.5-glia-α2). E-G: Representative sensorgrams of 4.7C (E), and RF117 (F) binding to HLA-DQ2.5:DQ2.5-glia-α1a, and 3.C11 binding to HLA-DQ2.5:DQ2.5-glia-α2 (G) (n≥ 2). RF117 denotes a mutant combining the sequence of 5.6A with the CDR H3 of 4.7C. H: The leads were reformatted to full-length hIgG1 and analyzed in ELISA against a panel of related soluble peptide:HLA-DQ2.5 complexes. In each set of 6 bars, from left to right, bar 1 is (a), bar 2 is (c), bar 3 is (b), bar 4 is (d), bar 5 is (e) and bar 6 is (f).

Figure 18. Antibodies stain engineered A20 mouse B cells. A20 cells were engineered to express HLA-DQ2.5 with covalently linked peptide. They were stained with the mother clones and the high affinity variants (n=2). A: Representative histograms are shown for the high affinity variants. B: Median fluorescence intensities are shown for all antibodies.

Figure 19. Antibodies stain plasma cells from celiac disease small intestinal biopsies. Single cell suspensions were prepared from either untreated HLA-

DQ2.5+ celiac disease patients (i.e. on a gluten-containing diet, n=8) or controls with a healthy mucosal histology (n=3). (A and B) Cells were gated as live, large lymphocytes, CD3-, CD11c-, CD14-, CD38+, CD27+, CD19+, CD45+ plasma cells in (A) celiac patients and (B) controls. Bound mIgG2b antibodies were detected with an Alexa-546-conjugated secondary antibody and the frequency of positive cells was calculated and compared to use of an isotype control antibody (isotype). The secondary antibody only (FMO) is also shown. Each celiac disease patient is shown in a unique symbol.

Figure 20. Determination of TCR-reconstructed SKW3 T cell peptide sensitivity and assessment of anti-pMHC mAb inhibition capacity.
(A - C) Representative dose-response curves (n =2) of T cell activation measured as % CD69-postive cells following co-cultivation of peptide-pulsed B cells (dump gated on CD19 expression) and the SKW3 T cells 380 (**A**), S16 (**B**) and 364 (**C**). Error bars illustrate mean ± SD of duplicates from one of two independent assays, and estimated EC50, quality of fit (R^2) values and the peptide used in pulsing are given within each graph. Based on the dose-response curves for each individual T cell, peptide concentrations of the indicated peptides resulting in about 60% activation were chosen baseline for an Ab inhibition assay (**D** – **F**), where the SKW3-380 (**D**), SKW3-S16 (**F**) and SKW3-364 (**F**) were treated as indicated with either 1 μM of the anti-pMHC mAbs, or 0.1 μM pan anti-HLA mAbs. The presented data are given as the % activation normalized to the absolute T cell activation in the absence of Ab, which was set to 100%. Error bars illustrate mean ± SD of duplicates.

Examples:

EXAMPLE 1

Identification of antibodies that specifically bind to HLA-DQ2.5:DQ2.5-glia-α1a

RESULTS

Phage selection of recombinant antibodies to HLA-DQ2.5 with bound DQ2.5-glia-α1a

To isolate HLA-DQ2.5:DQ2.5-glia-α1a specific binders, we performed phage selections using a naïve, fully-human scFv-phage library [Loset, G.A., et al., 2005]. We performed four rounds (R1-R4) of selection using recombinant soluble, biotinylated pMHC (peptide MHC complex) with covalently linked peptide. After R3, the polyclonal library outputs showed preferential HLA-DQ2.5:DQ2.5-glia-a1a reactivity compared to HLA-DQ2.5:CLIP2, with a large increase in antigen reactivity from R2 to R3 (Figure 1A). To remove low affinity clones, we performed a stringent R4 before single-clone scFv binding analysis of R2, R3 and R4 outputs. A total of 75 independent clones reacted preferentially with HLA-DQ2.5:DQ2.5-glia-a1a (Table S1), representing 11 unique clones, with a preferential usage of IGHV6-1, as well as IGKV1-9 and IGKV1-39 (Figure 1B).

We next expressed and purified all 11 unique scFv clones in *E. coli* (Figure 7A and B, data not shown) and performed SPR to analyze binding affinity and specificity using HLA-DQ2.5 with DQ2.5-glia-α1a or the control peptides, DQ2.5-glia-α2 and CLIP2. Several scFvs bound pMHC, and three (R2A1-8E, R3A2-9F (also referred to as 106) and R4A1-3A (also referred to as 107)) bound specifically to HLA-DQ2.5:DQ2.5-glia-α1a with a monomeric affinity ranging in the nanomolar range (Figure 1C, Figure 7C-E, Table S2). R3A2-9F was highly enriched, constituting 60 out of 75 binding clones in the soluble scFv screen. Although R3A2-9F and R4A1-3A were found to differ by only one amino acid, R4A1-3A appeared only once among the screened clones (Table S1).

The selected antibodies are highly specific towards HLA-DQ2.5:DQ2.5-glia-α1a

To increase the functional affinity of the interaction, we reformatted and expressed the three binders as human IgG1 (hIgG1) mAbs (Figure 8A). SPR confirmed pMHC-specific binding and a substantial gain in avidity, resulting in approximately 160-fold increase in half-life (Figure 8B). To confirm a requirement for DQ2.5-glia-α1a peptide recognition strictly in the context of HLA-DQ2.5, we performed competition ELISA using soluble pMHC and free peptide. Indeed, only soluble HLA-DQ2.5:DQ2.5-glia-α1a, and not peptide alone, competed with the plate-bound complex for binding to the mAbs (Figure 2A). Of note, DQ2.5-glia-α1a provided as part of a 33mer peptide fragment which binds efficiently to HLA-DQ2.5 [Shan, L., et al., 2002], was not able to inhibit mAb binding to pMHC (Figure 2B).

Next, we extended the specificity analysis with 7 HLA-DQ2.5-gluten-peptide complexes in ELISA. This panel included common epitopes from γ- and ω-gliadin to which CD patients mount T-cell responses. None of the mAbs bound any of the

complexes other than HLA-DQ2.5:DQ2.5-glia-α1a (Figure 2C), not even the highly similar DQ2.5-glia-ω1, which differs from DQ2.5-glia-α1a in p7 and p9 only. Taken together, these results show that the mAbs exclusively recognize DQ2.5-glia-α1a bound to HLA-DQ2.5 and are not cross-reactive with HLA-DQ2.5 in complex with the other gluten peptides tested.

Mapping fine-specificity of the candidate mAbs

To validate mAb binding to pMHC on cells, we utilized murine A20 B cells transduced with HLA-DQ2.5 with covalently linked DQ2.5-glia-α1a or CLIP2 peptides. When assessed for binding, all mAbs bound specifically to cells displaying the DQ2.5-glia-α1a epitope, while none bound CLIP2 (Figure 3A and Figure 9A).

To further map fine-specificity, we screened for binding against a panel HLA-DQ2.5:peptide or HLA-DQ2.2:peptide expressing A20 B cells (Figure 9B). Covalent attachment of the peptides to MHC largely eliminates effects of differences in peptide off-rates, enabling comparative assessment of binding. None of the mAbs bound the highly similar DQ2.5-glia-ω1 epitope or HLA-DQ2.2 with DQ2.5-glia-α1a (Figure 3B). We also corroborated this finding with SPR using the mAbs and soluble, recombinant pMHCs (Fig 9C-E). DQ2.5-glia-α1a and DQ2.5-glia-ω1 differ in p7 and p9 only (Figure 3C). Thus, we constructed pL7Q and pY9F variants of DQ2.5-glia-α1a to resemble DQ2.5-glia-ω1 in these positions. All three mAbs bound the pL7Q variant, albeit not as strongly as DQ2.5-glia-α1a (Figure 3B). However, while mAb R2A1-8E bound the pY9F variant, mAbs R3A2-9F and R4A1-3A did not (Figure 3B). Of the polymorphic residues that differ between HLA-DQ2.5 and HLA-DQ2.2, the α72 residue is the only one in position for direct interactions (Figure 3D). To map a potential effect of the HLA-DQ2.5 residue, we constructed the HLA-DQ2.5:DQ2.5-glia-α1a αS72I mutant (S in HLA-DQ2.5 and I in HLA-DQ2.2). The mAb R2A1-8E was the only one to bind the αS72I variant. As before, we did not observe binding to CLIP2 or DQ2.5-glia-α2 (Figure 3B). Furthermore, the native, non-deamidated DQ2.5-glia-α1a (DQ2.5-glia-α1a-Q) was not recognized.

To understand the molecular basis for the observed specificity of the mAbs, we built Fv homology models using the V region sequence of mAb R4A1-3A. These models represent the highly similar mAbs R3A2-9F and R4A1-3A, but not mAb R2A1-8E, which differs in sequence and thus cannot be rationalized based on the models. We then docked the models to the available crystal structure of HLA-DQ2.5:DQ2.5-glia-α1a [Kim, C.Y., et al., 2004]. The top three lowest-energy models were highly similar and positioned the scFv in a diagonal manner across the pMHC (Figure 3D). In all three models, the CDR-H3 was positioned close to p7, with

residues W111.1 and H112.1 within 5 Å of the L in p7 (Figure 3E). Although no direct interactions are indicated in the models, the pL7Q substitution could indirectly be sensed causing the small reduction in MFI as observed (Figure 3B). Similarly, both CDR-L1 and CDR-L3 are in close proximity to p9 (Figure 3F). Three residues are close enough to interact with the Y, and one of these residues, D28, potentially forms a H-bond with αS72 of the MHC, giving a molecular explanation to the lost binding of the highly similar mAbs R2A3-9F and R4A1-3A (Figure 3G). Taken together, fine-specificity analysis using single mutants revealed that the mAbs utilized distinct binding modes, and that mAbs R3A2-9F and R4A1-3A exhibited a greater specificity for DQ2.5-glia-α1a compared to mAb R2A1-8E.

Detection of cell surface HLA-DQ2.5:DQ2.5-glia-α1a complexes

As all efforts to characterize specificity and affinity of the antibodies were conducted using recombinant HLA-DQ2.5 with covalently coupled peptide, either soluble or cell-bound, we next examined if the mAbs could bind HLA-DQ2.5$^+$ cells loaded with soluble peptide. For this purpose, we isolated monocytes using PBMCs from a healthy HLA-DQ2.5$^+$ donor and *in vitro* differentiated to monocyte-derived DCs and loaded the cells with peptide. Using mAb R3A2-9F, we specifically detected cells presenting DQ2.5-glia-α1a (Figure 4A).

B cells and CD19$^+$ PCs are the major DQ2.5-glia-α1a presenting subsets in the intestinal mucosa of CD patients

Encouraged by the ability of the mAb R3A2-9F to specifically stain cells exogenously loaded with DQ2.5-glia-α1a peptide, we generated single-cell suspensions of intestinal biopsies from HLA-DQ2.5$^+$ untreated CD patients, and co-stained the freshly isolated cells with mouse IgG2b (mIgG2b) versions of mAb R3A2-9F together with antibodies specific for other APC surface markers (Figure 4B and Figure 10A and B). Unexpectedly, we observed binding of mAb R3A2-9F almost exclusively to PCs (large, viable, CD19$^{+/-}$CD27$^+$CD38$^+$) and B cells (smaller, viable, CD19$^+$CD38$^-$), whereas very few CD11c$^+$CD14$^-$ DCs and CD11c$^+$CD14$^+$ or CD11c$^-$CD14$^+$ macrophages stained positive (Figure 4B). Analysis of three patients analyzed in parallel showed an average of 27.4% and 35.4% mAb R3A2-9F positive PCs and B cells, respectively. Importantly, pre-blocking of FcγRs did not affect staining (Figure 10C).

We then compared the level of peptide presentation by B cells and PCs as detected by mAb R3A2-9F or R4A1-3A staining of both untreated CD and treated CD patients (i.e. on gluten-free diet) and matched with non-CD healthy controls.

Notably, these mAbs stained cells similarly. Small intestinal PCs can be separated into 3 major subsets with distinguished longevity based on CD19 and CD45 expression; $CD19^+CD45^+$ PCs which are dynamically exchanged, and $CD19^-CD45^+$ PCs and $CD19^-CD45^-$ PCs which are long-lived subsets and exhibits little and no replacement, respectively (herein these subsets are referred to as $CD19^+$, $CD45^+$, and $CD45^-$ PCs, respectively; Figure 11A). Of these PC subsets, we found the $CD19^+$ PCs to display most HLA-DQ2.5:DQ2.5-glia-α1a complexes, followed by the $CD45^+$ and the $CD45^-$ PCs, with an average of 19%, 11% and 7% positive cells among HLA-$DQ2.5^+$ untreated CD patients, respectively (Figure 5A and B). An average of 16% of the B cells were positive (Figure 5B). Further analysis of patients revealed that all PC subsets and the B cells of treated CD patients stained negative, comparable to both HLA-$DQ2.5^+$ and HLA-$DQ2.5^-$ healthy controls (Figure 5C and Figure 11B). Additionally, both HLA-$DQ8^+$ and HLA-$DQ2.2^+$ CD patients with active disease were negative. Possibly, there were a higher number of positive PCs from patients with high Marsh scores (Figure 5D). In summary, we found PCs and B cells to be the main cell types presenting DQ2.5-glia-α1a on HLA-DQ2.5, with the highest level of staining in the $CD19^+$ PC subset.

DQ2.5-glia-α1a presenting PCs express TG2-specific IgA

To further validate our observations, we sorted four populations of PCs by use of mAb R4A1-3A and TG2-antigen multimers; bulk PCs, bulk $TG2^+$ PCs, R4A1-$3A^+TG2^+$ PCs and R4A1-$3A^+TG2^-$ PCs. All groups of sorted cells were microscopically confirmed to be PCs, with the typical PC morphology characterized by large nuclei and little cytoplasm (Figure 6A). This further strengthens our observations from flow cytometry, largely excluding unspecific mAb binding by cells such as macrophages and DCs. Moreover, culturing and subsequent TG2-specific ELISPOT using the sorted PCs verified that the cells secrete IgA antibodies specific for TG2 (Figure 6B). Importantly, within the $TG2^+$ PC and the R4A1-$3A^+TG2^+$ PC populations spots were clearly visible, while none were found in the R4A1-$3A^+TG2^-$ sorted PC population, nor in the T-cell negative control. Among bulk PCs spots were only visible when using many cells, in line with the approximately 10% TG2-specific PCs in the inflamed mucosa of CD patients.

Intestinal PCs express MHC class II

Despite the fact that intestinal PCs appear to have a functional BCR, and thus Ag capturing capacity, they are thought to lack APC properties by virtue of transcriptional silencing of the MHC class II loci. The specific detection of gluten

peptide presentation on HLA-DQ2.5 requires MHC class II expression in human intestinal PCs in CD patients. To experimentally verify this, we performed flow cytometric staining showing that the $CD19^+$, $CD45^+$ and $CD45^-$ PCs all indeed express MHC class II, albeit to a lower level as compared to DCs, monocytes and macrophages or B cells (Figure 6C and Figure 12).

Table S1

Table S1. Overview of selection and candidate clones.

Selection round/strategy[a]	Input (cfu)	Output (cfu)	Enrichment factor[b]	# positive clones[c]	# unique clones[d]	# specific clones[e]
R1	$1.32x10^{11}$	$2.73x10^{6}$	ND	ND	ND	ND
R2A1	$6.50x10^{11}$	$5.11x10^{5}$	0.38	5/188	1	R2A1-8E
R2A2	$6.50x10^{11}$	$1.04x10^{6}$	7.73	3/188	3	0
R3A1	$7.35x10^{11}$	$1.78x10^{6}$	3.08	41/188	1	*
R3A2	$8.00x10^{10}$	$4.95x10^{5}$	3.87	9/188	2	R3A2-9F
R4A1	$3.83x10^{11}$	$3.09x10^{5}$	0.33	6/188	2	R4A1-3A/*
R4A2	$4.83x10^{10}$	$1.71x10^{5}$	0.57	11/188	5	0/*
Total	-	-	-	75/1128	11	3

[a] Selection was performed using two parallel strategies from R2-R4; A1 without soluble competitor and A2 with soluble competitor. In both cases the selection stringency was increased for each round.

[b] Enrichment factor was determined using the ratio from the current selection round divided by the ratio from the previous round. The ratio was obtained by dividing the phage output (cfu^{ampR}) on the phage input (cfu^{ampR}) in a selection round.

[c] Determined by ELISA after scoring clones with a signal/background ratio above background level (set by empty *E. coli* XL1-Blue) as positive.

[d] Determined by sequencing of single clones. Some clones are not included due to out-of-frame mutations or unattainable sequence.

[e] Determined by SPR binding analysis.

* Same clone as R3A2-9F

ND, not determined

Note; V_H of clone R4A1-3A contains the recognition sequence of one of the enzymes used to sub-clone the scFv cassette from the phagemid to the vector for soluble expression. As the cloning step was performed prior to screening of the libraries, clones with this particular sequence may have been lost. Thus, its frequency may be under-estimated in the selection output.

Table S2

Table S2. Kinetics of the scFv-HLA-DQ2.5:DQ2.5-glia-α1a interaction.

	Single cycle kinetics[a]				Steady state	
Clone	k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})	K_D (M)	SE K_D (M)	K_D (M)	SE K_D (M)
R2A1-8E	NA	NA	NA	NA	$2.03x10^{-7}$	$1.20x10^{-8}$
R3A2-9F	$1.29x10^{5}$	0.01262	$9.79x10^{-8}$	$5.63x10^{-8}$	$1.42x10^{-7}$	$2.20x10^{-8}$
R4A1-3A	$2.89x10^{5}$	0.02151	$7.43x10^{-8}$	$7.14x10^{-8}$	$6.70x10^{-8}$	$1.30x10^{-8}$

[a] Kinetics were determined by fitting data to a 1:1 Langmuir binding model.

[b] Steady state K_D was derived from the single cycle kinetics runs.

NA, not available.

DISCUSSION

In this study, we report the generation of mAbs highly specific for HLA-DQ2.5 in complex with one of the immunodominant T-cell epitopes in CD, DQ2.5-glia-α1a. By utilizing these mAbs, we identify B cells and PCs as the main APCs presenting gluten peptides in the inflamed intestine of CD patients.

TCR and TCR-like mAb binding to the same pMHC complex have been compared before, usually revealing distinct fine-specificities with mAb binding modes ranging from highly tilted to TCR-like docking. For the HLA-DQ2.5:DQ2.5-glia-α1a complex, binding experiments using 11 T-cell clones showed a striking dependence on p7, as a pL7A mutation completely abrogated binding for all clones, whereas alternations of all other positions resulted in clone-dependent effects. In the case of a model TCR clone, a pL7Q mutation reduced binding, while a pY9F mutation increased binding, presumably translating into HLA-DQ2.5:DQ2.5-glia-ω1 cross-reactivity. Among the three HLA-DQ2.5:DQ2.5-glia-α1a-specific mAbs described in this paper, R3A2-9F and R4A1-3A behaved similarly, while mAb R2A1-8E showed a distinct recognition pattern. All mAbs bound irrespective of p7 mutation, while p9 mutation abrogated binding for mAbs R3A2-9F and R4A1-3A, explaining the lack of binding to the DQ2.5-glia-ω1 epitope. R3A2-9F and R4A1-3A differ by one amino acid in the framework of V_L, while mAb R2A1-8E shares V_H with the two former mAbs, but utilizes a different V_L. While p7 appears solvent exposed and the pL7Q mutation reduced mAb binding, p9 is generally considered a buried anchor residue. However, crystallographic analysis of HLA-DQ2.5 in complex with DQ2.5-glia-α1a has shown that the p9 residue can either act as an anchor or be positioned outside of the pocket. Docked models of mAb R4A1-3A and HLA-DQ2.5:DQ2.5-glia-α showed that the CDR-L1 and CDR-L3 loops are in close proximity to p9 and αS72. Although there are no direct interactions with p9, D28 of CDR-L1 interacts with αS72, an interaction that would be disrupted after mutation to the αI72 found in HLA-DQ2.2, possibly explaining the lack of binding to HLA-DQ2.2 with DQ2.5-glia-α1a. The molecular basis for the lack of mAb binding to the DQ2.5-glia-α1a epitope with the corresponding native sequence remains unclear. The p6E is generated by TG2 mediated deamidation and acts as an anchor residue involved in an extensive H-bond network with both the peptide and MHC. It is conceivable that this H-bond network will rearrange in the presence of the native Q, which may then directly or indirectly influence the ability of the mAb to bind.

HLA-DQ2.5 is largely resistant to HLA-DM-mediated peptide exchange, resulting in an extraordinarily high level of CLIP peptides presented by HLA-DQ2.5$^+$ APCs.

As a consequence, the relative proportion of HLA-DQ2.5 loaded with other peptides is assumed to be low. Cross-reactivity to CLIP2 would limit the utility of the mAbs as specific reagents. As seen in both binding experiments using recombinant molecules in ELISA and SPR, as well as in flow cytometry after staining of $DQ2.5^+$ cells with covalently coupled CLIP2 peptide, CLIP2 is not detected. Each naturally processed antigenic pMHC complex has been estimated to occur in numbers of 10-1000 per cell. This contrasts the high density of TCR on T cells, estimated to about 50.000 molecules per cell, thus, in comparison with tetramer detection of a TCR, the use of TCR-like mAbs is challenging, particularly for detection of inefficiently loaded antigens. Still, we were able to detect both *in vitro* loaded cells and pMHC complexes generated *in vivo* after gluten consumption by CD patients.

The intestinal compartment of conventional APC is dominated by macrophages, with smaller populations of DCs, naïve and memory B cells. DCs have been suggested to participate in priming of T cells in CD. We detect very few DCs, which might in part be explained by their low density in the intestine, and by migration to the mesenteric lymph node after antigen uptake. Although the affinities of mAbs R3A2-9F and R4A1-3A are in line with those reported for other TCR-like mAbs isolated from naïve libraries, it might be too low to detect scarce cell populations.

B cells and PCs expressing Ig specific for gliadin and TG2 are characteristics of CD. The dominant B-cell lineage in the lamina propria is PCs, which are found at high densities, constituting 25-35% of the total mononuclear cell population, whereas there is only a minor population of memory B cells and very few naïve B cells. In CD, 1% and 10% of the PCs are specific for gliadin and TG2, respectively. The role of these cells and the antibodies they produce in disease development and maintenance has been unclear. Our findings indicate their involvement as APCs for gluten-reactive $CD4^+$ T cells. Comparing the 3 major subsets of small intestinal PCs, we found the $CD19^+$ subset to present DQ2.5-glia-α1a most efficiently. This subset is highly dynamic and undergoes constant renewal, whereas the $CD45^+$ and $CD45^-$ PCs are long-lived and more static, in particular the $CD45^-$ PCs where we detected the lowest level of peptide presentation. The observed lack of correlation between DQ2.5-glia-α1a presentation and serum anti-TG2 IgA titer is in line with the previous observation that the frequency of TG2-specific PCs does not correlate with serum Ab titers.

Although the conventional view is that B cells are not efficient activators of naïve T cells, B cells have been shown to be efficient APCs when they recognize the same antigen as the responding T cell. In a murine model of systemic lupus erythematosus (SLE), activation of naïve self-reactive T cells was shown to depend

on B cells. In CD, a hapten-carrier model has been suggested for efficient presentation of gluten peptides by TG2-specific B cells, whereby BCR-bound TG2 is itself associated with the gluten peptide, or has catalyzed the coupling of the peptide to neighboring molecules. The presence of DQ2.5-glia-α1a-presenting B cells builds on these observations and strengthens the hapten-carrier hypothesis in activation of T cells. The phenotype of the $CD19^{+}CD38^{-}$ B cells we identified has been thoroughly investigated. This population was found to constitute mostly memory B cells ($CD27^{+}IgD^{-}IgA^{+}$) with a minor population of naïve-mature B cells ($CD27^{-}IgD^{+}IgM^{+}$), most likely representing a variable contribution from isolated lymphoid follicles.

The ability of PCs to act as APCs is controversial, and conflicting results have been reported from human and murine studies. Murine PCs have been shown to process antigen and activate naïve T cells. This has proven much more difficult to verify for human PCs, despite the observation that IgA and IgM PCs in the bone marrow and lamina propria have functional BCR that is able to transmit intracellular signals and internalize antigen. Nevertheless, MHC expression and an ability to activate T cells have been demonstrated for human myelomas. Additionally, human bone marrow and splenic PCs have been shown to express MHC class II. Expression from the MHC class II locus is believed to be controlled by CIITA. Upon PC maturation, CIITA expression is lost, leading to silencing of MHC class II expression. However, epigenetic mechanisms as well as carcinogenesis have been shown to induce class II expression in PCs, both by reactivation of CIITA and in its absence. We have shown that the PCs present gluten peptides on HLA-DQ2.5, which indicates that PCs function as APCs.

In summary, we have isolated highly specific HLA-DQ2.5:DQ2.5-glia-α1a-specific mAbs, and we found PCs and B cells to be the main cell types presenting DQ2.5-glia-α1a in the intestinal lesion of CD patients. The mAbs are highly specific, detecting DQ2.5-glia-α1a solely in the context on HLA-DQ2.5. The lack of detection in $HLA\text{-}DQ2.2^{+}$ and $HLA\text{-}DQ8^{+}$ untreated CD patients strongly implies that our clear staining of $HLA\text{-}DQ2.5^{+}$ untreated CD patients is not an artifact caused by a highly inflamed tissue. The treatment for CD is to completely abstain from gluten. However, for a fraction of CD patients, this is not curative and this group is in need of novel therapeutic intervention. Up to 50% of the gluten-reactive $CD4^{+}$ T_H cells in the active CD lesion may be focused on either of the immunodominant DQ2.5-glia-α1a and DQ2.5-glia-α2 epitopes. Importantly, selective blocking of dominating epitopes in HLA-driven diseases has been shown to ameliorate disease. The previously unappreciated ability of PCs to act as APCs, and the observed

importance of B cells in gluten peptide presentation may also offer instructive clues for understanding of other T-cell driven autoimmune diseases.

