

METHOD AND COMPOSITION

Field of the invention

The invention relates to a method of selecting an immunotherapeutic agent for
5 treating a disease in an individual, and to treatment of the disease by administering the
immunotherapeutic agent or the cognate peptide antigen for the immunotherapeutic agent.
The invention also relates to an antigen binding molecule that binds to the peptide antigen.

Background to the invention

10 Allogeneic stem/immune cell transplantation (allo-SCT) is the most established,
commonly used cancer cellular immunotherapy. Allo-SCT has been in routine clinical use
since the 1960s. Over 20,000 allo-SCTs are performed worldwide annually, mainly for the
highest-risk blood cancers such as acute myeloid leukaemia (AML).

Allo-SCT involves transfer of blood stem and immune cells from a healthy person
15 to a patient. Allo-SCT is a very toxic treatment that is generally restricted to patients less
than 65 years old. Even then, allo-SCT has a 10 to 40% procedure-related mortality rate,
and around 20 to 40% of patients die of disease relapse. Only 30-70% of patients are alive,
and cured, after allo-SCT.

While many aspects of allo-SCT are poorly understood, the curative effect of allo-
20 SCT is known to rely on alloreactivity of donor T cells against cancer cells. In the case of
AML, this alloreactivity is known as Graft-versus-Leukaemia (GvL). It is desirable to
understand the mechanistic basis of graft-versus-disease responses, such as GvL, so that
the likelihood of a successful outcome can be maximized, and the safety of allo-SCT
improved.

25 A key problem in understanding the mechanistic basis of graft-versus-disease (e.g.
GvL) responses is identifying how donor T cells mediating curative responses target
tumour cells for recognition. T cells use their T cell receptors (TCRs) to scan target cells
for peptide antigens complexed to MHC molecules on their surface. However, the antigen-
MHC complexes on recipient tumour cells recognised by donor T cells have yet to be
30 characterised. Such characterisation is crucial to understanding curative graft-versus-
disease immune responses, and distinguishing the antigen-MHC complexes that contribute
to such responses from those that elicit pathogenic Graft-versus-Host Disease (GvHD).

Summary of the invention

The present invention relates to identifying the antigenic basis of beneficial graft-versus-disease and pathogenic graft-versus-host disease (GvHD) immune responses. The identification of antigens involved in graft-versus-disease immune responses allows the selection of immunotherapeutic agent(s) specific for antigens presented on diseased cells. The identification of antigens involved in GvHD immune responses allows the selection of immunotherapeutic agent(s) that do not target these antigens, thereby mitigating against GvHD.

In more detail, the present inventors have identified that target cells in an individual having a disease present peptide antigens on their surface that are capable of binding to a MHC molecule, and encoded by a germline variation in the diseased individual relative to an individual that does not have the disease. The present inventors have also identified antigen binding molecules that bind to the peptide antigens and may be used to effect immunotherapy against the disease. The present inventors have also identified that certain of the peptide antigens are also present on the surface of normal, non-diseased cells, and that targeting these peptide antigens may cause pathogenic graft-versus-host disease responses.

Accordingly, the present invention provides a method of selecting an immunotherapeutic agent for treating a disease in an individual, the method comprising: (a) identifying a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual; and (b) selecting an immunotherapeutic agent that comprises an antigen binding molecule that binds to the peptide antigen.

The present invention also provides:

- a method of treating a disease in an individual, the method comprising administering to the individual an immunotherapeutic agent that comprises an antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual;

- a method of treating a disease in an individual, the method comprising administering a composition comprising a peptide antigen to the individual and thereby inducing an immune response specific for the peptide antigen, wherein the peptide antigen is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual;
- an immunotherapeutic agent for use in a method of treating a disease in an individual, wherein the method comprises administering the therapeutic agent to the individual, and the immunotherapeutic agent comprises an antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual;
- a composition comprising a peptide antigen for use in a method of treating a disease in an individual, the method comprising administering the peptide antigen to the individual and thereby inducing an immune response specific for the peptide antigen, wherein the peptide antigen is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual;
- an antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual;
- a peptide antigen that is (i) encoded by a germline variation in an individual having a disease, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual ; - a polynucleotide encoding the antigen binding molecule or peptide antigen of the invention; and
- a vector comprising the polynucleotide of the invention.

30 **Brief description of the Figures**

Figure 1: Mismatched exome variants between patients and their stem cell transplant donors in 15 patient donor pairs. a) There are a greater number of germline

mismatched variants in unrelated compared with sibling transplants. **b)** 90.2% variants are single nucleotide variants (SNVs) and the commonest result on the coding sequence is missense (91.06%).

Figure 2: Predicted HLA-binding peptides in 15 patient donor pairs. On the x-axis individual patients. Y-axis number of predicted HLA-binding epitopes with germline variants. **a)** Number of predicted patient-donor mismatched HLA Class I-binding epitopes per patient. High affinity binders (rank affinity <0.5%) and low affinity binders (rank affinity 1.5-2%). **b)** Number of patient-donor mismatched HLA Class II-binding peptides per patient. High affinity binders (IC₅₀<150nM) and low affinity binders (IC₅₀150-500nM).

Figure 3: Characterisation of GvL T cell responses. **a)** IFN γ ELISpot results following stimulation of post-transplant PB with GvL peptide +/- antibodies blocking HLA pan-class I (W6/32), pan-class II (Tü39), HLA-DR (L243), -DQ (Tü169) and -DP(B7/21). Negative control without peptide (DMSO). **b)** Flow cytometry with intracellular cytokine staining showing % T cells positive for IFN γ , TNF α , CD107a after treatment with peptide vs no treatment.

Figure 4: Outline of AMADEUS Trial and sample collection. **a)** Outline of trial. **b)** Sample collection. Arrowheads indicate when samples are taken per trial protocol. (AML, acute myeloid leukaemia; MDS, myelodysplasia; MRD, minimal residual disease; allo-SCT, allogeneic stem cell transplant)

Figure 5: PADI4 expression in normal tissues and in cancers. **a)** Graph showing RNAseq data for PADI4 in 37 normal human tissues (data obtained from Human Protein Atlas (v18.1); Uhlén *et al.* Science 2015)). TPM = transcripts per million reads. The PADI4 SNP has an allele frequency of 4.27%, and is present in ~8% of the population, in either homozygous or heterozygous form. The graph shows that in normal tissues, PADI4 expression is highest in haematopoietic tissues (bone marrow and spleen). **b)** Graph showing RNAseq data for PADI4 in 21 human tumours (data obtained from Human Protein Atlas (v18.1); Uhlén *et al.* Science 2017)). **c)** Graph showing RNAseq data for PADI4 in 15 primary AML (acute myeloid leukaemia) samples.

Figure 6: Identifying Antigen-Specific T Cell Receptors. The following protocol was used to determine the sequence of TCRs recognising peptide 1 (SEQ ID NO: 1) or peptide 2 (SEQ ID NO: 2): 1. Culture post-transplant blood with peptide (identified

from IFN γ ELISpot screen) to enrich for antigen-specific T cells. 2. After peptide stimulation, FACS sort activated (IFN γ +) T cells and control (IFN γ -) T cells. 3. Single cell RNA sequencing with V(D)J enrichment. In peptide-activated (i.e. CD4+ IFN γ +) T cells, two clones are expanded. The two expanded clones (CD4+ IFN γ +) represent putative antigen-specific T cells. The large black bands (labelled 56.9% in the left panel and 11.0% in the right panel represents the sum of clonotypes with <0.1% frequency).

Figure 7: Cytokines/activation markers in putative antigen-specific T cells.

Single cell RNA sequencing of FACS sort activated (IFN γ +) T cells and control (IFN γ -) T cells shows that putative antigen-specific T cells express multiple cytokines (IFN γ , TNF α) and activation markers (FASLG, IL2RA, TNFRSF9, GZMB) in response to peptide stimulation.

Figure 8: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX289 peptide 52. After peptide stimulation and IFN γ catch, there were two expanded clones (27.3% and 10.7%). These clones were present at lower frequency in the control (IFN γ -) repertoire.

Figure 9: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX289 peptide 40. After peptide stimulation and IFN γ catch, there was one very expanded clone (85.2%) This clone was not present in the control (IFN γ -) repertoire. (Note – negative control sorted as IFN γ - population from Peptide 52 culture).

Figure 10: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX289 overlapping peptides 73/74. After peptide stimulation and IFN γ catch, there were two large clones, and one smaller clone. These clones were not present in the control (IFN γ -) repertoire. (Note – negative control sorted as IFN γ - population from Peptide 52 culture).

Figure 11: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX289 peptide 221. After peptide stimulation and IFN γ catch, there were two large clones. These clones were not present in the control (IFN γ -) repertoire. (Note – negative control sorted as IFN γ - population from Peptide 52 culture).

Figure 12: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX289

overlapping peptides 75/205. After peptide stimulation and IFN γ catch, there were three expanded clones. These clones were not present in the control (IFN γ -) repertoire. (Note – negative control sorted as IFN γ - population from Peptide 52 culture).

Figure 13: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX802 overlapping peptides 321/322. After peptide stimulation and IFN γ catch, there were two large clone. Clone 1 was present in the control (IFN γ -) repertoire, but clone 2 was absent.

Figure 14: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX628 peptides 80/81. After peptide stimulation and IFN γ catch, there were two expanded clones (55.1% and 13.5%). These clones were present at lower frequency in the control (IFN γ -) repertoire.

Figure 15: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX747 overlapping peptides 157/158. After peptide stimulation and IFN γ catch, multiple clones were expanded at modest size. All were present at lower frequency in the control (IFN γ -) repertoire.

Figure 16: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX885 overlapping peptides 559/560. After peptide stimulation and IFN γ catch, there was one very expanded clone (96.5%). This clones was also present at high frequency in the control (IFN γ -) repertoire. (Note - Negative control population sorted from the same culture as Activated.)

Figure 17: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX885 overlapping peptides OX628-308/309. After peptide stimulation and IFN γ catch, there was one large clone (76.1%). This clones was present at low frequency in the control (IFN γ -) repertoire. (Note – negative control sorted as IFN γ - population from Peptide 559/560 culture).

Figure 18: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX993

overlapping peptides 413/414. Four clones were expanded after peptide stimulation and IFN γ catch, compared to the control (IFN γ -) repertoire.

Figure 19: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX1149 peptide 190. Three clones were expanded after peptide stimulation and IFN γ catch, compared to the control (IFN γ -) repertoire.

Figure 20: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX1149 peptide 290. After peptide stimulation and IFN γ catch, there were three expanded clones. These clones were not present in the control (IFN γ -) repertoire. (Note – negative control sorted as IFN γ - population from Peptide 190 culture).

Figure 21: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX289 peptide 284. The dominant clone in the negative control (IFN γ -) repertoire was larger in the activated repertoire (96.0% vs 65.1%).

Figure 22: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX289 peptide 9. The dominant clone in the negative control (IFN γ -) repertoire was larger in the activated repertoire (91.1% vs 65.1%). (Note – negative control sorted as IFN γ - population from Peptide 284 culture, not Peptide 9 culture).

Figure 23: Identifying Antigen-Specific T Cell Receptors. The protocol set out in Example 5 was used to determine the sequence of TCRs recognising OX289 peptide 67. The two largest clones in the activated repertoire are not present in the control repertoire. (Note – negative control sorted as IFN γ - population from Peptide 284 culture).

Detailed description of the invention

The present inventors have, for the first time, identified peptide antigens targeted by graft-versus-disease (such as graft-versus-cancer or graft-versus-leukemia, GvL) and graft-versus-host disease immune responses. The inventors have also identified cognate antigen binding molecules, such as T cell receptors (TCRs), that recognise the peptide antigens targeted by graft-versus-disease responses and can therefore be used to provide immunotherapy against the disease.

In more detail, the present inventors have demonstrated that the graft-versus-disease and graft-versus-host disease immune responses are primarily specific for peptide antigens that are encoded by a germline variation in the diseased individual and present on the surface of cells targetted by allogeneic haemopoietic stem cell transplantation.

5 With knowledge of the antigenic basis of the graft-versus-disease immune response, it is possible to select donor-patient pairings for allo-SCT that maximise the likelihood of a successful treatment outcome. It is also possible to provide an immunotherapeutic agent that comprises an antigen binding molecule (such as a T cell receptor, T cell receptor fragments, chimeric antigen receptor (CAR), antibody, antibody
10 fragment, or bi-specific T cell engager (BiTE)) that mimics the antigen specificity of donor T cells capable of mounting an effective graft-versus-disease immune response. In this way, the graft-versus-disease immune response usually associated with allo-SCT may be harnessed for use in off-the-shelf or autologous approaches to treatment. It is also possible to prime immune cells present in a patient to mount an response against disease-associated
15 target cells by administering a relevant peptide antigen as a vaccine. Any of these approaches may be used in combination.

 Knowledge of the antigenic basis of the graft-versus-host immune response may also be used to select donor-patient pairings for allo-SCT. In particular, donor cells that recognise peptide antigens present on non-target cells (such as normal cells in healthy
20 tissue) can be avoided. Immunotherapeutic agents that comprise an antigen binding molecule that mimics the antigen specificity of such donor cells can likewise be avoided, as can the priming of immune cells present in the patient and specific for the graft-versus-host peptide antigen.

 To identify the antigenic basis of the graft-versus-disease and graft-versus-host
25 disease immune response, the inventors compared the sequence of patient and donor genomic DNA to identify germline coding variants mismatched between the patient and donor. In the exemplified embodiment, the patient is an AML patient and the donor is a donor without AML. However, the type of antigen identified as the basis of the graft-versus-AML response (namely, a MHC -restricted peptide antigen that is encoded by a
30 germline variation in the patient and present on the surface of target cells) may also be expressed by target cells associated with other diseases, such as other types of cancer. In addition, as the graft-versus-AML response targets a germline variant (rather than, for

example, a disease-specific neo-epitope or tumour associated antigen), the peptide antigen may be expressed by different types of target cells in different individuals, such as target cells derived from different tissues. For example, the same peptide antigen may be expressed on the surface of an AML cell in one individual, and on the surface of a solid
5 tumour cell in another individual.

Accordingly, the approach employed by the inventors has wide-reaching impact on the treatment of diseases such as cancer. The approach allows an effective immunotherapeutic agent or peptide antigen vaccine to be selected for different individuals having different types of disease, for example different types of cancer. Furthermore, a
10 single immunotherapeutic agent having a single antigen specificity may be useful in treating different diseases in different individuals each comprising a particular germline variation, depending on the type of target cell upon whose surface the peptide antigen is expressed. This may especially be the case for germline variation-encoded peptides that are expressed by target cells from two or more patients, as these may represent so-called
15 “*public*” antigens, which frequently occur in the population (e.g. have a frequency of 0.05 or greater).

The various aspects of the invention are described in detail below.

Method of selecting an immunotherapeutic agent

20 The invention provides a method of selecting an immunotherapeutic agent for treating a disease in an individual, the method comprising (a) identifying a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual; and (b) selecting an
25 immunotherapeutic agent that comprises an antigen binding molecule that binds to the peptide antigen. Preferably, the antigen binding molecule binds to the peptide antigen when the peptide antigen is bound to the MHC molecule. That is, the antigen binding molecule may bind to a peptide-MHC complex comprising the peptide antigen.

Identification of the peptide antigen and selection of an immunotherapeutic agent
30 that comprises an antigen binding molecule that binds to the peptide antigen maximises the likelihood that administration of the immunotherapeutic agent to the individual will result in successful treatment of the disease. In essence, the antigen binding ability of the antigen

binding molecule comprised in the immunotherapeutic agent can be matched to the antigen expression profile of the target cell, increasing the probability that the target cell is bound by the antigen binding molecule to effect treatment of the disease.

Absence of the peptide antigen on the surface of non-target cells minimizes the risk of graft-versus-host disease resulting from administration of the immunotherapeutic agent to the individual. In this case, the immunotherapeutic agent selectively binds to target cells, but does not bind to non-target cells. Target cells and non-target cells are described in detail below.

10 Medicaments and methods of treatment

The invention provides a method of treating a disease in an individual, the method comprising administering to the individual an immunotherapeutic agent that comprises an antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. The invention also provides an immunotherapeutic agent for use in a method of treating a disease in an individual, wherein the method comprises administering the immunotherapeutic agent to the individual, and the immunotherapeutic agent comprises an antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual.

The peptide antigen is present on the surface of target cells, because it is bound to cell surface MHC molecules. Following administration of the immunotherapeutic agent, the antigen binding molecule specifically binds to target cells via the peptide antigen. Binding may effect treatment of the disease in a variety of ways, depending on the nature of antigen binding molecule and/or immunotherapeutic agent. For example, the immunotherapeutic agent may comprise a T cell expressing a T cell receptor (TCR) as the antigen binding molecule. Binding of the T cell receptor to the peptide antigen-MHC complex may trigger activation of the T cell and result in, for example, cytolysis of the target cell and/or the production of cytokines (such as interferon gamma (IFN γ) and/or tumour necrosis factor alpha (TNF α)) that are detrimental to the target cell. The

immunotherapeutic agent may, for example, comprise an antigen binding molecule that comprises an antibody or antibody fragment. Binding of the antibody or antibody fragment to the peptide antigen may decorate the target cell with an opsonin, marking the target cell for phagocytosis or destruction via the classical complement pathway. The antibody/antibody fragment may be bound to a chemotherapeutic agent, and so binding of the antibody or antibody fragment to the peptide antigen may deliver the chemotherapeutic agent to the target cell. The immunotherapeutic agent may, for example, comprise an antigen binding molecule comprising a bi-specific T cell engager (BiTE). The BiTE may simultaneously bind to (i) the peptide antigen and (ii) a molecule (e.g. CD3) expressed on the surface of a T cell, to form a link between the target cell and the T cell that is independent of the antigen specificity of the T cell. Binding of the surface molecule on the T cell may activate the T cell and lead, for example, to cytolytic activity against the target cell.

Absence of the peptide antigen on the surface of non-target cells minimizes the risk of graft-versus-host disease resulting from administration of the immunotherapeutic agent to the individual. In this case, the immunotherapeutic agent selectively binds to target cells, but does not bind to non-target cells. Target cells and non-target cells are described in detail below.

The step of administering the immunotherapeutic agent to the individual may, for example, comprise administering two or more immunotherapeutic agents to the individual, wherein each immunotherapeutic agent comprises an antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. For instance, the individual may be administered with three or more, four or more, five or more six or more, seven or more, eight or more, nine or more, or ten or more immunotherapeutic agents each comprising an antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. Each immunotherapeutic agent administered to the individual may, for example, comprise an

antigen binding molecule that binds to a different peptide antigen. Each different peptide antigen may be encoded by a different germline variation in the individual.

The step of administering the immunotherapeutic agent to the individual may, for example, comprise administering a single immunotherapeutic agent to the individual, 5 wherein the single immunotherapeutic agent comprises two or more antigen binding molecules that each bind to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. For instance, the individual may be administered with a single 10 immunotherapeutic agent comprising three or more, four or more, five or more six or more, seven or more, eight or more, nine or more, or ten or more antigen binding molecules that each bind to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in 15 the individual. Each antigen binding molecule comprised in the single immunotherapeutic agent may, for example, bind to a different peptide antigen. Each different peptide antigen may be encoded by a different germline variation in the individual.

In another aspect, the invention provides a method of treating a disease in an 20 individual, the method comprising administering a composition comprising a peptide antigen to the individual and thereby inducing an immune response specific for the peptide antigen, wherein the peptide antigen is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the 25 individual. The invention also provides a composition comprising a peptide antigen for use in a method of treating a disease in an individual, the method comprising administering the peptide antigen to the individual and thereby inducing an immune response specific for the peptide antigen, wherein the peptide antigen is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface 30 of a target cell in the individual and optionally absent on the surface of non-target cells in the individual.

Following administration of the peptide antigen, components of the individual's own immune system may be primed to mount an immune response against target cells. For instance, administration of the peptide antigen may stimulate expansion of T cells and/or B cells specific for the peptide antigen. Administration of the peptide antigen may stimulate activation of T cells and/or B cells specific for the peptide antigen. In this way, the T cell and/or B cell responses directed against the target cell may be induced. Absence of the peptide antigen on the surface of non-target cells minimizes the risk of graft-versus-host disease resulting from the primed immune response.

The step of administering the peptide antigen to the individual may, for example, comprise administering two or more peptide antigens to the individual, wherein each peptide antigen is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. For instance, the individual may be administered with three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more peptide antigens each (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. Each peptide antigen administered to the individual may, for example, be encoded by a different germline variation in the individual. The peptide antigens may be comprised in the same composition.

The method of treating disease in an individual may further comprise administering to the individual immune cells specific for the peptide antigen. In other words, the individual may be administered with (i) the peptide antigen, and (ii) immune cells specific for the peptide antigen. Following administration of the peptide antigen, the cells specific for the peptide antigen may be primed to mount an immune response against target cells. This may facilitate a therapeutic effect in the event that components of the individual's own immune system are tolerant to the peptide antigen. The peptide antigen and immune cells specific for the peptide antigen may be comprised in the same composition. Absence of the peptide antigen on the surface of non-target cells minimizes the risk of graft-versus-host disease resulting from the primed immune response.

If the individual is administered with a plurality of peptide antigens, as described above, the method may comprise administering to the individual immune cells specific for each of the peptide antigens. The administered immune cells may, for example, comprise separate immune cells each specific for one of the peptide antigens. The administered
5 immune cells may, for example, comprise one or more immune cells each specific for a plurality of the peptide antigens. For example, if the individual is administered with peptide antigen X and peptide antigen Y, the method may comprise administering (a) immune cells specific for peptide antigen X and immune cells specific for peptide antigen Y or (b) immune cells individually specific for both peptide antigen X and peptide antigen
10 Y. In any case, the peptide antigens and immune cells specific for the peptide antigens may be comprised in the same composition.

Alternatively, the peptide antigen and the immune cells specific for the peptide antigen may be comprised in different compositions. In this case, the composition comprising the peptide antigen and the composition comprising the immune cells specific
15 for the peptide antigen may be administered to the individual together. That is, the composition comprising the peptide antigen and the composition comprising the immune cells specific for the peptide antigen may be administered to the individual at substantially the same time. The composition comprising the peptide antigen and the composition comprising the immune cells specific for the peptide antigen may be administered to the
20 individual separately. That is, the composition comprising the peptide antigen and the composition comprising the immune cells specific for the peptide antigen may be administered to the individual at different times. For example, the method may comprise administering the individual with (i) the composition comprising the peptide antigen and, subsequently, (ii) the composition comprising immune cells specific for the peptide
25 antigen. Preferably, the method comprises administering the individual with (i) the composition comprising the immune cells specific for the peptide antigen and, subsequently, (ii) the composition comprising the peptide antigen.

The immune cells specific for the peptide antigen may, for example, comprise T cells, B cells, NK cells, NKT cells, macrophages and/or monocytes. Preferably, the cells
30 specific for the peptide antigen comprise T cells and/or B cells. More preferably, the immune cells specific for the peptide antigen comprise T cells. The immune cells specific for the peptide antigen may exist in nature. For example, the immune cells specific for the

peptide antigen may be obtained from a donor. The donor may, for example, be donor whose genome does not comprise the germline variation. Preferably, the donor does not have the disease. The immune cells specific for the peptide antigen may, for example, be engineered cells. The engineered immune cells may be autologous or allogeneic with
 5 respect to the individual. The immune cells may be engineered to comprise a receptor conferring specificity for the peptide antigen. For example, the immune cells may comprise a T cell receptor or a chimeric antigen receptor (CAR) specific for the peptide antigen.

The immune response induced by administration of the peptide antigen may be an
 10 adaptive immune response. For example, the immune response may comprise a T cell response, a B cell response and/or a NKT cell response. Preferably, the immune response comprises a T cell response. The T cell response may comprise a CD4+ T cell response. The T cell response may comprise a CD8+ T cell response. Preferably, the MHC molecule to which the peptide antigen is capable of binding is a MHC class II molecule, and T cell
 15 response comprises a CD4+ T cell response. Preferably, the MHC molecule to which the peptide antigen is capable of binding is a MHC class I molecule, and T cell response comprises a CD8+ T cell response.

The CD4+ T cells and/or CD8+ T cells involved in the T cell response may have cytolytic effector function. The CD4+ T cells and/or CD8+ T cells may express markers
 20 of cytolytic effector function. For example, the CD4+ T cells and/or CD8+ T cells may express one or more of perforin, granzyme A, granzyme B, Fas, FasL and TRAIL. The CD4+ T cells and/or CD8+ T cells involved in the T cell response may express CD107a, a degranulation marker.

The CD4+ T cells and/or CD8+ T cells involved in the T cell response may secrete
 25 one or more cytokines. For example, the CD4+ T cells and/or CD8+ T cells may secrete interferon gamma (IFN γ). The CD4+ T cells and/or CD8+ T cells may secrete tumour necrosis factor alpha (TNF α).

The immune response induced by administration of the peptide antigen may be an innate immune response. For example, the immune response may comprise a NK cell
 30 response, a macrophage response, a dendritic cell response, or a monocyte response.

The method may further comprise administering to the individual an adjuvant. The adjuvant may, for example, comprise one or more of incomplete Freund's adjuvant (IFA),

montanide, an aluminium adjuvant (alum), a microparticle, a nanoparticle, a Toll-like receptor (TLR) agonist, a cytokine, or an antibody. The aluminium adjuvant may comprise aluminium hydroxide and/or aluminium phosphate. The microparticle or nanoparticle may, for example, comprise a liposome, a synthetic polymer (such as polystyrene, poly(lactide-co-glycolide) PLG, poly(lactic acid) PLA and/or PLGA), a natural polymer (such as
 5 gelatin, collagen and/or chitosan), and/or a carbon nanotube. The TLR agonist may comprise, for example, Pam₃CSK₄, Poly-ICLC, MPLA, Imiquimod, and/or CpG. The cytokine may comprise, for example, IL-2, GM-CSF, IFN or CDN. The antibody may, for example, comprise an anti-PD1 antibody or an anti-CTLA-4 antibody. Preferably, the
 10 adjuvant is administered together with the peptide antigen. That is, the adjuvant and the peptide antigen may be administered to the individual at substantially the same time. For example, the adjuvant and the peptide antigen may be comprised in the same composition. In other words, the composition comprising the peptide antigen may further comprise the adjuvant.

15

Disease

The disease may be any disease, such as a disease that results in or from the presence of an undesirable cell in the individual. An undesirable cell may, for example, be involved in the aetiopathogenesis of the disease. An undesirable cell may, for example,
 20 cause harm in the individual. Targeting the undesirable cell with the immunotherapeutic agent may impair the function of the undesirable of the cell or kill the undesirable cell, thereby treating the disease. The undesirable cell may express MHC class II. The undesirable cell may express MHC class I. The undesirable cell may be a target cell.

The disease may, for example, be cancer. In this case, the undesirable cell may be
 25 a cancer cell. The cancer may, for example, be anal cancer, bile duct cancer (cholangiocarcinoma), bladder cancer, blood cancer, bone cancer, bowel cancer, brain tumours, breast cancer, colorectal cancer, cervical cancer, endocrine tumours, Ewing's sarcoma, eye cancer (such as ocular melanoma), fallopian tube cancer, gall bladder cancer, head and/or neck cancer, Kaposi's sarcoma, kidney cancer, larynx cancer, leukaemia, liver
 30 cancer, lung cancer, lymph node cancer, lymphoma, melanoma, mesothelioma, myeloma, neuroendocrine tumours, ovarian cancer, oesophageal cancer, pancreatic cancer, penis cancer, primary peritoneal cancer, prostate cancer, Pseudomyxoma peritonei, skin cancer,

small bowel cancer, soft tissue sarcoma, spinal cord tumours, stomach cancer, testicular cancer, thymus cancer, thyroid cancer, trachea cancer, unknown primary cancer, vagina cancer, vulva cancer or endometrial cancer. The leukaemia is preferably acute lymphoblastic leukaemia, acute myeloid leukaemia (AML), chronic lymphocytic
 5 leukaemia or chronic myeloid leukaemia. The lymphoma may be Hodgkin lymphoma or non-Hodgkin lymphoma. The cancer may, for example, be acute myeloid leukaemia (AML). The cancer cell may, for example, be an AML cell.

The disease may, for example, be an autoimmune disease. In this case, the undesirable cell may be an immune cell. The immune cell may, for example, be a
 10 lymphocyte, such as a T cell or a B cell. The lymphocyte may comprise an antigen receptor that is specific for a self-antigen. The autoimmune disease may, for example, be alopecia areata, autoimmune encephalomyelitis, autoimmune hemolytic anemia, autoimmune hepatitis, dermatomyositis, diabetes (type 1), autoimmune juvenile idiopathic arthritis, celiac disease, glomerulonephritis, Graves' disease, Guillain-Barré syndrome, idiopathic
 15 thrombocytopenic purpura, myasthenia gravis, autoimmune myocarditis, multiple sclerosis, pemphigus/pemphigoid, pernicious anemia, polyarteritis nodosa, polymyositis, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, scleroderma/systemic sclerosis, Sjögren's syndrome, systemic lupus erythematosus, autoimmune thyroiditis, uveitis or vitiligo.

The disease may, for example, be an allergic disease. In this case, the undesirable
 20 cell may be an immune cell. The immune cell may, for example, be a lymphocyte, such as a T cell or a B cell. The lymphocyte may comprise an antigen receptor that is specific for an allergen. The allergic disease may, for example, be atopic dermatitis, allergic airway inflammation or perennial allergic rhinitis.

The disease may, for example, be a fibrosing disease. A fibrosing disease is a
 25 disease in which inflammation and/or tissue damage leads to fibrosis. In this case, the undesirable cell may be a fibroblast. The undesirable cell may, for example, be a lymphocyte, such as a T cell or a B cell. The fibrosing disease may, for example, be pulmonary fibrosis (such as cystic fibrosis or idiopathic pulmonary fibrosis), myocardial fibrosis (such as interstitial fibrosis or replacement fibrosis), cirrhosis, bridging fibrosis of the
 30 liver, glial scar, arterial stiffness, arthrofibrosis, Crohn's disease, Dupuytren's contracture, keloid, mediastinal fibrosis, myelofibrosis, Peyronie's disease, nephrogenic systemic fibrosis, retroperitoneal fibrosis, scleroderma, systemic sclerosis, or adhesive capsulitis

Individual

Preferably, the individual is a human individual. Alternatively, the individual may be a non-human mammal. For instance, the individual could be a pet mammal (such as a cat, a dog, a horse, a rabbit or a guinea pig), a commercially farmed mammal (such as an ox, a sheep, a goat or a pig), or a laboratory mammal, (such as a mouse or a rat). The individual may be an infant, a juvenile or an adult. The individual may be known to have the disease, or suspected to have the disease. The terms "*individual*" and "*patient*" may be used interchangeably.

10

Peptide antigen

The methods, medicaments and medical uses described above involve a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. The invention further provides such peptide antigen. That is, the invention further provides a peptide antigen (such as an isolated peptide antigen) that is (i) encoded by a germline variation in an individual having a disease, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. Any of the aspects described above in connection with the methods, medicaments and medical uses of the invention may also apply to the peptide antigen of the invention.

15

The term "*peptide*" relates to a short chain of amino acids, linked by peptide (-CO-NH-) bonds. The peptide antigen may, for example, comprise or consist of 10 to 20 amino acids, such as 11 to 19, 12 to 18, 13 to 17, or 14 to 16 amino acids. Preferably, the peptide antigen comprises or consists of 13 to 17 amino acids. The peptide antigen may, for example, comprise 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acids. The peptide antigen may consist of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acids.

20

The peptide antigen may comprise or consist of an epitope. The epitope may, for example, be a CD4⁺ T cell epitope, a B cell epitope, or an antibody epitope. A CD4⁺ T cell epitope is a peptide that is capable of (i) presentation by a MHC molecule and (ii) binding to a T cell receptor (TCR) present on a CD4⁺ T cell. Preferably, binding of the

25

- TCR results in activation of the CD4+ T cell. CD4+ T cell activation may lead to increased proliferation, cytokine production and/or cytotoxic effects. A B cell epitope is a peptide that is capable of binding to a B cell receptor (BCR) present on a B cell. Preferably, binding of the BCR results in activation and/or maturation of the B cell. B cell
- 5 activation may lead to increased proliferation, and/or antibody production. An antibody epitope is a peptide that is capable of binding to the paratope of an antibody.

Various peptide antigens are identified in the Examples, and include:

- LTISLLDTFNLELPEAVVFQ (SEQ ID NO: 1)
ISLLDTFNLELPEAVVFQDS (SEQ ID NO: 2)
- 10 SLLDTFNLELPEAVVF (SEQ ID NO: 3)
LDTFNLELPEAVVFQ (SEQ ID NO: 4)
AASCEPLASVLRAKLTSRSS (SEQ ID NO: 380)
GAGPDPLRLHGHLVPVRTSCP (SEQ ID NO: 381)
TQRSVLLCKVVGARGVGKSA (SEQ ID NO: 382)
- 15 KVVVGARGVGKSAFLQAFLGR (SEQ ID NO: 383)
GQKSPRFRRVSCFLRLGRST (SEQ ID NO: 384)
RFRRVSCFLRLGRSTLLELE (SEQ ID NO: 385)
ALAFLLISIAANLSLLLSR (SEQ ID NO: 386)
EVQDCLKQLMMSLLQLYRFS (SEQ ID NO: 387)
- 20 GYSPSLHILAIGTRSGAIKL (SEQ ID NO: 388)
VATFPVYTMVAIPIVCKD (SEQ ID NO: 389)
PPLYRQRYQFIKNLVDQHEP (SEQ ID NO: 390)
PLYRQRYQFIKNLVDQHEPK (SEQ ID NO: 391)
VSRPELLRESISAFLVPMPT (SEQ ID NO: 392)
- 25 TDRA LQNKSISAFLVPMPTP (SEQ ID NO: 393)
NPLSPYLNVDPRYLVDQDT (SEQ ID NO: 394)
EPPVDICLSKAISSSLKGFL (SEQ ID NO: 395)
GETGMFSLSTIRGHQYATY (SEQ ID NO: 396)
MNYVSKRLPFAARLNTPMGP (SEQ ID NO: 397)
- 30 LGS LGLIFALT LNRHKYPLN (SEQ ID NO: 398)
LGLIFALT LNRHKYPLNLYL (SEQ ID NO: 399)
APISLSSFFNVSTLEREVD (SEQ ID NO: 400)

- LELGAGTGLASIIAATMART (SEQ ID NO: 401)
 AGTGLASIIAATMARTVYCT (SEQ ID NO: 402)
 VPREYVRALNATKLERVFAK (SEQ ID NO: 403)
 LHRDKALLKRLKGMQKKRP (SEQ ID NO: 404)
 5 KALLKRLKGMQKKRPSDVQ (SEQ ID NO: 405)
 ITVQTVYVQHLITFLDRPIQ (SEQ ID NO: 406)
 QTVYVQHLITFLDRPIQMCC (SEQ ID NO: 407)
 PGLISMFSSSQELGAALAQL (SEQ ID NO: 408)
 WRVRIALALKGIDYETVPIN (SEQ ID NO: 409)
 10 VRIALALKGIDYETVPINLI (SEQ ID NO: 410)
 DRAEKFNRGIRKLGITPEGQ (SEQ ID NO: 411)
 EKFNRGIRKLGITPEGQSYL (SEQ ID NO: 412)

- The peptide antigen may comprise or consist of SEQ ID NO: 3. The peptide antigen may, for example, consist of 10 to 20 (such as 11 to 19, 12 to 18, 13 to 17, or 14 to
 15 16) amino acids and comprise SEQ ID NO: 3. For example, the peptide antigen may comprise or consist of SEQ ID NO: 1. The peptide antigen may comprise or consist of SEQ ID NO: 4. The peptide antigen may, for example, consist of 10 to 20 (such as 11 to 19, 12 to 18, 13 to 17, or 14 to 16) amino acids and comprise SEQ ID NO: 4. For example, the peptide antigen may comprise or consist of SEQ ID NO: 2. The peptide antigen may
 20 comprise any one of SEQ ID NOs: 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411 and 412. The peptide antigen may consist of any one of SEQ ID NOs: 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411 and 412.

25

Target cell

- The peptide antigen is present on the surface of a target cell in the individual. The target cell may express MHC class II. The target cell may express MHC class I. The target cell may be an undesirable cell. The target cell may be involved in the
 30 actiopathogenesis of the disease. The target cell may cause harm in the individual.

The target cell may, for example, be a cancer cell. The cancer may, for example, be an anal cancer cell, a bile duct cancer (cholangiocarcinoma) cell, a bladder cancer cell, a

blood cancer cell, a bone cancer cell, a bowel cancer cell, a brain tumour cell, a breast cancer cell, a colorectal cancer cell, a cervical cancer cell, an endocrine tumour cell, an eye cancer (such as ocular melanoma) cell, a fallopian tube cancer cell, a gall bladder cancer cell, a head and/or neck cancer cell, a Kaposi's sarcoma cell, a kidney cancer cell, a larynx cancer cell, a leukaemia cell, a liver cancer cell, a lung cancer cell, a lymph node cancer cell, a lymphoma cell, a melanoma cell, a mesothelioma cell, a myeloma cell, a neuroendocrine tumour cell, an ovarian cancer cell, an oesophageal cancer cell, a pancreatic cancer cell, a penis cancer cell, a primary peritoneal cancer cell, a prostate cancer cell, a Pseudomyxoma peritonei cell, a skin cancer cell, a small bowel cancer cell, a soft tissue sarcoma cell, a spinal cord tumour cell, a stomach cancer cell, a testicular cancer cell, a thymus cancer cell, a thyroid cancer cell, a trachea cancer cell, an unknown primary cancer cell, a vagina cancer cell, a vulva cancer cell or an endometrial cancer cell. The leukaemia may be acute lymphoblastic leukaemia, acute myeloid leukaemia (AML), chronic lymphocytic leukaemia or chronic myeloid leukaemia. The lymphoma may be Hodgkin lymphoma or non-Hodgkin lymphoma. Preferably, the cancer cell is an AML cell.

The target cell may, for example, be an immune cell. For instance, the immune cell may be a lymphocyte, such as a T cell or a B cell. The lymphocyte may comprise an antigen receptor that is specific for a self-antigen. Specificity for the self-antigen may, for example, cause alopecia areata, autoimmune encephalomyelitis, autoimmune hemolytic anemia, autoimmune hepatitis, dermatomyositis, diabetes (type 1), autoimmune juvenile idiopathic arthritis, celiac disease, glomerulonephritis, Graves' disease, Guillain-Barré syndrome, idiopathic thrombocytopenic purpura, myasthenia gravis, autoimmune myocarditis, multiple sclerosis, pemphigus/pemphigoid, pernicious anemia, polyarteritis nodosa, polymyositis, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, scleroderma/systemic sclerosis, Sjögren's syndrome, systemic lupus erythematosus, autoimmune thyroiditis, uveitis or vitiligo. The lymphocyte may comprise an antigen receptor that is specific for an allergen. Specificity for the allergen may, for example, cause atopic dermatitis, allergic airway inflammation or perennial allergic rhinitis.

The target cell may, for example, be a fibroblast.

The peptide antigen is present on the surface of the target cell. The peptide antigen may be considered to be present on the surface of the target cell if any method for

determining surface presence shows that the target cell presents a detectable level of the peptide antigen on its surface. Methods for determining surface presence are known in the art. Surface expression may, for example, be determined by immunoprecipitation of MHC molecules from the target cell, and mass spectrometry of eluted MHC-bound peptides.

- 5 Surface presence may, for example, be determined by flow cytometry. For instance, flow cytometry may be used to measure the mean fluorescent intensity (MFI) of the peptide antigen. MFI measures intensity, time average energy flux measured in watts per square metre.

10 Non-target cell

As set out above, the peptide antigen is present on the surface of a target cell in an individual having a disease. In any of the aspects described herein, the peptide antigen is preferably absent on the surface of non-target cells in the individual.

- Target cells are described in detail above. A non-target cell may be any
15 endogenous cell in the individual that is not a target cell. In other words, a non-target cell may be any endogenous cell that (a) is not an undesirable cell, (b) is not involved in the aetiopathogenesis of the disease, and/or (c) does not cause harm in the individual. Accordingly, a non-target cell may be a desirable cell. A non-target cell may be a non-pathogenic cell. A non-target cell may be a harmless cell. In other words, a non-target cell
20 may be a healthy or normal cell. A non-target cell may, for example, be a non-cancer cell such as a non-AML cell.

The non-target cell may express MHC class II. The non-target cell may express MHC class I.

- The term “absent on the surface of non-target cells” may be used interchangeably
25 with the term “undetectable on the surface of non-target cells”. Accordingly, the peptide antigen may be considered to be absent on the surface of a non-target cell if any method for determining surface presence shows that the peptide antigen is undetectable on the surface of the non-target cell. Methods for determining surface presence (and thus surface absence) are known in the art. Surface expression may, for example, be determined by
30 immunoprecipitation of MHC molecules from the target cell, and mass spectrometry of eluted MHC-bound peptides. Surface presence may, for example, be determined by flow cytometry. For instance, flow cytometry may be used to measure the mean fluorescent

intensity (MFI) of the peptide antigen. MFI measures intensity, time average energy flux measured in watts per square metre.

The peptide antigen may be absent on the surface of a particular type of non-target cells. For example, the peptide antigen may be absent on the surface of non-target cells in a particular tissue. The peptide antigen may be absent on the surface of non-target cells in a particular organ. For instance, the peptide antigen may be absent on the surface of non target cells in the anus, bile duct , bladder, blood, bone, bowel, brain, breast , colon, rectum, cervix, endocrine organs, eye, fallopian tube, gall bladder, head, neck, kidney, larynx, liver, lung, lymph node, muscle, peripheral nerves, ovary, oesophagus, pancreas, penis, peritoneum , prostate, skin, spinal cord, stomach , testicles , thymus , thyroid , trachea, vagina, vulva and/or endometrium, alone or in any combination.

The peptide antigen may be absent on the surface of any number or proportion of non-target cells in the individual. For instance, the peptide antigen may be absent on the surface of all non target cells. The peptide antigen may be absent on the surface of 70% or more of non-target cells in the individual. For example, the peptide antigen may be absent on the surface of 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 96 % or more, 97% or more, 98% or more, or 99% or more of non-target cells in the individual. In other words, the peptide antigen may be present on no more than 1%, no more than 2%, no more than 3%, no more than 5%, no more than 10%, no more than 15%, no more than 20%, no more than 25%, or no more than 30% of non-target cells in the individual. The peptide antigen may be absent on the surface of any proportion or number of non-target cells in a particular tissue. The peptide antigen may be absent on the surface of any proportion or number of non-target cells in a particular organ. For instance, the peptide antigen may be absent on the surface of any proportion or number of non target cells in the anus, bile duct , bladder, blood, bone, bowel, brain, breast , colon, rectum, cervix, endocrine organs, eye, fallopian tube, gall bladder, head, neck, kidney, larynx, liver, lung, lymph node, muscle, peripheral nerves, ovary, oesophagus, pancreas, penis, peritoneum , prostate, skin, spinal cord, stomach , testicles , thymus , thyroid , trachea, vagina, vulva and/or endometrium, alone or in any combination.

30

Germline variation

The peptide antigen is encoded by a germline variation in the individual. A germline variation is a change in the genetic structure that is inherited from a parent, and capable of being passed to offspring. Accordingly, the peptide antigen is not encoded by a somatic mutation specific to the target cell. In other words, the peptide antigen is not a neoantigen and does not comprise a neo-epitope. The peptide antigen is not a tumour-specific antigen (TSA).

For this reason, the peptide antigen may be present on the surface different types of target cells in different individuals, such as target cells derived from different tissues. For example, the peptide antigen may be present on the surface of an AML cell in one individual, and on the surface of a solid tumour cell in another individual. A single immunotherapeutic agent may therefore be used to treat different diseases in different individuals each comprising the germline variation, depending on the type of target cell upon whose surface the peptide antigen is expressed.

Preferably, the peptide antigen binds to an antigen binding domain that is expressed by an immune cell from a donor whose genome does not comprise the germline variation. Preferably, the donor does not have the disease. The donor may be an actual or prospective donor. The antigen binding domain may, for example, be a T cell receptor, a B cell receptor, an antibody, or an antibody fragment. The antibody fragment may be a fragment antigen-binding (Fab) fragment, a F(ab')₂ fragment, a single chain variable fragment (scFv), a scFv-Fc. The immune cell may be a T cell, a B cell, or a plasma cell, for example. Preferably, the immune cell is a T cell. The immune cell may recognise the peptide antigen as "*foreign*" or "*non-self*". The peptide antigen may be immunogenic with respect to the donor. The peptide antigen may be a minor histocompatibility antigen.

In other words, the germline variation may be a variation relative to the genome of the donor or prospective donor. The germline variation may give rise to polymorphism between the individual and the donor. Polymorphism may, for example, exist between a protein or peptide in the individual, and a corresponding protein or peptide in the donor. The germline variation may render the peptide antigen immunogenic with respect to the donor. The germline variation may encode a minor histocompatibility antigen.

The germline variation may comprise one or more nucleotide substitutions, insertions and/or deletions relative to the donor genome. For example, the germline variation may comprise two or more, three or more, four or more, or five or more

nucleotide substitutions relative to the donor genome. The germline variation may comprise two or more, three or more, four or more, or five or more nucleotide insertions relative to the donor genome. The germline variation may comprise two or more, three or more, four or more, or five or more nucleotide deletions relative to the donor genome.

- 5 The amino acid substitution may, for example, be a conservative amino acid substitution. The amino acid substitution may, for example, be a non-conservative amino acid substitution.

- Conservative substitutions replace amino acids with other amino acids of similar chemical structure, similar chemical properties or similar side-chain volume. The amino acids introduced may have similar polarity, hydrophilicity, hydrophobicity, basicity, acidity, neutrality or charge to the amino acids they replace. Alternatively, the conservative substitution may introduce another amino acid that is aromatic or aliphatic in the place of a pre-existing aromatic or aliphatic amino acid. Conservative amino acid changes are well-known in the art and may be selected in accordance with the properties of the 20 main amino acids as defined in Table 1 below. Where amino acids have similar polarity, this can also be determined by reference to the hydropathy scale for amino acid side chains in Table 2.

Table 1 – Chemical properties of amino acids

Ala	aliphatic, hydrophobic, neutral	Met	hydrophobic, neutral
Cys	polar, hydrophobic, neutral	Asn	polar, hydrophilic, neutral
Asp	polar, hydrophilic, charged (-)	Pro	hydrophobic, neutral
Glu	polar, hydrophilic, charged (-)	Gln	polar, hydrophilic, neutral
Phe	aromatic, hydrophobic, neutral	Arg	polar, hydrophilic, charged (+)
Gly	aliphatic, neutral	Ser	polar, hydrophilic, neutral
His	aromatic, polar, hydrophilic, charged (+)	Thr	polar, hydrophilic, neutral
Ile	aliphatic, hydrophobic, neutral	Val	aliphatic, hydrophobic, neutral
Lys	polar, hydrophilic, charged(+)	Trp	aromatic, hydrophobic, neutral
Leu	aliphatic, hydrophobic, neutral	Tyr	aromatic, polar, hydrophobic

Table 2 - Hydropathy scale

	Side Chain	Hydropathy
5	Ile	4.5
	Val	4.2
	Leu	3.8
	Phe	2.8
10	Cys	2.5
	Met	1.9
	Ala	1.8
	Gly	-0.4
	Thr	-0.7
15	Ser	-0.8
	Trp	-0.9
	Tyr	-1.3
	Pro	-1.6
	His	-3.2
20	Glu	-3.5
	Gln	-3.5
	Asp	-3.5
	Asn	-3.5
	Lys	-3.9
25	Arg	-4.5

MHC binding

The peptide antigen is capable of binding to a MHC molecule.

The MHC molecule may be a MHC class I molecule. The MHC class I molecule
 30 may be a human MHC class I molecule. That is, the MHC class I molecule may be a HLA
 class I molecule.

The peptide antigen may be capable of binding to one or more HLA class I molecules. For example, the peptide antigen may be capable of binding to one or more of (i) a HLA-A molecule, (ii) a HLA-B molecule, and (iii) a HLA-C molecule. For instance, the peptide antigen may be capable of binding to (i); (ii); (iii); (i) and (ii); (i) and (iii); (ii) and (iii); or (i), (ii) and (iii).

The MHC molecule may preferably be a MHC class II molecule. The expression of MHC class II molecule is traditionally limited to professional antigen-presenting cells. However, upregulation of MHC class II expression has been demonstrated for some target cells associated with certain diseases in a patient, such as AML. The MHC class II molecule may be a human MHC class II molecule. That is, the MHC class II molecule may be a HLA class II molecule.

The peptide antigen may be capable of binding to one or more HLA class II molecules. For example, the peptide antigen may be capable of binding to one or more of (i) a HLA-DP molecule, (ii) a HLA-DM molecule, (iii) a HLA-DOA molecule, (iv) a HLA-DOB molecule, (v) a HLA-DQ molecule, and (vi) a HLA-DR molecule. For instance, the peptide antigen may be capable of binding to (i); (ii); (iii); (iv); (v); (vi); (i) and (ii); (i) and (iii); (i) and (iv); (i) and (v); (i) and (vi); (ii) and (iii); (ii) and (iv); (ii) and (v); (ii) and (vi); (iii) and (iv); (iii) and (v); (iii) and (vi); (iv) and (v); (iv) and (vi); (v) and (vi); (i), (ii) and (iii); (i), (ii) and (iv); (i), (ii) and (v); (i), (ii) and (vi); (i), (iii) and (iv); (i), (iii) and (v); (i), (iii) and (vi); (i), (iv) and (v); (i), (iv) and (vi); (i), (v) and (vi); (ii), (iii) and (iv); (ii), (iii) and (v); (ii), (iii) and (vi); (ii), (iv) and (v); (ii), (iv) and (vi); (ii), (v) and (vi); (iii), (iv) and (v); (iii), (iv) and (vi); (iii), (v), (vi); (iv), (v) and (vi); (i), (ii), (iii) and (iv); (i), (ii), (iii) and (v); (i), (ii), (iii) and (vi); (i), (ii), (iv) and (v); (i), (ii), (iv) and (vi); (i), (ii), (v) and (vi); (i), (iii), (iv) and (v); (i), (iii), (iv) and (vi); (i), (iii), (v) and (vi); (i), (iv), (v) and (vi); (ii), (iii), (iv) and (v); (ii), (iii), (iv) and (vi); (ii), (iii), (v) and (vi); (ii), (iv), (v) and (vi); (iii), (iv), (v) and (vi); (i), (ii), (iii), (iv) and (v); (i), (ii), (iii), (iv) and (vi); (i), (ii), (iii), (v) and (vi); (i), (ii), (iv), (v) and (vi); (i), (iii), (iv), (v) and (vi); (ii), (iii), (iv), (v) and (vi); (i), (ii), (iii), (iv), (v) and (vi).

Methods for determining MHC (or HLA) binding ability are known in the art. For example, *in silico* analysis may be used to predict the affinity with which a peptide antigen binds to a MHC (or HLA) molecule. Mass spectrometry may be used to identify a peptide eluted from a MHC (or HLA) molecule immunoprecipitated from a target cell.

Various biochemical assays for determining peptide-MHC (or peptide-HLA) binding are also available.

Antigen binding molecule

5 The invention provides an antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in an individual having a disease, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. Such an antigen binding molecule is comprised in the immunotherapeutic agent selected or
10 administered in the methods and medical uses described herein.

 The antigen binding molecule may, for example, be a T cell receptor (TCR), a chimeric antigen receptor (CAR), an antibody, antibody fragment or bi-specific T cell engager (BiTE). The antibody fragment may comprise a fragment antigen-binding (Fab) fragment, a F(ab')₂ fragment, a single chain variable fragment (scFv), a scFv-Fc, or a
15 single domain antibody. Preferably, the antigen binding molecule is a TCR or a CAR.

 The antigen binding molecule binds to the peptide antigen. The antigen binding molecule may, for example, bind to the peptide antigen when it is bound to a MHC molecule. That is, the antigen binding molecule may bind to a MHC-peptide antigen complex. Preferably, the binding between the peptide antigen and the antigen binding
20 molecule is non-covalent. The binding may be mediated by, for example, electrostatic interaction, hydrogen bonds, van der Waals forces and/or hydrophobic interactions. Methods for detecting binding between a peptide and an antigen binding molecule are well-known in the art in include, for example, enzyme-linked immunosorbent assay (ELISA), enzyme-linked immune absorbent spot (ELISpot) assay, and flow cytometry.
25 Methods for functional testing of an antigen binding molecule are also known in the art. For example, cells may be engineered to express the antigen binding molecule. For instance, when the antigen binding molecule is a TCR, a lentiviral vector may be used to insert the alpha and beta chains of the TCR into T cells, such as human T cells. Then, the peptide antigen is added to a culture containing the cells that express the antigen binding
30 molecule. Cell activation (such as T cell activation) may be measured by well-known techniques, such as (1) an ELISpot for IFN γ secretion, or (2) flow cytometry following immunostaining for intracellular cytokines and/or surface markers of activation. Technique

(1) may, for example, be performed after 18 hours of peptide simulation. Technique (2) may, for example, be performed after 6 to 8 hours of peptide simulation.

The antigen binding molecule may comprise an antigen binding domain that is expressed by an immune cell from a donor whose genome does not comprise the germline variation. The immune cell may, for example, be a T cell or NKT cell. The antigen binding domain may, for example, comprise all or part of a TCR alpha chain, such as a TCR alpha chain disclosed herein. The antigen binding domain may comprise all or part of a TCR beta chain, such as a TCR beta chain disclosed herein. The antigen binding domain may comprise all or part of a TCR alpha chain (such as a TCR alpha chain disclosed herein) and all or part of a TCR beta chain (such as a TCR beta chain disclosed herein).

The antigen binding domain may comprise one or more of the complementarity determining regions (CDRs) from the alpha chain of a TCR. For example, the antigen binding domain may comprise two or three of the complementarity determining regions (CDRs) from the alpha chain of a TCR. The antigen binding domain may comprise one or more of the complementarity determining regions (CDRs) from the beta chain of a TCR. For example, the antigen binding domain may comprise two or three of the CDRs from the beta chain of a TCR. The antigen binding domain may comprise one or more of the CDRs from the alpha chain and one or more of the CDRs from the beta chain of a TCR. For example, the antigen binding domain may comprise (i) one of the CDRs from the alpha chain and one of the CDRs from the beta chain, (ii) one of the CDRs from the alpha chain and two of the CDRs from the beta chain, (iii) one of the CDRs from the alpha chain and three of the CDRs from the beta chain, (iv) two of the CDRs from the alpha chain and one of the CDRs from the beta chain, (v) two of the CDRs from the alpha chain and two of the CDRs from the beta chain, (vi) two of the CDRs from the alpha chain and three of the CDRs from the beta chain, (vii) three of the CDRs from the alpha chain and one of the CDRs from the beta chain, (viii) three of the CDRs from the alpha chain and two of the CDRs from the beta chain, or (ix) three of the CDRs from the alpha chain and three of the CDRs from the beta chain. The antigen binding domain may comprise one or more of (a) CDR1 from the alpha chain; (b) CDR2 from the alpha chain; (c) CDR3 from the alpha chain; (d) CDR1 from the beta chain; (e) CDR2 from the beta chain; and (f) CDR3 from the beta chain. For example, the antigen binding domain may comprise: (a); (b); (c); (d);

(e); (f); (a) and (b); (a) and (c); (a) and (d); (a) and (e); (a) and (f); (b) and (c); (b) and (d); (b) and (e); (b) and (f); (c) and (d); (c) and (e); (c) and (f); (d) and (e); (d) and (f); (e) and (f); (a), (b), (c); (a), (b), (d); (a), (b) and (e); (a), (b) and (f); (a), (c) and (d); (a), (c) and (e); (a), (c) and (f); (a), (d) and (e); (a), (d) and (f); (a), (e) and (f); (b), (c) and (d); (b), (c) and (e); (b), (c) and (f); (b), (d) and (e); (b), (d) and (f); (b), (e) and (f); (c), (d) and (e); (c), (d) and (f); (c), (e) and (f); (d), (e) and (f); (a), (b), (c) and (d); (a), (b), (c) and (e); (a), (b), (c) and (f); (a), (b), (d) and (e); (a), (b), (d) and (f); (a), (b), (e) and (f); (a), (c), (d) and (e); (a), (c), (d) and (f); (a), (c), (e) and (f); (a), (d), (e) and (f); (b), (c), (d) and (e); (b), (c), (d) and (f); (b), (c), (e), (f); (b), (d), (e) and (f); (c), (d), (e) and (f); (a), (b), (c), (d) and (e); (a), (b), (c), (d) and (f); (a), (b), (c), (e) and (f); (a), (b), (d), (e) and (f); (a), (c), (d), (e) and (f); (b), (c), (d), (e) and (f); (a), (b), (c), (d), (e) and (f). Preferably, the antigen binding domain comprises CDR3 from the alpha chain of a TCR and CDR3 from the beta chain of the TCR. In any case, the TCR may for example be any TCR disclosed herein.

Exemplary antigen binding domains are set out in the Examples (see Example 1, and Table 5 in Example 5). The antigen binding domain may, for example, comprise a CDR3 from any one or more of the exemplified antigen binding domains. The antigen binding domain may, for example, comprise a CDR3 from an exemplified TCR alpha chain, and a CDR3 from an exemplified TCR beta chain. The antigen binding domain may, for example, comprise CDR1, CDR2 and CDR3 from an exemplified TCR alpha chain, and CDR1, CDR2 and CDR3 from an exemplified TCR beta chain.

The antigen binding domain may, for example, comprise any one or more of the exemplified antigen binding domains. The antigen binding domain may, for example, comprise an exemplified TCR alpha chain and an exemplified TCR beta chain.