MATERIALS AND METHODS

Human and animal material

Duodenal biopsy material was obtained according to approved protocols (Regional Ethics Committee of South-Eastern Norway approval 2010/2720 S-97201), and all subjects gave informed written consent. CD diagnosis was given according to the British Society for Gastroenterology guidelines including clinical history, anti-TG2 serological testing, HLA typing and histological analysis of small intestinal biopsies obtained by esophagogastroduodenoscopy and forceps sampling from the duodenum.

Recombinant pMHC expression and purification

Recombinant HLA-DQ2.5 or HLA-DQ2.2 with covalently coupled gluten-derived peptides containing the T-cell epitopes DQ2.5-glia-α1a (QLQPFPQPELPY, underlined 9mer core sequence), DQ2.5-glia-α2 (PQPELPYPQPE), DQ2.5-glia-ω1 (QQPFPQPEQPFP), DQ2.5-glia-ω2 (FPQPEQPFPWQP), DQ2.5-glia-γ1 (PEQPQQSFPEQERP), DQ2.5-glia-γ2 (QGIIQPEQPAQL), DQ2.5-glia-γ3 (TEQPEQPYPQP), DQ2.5-glia-γ4c (TEQPEQPFPQP) and CLIP2 (MATPLLMQALPMGAL) were generated as previously described [Fallang, L.E., et al., 2008, Quarsten, H., et al., 2001]. Briefly, insect cell produced soluble, recombinant pMHC was affinity purified using mAb 2.12.E11 [Viken, H.D., et al., 1995] specific for DQ2 and occasionally by size exclusion using Superdex 200, followed by site-specific biotinylation using BirA (Avidity). Recombinant pMHC used for SPR was further purified by size exclusion using Superdex 200 after biotinylation.

Selection and rescue of scFv phage libraries

HLA-DQ2.5:DQ2.5-glia-α1a-specific binders were isolated from a naïve human scFv library (described in Loset, G.A., et al., 2005). Dynabeads MyOne Streptavidin T1 beads (Invitrogen) and phages ($1.32x10^{11}$ cfu^{ampR} in R1) were blocked 1 h using either 4% non-fat skim milk powder or 2% BSA (essentially fatty acid free) in PBS, alternating the blocking reagent for each selection round. 1 ml pre-blocked phage samples were incubated 1 h with 80 nM biotinylated HLA-DQ2.5:CLIP2 for negative selection (R1, R2, R3), before transfer to tubes containing beads and further

incubated for 30 min. Beads containing captured HLA-DQ2.5:CLIP2 with bound phage were absorbed on a magnet and supernatant containing unbound phage was transferred to new tubes and incubated 1 h with 80 nM biotinylated HLA-DQ2.5:DQ2.5-glia-α1a for positive selection, before transfer to beads as before. After 5 washes with PBS with 0.05% Tween-20 (PBST) and 5 washes with PBS (a brief vortex between each wash), bound phages were eluted by 30 min incubation with 0.5 ml trypsin/EDTA. In subsequent rounds, all samples were selected using two strategies; alterative 1 as in R1, and alternative 2, by addition of 16.6 nM non-biotinylated HLA-DQ2.5:DQ2.5-glia-α1a competitor in solution [Zahnd, C., et al., 2010]. All incubations were performed using rotation at room temperature (RT). The selection stringency was increased for each round; washing 10 + 10 in R2, 20 + 20 in R3 and R4, decreasing antigen amount 10 times for each round, and 100 times for R4. The eluted output was used to infect 9.5 ml *E. coli* XL1-Blue (Stratagene) at OD_{600nm} 0.6 in 2x YT-TG (30 µg/ml tetracycline and 0.1 M glucose). Additional 0.05 M glucose was added to the cultures immediately before infection to ensure complete shutdown of the lac promoter. Infection was allowed for 30 min/80 rpm/37°C, followed by 30 min/220 rpm/37°C incubation. Cultures were harvested by centrifugation, plated onto Bio-Assay dishes (NUNC) containing 2x-YT-TAG (30 µg/ml tetracycline, 100 µg/ml ampicillin, and 0.1 M glucose) and incubated overnight at 30°C. Cells were scraped and re-inoculated to OD_{600nm} 0.05 in 50 ml 2x YT-TAG. M13K07 (GE Healthcare) at MOI 20 was added at OD_{600nm} 0.1-0.2 and allowed to infect as before, followed by medium replacement to 2x YT-AK (100 µg/ml ampicillin and 50 µg/ml kanamycin), and incubated overnight at 30°C. Cultures were centrifuged and supernatants were filtrated using 0.22 µm filters. Virions were purified and concentrated by PEG precipitation as described [Marks, J.D., et al., 1991]. Phage was spot-titrated onto nitrocellulose filters essentially as before [Koch, J. et al., 2000]. Antigen-specific clones identified after selection were sequenced by GATC Biotech.

Reformatting from phage to soluble expression

scFv cassettes encoding selected clones were retrieved either by batch-cloning a midi-prepped library glycerol stock (for R3 screening) or by PCR amplification directly from the phage stocks (for R2 and R4 screening). Briefly, the scFv cassette was cloned as NcoI/NotI fragment from the phagemid pSEX81 pL-NBLκ into pFKPEN [Gunnarsen, K.S., et al., 2010], placing the scFv in-frame with c-myc and his-tags, and transformed into *E. coli* XL1-Blue. Alternatively, the scFv cassette was retrieved directly from the PEG precipitated phages stocks by PCR using Phusion

HotStart DNA polymerase (Thermo Scientific). 1µl phage stocks were used with 0.5µM primers scTCR_fw 5'-CTCAGCCGGCCATGGCC-3' (SEQ ID NO: 516) and scTCR_rv 5'-TTTGGATCCAGCGGCCGC-3' (SEQ ID NO:517), 0.2mM dNTPs, annealing temperature 60°C. The PCR was purified from agarose gel and the scFv cassette cloned as NcoI/NotI fragment into pFKPEN.

Soluble prokaryotic protein expression and purification

Soluble prokaryotic expression both for library screening and large-scale single-clone production was performed essentially as before [Gunnarsen, K.S., et al., 2010]. For single clone screening in 96-deep well plates, single colonies were picked and inoculated into 400 µl LB-AG, sealed with AirPore Tape Sheet (QIAGEN) and incubated with shaking at 750 rpm/37°C overnight using Titramax (Heidolph). 50 µl of the cultures were transferred to plates containing fresh LB-AG and incubated with shaking at 600 rpm/4 h/37°C before medium replacement to 450 µl LB-A supplemented with 0.1 mM IPTG. The plates were incubated with shaking at 600 rpm/30°C overnight. For large-scale scFv expression, the cells were inoculated into 1 L 2x YT-AG in baffled shaker flasks, and incubated at 37°C/220 rpm overnight. The cultures were then re-inoculated to OD_{600nm} 0.025 using 1 L 2x YT-AG. Medium was replaced to 2x-YT-A when the cultures reached OD_{600nm} 0.6 and incubation continued overnight at 30°C/250 rpm. Periplasmic fractions containing expressed scFv were harvested by resuspension of cell pellets in ice-cold periplasmic extraction solution (50 mM Tris-HCl, 20% sucrose, 1 mM EDTA, pH 8) supplemented with 1 mg/ml lysozyme and 0.1 mg/ml RNase A, using 300 µl for 96-well cultures and 80 ml for 1 L cultures, and incubate for 1 h/rotation/4°C. Periplasmic fraction were harvested by centrifugation and protein either used directly in screening or filtered (0.22 µm filters) and purified by IMAC (HiTrap, GE Healthcare) followed by size exclusion using HiLoad Superdex 200 (GE Healthcare) run in PBS supplemented with 150 mM NaCl and pH adjusted according to the pI of the proteins. Superdex 200 3.2/300 was used for analytical size exclusion.

SDS-PAGE

To visualize purified protein, 2 µg was mixed with BOLT™ LDS sample buffer, heated 5 min at 95°C before separation on 12% NUPAGE BT gels in BOLT™ MES SDS running buffer (reagents from Novex) at 165 V/35 min along with Spectra prestained multicolor broad-range ladder (Thermo Scientific). Gels were stained with coomassie gel stain. Samples were in some cases reduced using DTT.

ELISA

96-well MaxiSorp microtiter plates (Nunc) were coated overnight at 4°C with NeutrAvidin (Avidity, 10 ug/ml in PBS), before blocking with 4% skim milk powder in PBS (w/v). Biotinylated pMHC was captured onto the NeutrAvidin. Due to variations in biotinylation levels, different pMHCs were normalized to give the same signal as 63 ng/well of HLA-DQ2.5:DQ2.5-glia-α1a in ELISA with mAb 2.12.E.11 detection. Phage, periplasmic fractions containing scFvs, or 0.5 µg/ml hIgG1 diluted in PBS with 0.05% Tween-20 (PBST) were added to the wells, and detected with either anti-M13-HRP (Amersham Biosciences, 1:5000), anti-His-tag-HRP (AbD Serotech, 1:5000), or polyclonal anti-human IgG Fc-ALP (Sigma, 1:2000) in PBST, respectively. 0.2 µg/ml mAb 2.12.E11 [Viken, H.D., et al., 1995] was detected using polyclonal anti-mouse IgG Fc-ALP (Sigma, 1:2000). HRP ELISAs were developed by addition of TMB solution (Calbiochem), while ALP ELISAs were developed with 1mg/ml phosphatase substrate in diethanolamine buffer before absorbance reading at 620nm (450nm in the case of HCl addition) or 405nm, respectively. Assays were performed at RT with duplicate wells, except for single clone screenings with only one well per sample. Between each layer, the plates were washed 3x with PBST. In competition ELISAs, 0.1 µg/ml hIgG1 was pre-incubated 30 min with non-biotinylated pMHC or peptides 2-fold diluted from 1 µM. Deamidated gliadin peptides used were 12mer DQ2.5-glia-α1a (QLQPFPQPELPY), 12mer DQ2.5-glia-α2 (PQPELPYPQPQL) (SEQ ID NO: 524) and 33mer (LQLQPFPQPELPYPQPELPYPQPELPYPQPQPF).

Binding analysis by SPR

Binding specificity, affinity, and kinetics was determined on Biacore T100 (T200 sensitivity enhanced) (GE Healthcare). 1000 RU of NeutrAvidin (Avidity) diluted in acetate buffer pH 4.5 was immobilized on CM3 sensor chips (GE Healthcare) by amine coupling, before capture of 150-300 RU biotinylated pMHC. Samples were 3-fold diluted from 2 µM in PBS supplemented with 150 mM NaCl and 0.05% surfactant P20 for estimation of scFv affinity and binding kinetics. Data were acquired at 30 ul/min using the single cycle kinetics method (data collection rate 10 Hz), with an association time 120 sec and a final dissociation of 600 sec. Alternatively, a kinetic/affinity method was employed using the same conditions as above, with association times as indicated in the figure panels. For half-life comparisons of scFv and hIgG1 variants, 0.25 µM was used of each protein, with association time 120 sec and dissociation of at least 600 sec. All experiments were performed at 25°C. The surface was regenerated by a 10 sec injection of Glycine-

HCl pH 2.2 at 10 ul/min. Presence of functionally folded pMHC was verified after running samples by injection of 0.2 µM mAb SPV-L3, binding only correctly folded DQ2. NeutrAvidin reference flow cell values were subtracted before data analysis using Biacore T200 Evaluation Software, version 1.0 and RI set to constant. A 1:1 Langmuir binding model was used for determination of K_D. Figures were prepared using GraphPad Prism 7.

IgG cloning and eukaryotic protein expression and purification

Synthetic gene fragments encoding V_H and V_L from the selected scFvs together with intronic splice donor sites (Genscript) were cloned as BsmI-BsiWi fragment into the IgG genomic expression vectors $pLNOH2_{NIP}$ and $pLNOk_{NIP}$ [Norderhaug, L., et al., 1997], encoding constant human gamma1 with N297G mutation and constant human kappa domains, respectively, exchanging the existing specificity for the hapten NIP [Neuberger, M.S., 1983]. Alternatively, synthetic gene fragments encoding V_H and V_L were ordered together with codon optimized mouse gamma2b or mouse kappa cDNA, respectively, and cloned as BsmI-BamHI fragments into the vectors described above. *E. coli* Top10F (Life Technologies) were transformed with the resulting plasmids before preparation of DNA. HEK293E cells (ATCC) were co-transfected with the expression vectors encoding Ig H and L chains using Lipofectamine 2000 (Invitrogen) and grown in DMEM supplemented with 10% fetal calf serum, 2 mM L-glutamine, 50 U/ml Streptomycin and 50 U/ml Penicillin. Medium was collected and replaced every day/every second day for two weeks, followed by filtration (0.22 µm) and purification on either HiTrap protein L (GE Healthcare) or a NIP-coupled column (in-house prepared) using 0.2 M glycine-HCl pH 3.0 for elution followed by rapid neutralization using 1 Tris-HCl pH 8. Protein containing fractions were further purified by size exclusion on HiLoad Superdex 200 (GE Healthcare) run in PBS supplemented with 150 mM NaCl and pH adjusted according to the pI of the proteins.

Retroviral transduction of A20 murine B cells and flow cytometry

A20 B cells expressing HLA-DQ2.5 with the covalently attached DQ2.5-glia-α1a (deamidated=E, native=Q, pL7Q and pY9F variants), DQ2.5-glia-ω1, DQ2.5-glia-α2 as well as HLA-DQ2.5:CLIP2 have been described. The construct encoding HLA-DQ2.5:DQ2.5-glia-α1a-Sα72I was generated by cloning a BglII/BamHI codon-optimized synthetic DNA fragment (Genscript) encoding the HLA-DQ2.5 α-chain (*DQA1*05:01*) with the Sα72I mutation into the pMIG-II-eGFP retroviral plasmid (Holst J, Vignali KM, Burton AR, Vignali DA., *Nat Methods*. 2006;3(3):191–197)

already encoding HLA-DQ2.5:DQ2.5-glia-α1a. HLA-DQ2.2:DQ2.5-glia-α1a was generated by exchange of the HLA-DQ2.5 α-chain (*DQA1*05:01*) with a BglII/BamHI codon-optimized synthetic DNA fragment encoding the HLA-DQ2.2 α-chain (*DQA1*02:01*). The constructs were made to have identical ectodomains as in the soluble, recombinant pMHCs. The resulting pMIG-II-eGFP-rDQ2.5:peptide plasmids and the pAmpho plasmid were then co-transfected (Lipofectamine 2000, Invitrogen) into GP2-293 packaging cells (Clontech), before virus-containing supernatants were collected 48 and 72 h after transduction and cell debris removed by centrifugation and filtration (0.45 µm). Fifty thousand A20 cells were incubated with 1.3 ml of virus-containing supernatant supplemented with 10 µg/ml polybrene and centrifuged 3000g at 32°C for 90 min. The supernatant was then discarded and the cells cultured in RPMI with 10% FCS for 5 days, before cells were sorted using FACSAria II (BD Biosciences) based on eGFP expression level. The A20 B cells were cultivated in RPMI-10% FCS. Data was analyzed using FlowJo software V10.

Differentiation and flow cytometric detection of peptide-loaded monocyte-derived DCs

Monocyte-derived DCs were prepared from PBMCs from DR3/DQ2-positive blood donors [Qiao, S.W., et al., 2004]. Briefly, monocytes were positively selected from PBMCs using anti-CD14 MicroBeads (Miltenyi Biotec) and cultured in RPMI 1640 with 10% FCS containing 1000 U/ml GM-CSF and 500 U/ml IL-4 (both from R&D Systems). On day 6, DCs were matured using 150 ng/ml LPS for 48 h, supplemented with 40 µM deamidated DQ2.5-glia-α1a peptide (QLQPFPQPELPY) after 24 h. For flow cytometry, cells were washed twice with flow buffer buffer (PBS with 2% FCS) in V-bottomed 96-well plates, incubated for 45 min on ice with 10 µg/ml of mAb R3A2-9F or isotype control mAb. After washing, the cells were incubated as before with 2 µg/ml F(ab')2 anti-human IgG-biotin (Southern Biotech), followed by 30 min incubation with streptavidin-RPE (Invitrogen). After staining, cells were washed once with flow buffer and immediately analyzed on FACSCalibur (BD Biosciences), and data were analyzed with FlowJo 10.0.7 software (Tree Star). All antibodies were diluted in flow buffer.

Isolation of single-cell suspensions from duodenal biopsies and flow cytometry

To obtain single-cell suspensions from duodenal biopsies, epithelial cells were removed by three washing steps with PBS containing 2mM EDTA and 1% FCS for

15 min at 37°C. The remaining lamina propria was minced and digested in RPMI containing 2.5 mg/ml liberase and 20 U/ml DNase I (both from Roche) at 37 °C for 1 h. Cells were passed through 100 µM cell strainers (Falcon) and washed three times in PBS. Single-cell suspensions from lamina propria were stained in V-bottomed 96-well plates with either 10 µg/ml mIgG2b mAb R3A2-9F and R4A1-3A or isotype control mAb (mIgG2b/κ, Sigma) for 30 min, followed by staining with 1 µg/ml secondary antibody goat anti-mouse IgG2b conjugated to either Alexa-488 or FITC (Southern Biotech). Cells were subsequently stained with the following fluorochrome-conjugated mAbs targeting human cell-surface markers for 30 min on ice; CD14-APC-Cy7 (clone HCD14), CD45-v510 (clone H130), HLA-DR-bv605 (clone L243) (all Biolegend) and CD11c-v450 (clone B-Ly6); or CD3-APC (clone OKT3, eBioscience), CD11c-APC (clone S-HCl-3), CD14-APC (clone HCD14), CD45-BV510 (clone HI30), HLA-DR-BV605 (clone L243), CD19-PE-Cy7 (clone HIB19), CD38-APC-Cy7 (clone HIT2) and CD27-BV421 ((clone O323) all from Biolegend). For panHLA detection single-cell suspensions were stained with 10 µg/ml anti-human DR/DQ/DP/Dx (clone CR3/43, Santa Cruz Biotechnology) or isotype control mAb (mouse IgG1/κ, clone MOPC-21,BD Pharmingen; or clone AD1.1.10, AbD Serotec) followed by 1 µg/ml secondary mAb anti-mouse IgG1-PE (clone A85-1, BD Biosceinces) or Ab anti-mouse-PE (BD Pharmingen), before staining with the following fluorochrome-conjugated mAbs targeting human cell-surface markers; CD3-FITC (clone OKT3, Biolegend), CD11c-BV450 (clone Bly-6, BD Horizon), CD14-Pacific Blue (clone M5E2, BD Pharmingen), CD45-BV510, CD19-PE-Cy7, CD38-APC-Cy7. Additionally, cells were occasionally stained with fluorescent TG2 multimers where prepared by preincubation of biotinylated TG2 with either streptavidin-RPE (Life Technologies) or Strep-tactin-APC (iba solutions for life sciences). Propidium iodide was used to exclude dead cells and FcRs were blocked using human FcR Blocking Reagent (Miltenyi Biotec). All antibodies and reagents were diluted in PBS containing 5% FCS and 0.1% sodium azide and incubations were performed on ice. Cells were washed between each staining layer. After staining, cells were washed once and immediately acquired on LSR Fortessa cytometer (BD Biosciences), and data were analyzed with FlowJo 10.0.7 software (Tree Star).

Sorting of PCs, validation of morphology by light microscopy and TG2 ELISPOT

Single-cells suspensions from duodenal biopsies were stained with Alexa-488-conjugated hIgG1 R3A2-9F or hIgG1 anti-RSV as isotype controls mAbs (both in-

house conjugated) together with the following antibodies against cell-surface markers; CD4, CD8 and CD14-Pacific Blue (Biolegend), CD11c-BV450 (BD Biosciences), CD27-PE-Cy7 (eBioscience), IgA-PE (Southern Biotech), and multimerised TG2 (Strep-tactin-APC, iba solutions for life sciences). PCs were sorted using FACSAriaII (BD Biosciences) directly into RPMI1640 without phenol red using a 100 µM nozzle. Sorted cells were spun down, resuspended in fresh medium and kept in culture at 37°C, 5% CO_2 over night before imaging live cells in culture using a 40x NA 0.5 objective on an inverted Leica DM IL microscope equipped with a Axiocam MRc camera (Zeiss).

MultiScreenHTS IP Filter Plate (0.45 µm) ELISPOT plates (Millipore) were activate with a 1 min incubation with 20 µl 35% ethanol, solution discarded and wells washed 3x with 200 µl PBS before coating with 100 µl 5 µg/ml TG2 (Phadia) in PBS or PBS only to negative control wells and incubated overnight at 4°C. Wells were 3x washed with 200 µl PBS and block with 200 µl 1% w/v BSA in PBS for 2 h at RT. Sorted cells were added in a total volume of 100 µl and plates incubated at 37°C, 5% CO_2 for 3 days. Cell were aspired and wells washed 3x with 200 µl PBS and 6x with 200 µl PBST before incubation with AP-conjugated goat anti-human IgA (Sigma, 1:2000) in 100 µl 1% BSA in PBST for 1.5 h at RT. Wells were wash 6x with 200 µl PBST, 3x with 200 µl PBS, 2x with 200 µl dH_2O, followed by detection of spots by addition of 100 µl BCIP/NBT solution (AP Conjugate Substrate Kit, Bio-Rad). The reaction was stopped with extensively washing under running water. Plates were dried and read by ImmunoSpot Analyzer. Spots were counted manually. The BW58$\alpha^-\beta^-$.human CD4 T cell hybridoma transduced with TCR364 was used as negative control.

Antibody modeling

Antibody homology models were generated essentially as described in [Weitzner, B.D., et al., 2017]. The sequences of the light and heavy variable regions were saved in fasta format, aligned to homologs with known structure, and grafted together into models using Rosetta Antibody. Multiple templates of the V_L–V_H orientation [Marze, N.A., et al., 2016] were used, resulting in 10 grafted models. The grafted models were further refined by *de novo* CDR H3 loop modeling and the V_L-V_H docking. During modeling, the CDR H3 was constrained to the kinked conformation with a harmonic potential [Weitzner, B.D. and J.J. Gray, 2017]. We obtained a total of 2,800 Fv models. Models for docking were selected based on low Rosetta energy and good V_L-V_H orientation. To keep some of the diversity generated by the multi-template grafting, we considered models from at least three

different V_L-V_H orientation templates. In the end, 10 Fv models were docked to the pMHC complex, using SnugDock [Sircar, A. and J.J. Gray, 2010].

Antibody docking to pMHC

A crystal structure of unliganded HLA-DQ2.5:DQ2.5-glia-α1a is available in the PDB (1S9V, [Kim, C.Y., et al., 2004]) and was used as the docking partner for the antibody models. To alleviate pre-existing steric clashes, the structure was "relaxed" in the Rosetta energy function [Conway et al., 2014]. The top 10 Fv models and the relaxed pMHC structure were prepared for docking by running the ensemble prepack protocol as described in [Weitzner, B.D., et al., 2017]. The initial orientation was chosen based on the solved TCR:pMHC interaction (4OZI, [Petersen, J., et al., 2014]). Docking consisted of an initial spin around the Ab–Ag center-of-mass axis and uniformly sampled from 0 to 360 °, and additional random perturbations consisting of small translations and rotations, with values sampled from Gaussian distributions centered at 3 Å and 8 °, respectively. During docking, the flexible CDR H2 and H3 loops were refined by kinematic loop closure and the V_L-V_H orientation was refined by V_L–V_H docking. A total of 1,000 models were generated using SnugDock. The final models were picked based on low Rosetta energy, reasonable orientation relative to the pMHC, and agreement with experimentally observed specificities.

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EXAMPLE 2

Identification of antibodies that specifically bind to HLA-DQ2.5:DQ2.5-glia-α2

Antibodies with specificity for HLA-DQ2.5:DQ2.5-glia-α2 were isolated by use of phage display. Three rounds of selection against the target complex were performed using a large, naïve human single chain fragment variable (scFv) library and different display formats (high valence vs. low valence display, pIII fusions vs. pIX fusions). Single clones were isolated from the selection output and screened for target binding and cross-reactivity to related pMHC complexes. All the scFv identified that bind specifically to HLA-DQ2.5:DQ2.5-glia-α2 use a VH1 gene segment.

The sequences of identified clones 6 (also referred to as 206), 17 (also referred to herein as 217), 18 (also referred to herein as 218), 20 (also referred to herein as

220), 21 (also referred to herein as 221), 23 (also referred to herein as 223), 26 (also referred to herein as 226 or 26I) and 28 (also referred to herein as 228) are set forth elsewhere herein.

These clones in the scFv format, were tested for their specificity and affinity for HLA-DQ2.5:DQ2.5-glia-α2 using surface plasmon resonance (SPR) experiments.

First the target antigen was immobilized on a NeutrAvidin coated chip and binding of candidates (scFv clones) was tested briefly. The above mentioned clones demonstrated binding to the target antigen.

The clones were analyzed in single cycle kinetics experiments regarding their binding to HLA-DQ2.5:DQ2.5-glia-α2, HLA-DQ2.5:DQ2.5-glia-α1a, HLA-DQ2.5:DQ2.5-glia-ω2 (Figure 13). Binding to HLA-DQ2.5:DQ2.5-glia-α2 was observed for the above clones and dissociation constants Kd were calculated from two independent experiments with different ligand concentrations. The same single cycle kinetics method was used to analyze binding to HLA-DQ2.5:DQ2.5-glia-α1a and HLA-DQ2.5:DQ2.5-glia-ω2.

The clones demonstrated specificity for the HLA-DQ2.5:DQ2.5-glia-α2 (Figure 13) In particular, none of the clones, demonstrated significant cross-reactivity to HLA-DQ2.5:DQ2.5-glia-α1a.

The affinities of the scFvs for HLA-DQ2.5:DQ2.5-glia-α2 were in the range of approximately 10 nM to 5 µM (Table Y).