The antigen binding domain may, for example, comprise (a) a CDR3 from one or more of SEQ ID NOs: 6, 10, 12 16, 20, 206, 208, 211, 213, 215, 218, 221, 222, 224, 226, 228, 230, 232, 233, 235, 237, 239, 241, 243, 244, 246, 248, 250, 252, 254, 256, 258, 260, 261, 263, 266, 268, 270, 272, 274, 276, 278, 280, 282, 283, 285, 287, 288, and 290; and/or (b) a CDR3 from one or more of SEQ ID NOs: 8, 14, 18, 22, 207, 209, 210, 212, 214, 216, 217, 219, 220, 223, 225, 227, 229, 231, 234, 236, 238, 240, 242, 245, 247, 249, 251, 253, 255, 257, 259, 262, 264, 265, 267, 269, 271, 273, 275, 277, 279, 281, 284, 286, 289, 291, and 292. The antigen binding molecule may, for example, comprises (a) CDR1, CDR2 and CDR3 from one or more of SEQ ID NOs: 6, 10, 12 16, 20, 206, 208, 211, 213, 215,

218, 221, 222, 224, 226, 228, 230, 232, 233, 235, 237, 239, 241, 243, 244, 246, 248, 250, 252, 254, 256, 258, 260, 261, 263, 266, 268, 270, 272, 274, 276, 278, 280, 282, 283, 285, 287, 288, and 290; and/or (b) CDR1, CDR2 and CDR3 from one or more of SEQ ID NOs: 8, 14, 18, 22, 207, 209, 210, 212, 214, 216, 217, 219, 220, 223, 225, 227, 229, 231, 234, 236, 238, 240, 242, 245, 247, 249, 251, 253, 255, 257, 259, 262, 264, 265, 267, 269, 271, 273, 275, 277, 279, 281, 284, 286, 289, 291, and 292. The antigen binding molecule may, for example, comprises (a) one or more of SEQ ID NOs: 6, 10, 12, 16, 20, 206, 208, 211, 213, 215, 218, 221, 222, 224, 226, 228, 230, 232, 233, 235, 237, 239, 241, 243, 244, 246, 248, 250, 252, 254, 256, 258, 260, 261, 263, 266, 268, 270, 272, 274, 276, 278, 280, 282, 283, 285, 287, 288, and 290; and/or (b) one or more of SEQ ID NOs: 8, 14, 18, 22, 207, 209, 210, 212, 214, 216, 217, 219, 220, 223, 225, 227, 229, 231, 234, 236, 238, 240, 242, 245, 247, 249, 251, 253, 255, 257, 259, 262, 264, 265, 267, 269, 271, 273, 275, 277, 279, 281, 284, 286, 289, 291, and 292.

The antigen binding domain may, for example, comprise CDR3 from one or more of SEQ ID NOs: 6, 8, 10, 12, 14, 16, 18, 20 and 22. For example, the antigen binding domain may comprise (a) CDR3 from each of SEQ ID NOs: 6 and 8; (b) CDR3 from each of SEQ ID NOs: 10 and 14, or 12 and 14; (c) CDR3 from each of SEQ ID NOs: 16 and 18; (d) CDR3 from each of SEQ ID NOs: 10 and 14; or (e) CDR3 from each of SEQ ID NOs: 20 and 22.

The antigen binding domain may, for example, comprise CDR1, CDR2 and CDR3 from one or more of SEQ ID NOs: 6, 8, 10, 12, 14, 16, 18, 20 and 22. For example, the antigen binding domain may comprise (a) CDR1, CDR2 and CDR3 from each of SEQ ID NOs: 6 and 8; (b) CDR1, CDR2 and CDR3 from each of SEQ ID NOs: 10 and 14, or 12 and 14; (c) CDR1, CDR2 and CDR3 from each of SEQ ID NOs: 16 and 18; (d) CDR1, CDR2 and CDR3 from each of SEQ ID NOs: 10 and 14; or (e) CDR1, CDR2 and CDR3 from each of SEQ ID NOs: 20 and 22.

The antigen binding domain may, for example, comprise a CDR3 encoded within one or more nucleic acid sequences comprising or consisting of SEQ ID NOs: 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23 to 31. For example, the antigen binding domain may comprise a CDR3 encoded within (a) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 5 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 7; (b) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 9, a nucleic acid

sequence comprising or consisting of SEQ ID NO: 11, and a nucleic acid sequence comprising or consisting of SEQ ID NO: 13; (c) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 15 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 17; (d) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 9 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 13; or (e) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 19 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 21. The antigen binding domain may, for example, comprise a CDR3 encoded within (a) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 23 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 24; (b) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 25 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 27, or each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 26 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 27; (c) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 28 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 29; (d) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 25 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 27; or (e) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 30 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 31.

The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within one or more nucleic acid sequences comprising or consisting of SEQ ID NOs: 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23 to 31. For example, the antigen binding domain may comprise a CDR1, CDR2 and CDR3 encoded within (a) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 5 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 7; (b) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 9, a nucleic acid sequence comprising or consisting of SEQ ID NO: 11, and a nucleic acid sequence comprising or consisting of SEQ ID NO: 13; (c) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 15 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 17; (d) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 9 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 13; or (e) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 19 and a nucleic acid sequence comprising or

consisting of SEQ ID NO: 21. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within (a) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 23 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 24; (b) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 25 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 27, or each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 26 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 27; (c) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 28 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 29; (d) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 25 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 27; or (e) each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 30 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 31.

The antigen binding domain may, for example, comprise one or more of SEQ ID NOs: 6, 8, 10, 12, 14, 16, 18, 20 and 22. For example, the antigen binding domain may comprise (a) SEQ ID NOs: 6 and 8; (b) SEQ ID NOs: 10 and 14 or 12 and 14; (c) SEQ ID NOs: 16 and 18; (d) SEQ ID NOs: 10 and 14; or (e) SEQ ID NOs: 20 and 22. The antigen binding domain may, for example, be encoded by one or more nucleic acid sequences comprising or consisting of SEQ ID NOs: 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23 to 31. For example, the antigen binding domain may be encoded by (a) a nucleic acid sequence comprising or consisting of SEQ ID NO: 5 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 7; (b) a nucleic acid sequence comprising or consisting of SEQ ID NO: 9, a nucleic acid sequence comprising or consisting of SEQ ID NO: 11, and a nucleic acid sequence comprising or consisting of SEQ ID NO: 13; (c) a nucleic acid sequence comprising or consisting of SEQ ID NO: 15 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 17; (d) a nucleic acid sequence comprising or consisting of SEQ ID NO: 9 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 13; or (e) a nucleic acid sequence comprising or consisting of SEQ ID NO: 19 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 21. Preferably, the antigen binding domain is encoded by (a) a nucleic acid sequence comprising or consisting of SEQ ID NO: 23 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 24; (b) a nucleic acid sequence comprising or consisting of SEQ ID NO: 25 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 27, or a

nucleic acid sequence comprising or consisting of SEQ ID NO: 26 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 27; (c) a nucleic acid sequence comprising or consisting of SEQ ID NO: 28 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 29; (d) a nucleic acid sequence comprising or consisting of SEQ ID NO: 25 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 27; or (e) a nucleic acid sequence comprising or consisting of SEQ ID NO: 30 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 31.

The antigen binding domain may, for example, comprise a CDR3 from one or more of SEQ ID NOs: 206, 207, 208, 209, 210, 211, 210, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 289, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 27, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291 and 292. For example, the antigen binding domain may comprise a CDR3 from two of SEQ ID NOs: 206, 207, 208, 209, 210, 211, 210, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 289, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 27, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291 and 292, in any combination. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID NOs: 206 and 207. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 208 and 209, or from each of 208 and 210. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 211 and 212. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 213 and 214. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos: 215 and 216, or from each of SEQ ID Nos: 215 and 217. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 218 and 219, or from each of SEQ ID Nos: 218 and 220. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 221 and 223, or from each of SEQ ID Nos: 222 and 223. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 224 and 225. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 226 and

227. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 228 and 229. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 230 and 231. The antigen binding domain may, for example, comprise SEQ ID Nos 232 and 234, or 233 and 234. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 235 and 236. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 237 and 238. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 239 and 240. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 241 and 242. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 243 and 245, or from each of SEQ ID Nos: 244 and 245. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 246 and 247. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 248 and 249. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 250 and 251. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 252 and 253. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 254 and 255. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 256 and 257. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 258 and 259. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 260 and 262, or from each of SEQ ID Nos: 261 and 262. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 263 and 264, or from each of SEQ ID NOs: 263 and 265. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 266 and 267. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 268 and 269. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 270 and 271. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 272 and 273. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 274 and 275. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 276 and 277. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 278 and 279. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 280 and 281. The antigen binding domain may, for example,

comprise a CDR3 from each of SEQ ID Nos 282 and 284, or 283 and 284. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 285 and 286. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 287 and 289, or from each of SEQ ID Nos: 288 and 289. The antigen binding domain may, for example, comprise a CDR3 from each of SEQ ID Nos 290 and 291, or from each of SEQ ID Nos: 290 and 292.

The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from one or more of SEQ ID NOs: 206, 207, 208, 209, 210, 211, 210, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 289, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 27, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291 and 292. For example, the antigen binding domain may comprise a CDR1, CDR2 and CDR3 from two of SEQ ID NOs: 206, 207, 208, 209, 210, 211, 210, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 289, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 27, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291 and 292, in any combination. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID NOs: 206 and 207. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 208 and 209, or from each of 208 and 210. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 211 and 212. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 213 and 214. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos: 215 and 216, or from each of SEQ ID Nos: 215 and 217. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 218 and 219, or from each of SEQ ID Nos: 218 and 220. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 221 and 223, or from each of SEQ ID Nos: 222 and 223. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 224 and 225.

The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 226 and 227. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 228 and 229. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 230 and 231. The antigen binding domain may, for example, comprise SEQ ID Nos 232 and 234, or 233 and 234. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 235 and 236. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 237 and 238. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 239 and 240. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 241 and 242. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 243 and 245, or from each of SEQ ID Nos: 244 and 245. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 246 and 247. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 248 and 249. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 250 and 251. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 252 and 253. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 254 and 255. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 256 and 257. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 258 and 259. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 260 and 262, or from each of SEQ ID Nos: 261 and 262. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 263 and 264, or from each of SEQ ID NOs: 263 and 265. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 266 and 267. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 268 and 269. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 270 and 271. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ

ID Nos 272 and 273. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 274 and 275. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 276 and 277. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 278 and 279. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 280 and 281. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 282 and 284, or 283 and 284. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 285 and 286. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 287 and 289, or from each of SEQ ID Nos: 288 and 289. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 from each of SEQ ID Nos 290 and 291, or from each of SEQ ID Nos: 290 and 292.

The antigen binding domain may, for example, comprise a CDR3 encoded within one or more (such as two more more) nucleic acid sequences comprising or consisting of SEQ ID NOs: 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378 or 379. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 293 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 294. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of 295 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 296, or a within each of nucleic acid sequence comprising or consisting of 295 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 297. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of 298 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 299. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of 300 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 301. The antigen binding

domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of 302 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 303, or within each of a nucleic acid sequence comprising or consisting of 302 and a nucleic acid sequence comprising or consisting of SEQ ID

5 NO:304, The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 305 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 306, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 305 a nucleic acid sequence comprising or consisting of SEQ ID NO: 307. The antigen binding domain may, for

10 example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 308 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 309, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 308 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 310. The antigen binding domain may, for example, comprise a CDR3 encoded within

15 each of a nucleic acid sequence comprising or consisting of 311 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 312. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 313 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 314. The antigen binding domain may, for example, comprise a CDR3

20 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 315 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 316. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 317 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 318. The antigen binding domain may,

25 for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 319 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 321, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 320 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 321, The antigen binding domain may, for example, comprise a CDR3 encoded within

30 each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 322 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 323. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence

comprising or consisting of SEQ ID NO: 324 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 325. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 326 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 327. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 328 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 329. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 330 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 332, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 331 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 332. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 333 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 334. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 335 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 336. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 337 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 338. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 339 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 340. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 341 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 342. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 343 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 344. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 345 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 346. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 347 and a nucleic acid sequence comprising or consisting of

SEQ ID NO: 349, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 348 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 349. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of a nucleic acid sequence

5 comprising or consisting of SEQ ID NO: 350 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 351, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 350 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 352. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO:

10 353 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 354. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 355 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 356. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising

15 or consisting of SEQ ID NO: 357 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 358. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 359 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 360. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid

20 sequence comprising or consisting of SEQ ID NO: 361 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 362. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 363 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 364. The antigen binding domain may, for example, comprise a CDR3

25 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 365 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 366. The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 367 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 368. The antigen binding domain may,

30 for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 369 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 371, or within each of a nucleic acid sequence comprising or consisting of

SEQ ID NO: 370 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 371, The antigen binding domain may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 372 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 373. The antigen binding domain
 5 may, for example, comprise a CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 374 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 376, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 375 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 376. The antigen binding domain may, for example, comprise a CDR3
 10 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 377 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 378, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 377 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 379.

The antigen binding domain may, for example, comprise a CDR1, CDR2 and
 15 CDR3 encoded within one or more (such as two or more) nucleic acid sequences comprising or consisting of SEQ ID NOs: 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355,
 20 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378 or 379. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 293 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 294. The antigen binding domain may, for example, comprise a CDR1,
 25 CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of 295 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 296, or a within each of nucleic acid sequence comprising or consisting of 295 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 297. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid
 30 sequence comprising or consisting of 298 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 299. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or

consisting of 300 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 301. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of 302 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 303, or within each of a nucleic acid sequence comprising or consisting of 302 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 304, The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 305 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 306, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 305 a nucleic acid sequence comprising or consisting of SEQ ID NO: 307. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 308 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 309, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 308 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 310. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of 311 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 312. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 313 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 314. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 315 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 316. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 317 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 318. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 319 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 321, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 320 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 321, The antigen binding domain may, for example, comprise a

CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 322 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 323. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 324 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 325. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 326 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 327. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 328 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 329. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 330 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 332, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 331 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 332. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 333 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 334. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 335 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 336. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 337 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 338. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 339 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 340. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 341 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 342. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid

sequence comprising or consisting of SEQ ID NO: 343 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 344. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 345 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 346. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 347 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 349, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 348 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 349. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of a nucleic acid sequence comprising or consisting of SEQ ID NO: 350 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 351, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 350 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 352. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 353 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 354. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 355 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 356. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 357 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 358. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 359 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 360. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 361 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 362. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 363 and a nucleic acid sequence

comprising or consisting of SEQ ID NO: 364. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 365 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 366. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 367 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 368. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 369 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 371, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 370 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 371. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 372 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 373. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 374 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 376, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 375 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 376. The antigen binding domain may, for example, comprise a CDR1, CDR2 and CDR3 encoded within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 377 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 378, or within each of a nucleic acid sequence comprising or consisting of SEQ ID NO: 377 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 379.

25 The antigen binding domain may, for example, comprise one or more of SEQ ID NOs: 206, 207, 208, 209, 210, 211, 210, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 289, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 27, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291 and 292. For example, the antigen binding domain may comprise two of SEQ ID NOs: 206, 207, 208, 209, 210, 211, 210, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226,

227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 289, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 27, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291 and 292, in any combination. The
5 antigen binding domain may, for example, comprise SEQ ID NOs: 206 and 207. The antigen binding domain may, for example, comprise SEQ ID Nos 208 and 209, or 208 and 210. The antigen binding domain may, for example, comprise SEQ ID Nos 211 and 212. The antigen binding domain may, for example, comprise SEQ ID Nos 213 and 214. The antigen binding domain may, for example, comprise SEQ ID Nos 215 and 216, or 215 and
10 217. The antigen binding domain may, for example, comprise SEQ ID Nos 218 and 219, or 218 and 220. The antigen binding domain may, for example, comprise SEQ ID Nos 221 and 223, or 222 and 223. The antigen binding domain may, for example, comprise SEQ ID Nos 224 and 225. The antigen binding domain may, for example, comprise SEQ ID Nos 226 and 227. The antigen binding domain may, for example, comprise SEQ ID Nos
15 228 and 229. The antigen binding domain may, for example, comprise SEQ ID Nos 230 and 231. The antigen binding domain may, for example, comprise SEQ ID Nos 232 and 234, or 233 and 234. The antigen binding domain may, for example, comprise SEQ ID Nos 235 and 236. The antigen binding domain may, for example, comprise SEQ ID Nos 237 and 238. The antigen binding domain may, for example, comprise SEQ ID Nos 239
20 and 240. The antigen binding domain may, for example, comprise SEQ ID Nos 241 and 242. The antigen binding domain may, for example, comprise SEQ ID Nos 243 and 245, or 244 and 245. The antigen binding domain may, for example, comprise SEQ ID Nos 246 and 247. The antigen binding domain may, for example, comprise SEQ ID Nos 248 and 249. The antigen binding domain may, for example, comprise SEQ ID Nos 250 and 251.
25 The antigen binding domain may, for example, comprise SEQ ID Nos 252 and 253. The antigen binding domain may, for example, comprise SEQ ID Nos 254 and 255. The antigen binding domain may, for example, comprise SEQ ID Nos 256 and 257. The antigen binding domain may, for example, comprise SEQ ID Nos 258 and 259. The antigen binding domain may, for example, comprise SEQ ID Nos 260 and 262, or 261 and
30 262. The antigen binding domain may, for example, comprise SEQ ID Nos 263 and 264, or 263 and 265. The antigen binding domain may, for example, comprise SEQ ID Nos 266 and 267. The antigen binding domain may, for example, comprise SEQ ID Nos 268 and

269. The antigen binding domain may, for example, comprise SEQ ID Nos 270 and 271. The antigen binding domain may, for example, comprise SEQ ID Nos 272 and 273. The antigen binding domain may, for example, comprise SEQ ID Nos 274 and 275. The antigen binding domain may, for example, comprise SEQ ID Nos 276 and 277. The antigen binding domain may, for example, comprise SEQ ID Nos 278 and 279. The antigen binding domain may, for example, comprise SEQ ID Nos 280 and 281. The antigen binding domain may, for example, comprise SEQ ID Nos 282 and 284, or 283 and 284. The antigen binding domain may, for example, comprise SEQ ID Nos 285 and 286. The antigen binding domain may, for example, comprise SEQ ID Nos 287 and 289, or 288 and 289. The antigen binding domain may, for example, comprise SEQ ID Nos 290 and 291, or 290 and 292.

The antigen binding domain may, for example, be encoded by one or more nucleic acid sequences comprising or consisting of SEQ ID NOs: 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378 or 379. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 293 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 294. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of 295 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 296, or a nucleic acid sequence comprising or consisting of 295 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 297. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of 298 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 299. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of 300 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 301. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of 302 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 303, or a nucleic acid sequence comprising or consisting of 302 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 304. The antigen

binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 305 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 306, or a nucleic acid sequence comprising or consisting of SEQ ID NO: 305 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 307. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 308 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 309, or a nucleic acid sequence comprising or consisting of SEQ ID NO: 308 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 310. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of 311 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 312. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 313 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 314. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 315 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 316. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 317 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 318. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 319 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 321, a nucleic acid sequence comprising or consisting of SEQ ID NO: 320 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 321, The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 322 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 323. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 324 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 325. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 326 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 327. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 328 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 329. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting

of SEQ ID NO: 330 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 332, or a nucleic acid sequence comprising or consisting of SEQ ID NO: 331 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 332. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ

5 ID NO: 333 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 334. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 335 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 336. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 337 and a

10 nucleic acid sequence comprising or consisting of SEQ ID NO: 338. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 339 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 340. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 341 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 342. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 343 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 344. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 345 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 346. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 347 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 349, or a nucleic acid sequence comprising or consisting of SEQ ID NO: 348 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 349. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of a nucleic acid sequence comprising or consisting of SEQ ID NO: 350 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 351, or a nucleic acid sequence comprising or consisting of SEQ ID NO: 350 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 352. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 353 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 354. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO:

30

355 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 356. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 357 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 358. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 359 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 360. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 361 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 362. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 363 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 364. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 365 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 366. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 367 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 368. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 369 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 371, or a nucleic acid sequence comprising or consisting of SEQ ID NO: 370 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 371, The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 372 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 373. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 374 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 376, or a nucleic acid sequence comprising or consisting of SEQ ID NO: 375 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 376. The antigen binding domain may, for example, be encoded by a nucleic acid sequence comprising or consisting of SEQ ID NO: 377 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 378, or a nucleic acid sequence comprising or consisting of SEQ ID NO: 377 and a nucleic acid sequence comprising or consisting of SEQ ID NO: 379.

The immune cell may, for example, be a B cell or a plasma cell. The antigen binding domain may, for example, comprise all or part of a light chain from an antibody or

a B cell receptor (BCR). The antigen binding domain may comprise all or part of a heavy chain of an antibody or a BCR. The antigen binding domain may comprise all or part of a light chain and all or part of a heavy chain of an antibody or a BCR. The antigen binding domain may comprise the three CDRs from the light chain of an antibody or a BCR. The antigen binding domain may comprise the three CDRs from the heavy chain of an antibody or a BCR. The antigen binding domain may comprise the three CDRs from the light chain and the three CDRs from the heavy chain of an antibody or a BCR. The antigen binding domain may comprise the variable region of an antibody or BCR. The antigen binding domain may comprise a Fab or (Fab')₂ from an antibody or BCR.

10 The antigen binding molecule may comprise a variant of an antigen binding domain that is expressed by an immune cell from a donor whose genome does not comprise the germline variation. Antigen binding domains are described in detail in the preceding paragraphs. Over the entire length of the amino acid sequence of the antigen binding domain, a variant will preferably have at least 50% identity to that sequence. More preferably, the variant will have at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity to the amino acid sequence of the antigen binding domain. The variant retains the antigen binding ability of the antigen binding domain.

20 The antigen binding molecule may comprise or consist of an antigen binding molecule that is expressed by an immune cell from a donor whose genome does not comprise the germline variation. The immune cell may, for example, be a T cell or NKT cell. The antigen binding molecule may be a TCR. The immune cell may be a B cell or a plasma cell. The antigen binding molecule may be an antibody or a BCR.

25 The antigen binding molecule may comprise a variant of an antigen binding molecule that is expressed by an immune cell from a donor whose genome does not comprise the germline variation. Antigen binding molecules are described in the preceding paragraph. Over the entire length of the amino acid sequence of the antigen binding molecule, a variant will preferably have at least 50% identity to that sequence. More preferably, the variant will have at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity to the amino acid sequence of the antigen binding molecule. The variant retains the antigen binding ability of the antigen binding molecule.

The variant may comprise the CDRs of the antigen binding molecule expressed by an immune cell from a donor whose genome does not comprise the germline variation. For example, the variant may comprise the three CDRs from the alpha chain of a TCR expressed by the immune cell. The variant may comprise the three CDRs from the beta chain of a TCR expressed by the immune cell. The variant may comprise three CDRs from the alpha chain and the three CDRs from the beta chain of a TCR expressed by the immune cell. The variant may comprise the three CDRs from the light chain of an antibody or a BCR expressed by the immune cell. The variant may comprise the three CDRs from the heavy chain of an antibody or a BCR expressed by the immune cell. The variant may comprise the three CDRs from the light chain and the three CDRs from the heavy chain of an antibody or a BCR expressed by the immune cell.

Immunotherapeutic agent

The immunotherapeutic agent comprises an antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. Antigen binding molecules and peptide antigens are described in detail above.

The immunotherapeutic agent may further comprise an immune cell that expresses the antigen binding molecule on its surface. The immune cell may be autologous with respect to the individual. The immune cell may be allogeneic with respect to the individual. The immune cell may be derived from a donor whose genome does not comprise the germline variation. Preferably, the donor does not have the disease. The immune cell may, for example, be a T cell, a B cell, a NKT cell, a NK cell, a monocyte or a macrophage. Preferably, the immune cell is a T cell. The T cell may be a CD4⁺ T cell or a CD8⁺ T cell. Preferably, the T cell is CD4⁺ T cell.

The antigen binding molecule expressed on the surface of the immune cell may be derived from the donor. For instance, the immune cell may be a donor-derived T cell or NKT cell. The antigen binding molecule expressed on the surface of the donor-derived immune cell may be a donor-derived TCR. In this way, the donor-derived immune cell may naturally have specificity for the peptide antigen. The immunotherapeutic agent may be administered to the individual to provide an allogeneic immune cell transplant.

Following administration, peptide antigen on target cells may bind to the antigen binding molecule, leading to immune cell activation and an immune response against target cells expressing the peptide antigen. Accordingly, the disease in the individual may be treated.

The antigen binding molecule expressed on the surface of the immune cell may be
5 a T cell receptor (TCR) or a chimeric antigen receptor (CAR). Expression of a TCR or CAR specific for the peptide antigen may confer specificity for the peptide antigen onto an immune cell that is autologous or allogeneic with respect to the individual, and that otherwise would not recognise the peptide antigen. In this way immune cells specific for the peptide antigen can be engineered. Preferably, the immune cell is a T cell. Preferably,
10 the T cell is a CD4⁺ T cell. Following administration of engineered immune cells to the individual, peptide antigen on target cells may bind to the CAR, leading to immune cell activation and an immune response against target cells expressing the peptide antigen. Accordingly, the disease in the individual may be treated.

The immunotherapeutic agent may be administered by any route. Suitable routes
15 include, but are not limited to, the intravenous, intramuscular, intraperitoneal, subcutaneous, intradermal, and transdermal routes.

The immunotherapeutic agent is administered in a manner compatible with the dosage formulation and in such amount will be therapeutically effective. The quantity to be administered depends on the subject to be treated, the disease to be treated, and the
20 capacity of the individual's immune system. Precise amounts of the immunotherapeutic agent required to be administered may depend on the judgement of the practitioner and may be peculiar to each individual.

The immunotherapeutic agent may comprise a pharmaceutically acceptable carrier or diluent. Thus, the immunotherapeutic agent may be provided as a pharmaceutical
25 composition. Typically, such compositions are prepared as liquid suspensions of antigen binding molecules and/or cells. The antigen binding molecules and/or cells may be mixed with an excipient which is pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, of the like and combinations thereof. The pharmaceutical composition may be formulated using
30 any suitable method. Formulation of antigen binding molecules and/or cells with standard pharmaceutically acceptable carriers and/or excipients may be carried out using routine methods in the pharmaceutical art. The exact nature of a formulation will depend upon

several factors including the cells to be administered and the desired route of administration. Suitable types of formulation are fully described in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Company, Eastern Pennsylvania, USA. In addition, if desired, the pharmaceutical compositions may contain minor amounts
5 of auxiliary substances such as wetting or emulsifying agents, and/or pH buffering agents.

Polynucleotide

The invention further provides a polynucleotide encoding the antigen binding molecule or peptide antigen of the invention. That is, the invention provides a
10 polynucleotide encoding an antigen binding molecule that is (i) encoded by a germline variation in an individual having a disease, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. The invention also provides a polynucleotide encoding a peptide antigen that is (i) encoded by a germline variation in an individual
15 having a disease, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. Any of the aspects describe above in connection with the antigen binding molecule or the peptide of the invention may also apply to the polynucleotide of the invention.

20 The polynucleotide may comprise RNA. The polynucleotide may comprise DNA. The polynucleotide may comprise RNA and DNA.

The polynucleotide may, for example, comprise one or more of SEQ ID NOs: 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 24, 25, 26, 27, 28, 29, 30, 31, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316,
25 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378 or 379.

30 Vector

The invention provides a vector comprising the polynucleotide of the invention. That is, the invention provides a vector comprising a polynucleotide encoding an antigen

binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual. The invention also provides a vector comprising a polynucleotide
 5 encoding a peptide antigen that is (i) encoded by a germline variation in an individual having a disease, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual.

The vector may be a viral vector. The viral vector may, for example, be a
 10 lentivirus, a retrovirus, an adenovirus, an adeno-associated virus (AAV), a vaccinia virus or a herpes simplex virus. Methods for producing and purifying such vectors are known in the art. The retrovirus may be a gamma-retrovirus. The lentivirus may be a modified HIV virus suitable for use in delivering genes. The lentivirus may be a SIV, FIV, or equine infectious anemia virus (EQIA) based vector. The viral vector may comprise a targeting
 15 molecule to ensure efficient transduction with the nucleic acid sequence or nucleic acid construct. The targeting molecule will typically be provided wholly or partly on the surface of the viral vector in order for the molecule to be able to target the virus to cells. The viral vector is preferably replication deficient.

The vector may be a non-viral vector. Preferably, the non-viral vector is a DNA
 20 plasmid, a naked nucleic acid, a nucleic acid complexed with a delivery vehicle, or an artificial virion. The non-viral vector may be a human artificial chromosome, as described in e.g. Kazuki et al., Mol. Ther. 19(9): 1591-1601 (2011), and Kouprina et al., Expert Opinion on Drug Delivery 11(4): 517-535 (2014). When the non-viral vector is a nucleic acid complexed with a delivery vehicle, the delivery vehicle may be a liposome, virosome, or
 25 immunoliposome. Integration of a plasmid vector may be facilitated by a transposase such as sleeping beauty or PiggyBAC.

Examples

30 Example 1 - Identifying the antigenic basis of GvL

Given the low mutational burden in AML, HLA-bound GvL antigens are likely to result from mismatched expressed germline variants between patient and donor (i.e. minor

histocompatibility antigens) rather than neoantigens. It remains unclear whether donor GvL responses are driven by public antigens (those with a frequency >0.05 in the population) or low frequency, private antigens.

We implemented an unbiased approach to identify GvL antigens in bone marrow samples from 15 AML patients treated with allo-SCT (12/15 have been cured; 3/15 died from relapsed disease). We first performed whole exome sequencing (WES) of patient and donor DNA to identify coding variants mismatched between patient and donor, and then RNA-Seq to identify all variants mismatched between patient AML cells and donor that were expressed on patient AML cells. As expected, more germline mismatched variants were identified in unrelated compared with sibling donor transplants (5744 vs 3253 variants, Figure 1a and b).

Of all variants, 98.7% were germline and only 1.3% were AML-specific somatic mutations. A mean of 28.6% variants were detectable in RNA-Seq reads. Of all variants, 47.8% are present in 2 or more patients. Variants present in multiple patients are more likely to have importance for clinical translation. From these variants, putative GvL antigens were identified using two methods:

1. In silico prediction of HLA-binding affinity, using exome-identified variants and RNA-Seq expression data from AML.
2. Mass spectrometry of peptides presented by HLA class I and II.

First, we identified putative GvL antigens by integrating WES-identified variants, RNA-Seq expression data and patient-specific HLA alleles. Then we performed in silico HLA class I and II-binding prediction using NetMHCpan 4.0 and NetMHCIIpan 3.0, utilising artificial neural networks trained on HLA-binding data. For HLA class I and II, between 150 and 700 mismatched HLA-binding epitopes were predicted for each patient (Figure 2). An average of 2864 genes contained potential immunogenic variants/patient. 56% of these genes are expressed in AML blasts by RNA-Seq.

In our second approach, we immunoprecipitated HLA Class I and II from AML blasts, eluted HLA-bound peptides and analysed them by mass spectrometry. Patient-specific proteome databases were produced using the exome-identified variants. Peptide

sequences were then identified from the mass spectra with reference to these databases. Immunopeptidome analysis revealed 2.1 patient-donor mismatched peptides per patient (compared to the 150-700 mismatched peptides from computational approaches). This was unsurprising as immunopeptidome analysis identifies only a subset of highest affinity, well ionising HLA-bound peptides. Nevertheless, it did confirm some predicted mis-matched peptides.

Characterising the GvL T cell response

For any individual patient, it is not known whether GvL responses are mediated by a small number of dominant T cell clones or whether a large number of clones contribute to the anti-AML response. To begin to address this, we established a generic workflow. As a proof of principle, we studied one patient in detail. We screened a library of 335 mismatched peptides identified by *in silico* prediction and mass spectrometry for their ability to activate donor-derived T cells taken from the patient post-allo-SCT, using sensitive cultured IFN γ ELISpot assays. This patient had strong T cell responses to two overlapping peptides (SEQ ID NOs: 3 and 4, see below), targeting the same germline mismatched variant.

The single nucleotide polymorphism (SNP) producing the immunogenic peptides is a C $\rightarrow$ T substitution in PADI4 (peptidyl arginine deiminase 4), which results in a serine (S) $\rightarrow$ phenylalanine (F) amino acid substitution. (dbSNP ID = rs1748020). Expression of PADI4 in normal human tissue, in human tumours, and in primary AML samples is shown in Figure 5. In the initial IFN γ ELISpot screen, 2 peptides overlapping this PADI4 SNP elicited T cell responses:

Peptide 1 (SEQ ID NO: 1)
LTISLLDTFNLELPEAVVFQ

Peptide 2 (SEQ ID NO: 2)
ISLLDTFNLELPEAVVFQDS

Subsequent ELISpot experiments were used to identify nested peptides within these longer sequences that produce the strongest T cell responses:

Nested peptide 1 (SEQ ID NO: 3)

SLLDTFNLELPEAVVF

5 Nested peptide 2 (SEQ ID NO: 4)

LDTFNLELPEAVVFQ

Using IFN γ ELISpots with HLA-blocking antibodies we demonstrated that allo-AML responses were HLA-DP restricted (Figure 3a). Supporting this observation, immunophenotyping of peptide-responsive T cells identified by production of cytokines (IFN γ , TNF α) and expression of the degranulation marker (CD107a) revealed this response was mediated by CD4+, but not CD8+, T cells (Figure 3b). All of SEQ ID Nos: 1 to 4 were demonstrated to elicit HLA-DP restricted T cell responses by IFN γ ELISpot using HLA-blocking antibodies.

15 In line with our observations, importance of HLA class II is supported by recent evidence of downregulation of HLA class II expression on AML blasts post-allo-SCT relapse in one third of patients, i.e. it is a common mechanism of immune evasion. Notably this germline polymorphism is present in 8% of the Caucasian population and the DP allele in ~60% of the Caucasian population, suggesting this may be a widely applicable target GvL antigen.

The following protocol was used to determine the sequence of TCRs recognising peptide 1 (SEQ ID NO: 1) or peptide 2 (SEQ ID NO: 2):

1. Culture post-transplant blood with peptide (identified from IFN γ ELISpot screen) to enrich for antigen-specific T cells.
- 25 2. After peptide stimulation, FACS sort activated (IFN γ +) T cells and control (IFN γ -) T cells.
3. Single cell RNA sequencing with V(D)J enrichment.

As demonstrated in Figure 6, single cell sequencing identified two expanded clones (clone 1 and clone 2) within the CD4+ IFN γ + population. The two expanded clones represent putative antigen-specific T cells. As shown in Figure 7, putative antigen-specific T cells express multiple cytokines (IFN γ , TNF α) and activation markers (FASLG, IL2RA, TNFRSF9, GZMB) in response to peptide stimulation.

Single cell RNA sequencing was further used to determine the sequence of TCRs recognising nested peptide 1 (SEQ ID NO: 3) or nested peptide 2 (SEQ ID NO: 4). SEQ ID NOs: 5 to 22 provide the sequences of the alpha and beta chains from the five most frequent T cell clones in an experiment that enriched for antigen-specific T cells. Clone 2 contains two alpha sequences and one beta. Clone 4 has one of these alpha chains and the same beta, demonstrating that clones 2 and 4 are very likely to recognise the same epitope.

Clone 1 - TCR α

10 Nucleotide sequence (SEQ ID NO: 5)

CAGAAGCCTCACACAGCCCAGTAACTTTGCTAGTACCTCTTGAGTGCAAGGTG
 GAGAATTAAGATCTGGATTTGAGACGGAGCACGGAACATTTCACTCAGGGGAA
 GAGCTATGAACATGCTGACTGCCAGCCTGTTGAGGGCAGTCATAGCCTCCATC
 15 TGTGTTGTATCCAGCATGGCTCAGAAGGTAAGTCAAGCGCAGACTGAAATTTC
 TGTGGTGGAGAAGGAGGATGTGACCTTGGACTGTGTGTATGAAACCCGTGATA
 CTAATTATTACTTATTCTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCC
 TTATTCGTCGGAACCTCTTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTT
 GGAACCTCCAGAAATCCACCAGTTCCTTCAACTTCACCATCACAGCCTCACAA
 20 GTCGTGGACTCAGCAGTATACTTCTgtgctctgagtgaacggccgtatggtggtgctacaaacaagctcatct
 ttGGAACCTGGCACTCTGCTTGCTGTCCAGCCAAATATCCAGAACCCTGACCCTGC
 CGTGTACCAGCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTAC
 CGATTTTGATTCTCAAACAAATGTGTACAAAGTAAGGATTCTGATGTGTATAT
 CACAGACAAAACCTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTG
 25 CTGTGGCCTGGAGCAACAAATCTGACTTTGCATGTGCAAACGCCTTCA

(Consensus sequence ends before completion of TRAC)

Amino acid sequence (SEQ ID NO: 6)

30

MLTASLLRAVIASICVVSSMAOKVTOAQTEISVVEKEDVTLDCVYETRDTTYLYF
 WYKOPPSGELVFLIRRNSEDEQNEISGRYSWNFOKSTSSFNFTITASQVVDSAVYF_c

alserpyggatnkliFGTGTLAVQPNIQNPDPVYQLRDSKSSDKSVCLFTDFDSQTNVSQ
SKDSDVYITDKTVLDMRSMDFKSNSAVAWSNKSDFACANAF

(Consensus sequence ends before completion of TRAC)

5

not underlined = 5' UTR

..... = TRAV19

_____ = TRAJ32

----- = TRAC

10 lower case = CDR3 (17-aa length)

Clone 1 - TCR β

Nucleotide consensus sequence (SEQ ID NO: 7)

15

AAAATGCCCTCCTTTCCTCCACAGGACCAGATGCCTGAGCTAGGAAAGGCCT
 CATTCTGCTGTGATCCTGCCATGGATACCTGGCTCGTATGCTGGGCAATTTT
 AGTCTCTTGAAAGCAGGACTCACAGAACCTGAAGTCACCCAGACTCCCAGCCA
 TCAGGTCACACAGATGGGACAGGAAGTGATCTTGGCTGTGTCCCATCTCTA

20

ATCACTTATACTTCTATTGGTACAGACAAATCTTGGGGCAGAAAGTCGAGTTT
 TGGTTTCCTTTTATAATAATGAAATCTCAGAGAAGTCTGAAATATTCGATGATC
 AATTCTCAGTTGAAAGGCCTGATGGATCAAATTTCACTCTGAAGATCCGGTCC
 ACAAAGCTGGAGGACTCAGCCATGTACTTCTgtgccagcagtgaaacgcaggacgcaacctgcctac
 gagcagctacttcGGGCCGGGCACCAGGCTCACGGTCACAGAGGACCTGAAAAACGTG

25

TTCCCACCCGAGGTCGCTGTGTTTGAGCCATCAGAAGCAGAGATCTCCCACAC
 CAAAAGGCCACACTGGTATGCCTGGCCACAGGCTTCTACCCCGACCACGTGG
 AGCTGAGCTGGTGGGTGAATGGGAAGGAGGTGCACAGTGGGGTCAGCACAGA
 CCCGCAGCCCCTCAAGGAGCAGCCCGCCCTCAATGACTCCAGATACTGCCTGA
 GCAGCCGCCTGAGGGTCTCGGCCACCTTCTGGCAGAACCCCGCAACCACTTC

30

CGCTGTCAAGTCCAGTTCTACGGGCTCTCGGAGAATGACGAGTGG

(Consensus sequence ends before completion of TRBC2)

Amino acid consensus sequence (SEQ ID NO: 8)

MDTWLVCWAIFSLKAGLTEPEVTOTPSHQVTOMGQEVILRCVPISNHLIFYWYR
 5 QILGQKVEFLVSFYNNEISEKSEIFDDQFSVERPDGSNFTLKIRSTKLEDSAMYFcass
errtqpayeqyfGPGTRLTVTEDLKNVFPPEVAVFEPSEAEISHTQKATLVCLATGFYPD
HVELSWWWNGKEVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNH
FRCQVQFYGLSENDEW

10 (Consensus sequence ends before completion of TRBC2)

not underlined = 5' UTR

..... = TRBV2

===== = TRBJ2-7

15 ----- = TRBC2

lower case = CDR3 (16-aa length)

Clone 2 – TCR α (1)

20 Nucleotide consensus sequence (SEQ ID NO: 9)

AAAGCAGATTCTTTTATGATTTTTAAAGTAGAAATATCCATTCTAGGTGCATT
 TTTTAAGGGTTTAAAATTTGAATCCTCAGTGAACCAGGGCAGAGAAGAATGAT
 GAAATCCTTGAGAGTTTTACTAGTGATCCTGTGGCTTCAGTTGAGCTGGGTTTG
 25 GAGCCAACAGAAGGAGGTGGAGCAGAATTCTGGACCCCTCAGTGTTCCAGAG
GGAGCCATTGCCTCTCTCAACTGCACTTACAGTGACCGAGGTCCCAGTCCTTC
TTCTGGTACAGACAATATTCTGGGAAAAGCCCTGAGTTGATAATGTCCATATA
CTCCAATGGTGACAAAGAAGATGGAAGGTTTACAGCACAGCTCAATAAAGCC
AGCCAGTATGTTTCTCTGCTCATCAGAGACTCCCAGCCCAGTGATTCAGCCACC
 30 TACCTCtgtgccgtccggggcaggcaggaactgctgactttGGGAAGGGAACCACTTATCAGT
GAGTTCCAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACTCTA
AATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAACAAATG

TGTCACAAAGTAAGGATTCTGATGTGTATATCACAGACAAAACCTGTGCTAGAC
ATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTGGCCTGGAGCAACAAATC
TGACTTTGCATGTGCAAACGCCTTCA

5 (Consensus sequence ends before completion of TRAC)

Amino acid consensus sequence (SEQ ID NO: 10)

MKSLRVLLVILWLQLSWVWSQOKEVEQNSGPLSVPEGAIASLNCTYSDRGSSQSF
 10 WYROYSGKSPELIMSIYSNGDKEDGRFTAOLNKASQYVSLLRDSQPSDSATYL_{cav}
rgqagtalifGKGTTLSVSSNIQNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDS
DVYITDKTVLDMRSMDFKSNSAVAWSNKSDFA CANAF

(Consensus sequence ends before completion of TRAC)

15

Not underlined = 5' UTR

..... = TRAV12-2

==== = TRAJ15

----- = TRAC

20 Lower case = CDR3 (13-aa length)

Clone 2 – TCR α (2)

Nucleotide consensus sequence (SEQ ID NO: 11)

25

CAGAAAGCCTCACACAGCCCAGTAACTTTGCTAGTACCTCTTGAGTGCAAGGTG
 GAGAATTAAGATCTGGATTTGAGACGGAGCACGGAACATTTCACTCAGGGGAA
 GAGCTATGAACATGCTGACTGCCAGCCTGTTGAGGGCAGTCATAGCCTCCATC
TGTGTTGTATCCAGCATGGCTCAGAAGGTAACCTCAAGCGCAGACTGAAATTTC
 30 TGTGGTGGAGAAGGAGGATGTGACCTTGGACTGTGTGTATGAAACCCGTGATA
CTACTTATTACTTATTCTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCC
TTATTCGTCGGAACCTCTTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTT

GGA~~ACTTCCAGAAATCCACCAGTTCCTTCAACTTCACCATCACAGCCTCACAA~~
 GTCGTGGACTCAGCAGTATACTTC~~gtgctctccggcaggaaacacaccttgtctti~~GGAAAGGG
 CACAAGACTTTCTGTGATTGCAAATATCCAGAACCCTGACCCTGCCGTGTACCA
 GCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGA
 5 TTCTCAAACAAATGTGTACAAAGTAAGGATTCTGATGTGTATATCACAGACA
 AA~~ACTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTGGCC~~
 TGGAGCAACAAATCTGACTTTGCATGTGCAAACGCCTTCA

(Consensus sequence ends before completion of TRAC)

10

Amino acid consensus sequence (SEQ ID NO: 12)

MLTASLLRAVIASICVSSMAOKVTOAQTEISVVEKEDVTLDCVYETRDTTYYLE
 WYKOPPSGELVFLIRNSFDEQNEISGRYSWNFOKSTSSFNFTITASQVVD~~SAVYFc~~
 15 ~~alpagn~~tplvfGKGTRLSVIANIQNPDPVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKD
 SDVYITDKTVLDMRSMDFKSN~~SAVAWSNKSDFACANAF~~

(Consensus sequence ends before completion of TRAC)

20 Not underlined = 5' UTR

..... = TRAV19

===== = TRAJ29

----- = TRAC

Lower case = CDR3 (12-aa length)

25

Clone 2 – TCRβ

Nucleotide consensus sequence (SEQ ID NO: 13)

30 CTCAGAGGACCAGTATCCCTCACAGGGTGACACCTGACCAGCTCTGTCCCACC
 TGGCCATGGGCTCCAGGTACCTCTGATGGGAAGACCTTTGTCTCTTGGGAACA
 AGTGAATCCTTGGCACAGGCCAGTGGATTCTGCTGTGCAGAACAGAGAGCAG

TGGACCTCAGGAGGCCTGCAAGGGGAGGACATAGGACAGTGACATCACAGTA
 TGCCCCCTCCCACCAGGAAAAGCAAGGCTGAGAATTTAGCTCTTTCCCAGGAGG
 ACCAAGCCCTGAGCACAGACACAGTGCTGCCTGCCCCTTTGTGCCATGGGCTC
 CAGGCTGCTCTGTTGGGTGCTGCTTTGTCTCCTGGGAGCAGGCCCAGTAAAGG
 5 CTGGAGTCACTCAAACCTCCAAGATATCTGATCAAAACGAGAGGACAGCAAGTG
 ACACTGAGCTGCTCCCCTATCTCTGGGCATAGGAGTGTATCCTGGTACCAACA
 GACCCCAGGACAGGGCCTTCAGTTCCTCTTTGAATACTTCAGTGAGACACAGA
 GAAACAAAGGAACTTCCCTGGTCGATTCTCAGGGCGCCAGTTCTCTAACTCT
 CGCTCTGAGATGAATGTGAGCACCTTGGAGCTGGGGGACTCGGCCCTTTATCTT
 10 tgccgagcagcttgactgggggaaactatggctacacctcGGTTCGGGGACCAGGTTAACCGTTGTA
GAGGACCTGAACAAGGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
AGCAGAGATCTCCACACCCAAAAGGCCACACTGGTGTGCCTGGCCACAGGCT
TCTTCCCTGACCACGTGGAGCTGAGCTGGTGGGTGAATGGGAAGGAGGTGCAC
AGTGGGGTCAGCACGGACCCGCAGCCCCTCAAGGAGCAGCCCGCCCTCAATG
 15 ACTCCAGATACTGCCTGAAGATCGGAAGAGC

(Consensus sequence ends before completion of TRBC1)

Amino acid consensus sequence (SEQ ID NO: 14)

20 MGRLLCWVLLCLLGAGPVKAGVTOTPRYLIKTRGOQVTLSCSPISGHRVSWYO
 OTPGOGLOFLEFYFSETORNKGNFPGRFSGROFSNSRSEMNVSTLELGDSALYLcas
sltggnvygtfGSGTRLTVVEDLNKVFPPEVAVFEPSEAEISHTQKATLVCLATGFFPDH
VELSWWVNGKEVHSGVSTDPOPLKEOPALNDSRYCLKIGR

25

(Consensus sequence ends before completion of TRBC1)

Not underlined = 5' UTR

..... = TRBV5-1
 30 _____ = TRBD1
 _____ = TRBJ1-2
 ----- = TRBC1

Lower case = CDR3 (14-aa length)

Clone 3 – TCR α

5 Nucleotide consensus sequence (SEQ ID NO: 15)

CCAAAACAAGAGACTTGCCTAGCCCAACCTTCCTCACGCTCGCTATTCTCAAG
 ACCTGGGTTCCAGCCACTTTCCTACTGGCCCCGAGGAGAATTTCCAAAGAGAC
 GCCTGCAGTGTTTCCACAGCTCAGCCATGCTCCTGTTGCTCATACCACTGCTGG
 10 GGATGATTTTGGCCCTGAGAGATGCCAGAGCCCAGTCTGTGAGCCAGCATAAC
CACCACGTAATTCTCTCTGAAGCAGCCTCACTGGAGTTGGGATGCAACTATTCC
TATGGTGGAAGTGTAAATCTCTTCTGGTATGTCCAGTACCCTGGTCAACACCTT
CAGCTTCTCCTCAAGTACTTTTCAGGGGATCCACTGGTTAAAGGCATCAAGGG
CTTTGAGGGCTGAATTTATAAAGAGTAAATTCTCCTTTAATCTGAGGAAACCCTC
 15 TGTGCAGTGGAGTGACACAGCTGAGTACTTCgtgccgtaggcaccaatgcaggcaatcaaccttt
GGGGATGGGACTACGCTCACTGTGAAGCCAAATATCCAGAACCCCTGACCCTGC
CGTGTACCAGCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTAC
CGATTTTGATTCTCAAACAAATGTGTCACAAAGTAAGGATTCTGATGTGTATAT
CACAGACAAAAGTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTG
 20 CTGTGGCCTGGAGCAACAAATCTGACTTTGCATGTGCAAACGCCTTCA

(Consensus sequence ends before completion of TRAC)

Amino acid consensus sequence (SEQ ID NO: 16)

25 MLLLLIPVLGMIFALRDARAQSVSOHNHHVILSEAASLELGCNYSYGGTVNLFWY
VQYPGOHLQLLLKYFSGDPLVKGIKGFEAEFIKSKFSFNLRKPSVQWSDTAEYFcav
gtnagkstfGDGTTLTVKPNIQNPDPVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDS
DVYITDKTVLDMRSMDFKSN SAVAWSNKSD FACANAF

30

(Consensus sequence ends before completion of TRAC)

Not underlined = 5' UTR

..... = TRAV8-1

===== = TRAJ27

----- = TRAC

5 Lower case = CDR3 (12-aa length)

Clone 3 – TCRβ

Nucleotide consensus sequence (SEQ ID NO: 17)

10

ACCTGGAGCCCCCAGAACTGGCAGACACCTGCCTGATGCTGCCATGGGCCCCC
 AGCTCCTTGGCTATGTGGTCCTTTGCCCTTAGGAGCAGGCCCCCTGGAAGCCC
 AAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAGAAGTTAAC
 AGTGACTTGTCTCAGAATATGAACCATGAGTATATGTCCTGGTATCGACAAG
 15 ACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTTGAGGTGACT
 GATAAGGGAGATGTTCCCTGAAGGGTACAAAGTCTCTCGAAAAGAGAAGAGGA
 ATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACCCAGACCTCTCTGTACTTCtg
 tggcagcagccgaaagggactagcgggaggcgccccaccggggagctgtttttGGAGAAGGCTCTAGGCTG
 ACCGTA CTGGAGGACCTGAAAAACGTGTTCCCACCCGAGGTGCGTGTGTTTGA
 20 GCCATCAGAAGCAGAGATCTCCACACCCAAAAGGCCACACTGGTGTGCCTGG
 CCACAGGCTTCTACCCCGACACGTGGAGCTGAGCTGGTGGGTGAATGGGAAG
 GAGGTGCACAGTGGGGTCAGCACGGACCCGCAGCCCCTCAAGGAGCAGCCCG
 CCCTCAATGACTCCAGATACTGCCTGA

25 (Consensus sequence ends before completion of TRBC2)

Amino acid consensus sequence (SEQ ID NO: 18)

MGPQLLG YVVLCLLGAGPLEAQVTNPRYLITVTGKKLTVTCSONMNHEYMSW
 30 YRODPGLGLROIYYSMNVEVTDKGDVPEGYKVS RKEKRNEPLILESPSPNOTSLYF
 cassrkglagggptgelffGEGSRLTVLEDLKNVPPEVAVFEPSEAEISHTQKATLVCLATG
 FYPDHVELSWVWNGKEVHSGVSTDPQPLKEQPALNDSRYCL

(Consensus sequence ends before completion of TRBC2)

Not underlined = 5' UTR

5 = TRBV27

_____ = TRBD2

===== = TRBJ2-2

----- = TRBC2

Lower case = CDR3 (19-aa length)

10

Clone 4

TCR α (1) and TCR β from Clone 2

15 **Clone 5 – TCR α**

Nucleotide consensus sequence (SEQ ID NO: 19)

AGGAAAAGTTGAGGGGGCTTGACAGACAGAAATTCTAAACTGATGCTTATCTG
 20 TGTGTAAAGAAAGGATTACTGATTCCCAATGAATATATCTTCAGCAATTCTAA
 ATTTGGACAAAGTGAGGGAAGTGCTTCCTTTGACAGAGACAGCTTTAAGTGAAA
 GCACTTGTGAAAGGGCGGGGCCTGCTGAAAGAATTCAGTTGAGGGTGAATTTA
 CAGAGTTTCAGCTGGTTGGGAAGACTGGAAGACCACCTGGGCTGTCATTGAGC
 TCTGGTGCCAGGAGGAATGGACAAGATCTTAGGAGCATCATTTTTAGTTCTGT
 25 GGCTTCAACTATGCTGGGTGAGTGGCCAACAGAAGGAGAAAAGTGACCAGCA
GCAGGTGAAACAAAGTCCTCAATCTTTGATAGTCCAGAAAGGAGGGATTTCAA
TTATAAACTGTGCTTATGAGAACACTGCGTTTGACTACTTTCCATGGTACCAAC
AATTCCTGGGAAAGGCCCTGCATTATTGATAGCCATACGTCCAGATGTGAGT
GAAAAGAAAGAAGGAAGATTCACAATCTCCTTCAATAAAAAGTGCCAAGCAGT
 30 TCTCATTGCATATCATGGATTCCCAGCCTGGAGACTCAGCCACCTACTTctgtgcag
ctgtgacaggaggaggtgctgacggactcaccttGGCAAAGGGACTCATCTAATCATCCAGCCCT
ATATCCAGAACCCCTGACCCTGCCGTGTACCAGCTGAGAGACTCTAAATCCAGT

GACAAGTCTGTCTGCCTATTACCGATTTTGATTCTCAAACAAATGTGTCACAA
AGTAAGGATTCTGATGTGTATATCACAGACAAAACCTGTGCTAGACATGAGGTC
TATGGACTTCAAGAGCAACAGTGCTGTGGCCTGGAGCAACAAATCTGACTTTG
CATGTGCAAACGCCTTCA

5

(Consensus sequence ends before completion of TRAC)

(5' UTR sequence of consensus and reference differ – reference shown)

10 Amino acid consensus sequence (SEQ ID NO: 20)

MDKILGASFLVLWLQLCWVSGOOKEKSDOOOVKOSPOSLIVOKGGISIINCAYEN
TAFDYFPWYQOFPKGKGPALLIAIRPDVSEKKEGRTISENKSAAKQFSLHIMDSOPGD
SATYFcaaytgggagdlfGKGTHLIQPYIQNPDPVYQLRDSKSSDKSVCLFTDFDSQTN
15 VSQSKDSDVYITDKTVLDMRSMDFKSNsAVAWSNKsDFACANAF

(Consensus sequence ends before completion of TRAC)

Not underlined = 5' UTR

20 = TRAV23DV6

===== = TRAJ45

----- = TRAC

Lower case = CDR3 (14-aa length)

25 **Clone 5 – TCR β**

Nucleotide consensus sequence (SEQ ID NO: 21)

AGCTGTGAGGTCTGGTTCCCCGACGTGCTGCAGCAAGTGCCTTTGCCCTGCCTG
30 TGGGCTCCCTCCATGGCCAACCTCTGCTATGGACACCAGAGTACTCTGCTGTGCG
GTCATCTGTCTTCTGGGGGCAGGTCTCTCAAATGCCGGCGTCATGCAGAACCC
AAGACACCTGGTCAGGAGGAGGGGACAGGAGGCAAGACTGAGATGCAGCCCA

ATGAAAGGACACAGTCATGTTTACTGGTATCGGCAGCTCCCAGAGGAAGGTCT
 GAAATTCATGGTTTATCTCCAGAAAGAAAATATCATAGATGAGTCAGGAATGC
 CAAAGGAACGATTTTCTGCTGAATTTCCCAAAGAGGGCCCCAGCATCCTGAGG
 ATCCAGCAGGTAGTGCGAGGAGATTTCGGCAGCTTATTTCTgtgccagctccccagggtta
 5 caatgagcagttcttcGGGCCAGGGACACGGCTCACCGTGCTAGAGGACCTGAAAAACG
 TGTTCCCAACCCGAGGTCTGCTGTGTTTGTAGCCATCAGAAGCAGAGATCTCCCAC
 ACCCAAAAGGCCACACTGGTGTGCCTGGCCACAGGCTTCTACCCCGACCACGT
 GGAGCTGAGCTGGTGGGTGAATGGGAAGGAGGTGCACAGTGGGGTCAGCACG
 GACCCGCAGCCCCTCAAGGAGCAGCCCGCCCTCAATGACTCCAGATACTGCCT
 10 GA

(Consensus sequence ends before completion of TRBC2)

Amino acid consensus sequence (SEQ ID NO: 22)

15 MDTRVLCCAVICLLGAGLSNAGVMONPRHLVRRRGQEARLRCSPMKGHSHVYW
 YROLPEEGLKFMVYLOKENIIDESGMPKERESAEFPKEGPSILRIOQVVRGDSAAYE
 casspdyneqffGPGTRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKATLVCLATGFYPD
 HVELSWWWNGKEVHSGVSTDPOPLKEOPALNDSRYCL

20

(Consensus sequence ends before completion of TRBC2)

Not underlined = 5' UTR

..... = TRBV18

25 _____ = TRBD1

_____ = TRBJ2-1

----- = TRBC2

Lower case = CDR3 (13-aa length)

30 SEQ ID NOs: 23 to 31 provide human codon optimised versions of SEQ ID NOs:
 5, 7, 9, 11, 13, 15, 17, 19 and 21 respectively. These human codon optimised sequences
 encode the same amino acid sequences as SEQ ID NOs: 5, 7, 9, 11, 13, 15, 17, 19 and 21,

but may be more readily expressed in human cells than the original nucleotide sequences. Thus, the human codon optimised sequences may be used in therapeutic applications in preference to the original nucleotide sequences. For each of SEQ ID NOs: 23 to 31:

5 ___ – Restriction site / Murine constant

 – V region

 ===== – D region

 ----- – V region

10 **Clone 1 – TCR α (SEQ ID NO: 23)**

GCGGCCGCGCCACCATGCTTACAGCTTCTCTGCTGAGAGCCGTGATCGCCAGC
ATCTGTGTGGTGTCTAGCATGGCCCAGAAAGTGACACAGGCCAGACCGAGAT
CAGCGTGGTGGAAAAAGAAGATGTGACCCCTGGACTGCGTGTACGAGACACGG
GACACCACCTACTACCTGTTCTGGTACAAGCAGCCTCCTAGCGGCGAGCTGGT
15 GTTCTGTGATCAGACGGAACAGCTTCGACGAGCAGAACGAGATCTCCGGCCGGT
ACAGCTGGAACTTCCAGAAGTCCACCAGCAGCTTCAACTTCACCATCACCGCC
AGCCAGGTGGTGGATAGCGCCGTGTATTTTTCGCGCCCTGAGCGAGAGGCCTTA
CGGCGGAGCTACAAACAAGCTGATCTTCGGCACCCGGCACACTGCTGGCTGTTC
AACCTA ACATCCAGAACCCCGACCCCGCGG

20

Clone 1 – TCR β (SEQ ID NO: 24)