Table Y (dissociation constants (K_D))

	KD* (affinity **)	KD (kinetics***)
scFv 6	(20 ± 10) nM	(12.6 ± 0.9) nM
scFv 17	(4,900 ± 200) nM	(5,080 ± 20) nM
scFv 18	(2,700 ± 800) nM	(2,400 ± 600) nM
scFv20	(900 ± 200) nM	(730 ± 70) nM
scFv 21	(700 ± 100) nM	(590 ± 70) nM
scFv23	(2,300 ± 300) nM	(2,200 ± 300) nM
scFv 26	(300 ± 100) nM	(170 ± 50) nM
scFv 28	(240 ± 80) nM	(110 ± 70) nM

*) Dissociation constants KD were determined as mean values from two separate single cycle kinetics experiments with different scFv concentrations. Errors were calculated as standard deviations.

**) KD was determined by using a fit to the responses for different concentrations.

***) KD was also determined by estimating the on- and off-rates. For all candidates the dissociation constants estimated with the two methods have overlapping errors.

The ELISA was performed as essentially *as per* the method in Example 1. Briefly, 96-well MaxiSorp microtiter plates (Nunc) were coated overnight at 4°C with NeutrAvidin (Avidity, 10 ug/ml in PBS), before blocking with 4% skim milk (SM) powder in PBS (w/v). Biotinylated pMHC was captured onto the NeutrAvidin.

The biotinylated pMHCs captured were:

HLA-DQ2.5:DQ2.5-glia-α2 (native (P4Q))

HLA-DQ2.5:DQ2.5-glia-α2 (deamidated P4E)

HLA-DQ2.5:DQ2.5-glia-ω2

HLA-DQ2.5:DQ2.5-α1a

HLA-DQ2.5:DQ2.5-hor3

HLA-DQ2.5:DQ2.5-glia-γ2

HLA-DQ2.5:CLIP2

Due to variations in biotinylation levels, the different pMHCs were normalized to give the same signal as 63 ng/well of HLA-DQ2.5:DQ2.5-glia-α1a in ELISA with mAb 2.12.E.11 detection (2.12.E.11 is a monoclonal antibody specific for the DQ2 β-chain). 0.5 µg/ml hIgG1 (antibodies 206, 220 and 228) was diluted in PBS with 0.05% (v/v) Tween-20 (PBST) were added to the wells, and detected with polyclonal anti-human IgG Fc-AP (Sigma, 1:2000) in PBST. mAb 2.12.E11 (0.2 µg/ml) was detected using polyclonal anti-mouse IgG Fc-AP (Sigma, 1:2000). AP ELISAs were developed with 1mg/ml phosphatase substrate in diethanolamine buffer before absorbance reading at 405nm. Assays were performed at RT with duplicate wells. Between each layer, the plates were washed 3x with PBST.

The ELISA results (Figure 14A) indicate that the antibodies show preferential binding to the HLA-DQ2.5:DQ2.5-glia-α2 molecules as compared to the other tested pMHCs.

Figure 14B is a control experiment which demonstrates that the 107 antibody (hIgG1), which specifically binds to HLA-DQ2.5:DQ2.5-glia-α1a, does not bind to any of the other tested pMHCs, and also that an isotype control does not bind to any

of the tested pMHCs. Figure 14C is a control experiment which shows consistent pMHC immobilization levels.

EXAMPLE 3

Affinity matured antibodies

Affinity matured antibodies that specifically bind to HLA-DQ2.5:DQ2.5-glia-α1a or that specifically bind to HLA-DQ2.5:DQ2.5-glia-α2 were generated.

Starting from the 107 (R4A1-3A) "mother clone" that specifically binds HLA-DQ2.5:DQ2.5-glia-α1a, affinity matured second generation clones were generated. The sequences of six such clones are set forth elsewhere herein, 4.5D (or 107-4.5D), 4.6D (or 107-4.6D), 4.6C (or 107-4.6C), 4.7C (or 107-4.7C), 5.6A (or 107-5.6A) and 15.6A (107-15.6A).

Starting from the 206 "mother clone" that specifically binds HLA-DQ2.5:DQ2.5-glia-α2, affinity matured second generation clones were generated. The sequences of six such clones are set forth elsewhere herein, 2.B11 (or 206-2B11), 3D.8 (or 206-3D.8), 3.C7 (or 206-3.C7), 3.C11 (or 206-3.C11), 3.F6 (or 206-3.F6) and 12.F6 (206-12.F6).

ELISA

To assess the specificity of the affinity matured clones ELISA experiments were performed. ELISA wells were coated with NeutrAvidin (10 µg/mL), blocked with PBS supplemented with 0.05 % tween and 5 % skim milk powder, biotinylated forms of HLA-DQ2.5:CLIP, HLA-DQ2.5:DQ2.5-glia-α1a, and HLA-DQ2.5:DQ2.5-glia-α2 molecules were immobilised and the scFv were added (10 µg/mL in PBS). The scFv were detected with a mouse anti-myc antibody and a secondary anti-mouse antibody coupled to horseradish peroxidase (HRP). The reaction was stopped by adding 1M HCl to the wells. Absorbance was read at 450 nm.

As shown in this ELISA experiment (Figure 15), all tested affinity matured scFvs are specific to the relevant HLA-DQ2.5:DQ2.5-peptide antigen (pMHC) and do not cross-react to HLA-DQ2.5 with the other α-gliadin or CLIP bound.

SURFACE PLASMON RESONANCE (SPR)

To assess the affinity improvement, we performed Surface Plasmon Resonance (SPR) experiments (Figure 16). We immobilized Neutravidin on a CM3 sensor chip and captured biotinylated pMHC (HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2). The different scFv were run over the pMHC molecules. We confirmed that there is no cross-reactivity between the two targets.

All of the affinity matured antibodies showed improved affinity relative to their respective mother clone. The affinity matured scFv bound their targets and showed different off-rates. All of them showed improved off-rates compared to the mother clone. None of them was cross-reactive to the other α-gliadin pMHC complex (only depicted in Figure 16 for 12.F6, 3.F6, 15.A6, and 4.7C).

Based on the rate of the decaying signal, we ranked the antibodies and chose 4.7C and 2.B11 as lead candidates for high affinity binding to HLA-DQ2.5:DQ2.5-glia-α1a and HLA-DQ2.5:DQ2.5-glia-α2, respectively. This also matches the results obtained in ELISA experiments where these candidates showed the highest signals.

EXAMPLE 4

Antibody modelling/docking

To assess the “footprint” (or “recognition motif” or “codon”) to which antibodies of the present invention may bind, antibody modelling was done using the 107 antibody that specifically binds to HLA-DQ2.5:DQ2.5-glia-α1a and the 206 antibody that specifically binds to HLA-DQ2.5:DQ2.5-glia-α2.

Methods

We chose to use the RosettaAntibody and SnugDock applications (software) to generate models of the docked complexes of the antibodies with their pMHC targets. Both applications belong to the Rosetta software suite for macromolecular structure prediction and design.

RosettaAntibody’s performance was tested in the antibody modeling assessment II (AMA-II) [B. D. Weitzner, et al. 2014]. It predicted all framework regions and 76 % of non-H3 CDR loops at sub-Ångström accuracy. RosettaAntibody further produced the best H3 models for 4 out of 11 targets compared to competitors. It can be

regarded as among the best available computational methods for prediction of antibody structures.

SnugDock's ability to correctly predict antibody:antigen complexes was benchmarked on 15 solved structures when the software was first published [A. Sircar and J. J. Gray, 2010]. When analyzing the top10 lowest energy models produced by SnugDock in combination with a method called EsembleDock (Chaudhury and Gray, 2008), a model of at least acceptable quality was found in 14 out of the 15 candidates.

Antibody homology models were obtained essentially as described in [B. D. Weitzner, 2016a]. The amino acid sequences of the light and heavy variable regions in fasta format were aligned to homologs with solved crystal structure, and grafted together into models using Rosetta Antibody. To improve the accuracy we used multiple templates of the V_L–V_H orientation [N. A. Marze and J. J. Gray, 2016], resulting in 10 grafted models. The grafted models were refined by *de novo* CDR H3 loop modeling and V_L-V_H docking. The CDR3 loop of the heavy chain was constrained to the kinked conformation with a harmonic potential [B. D. Weitzner and J. J. Gray, 2016b]. We obtained 2,800 Fv models. We selected models for docking based on low Rosetta energy and V_L-V_H orientations within the ranges that are observed in solved antibody structures. In order to maintain structural diversity generated by the multi-template grafting, we considered models from at least three different V_L-V_H orientation templates. 10 Fv models were docked to the pMHC complex, using SnugDock [A. Sircar and J. J. Gray, 2010].

We used the crystal structure of the binary complex of HLA-DQ2.5:DQ2.5-glia-α1a (PDB ID 1S9V [C.-Y. Kim, 2004]) and the crystal structure of HLA-DQ2.5:DQ2.5-glia-α2 in complex with T cell receptor JR5.1 (PDB ID 4OZF [Petersen et al., 2014]) as docking partners.

The pMHC structures were first "relaxed" in the Rosetta energy function [Conway et al., 2014] to remove pre-existing steric clashes. The top 10 Fv models and the relaxed pMHC structure were prepared for docking by running the ensemble prepack protocol as described in [Weitzner et al, 2016a]. The initial orientation was selected based on the solved TCR:pMHC interaction (4OZI and 4OZF [J. Petersen, 2014]). Docking consisted of an initial spin around the Ab–Ag center-of-mass axis uniformly sampled from 0 to 360 °, and additional random perturbations consisting of small translations and rotations, with values sampled from Gaussian distributions centered at 3 Å and 8 °, respectively. The flexible CDR2 and CDR3 loops of the

heavy chain were refined by kinematic loop closure and the V_L-V_H orientation was refined by V_L–V_H docking. For each antibody, 1,000 models were generated using SnugDock. The final models were picked based on low Rosetta energy, reasonable TCR-like orientation relative to the pMHC, as well as agreement with experimentally observed specificities.

The recognition motif was identified by visual inspection of the three and four lead docking models of 107 (0063, 0158, 0195) and 206 (0064, 0083, 0107, 0265), respectively.

Results

A diagonal binding mode of the antibodies across the pMHC groove, similar to the one observed for TCRs. This has been observed for TCR like antibodies before and is supported by our docking models.

The docking models predict the variable light chain of 107 and 206 to be positioned mostly over MHC and the C terminal end of the peptide. The variable heavy chain is positioned over both MHC and peptide.

Based on the strong enrichment of different IGVH gene families during the phage display selections (IGVH6-1 for the α1a selection and IGVH1-69 for the α2 selection) it is likely that the heavy chains contribute strongly to peptide specificity.

The models of 107 and 206 in complex with pMHC predict CDR3 loop of the light chain to be oriented to the *DQB1*02* chain of MHC. CDR1 loop of the light chain is oriented towards to *DQA1*05* chain.

Because of the sequence conservation and the closely related IGKV-1 genes used by 107 and 206, we think that IGKV-1 drives binding to the MHC, HLA-DQ2.5.

This is exemplified by IGKV1-9 and IGKV1-12 gene usage for the 107 and 206 antibodies, respectively.

The models show VH6-1 (for antibody 107) and VH1-69 (for antibody 206) to be supporting binding to DQB 02:05 (MHC contacts) and additionally harboring peptide specificity.

Based on the antibody modelling, the recognition motif in the conserved stretches of the antibody light chain is predicted to be comprised of a set of residues including but not limited to an N at position 92 of the VL chain of the 107 or 206 antibodies (which is in CDR3), an S at position 93 of the light chain of the 107 or 206 antibodies (which is in CDR3), and a Y at position 94 of the light chain of the 107 and 206 antibodies (which is in CDR3), a D at position 28 of the of the VL chain of the 107 or 206 antibodies (which is in CDR1), and an S at position 30 of the VL chain of the 107 and 206 antibodies (which is in CDR1).

These light chain residues are predicted to interact with a set of MHC residues including a Y at position 60 of the MHC beta chain, a Q at position 64 of the MHC beta chain, a D at position 66 of the MHC beta chain, an R at position 70 of the MHC beta chain, an H at position 68 in the MHC alpha chain, an S at position 72 of the MHC alpha chain, and an R at position 76 of the MHC alpha chain.

Thus, this antibody modeling study indicates that, surprisingly, the 107 antibody that specifically binds to HLA-DQ2.5:DQ2.5-glia-α1a and the 206 antibody that specifically binds to HLA-DQ2.5:DQ2.5-glia-α2, despite having different antigen specificities, share a common recognition motif which recognises the HLA-DQ2.5 MHC molecule. This recognition motif involves residues found in the variable light chain of the antibodies, as discussed above.

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EXAMPLE 5

Biophysical characterization of affinity matured pMHC-specific antibodies

In order to assess improvements in binding strength of the 107 and 206 derived binders and to choose lead clones, we performed SPR (surface plasmon resonance) and ranked the antibodies based on off-rates (Fig. 17A+B and Table Z). Strongly improved off-rates were observed for all clones tested. As expected, the 107-derived clones 5.6A and 15.6A, both from the random, error-prone library (i.e. clones derived from a random library made by error prone PCR across the entire scFv), had less pronounced improvements in off-rate compared to the CDR3 mutants (i.e. mutants derived from a library of CDR3 mutated clones). Based on these results, we chose

4.7C and 3.C11 as leads for binding to HLA-DQ2.5:DQ2.5-glia-α1a and HLA-DQ2.5:DQ2.5-glia-α2, respectively.

We next assessed the thermostability of all Fab fragments by determining their melting temperatures by nanoDSF (nano differential scanning fluorimetry) (Fig. 17C+D). Whereas most HLA-DQ2.5:DQ2.5-glia-α1a binders had improved thermostability compared to 107, the HLA-DQ2.5:DQ2.5-glia-α2 binders surprisingly had slightly lower melting temperatures than the 206 mother clone. The lead clones 4.7C and 3.C11 had the highest thermostabilities among the selected clones from the targeted libraries (i.e. from the library of CDR3 mutated clones). In line with the rational for generating the random mutagenesis libraries, the mutants 5.6A and 15.6A had the highest improvements in thermostability, with 5.6A being the highest with a melting temperature 3.3 °C higher than 107.

To harness both the improved off-rate and improved thermostability of the HLA-DQ2.5:DQ2.5-glia-α1a binders, a combination mutant, RF117, was generated, combining the lowest off-rate CDR3 loop (4.7C) with the most stable clone (5.6A). Affinities of the lead antibodies were determined in SPR (Fig. 17E-G). In concordance with the improved (lower) off-rates, all candidates had a strong improvement in affinity, with 4.7C, and 3C11 having K_Ds of 170±40 pM and 88±11 pM, respectively (Table Z). This is a 400-fold improvement for 4.7C and a 2,600-fold improvement for 3.C11. The combination mutant RF117 had a K_D of 20±17 pM, an approximately 3,600-fold improvement. To our knowledge, RF117 has the highest reported monomeric affinity of a pMHC-specific antibody in any human system.

The 2nd generation antibodies were then expressed as full-length hIgG1 and tested for specific binding in ELISA (Fig. 17H). In agreement with previous results, both 4.7C and RF117 bound exclusively to the target complex HLA-DQ2.5:DQ2.5-glia-α1a and 3.C11 was specific for HLA-DQ2.5:DQ2.5-glia-α2.

Table Z. Kinetics and affinity of affinity matured variants.

	Kinetics and affinity				Steady state[c]	
Clone	k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})	K_D (M)	SE K_D (M)	K_D (M)	SE K_D (M)
HLA-DQ2.5:DQ2.5-glia-α1a binders						
scFv 107[a]	$2.89x10^5$	0.02151	$7.43x10^{-8}$	$7.44x10^{-8}$	$6.70x10^{-8}$	$1.30x10^{-8}$
Fab 107[a]	$2.24x10^5$	0.01601	$7.14x10^{-8}$	$5.54x10^{-8}$	$7.41x10^{-8}$	$1.20x10^{-9}$
Fab 107[b]	$2.377x10^5$	0.01698	$7.145x10^{-8}$		NA	NA
Fab 4.7C[b]	$3.776x10^5$	$9.819x10^{-5}$	$2.600x10^{-10}$		NA	NA
Fab 4.5D[b]	$3.830x10^5$	$1.657x10^{-3}$	$4.327x10^{-9}$		NA	NA

Fab 4.6C[b]	$6.972x10^{5}$	$2.617x10^{-4}$	$3.754x10^{-10}$		NA	NA
Fab 4.6D[b]	$4.638x10^{5}$	$5.413x10^{-4}$	$1.167x10^{-9}$		NA	NA
Fab 5.6A[b]	$1.002x10^{6}$	$3.442x10^{-3}$	$3.436x10^{-9}$		NA	NA
Fab 15.6A[b]	$5.883x10^{5}$	$2.209x10^{-3}$	$3.755x10^{-9}$		NA	NA
Fab 4.7C	$9.007x10^{5}$	$1.770x10^{-4}$	$1.966x10^{-10}$	$5.40x10^{-7}$	NA	NA
Fab 4.7C	$6.697x10^{5}$	$9.685x10^{-5}$	$1.446x10^{-10}$	$5.60x10^{-7}$	NA	NA
Fab RF117	$1.829x10^{6}$	$5.861x10^{-5}$	$3.024x10^{-11}$	$3.70x10^{-7}$	NA	NA
Fab RF117	$2.048x10^{6}$	$1.550x10^{-5}$	$7.569x10^{-12}$	$5.60x10^{-7}$	NA	NA
HLA-DQ2.5:DQ2.5-glia-α2 binders						
Fab 206[a]	$1.02x10^{6}$	0.2291	$2.24x10^{-7}$	$2.25x10^{-7}$	$2.54x10^{-7}$	$2.70x10^{-9}$
Fab 206[b]	$1.077x10^{6}$	0.2462	$2.280x10^{-7}$		NA	NA
Fab 2.B11[b]	$2.208x10^{6}$	$3.285x10^{-4}$	$1.488x10^{-10}$		NA	NA
Fab 3.C11[b]	$1.669x10^{6}$	$6.967x10^{-6}$	$4.174x10^{-11}$		NA	NA
Fab 3.C7[b]	$2.006x10^{6}$	$7.111x10^{-4}$	$3.544x10^{-10}$		NA	NA
Fab 3.D8[b]	$1.545x10^{6}$	$1.729x10^{-3}$	$1.119x10^{-9}$		NA	NA
Fab 3.F6[b]	$8.096x10^{5}$	$1.225x10^{-3}$	$1.513x10^{-9}$		NA	NA
Fab 12.F6[b]	$8.039x10^{5}$	$7.456x10^{-4}$	$9.275x10^{-10}$		NA	NA
Fab 3.C11	$1.190x10^{6}$	$1.126x10^{-4}$	$9.462x10^{-11}$	$3.10x10^{-7}$	NA	NA
Fab 3.C11	$1.387x10^{6}$	$1.118x10^{-4}$	$8.064x10^{-11}$	$1.30x10^{-7}$	NA	NA
Fab 3.C11	$1.335x10^{6}$	$1.206x10^{-4}$	$9.039x10^{-11}$	$1.20x10^{-7}$	NA	NA

Kinetics were determined by fitting data to a 1:1 Langmuir binding model.
[a] Determined from single cycle kinetics.
[b] Determined from one concentration of protein in off-rate screening.
[c] Steady state K_D was derived from the single cycle kinetics runs.
NA, not available.

Materials and Methods

ELISA

EIA/RIA plates were coated with 10 µg/ml NeutrAvidin in PBS (100 µl/well) and incubate overnight at 4 °C. Plates were blocked with 5% skim milk powder in PBS-T (300 µl/well) for 1 h/RT with agitation. Biotinylated pMHCs were prepared *as per* in Example 1 herein. Equal amounts of biotinylated pMHC (normalized to 300 ng/ml) were captured for 1 h/RT and followed by addition of 0.5 µg/ml purified pMHC-specific antibodies. hIgG1 were detected with anti-hIgG-ALP (Sigma Aldrich, 1:3,000). All antibodies were diluted in PBS-T. Plates were developed with TMB solution (Calbiochem) and the enzymatic reaction stopped by addition of 1 M HCl and read at 450 nm or developed with 1 mg/ml phosphatase substrate (Sigma Aldrich) in dietanolamine buffer and read at 405 nm using a microplate reader (Tecan sunrise).

SPR

Kinetics of antibody binding to pMHC were determined using a Biacore T200 (GE Healthcare). Briefly, NeutrAvidin (10 µg/ml in 10 mM sodium acetate, pH 4.5) was

coupled onto a CM3 sensor chip to 1000 response units (RU) by amine coupling. Biotinylated pMHCs were prepared *as per* in Example 1 herein. Soluble, recombinant, biotinylated pMHC (1 µg/ml) was then captured at approximately 80-90 RU by passing over the flow cells at 10 µl/min. Antibody samples (scFv or Fab fragments) in PBS supplemented with 150 mM NaCl and 0.05% (v/v) surfactant P20 were run over the surface at various concentrations using either single cycle kinetics or a multi cycle method. For off-rate ranking, all samples were used at 0.5 µM. Binding experiments were performed at 25°C with a flow-rate of 30 µl/min. The surface was regenerated using either Glycine-HCl pH 2.2 or Diethylamine pH 11 when necessary. Binding data were buffer subtracted and NeutrAvidin-reference-cell subtracted using the T200 Evaluation Software v1.0. Kinetic constants were determined by fitting the data to a 1:1 Langmuir binding model.

EXAMPLE 6

Structural basis for improved affinity

In an effort to visualize the interaction interfaces, docking models of the two leads, 4.7C and 3.C11, were generated. Interestingly, the mutations responsible for the increased affinity of 4.7C, are not seen to be directly involved in binding to the pMHC, but rather to stabilize the CDR H3 loop with additional hydrogen bonds. The overall docking geometry does not appear to be changed. In contrast, 3.C11 is predicted to form several new interactions with pMHC via the CDR H1 loop as a result of the increased loop length (2 amino acids). In the model, the mutated CDR H1 loop is positioned where the CDR H3 loop was in the mother clone. This suggests that it takes over the function of the CDR H3 loop, which is displaced to the periphery of the interface. The interfaces were further analyzed using Rosetta's InterfaceAnalyzer. The solvent accessible surface area (SASA) of the interface increased from the mother clones to the high affinity variants in both cases, and Rosetta further estimated lower binding energies for the improved variants. The binding energies are also improved when normalized to the interface SASA, meaning that the gained affinity is likely both due to a larger interface surface and to improved interactions across the interface.

Materials and Methods

Antibody modeling

Structural models of Fv fragments were generated as described (Weitzner et al. 2017 and *supra*). CDR loops and framework regions were separately aligned to homologs with known structures and grafted together using RosettaAntibody. We used 10 templates for the V_L/V_H orientation (Marze and Gray 2016, *supra*) resulting in 10 grafted models. The grafted relaxed models were further improved by de novo CDR H3 modeling and VL/VH docking. The CDR H3 was constrained to a kinked conformation (Weitzner and Gray 2016, *supra*) and a total of 2,800 Fv models were generated. The 10 final models were selected based on low Rosetta energy and V_L/V_H orientations within the natural distribution. Models were taken from at least three initial grafted templates to maintain diversity.

Antibody docking to pMHC

Crystal structures of HLA-DQ2.5:DQ2.5-glia-α1a (1S9V) (Kim et al. 2004) and HLA-DQ2.5:DQ2.5:glia-α2 (4OZF) (Petersen et al. 2014, *supra*) were retrieved from the PDB and "relaxed" into the Rosetta energy function. We used the cocrystal structure with the T-cell receptor (4OZI) (Petersen et al. 2014, *supra*) as a template for an initial orientation of the Fv models relative to the pMHC. We used SnugDock+EnsembleDock starting with 10 antibody Fv models (Sircar and Gray 2010, *supra*) to generate 1,000 docking models for each antibody. Random moves during docking consisted of a spin around the antibody:antigen center-of-mass axis sampled from 0 – 360 °, and additional random translations and rotations, sampled from Gaussian distributions centered a 3 Å and 8 °, respectively. CDRs H2 and H3 were refined by kinematic loop closure and V_L/V_H orientations were improved by V_L/V_H docking. The final models were ranked and selected based on low Rosetta energy, occurrence of "energy funnels", and an orientation relative to the pMHC that agrees with the observed specificities. Rosetta's InterfaceAnalyzer application was used to obtain information about binding energies and interfaces.

EXAMPLE 7

Detection of cell-surface pMHC

Having demonstrated specificity and improved affinity to soluble, recombinant, biotinylated pMHC molecules, we tested whether the antibodies would stain pMHC complexes on the surface of cells. To this end, A20 mouse B cells were engineered to express variants of covalently linked pMHC complexes. Functional cell-surface pMHC expression was verified and the A20 cells were stained with the engineered hIgG1 variants (Figure 18A+B). 107 and its offspring 4.7C and RF117 bound the

deamidated target specifically. The high affinity clone 3.C11 bound to both native and deamidated HLA-DQ2.5:DQ2.5-glia-α2.

Materials and Methods

B cell lines

The murine A20 B cell lymphoma had previously been engineered to express HLA-DQ2.5 or HLA-DQ2.2 with different peptide variants covalently linked to the MHC β-chain (Kristin Støen Gunnarsen et al. 2017, JCI Insight 2 (17) doi:10.1172/jci.insight95193). Notably, the ectodomains are identical as in the soluble pMHC molecules used for selection, screening and characterization of antibody binding by SPR and ELISA. All cells were cultured under standard conditions in RPMI 1650 supplemented with 10% FCS, 0.1 mg/ml Streptomycin and 100 U/ml Penicillin.

Flow cytometry

A20 murine B cells were stained for flow cytometry experiments using the pMHC-specific antibodies. For staining A20 B cells, pMHC-specific hIgG1 antibodies were used at 5 µg/mL together with rat anti-mouse CD16/CD32 block (BD, 1:200). Bound hIgG1 were detected with biotinylated goat F(ab')2 anti-human IgG (Southern Biotech, 2 µg/ml) followed by streptavidin R-PE (Invitrogen, 2µg/ml). All stainings were performed on ice using V-bottom shaped 96-well plates and an equal number of cells were used in each staining (at least 100,000).all PBS supplemented with 2% FCS was used to wash cells and for dilution of antibodies and streptavidin.