CCATGGATACCTGGCTCGTGTGCTGGGCCATCTTCAGCCTGCTGAAAGCCGGA
CTGACCGAGCCTGAAGTGACCCAGACACCTAGCCACCAAGTGACACAGATGG
GCCAAGAAGTGATCCTGCGCTGCGTGCCCATCAGCAACCACCTGTACTTCTAC
25 TGGTACAGACAGATCCTGGGCCAGAAAGTGGAATTCCTGGTGTCTTCTACAA
CAACGAGATCAGCGAGAAGTCCGAGATCTTCGACGACCAGTTCAGCGTGGA
AGACCCGACGGCAGCAACTTCACCCTGAAGATCAGAAGCACCAAGCTCGAGG
ACAGCGCCATGTACTTTTTCGCGCCAGCAGCGAGAGAAGAACCAGCCTGCCTAC
GAGCAGTACTTCGGGCCCTGGCACAAGACTGACCGTGACAG AGGACCTGCGG
30 AACGTGACCCCCCCCCAAGGTGTCCCTGTTCGAGCCCAGCAAGGCCGAGATCGC
CAACAAGCAGAAAGCCACACTGGTCTGTCTGGCTAGGGGCTTCTTCCCCGACC
ACGTG

Clone 2 - TCR α (1) (SEQ ID NO: 25)

GCGGCCGCGCCACCATGAAGTCTCTGAGAGTGCTGCTGGTCATCCTGTGGCTG
CAGCTGTCTTGGGTCTGGTCCCAGCAGAAAGAGGTGGAACAGAACAGCGGCCC
5 TCTGTCTGTTTCTGAAGGCGCTATCGCCAGCCTGAACTGCACCTACAGCGATAG
AGGCAGCCAGAGCTTCTTCTGGTACAGACAGTACAGCGGCAAGAGCCCCGAG
CTGATCATGAGCATCTACAGCAACGGCGACAAAGAGGACGGCCGGTTTACAGC
CCAGCTGAACAAGGCCAGCCAGTACGTGTCCCTGCTGATCAGAGATAGCCAGC
CTAGCGACAGCGCCACCTATCTGTGTGCCGTAGAGGCCAGGCTGGCACAGCC
10 CTGATCTTTGGCAAGGGCACAACACTGAGCGTGTCCAGCA ACATCCAGAACCC
CGACCCCGCGG

Clone 2 - TCR α (2) (SEQ ID NO: 26)

GCGGCCGCGCCACCATGCTTACAGCTTCTCTGCTGAGAGCCGTGATCGCCAGC
15 ATCTGTGTGGTGTCTAGCATGGCCCAGAAAGTGACACAGGCCAGACCGAGAT
CAGCGTGGTGGAAAAAGAAGATGTGACCCTGGACTGCGTGTACGAGACACGG
GACACCACCTACTACCTGTTCTGGTACAAGCAGCCTCCTAGCGGCGAGCTGGT
GTTCTGATCAGACGGAACAGCTTCGACGAGCAGAACGAGATCTCCGGCCGGT
ACAGCTGGAAGTTCCAGAAGTCCACCAGCAGCTTCAACTTCACCATCACCGCC
20 AGCCAGGTGGTGGATAGCGCCGTGTACTTTTGTGCCCTGCCTGCCGGAATAC
CCCTCTGGTGTGTTGGCAAGGGCACCAGACTGTCTGTGATCGCCA ACATCCAGA
ACCCCGACCCCGCGG

Clone 2 - TCR β (SEQ ID NO: 27)

25 CCATGGGCAGCAGACTGCTGTGTTGGGTGCTGCTGTGTCTGCTTGGAGCCGGA
CCTGTGAAAGCTGGCGTGACCCAGACACCTAGATACCTGATCAAGACCAGAGG
CCAGCAAGTGACCCTGAGCTGCTCTCCTATCAGCGGCCACAGAAGCGTGTCT
GGTATCAGCAGACACCTGGACAGGGCCTGCAGTTCCTGTTTCGAGTACTTCAGC
GAGACACAGCGGAACAAGGGCAACTTCCCCGGCAGATTTTCCGGCAGACAGTT
30 CAGCAACAGCCGAGCGAGATGAACGTGTCCACACTGGAAGTGGGCGACAGC
GCCCTGTATCTGTGTGCCTCTTCTCTGACCGGCGGCAACTACGGCTACACATT
GGCAGCGGCACCAGACTGACAGTGGTTCG AGGACCTGCGGAACGTGACCCCC

CCCAAGGTGTCCCTGTTTCGAGCCCAGCAAGGCCGAGATCGCCAACAAGCAGA
AAGCCACACTGGTCTGTCTGGCTAGGGGCTTCTTCCCCGACCACGTG

Clone 3 – TCR α (SEQ ID NO: 28)

5 GCGGCCGCGCCACCATGTTGTTGCTGCTGATTCTGTGCTGGGCATGATCTTCG
CCCTGAGGGATGCTAGAGCCCAGTCCGTGTCTCAGCACAACCACCACGTGATC
CTGTCTGAGGCCGCCTCTCTGGAAGTGGGCTGCAATTACAGCTACGGCGGCAC
CGTGAACCTGTTTTGGTACGTGCAGTACCCCGGCCAGCATCTCCAGCTGCTGCT
GAAGTACTTTAGCGGCGACCCTCTGGTCAAGGGCATCAAGGGATTTCGAGGCCG
10 AGTTCATCAAGAGCAAGTTCAGCTTCAACCTGCGGAAGCCCAGCGTGCAGTGG
AGCGATACAGCCGAGTACTTTTGTGCCGTGGGCACCAATGCCGGCAAGAGCAC
ATTTGGCGACGGCACCACTGACCGTGAAGCCTA ACATCCAGAACCCCGA
CCCCGCGG

15 **Clone 3 – TCR β (SEQ ID NO: 29)**

CCATGGGCCCTCAGCTGCTGGGATATGTGGTGTGTCTGCTTGGAGCCGGA
CCTCTGGAAGCCCAAGTGACACAGAACCCAGATACCTGATCACCGTGACCGG
CAAGAACTGACCGTGACCTGCAGCCAGAACATGAACCACGAGTACATGAGC
TGGTACAGACAGGACCCTGGCCTGGGCCTGAGACAGATCTACTACAGCATGAA
20 CGTGGAAGTGACCGACAAGGGCGACGTGCCCCGAGGGCTACAAGGTGTCCAGA
AAAGAGAAGCGGAACTTCCCACTGATCCTGGAAAGCCCATCTCCTAACCAGAC
CAGCCTGTACTTCTGCGCCAGCAGCAGAAAAGGACTGGCTGGCGGAGGACCTA
CCGGCGAGCTGTTTTTTGGCGAGGGCAGCAGACTGACAGTGCTCG AGGACCTG
CGGAACGTGACCCCCCCCCAAGGTGTCCCTGTTTCGAGCCCAGCAAGGCCGAGAT
25 CGCCAACAAGCAGAAAGCCACACTGGTCTGTCTGGCTAGGGGCTTCTTCCCCG
ACCACGTG

Clone 5 – TCR α (SEQ ID NO: 30)

GCGGCCGCGCCACCATGGATAAGATTCTGGGCGCCAGCTTCCTGGTGTGTGG
30 CTGCAACTTTGTTGGGTGTCCGGCCAGCAGAAAGAGAAGTCCGACCAGCAGCA
AGTGAAACAGAGCCCTCAGAGCCTGATCGTGCAGAAAGGCGGCATCAGCATC
ATCAACTGCGCCTACGAGAATACCGCCTTCGACTACTTCCCCTGGTATCAGCA

GTTCCCCGGCAAGGGACCTGCTCTGCTGATCGCCATTAGACCCGACGTGTCCG
 AGAAGAAAGAGGGCAGATTCACCATCAGCTTCAACAAGAGCGCCAAGCAGTT
 CAGCCTGCACATCATGGATAGCCAGCCTGGCGACAGCGCCACCTATTTTTGTG
 CTGCTGTTACAGGCGGCGGAGCCGATGGCCTGACATTTGGAAAGGGCACCCAC
 5 CTGATCATCCAGCCTT ACATCCAGAACCCCGACCCCGCGG

Clone 5 – TCR β (SEQ ID NO: 31)

CCATGGACACCAGAGTGCTGTGCTGCGCCGTGATCTGTCTGCTTGGAGCCGGA
 CTGTCTAATGCCGGCGTGATGCAGAACCCAGACACCTCGTTCGGAGAAGAGG
 10 CCAAGAGGCCAGACTGAGATGCAGCCCTATGAAGGGCCACAGCCATGTGTACT
 GGTACAGACAGCTGCCCGAAGAGGGCCTGAAGTTCATGGTGTACCTGCAGAAA
 GAGAACATCATCGACGAGAGCGGCATGCCCAAAGAGCGGTTCTCTGCCGAGTT
 TCCCAAAGAGGGCCCCAGCATCCTGAGAATCCAGCAGGTTGTGCGGGGAGATA
 GCGCCGCCTACTTTTGTGCTAGCAGCCCTCAGGGCTACAACGAGCAGTTTTTCG
 15 GCCCTGGCACCAGACTGACAGTGCTCG AGGACCTGCGGAACGTGACCCCCC
 CCAAGGTGTCCCTGTTCGAGCCCAGCAAGGCCGAGATCGCCAACAAGCAGAA
 AGCCACACTGGTCTGTCTGGCTAGGGGCTTCTTCCCCGACCACGTG

Conclusion

20 The data provides the evidence that this is the first time any group has successful
 implemented the type of unbiased approach employed here to identify GvL antigens and
 we have also identified the cognate TCRs recognising the antigen. This opens new field in
 immunology and development of antigen-binding molecule based therapies, including
 TCR based therapies, and peptide vaccination with the antigens identified.

25

Example 2 – Further identifying the antigenic basis of GvL

The generic workflow established in Example 1 was used to identify the antigenic
 basis of GvL in further patients. In brief, mismatched peptides identified by *in silico*
 prediction and mass spectrometry for each patient were screened for their ability to activate
 30 donor-derived T cells taken from the patient post-allo-SCT, using IFN γ ELISpot assays.
 HLA restriction was investigated using IFN γ ELISpots with HLA-blocking antibodies.
 The nature and frequency of peptide-responsive T cells (i.e. cells producing cytokines

(IFN γ , TNF α) and expression of the degranulation marker (CD107a) following peptide contact) were assessed by culturing post-transplant blood with peptide for 12 days and then stimulating with the peptide. Responses were assessed by flow cytometry.

Results are shown in Table 3.

5 In Table 3, the mismatched peptide sequence expressed by the patient is indicated in column D. The amino acid mismatched between patient and donor is underlined. In many cases, there are 2 peptides covering the same genetic variant that both elicit T cell responses.

 The genetic variant leading to the patient-donor mismatch is described in columns
10 F/G/H/I. The dbSNP ID (Column I) refers to an online database of previously described inherited genetic variants.

 Column J indicates whether the T cell response is directed against the variant or reference amino acid sequence. The reference amino acid sequence used was NCBI Human Reference Genome Build hg38, which is also referred to as GRCh38
15 (https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.26). In most cases, the donor is homozygous for the reference allele and the patient is heterozygous, so the T cell response is directed against the variant sequence. However, particularly for common genetic variants, responses may be directed against the reference sequence. In these cases, the donor is homozygous for the variant allele and the patient is either homozygous reference
20 or heterozygous.

 Column K shows the allele frequency of the variant in the population and is taken from the gnomAD database.

 Columns L/M/N/O show results from HLA restriction and immunophenotyping experiments.
25

Table 3	A	B	C	D	E
	Number	Patient	Peptide(s)	Gyl. peptide amino acid sequence (mismatch underlined)	Donor sequence
i	1	OX866	OX866-021	LTISLLDT <u>E</u> NLELPEAVVFQ	LTISLLDTSNLELPEAVVFQ
ii			OX866-022	ISLLDT <u>E</u> NLELPEAVVFQDS	ISLLDTSNLELPEAVVFQDS
iii	2	OX1149	OX1149-190	AASCEPLASVLR <u>A</u> KTSRSS	AASCEPLASVLRAKTPSRSS
iv	3	OX1149	OX1149-290	GAGDPRLRL <u>H</u> GHLPVRTSCP	GAGDPRLRLRGHLPVRTSCP
v	4	OX813	OX813-101	TQRSVLLCKVVG <u>A</u> RGVGSKA	TQRSVLLCKVVGACGVGSKA
vi			OX813-102	KVVG <u>A</u> RGVGSKAFLQAFLGR	KVVGACGVGSKAFLQAFLGR
vii	5	OX802	OX802-321	GQKSPRFR <u>R</u> VSFLRLGRST	GQKSPRFRRTVCFRLGRST
viii			OX802-322	RFRRV <u>S</u> CFRLRLGRSTLLELE	RFRRVTCFRLRLGRSTLLELE
ix	6	OX289	OX289-009	ALAFLLISJAANLSLLSR	ALAFLLISTAANLSLLSR
x	7	OX289	OX289-040	EVQDCLKQLMMSL <u>Q</u> LYRFS	EVQDCLKQLMMSLLRLYRFS
xi	8	OX289	OX289-052	GYSPL <u>H</u> ILAIGTRSGAIKL	GYSPLRLILAIGTRSGAIKL
xii	9	OX289	OX289-067	VATFPVYTM <u>V</u> AIPVCKD	VATFPVYTMGAIPVCKD
xiii	10	OX289	OX289-073	PPLYRQRYQF <u>K</u> NLVDQHEP	PPLYRQRYQFVKNLVDQHEP
xiv			OX289-074	PLYRQRYQF <u>K</u> NLVDQHEPK	PLYRQRYQFVKNLVDQHEPK
xv	11	OX289	OX289-075	VSRPELLRES <u>I</u> SAFLVPMPT	VSRPELLREGISAFLVPMPT
xvi			OX289-205	TDALQNK <u>S</u> ISAFLVPMPTP	TDALQNKGISAFLVPMPTP
xvii	12	OX289	OX289-180	NPLSPYLNVDPRYLVDQT	NPLCPYLNVDPRYLVDQT
xviii	13	OX289	OX289-221	EPPVDICLSKA <u>I</u> SSSLKGFL	EPPVDICLSKANSSSLKGFL
xix	14	OX289	OX289-284	GETGMFSL <u>S</u> TIRGHQYATY	GETGMFSLCTIRGHQYATY
xx	15	OX289	OX1038-614	MNYVSK <u>R</u> LPAARLNTPMGP	MNYVSKSLPFAARLNTPMGP
xxi	16	OX747	OX747-157	LGLGLIFAL <u>T</u> LNHRHKYPLN	LGLGLIFALILNRHKYPLN
xxii			OX747-158	LGLIFAL <u>T</u> LNHRHKYPLNLYL	LGLIFALILNRHKYPLNLYL
xxiii	17	OX747	OX747-185	APISLSSFF <u>N</u> VSTLEREVD	APISLSSFFSVSTLEREVD
xxiv	18	OX747	OX747-190	LELGAGTGL <u>S</u> IAATMART	LELGAGTGLTSIAATMART
xxv			OX747-191	AGTGL <u>S</u> IAATMARTVYCT	AGTGLTSIAATMARTVYCT
xxvi	19	OX747	OX628-305	VPREYV <u>R</u> ALNATKLERVFAK	VPREYIRALNATKLERVFAK
xxvii	20	OX993	OX993-413	LHRDKALLKRLKG <u>M</u> QKKRP	LHRDKALLKRLKGVQKKRP
xxviii			OX993-414	KALLKRLKG <u>M</u> QKKRPSDVQ	KALLKRLKGVQKKRPSDVQ
xxix	21	OX628	OX628-80	ITVQTVYVQH <u>L</u> ITFLDRPIQ	ITVQTVYVQHPITFLDRPIQ
xxx			OX628-81	QTVYVQH <u>L</u> ITFLDRPIQMCC	QTVYVQHPITFLDRPIQMCC
xxxi	22	OX628	OX628-564	PGLIS <u>M</u> FSSSQELGAALAQL	PGLISVFSSSQELGAALAQL
xxxii	23	OX885	OX885-559	WRVRIALALKGIDY <u>E</u> TVPIN	WRVRIALALKGIDYKTVPIN
xxxiii			OX885-560	VRIALALKGIDY <u>E</u> TVPINLI	VRIALALKGIDYKTVPINLI
xxxiv	24	OX885	OX628-308	DRAEKFN <u>R</u> GIRKL <u>G</u> ITPEGQ	DRAEKFNRGIRKLGVITPEGQ
xxxv			OX628-309	EKFNRGIRKL <u>G</u> ITPEGQSYL	EKFNRGIRKLGVITPEGQSYL

Table 3 cont.		F	G	H	I	J	K
	Gene	Chromosome	Position (hg38)	dbSNP ID	T cell response against reference or variant amino acid sequence		Allele frequency (%)
i	PADI4	1	17342114	rs1748020	Variant		4.27
ii							
iii	RNH1	11	499120	rs17585	Variant		11.21
iv	SLC26A6	3	48632014	rs13324142	Variant		9.84
v	RHOT2	16	672331	rs3177338	Reference		51.51
vi							
vii	COA6	1	234373513	rs10910420	Reference		52.52
viii							
ix	NAGPA	16	5025632	rs7188856	Variant		30.07
x	RNF123	3	49700521	rs35620248	Variant		5.07
xi	LLGL2	17	75556104	rs1671036	Variant		50.19
xii	ENDOD1	11	95129413	rs3740861	Variant		25.36
xiii	HENMT1	1	108657486	rs36100901	Variant		1.93
xiv							
xv	ACADS	12	120738280	rs1799958	Variant		26.58
xvi							
xvii	TMM23B	10	49945053	rs148307270	Variant		9.11
xviii	LRR1	14	49607404	rs17121605	Variant		20.48
xix	FTSJ3	17	63823837	rs2727288	Reference		64.78
xx	LGALS8	1	236543562	rs2243525	Reference		72.36
xxi	TMBIM4	12	66152320	rs8793	Variant		43.73
xxii							
xxiii	DOCK8	9	334337	rs10970979	Reference		24.54
xxiv	METTL22	16	8635267	rs2302607	Reference		22.2
xxv							
xxvi	DCAF13	8	103420317	rs3134253	Variant		23.64
xxvii	DENND6B	22	50313721	rs68178377	Variant		31.06
xxviii							
xxix	LITAF	16	11553659	rs761746674	Variant		0.00122
xxx							
xxxi	PGLS	19	17511703	rs368232818	Variant		0.88
xxxii	GSTZ1	14	77326864	rs7975	Reference		30.57
xxxiii							
xxxiv	WASHC4	12	105152394	rs1663564	Variant		94.67
xxxv							

Table 3 cont		M	
	L		
	HLA restriction	Restricting HLA allele	
i	HLA-DP	DPA1*01:03-DPB1*04:01	
ii			
iii	HLA-DR	DRB1*13:01 / DRB1*11:02:01 / DRB3*02:02/28/29N / DRB3*01:01/04	
iv	HLA-DR	DRB1*13:01 / DRB1*11:02:01 / DRB3*02:02/28/29N / DRB3*01:01/04	
v	Indeterminate	A*68:01:01 / A*11:01:01 // B*55:01:01 / B*15:01:01 // C*03:04:01 / C*03:03:01 // DRB1*14:54 / DRB1*15:01 / DRB3*02:02/28/29N / DRB5*01:01:01 // DQA1*01:02/06 / DQA1*01:01/04/05/07 / DQB1*06:02:10 / DQB1*05:03:01 // DPB1*05:01 / DPB1*04:01:01	
vi			
vii	Not tested	DRB1*03:01 / DRB1*11:01 / DRB3*02:02/03/05/06/11/13-29N // DQA1*05:05/08-11 / DQA1*05:01 / DQB1*02:01 / DQB1*03:01 // DPB1*04:01/121:01	
viii			
ix	Class I	A*02:05 / A*23:01/05/06/08/10/11-19 // B*44-03/13/26/30/32/36-61 / B*58:01/04/11/13/15 // C*04:01/05/08/10/12/16-33 / C*07-01/06/16/18/20/21/24-57	
x	Likely HLA-DP	DPB1*04:01:01 / DPB1*02:01	
xi	Likely HLA-DR	DRB1*03:01 / DRB1*07:01:01 / DRB3*02:02/05/11/13/14/17-23 / DRB4*01:01-05/07	
xii	Likely Class I	A*02:05 / A*23:01/05/06/08/10/11-19 // B*44-03/13/26/30/32/36-61 / B*58:01/04/11/13/15 // C*04:01/05/08/10/12/16-33 / C*07-01/06/16/18/20/21/24-57	

xiii	Not tested	DRB1*03:01 / DRB1*07:01:01 / DRB3*02:02/05/11/13/14/17-23 / DRB4*01:01-05/07 /// DQB1*02:02 / DQB1*02:01/02/04 ///
xiv		DPB1*04:01:01 / DPB1*02:01
xv	Not tested	DRB1*03:01 / DRB1*07:01:01 / DRB3*02:02/05/11/13/14/17-23 / DRB4*01:01-05/07 /// DQB1*02:02 / DQB1*02:01/02/04 ///
xvi		DPB1*04:01:01 / DPB1*02:01
xvii	Likely HLA-DR	DRB1*03:01 / DRB1*07:01:01 / DRB3*02:02/05/11/13/14/17-23 / DRB4*01:01-05/07
xviii	Likely Class II	DRB1*03:01 / DRB1*07:01:01 / DRB3*02:02/05/11/13/14/17-23 / DRB4*01:01-05/07 /// DQB1*02:02 / DQB1*02:01/02/04 ///
xix	Class I	DPB1*04:01:01 / DPB1*02:01 A*02:05 / A*23:01/05/06/08/10/11-19 /// B*44:03/13/25/30/32/36-51 / B*58:01/04/11/13/15 /// C*04:01/05/08/10/12/16-33 / C*07:01/06/16/18/20/21/24-57
xx	Indeterminate	A*02:05 / A*23:01/05/06/08/10/11-19 /// B*44:03/13/26/30/32/36-51 / B*58:01/04/11/13/15 /// C*04:01/05/08/10/12/16-33 / C*07:01/06/16/18/20/21/24-57 /// DRB1*03:01 / DRB1*07:01:01 / DRB3*02:02/05/11/13/14/17-23 / DRB4*01:01-05/07 ///
xxi	Not tested	DQB1*02:02 / DQB1*02:01/02/04 /// DPB1*04:01:01 / DPB1*02:01 DRB1*04:04:01 / DRB1*13:02:01 / DRB3*03:01 / DRB4*01:03 /// DQA1*01:02/06/08/09 / DQA1*03:01-03 / DQB1*03:02:01 / DQB1*06:04:01 /// DPB1*10:01 / DPB1*03:01:01

xxii		
xxiii	HLA-DR	DRB1*04:04:01 / DRB1*13:02:01 / DRB3*03:01 / DRB4*01:03
xxiv	HLA-DR	DRB1*04:04:01 / DRB1*13:02:01 / DRB3*03:01 / DRB4*01:03
xxv		
xxvi	Indeterminate	A*01:01:01 // B*51:01:01 / B*40:01 // C*03:04:01 / C*06:02:01 // DRB1*04:04:01 / DRB1*13:02:01 / DRB3*03:01 / DRB4*01:03 // DQA1*01:02:06/08/09 / DQA1*03:01:03 / DQB1*03:02:01 / DQB1*06:04:01 // DPB1*10:01 / DPB1*03:01:01
xxvii	HLA-DR	DRB1*01:01 / DRB1*11:01 / DRB3*02:02/28/29N
xxviii		
xxix	HLA-DR	DRB1*03:01 / DRB1*15:01 / DRB3*01:01/04 / DRB5*01:01:01
xxx		
xxxi	Not tested	A*24:02 / A*03:01:01 // B*44:02:01 / B*08:01 // C*07:01 / C*05:01 // DRB1*03:01 / DRB1*15:01 / DRB3*01:01/04 / DRB5*01:01:01 // DQA1*01:02/06 / DQA1*05:01 / DQB1*02:01:01 / DQB1*06:02:01 // DPB1*04:01:01
xxxii	Not tested	DRB1*11:04:01 / DRB1*04:05:01 / DRB3*02:02/28/29N / DRB4*01:03 // DQA1*03:01:03 / DQA1*05:05/08/09/11 / DQB1*03:01:01 / DQB1*03:02:01 // DPB1*04:01:01 / DPB1*04:02:01
xxxiii		
xxxiv	Not tested	DRB1*11:04:01 / DRB1*04:05:01 / DRB3*02:02/28/29N / DRB4*01:03 // DQA1*03:01:03 / DQA1*05:05/08/09/11 / DQB1*03:01:01 / DQB1*03:02:01 // DPB1*04:01:01 / DPB1*04:02:01
xxxv		

Table 3		
cont	N	O
	CD4 / CD8 responses	Frequency of response (% IFNγ cells amongst CD4^{+} or CD8^{+} by FACS)
i	CD4	1.1
ii		
iii	CD4	3.62
iv	CD4	0.81
v	Indeterminate	Not detected
vi		
vii	CD4	5.47/3.23
viii		
ix	CD8	4.77
x	CD4	0.98
xi	CD4	1.27
xii	CD8	0.55
xiii	CD4	0.36/0.24
xiv		
xv	CD4	1.33/0.89
xvi		
xvii	CD4	0.98
xviii	CD4	0.74
xix	CD8	2.76
xx	Indeterminate	Not detected
xxi	CD4	0.325/0.45
xxii		
xxiii	Likely CD4	Not detected
xxiv	Likely CD4	Not detected
xxv		
xxvi	Indeterminate	Not detected
xxvii	Likely CD4	Not tested
xxviii		
xxix	CD4	2.36/1.12
xxx		
xxxi	Indeterminate	Not detected
xxxii	CD4	0.83
xxxiii		
xxxiv	CD4	1.96/1.06
xxxv		

Example 3 - Identifying putative GvL antigens in 50 patient-donor pairs by exome-seq, RNA-seq and peptide screening by IFN γ ELISpot

To identify common GvL antigens across a larger patient cohort and thus expand the repertoire of putative GvL antigens, the workflow described above (exome sequencing, RNA-Seq and in silico antigen prediction) is applied at scale to bio-banked AMADEUS trial samples. In addition to identifying multiple antigenic targets, the HLA restriction is identified in each case.

AMADEUS provides a unique opportunity to acquire samples and clinical metadata (Figure 4). It opened for recruitment 06/2019 and is open in all UK allo-SCT transplant centres. Target recruitment is 324 patients over 3 years (108 patients recruited/year). 49 patients recruited until March 2020 (recruitment ahead of schedule). Recruitment suspended March (COVID) and re-opened in May. Projected number of relapses: year 1 – 21; year 2 – 49, year 3 – 59; year 4 – 24; year 5 – 10 patients.

Exome sequencing is performed 50 patient-donor pairs. For patients, AML cells are used for sequencing, with T cells as a germline control. For donors, DNA is available from NHS tissue typing centres. RNA sequencing of AML cells from each patient is also performed. Sequencing data is analysed to identify patient-donor mismatched peptides expressed on AML cells and predicted to bind patient-specific HLA molecules. These peptides are screened for their ability to activate donor-derived T cells from post-transplant blood samples, using *ex vivo* and sensitive cultured IFN γ ELISpot assays. Component peptides from pools that elicit ELISpot responses are individually tested to identify the peptide(s) recognised and the T cell phenotype (CD4 or CD8) and HLA restriction of the responding T cells is determined by flow cytometry analysis and antibody-blocking approaches (Figure 3).

Patient selection is based on identifying patients most likely to have mounted a GvL response. Patient selection excludes: (i) patients where GvL is unlikely to have occurred; and (ii) patients who relapse early, within 3 months, after allo-SCT. This is because these patients go into allo-SCT with too much disease and relapse before an adaptive GvL T cell response could control disease. Patient selection includes: (i) patients who have had CC-486 (around 40 patients) and patients who have not as controls (around 10 patients); (ii) patients who go into allo-SCT with low level disease (known as

measurable residual disease or MRD) that then slowly clears post allo-SCT, as disease clearance could have occurred through GvL; and (iii) patients who lose detectable MRD and then relapse late (after 12 months), as this may help to elucidate the mechanism of loss of GvL.

5 GvL antigens are shown to represent germline polymorphisms that could be targeted not only in AML but in multiple cancers. Given that peptide binding to HLA class II is often promiscuous, some peptides bind multiple HLA alleles.

Ultimately, we hope to develop ‘off the shelf’ engineered T cell therapies, combinations of which will be suitable for treating a large proportion of patients, based on
10 their genetic polymorphisms and HLA types.

Example 4 - Detailed characterisation GvL T cell responses and assessment of the role CC-486 (oral Azacitidine) in augmenting immune surveillance and disease control

There are multiple mechanisms by which AML could evade GvL including:
15 reduction in HLA presentation; increased immune checkpoint molecule expression by T cells and their ligands on AML blasts; expression of immunosuppressive molecules, for example, indoleamine 2,3-dioxygenase 1 (IDO1) and alteration of the pro- and anti-inflammatory cytokine milieu. Treatment with the DNA methyltransferase inhibitor, Azacitidine (aza) post-transplant has had a beneficial clinical effect but the mechanism is
20 unclear. On the one hand, aza may promote GvL; it upregulates expression of melanoma-associated antigen (MAGE) leading to a CD8⁺ T cell response. Alternatively, aza may exert a direct anti-leukaemic effect, buying time for a therapeutic GvL response to occur.

To establish how CC-486 works, patients from the Amadeus trial are studied in detail, as follows.

25

i. Longitudinal tracking of antigen-specific anti-AML T cell responses

Flow-cytometry-based methods are used to identify T cells responsive to antigenic peptides (mapped in IFN γ ELISpot assays) on the basis of activation marker upregulation, cytokine (IFN γ /TNF α) production or degranulation marker (CD107a) upregulation
30 following peptide stimulation, and/or using fluorescent-labelled HLA-peptide tetramers. Multiparameter flow cytometry panels (read out on a Cytex Aurora spectral flow cytometer or BD Symphony, which readily enables simultaneous analysis of at least 30 parameters)

are employed, to enable evaluation of naïve, memory, effector, regulatory T cells and maturation/differentiation markers (CD45RA/RO, CCR7, CD27, CD28, CD57); lineage-characteristic transcription factors (Tbet, Eomes, GATA3, ROR γ t, FoxP3); cytolytic effector function (perforin, granzymes A and B, Fas, FasL, TRAIL) and inhibitory
 5 receptors often co-expressed on exhausted T cells (PD-1, CTLA-4, LAG3, TIM3, TIGIT). NK cells that can have both effector and immunomodulatory roles are also studied.

Multiparameter flow cytometry-based analysis of antigen-specific T cell responses is performed on longitudinal, serial samples from each patient to track GvL T cell clonal dynamics and determine whether CC-486 promotes, sustains and amplifies GvL T cell
 10 responses, or not. This allows assessment of (i) the time post-transplant when maximal GvL clonal expansion is seen; (ii) correlation between GvL-specific T cell frequency and immunophenotype, amount of disease and clinical outcomes, CC-486 treatment, GvHD and amount of immunosuppression; (iii) GvL-specific T cell status at relapse. In addition to providing correlative data to suggest possible biological mechanisms of disease control
 15 by CC-486, it may also provide prognostic biomarker data. Loss of antigen-specific T cell clones is assessed by comparing patients who relapse post-allo-SCT with those who do not, and whether these T cells clones exhibit an exhausted phenotype.

ii. Assess how GvL response shapes post-transplant T cell repertoire

20 Bulk and single cell (sc) T cell receptor (TCR) sequencing of donor-derived AML-reactive T cells in patient's blood and bone marrow samples is performed. This is combined with whole transcriptome sequencing to get a further indication of the transcriptional state of antigen-specific T cell clones.

In a pilot experiment, we stimulated PBMCs from one patient with overlapping
 25 putative GvL peptides identified by IFN γ ELISpot mapping (see Figure 3), or control peptides, FACS-sorted responding T cells (identified by IFN γ -secretion using a catch reagent) and successfully subjected them to parallel single cell TCR/transcriptome sequencing (10X genomics platform) (Keskin, D.B. et al. *Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial*. Nature, 2019. **565**(7738): p.
 30 234-239). Analysis of the data has enabled identification of TCRs highly enriched in the peptide-responsive population, and simultaneous interrogation of their gene expression profile. Bulk TCR sequencing was also performed on an unstimulated *ex vivo* sample from

the same patient, to enable determination of the frequency of each peptide-responsive TCR within the *in vivo* T cell repertoire. This established a workflow in our laboratory that can readily be applied to the larger sample set from the AMADEUS trial.

Single cell sequencing allows:

- 5 (i) identification of paired TCR α and β chains of GvL T cell clones.
- (ii) characterisation of GvL T cell phenotype from the transcriptome.
- (iii) assessment of the size of antigen-specific T cell clones *ex vivo* and after stimulation.

10 iii. *Antigen-specific T cell-mediated AML cell killing*

Peptide-specific T cell clones are generated using our established single-cell cloning method (Brenna, E. et al. *CD4(+) T Follicular Helper Cells in Human Tonsils and Blood Are Clonally Convergent but Divergent from Non-Tfh CD4(+) Cells*. Cell Rep, 2020. **30**(1): p. 137-152 e) and/or donor-derived CD4 T cells are transduced with lentiviral
 15 vectors encoding paired TCR α and β chains to create antigen-specific T cell populations. These are tested using flow cytometry-based methods for *in vitro* activation (upregulation of CD69, CD25 and CD137), cytokine (IFN γ and TNF α production, degranulation (surface CD107a expression) and cytotoxicity (assessed by loss of fluorescent dye-labelled target cells) following incubation with patient AML cells loaded with relevant peptide (or and
 20 irrelevant peptide as a control). Antigens that are most polymorphic and patients with the most common HLA types are chosen. Cases where the T cell clones are the largest are prioritised.

AML patient-derived xenograft models in immunodeficient NSG/NSGW mice are created. In engrafting samples after establishment of AML, survival of mice and % of
 25 AML cells are compared after infusion of T cell clones, or patient T cells, transduced with either TCR recognizing a GvL antigen from that AML or recognizing a control peptide. In this way, it is possible to confirm that TCR-transduced T cells kill AML *in vivo* in patients using.

30 iv. *Quantitate residual AML cells in bone marrow samples*

Sensitive flow cytometry and next generation sequencing are used to accurately quantitate AML cells that remain after treatment. This is called measurable residual

disease analysis (MRD) at 2 time points (pre-trial entry, 3 months post allo-SCT). The sensitivity of this approach is 1 AML cells in 10^5 cells.

v. Assess HLA expression in AML blasts

- 5 RNA-Seq performed on AML cells at diagnosis is performed at post-transplant relapse to look for loss/reduction in expression of HLA, as a mechanism of immune evasion. Altered expression of transcriptional and signaling regulators of HLA expression (e.g. CIITA, RFX5, NFYA, NFYB, IL-1A, IL-1B, IRF8), genes regulating peptide processing, and ligands for inhibitory receptors expressed on T cells and
- 10 immunosuppressive factors is assessed. Cell surface HLA protein expression is also expressed by flow cytometry. This enables the study the role of CC-486 in modulating different modes of GvL failure.

Example 5

- 15 The following protocol was used to determine the sequence of TCRs recognising the alloreactive peptide antigens set out in Table 3 above:

1. Thaw post-transplant PBMCs from the patient from whom the peptide antigen was detected. Culture the cells with peptide, IL-2 and IL-7 for 12 days.
- 20 2. Rest cells overnight.
3. Stimulate cells with peptide for 6 hours.
4. Stain cells for FACS using antibodies and IFN γ catch reagent.
5. FACS sorting of activated (IFN γ +) CD4+ or CD8+ T cells and negative control (IFN γ -) populations.
- 25 6. 10X Chromium single cell RNA sequencing with V(D)J enrichment.

- T cells recognizing 18 of the 24 peptides set out in Table 3 (including PADI4) were detectable by FACS. Of these, 17 were detectable using IFN γ catch. Data are shown in Tables 4 and 5 below, and in Figures 8 to 23. In Table 5, clones were included that were
- 30 (a) greater in size than the largest clone in the control repertoire, or (b) >10% of the repertoire, even if not larger than the largest clone in the control repertoire.

Table 4 – Frequencies of peptide-specific responses

Patient	Peptide(s)	Gene	Allele frequency (%)	CD4 / CD8 responses	HLA restriction	Freq. of response (% IFN γ cells amongst CD4 $^{+}$ or CD8 $^{+}$ by FACS)
OX866	OX866-21/22	PADI4	4.27	CD4	HLA-DP	1.1
OX1149	OX1149-190	RNH1	11.21	CD4	HLA-DR	3.62
OX1149	OX1149-290	SLC26A6	9.84	CD4	HLA-DR	0.81
OX813	OX813-101/102	RHOT2	51.51	Not known	Not known	Not detected
OX802	OX802-321/322	COA6	52.52	CD4	Not tested	5.47/3.23
OX289	OX289-9	NAGPA	30.07	CD8	Class I	4.77
OX289	OX289-040	RNF123	5.07	CD4	HLA-DP	0.98
OX289	OX289-052	LLGL2	50.19	CD4	HLA-DR	1.27
OX289	OX289-067	ENDOD1	25.36	CD8	Not tested	0.55
OX289	OX289-073/074	HENMT1	1.93	CD4	Not tested	0.36/0.24
OX289	OX289-075/205	ACADS	26.58	CD4	Not tested	1.33/0.89
OX289	OX289-180	TIMM23B	9.11	CD4	HLA-DR	0.98
OX289	OX289-221	LRR1	20.48	CD4	HLA-DP	0.74
OX289	OX289-284	FTSJ3	64.78	CD8	Class I	2.78
OX289	OX1098-614	LGALS8	72.36	Likely CD4	HLA-DP	Not detected
OX747	OX747-157/158	TMBIM4	43.73	CD4	Not tested	0.325/0.45
OX747	OX747-185	DOCK8	24.54	Likely CD4	HLA-DR	Not detected
OX747	OX747-190/191	METTL22	22.2	Likely CD4	HLA-DR	Not detected
OX747	OX628-305	DCAF13	23.64	Not known	Not known	Not detected
OX993	OX993-413/414	DENND6B	31.06	CD4	HLA-DR	0.4
OX628	OX628-80/81	LITAF	0.00122	CD4	HLA-DR	2.36/1.12
OX628	OX628-564	PGLS	0.08	Not known	Not tested	Not detected
OX885	OX885-559/560	GSTZ1	30.57	CD4	Not tested	0.83
OX885	OX628-308/309	WASHC4	94.67	CD4	Not tested	1.96/1.06

Table 5 – TCR sequences from expanded T cell clones following peptide stimulation

Peptide	CD4 or CD8	Clone	Clone size (percent repertoire)	Chain	V gene	D gene	J gene	C gene	CDR1 aa (SEQ ID NO)	CDR1 nt (SEQ ID NO)	CDR2 aa (SEQ ID NO)	CDR2 nt (SEQ ID NO)	CDR3 aa (SEQ ID NO)	CDR3 nt (SEQ ID NO)	Full consensus aa (SEQ ID NO)	Full consensus nt (SEQ ID NO)
OX289 Peptide 40	CD4	1	85.2	TRA	TRAJ9-2		TRAJ10	TRAC	448	535	622	709	32	119	206	293
				TRB	TRBV20-1		TRBJ2-2	TRBC2	449	536	623	710	33	120	207	294
				TRA	TRAJ8-3		TRAJ3	TRAC	450	537	624	711	34	121	208	295
OX289 Peptide 52	CD4	1	27.3	TRB	TRBV2	TRBD1	TRBJ2-6	TRBC2	451	538	625	712	35	122	209	296
				TRB	TRBV20-1		TRBJ2-2	TRBC2	452	539	626	713	36	123	210	297
				TRA	TRAJ36/DV7		TRAJ22	TRAC	453	540	627	714	37	124	211	298
OX289 Peptides 73/74	CD4	1	32.3	TRB	TRBV12-3		TRBJ2-1	TRBC2	454	541	628	715	38	125	212	299
				TRA	TRAJ5		TRAJ16	TRAC	455	542	629	716	39	126	213	300
				TRB	TRBV27		TRBJ2-1	TRBC2	456	543	630	717	40	127	214	301
		2	25.6	TRA	TRAJ39		TRAJ58	TRAC	457	544	631	718	41	128	215	302
				TRB	TRBV27		TRBJ2-1	TRBC2	458	545	632	719	42	129	216	303
				TRB	TRBV27	TRBD1	TRBJ1-1	TRBC1	459	546	633	720	43	130	217	304
		3	8.67	TRA	TRAJ8-6		TRAJ56	TRAC	460	547	634	721	44	131	218	305
				TRB	TRBV7-2		TRBJ2-1	TRBC2	461	548	635	722	45	132	219	306
				TRB	TRBV7-2		TRBJ2-1	TRBC2	462	549	636	723	46	133	220	307
OX289 Peptides 75/205	CD4	1	42.4	TRA	TRAJ9-2		TRAJ17	TRAC	463	550	637	724	47	134	221	308
				TRA	TRAJ23/DV6		TRAJ42	TRAC	464	551	638	725	48	135	222	309
				TRB	TRBV20-1		TRBJ1-4	TRBC1	465	552	639	726	49	136	223	310
		2	16	TRA	TRAJ12-2		TRAJ41	TRAC	466	553	640	727	50	137	224	311
				TRB	TRBV6-5	TRBD2	TRBJ2-5	TRBC2	467	554	641	728	51	138	225	312
				TRA	TRAJ9-2		TRAJ23	TRAC	468	555	642	729	52	139	226	313
		3	13.9	TRB	TRBV20-1		TRBJ2-1	TRBC2	469	556	643	730	53	140	227	314
				TRA	TRAJ4		TRAJ23	TRAC	470	557	644	731	54	141	228	315
				TRB	TRBV5-1	TRBD2	TRBJ2-5	TRBC2	471	558	645	732	55	142	229	316
OX289 Peptide 221	CD4	1	65.4	TRA	TRAJ26-2		TRAJ57	TRAC	472	559	646	733	56	143	230	317
				TRB	TRBV20-1		TRBJ1-5	TRBC1	473	560	647	734	57	144	231	318

Peptide	CD4 or CD8	Clone	Clone size (percent repertoire)	Chain	V gene	D gene	J gene	C gene	CDR1 aa (SEQ ID NO)	CDR1 nt (SEQ ID NO)	CDR2 aa (SEQ ID NO)	CDR2 nt (SEQ ID NO)	CDR3 aa (SEQ ID NO)	CDR3 nt (SEQ ID NO)	Full consensus aa (SEQ ID NO)	Full consensus nt (SEQ ID NO)
OX802 Peptides 321/322	CD4	1	47.4	TRA	TRAV1-1		TRAJ41	TRAC	474	561	648	735	58	145	232	319
				TRA	TRAV2		TRAJ4	TRAC	475	562	649	736	59	146	233	320
		2	20	TRB	TRBV11-3		TRBJ2-7	TRBC2	476	563	650	737	60	147	234	321
				TRA	TRAV2		TRAJ4	TRAC	477	564	651	738	61	148	235	322
				TRB	TRBV11-3		TRBJ2-7	TRBC2	478	565	652	739	62	149	236	323
OX628 Peptides 80/81	CD4	1	55.1	TRA	TRAV35		TRAJ54	TRAC	479	566	653	740	63	150	237	324
				TRB	TRBV6-6		TRBJ1-1	TRBC1	480	567	654	741	64	151	238	325
		2	13.5	TRA	TRAV35		TRAJ31	TRAC	481	568	655	742	65	152	239	326
				TRB	TRBV29-1		TRBJ1-1	TRBC1	482	569	656	743	66	153	240	327
				TRA	TRAV12-2		TRAJ52	TRAC	483	570	657	744	67	154	241	328
OX747 Peptides 157/158	CD4	1	15.5	TRB	TRBV3-1		TRBJ2-7	TRBC2	484	571	658	745	68	155	242	329
				TRA	TRAV41		TRAJ32	TRAC	485	572	659	746	69	156	243	330
		2	9.8	TRA	TRAV41		TRAJ58	TRAC	486	573	660	747	70	157	244	331
				TRB	TRBV6-5		TRBJ1-3	TRBC1	487	574	661	748	71	158	245	332
				TRA	TRAV19		TRAJ34	TRAC	488	575	662	749	72	159	246	333
		3	8.7	TRB	TRBV5-4		TRBJ1-2	TRBC1	489	576	663	750	73	160	247	334
				TRA	TRAV12-2		TRAJ50	TRAC	490	577	664	751	74	161	248	335
		4	7.9	TRB	TRBV24-1		TRBJ1-2	TRBC1	491	578	665	752	75	162	249	336
				TRA	TRAV19		TRAJ30	TRAC	492	579	666	753	76	163	250	337
				TRB	TRBV18	TRBD1	TRBJ1-3	TRBC1	493	580	667	754	77	164	251	338
OX885 Peptides 559/560	CD4	5	7.7	TRA	TRAV35		TRAJ58	TRAC	494	581	668	755	78	165	252	339
				TRB	TRBV19	TRBD1	TRBJ1-5	TRBC1	495	582	669	756	79	166	253	340
		1	96.5	TRA	TRAV22		TRAJ43	TRAC	496	583	670	757	80	167	254	341
				TRB	TRBV12-5		TRBJ1-5	TRBC1	497	584	671	758	81	168	255	342

Peptide	CD4 or CD8	Clone	Clone size (percent repertoire)	Chain	V gene	D gene	J gene	C gene	CDR1 aa (SEQ ID NO)	CDR1 nt (SEQ ID NO)	CDR2 aa (SEQ ID NO)	CDR2 nt (SEQ ID NO)	CDR3 aa (SEQ ID NO)	CDR3 nt (SEQ ID NO)	Full consensus aa (SEQ ID NO)	Full consensus nt (SEQ ID NO)
OX885 Peptides OX628-308/309	CD4	1	76.1	TRA	TRAV26-1		TRAJ27	TRAC	498	585	672	759	82	169	256	343
				TRB	TRBV27		TRBJ2-3	TRBC2	499	586	673	760	83	170	257	344
		2	16.2	TRA	TRAV8-6		TRAJ10	TRAC	500	587	674	761	84	171	258	345
				TRB	TRBV10-2	TRBD1	TRBJ1-5	TRBC1	501	588	675	762	85	172	259	346
OX993 Peptides 413/414	CD4	1	26.7	TRA	TRAV13-2		TRAJ28	TRAC	502	589	676	763	86	173	260	347
				TRA	TRAV13-2		TRAJ12	TRAC	503	590	677	764	87	174	261	348
		2	13.7	TRB	TRBV7-9		TRBJ1-1	TRBC1	504	591	678	765	88	175	262	349
				TRA	TRAV8-4		TRAJ8	TRAC	505	592	679	766	89	176	263	350
		3	11.6	TRB	TRBV6-5		TRBJ2-2	TRBC2	506	593	680	767	90	177	264	351
				TRB	TRBV6-5		TRBJ1-6	TRBC1	507	594	681	768	91	178	265	352
		1	18.3	TRA	TRAV5		TRAJ9	TRAC	508	595	682	769	92	179	266	353
				TRB	TRBV6-5		TRBJ2-2	TRBC2	509	596	683	770	93	180	267	354
		2	17.3	TRA	TRAV17		TRAJ17	TRAC	510	597	684	771	94	181	268	355
				TRB	TRBV2		TRBJ2-2	TRBC2	511	598	685	772	95	182	269	356
OX1149 Peptide 190	CD4	3	9	TRA	TRAV17		TRAJ45	TRAC	512	599	686	773	96	183	270	357
				TRB	TRBV2		TRBJ2-7	TRBC2	513	600	687	774	97	184	271	358
		4	5.7	TRA	TRAV13-1		TRAJ53	TRAC	514	601	688	775	98	185	272	359
				TRB	TRBV12-4	TRBD1	TRBJ2-7	TRBC2	515	602	689	776	99	186	273	360
		5	4.8	TRA	TRAV17		TRAJ7	TRAC	516	603	690	777	100	187	274	361
				TRB	TRBV2		TRBJ1-2	TRBC1	517	604	691	778	101	188	275	362
		5	4.8	TRA	TRAV29/DV5		TRAJ52	TRAC	518	605	692	779	102	189	276	363
				TRB	TRBV30		TRBJ2-5	TRBC2	519	606	693	780	103	190	277	364

Peptide	CD4 or CD8	Clone	Clone size (percent repertoire)	Chain	V gene	D gene	J gene	C gene	CDR1 aa (SEQ ID NO)	CDR1 nt (SEQ ID NO)	CDR2 aa (SEQ ID NO)	CDR2 nt (SEQ ID NO)	CDR3 aa (SEQ ID NO)	CDR3 nt (SEQ ID NO)	Full consensus aa (SEQ ID NO)	Full consensus nt (SEQ ID NO)
OX1149 Peptide 290	CD4	1	20.4	TRA	TRAV13-1		TRAJ34	TRAC	520	607	694	781	104	191	278	365
		2	7	TRB	TRBV5-1	TRBD1	TRBJ1-2	TRBC1	521	608	695	782	105	192	279	366
				TRA	TRAV10		TRAJ36	TRAC	522	609	696	783	106	193	280	367
				TRB	TRBV5-1		TRBJ2-3	TRBC2	523	610	697	784	107	194	281	368
		3	4.8	TRA	TRAV26-2		TRAJ48	TRAC	524	611	698	785	108	195	282	369
				TRA	TRAV34		TRAJ42	TRAC	525	612	699	786	109	196	283	370
				TRB	TRBV2		TRBJ1-1	TRBC1	526	613	700	787	110	197	284	371
		1	91.1	TRA	TRAV12-1		TRAJ40	TRAC	527	614	701	788	111	198	285	372
				TRB	TRBV20-1	TRBD1	TRBJ1-2	TRBC1	528	615	702	789	112	199	286	373
OX289 Peptide 67	CD8	1	81.1	TRA	TRAV27		TRAJ30	TRAC	529	616	703	790	113	200	287	374
				TRA	TRAV22		TRAJ33	TRAC	530	617	704	791	114	201	288	375
				TRB	TRBV11-2		TRBJ2-1	TRBC2	531	618	705	792	115	202	289	376
OX289 Peptide 284	CD8	1	96	TRA	TRAV12-1		TRAJ40	TRAC	532	619	706	793	116	203	290	377
				TRB	TRBV20-1	TRBD1	TRBJ1-2	TRBC1	533	620	707	794	117	204	291	378
				TRB	TRBV20-1		TRBJ2-2	TRBC2	534	621	708	795	118	205	292	379

TABLE OF SEQUENCES

SEQ ID NO:	Sequence
1	LTISLLDTFNLELPEAVVFQ
2	ISLLDTFNLELPEAVVFQDS
3	SLLDTFNLELPEAVVF
4	LDTFNLELPEAVVFQ
5	CAGAAGCCTCACACAGCCAGTAACCTTTGCTAGTACCTCTTGAGTGCAAGGTGGAGAATTAAGATCTGGATTTGAGACGGAGCACGGAACATTTCACTCAGGGGAAGAGCTATGAACATGCTGACTGCCAGCCGTGTGAGGGCAGTCATAGCCTCCATCTGTGTTGTATCCAGCATGGCTCAGAAGGTAACCTCAAGCGCAGACTGAAATTTCTGTGGTGGAGAAGGAGGATGTGACCTTGAGCTGTGTATGAAACCCGTGATACTACTTATTACTTATTCTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCTTATTCGTCGGAACCTCTTTTGTGAGCAAAATGAAATAAGTGGTGGTATTCTTGAACTTCCAGAAATCCACCAGTTCCTTCAACTTCACCATCACAGCCTCACAAGTCGTGGACTCAGCAGTATACTTCgtgctctgagtgaaacggcgatgggtgctacaacaagctcatcttGGAAGTGGCACTCTGCTTGTGTCCAGCCAAATATCCAGAACCCTGACCCTGCGTGATACCAGCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAACAAATGTGTACAAAGTAAGGATTCTGATGTGTATATCACAGACAAAAGTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGTGTGGCCTGGAGCAACAAATCTGACTTTGCATGTGCAACGCCCTCA
6	MLTASLLRAVIASICVVSMAQKVTAQTEISVVEKEDVTLDCVYETRDTTYLFWYKQPPSGELVFLIRRNSFDEQNEISGRYSWNFQKSTSSFNTITASQVVDASVYFcalserypygatnkliFGTGLLAVQPNINPDPNAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKSDSVYITDKTVLDMRSMDFKNSNAVAWSNKSDFACANAF
7	AAAATGCCCTCCTTTCTCCACAGGACCAGATGCCTGAGCTAGGAAAGCCCTATTCCTGCTGTGATCCTGCCATGGATACCTGGCTCGTATGCTGGGCAATTTTAGTCTCTTGAAAGCAGGACTCACAGAACCTGAAGTCACCCAGACTCCCAGCCATCAGGTCACACAGATGGGACAGGAAGTGATCTTGCGCTGTGTCCCCATCTCTAATCACTTATACTTCTATTGGTACAGACAAATCTTGGGGCAGAAAGTCGAGTTTCTGGTTTCTTTTATAATAATGAAATCTCAGAGAAGTCTGAAATATTGATGATCAATTCTCAGTTGAAAGGCCTGATGGATCAAATTTCACTCTGAAGATCCGGTCCACAAAGCTGGAGGACTCAGCCATGTACTTCgtgccagcagtgaaacgcaggacgcaacctgcctacgagcagtgacttcGGGCCGGGCACCAGGCTCACGGTCACAGAGGACCTGAAAAACGTGTTCCACCCGAGGTGCTGTGTTGAGCCATCAGAAGCAGAGATCTCCACACCCAAAAGGCCACACTGGTATGCCTGGCCACAGGCTTCTACCCCGACCACGTGGAGCTGAGCTGGTGGTGAATGGGAAGGAGGTGCACAGTGGGGTCAGCACAGACCCGAGCCCTCAAGGAGCAGCCGCCCTCAATGACTCCAGATACTGCCTGAGCAGCCGCTGAGGGTCTCGGCCACCTTCTGGCAGAACCCCCGAACCACTTCCGCTGTCAAGTCCAGTTCTACGGGCTCTCGGAGAATGACGAGTGG
8	MDTWLVCAWIFSLKAGLTEPEVTQTPSHQVTQMGEVILRCVPISNHLFYFYWRQILGQKVEFLVSFYNNEISEKSEIFDDQFSVERPDGSNFTLKIRSTKLEDSAMYFcasserrtqpayeqlfGPGTRLTVTEDLKNVFPPEVAVFEPSEAEISHTQKATLVCLATGFYPDHVELSWVWNGKEVHSGVSTDPQLKEQPALNDSRYCLSSRLRVSATFWQNPРНHFRQVQFYGLSENDEW
9	AAAGCAGATTCTTTTATGATTTTAAAGTAGAAATATCCATTCTAGGTGCATTTTAAAGGGTTAAAAATTTGAATCCTCAGTGAACCAGGGCAGAGAAGAATGATGAAATCCTTGAGAGTTTTACTAGTGATCCTGTGGCTTCAGTTGAGCTGGGTTTGGAGCCAACAGAAGGAGGTGGAGCAGAATCTGGACCCCTCAGTGTTCCAGAGGGAGCCATTGCCTCTCTCAACTGCACTTACAGTGACCGAGGTTCCAGTCTCTTCTTGGTACAGACAATATTCTGGGAAAAGCCCTGAGTTGATAATGTCCATATACTCCAATGGTGCAAAAGAAGATGGAAGGTTTACAGCACAGCTCAATAAAGCCAGCCAGTATGTTTCTCTGCTCATCAGAGACTCCAGCCCAGTGATTAGCCACCTACCTCgtgccgtccggggcaggcaggaaactgctcgtatcttGGGAAGGGAACCACTTATCAGTGAGTTCCAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACTCTAAATCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAACAAATGTGTACAAAGTAAGGATTCTGATGTGTATATCACAGACAAAAGTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGTGTGGCCTGGAGCAACAAATCTGACTTTGCAATGTGCAAAACGCCCTCA
10	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGAIASLNCTYSDRGSQSFFWYRQYSGKSPELIMSIYNSGDKEDGRFTAQLNKASQYVSLIRDSQPSDSATYLCavrgqagtalifGKGTTLSVSSNIQNPDPNAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKSDSVYITDKTVLDMRSMDFKNSNAVAWSNKSDFACANAF