Data was acquired using an Attune NxT flow cytometer and analyzed using FlowJo software v10.4.1.

EXAMPLE 8

Staining human small intestinal biopsy material

We generated fresh single-cell suspensions of intestinal biopsies from either untreated HLA-DQ2.5+ celiac disease patients or control patients and stained them with the pMHC specific mIgG2b antibodies as well as antibodies against different APC surface markers (Fig. 19). We have previously detected the highest levels of DQ2.5-glia-α1a presentation on CD19+CD45+ plasma cells (see Example 1 herein). These cells have been characterized in the small intestinal mucosa and were found

to be dynamically exchanged (Landsverk et al. 2017, *Journal of Experimental Medicine*, 214(2):309-317). The high affinity variants also stain CD19+CD45+ plasma cells and confirm that these cells present gliadin peptides in celiac disease patients. 4.7C stains a similar percentage of cells as the 107 mother clone, while 3.C11 appears to stain a slightly higher number of cells. Two out of six samples are consistently negative for pMHC using all three antibodies. Only one sample (#5) is negative for staining with the mother clone but has a positive population when stained with 4.7C and especially 3.C11. The two control subjects confirm that there is little background staining with all antibodies used.

Materials and Methods

Human material

Duodenal biopsy material was obtained according to approved protocols (Regional Ethics Committee of South-Eastern Norway approval 2010/2720 S-97201), and all subjects gave informed written consent. CD (celiac disease) diagnosis was given according to the British Society for Gastroenterology guidelines including clinical history, anti-TG2 serological testing, HLA typing and histological analysis of small intestinal biopsies obtained by esophagogastroduodenoscopy and forceps sampling from the duodenum (Ludvigsson et al. 2014, *Gut*, 63 (8):1210-28). Small intestinal resections (duodenum-proximal jejunum tissue) were obtained from nonpathological small intestine during Whipple procedure (pancreatoduodenectomy) of pancreatic cancer patients who gave informed written consent (approval 2010/2720 S-97201). Only material with confirmed normal histology was included.

Isolation of single-cell suspensions from duodenal biopsies and small intestinal resections and flow cytometry

Single-cell suspensions from duodenal biopsies or from small intestinal resection were prepared as described (Landsverk et al. 2017, *supra*) and analyzed by flow cytometry as detailed in the Table below.

Antibodies used for Staining of pMHC on APCs in human biopsy material and anlysis by flow cytometry:

Antigen	Conjugate	Clone	Supplier	Dilution
mIgG2b 107/4.7C/3.C11	-	107, 4.7C, 3.C11	In-house	10 µg/ml

Isotype control	-	OMV	In-house	10 µg/ml
mIgG	Alexa-546	Polyclonal	Invitrogen	1 µg/ml
CD3	FITC	OKT3	Biolegend	1:20
CD11c	APC	S-HCl-3	BD Biosciences	1:20
CD14	APC	HCD14	Biolegend	1:20
CD14	APC-Cy7	HCD14	Biolegend	1:20
HLA-DR	BV605	L243	Biolegend	1:20
CD45	BV510	H130	Biolegend	1:20
CD19	PE-Cy7	HIB19	Biolegend	1:20
CD38	APC-Cy7	HIT2	Biolegend	1:20
CD27	BV421	O323	Biolegend	1:20

EXAMPLE 9

Inhibition of T cell activation using affinity maturated mAbs 4.7C and 3.C11

RESULTS

The anti-pMHC specific mAbs 4.7C (also referred to herein as 107-4.7C) and 3.C11 (also referred to herein as 206-3.C11) exhibit strong HLA and peptide dependent *in vitro* inhibitory capacity of T cell activation

To assess whether or not the affinity maturated lead candidate mAb clones 4.7C and 3.C11 have relevant T cell inhibitory capacity, and thus might function as disease (e.g. celiac disease) modifying agents, we generated T cell receptor (TCR) reconstructed SKW3 T cells clones expressing three different human TCRs derived from celiac patients. Two of these TCRs are specific for DQ2.5:DQ2.5-glia-α2 (clone S16 and 364), whereas the last TCR is specific for DQ2.5:DQ2.5-glia-α1a (clone 380). We then characterized the peptide dose-response of T cell activation using a human HLA-DQ2.5 positive B cells line (Raji) as antigen presenting cells (APCs) loaded with exogenous peptide. For the subsequent T cell inhibition, we fixed the amount of exogenous specific peptide to the concentration resulting in about 60% of full T cell activation (Figure 20, A – C). After having loaded the APC with peptide, we then added the pMHC-specific and control Abs followed by adding T cells and continue incubation ON (overnight). When measuring the resulting T cell activation, indeed we observed an interference of T cell activation directly conferred by the Abs (Figure 20, D-F). In the case of the mAb 4.7C, there was an about 20% reduction in T cell activation, but only where the APC was loaded with the peptide containing the

correct epitope (Fig. 20, D). Correspondingly, the pan anti-DQ Ab (clone SPVL3) exhibited a close to complete inhibition, whereas the pan anti-DR Ab (clone L243) had no apparent effect (Fig. 20, D). Importantly, the mAb 3.C11 had no inhibitory effect on this SKW3-380 T cell activation underscoring the peptide specificities of these anti-pMHC mAbs. Conversely, the situation was opposite when the mAb 3.C11 was used to inhibit activation of the SKW3-S16 and 364 T cells (Figure 20, E and F). Here, a complete inhibition on par with the pan anti-DQ Ab was seen in the case of both T cells, whereas the 4.7C had a negligible effect. Thus, we conclude that the observed T cell inhibitory capacity seen with mAb 4.7C and 3.C11 is both peptide and DQ dependent underscoring the high specificity and strong target binding capacity of these mAbs.

MATERIALS AND METHODS

IgG protein expression and purification

Purified full-length human IgG1 protein harboring the VH and VL domains of the identified affinity maturated clones 4.7C and 3.C11 were custom produced in HEK293 cells by Genscript based on the provided VH and VL domain amino acid sequences.

Retroviral transduction of human SKW3 T cells and flow cytometry

The human T cell line SKW3 and the retroviral vector pMSCV were purchased from CLS Cell Lines Service GmbH and Clontech Laboratories, Inc, respectively. Based on the published T cell receptor (TCR) sequences (PMID: 24777060 – Petersen *et al*., 2014, *Nat. Struct. Mol. Biol*. 21(5):480-8, 28878121 – Gunnarsen *et al*., 2017, *JCI Insight*, 2 (17), and 29649333 – Gunnarsen *et al*., 2018, *PLoS One*, 13(4)e0195868), TCRs 380, 364 and s16 were reconstructed by gene synthesis as human/mouse chimeric TCRs as described (PMID: 28878121, *supra*), and cloned into pMSCV (performed by Genscript). Retroviral transduction of the SKW3 cells was performed using the Retro-X Universal Packaging System (Clonetech) according to the manufacturer's instructions. Stable, homogenous TCR-redirected SKW3 T cells were obtained by standard cell expansion and FACS sorting using a FACSAria II cytometer (BD Biosciences) based on their TCR expression levels assessed by H57-Alexa647 (Thermo Fisher Scientific) antibody staining. The TCRs transduced SKW3 cells were validated for peptide-specific activation using a panel of known agonistic and antagonistic peptides, essentially as described (PMID: 28878121, *supra*), using CD69 up-regulation as activation marker assessed by anti-

hCD69-APC (BD Biosciences) antibody staining. Data was acquired on a BD Accuri C6 cytometer (BD Biosciences) and analyzed using FlowJo software V10 (Tree Star).

T cell activation and inhibition assays

For T cell activation assays 50,000 Raji cells, which natively express HLA-DQ2.5 (PMID: 19845894 – Bentley *et al*., 2009, *Tissue Antigens*, 74(5):393-403), were incubated in RPMI/10% FCS at 37°C/ON with titrated amounts of peptide (as indicated in the figures), followed by washing to remove remaining free peptide and addition of 40,000 SKW3 T cells and growth 37°C/ON (overnight) before being analysed in flow. The following peptides were used (epitopes are underlined): DQ2.5-glia-α1a (QLQPFPQPELPY) and DQ2.5-glia-α2 (PQPELPYPQPE). As a control, Cell Stimulation Cocktail containing PMA and ionomycin (eBioscience, 1:500) was added to wells containing SKW T cells only. Data analysis (EC50 determination) and figures were prepared using GraphPad Prism 7. Based on the established dose-response in T cell activation, a peptide concentration estimated to result in about 60% T cell activation (measured as CD69 upregulation) was chosen for the inhibitory assays. Following ON (overnight) incubation with peptide as above and washing, either 1 μM (final concentration) mAb 4.7C or 3.C11 were added to the Raji cells, before T cells were added and incubation continued ON. The resulting T cell activation was measured as above. As control Abs, either 0.1 μM (final concentration) of pan-anti-DR (clone L243: Thermo Scientific) of pan-anti-DQ (clone SPVL3: BD Biosciences) was added on parallel. Relative inhibitory capacity was estimated by normalizing the data according to the T cell activation in the absence of mAb, which was set to 100% activation (gray left bar in Figure 20, D – F).

CLAIMS

1. An antigen binding protein which binds to HLA-DQ2.5:DQ2.5 presenting a gliadin peptide, said antigen binding protein comprising at least one light chain variable domain and at least one heavy chain variable domain, each domain comprising three complementarity determining regions (CDRs), wherein

(a) said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α2 and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:425 ($GGTX_4X_5X_6X_7X_8X_9X_{10}X_{11}$) wherein

X_4 is F or S or N or V or G or Y;

X_5 is S or T or Q or L or R or N;

X_6 is S or G or M or E or P;

X_7 is Y or F or G or R;

X_8 is A or G or I or Y or V or M;

X_9 is no amino acid or any amino acid, preferably no amino acid or G or Y or H or S;

X_{10} is no amino acid or any amino acid, preferably no amino acid or A or G; and

X_{11} is no amino acid or any amino acid, preferably no amino acid or A;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:427 ($IIPIFGTX_8$) wherein

X_8 can be any amino acid, preferably A or V;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:429 ($ARX_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}$) wherein

X_3 is D or V or G;

X_4 is V or A or Y or R or Q;

X_5 is Q or I or Y or N or P or V or G;

X_6 is R or G or Y or T or S or I or P or L;

X_7 is M or G or V or D or Y or P or L or I;

X_8 is G or F or S or C or Y or P or W;

X_9 is M or F or S or D or T;

X_{10} is D or G or A or S or Y or R;

X_{11} is V or Y or L or G or E;

X_{12} is no amino acid or any amino acid, preferably no amino acid or F or D or S or W or Y or L;

X_{13} is no amino acid or any amino acid, preferably no amino acid or D or Y or C or F or G or V;

X_{14} is no amino acid or any amino acid, preferably no amino acid or Y or M;

X_{15} is no amino acid or any amino acid, preferably no amino acid or S or Y or D or F;

X_{16} is no amino acid or any amino acid, preferably no amino acid or P or F or V or Q;

X_{17} is no amino acid or any amino acid, preferably no amino acid or H or D;

X_{18} is no amino acid or any amino acid, preferably no amino acid F or Y;

X_{19} is no amino acid or any amino acid, preferably no amino acid or D; and

X_{20} is no amino acid or any amino acid, preferably no amino acid or Y;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:419 ($X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$) wherein

X_1 is Q or G;

X_2 is D or S or T or N;

X_3 is I or V or S;

X_4 is S or L or N or I;

X_5 is N or S or Y or D or T or K;

X_6 is W or N or S or V or Y;

X_7 is no amino acid or any amino acid, preferably no amino acid or S or G;

X_8 is no amino acid or any amino acid, preferably no amino acid or N or G;

X_9 is no amino acid or any amino acid, preferably no amino acid or N or Y;

X_{10} is no amino acid or any amino acid, preferably no amino acid or K or G;

X_{11} is no amino acid or any amino acid, preferably no amino acid or N or Y; and

X_{12} is no amino acid or any amino acid, preferably no amino acid or Y;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:421 (X_1X_2S) wherein

X_1 can be any amino acid, preferably D or G or W;

X_2 can be any amino acid, preferably S or A or V;

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:423 ($X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}$) wherein

X_1 is Q or S;

X_2 is Q or S or H;

X_3 is F or Y;

X_4 is N or Y or D or T;

X_5 is S or N or D or W;

X_6 is Y or W or T or S or L;

X_7 is P or G;

X_8 is L or T or P or R;

X_9 is no amino acid or any amino acid, preferably no amino acid or T or V or R;

X_{10} is no amino acid or any amino acid, preferably no amino acid or L or F; and

X_{11} is no amino acid or any amino acid, preferably no amino acid or T; or wherein

(b) said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α1a and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:5 (GDSVSSNSAA), or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:5;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:6 (TYYRSKWYN), or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:6;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:417 ($ARDX_4X_5X_6GWX_9X_{10}YGMDV$) wherein

X_4 can be any amino acid, preferably S or R;

X_5 can be any amino acid, preferably S or T;

X_6 can be any amino acid, preferably S or T;

X_9 can be any amino acid, preferably H or N or G; and

X_{10} can be any amino acid, preferably P or A;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:8 (HDISSY) , or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:8;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:9 (AAS) or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:9; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:415 ($QX_2LNSYPLX_9X_{10}$) wherein

X_2 can be any amino acid, preferably Q or D;

X_9 can be any amino acid or no amino acid, preferably no amino acid or L; and

X_{10} can be any amino acid or no amino acid, preferably no amino acid or T.

2. The antigen binding protein of claim 1, wherein

(a) said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α2 and comprises a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:426;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:428;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:430;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:420;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:422; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:424; or wherein

(b) said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α1a and comprises a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:5, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:5;
a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:6, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:6;
a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:418;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:8 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:8;
a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:9 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:9; and
a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:520 or SEQ ID NO:416.

3. The antigen binding protein of claim 1 or claim 2, wherein said antigen binding protein comprises a light chain variable domain that comprises

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:435;
a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:437; and
a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:439.

4. The antigen binding protein of any one of claims 1 to 3, wherein said antigen binding protein comprises a light chain variable domain that comprises

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:436;
a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:438; and
a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:521 or SEQ ID NO:440.

5. The antigen binding protein of any one of claims 1 to 4, wherein said heavy chain variable region comprises
a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:522 or SEQ ID NO:441 or;
a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:42 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:42, or SEQ ID NO:168 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:168; and
a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:443.

6. The antigen binding protein of any one of claims 1 to 5, wherein said heavy chain variable region comprises
a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:523 or SEQ ID NO:442;
a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:42 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:42, or SEQ ID NO:168 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:168; and
a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:443.

7. The antigen binding protein of any one of claims 1 to 6, wherein said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:368 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:368,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:369 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:369, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:370 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:370; and

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:365 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:365,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:366 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:366, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:367 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:367.

8. The antigen binding protein of any one of claims 1 to 6, wherein said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α1a and comprises

a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:41, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:41;

a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:42, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:42;

a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:431;

a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:44 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:44;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:45 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:45; and

a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:46 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:46.

9. The antigen binding protein of any one of claims 1 to 6 or claim 8, wherein said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α1a and comprises
a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:41, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:41;
a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:42, or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:42;
a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:432;
a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:44 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:44;
a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:45 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:45; and
a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:46 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:46.

10. The antigen binding protein of any one of claims 1 to 7, wherein said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α2 and comprises
a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:433;
a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:168 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:168;
a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:169 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:169;
a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:170 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:170;

a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:171 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:171; and
a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:172 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:172.

11. The antigen binding protein of any one of claims 1 to 7 or claim 10, wherein said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α2 and comprises
a variable heavy (VH) CDR1 comprising the amino acid sequence of SEQ ID NO:434;
a variable heavy (VH) CDR2 comprising the amino acid sequence of SEQ ID NO:168 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:168;
a variable heavy (VH) CDR3 comprising the amino acid sequence of SEQ ID NO:169 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:169;
a variable light (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:170 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:170;
a variable light (VL) CDR2 comprising the amino acid sequence of SEQ ID NO:171 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:171; and
a variable light (VL) CDR3 comprising the amino acid sequence of SEQ ID NO:172 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:172.

12. The antigen binding protein of any one of claims 1 to 6 or claims 8 or 9, wherein said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:116 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:116,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:117 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:117, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:118 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:118; and

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:113 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:113,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:114 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:114, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:115 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:115.

13. The antigen binding protein of any one of claims 1 to 6 or claims 8 or 9, wherein said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α1a, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:503 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:503,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:504 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:504, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:505 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:505; and

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:500 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:500,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:501 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:501, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:502 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:502.

14. The antigen binding protein of any one of claims 1 to 6, or claims 10 or 11, wherein said antigen binding protein binds to HLA-DQ2.5:DQ2.5-glia-α2, said antigen binding protein comprising at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, wherein said light chain variable region comprises:

(a) a variable light (VL) CDR1 that comprises the amino acid sequence of SEQ ID NO:314 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:314,

(b) a VL CDR2 that comprises the amino acid sequence of SEQ ID NO:315 or a sequence containing 1 amino acid substitution, addition or deletion relative to SEQ ID NO:315, and

(c) a VL CDR3 that comprises the amino acid sequence of SEQ ID NO:316 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:316; and

wherein said heavy chain variable region comprises:

(d) a variable heavy (VH) CDR1 that comprises the amino acid sequence of SEQ ID NO:311 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:311,

(e) a VH CDR2 that comprises the amino acid sequence of SEQ ID NO:312 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:312, and

(f) a VH CDR3 that comprises the amino acid sequence of SEQ ID NO:313 or a sequence containing 1, 2 or 3 amino acid substitutions, additions or deletions relative to SEQ ID NO:313.

15. The antigen binding protein of any one of claims 1 to 14, wherein said antigen binding protein is an antibody.

16. A composition comprising an antigen binding protein of any one of claims 1 to 15 and a diluent, carrier or excipient.

17. An immunoconjugate comprising an antigen binding protein of any one of claims 1 to 15 attached to a therapeutic or diagnostic agent.

18. A nucleic acid comprising a nucleotide sequence that encodes an antigen binding protein of any one of claims 1 to 15.

19. An antigen binding protein of any one of claims 1 to 15 for use in therapy or diagnosis.

20. An antigen binding protein of any one of claims 1 to 15 for use in the treatment or diagnosis of celiac disease.

21. A method of treating celiac disease which method comprises administering to a patient in need thereof a therapeutically effective amount of an antigen binding protein of any one of claims 1 to 15.

22. Use of an antigen binding protein of any one of claims 1 to 15 in the manufacture of a medicament for use in the treatment of celiac disease.

23. A method of diagnosing celiac disease in a mammal comprising the steps of:

(a) contacting a test sample taken from said mammal with one or more of the antigen binding proteins of any one of claims 1 to 15;
(b) measuring the presence and/or amount and/or location of antigen binding protein-antigen complex in the test sample; and, optionally
(c) comparing the presence and/or amount of antigen binding protein-antigen complex in the test sample to a control.

24. A method of detecting HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2, comprising contacting a composition suspected of containing HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2 with an antigen binding protein of any one of claims 1 to 15 under conditions effective to allow the formation of HLA-DQ2.5:DQ2.5-glia-α1a or HLA-DQ2.5:DQ2.5-glia-α2/antigen binding protein complexes and detecting the complexes so formed.

25. A method of producing an antigen binding protein of any one of claims 1 to 15, comprising the steps of (i) culturing a host cell comprising one or more of the nucleic acids of claim 18 under conditions suitable for the expression of the encoded antibody or protein, and (ii) isolating or obtaining the antigen binding protein from the host cell or from the growth medium/supernatant.

26. The method of claim 25, further comprising a step of purification of the antigen binding protein product and/or formulating the antigen binding protein into a composition including at least one additional component, such as a pharmaceutically acceptable carrier or excipient.

Figure 1

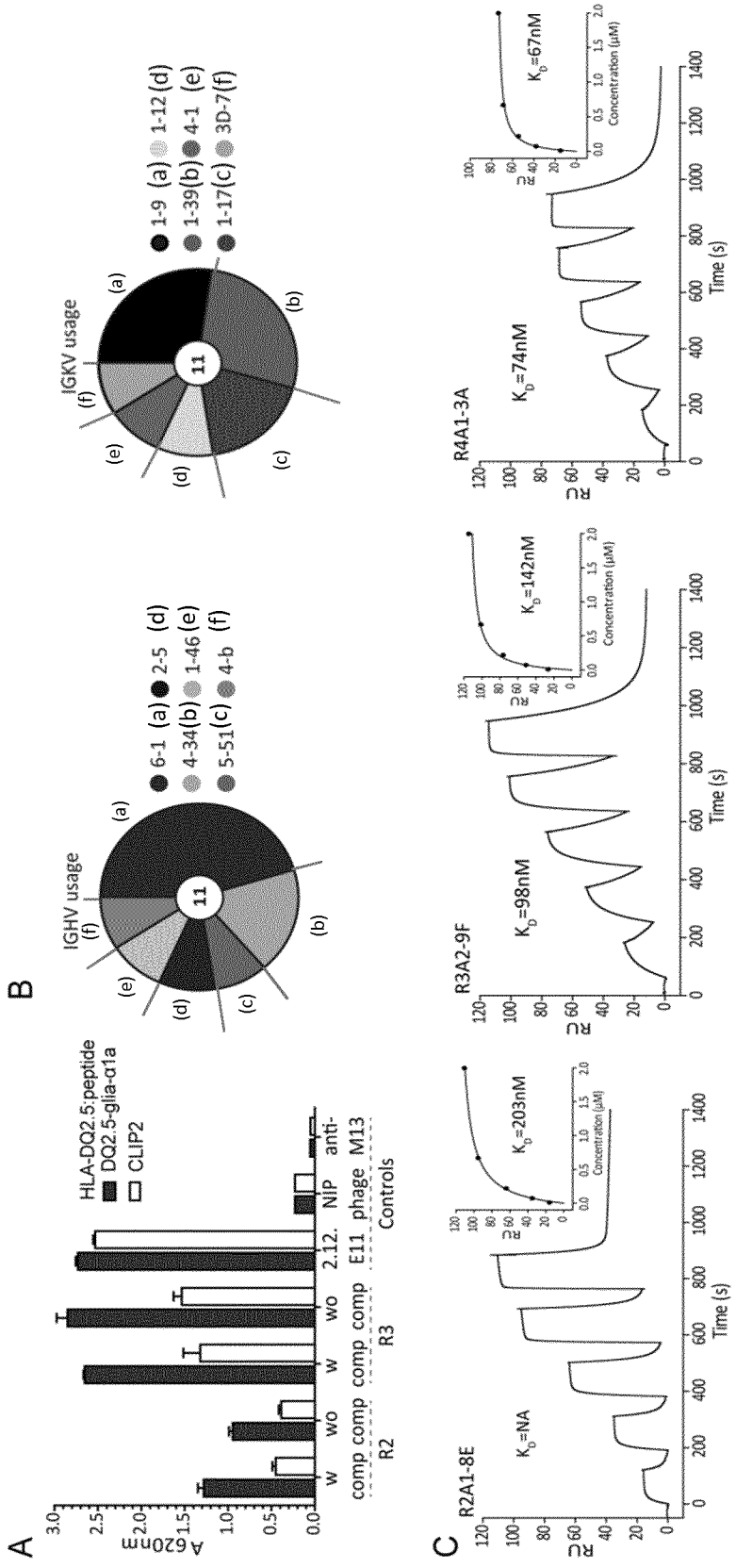

A
HLA-DQ2.5:peptide
DQ2.5-glia-α1a
CLIP2
A620nm
w wo w wo 2.12. NIP anti-
comp comp comp comp E11 phage M13
R2 R3 Controls
B
IGHV usage
6-1 (a) 2-5 (d)
4-34(b) 1-46 (e)
5-51(c) 4-b (f)
IGKV usage
1-9 (a) 1-12 (d)
1-39(b) 4-1 (e)
1-17(c) 3D-7(f)
C
R2A1-8E
K_D=NA
K_D=203nM
R3A2-9F
K_D=98nM
K_D=142nM
R4A1-3A
K_D=74nM
K_D=67nM
RU
Time (s)
Concentration (μM)