11	CAGAAGCCTCACACAGCCCAGTAACCTTTGCTAGTACCTCTTGAGTGCAAGGTGGAGAATTAAGATCTGGATTTGAGACGGAGCACGGAACATTTCACTCAGGGGAAGAGCTATGAACATGCTGACTGCCAGCCGTGTGAGGGCAGTCATAGCCTCCATCTGTGTTGTATCCAGCATGGCTCAGAAAGGTAACCTCAAGCGCAGACTGAAATTTCTGTGGTGGAGAAGGAGGATGTGACCTTGGACTGTGTGTATGAAACCCGTGATACTACTTATTACTTATTCTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCTTATTCGTGCGAACTCTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTTGGAACCTCCAGAAATCCACCAAGTTCCTTCAACTTCACCATCACAGCCTCACAAGTCGTGGACTCAGCAGTATACTTCgtgctctccggcaggaaacacacctctgtctttGGAAAGGGCACAAGACTTTCTGTGATTGCAAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAAACAAATGTGTCAAAAGTAAGGATTCTGATGTGTATATCACAGACAAAACCTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTGGCCTGGAGCAACAACTGACTTTGCATGTGCAAAACGCCCTTCA
12	MLTASLLRAVIASICVVSSMAQKVTAQTEISVVEKEDVTLDCVYETRDTTYLFWYKQPPSGELVFLIRRNSEFDEQNEISGRYSWNFKSTSSFNFTITASQVVDASVYFcalpagnlplvGKTRLSVIANIQNPDPVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKSDSVYITDKTVLDMRSMDFKSNSAVAWSNKSDFACANAF
13	CTCAGAGGACCACTATCCCTCACAGGGTGACACCTGACCAGCTCTGTCCACCTGGCCATGGGCTCAGGTACCTCTGATGGGAAGACCTTTGTCTCTTGGGAACAAGTGAATCCTTGGCACAGGCCCAAGTGATTCTGCTGTGCAGAACAGAGAGCAGTGGACCTCAGGAGGCCCTGCAAGGGGAGGACATAGGACAGTGACATCACAGTATGCCCCCTCCACCAAGCAAGGCTGAGAATTTAGCTCTTTCCAGGAGGACCAAGCCCTGAGCACAGACAGTGTCTGCCTGCCCTTTGTGCCATGGGCTCCAGGCTGCTCTGTTGGGTGCTGCTTTGTCTCCTGGGAGCAGGCCAGTAAAGGCTGGAGTCACTCAAACCTCAAGATATCTGATCAAAACGAGAGGACAGCAAGTGACACTGAGCTGCTCCCTATCTCTGGGCATAGGAGTGATTCCTGGTACCAACAGACCCCCAGGACAGGGCCTTCAGTTCCTTTGAATACTTCAGTGAGACACAGAGAAACAAAGGAACTTCCCTGGTGCATTCTCAGGGCGCCAGTTCTCTAACTCTGCTCTGAGATGAATGTGAGCACCTTGGAGCTGGGGGACTCGGCCCTTTATCTTgcgccagcagcttgactgggggaaactatggctacaccltcGGTTTCGGGGACCAGGTTAACCGTTGTAGAGGACCTGAACAAGGTGTTCCACCCGAGCTGCTGTGTTTGGCCATCAGAAGCAGAGATCTCCACACCCAAAAGGCCACACTGGTGTGCTGGCCACAGGCTTCTCCCTGACCACGTGGAGCTGAGCTGGTGGGTGAATGGGAAGGAGGTGCACAGTGGGGTCAGCACGGACCCGACGCCCTCAAGGAGCAGCCCGCCCTCAATGACTCCAGATACTGCCTGAAGATCGGAAGAGC
14	MGSRLLCWVLLCLLGGAPVKAGVTQTPRYLIKTRGQVTLSCSPISGHRVSWYQQTPGQGLQFLFEYFSETQRNKGNFPRGFSGRQFSNSRSEMNVSTLELGDSALYLcassltggnnygytfGSGTRLTVEDLNKVPPEVAVFEPSEAEISHTQKATLVCLATGFFPDHVELSWWVNGKEVHSGVSTDPQLKEQPALNDSRYCLKIGR
15	CCAAAACAAGAGACTTGCCTAGCCCAACCTTCCTCACGCTCGCTATTCTCAAGACCTGGGTTCCAGCACACTTTCCTACTGGCCCCGAGGAGAATTTCAAAGAGACGCCTGCAGTGTTTCCACAGCTCAGCCATGCTCCTGTTGCTCATACCACTGCTGGGGATGATTTTTGCCCTGAGAGATGCCAGAGCCCAGTCTGTGAGCCAGCATAACCACCACGTAATTCTCTGAAGCAGCCTCACTGGAGTTGGGATGCAACTATTCCATGGTGGAACTGTTAATCTCTTCTGGTATGTCCAGTACCCTGGTCAACACCTTCAGCTCTCCCTCAAGTACTTTTTCAGGGGATCCACTGGTTAAAGGCATCAAGGGCTTTGAGGCTGAATTTATAAAGAGTAAATCTCCTTTAATCTGAGGAAACCCTCTGTGCAGTGGAGTGACACAGCTGAGTACTTCgtgacctaggcaccaatgcaggcaaatcaacctttGGGGATGGGACTACGCTCACTGTGAAGCCAAATATCCAGAACCCTGACCCTGCGTGATACCAGCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAAACAAATGTGTCAAAAGTAAGGATTCTGATGTGTATATCACAGACAAAACCTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTGGCCTGGAGCAACAACTGACTTTGCATGTGCAAAACGCCCTTCA
16	MLLLLIPVLGMIFALRDARAQSVSQHNHHVILSEAASLELGCNYSYGGTVNLFWYVQYPGQHLQLLLKYFSGDPLVKIGKFEAEFIKSKFSFNLKPSVQWSDTAIEYFcavgtgnagkstfGDGTTLTVKPNIQNPDPVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKSDSVYITDKTVLDMRSMDFKSNSAVAWSNKSDFACANAF
17	ACCTGGAGCCCCCAGAACTGGCAGACACCTGCCTGATGCTGCCATGGGCCCCAGCTCCTTGGCTATGTGGTCCTTTGCTTCTAGGAGCAGGCCCTTGGAAAGCCCAAGTGACCAGAACCAAGATACCTCATCACAGTGACTGGAAAGAAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCCTGGTATCGACAAGACCCAGGGCTGGGCTTAAAGGCAGATCTACTATTCAATGAATGTTGAGGTGACTGATAAGGGAGATGTTCTGAAGGTACAAAGTCTCTCGAAAAGAGAAGAGGAATTTCCCTGATCCTGAGAGTGCAGGAGCCCCAACAGACCTCTCTGACTTCgtgacctaggcaccaatgcaggcaaatcaacctttGGGGATGGGACTACGCTCACTGTGAAGCCAAATATCCAGAACCCTGACCCTGCGTGATACCAGCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAAACAAATGTGTCAAAAGTAAGGATTCTGATGTGTATATCACAGACAAAACCTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTGGCCTGGAGCAACAACTGACTTTGCATGTGCAAAACGCCCTTCA

	GTGGGGTCAGCACGGACCCGCAGCCCCCTCAAGGAGCAGCCCGCCCTCAATGACTCCAGATACTGCCTGA
18	MGPQLLGYYVLCLLGAGPLEAQVTQNPRLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVEVTDKGDVPEGYKVSREKRNFLILESPSPNQTSLYFcassrklagggptgelffGEGSRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKATLVCLATGFYPDHVELSWWWNGKEVHSGVSTDPQLKEQPALNDSRYCL
19	AGGAAAAGTTGAGGGGGCTTGACAGACAGAAATTTCTAACTGATGCTTATCTGTGTGTAAGAAAGGATTACTGATTTCCCAATGAATATATCTTCAGCAATTTCTAAATTTGGACAAAGTGGGGAAGTGCTTCCTTTGACAGAGACAGCTTTAAGTGAAGCACTTGTAAGGGCGGGGGCTGCTGAAAGAATTCAGTTGAGGGTGAATTTACAGAGTTTCAGCTGGTTGGGAAGACTGGAAGACCACCTGGGCTGTCATTGAGCTCTGGTGCCAGGAGGAATGGACAAGATCTTAGGAGCATCATTTTTAGTTCTGTGGCTTCAACTATGCTGGGTGAGTGGCCAACAGAAGGAGAAAAGTGACCAGCAGCAGGTGAAACAAAGTCCCTCAATCTTTGATAGTCCAGAAAAGGAGGATTTCATTATAAACTGTGCTTATGAGAACACTGCGTTTGACTACTTTCCATGTACCAACAATTCCCTGGGAAAGGCCCTGCATTATTGATAGCCATACGTCCAGATGTGAGTGAAAAGAAAGAAGGAAGATTCACAATCTCCTTCAATAAAAGTGCCAAGCAGTTCTCATTGCATATCATGGATCCAGCCTGGAGACTCAGCCACCTACTTCgtgcagctgtgacaggaggaggtgtgacggactcacctttGGCAAAGGGACTCATCTAATCATCCAGCCCTATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACTCTAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAACAAATGTGTCAAAAGTAAGGATTCTGATGTGTATATCACAGACAAAAGTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTCTGTGGCTGGAGCAACAAATCTGACTTTGTCATGTGCAAAACGCCTTCA
20	MDKILGASFLVLWLQCLWVSGQQKEKSDQQQVKQSPQSLIVQKGGISIINCAYENTAFDYFPWYQQFPGKGPALLIAIRPDVSEKKEGRFTISFNKSAKFSLHIMDSQPQDSATYFcaavtgggagdlfGKGTHLIIQPIQNPDPVAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKNSAVAWSNKSDFACANAF
21	AGCTGTGAGGTCTGGTTCCCCGACGTGCTGCAGCAAGTGCCCTTGGCCTGCCTGTGGGCTCCCTCCATGGCCAACTCTGCTATGGACACCAGACTCTGCTGTGCGGTCTGCTGCTTCTGGGGGCAGGTCTCTCAAATGCCGGCGTCATGCAGAACCAAGACACCTGGTCAGGAGGAGGGACAGGAGGCAAGACTGAGATGCAGCCCAATGAAAGGACACAGTCATGTTTACTGGTATCGGCAGCTCCAGAGGAAGGTCTGAAATTCATGGTTTATCTCCAGAAAAGAAAATATCATAGATGAGTCAGGAATGCCAAGGAACGATTTTCTGCTGAATTTCCCAAAGAGGGCCCCAGCATCCTGAGGATCCAGCAGGTAGTGCAGGAGGATTCGGCAGCTTATTTCTgtgccagctccccccagggttacaatgagcaglttcttGGGCCAGGGACACGGCTCACCGTGTAGAGGACCTGAAAAACGTGTTCCACCCGAGGTGCTGTGTTTGAGCCATCAGAAGCAGAGATCTCCACACCCAAAAGGCCACACTGGTGTGCTGGCCACAGGCTTCTACCCCGACACAGTGGAGTGA GCTGGTGGGTGAATGGGAAGGAGGTGCACAGTGGGGTCAGCACGGACCCGCAGCCCCCTCAAGGAGCAGCCCGCCCTCAATGACTCCAGATACTGCCTGA
22	MDTRVLCCAVICLLGAGLSNAGVMQNPRLVRRRGQEARLRCSPMKGHSHVYWRQLPEEGLKFMVYLQKENIIDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAAYFcasspggyneqffGPGTRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKATLVCLATGFYPDHVELSWWWNGKEVHSGVSTDPQLKEQPALNDSRYCL
23	GCGGCCGCGCCACCATGCTTACAGCTTCTCTGCTGAGAGCCGTGATCGCCAGCATCTGTGTGGTGTCTAGCATGGCCAGAAAAGTGACACAGGCCAGACCCAGATCAGCGTGGTGAAAAAGAAAGATGTGACCCCTGGACTGCGTGTACGAGACACGGGACACCACTACTACCTGTTCTGGTACAAGCAGCCTCCTAGCGCGAGCTGGTGTTCCTGATCAGACGGAACAGCTTCGACGAGCAGAACGAGATCTCCGGCCGGTACAGCTGGAACCTCCAGAAAGTCCACAGCAGCTTCAACTTACCATACCGCCAGCCAGGTGGTGATAGCGCCGTGATTTTTGCGCCCTGAGCGAGAGGCCTTACGGCGGAGCTACAAACAAGCTGATCTTCGGCACCGGCACACTGCTGGCTGTTCAACCTA ACATCCAGAACCCCGACCCCGCGG
24	CCATGGATACCTGGCTCGTGTGCTGGGCCATCTTCAGCCTGCTGAAAGCCGGAAGTACCCAGCCTGAAGTGACCCAGACACCTAGCCACCAAGTGACACAGATGGGCCAAGAAGTGATCCTGCGCTGCGTGC CCATCAGCAACCACCTGTACTTCTACTGGTACAGACAGATCCTGGGCCAGAAAAGTGGAATTCCTGGTGTCCCTTCTACAACAACGAGATCAGCGAGAAGTCCGAGATCTTCGACGACCAGTTCAGCGTGGAAGACCCGACGGCAGCAACTTCACCTGAAGATCAGAAGCACCAAGCTCGAGGACAGCGCCATGTACTTTCGCGCCAGCAGCGAGAGAAGAACCAGCCTGCCTACGAGCAGTACTTCGGCCCTGGCACAAGACTGACCGTGACAG AGGACCTGCGG AACGTGACCCCCCAGGTGTCCCTGTTTCGAGCCAGCAAGGCCGAGATCGCCAACAAGCAGAAA GCCACACTGGTCTGTCTGGCTAGGGGCTTCTTCCCGACACGTG
25	GCGGCCGCGCCACCATGAAGTCTCTGAGAGTCTGCTGGTCATCCTGTGGCTGCAGCTGTCTTGGGTCTGGTCCAGCAGAAAGAGGTGGAACAGAACAGCGGCCCTCTGTCTGTTCTGAAAGCGCTATCGCCAGCCTGAACTGCACCTACAGCGATAGAGGCAGCCAGAGCTTCTTCTGGTACAGACAGTACAGCGCAAGAGCCCCGAGCTGATCATGAGCATCTACAGCAACGGCGACAAAGAGGACGGCCGGTTTACA

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26	GCGGCCGCGCCACCATGCTTACAGCTTCTCTGCTGAGAGCCGTGATCGCCAGCATCTGTGTGGTGT CTAGCATGGCCAGAAAAGTGACACAGGCCAGACCGAGATCAGCGTGGTGGAAAAAGAAGATGTGA CCCTGGACTGCGTGTACGAGACACGGGACACCACCTACTACCTGTTCTGGTACAAGCAGCCTCCTA GCCGCGAGCTGGTGTTCCTGATCAGACGGAACAGCTTCGACGAGCAGAACGAGATCTCCGGCCGG TACAGCTGGAACCTCCAGAAGTCCACCAGCAGCTTCAACTTCACCATCACCGCCAGCCAGGTGGTG GATAGCGCCGTGTACTTTTGTGCCCTGCCTGCCGGAATACCCCTCTGGTGTGGCAAGGGCACC AGACTGTCTGTGATCGCCA ACATCCAGA ACCCCGACCCCGCGG
27	CCATGGGCAGCAGACTGCTGTGTTGGGTGCTGCTGTGTCTGCTTGGAGCCGGACCTGTGAAAGCTG GCGTGACCCAGACACCTAGATACCTGATCAAGACCAGAGGCCAGCAAGTGACCCCTGAGCTGCTCTC CTATCAGCGGCCACAGAAGCGTGTCTGGTATCAGCAGACACCTGGACAGGGCCTGCAGTTCCCTGT TCGAGTACTTCAGCGAGACACAGCGGAACAAGGGCAACTTCCCCGGCAGATTTTCCGGCAGACAGT TCAGCAACAGCCGAGCGAGATGAACGTGTCCACACTGGAAGTGGGCGACAGCGCCCTGTATCTGT GTGCCTCTTCTCTGACCGGCGCAACTACGGCTACACATTTGGCAGCGGCACCAGACTGACAGTGG TCG AGGACCTGCGGAACGTGACCCCC CCCAAGGTGTCCCTGTTTCGAGCCAGCAAGGCCGAGATCGCCAACAAGCAGAAAGCCACACTGGTC TGCTGGCTAGGGGCTTCTTCCCCGACCACGTG
28	GCGGCCGCGCCACCATGTTGTTGCTGCTGATTCTCTGTGCTGGGCATGATCTTCGCCCTGAGGGATG CTAGAGCCAGTCCGTGTCTCAGCACAAACCACCGTATCCTGTCTGAGGCCGCCTCTCTGGAAC TGGGCTGCAATTACAGCTACGCGCGCACCGTGAACCTGTTTTGGTACGTGCAGTACCCCGGCCAGC ATCTCCAGCTGCTGCTGAAGTACTTTAGCGGCGACCCCTCTGGTCAAGGGCATCAAGGGATTGAGG CCGAGTTCATCAAGAGCAAGTTCAGCTTCAACCTGCGGAAGCCAGCGTGCAGTGGAGCGATACAG CCGAGTACTTTTGTCCGTGGGCACCAATGCCGGCAAGAGCACATTTGGCGACGGCACCACTGA CCGTGAAGCCTA ACATCCAGAACCCCGA CCCCAGCGG
29	CCATGGGCCCTCAGCTGCTGGGATATGTGGTGCTGTGTCTGCTTGGAGCCGGACCTCTGGAAGCCC AAGTGACACAGAACCCAGATACCTGATCACCGTGACCGGCAAGAACTGACCGTGACCTGCAGCC AGAACATGAACCACGAGTACATGAGCTGGTACAGACAGGACCCTGGCCTGGGCCTGAGACAGATCT ACTACAGCATGAACGTGGAAGTGACCGACAAGGGCGACGTGCCCCGAGGGCTACAAGGTGTCCAGA AAAGAGAAGCGGAACCTCCCACTGATCCTGGAAGCCCATCTCCTAACAGACCAGCCTGTACTTCT GCGCCAGCAGCAGAAAAGGACTGGCTGGCGGAGGACCTACCGCGAGCTGTTTTTGGCGAGGGC AGCAGACTGACAGTGCTCG AGGACCTG CGGAACGTGACCCCCCCCCAAGGTGTCCCTGTTTCGAGCCAGCAAGGCCGAGATCGCCAACAAGCA GAAAGCCACACTGGTCTGTCTGGCTAGGGGCTTCTTCCCCGACCACGTG
30	GCGGCCGCGCCACCATGGATAAGATTCTGGGCGCCAGCTTCTGGTGCTGTGGCTGCAACTTTGTT GGGTGTCCGGCCAGCAGAAAGAGAAGTCCGACCAGCAGCAAGTGAAACAGAGCCCTCAGAGCCTG ATCGTGCAGAAAGGCGCATCAGCATCATCAACTGCGCCTACGAGAATACCGCCTTCGACTATCC CCTGGTATCAGCAGTTCCCCGGCAAGGGACCTGCTCTGCTGATCGCCATTAGACCCGACGTGTCCG AGAAGAAAGAGGGCAGATTACCATCAGCTTCAACAAGAGCGCCAAGCAGTTACGCTGCACATCA TGGATAGCCAGCCTGGCGACAGCGCCACCTATTTTGTGCTGCTGTTACAGGCGGCGAGCCGATG GCCTGACATTTGGAAGGGCACCCACCTGATCATCCAGCCTT ACATCCAGAACCCCGACCCCGCGG
31	CCATGGACACCAGAGTGCTGTGCTGCGCCGTGATCTGTCTGCTTGGAGCCGGACTGTCTAATGCCG GCGTGATGCAGAACCCAGACACCTCGTTCCGAGAAGAGGCCAAGAGGCCAGACTGAGATGCAGC CCTATGAAGGGCCACAGCCATGTGTAAGTACGACAGCTGCCGAAGAGGGCCTGAAGTTCATG GTGTACCTGCAGAAAGAGAACATCATCGACGAGAGCGGCATGCCCAAAGAGCGGTTCTCTGCCGAG TTTCCCAAAGAGGGCCCCAGCATCCTGAGAATCCAGCAGGTTGTGCGGGGAGATAGCGCCGCTAC TTTTGTGCTAGCAGCCCTCAGGGCTACAACGAGCAGTTTTTTCGGCCCTGGCACCAGACTGACAGTG CTCG AGGACCTGCGGAACGTGACCCCC CCAAGGTGTCCCTGTTTCGAGCCAGCAAGGCCGAGATCGCCAACAAGCAGAAAGCCACACTGGTCT GTCTGGCTAGGGGCTTCTTCCCCGACCACGTG
32	CALIPTGGGNKLTf
33	CSARLAHSGTNTGELFF
34	CAVGAYSSASKIIF
35	CASRDRGSGANVLTF
36	CSGGWGPNTGELFF

37	CAVGHFSSRSSGSARQLTF
38	CASSLKVGVDSSYNEQFF
39	CAESPSDGGKLLF
40	CASSLRQGISPEQFF
41	CAVEETSGSRLTF
42	CASSLRQGISPEQFF
43	CASSERQGITEAFF
44	CAVSGTGANSKLTf
45	CASSDPISGRGDEQFF
46	CASSFGGGAWNEQFF
47	CALRHKAAGNKLTf
48	CAALFDGGSQGNLIF
49	CSASGPEKLFF
50	CASRGLAGETQYF
51	CAVIPNSGYALNF
52	CALRGRNQGGKLIF
53	CSARLSSGGGYEQFF
54	CLVVPVYNQGGKLIF
55	CASSSGTSGMGETQYF
56	CILRDVGGSEKLVF
57	CSAKGLENQPQHF
58	CAVLKKGYALNF
59	CAVAGGYNKLIF
60	CASSLEAGDSYEQYF
61	CAVTGGYNKLIF
62	CASSLEAGDSYEQYF
63	CAGHQIQAQKLVF
64	CASSYSGMNTEAFF
65	CAGANNNARLMF
66	CSVTPGGGVNTEAFF
67	CAVSAGGTSYGKLTf
68	CASSQVLRGEQYF
69	CAVSTGGATNKLIF
70	CAVQEGETSGSRLTF
71	CASSPGFNGNTIYF
72	CALSEATYNTDKLIF
73	CASSSTGTDYGYTF
74	CAGRQTSYDKVIF
75	CATSDVTGQGEMRGYTF
76	CALSEMNRDDKIIF
77	CASSPTGVSGNTIYF
78	CAGQKQKTSGSRLTF
79	CASSSPRDRVGQPQHF
80	CAARRVDNNNDMRF
81	CASGLAQPPHF
82	CIVRVAVTNAGKSTF
83	CASRYYSADTQYF
84	CAVSGVLTGGGNKLTF
85	CASSEGTVSNQPQHF
86	CAEIGSGAGSYQLTF
87	CAENQGGSSYKLIF
88	CASSSQSGVDTEAFF
89	CAVSPPAQKLVF
90	CASQETGVGGELFF
91	CASSTTAVVSPLHF

92	CAEKKEGFKTIF
93	CASQETGVGGELFF
94	CATDEAAGNKLTf
95	CASKRESLATGELFF
96	CAAMYSGGGADGLTF
97	CASSTQGGAYEQYF
98	CAARGGSNYKLTF
99	CASSTGGEQYF
100	CATKGGNNRLAF
101	CASSAWTGETGYTF
102	CAATRAGGTSYKLTf
103	CAWSVLAGVSQYF
104	CAASIATDKLIF
105	CASSWRGQGEQYF
106	CVVTGGANNLFF
107	CASSEAGEWTQYF
108	CILVEGNEKLTF
109	CGADVQGSQGNLIF
110	CASRLGGRTTEAFF
111	CVVDFYTSQTYKYIF
112	CSARDREAAGYGYTF
113	CAGLDDKIIF
114	CAVAGSNYQLIW
115	CASSDPISGRGDEQFF
116	CVVNKATSGTYKYIF
117	CSARDREAAGYGYTF
118	CSARLAHSGTNTGELFF
119	TGTGCTCTGATTCCCACGGGAGGAGGAAACAACTCACCTTT
120	TGCAGTGCTAGATTGGCCCATAGCGGGACCAACACCGGGGAGCTGTTTTT
121	TGTGCTGTGGGTGCGTACAGCAGTGCTTCCAAGATAATCTTT
122	TGTGCCAGCAGGGACAGGGGATCTGGGGCCAACGTCCTGACTTTC
123	TGCAGTGGGGGTGGGGACCTAACACCGGGGAGCTGTTTTT
124	TGTGCTGTGGGGCACTTCTCATCTCGGTCTCTGTTCTGCAAGGCAACTGACCTTT
125	TGTGCCAGCAGTTTAAAGGTCGGTGTAGACAGCTCCTACAATGAGCAGTTCTTC
126	TGTGCAGAGAGCCCTTCAGATGGCCAGAAGCTGCTCTT
127	TGTGCCAGCAGTTTGAGACAGGGTATAAGTCCTGAGCAGTTCTTC
128	TGTGCCGTGGAAGAAACAGTGGCTCTAGGTTGACCTTT
129	TGTGCCAGCAGTTTGAGACAGGGTATAAGTCCTGAGCAGTTCTTC
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132	TGTGCCAGCAGCGACCCATTAGCGGGAGAGGGGATGAGCAGTTCTTC
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134	TGTGCTCTGAGGCACAAAGCTGCAGGCAACAAGCTAACTTTT
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136	TGCAGTGCTAGCGGCCCTGAAAACTGTTTTT
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138	TGTGCCGTGATCCCGAATTCCGGGTATGCACTCAACTTC
139	TGTGCTCTGAGGGGCCGAACAGGGAGGAAAGCTTATCTTC
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141	TGCCTCGTGGTCCCTGTTTATAACCAGGGAGGAAAGCTTATCTTC
142	TGCGCCAGCAGCTCGGGGACTAGCGGGATGGGAGAGACCCAGTACTTC
143	TGCATCCTGAGAGACGTGGGCGGATCTGAAAAGCTGGTCTTT
144	TGCAGTGCCAAAGGCCTCGAAAATCAGCCCCAGCATTTT
145	TGCGCTGTCTTAAAAAGGGGTATGCACTCAACTTC
146	TGTGCTGTGGCTGGTGGCTACAATAAGCTGATTTTT

147	TGTGCCAGCAGCTTAGAAGCGGGGGACTCCTACGAGCAGTACTTC
148	TGTGCTGTGACTGGTGGCTACAATAAGCTGATTTT
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150	TGTGCTGGGCACCAAATTCAGGGAGCCCAGAAGCTGGTATTT
151	TGTGCCAGCAGTTACTCGGGGATGAACACTGAAGCTTTCTTT
152	TGTGCTGGGGCGAATAACAATGCCAGACTCATGTTT
153	TGCAGCGTCACTCCGGGGGGCGGGGTGAACACTGAAGCTTTCTTT
154	TGTGCCGTGAGCGCTGGTGGTACTAGCTATGGAAAGCTGACATTT
155	TGTGCCAGCAGCCAAGTTCTTAGGGGTGAGCAGTACTTC
156	TGTGCTGTCAGTACTGGTGGTGTACAACAAGCTCATCTTT
157	TGTGCTGTTTCAGGAGGGAGAAACCAAGTGGCTCTAGGTTGACCTTT
158	TGTGCCAGCAGTCCAGGGTTTAAATGGAAACACCATATATTTT
159	TGTGCTCTGAGTGAGGCAACATATAACACCGACAAGCTCATCTTT
160	TGTGCCAGCAGCTCCACCGGGACGGACTATGGCTACACCTTC
161	TGTGCCGGGAGGCAAACCTCCTACGACAAGGTGATATTT
162	TGTGCCACCACTGATGTGACTGGGCAGGGCGAGATGCGTGGCTACACCTTC
163	TGTGCTCTGAGTGAGATGAACAGAGATGACAAGATCATCTTT
164	TGTGCCAGCTCACCGACAGGGTCTCTGGAACACCATATATTTT
165	TGTGCTGGGCAGCAAAAAACCAAGTGGCTCTAGGTTGACCTTT
166	TGTGCCAGTAGTTCCCCCGGGACAGGGTCGGTCAGCCCCAGCATTTT
167	TGTGCTGCCCGTCGGGTGCAACAATAACAATGACATGCGCTTT
168	TGTGCTAGTGGTTTAGCTCAGCCCCAGCATTTT
169	TGCATCGTCAGAGTCGCGGTAACCAATGCAGGCAAATCAACCTTT
170	TGTGCCAGCAGATATTATAGCGCGGATACGCAGTATTTT
171	TGTGCTGTGAGTGGGGTACTCACGGGAGGAGGAAACAACTCACCTTT
172	TGCGCCAGCAGTGAGGGGACAGTTAGCAATCAGCCCCAGCATTTT
173	TGTGCAGAGATCGGGTCTGGGGCTGGGAGTTACCAACTCACTTTC
174	TGTGCAGAGAATCAGGGAGGCAGCAGCTATAAATTGATCTTC
175	TGTGCCAGCAGCTCTCAGTCGGGTGTGGACACTGAAGCTTTCTTT
176	TGTGCTGTGAGTCCCCCGCGCAGAACTTGATTTT
177	TGTGCCAGCCAAGAGACAGGGGTTGGCGGGGAGCTGTTTTTTT
178	TGTGCCAGCAGTACGACAGCCGTGGTTTCACCCCTCCACTTT
179	TGTGCAGAGAAGAAGGAAGGCTTCAAACTATCTTT
180	TGTGCCAGCCAAGAGACAGGGGTTGGCGGGGAGCTGTTTTTTT
181	TGTGCTACGGACGAGGCTGCAGGCAACAAGCTAACTTTT
182	TGTGCCAGCAAAAGGGAATCACTAGCCACCGGGGAGCTGTTTTTTT
183	TGTGCTGCCATGTATTCAGGAGGAGGTGCTGACGGACTCACCTTT
184	TGTGCCAGCAGTACCCAGGGACAGGCCTACGAGCAGTACTTC
185	TGTGCAGCAAGAGGAGGTAGCAACTATAAACTGACATTT
186	TGTGCCAGCAGCACAGGGGGCGAGCAGTACTTC
187	TGTGCTACAAAGGGTGGGAACAACAGACTCGCTTTT
188	TGTGCCAGCAGTGCCCTGGACAGGGGAGACGGGCTACACCTTC
189	TGTGCAGCAACCCGCGCTGGTGGTACTAGCTATGGAAAGCTGACATTT
190	TGTGCCTGGAGTGTACTAGCAGGGGTTTCCAGTACTTC
191	TGTGCAGCAAGTATAGCCACCGACAAGCTCATCTTT
192	TGCGCCAGCAGCTGGAGGGGACAGGGGGAAGGCTACACCTTC
193	TGTGTGGTGACCGGGGGGGCAAACAACCTCTTCTTT
194	TGCGCCAGCAGTGAGGCTGGGGAGTGACGCAGTATTTT
195	TGCATCCTGGTAGAAGGAAATGAGAAATTAACCTTT
196	TGTGGAGCAGACGTACAAGGAAGCCAAGGAAATCTCATCTTT
197	TGTGCCAGCAGGCTGGGGGGAAGGACCACTGAAGCTTTCTTT
198	TGTGTGGTGGATTTTATACCTCAGGAACCTACAAATACATCTTT
199	TGCAGTGCTAGAGATCGGGAGGCGGCCGGCTATGGCTACACCTTC
200	TGTGCAGGGTTAGATGACAAGATCATCTTT
201	TGTGCTGTGGCGGGTAGCAACTATCAGTTAATCTGG