Figure 2

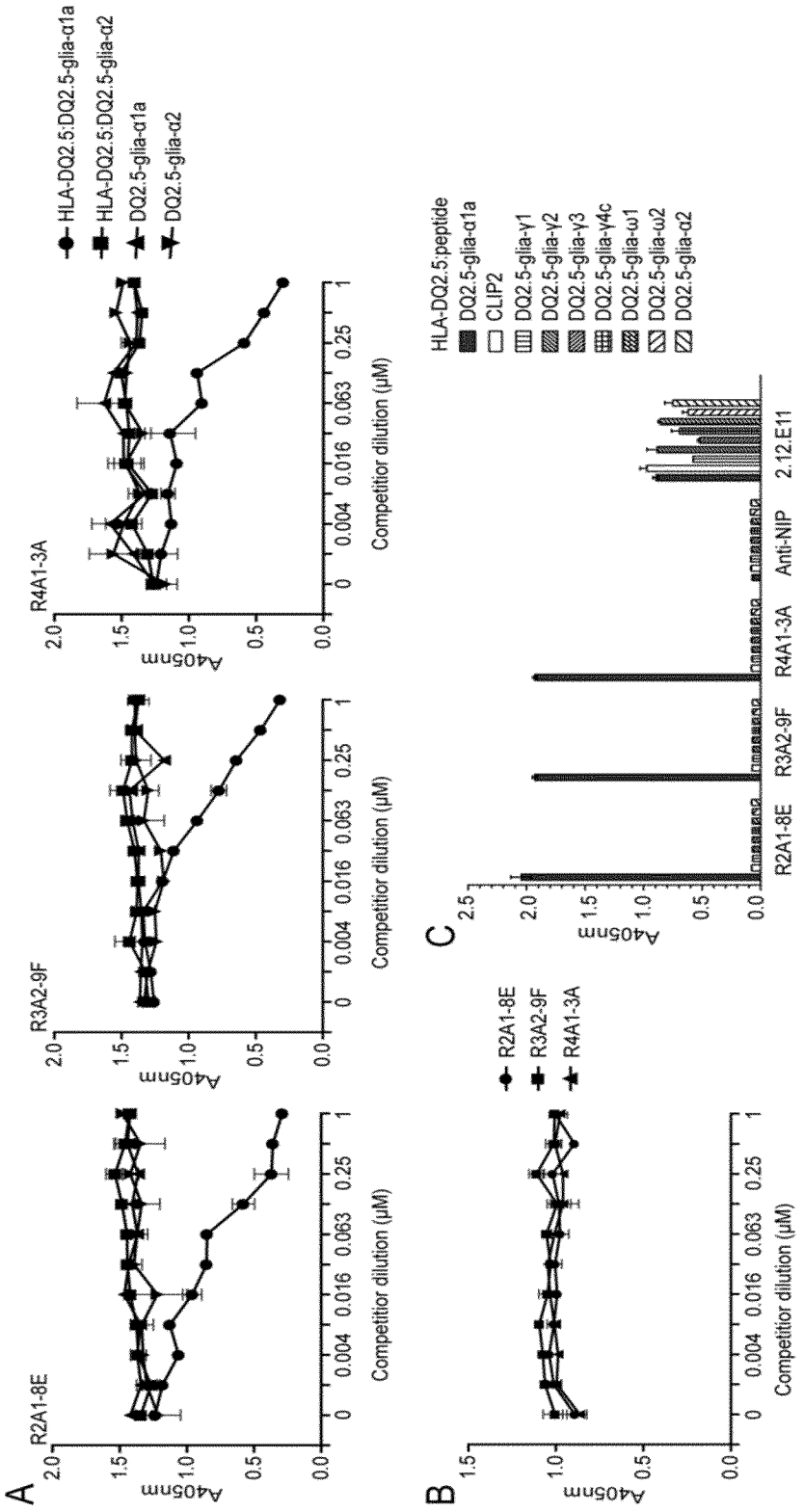

A
R2A1-8E
R3A2-9F
R4A1-3A
A405nm
Competitior dilution (μM)
0
0.004
0.016
0.063
0.25
1
B
R2A1-8E
R3A2-9F
R4A1-3A
C
HLA-DQ2.5:peptide
DQ2.5-glia-α1a
CLIP2
DQ2.5-glia-γ1
DQ2.5-glia-γ2
DQ2.5-glia-γ3
DQ2.5-glia-γ4c
DQ2.5-glia-ω1
DQ2.5-glia-ω2
DQ2.5-glia-α2
R2A1-8E
R3A2-9F
R4A1-3A
Anti-NIP
2.12.E11
HLA-DQ2.5:DQ2.5-glia-α1a
HLA-DQ2.5:DQ2.5-glia-α2
DQ2.5-glia-α1a
DQ2.5-glia-α2

Figure 3

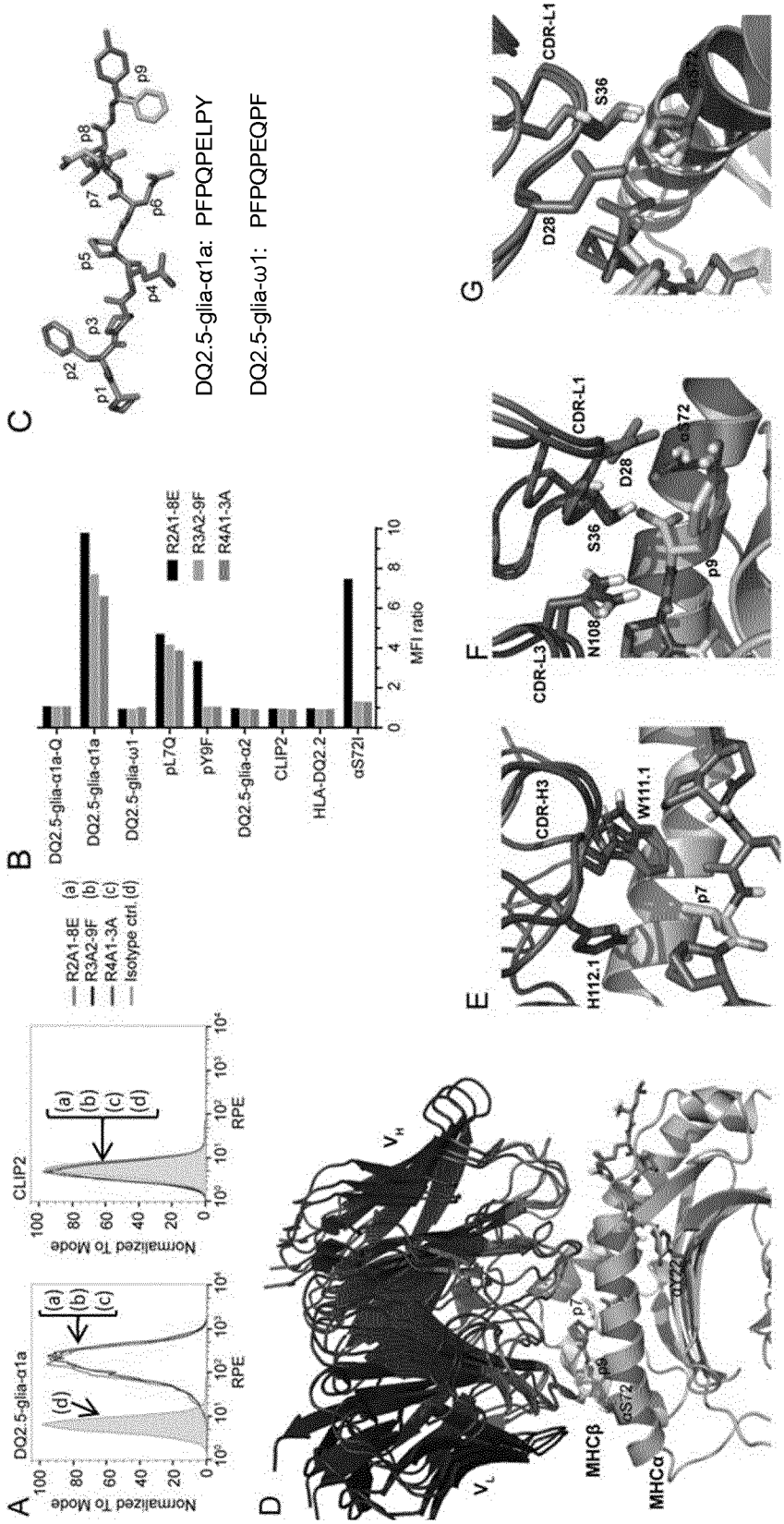

A
DQ2.5-glia-α1a
CLIP2
Normalized To Mode
RPE
(a)
(b)
(c)
(d)
B
R2A1-8E
R3A2-9F
R4A1-3A
Isotype ctrl
DQ2.5-glia-α1a-Q
DQ2.5-glia-α1a
DQ2.5-glia-ω1
pL7Q
pY9F
DQ2.5-glia-α2
CLIP2
HLA-DQ2.2
αS72I
MFI ratio
C
DQ2.5-glia-α1a: PFPQPELPY
DQ2.5-glia-ω1: PFPQPEQPF
D
VH
VL
MHCβ
MHCα
E
CDR-H3
H112.1
W111.1
F
CDR-L3
CDR-L1
N108
S36
D28
G
CDR-L1
S36
D28

Figure 4

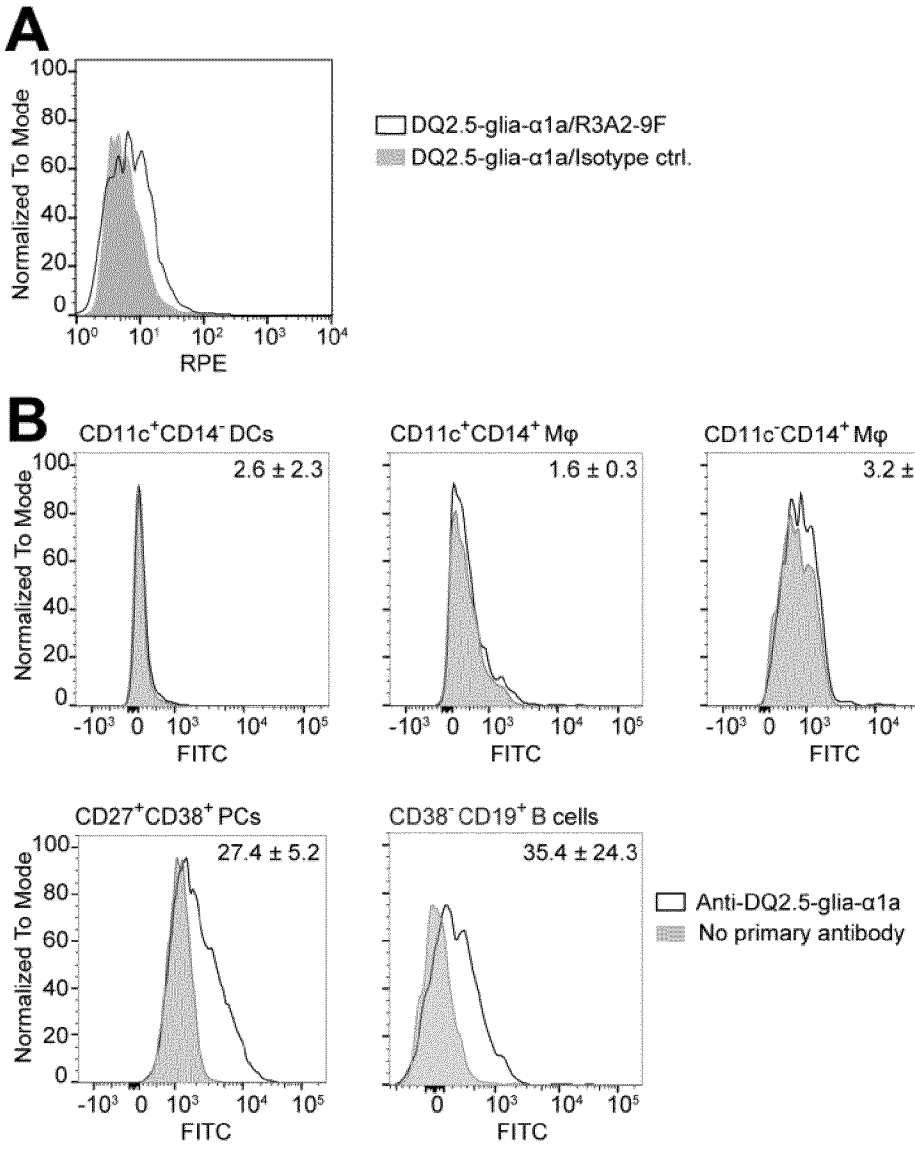

A
Normalized To Mode
RPE
DQ2.5-glia-α1a/R3A2-9F
DQ2.5-glia-α1a/Isotype ctrl.
B
CD11c+CD14- DCs
2.6 ± 2.3
CD11c+CD14+ Mφ
1.6 ± 0.3
CD11c-CD14+ Mφ
3.2 ± 0.4
CD27+CD38+ PCs
27.4 ± 5.2
CD38- CD19+ B cells
35.4 ± 24.3
FITC
Anti-DQ2.5-glia-α1a
No primary antibody

Figure 5

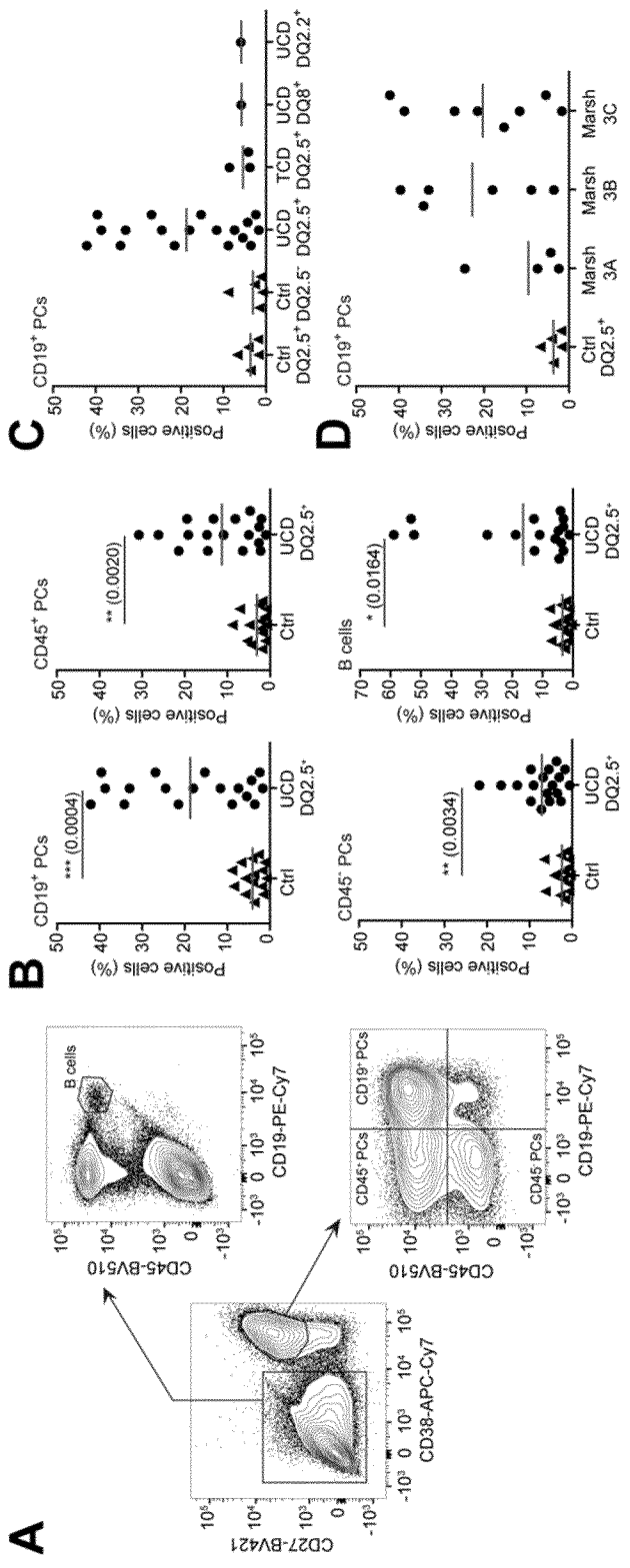

A
CD27-BV421
CD38-APC-Cy7
B cells
CD45-BV510
CD19-PE-Cy7
CD45⁺ PCs
CD19⁺ PCs
CD45⁻ PCs
B
CD19⁺ PCs
*** (0.0004)
Positive cells (%)
Ctrl
UCD DQ2.5⁺
CD45⁺ PCs
** (0.0020)
B cells
* (0.0164)
CD45⁻ PCs
** (0.0034)
C
CD19⁺ PCs
Ctrl DQ2.5⁺
Ctrl DQ2.5⁻
UCD DQ2.5⁺
TCD DQ2.5⁺
UCD DQ8⁺
UCD DQ2.2⁺
D
CD19⁺ PCs
Ctrl DQ2.5⁺
Marsh 3A
Marsh 3B
Marsh 3C

Figure 6

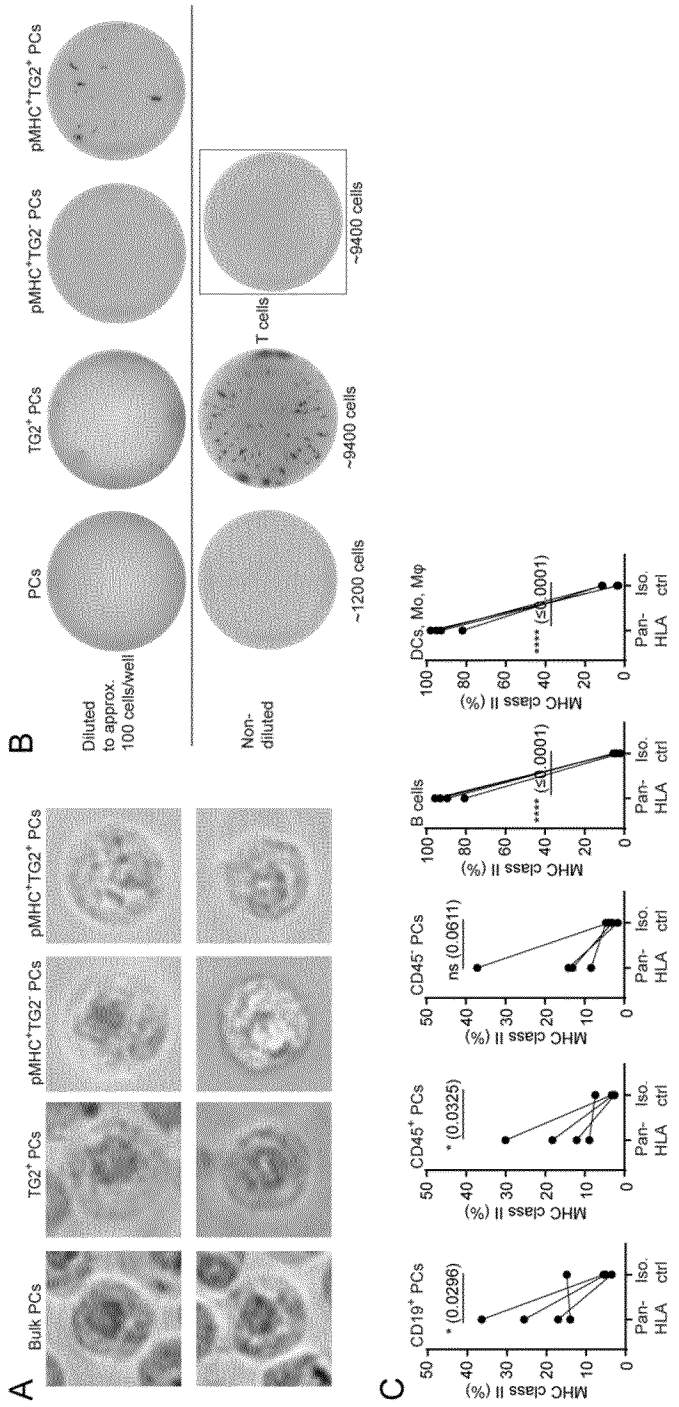
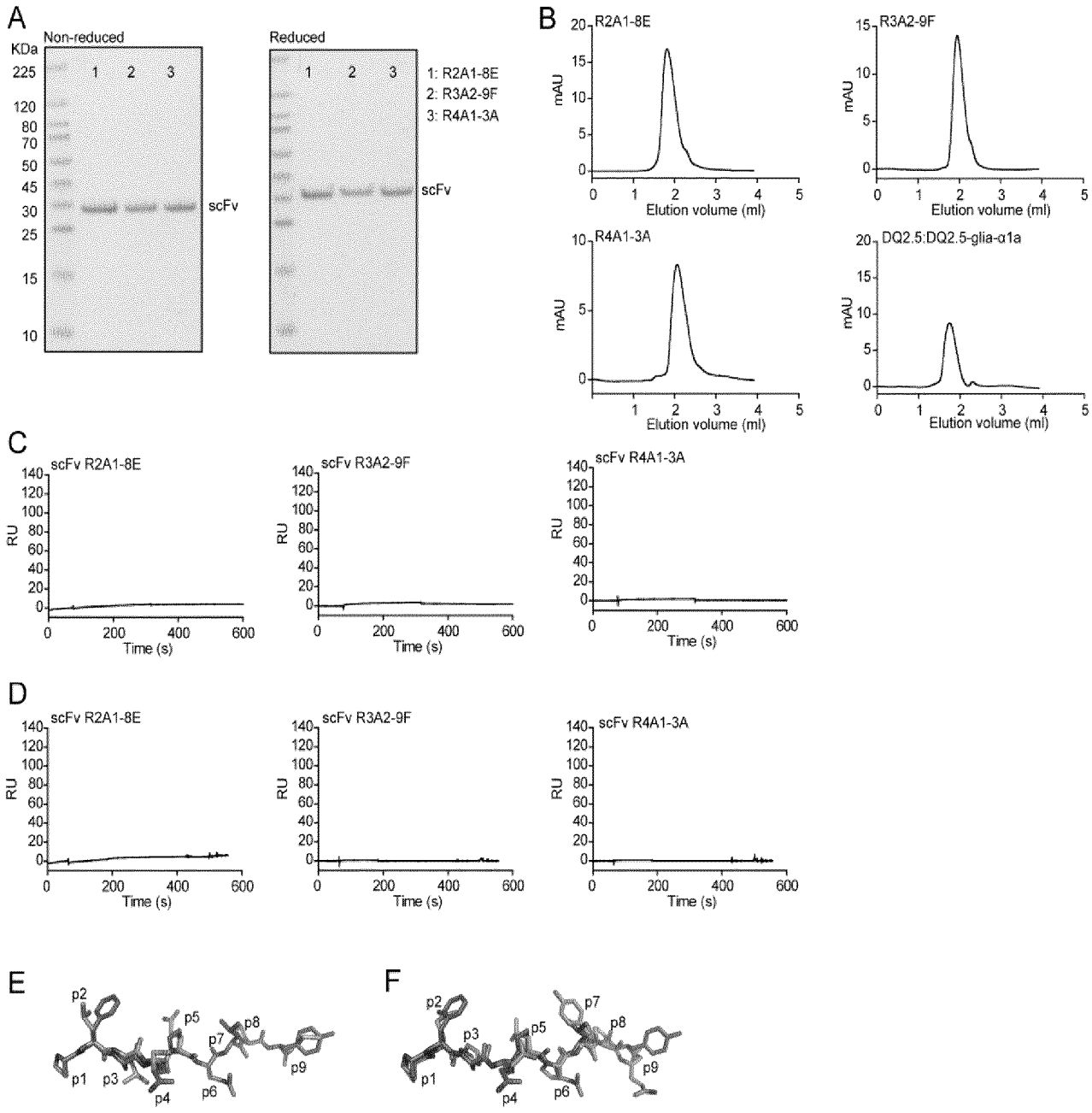

A
Bulk PCs
TG2+ PCs
pMHC+TG2- PCs
pMHC+TG2+ PCs
B
PCs
TG2+ PCs
pMHC+TG2- PCs
pMHC+TG2+ PCs
Diluted to approx. 100 cells/well
Non-diluted
~1200 cells
~9400 cells
T cells
~9400 cells
C
CD19+ PCs
* (0.0296)
CD45+ PCs
* (0.0325)
CD45- PCs
ns (0.0611)
B cells
**** (≤0.0001)
DCs, Mo, Mφ
**** (≤0.0001)
MHC class II (%)
Pan-HLA
Iso. ctrl

Figure 7



DQ2.5-glia-α1a: PFPQPELPY

CLIP2: PLLMQALPM

DQ2.5-glia-α1a: PFPQPELPY

DQ2.5-glia- α2: PQPELPYPQ

Figure 8

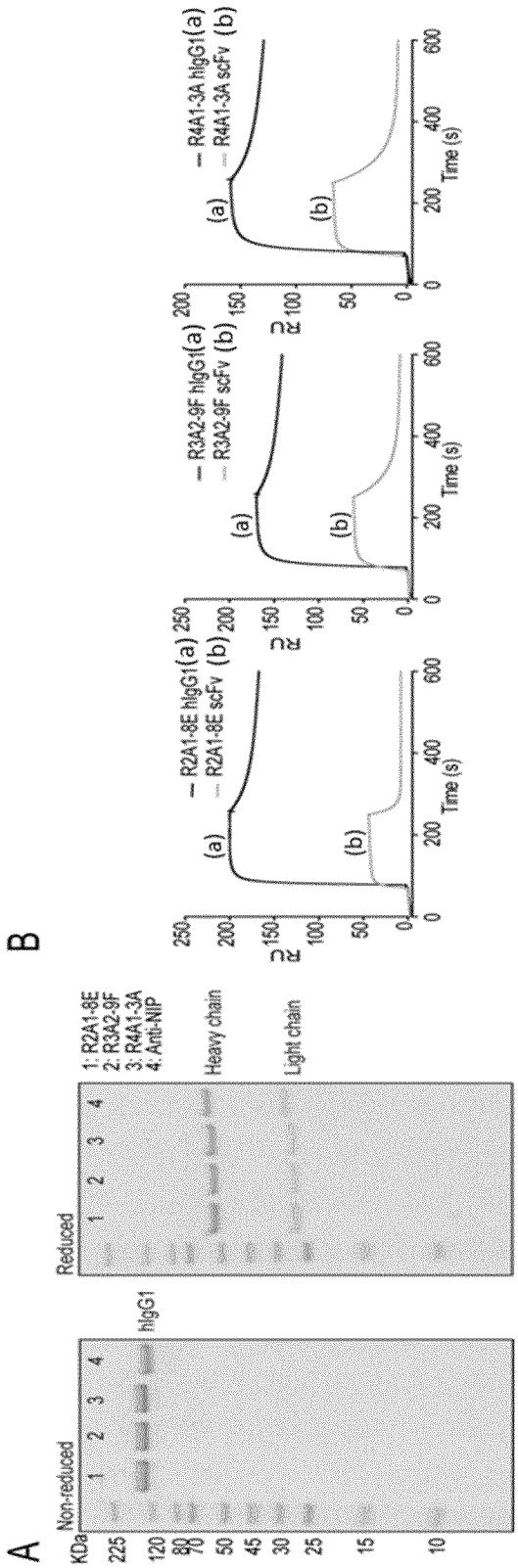

A
Non-reduced
KDa
225
120
80
70
50
45
30
25
15
10
1 2 3 4
hIgG1
Reduced
1 2 3 4
1: R2A1-8E
2: R3A2-9F
3: R4A1-3A
4: Anti-NIP
Heavy chain
Light chain
B
R2A1-8E hIgG1 (a)
R2A1-8E scFv (b)
R3A2-9F hIgG1(a)
R3A2-9F scFv (b)
R4A1-3A hIgG1(a)
R4A1-3A scFv (b)
(a)
(b)
RU
Time (s)

Figure 9

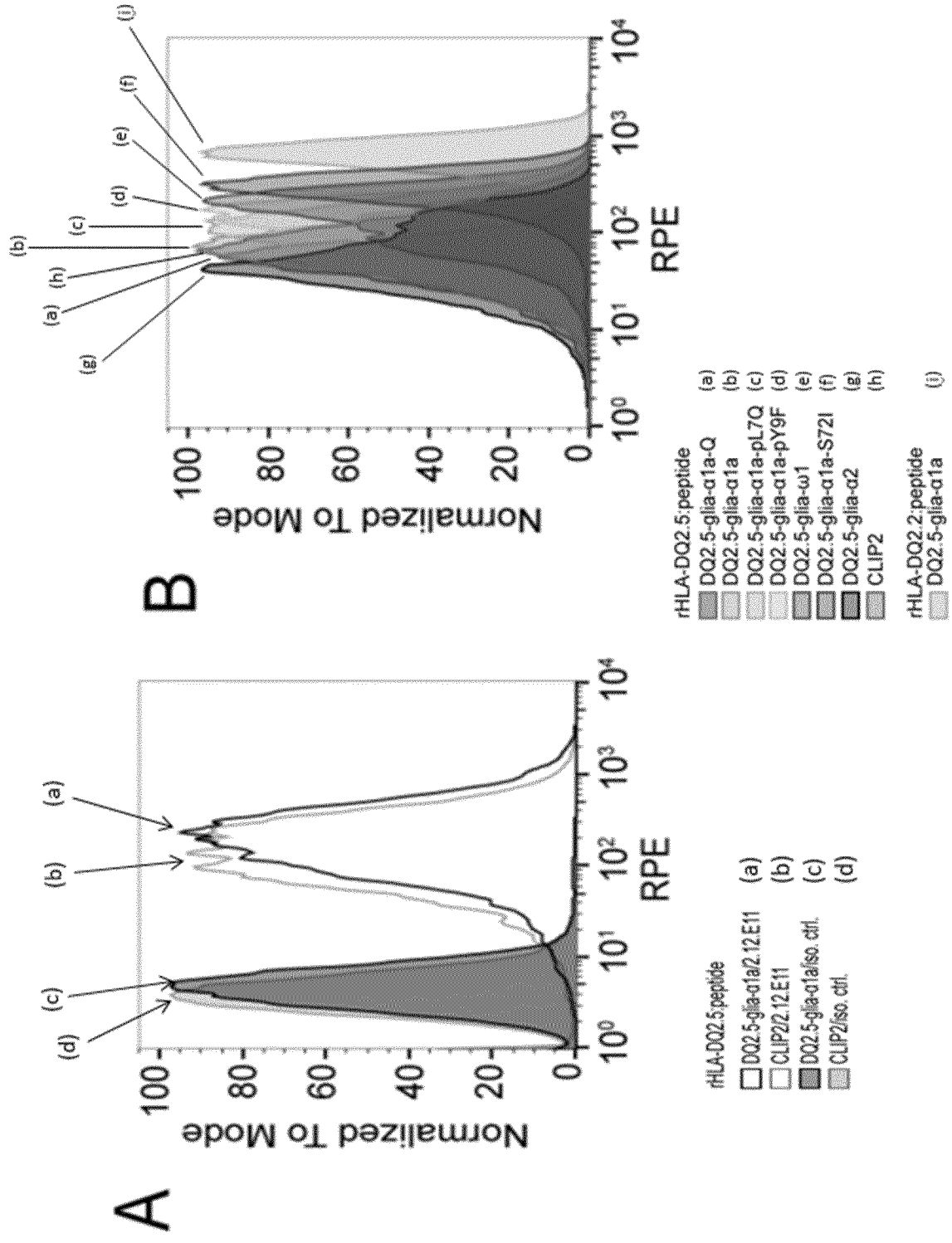

A
Normalized To Mode
RPE
rHLA-DQ2.5:peptide
DQ2.5-glia-α1a2.12.E11 (a)
CLIP2/2.12.E11 (b)
DQ2.5-glia-α1a/iso. ctrl. (c)
CLIP2/iso. ctrl. (d)
B
Normalized To Mode
RPE
rHLA-DQ2.5:peptide
DQ2.5-glia-α1a-Q (a)
DQ2.5-glia-α1a (b)
DQ2.5-glia-α1a-pL7Q (c)
DQ2.5-glia-α1a-pY9F (d)
DQ2.5-glia-ω1 (e)
DQ2.5-glia-α1a-S72I (f)
DQ2.5-glia-α2 (g)
CLIP2 (h)
rHLA-DQ2.2:peptide (i)
DQ2.5-glia-α1a

Figure 9 continued

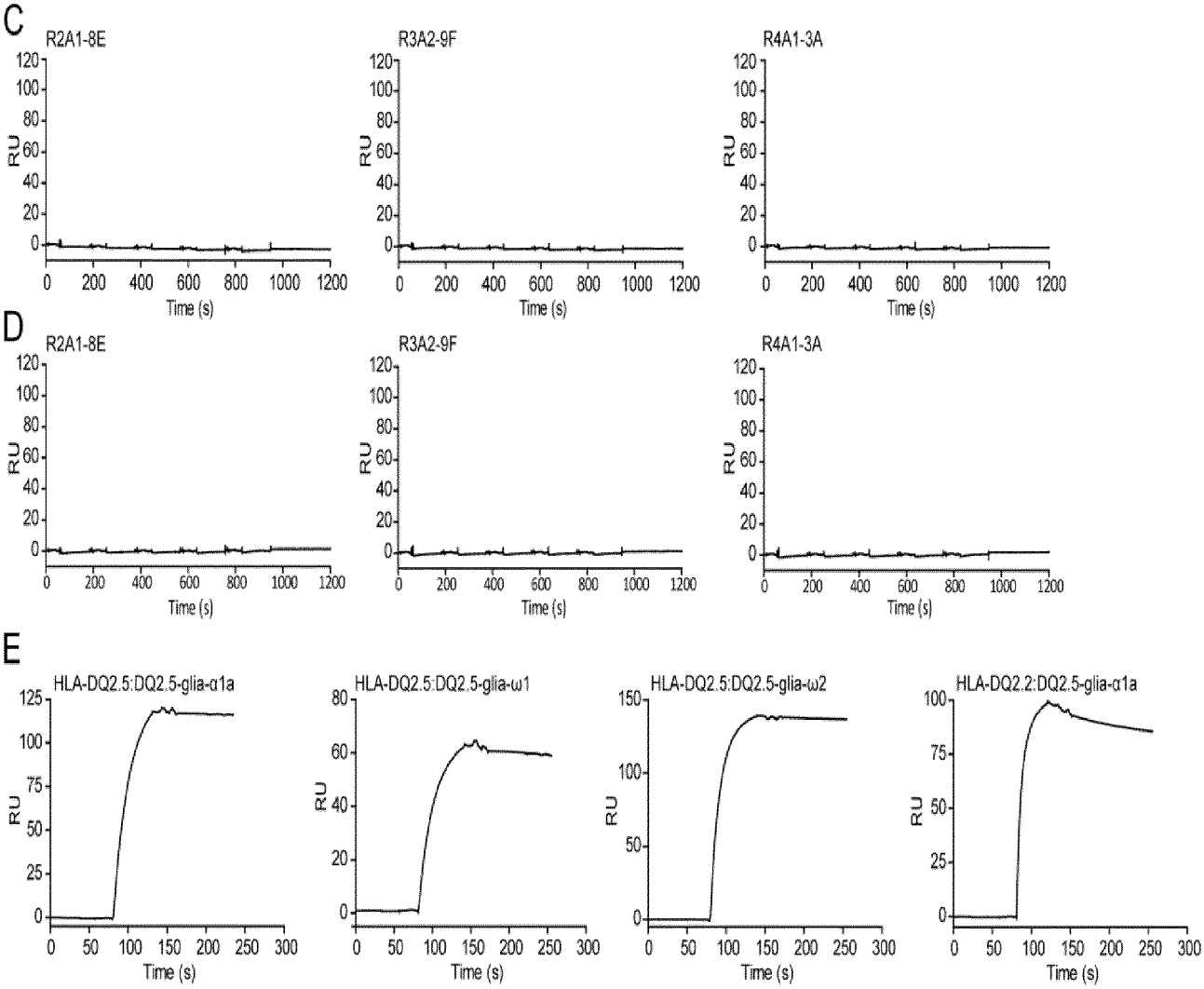


Figure 10

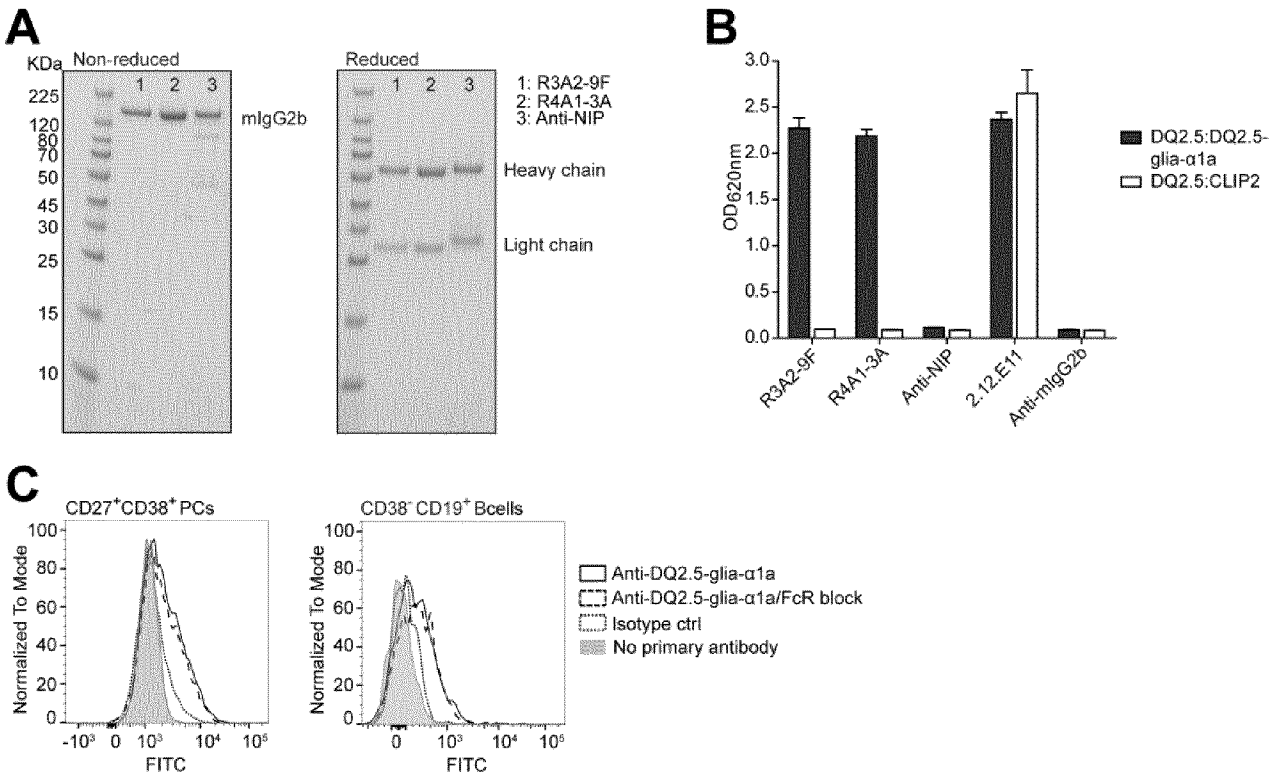

A
KDa
Non-reduced
Reduced
1 2 3
225
120
80
70
50
45
30
25
15
10
mIgG2b
1: R3A2-9F
2: R4A1-3A
3: Anti-NIP
Heavy chain
Light chain
B
OD620nm
3.0
2.5
2.0
1.5
1.0
0.5
0.0
R3A2-9F
R4A1-3A
Anti-NIP
2.12.E11
Anti-mIgG2b
DQ2.5:DQ2.5-glia-α1a
DQ2.5:CLIP2
C
CD27+CD38+ PCs
CD38- CD19+ Bcells
Normalized To Mode
100
80
60
40
20
0
-10³ 0 10³ 10⁴ 10⁵
FITC
Anti-DQ2.5-glia-α1a
Anti-DQ2.5-glia-α1a/FcR block
Isotype ctrl
No primary antibody

Figure 11

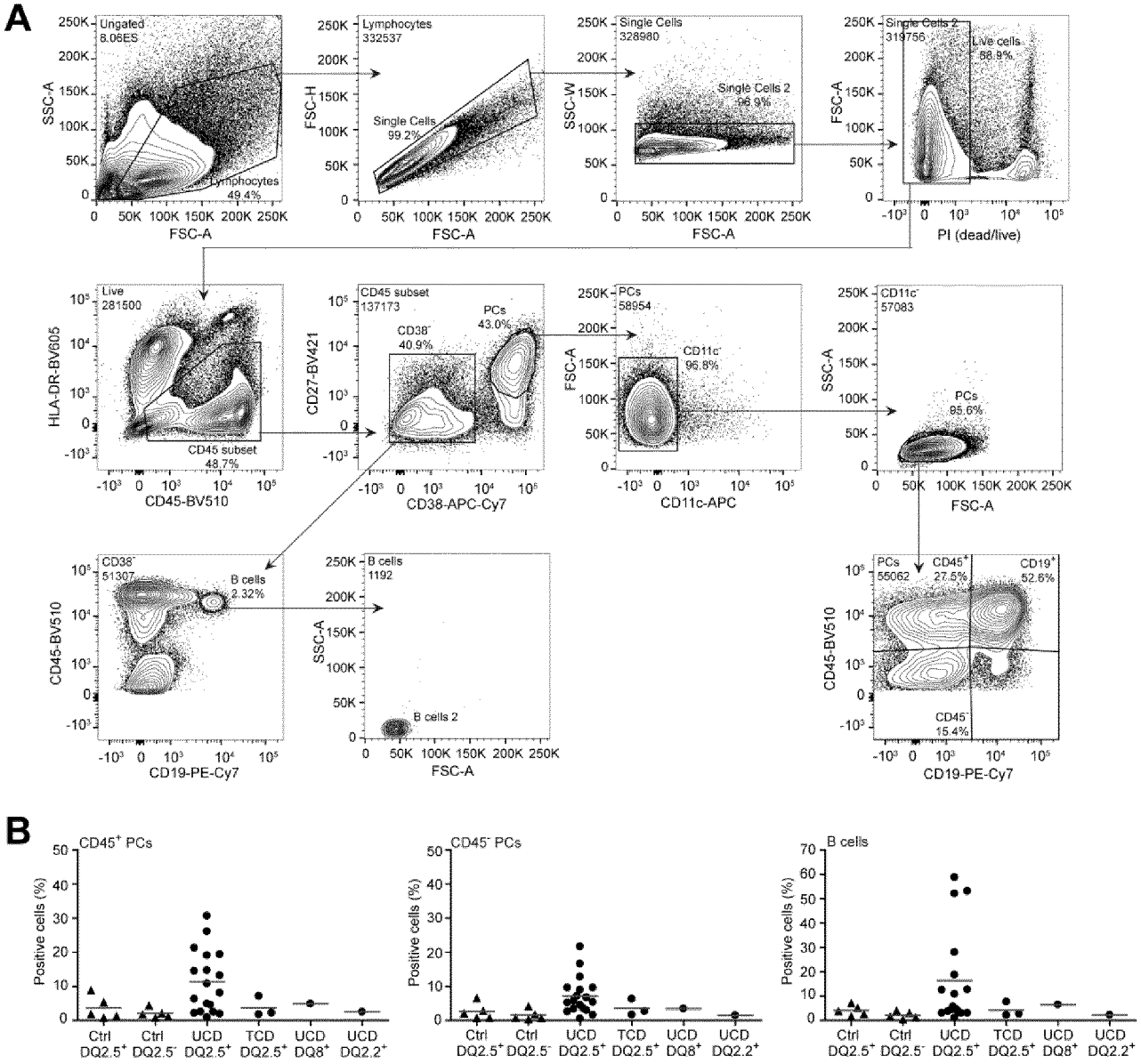

A
Ungated
8.06ES
Lymphocytes
49.4%
SSC-A
FSC-A
Lymphocytes
332537
Single Cells
99.2%
FSC-H
Single Cells
328980
Single Cells 2
96.9%
SSC-W
Single Cells 2
319756
Live cells
68.9%
PI (dead/live)
Live
281500
CD45 subset
48.7%
HLA-DR-BV605
CD45-BV510
CD45 subset
137173
CD38+
40.9%
PCs
43.0%
CD27-BV421
CD38-APC-Cy7
PCs
58954
CD11c+
96.8%
CD11c-APC
CD11c+
57083
PCs
85.6%
CD38+
51307
B cells
2.32%
CD19-PE-Cy7
B cells
1192
B cells 2
PCs
55062
CD45+
27.5%
CD19+
52.6%
CD45-
15.4%
B
CD45+ PCs
CD45- PCs
B cells
Positive cells (%)
Ctrl DQ2.5+
Ctrl DQ2.5-
UCD DQ2.5+
TCD DQ2.5+
UCD DQ8+
UCD DQ2.2+

Figure 12

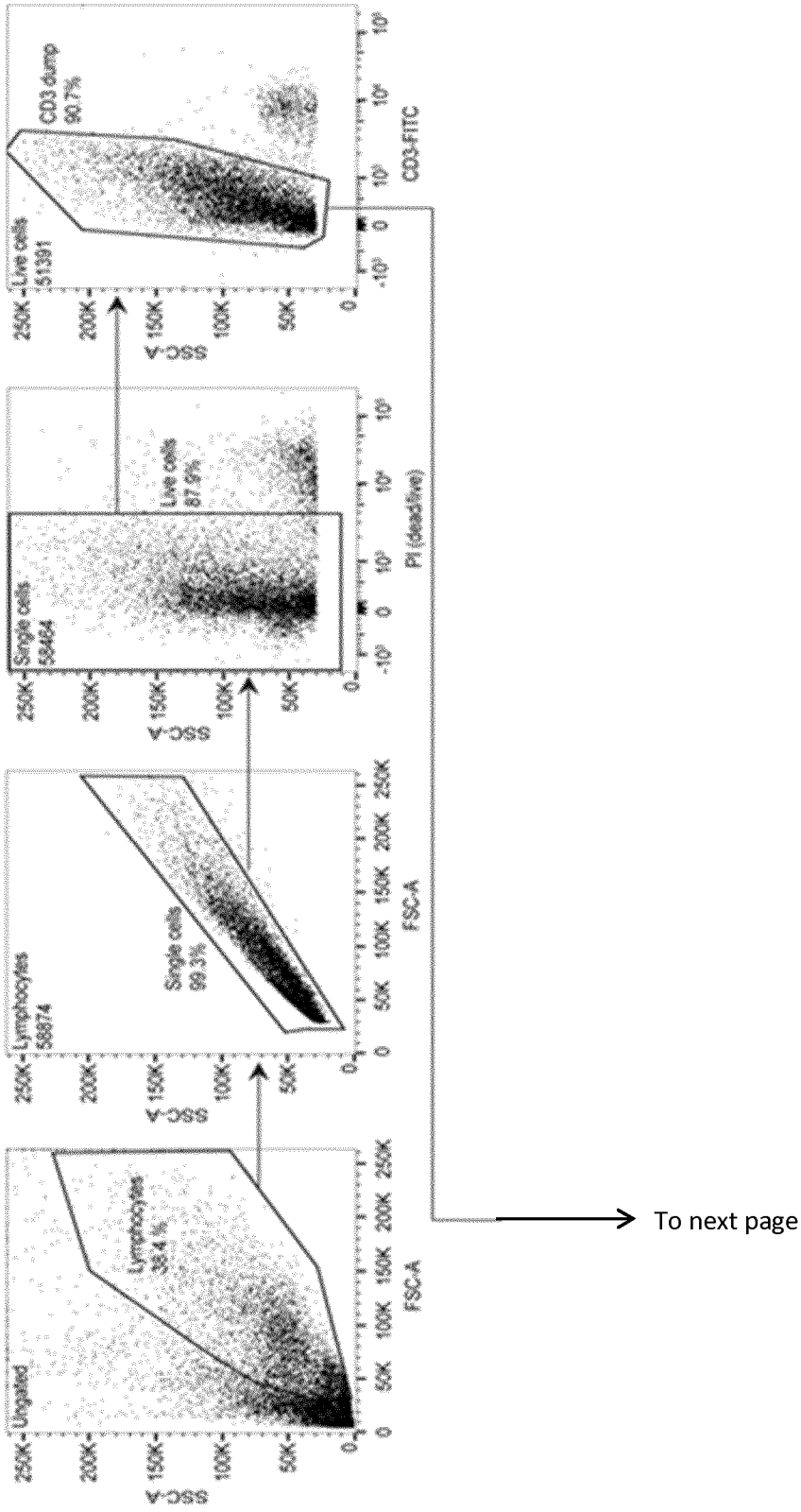

Ungated
Lymphocytes
39.4 %
SSC-A
FSC-A
Lymphocytes
58874
Single cells
99.3%
Single cells
58464
Live cells
87.9%
PI (dead/live)
Live cells
51391
CD3 dump
90.7%
CD3-FITC
To next page

Figure 12 continued

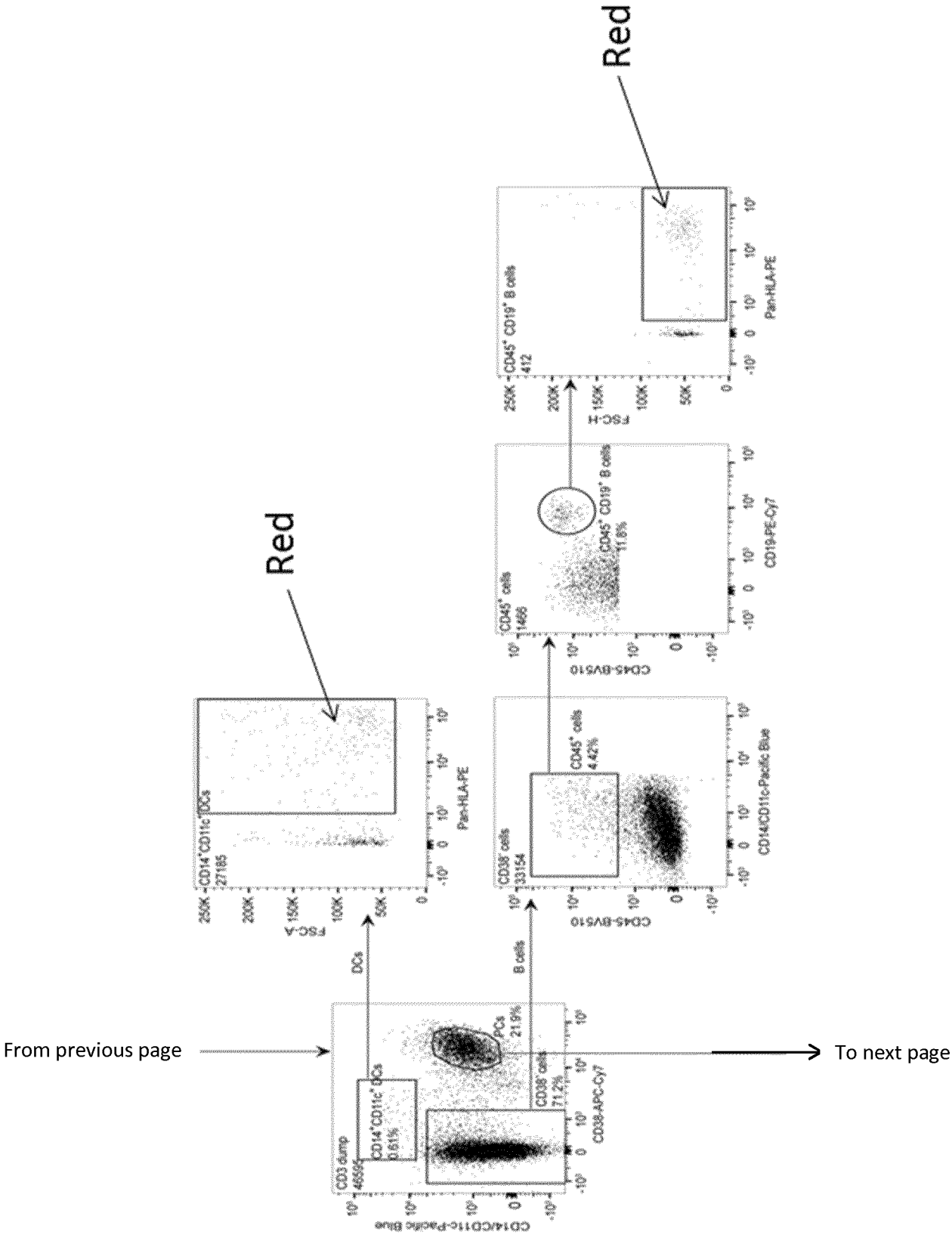


Figure 12 continued

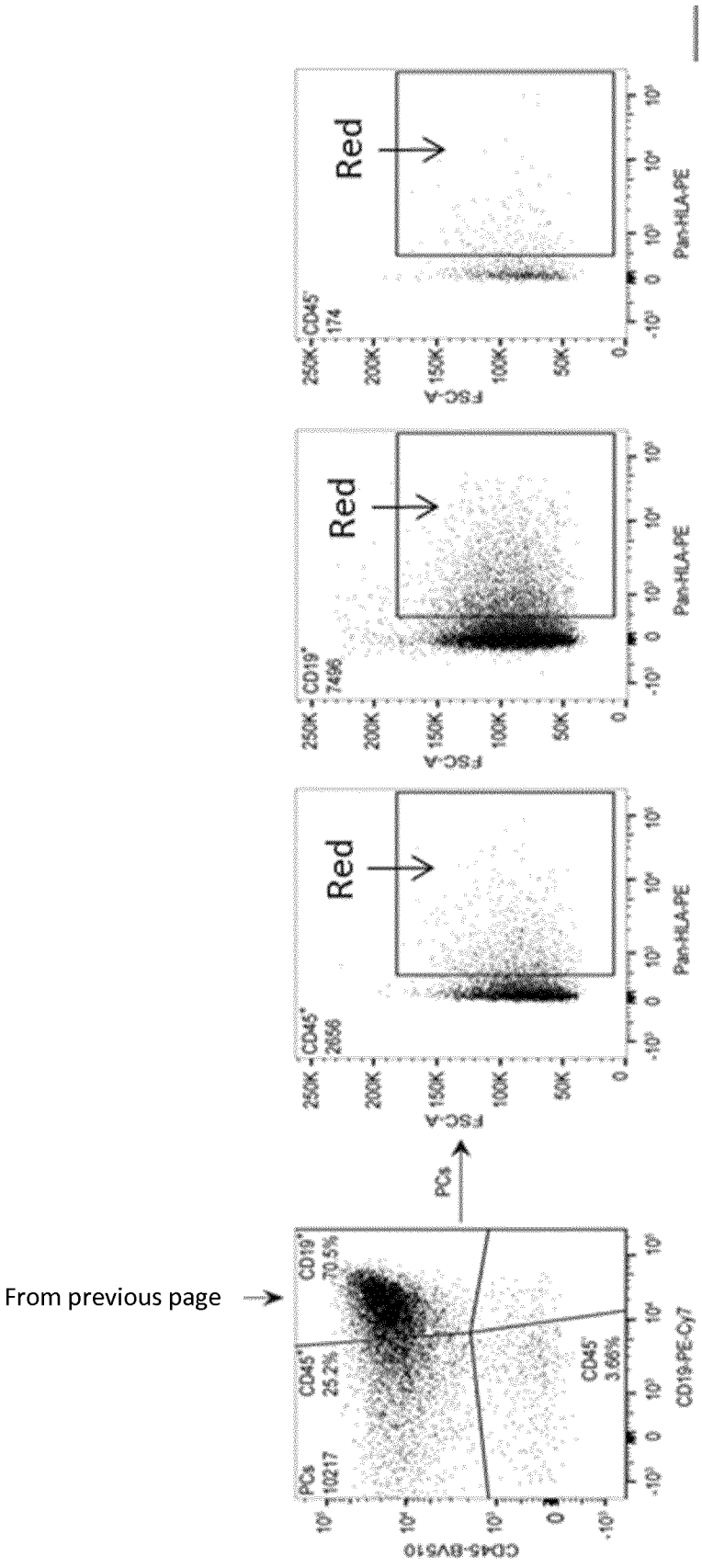


Figure 13

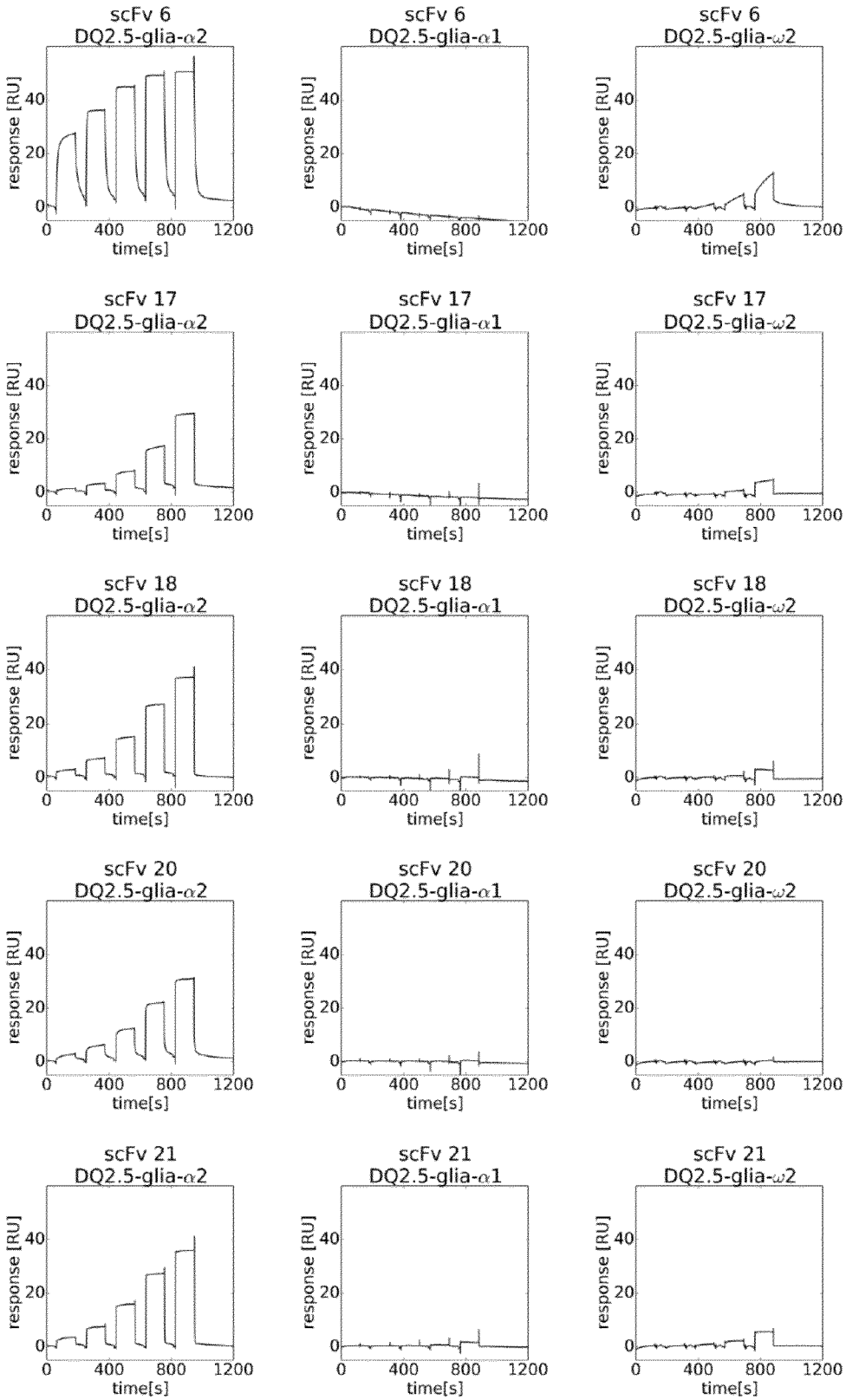

scFv 6
DQ2.5-glia-α2
scFv 6
DQ2.5-glia-α1
scFv 6
DQ2.5-glia-ω2
scFv 17
DQ2.5-glia-α2
scFv 17
DQ2.5-glia-α1
scFv 17
DQ2.5-glia-ω2
scFv 18
DQ2.5-glia-α2
scFv 18
DQ2.5-glia-α1
scFv 18
DQ2.5-glia-ω2
scFv 20
DQ2.5-glia-α2
scFv 20
DQ2.5-glia-α1
scFv 20
DQ2.5-glia-ω2
scFv 21
DQ2.5-glia-α2
scFv 21
DQ2.5-glia-α1
scFv 21
DQ2.5-glia-ω2
response [RU]
time[s]
0
20
40
0
400
800
1200

Figure 13 continued

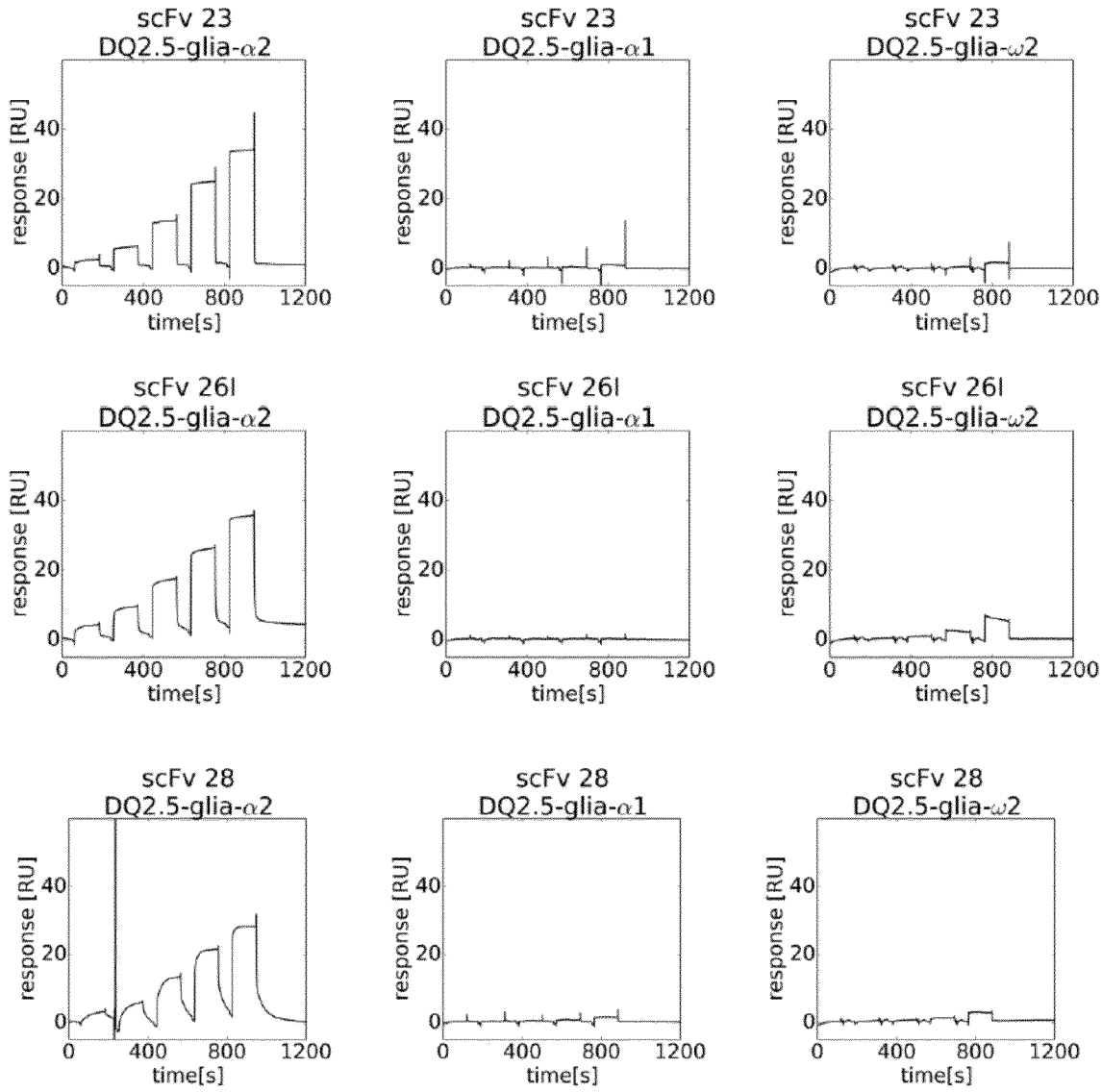


Figure 14

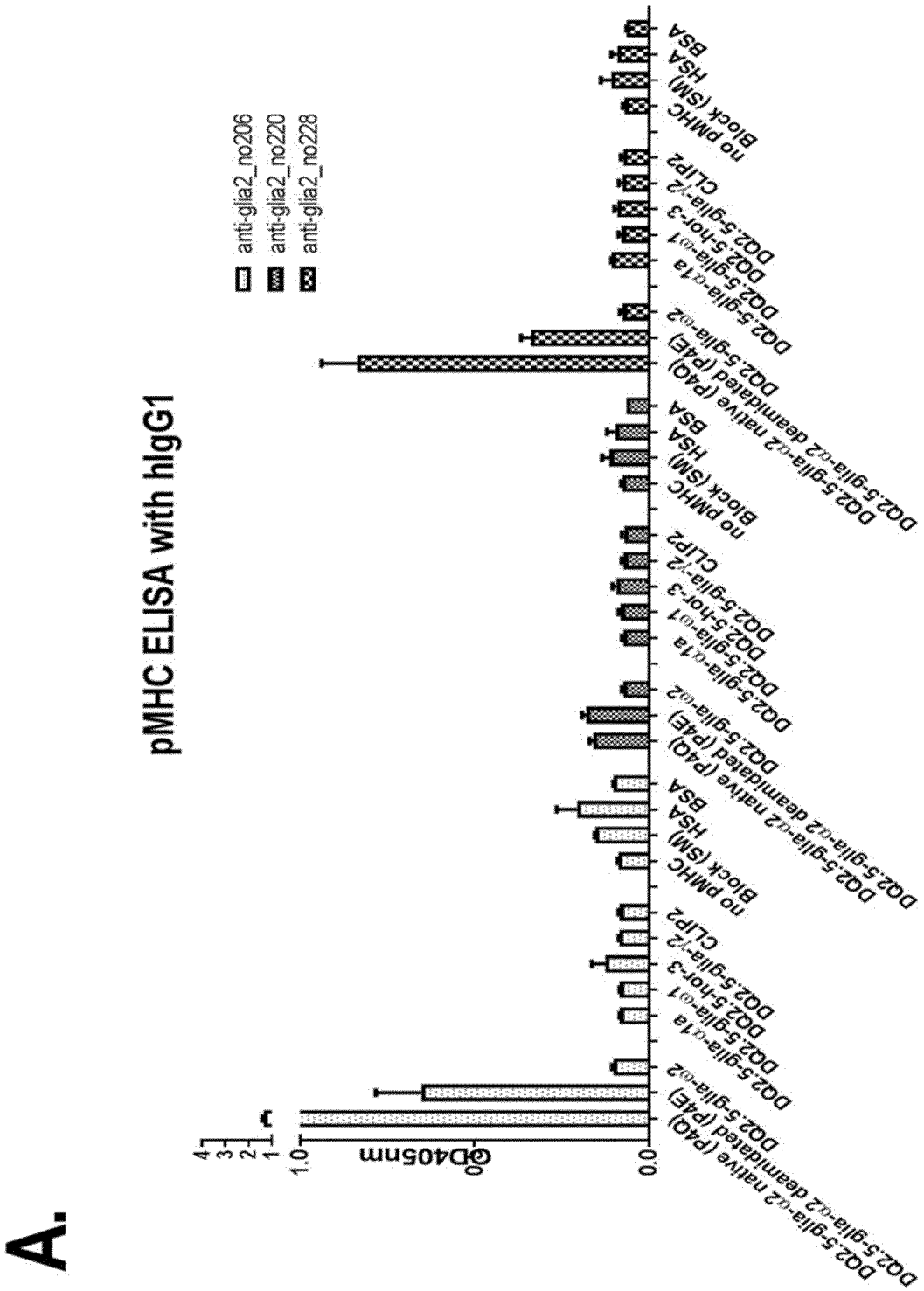

A.
pMHC ELISA with hIgG1
OD405nm
anti-glia2_no206
anti-glia2_no220
anti-glia2_no228
DQ2.5-glia-α2 native (P4Q)
DQ2.5-glia-α2 deamidated (P4E)
DQ2.5-glia-α2
DQ2.5-glia-α1a
DQ2.5-glia-ω1
DQ2.5-hor-3
DQ2.5-glia-γ2
CLIP2
no pMHC
Block (SM)
HSA
BSA

Figure 14 continued

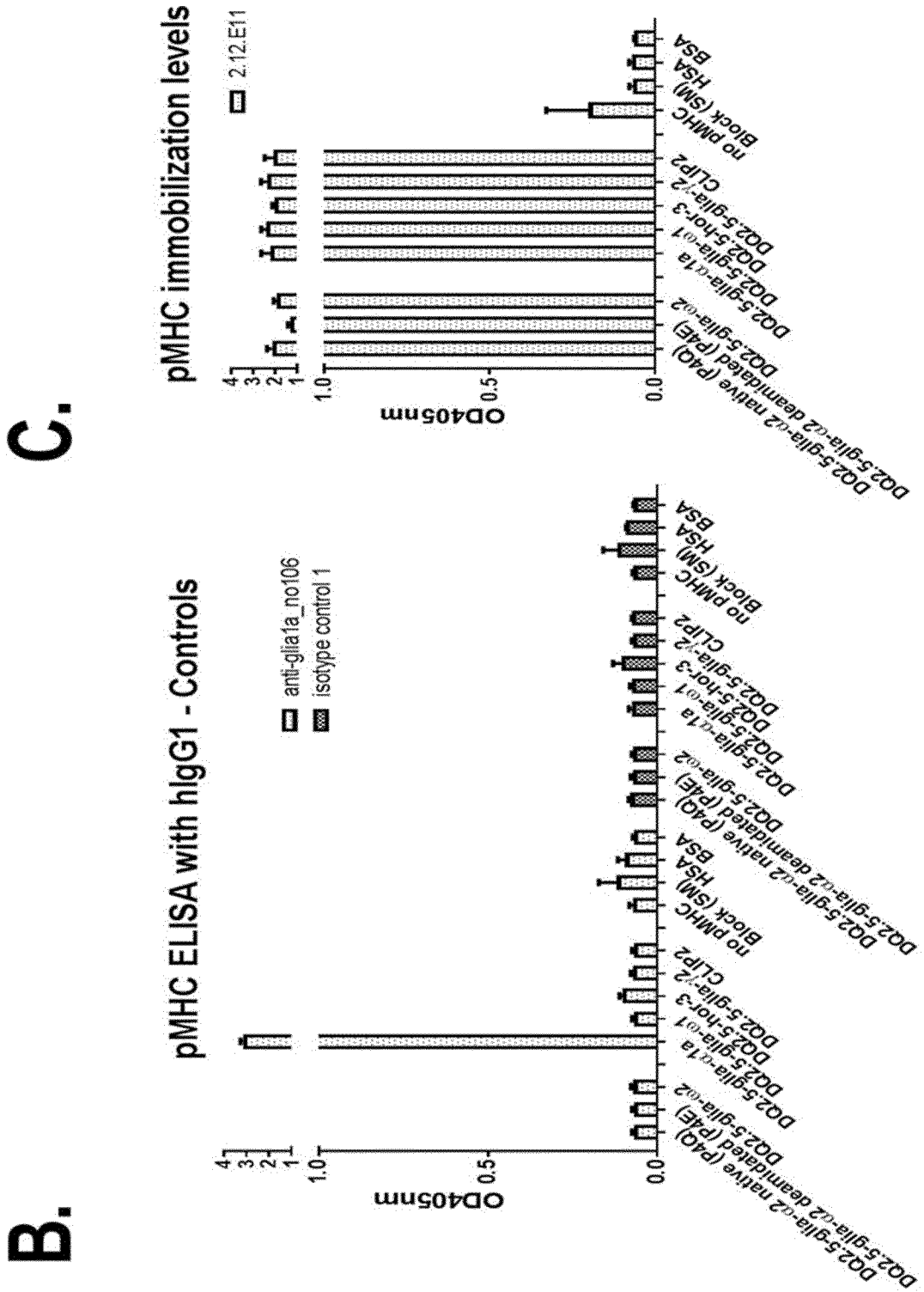


Figure 15

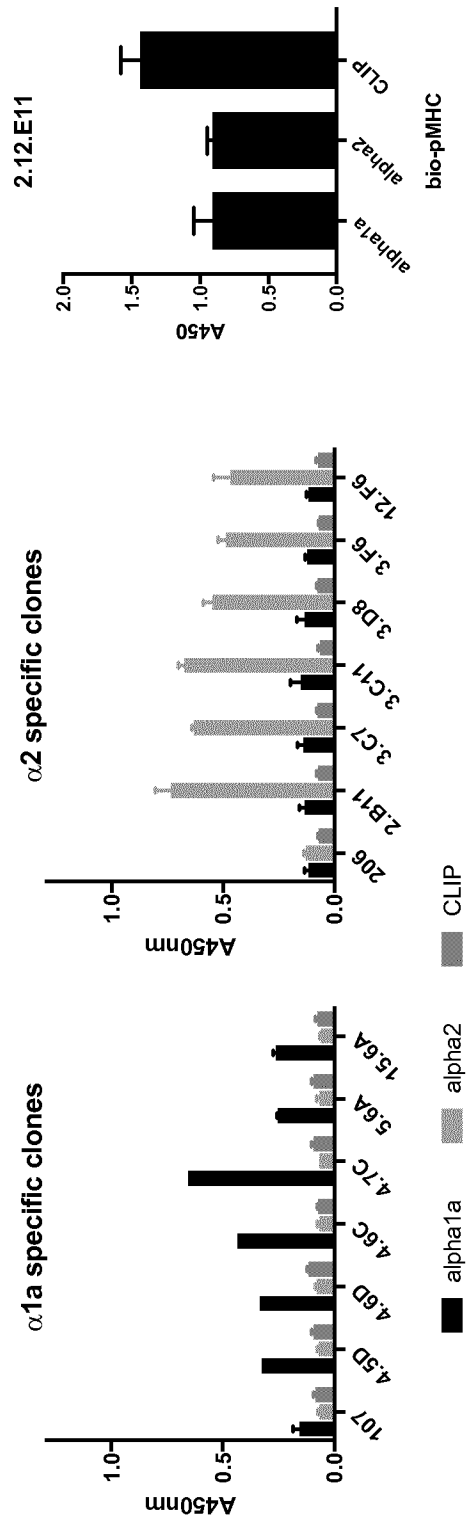

2.12.E11
bio-pMHC
alpha1a
alpha2
CLIP
A450
2.0
1.5
1.0
0.5
0.0
α2 specific clones
A450nm
2D6
2.B11
3.C7
3.C11
3.D8
3.F6
12.F6
α1a specific clones
10.7
4.5D
4.6D
4.6C
4.7C
5.6A
15.6A
alpha1a
alpha2
CLIP

Figure 16

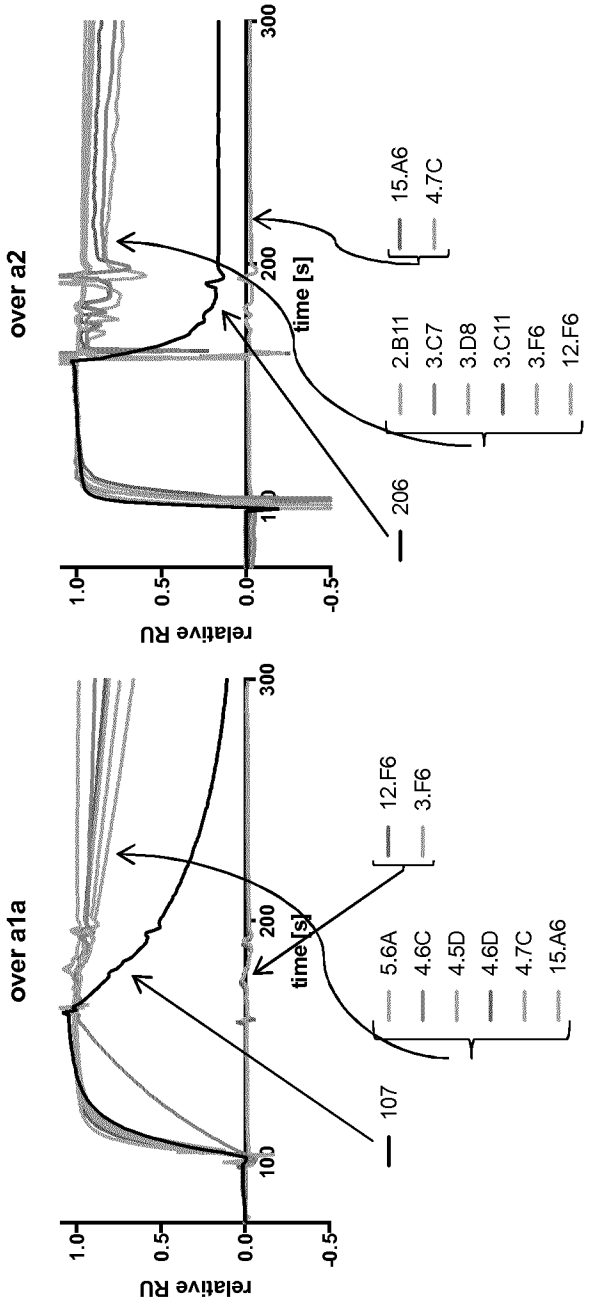

over a2
relative RU
1.0
0.5
0.0
-0.5
100
200
300
time [s]
206
15.A6
4.7C
2.B11
3.C7
3.D8
3.C11
3.F6
12.F6
over a1a
relative RU
1.0
0.5
0.0
-0.5
100
200
300
time [s]
107
12.F6
3.F6
5.6A
4.6C
4.5D
4.6D
4.7C
15.A6

Figure 17

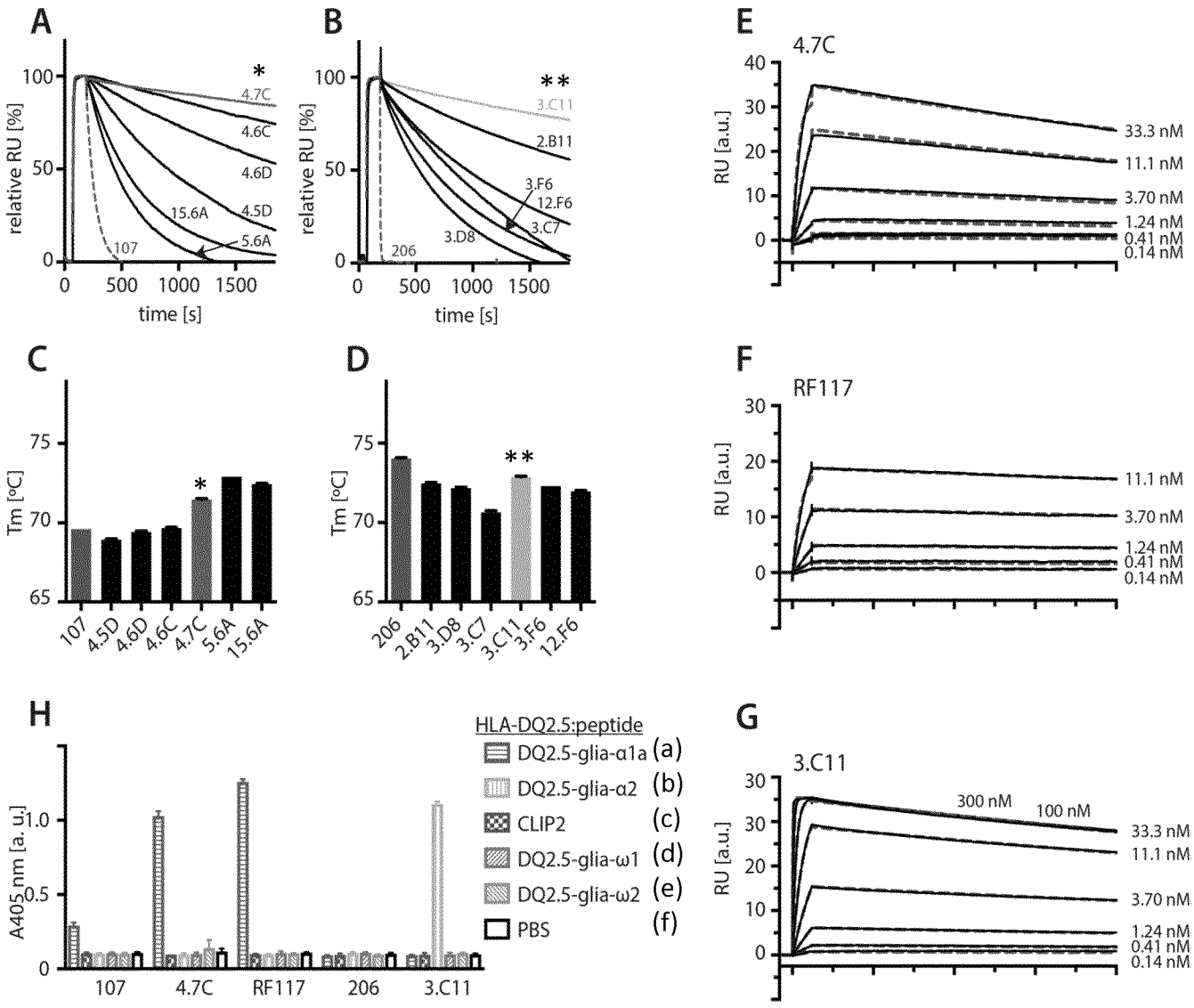

A
B
relative RU [%]
time [s]
4.7C
4.6C
4.6D
15.6A
4.5D
5.6A
107
3.C11
2.B11
3.F6
12.F6
3.C7
3.D8
206
C
D
Tm [°C]
107
4.5D
4.6D
4.6C
4.7C
5.6A
15.6A
206
2.B11
3.D8
3.C7
3.C11
3.F6
12.F6
E
4.7C
RU [a.u.]
33.3 nM
11.1 nM
3.70 nM
1.24 nM
0.41 nM
0.14 nM
F
RF117
G
3.C11
300 nM
100 nM
H
A405 nm [a. u.]
HLA-DQ2.5:peptide
DQ2.5-glia-α1a (a)
DQ2.5-glia-α2 (b)
CLIP2 (c)
DQ2.5-glia-ω1 (d)
DQ2.5-glia-ω2 (e)
PBS (f)

Figure 18

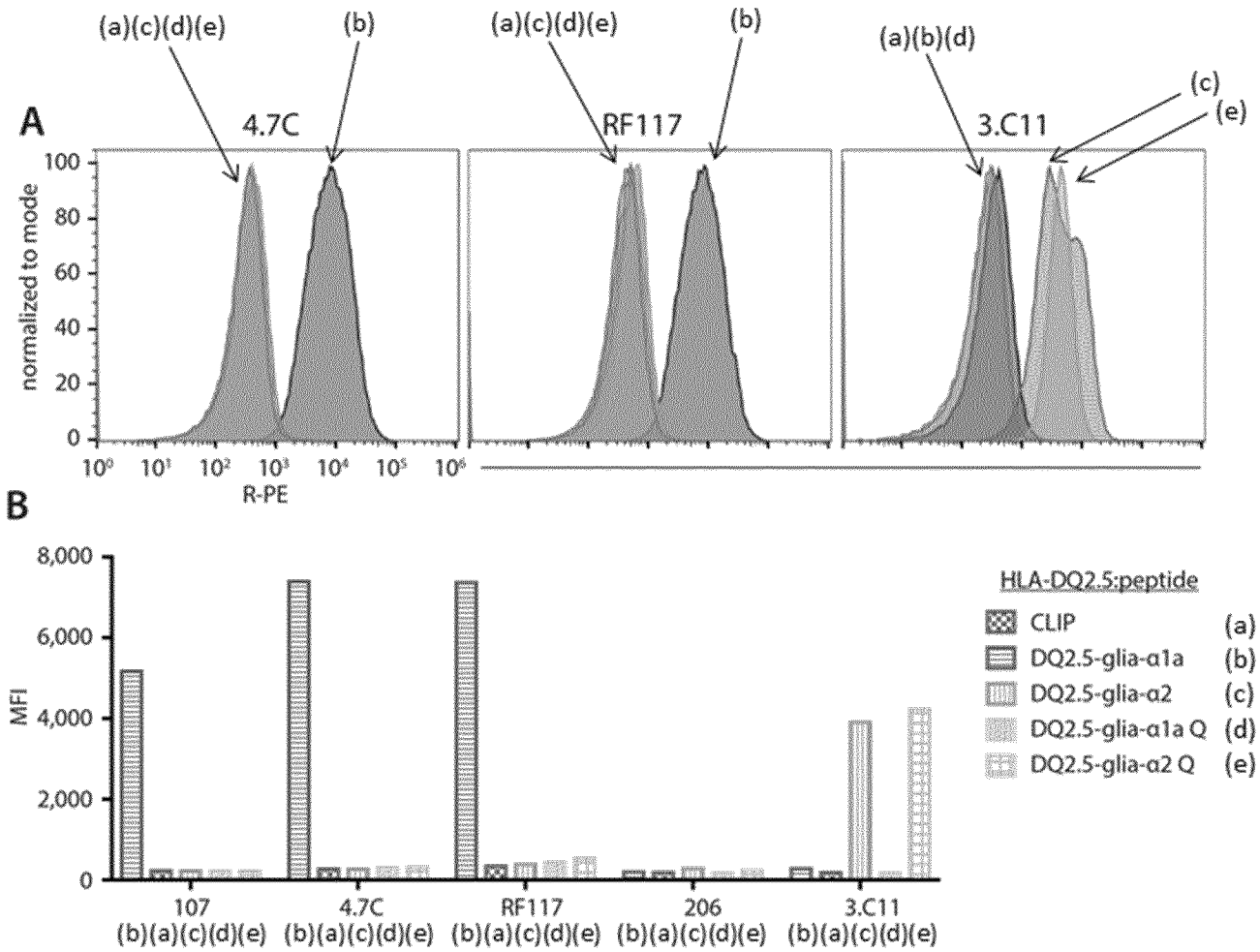

A
4.7C
RF117
3.C11
(a)(c)(d)(e)
(b)
(a)(b)(d)
(c)
(e)
normalized to mode
R-PE
B
MFI
107
4.7C
RF117
206
3.C11
(b)(a)(c)(d)(e)
HLA-DQ2.5:peptide
CLIP (a)
DQ2.5-glia-α1a (b)
DQ2.5-glia-α2 (c)
DQ2.5-glia-α1a Q (d)
DQ2.5-glia-α2 Q (e)

Figure 19

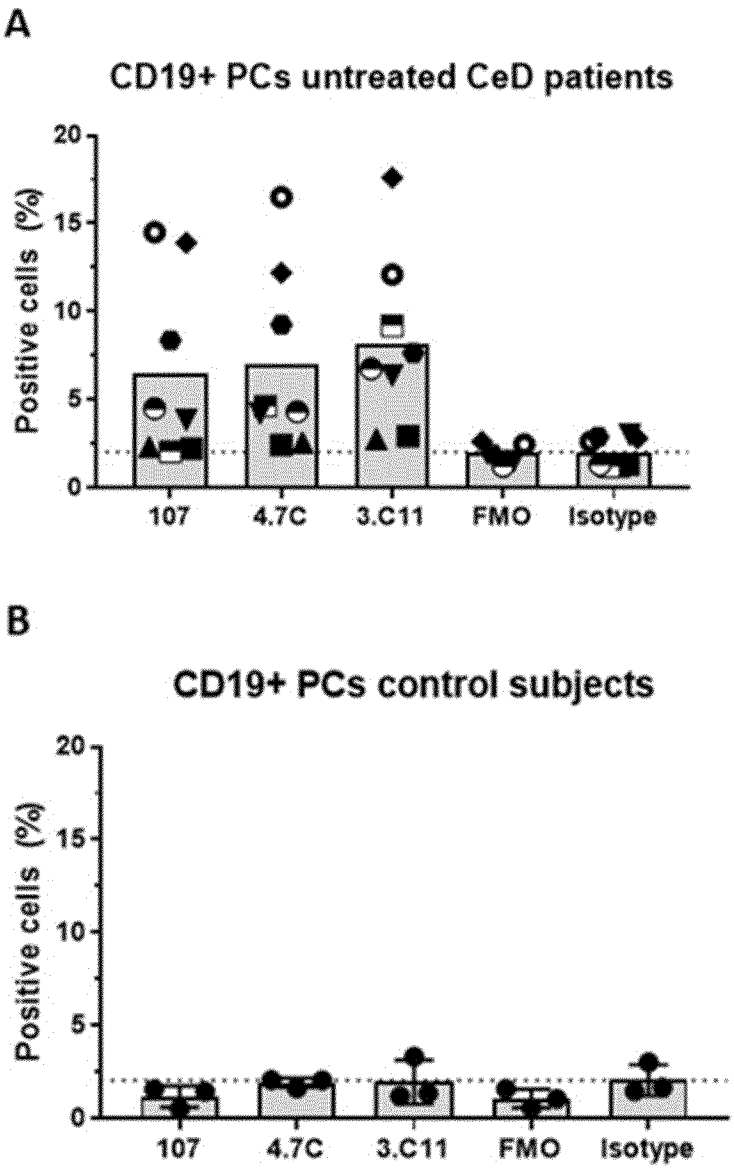

A
CD19+ PCs untreated CeD patients
Positive cells (%)
20
15
10
5
0
107
4.7C
3.C11
FMO
Isotype
B
CD19+ PCs control subjects
Positive cells (%)
20
15
10
5
0
107
4.7C
3.C11
FMO
Isotype

Figure 20

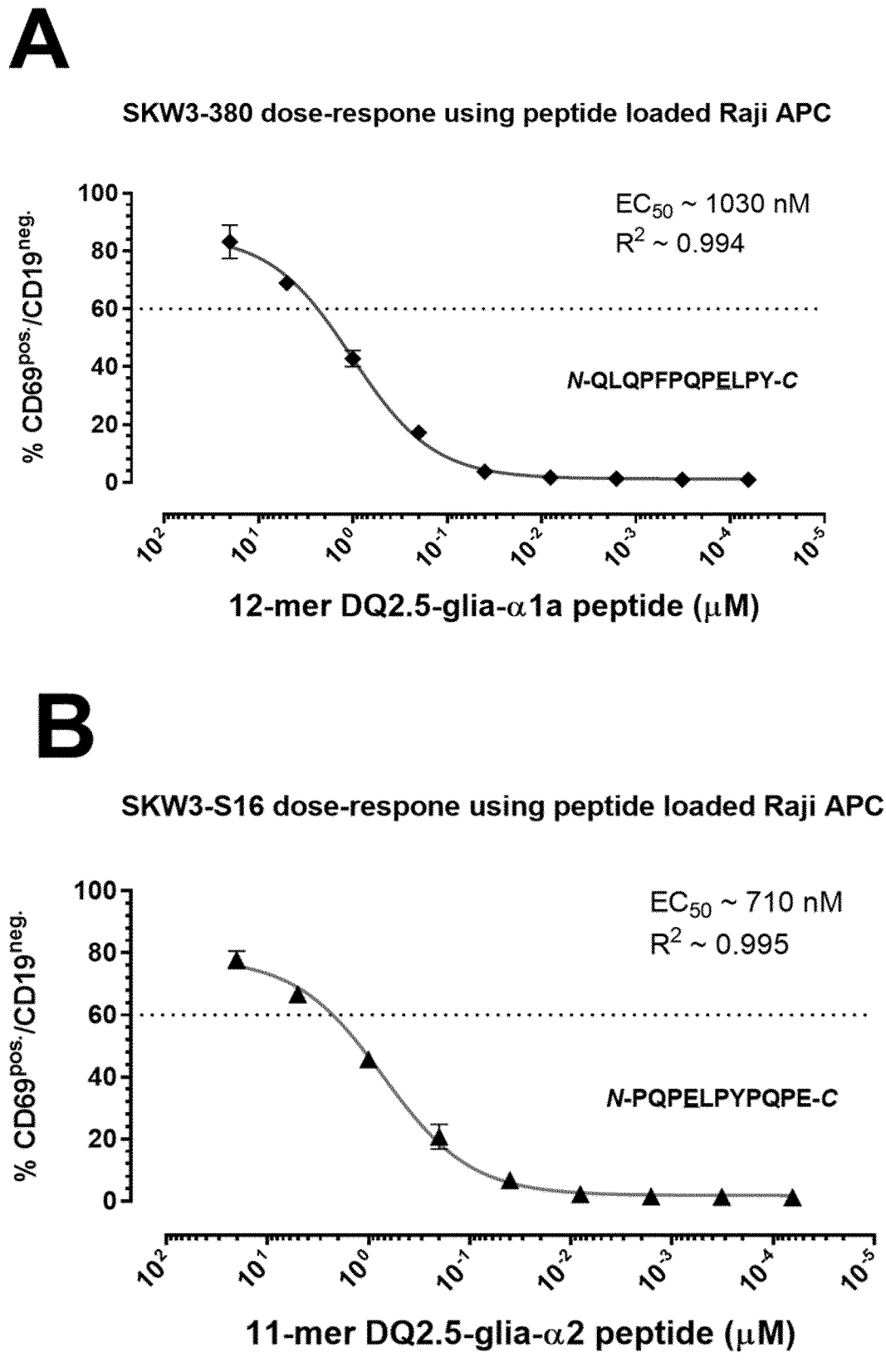
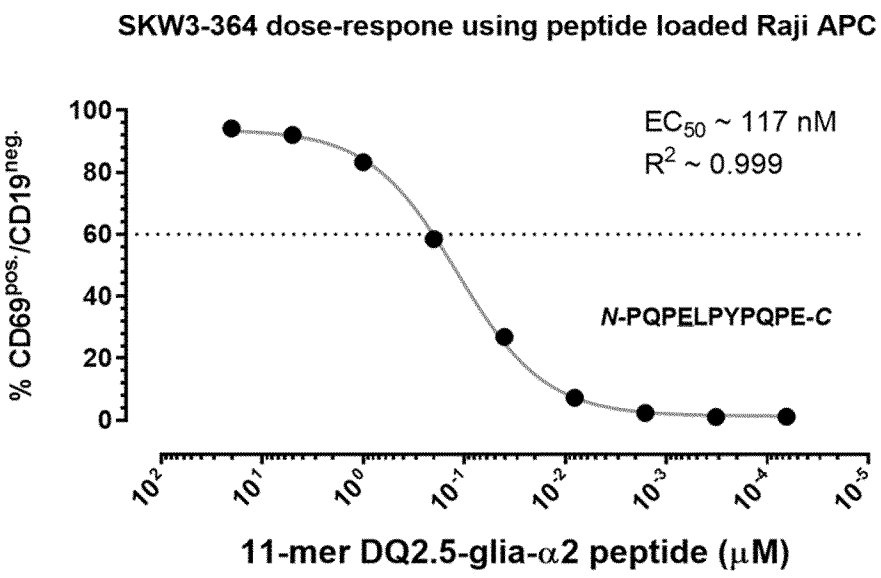

A
SKW3-380 dose-respone using peptide loaded Raji APC
EC50 ~ 1030 nM
R2 ~ 0.994
N-QLQPFPQPELPY-C
% CD69pos./CD19neg.
12-mer DQ2.5-glia-α1a peptide (μM)
B
SKW3-S16 dose-respone using peptide loaded Raji APC
EC50 ~ 710 nM
R2 ~ 0.995
N-PQPELPYPQPE-C
% CD69pos./CD19neg.
11-mer DQ2.5-glia-α2 peptide (μM)

Figure 20 continued

C



D

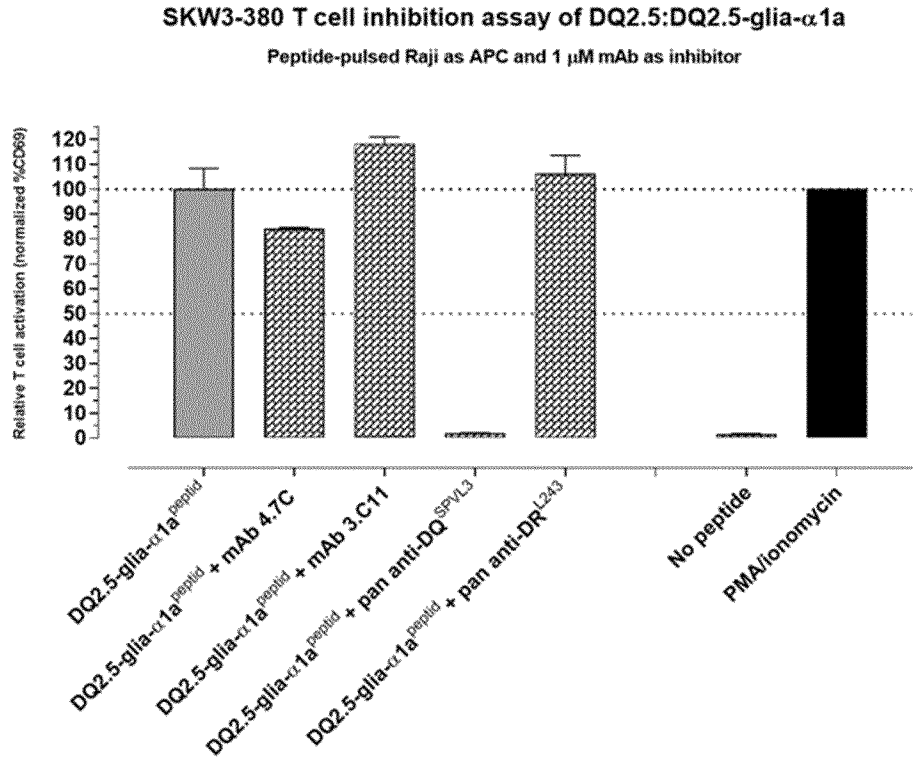
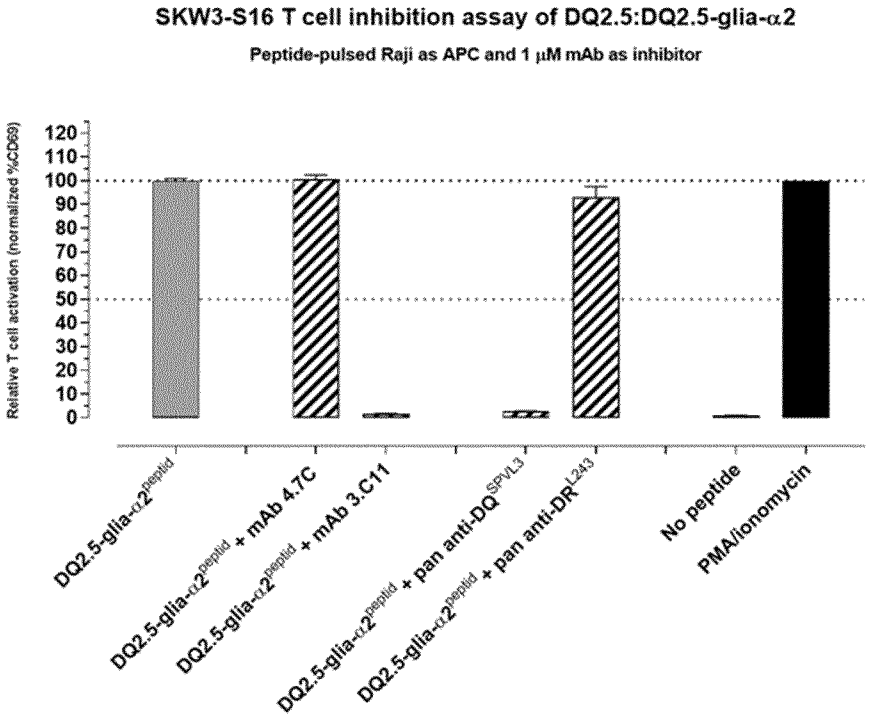
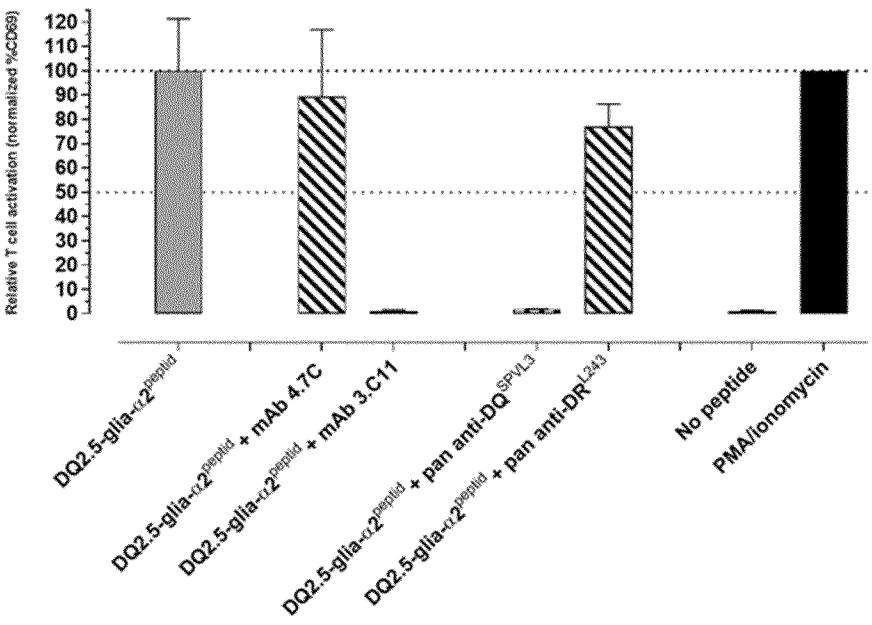


Figure 20 continued

E



F



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/053580

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/16 C07K16/28 A61P37/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/191839 A2 (OSLO UNIVERSITETSSYKEHUS HF [NO]) 4 December 2014 (2014-12-04) The ewhole document, in particular, the examples -----	1-15,19, 20,23
X	S.-W. QIAO ET AL: "Posttranslational Modification of Gluten Shapes TCR Usage in Celiac Disease", THE JOURNAL OF IMMUNOLOGY, vol. 187, no. 6, 17 August 2011 (2011-08-17), pages 3064-3071, XP055588335, ISSN: 0022-1767, DOI: 10.4049/jimmunol.1101526 The whole document, in particular, Fig.5 -----	1-15,19, 20,23
	-/--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 May 2019	03/06/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Chapman, Rob

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NICOLE HARTWIG PETERSEN ET AL: "Fast and efficient characterization of an anti-gliadin monoclonal antibody epitope related to celiac disease using resin-bound peptides", JOURNAL OF IMMUNOLOGICAL METHODS, ELSEVIER SCIENCE PUBLISHERS B.V.,AMSTERDAM, NL, vol. 365, no. 1, 21 December 2010 (2010-12-21), pages 174-182, XP028141200, ISSN: 0022-1759, DOI: 10.1016/J.JIM.2010.12.019 [retrieved on 2010-12-31] The whole document, in particular, sections 3.5 and 4.	1-26
X,P	WO 2018/155692 A1 (CHUGAI PHARMACEUTICAL CO LTD [JP]) 30 August 2018 (2018-08-30) the whole document	1-26
E	WO 2019/069993 A1 (CHUGAI PHARMACEUTICAL CO LTD [JP]) 11 April 2019 (2019-04-11) the whole document	1-26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2019/053580

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-26(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box II.2

Claims Nos.: 1-26(partially)

The present application comprises claims relating to several million possible antibodies (Markush formulae), imposing a severe and undue burden on all those wishing to ascertain the scope of the claim, which is not in compliance with the clarity requirement of Article 6 PCT. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search (PCT Guidelines, 9.19 and 9.24). Furthermore, the application relates to sequence combinations which may or may not generate an antibody with defined technical properties.

In view of the importance of the role played by each single amino acid in the binding of an antibody to its target, especially at the level of its CDRs (see Rudikoff et.al., PNAS 1982, Vol.79, pp. 1979-1983), a claim to an antibody which is structurally characterised by less than the full sequence of all the CDRs, and their specific order, cannot be seen to sufficiently disclose an antibody with any particular properties. Thus, it is apparent that a search of all possible combinations of claimed sequences would not be useful, since only an antibody defined by at least 6 CDRs (HCDR1-3, LCDR1-3) has any defined technical properties of binding. Antibodies that do no share a common, special technical property, are not considered to belong to the same invention (Rule 13.1 PCT).

The extent of the search was consequently limited to antibodies directed to a gliadin peptide, bound or unbound, and the 100% defined CDRs of the antibodies of claims 7 and 8, which appear to be a fair representation of the millions of potential antibodies claimed.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/053580

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014191839 A2	04-12-2014	AU 2014272810 A1	10-12-2015
		CA 2912365 A1	04-12-2014
		EP 2997368 A2	23-03-2016
		US 2016109443 A1	21-04-2016
		WO 2014191839 A2	04-12-2014
WO 2018155692 A1	30-08-2018	NONE	
WO 2019069993 A1	11-04-2019	NONE	