202	TGTGCCAGCAGCGACCCCATAGCGGGAGAGGGGATGAGCAGTTCTTC
203	TGTGTGGTGAACAAAGCCACCTCAGGAACCTACAAATACATCTTT
204	TGCAGTGCTAGAGATCGGGAGGCGGCCGGCTATGGCTACACCTTC
205	TGCAGTGCTAGATTGGCCCATAGCGGGACCAACACCGGGGAGCTGTTTTT
206	MNYSPLVSLILLLLGRTRGNSVTQMEGPVTLSEEAFLTINCTYTATGYPSLFWYVQYPGEGLQLLLKATK ADDKGSNKGFEATYRKETTSFHLEKGSVQVSDSAVYFCALIPTGGGNKLTFTGTQLKVELNIQNPDPAV YQLRD
207	MLLLLLLLGPGSGLGAVVSQHPSWWICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEGSK ATYEQGVEKDKFLINHASLTLSTLTVTSAHPEDSSFYIC SARLAHSGTNTGELFFGEGSRLTVLEDLKNVF PPEVAVFEPS
208	MLLELIPLLGIHFVLR TARASVTQPDHITVSE GASLELR CNYSYGATPYLFWYVQSPGQGLQLLLKYFSG DTLVQGIKGFEAEFKRSQSSFNLKPSVHWSDAAEYFCAVGAYSSASKIIFGSGTRLSIRPNIQNPDPNAVY QLRD
209	MDTWLVCWAIFSLKAGLTEPEVTQTPSHQVTQMGQEVILRCVPISNHLFYFYWYRQILGQKVEFLVSFYN NEISEKSEIFDDQFSVERPDGSNFTLKIRSTKLEDSAMYFCASRD RGSGANVLTFGAGSRLTVLEDLKNVF PPEVAVFEPS
210	MLLLLLLLGPGSGLGAVVSQHPSWWICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEGSK ATYEQGVEKDKFLINHASLTLSTLTVTSAHPEDSSFYICSGGWGPNTGELFFGEGSRLTVLEDLKNVFPPE VAVFEPS
211	MMKCPQALLAIFWLLLSWVSSDKVQSPSLVVEHGDVTNLNCSYEVTNFRSLLWYKQEKKAPTFLFML TSSGIEKKSGRLSSILDKKELSSILNITATQTGDSAIYLCVGHFSSRSSGSARQLTFGSGTQLTVLPDIQNP DPAVYQLRD
212	MDSWTFCCVSLCILVAKHTDAGVIQSPRHEVTMGQEVTLRCKPISGHNSLFWYRQTM MRGLELLIYFN NNVPIDDSGMPEDRFS AKMPNASFSTLKIQSEPRDSAVYFCASSLKVGVDSSYNEQFFGPGTRTLTVLE DLKNVFPPEVAVFEPS
213	MKTFAGFSFLWLQLDCMSRGEDVEQSFLSVREGDSSVINCTYTDSSSTYLWYKQEPGAGLQLLTYI FSNMDMKQDQRLTVLLNKKDKHLSLRIADTQTGDSAIYFCAESP SDGQKLLFARGTMLKVDLNIQNPDPA VYQLRD
214	MGPQLLGYVVLCLLGAGPLEAQVTQNPRLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYS MNVEVTDKGDVPEGYKVS RKEKRNFLILESPSPNQTSLYFCASSLRQGISP EQFFGPGTRTLTVLEDLKN VFPPEVAVFEPS
215	MKKLLAMILWLQLDRLSGELKVEQNPLFLSMQEGKNYTIYCNYSTTSDRLYWYRQDPGKSLESFLVLLSN GAVKQEGRLMASLDTKARLSTLHITAAVHDL SATYFCAVEETSGSRLTFGEGTQLTVNPDIQNPDPAVYQ LRD
216	MGPQLLGYVVLCLLGAGPLEAQVTQNPRLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYS MNVEVTDKGDVPEGYKVS RKEKRNFLILESPSPNQTSLYFCASSLRQGISP EQFFGPGTRTLTVLEDLKN VFPPEVAVFEPS
217	MGPQLLGYVVLCLLGAGPLEAQVTQNPRLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYS MNVEVTDKGDVPEGYKVS RKEKRNFLILESPSPNQTSLYFCASSERQGITEAFFGQGT RTLTVVEDLNKV FPPEVAVFEPS
218	MLLLLVPAFQVIFTLGGTRAQSVTQLDSQVPVFEAPVELRCNYS SVSVYLFWYVQYPNQGLQLLLKYL SGSTLVKINGFEAEFNKSQTSFHLRKPSVHISDTAEYFCAVSGTGANSKLTFGKGITLSVRPDIQNPDPA VYQLRD
219	MGTRLLFWWAFCLLGADHTGAGVSQSPSNKVTEKGDVELRCDPISGHTALYWYRQSLGQGLEFLIYFQ GNSAPDKSGLPSDRFSAERTGGSVSTLTIQRTQQEDSAVYLCASSDPISGRGDEQFFGPGTRTLTVLEDL KNVFPPEVAVFEPS
220	MGTRLLFWWAFCLLGADHTGAGVSQSPSNKVTEKGDVELRCDPISGHTALYWYRQSLGQGLEFLIYFQ GNSAPDKSGLPSDRFSAERTGGSVSTLTIQRTQQEDSAVYLCASSFGGAWNEQFFGPGTRTLTVLEDLK NVFPPEVAVFEPS
221	MNYSPLVSLILLLLGRTRGNSVTQMEGPVTLSEEAFLTINCTYTATGYPSLFWYVQYPGEGLQLLLKATK ADDKGSNKGFEATYRKETTSFHLEKGSVQVSDSAVYFCALRHKAAGNKLTFGGGTRVLVKPNIQNPDPA VYQLRD
222	MDKILGASFLVLWLQLCWVSGQKQEKSDQQQVKQSPQSLIVQKGGISIINCAYENTAFDYFPWYQQFPG KGPALLIAIRPDVSEKKEGRFTISFNKSAKQFSLHIMDSQP GDSATYFCAALFDGGSQGNLIFGKGT KLSV KPNIQNPDPNAVYQLRD

223	MLLLLLLGPGLGAVVSQHPSWWICKSGTSVKIECRSLDFQATTMFYWRQFPKQSLMLMATSNEGSK ATYEQGVEKDKFLINHASLTLSTLTVSAHPEDSSFYICSASGPEKLFSGTQLSVLEDLNKVPPEVAV FEPS
224	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGAIASLNCTYSRDRGSQSFFWYRQYSGKSPELIM FIYSNGDKEDGRFTAQLNKASQYVSLLRDSQPSDSATYLCVIPNSGYALNFGKGTSLLVTPHIQNPDP AVYQLRD
225	MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMTLQCAQDMNHEYMSWYRQDPGMGLRLIHYS VGAGITDQGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASRGLAGETQYFGPGTRLLVLEDLNKVF PPEVAVFEPS
226	MNYSPGLVSLILLLLGRTRGNSVTQMEGPVTLSEEAFLTINCTYTATGYPSLFWYVQYPGEGLQLLLKATK ADDKGSNKGFEATYRKETTSFHLEKGSVQVSDSAVYFCALGRNQGGKLIFFGQGTLSVKPNIQNPDP AVYQLRD
227	MLLLLLLGPGLGAVVSQHPSRVICKSGTSVKIECRSLDFQATTMFYWRQFPKQSLMLMATSNEGSK ATYEQGVEKDKFLINHASLTLSTLTVSAHPEDSSFYICSARLSSGGGYEQFFGPGTRTLVLEDLNKVFPP EVAVFEPS
228	MRQVARVIVFLTLSTLSLAKTTQPISMDSYEGQEVNITCSHNNIATNDYITWYQQFSPQGPRIIQQYKTKV TNEVASLFIAPDRKSSTLSLPRVSLSDTAVYYCLVVPVYNQGGKLIFFGQGTLSVKPNIQNPDP AVYQLRD
229	MGSRLLCWVLLCCLGAGPVKAGVTQTPRYLIKTRGQVTLSCSPISGHRVSWYQQTPGQGLQFLFEYF SETQRNKGNFPGRFSGRQFSNSRSEMNVTLELGDLSALYLCASSSGTSGMGETQYFGPGTRLLVLEDL KNVFPPEVAVFEPS
230	MKLVTSTVLLSLGIMGDAKTTQPNMESNEEPPVHLPCNHSTISGTDYIHWYRQLPSQGPPEYVIHGLTSN VNNRMASLAIEDRKSTLILHRATLRDAVYYCILRDVGGSEKLVFGKGTCLTVNPYIQNPDP AVYQLRD
231	MLLLLLLGPGLGAVVSQHPSWWICKSGTSVKIECRSLDFQATTMFYWRQFPKQSLMLMATSNEGSK ATYEQGVEKDKFLINHASLTLSTLTVSAHPEDSSFYICSAGLENQPHFGDGTLSILEDLNKVPPEV AVFEPS
232	MWGAFLLYVSMKMGGTAGQSLEQPSEVTAVEGAIVQINCTYQTSIFYGLSWYQQHGGAPTFLSYNAL DGLEETGRFSSFLSRSDSYGYLLQLQMKDSASYFCVAVLKKGALNFGKGTSLLVTPHIQNPDP AVYQLRD
233	MALQSTLGAVWLGLLLNSLWKVAESKDQVFQPTVASSEGAVVEIFCNHVSNSAYNFFWYLHFGPCAPR LLVKGSKPSQQGRYNMTYERFSSLLILQVREADAAVYYCAVAGGYNKLIFGAGTRLAVHPYIQNPDP AVYQLRD
234	MGTRLLCWVAFCLLVEELIEAGVVQSPRYKIEKKQPVAFWCNPISGHNTLYWYLQNLGQGPPELLIRYENE EAVDDSQLPKDRFSAERLKGVDSTLKIQAELGDSAVYLCASSLEAGDSYEQYFGPGTRTLTVTEDLKNV FPPEVAVFEPS
235	MALQSTLGAVWLGLLLNSLWKVAESKDQVFQPTVASSEGAVVEIFCNHVSNSAYNFFWYLHFGPCAPR LLVKGSKPSQQGRYNMTYERFSSLLILQVREADAAVYYCAVTGGYNKLIFGAGTRLAVHPYIQNPDP AVYQLRD
236	MGTRLLCWVAFCLLVEELIEAGVVQSPRYKIEKKQPVAFWCNPISGHNTLYWYLQNLGQGPPELLIRYENE EAVDDSQLPKDRFSAERLKGVDSTLKIQAELGDSAVYLCASSLEAGDSYEQYFGPGTRTLTVTEDLKNV FPPEVAVFEPS
237	MLLEHLLIILWMLTWVSGQQLNQSPQSMFIQEGEDVSMNCTSSSIFNTWLWYKQEPGEGPVLLIALYKA GELTSNGRLTAQFGITRKDSFLNISASIPSDVGIFYCAGHQIQAQKL VFGQGTSLTINPNIQNPDP AVYQLRD
238	MSISLLCCAAFPLLWAGPVNAGVTQTPKFRILKIGQSMTLQCTQDMNHNMYWYRQDPGMGLKLIYYSV GAGITDKGEVPNGYNVSRSTTEDFPLRLELAAPSQTSVYFCASSYSGMNTAEFFGQGTSLTVTEDLN KVPPEVAVFEPS
239	MLLEHLLIILWMLTWVSGQQLNQSPQSMFIQEGEDVSMNCTSSSIFNTWLWYKQDPGEGPVLLIALYKA GELTSNGRLTAQFGITRKDSFLNISASIPSDVGIFYCAGANNARLMFGDGTQLVVKPNIQNPDP AVYQLRD
240	MLSLLLLLLGLGSVFSAVISQKPSRDICQRGTSLTIQCQVDSQVTMMFWYRQQPGQSLTLIATANQSEA TYESGFVIDKFPISRPNLTFSTLTVSNMSPEDSSIYLCVTPGGGVNTEAFFGQGTSLTVTEDLN KVPPEVAVFEPS
241	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGAIASLNCTYSRDRGSQSFFWYRQYSGKSPELIM SIYSNGDKEDGRFTAQLNKASQYVSLLRDSQPSDSATYLCVAVSAGGTSYGLTFFGQGTSLTVHPN IQNPDP PAVYQLRD

242	MGCRLLCCVVFCLLQAGPLDTAVSQTPKYLVQTQMGNDKSIKCEQNLGHDTMYWYKQDSKKFLKIMFSYN NKELIINETVPNRFSKSPDKAHLNLHINSLELGDSSAVYFCASSQVLRGEQYFGPGTRTLTVTEDLKNVFPF EVAVFEPS
243	MVKIRQFLLAILWLQLSCVSAAKNEVEQSPQNLTAQEGEFITINCSYVSGISALHWLQQHPGGGIVSLFML SSGKKKHGRLIATINIQEKHSSLHITASHPRDSAVYICAVSTGGATNKLIFGTGLLAVQPNIQNPDPVAVYQL RD
244	MVKIRQFLLAILWLQLSCVSAAKNEVEQSPQNLTAQEGEFITINCSYVSGISALHWLQQHPGGGIVSLFML SSGKKKHGRLIATINIQEKHSSLHITASHPRDSAVYICAVQEGETSGSRLTFGEGTQLTVNPDIQNPDPVAVY QLRD
245	MSIGLLCCAALLSLLWAGPVNAGVTQTPKFQVLKTGQSMTLQCAQDMNHEYMSWYRQDPGMGLRLIHYS VGAGITDQGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASSPGFNGNTIYFEGESWLTVVEDLNK VFPPEVAVFEPS
246	MLTASLLRAVIASICVSSMAQKVTAQTEISVVEKEDVTLDVYETRDTTYLFWYKQPPSGELVFLIRR NSFDEQNEISGRYSWNFQKSTSSFNFTITASQVVDSSAVYFCALSEATYNTDKLIFGTGTRLQVFPNIQNPDP PAVYQLRD
247	MGPGLLCWALLCLLGAGSVETGVTQSPTHLIKTRGQQVTLRCSSQSGHNTVSWYQQALGQGPQFIFQY YREEENGRGNFPPRFSGLQFPNYSSSELNVNALELDDSSALYLCASSSTGTDYGYTFGSGTRTLTVVEDLNK VFPPEVAVFEPS
248	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGAIASLNCTYSRGSQSFFWYRQYSGKSPELIM FIYSNGDKEDGRFTAQLNKASQYVLLIRDSQPSDSATYLCAGRQTSYDKVIFGPGTSLSVIPNIQNPDP VAVYQLRD
249	MASLLFFCGAFYLLGTGSMADVTQTPRNRITKTGKRIMLECSQTKGHDRMYWYRQDPGLGLRLIYYSF DVKDINKGEISDGYSVSRQAQAKFSLSLSAIPNQALYFCATSDVTGQGEMRGYTFGSGTRTLTVVEDLN KVFPPEVAVFEPS
250	MLTASLLRAVIASICVSSMAQKVTAQTEISVVEKEDVTLDVYETRDTTYLFWYKQPPSGELVFLIRR NSFDEQNEISGRYSWNFQKSTSSFNFTITASQVVDSSAVYFCALSEMNRDDKIIFGKGTRLHILPNIQNPDP AVYQLRD
251	MDTRVLCCAVICLLGAGLSNAGVMQNPRLHVRRRGQEARLRCSPMKGHSHVYWYRQDPGLGLRLIYYSF LQKENIIDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAVFCASSPTGVSGNTIYFEGESWLTVVEDLN KVFPPEVAVFEPS
252	MLLEHLLIILWMLTWVSGQQLNQSPQSMFIQEGEDVSMNCTSSSIFNTWLWYKQDPGEGPVLLIALYKA GELTSNGRLTAQGITRKDSFLNISASIPSDVGIFYCAGQKTSGSRLTFGEGTQLTVNPDIQNPDPVAVYQ LRD
253	MSNQVLCCVLCFLGANTVDGGITQSPKYLFRKEGQNVTLSCQNLNHDAMYWYRQDPGQGLRLIYYS QIVNDFQKGDIAEGYSVSREKKEFPLTVTSAQNPTAFYLCASSSPRDRVGQPQHFGDGTLSILEDLN KVFPPEVAVFEPS
254	MKRILGALLGLLSAQVCCVRGIQVEQSPDLILQEGANSTLRCNFSDSVNNLQWFHQNPNWQQLINLFYIP SGTKQNGRLSATTVATERYSLYISSSQTTDSGVYFCAARRVDNNDMRFAGAGTRTLVKPNIQKPDPAV YQLRD
255	MATRLLCCVLCCLLGEELIDARVTQTPRHKVTEMGQEVMTMRCQPILGHNTVFWYRQTMQGLELLAYFR NRAPLDDSGMPKDRFSAEMPATLATLKIQPSERDSAVYFCASGLAQPHFGDGTLSILEDLNKFVFPF EVAVFEPS
256	MRLVARVTVFLTFGTIDAKTTQPPSMDCAEGRAANLPCNHSTISGNEYVYWYRQIHSQGPQYIIHGLKNN ETNEMASLIITEDRKSSTLILPHATLRDTAVYYCIVRVAVTNAGKSTFGDGTTLTVKPNIQKPDPAVYQLRD
257	MGPQLLGYVVLCLLGAGPLEAQVTQNPRLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYS MNVEVTDKGDVPEGYKVSREKERNFPLILESPSPNQTSYFCASRYYSADTYFGPGTRTLTVTEDLKNVF PPEVAVFEPS
258	MLLLLVPFQVIFTLGGTRAQSVTLQDSQVPVFEEAPVELRCNYSSSVSYLFWYVQYPNQGLQLLLKYL SGSTLVKINGFEAFNKSQTSFHLRKPSVHISDTAEYFCAVSGVLTGGGNKLTFTGTQLKVELNIQKPD PAVYQLRD
259	MGTRLFFYVALCLLWAGHRDAGITQSPRYKITETGRQVTLTMCHQTWSHSYMFYRQDLGHGLRLIYYS AADITDKGEVPDGYVVSRSKTENFPLTLESATRSQTSVYFCASSEGTVSNPQPHFGDGTLSILEDLNKF FPPEVAVFEPS
260	MAGIRALFMYLWLQLDWVSRGESVGLHPLTSLVQEGDNSIINCAYSNSASDYFIWYKQESGKGPQFIIDIR SNMDKRQGRVTVLLNKTVKHLSLQIAATQPGDSAVYFCAEIGSGAGSYQLTFGKGTKLSVIPNIQNPDP AVYQLRD

261	MAGIRALFMYLWLQLDWVSRGESVGLHLP T LSVQEGDNSIINCAYSNSASDYFIWYKQESGKGPQFIIDIR SNMDKRQGGQRVTLLNKT VKHLSLQIAATQPGDSAVYFCAENQGGSSYKLIFGSGTRLLVRPDIQNPDPA VYQLRD
262	MGTSLCCWMALC L L GADHADTGVSQNPRHKITKRGQNVTFRCDP I SEHNRLYWYRQTLGQGPEFLTYF QNEAQLEKSRLLSDRFS AERP KGSFSTLEIQRT EQGDSAMYL C ASSSQSGVDTEAFFGQGTRLT VVEDL NKVFPPEVAVFEPS
263	MLLLLVPVLEIFTLGGTRAQSVTLGSHVSVSEGALVLLRCNYSSSVPPYLFWYVQYPNQGLQLLLKYT TGATLVKGINGFEAEFKKSETSFHLTKPSAHMSDAAEYFCAVSPPAQKL VFGTGTRLLVSPNIQNPDPAV YQLRD
264	MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMTLQCAQDMNHEYMSWYRQDPGMGLRLIHYS VGAGITDQGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASQETGVGGELFFGEGSRLTVLEDLKN VFPPEVAVFEPS
265	MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMTLQCAQDMNHEYMSWYRQDPGMGLRLIHYS VGAGITDQGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASSTTAVVSP L HFGNGTRLT VTEDLKNV FPPEVAVFEPS
266	MKTFAGFSFLWLQLDCMSRGEDVEQSLFLSVREGDSSVINCTYTDSSSTYLWYKQEPGAGLQLLTYI FSNMDMKQDQRLTVLLNKKDKHLSLRIADTQTGDSAIYFCAEKGFKTIFGAGTRLFVKANIQNPDPAVY QLRD
267	MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMTLQCAQDMNHEYMSWYRQDPGMGLRLIHYS VGAGITDQGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASQETGVGGELFFGEGSRLTVLEDLKN VFPPEVAVFEPS
268	METLLGVSLVILWLQLARVNSQQGEEDPQALSIQEGENATMNC SYKTSINN LQWYRQNSGRGLVHLILIR SNEREKHSGRLRVTLDTSKKSSLLITASRAADTASYFCATDEAAGNKLTFGGGTRVLVKPNIQNPDPAV YQLRD
269	MDTWLVCWAIFSL L KAGLTEPEVTQTPSHQVTQMGEVILRCVPISNHLFYWYRQILGQKVEFLVSFYN NEISEKSEIFDDQFSVERPDGSNFTLKIRSTKLEDSAMYFCASKRESLATGELFFGEGSRLTVLEDLKNVF PPEVAVFEPS
270	METLLGVSLVILWLQLARVNSQQGEEDPQALSIQEGENATMNC SYKTSINN LQWYRQNSGRGLVHLILIR SNEREKHSGRLRVTLDTSKKSSLLITASRAADTASYFCAAMYSGGGADGLTFGKGTHLIIPYIQNPDPA VYQLRD
271	MDTWLVCWAIFSL L KAGLTEPEVTQTPSHQVTQMGEVILRCVPISNHLFYWYRQILGQKVEFLVSFYN NEISEKSEIFDDQFSVERPDGSNFTLKIRSTKLEDSAMYFCASSTQGQAYEQYFGPGTRLT VTEDLKNVF PPEVAVFEPS
272	MTSIRAVFIFLWLQLDLVNGENVEQHPSTLSVQEGDSAVIKCTYSDSASNYFPWYKQELGKRPLIIDIRS NVGEKKDQRIAVTLNKTAKHFS LHITETQPEDSAVYFCAARGGSNYKLTFGKGTLTVNPNIQNPDP PAVY QLRD
273	MGSWTLCCVSLC I L VAKHTDAGVIQSPRHEVTEMGQEVTLRCKPISGHDYLFWYRQTM MRGLLIYFN NNVPIDDSGMPEDRFS AKMPNASFSTLKIQ PSEPRDSAVYFCASSTGGEQYFGPGTRLT VTEDLKNVFP PEVAVFEPS
274	METLLGVSLVILWLQLARVNSQQGEEDPQALSIQEGENATMNC SYKTSINN LQWYRQNSGRGLVHLILIR SNEREKHSGRLRVTLDTSKKSSLLITASRAADTASYFCATKGNNRLAFGKGNQVVIPNIQNPDPAVY QLRD
275	MDTWLVCWAIFSL L KAGLTEPEVTQTPSHQVTQMGEVILRCVPISNHLFYWYRQILGQKVEFLVSFYN NEISEKSEIFDDQFSVERPDGSNFTLKIRSTKLEDSAMYFCASSAWTGETGYTFGSGTRLT VVEDLKNVF PPEVAVFEPS
276	MAMLLGASVLILWLQPDWVNSQQKNDDQVQKQNSPSLSVQEGRISILNCDYTN SMFDYFLWYKYPAE GPTFLISSIKDKNEDGRFTVFLNKS AKHLSLHIVPSQPGDSAVYFCAATRAGGTSY GKLTFGQG TILTVH PNIQNPDPAVYQLRD
277	MLCSLLALLGTFFGVRSQTIHQWPATLVQPVGSPLSLECTVEGTSNP NLYWYRQAAGRGLQLLFYSVGI GQISSEVPQNLSASRPQDRQFILSSKLLLSDSGFYLCAWSVLAGVSQYFGPGTRLLVLEDLKNVFPPEV AVFEPS
278	MTSIRAVFIFLWLQLDLVNGENVEQHPSTLSVQEGDSAVIKCTYSDSASNYFPWYKQELGKRPLIIDIRS NVGEKKDQRIAVTLNKTAKHFS LHITETQPEDSAVYFCAASIATDKLIFGTGTRLQVFPNIQNPDPAVYQLR D

279	MGSRLLCWVLLCCLLGAGPVKAGVTQTPRYLIKTRGQQVTLSCSPISGHRVSVWYQQTPGQGLQFLFEYF SETQRNKGNFGRFSGRQFSNSRSEMNVTLELGDLSALYLCASSWRGQGEYTFGSGTRLTVVEDLNK VFPPEVAVFEPS
280	MKKHLTTFLVILWLYFYRGNGKNQVEQSPQSLILEGKNCTLCQNYTVSPFSNLRWYKQDTGRGPVSLTI MTFSEKTSNGRYTATLDADTKQSSLHITASQLSDSASYICVVTGGANNLFFGTGTRLTVIPYIQNPDP AVYQLRD
281	MGSRLLCWVLLCCLLGAGPVKAGVTQTPRYLIKTRGQQVTLSCSPISGHRVSVWYQQTPGQGLQFLFEYF SETQRNKGNFGRFSGRQFSNSRSEMNVTLELGDLSALYLCASSEAGEWTQYFGPGTRLTVLEDLKNV FPPEVAVFEPS
282	MKLVTSITVLLSLGIMGDAKTTQPNMESNEEPPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSN VNNRMASLAIAEDRKSSTLILHRATLRDAAVYICILVEGNEKLTFTGTGTRLTIIPNIQNPDP AVYQLRD
283	METVLQVLLGILGFQAAWVSSQEQSPQSLIVQEGKNLTINCTSSKTLYGLYWYKQYGEGLIFLMMMLQ KGGEKESHEKITAKLDEKKQSSLHITASQPSHAGIYLCGADVQGSQGNLIFGKGTKLSVKPNIQNPDP AVYQLRD
284	MDTWLVCWAIFSLKAGLTEPEVTQTPSHQVTQMGEVILRCVPISNHLFYWYRQILGQKVEFLVSFYN NEISEKSEIFDDQFSVERPDGSNFTLKIRSTKLEDSAMYFCASRLGGRTEAFFGQGTGTRLTVEDLNK VFPPEVAVFEPS
285	MISLRVLLVILWLQLSWVWSQRKEVEQDPGPFNVPEGATVAFNCTYSNSASQSFFWYRQDCRKEPKLL MSVYSSGNEDGRFTAQLNRASQYISLLIRDSKLSDSATYLCVVDFTSGTYKYIFGTGTRLKVL ANIQNPDP AVYQLRD
286	MLLLLLLLGPGSGLGAVVSQHPRSVICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEGSK ATYEQGVEKDKFLINHASLTLSTLTVSAHPEDSSFYICSARDREAAGYGYTFGSGTRLTVEDLNK VFPPEVAVFEPS
287	MVLKFSVSILWIQLAWVSTQLLEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVT VVTGGEVKKLKRFTQFGDARKDSSLHITAAQPGDGLYLACAGLDDKIIIFGKGTRLHILPNIQNPDP AVYQLRD
288	MKRILGALLGLLSAQVCCVRGIQVEQSPDILIQEGANSTLRNCFSDSVNNLQWFHQNPNWGQLINL FYIPSGTKQNGRLSATTVATERYSLLYISSSQTTDSGVYFCAVAGSNYQLIWGAGTKLIIPDIQNPDP AVYQLRD
289	MGTRLLCWAALCCLLGAELTEAGVAQSPRYKIEKRQSVAFWCNPISGHATLYWYQQILGQGP KLLIQFQNGVVDSSQLPKDRFSAERLKGVDSTLKIQPAKLEDSAVYLCASSDPISGRGDEQFFGPG TRLTVLEDLKNVFPPEVAVFEPS
290	MISLRVLLVILWLQLSWVWSQRKEVEQDPGPFNVPEGATVAFNCTYSNSASQSFFWYRQDCRKEPKLL MSVYSSGNEDGRFTAQLNRASQYISLLIRDSKLSDSATYLCVNVKATSGTYKYIFGTGTRLKVL ANIQNPDP AVYQLRD
291	MLLLLLLLGPGSGLGAVVSQHPSWVICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEGSK ATYEQGVEKDKFLINHASLTLSTLTVSAHPEDSSFYICSARDREAAGYGYTFGSGTRLTVEDLNK VFPPEVAVFEPS
292	MLLLLLLLGPGSGLGAVVSQHPSWVICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEGSK ATYEQGVEKDKFLINHASLTLSTLTVSAHPEDSSFYICSAHLAHSNTGELFFGEGSRLTVLEDLKNV FPPEVAVFEPS
293	GACTGTGATTTCTTCATGTTAAGGATCAAGACCATTATTTGGGTAACACACTAAAGATGA ACTATTCTCAGGCTTAGTATCTCTGATACTCTTACTGCTTGAAGAACCCGTGGAATT CAGTGACCCAGATGGAAGGCCAGTGACTCTCTCAGAAGAGGCCTTCTGACTATAAACTGCACGTACACAGCCACAGGATA CCCTTCCCTTTCTGGTATGTCCAATATCCTGGAGAAGGTCTACAGCTCCTCCTGAAAGCCACGAAG GCTGATGACAAGGGAAGCAACAAAGGTTTTGAAGCCACATACCGTAAAGAAACCACTTCTTTCCACT TGGAGAAAGGCTCAGTTCAAGTGTGACTCAGCTCAGCGGTGACTTCTGTGCTCTGATTCCACGGGAG GAGGAAACAACTCACCTTTGGGACAGGCACTCAGCTAAAAGTGGAACCTCAATATCCAGAACCCTGA CCCTGCCGTGTACCAGCTGAGAGACT
294	GTCATCCCTCCTCGCTGGTGAATGGAGGCACTGGTCACAACTCTCCCCAGAGAAGGTGGTGTGAGG CCATCACGGAAGATGCTGCTGCTTCTGCTGCTTCTGGGGCCAGGCTCCGGGCTTGGTGTGCTGCTC TCTCAACATCCGAGCTGGGTATCTGTAAGAGTGGAACCTCTGTGAAGATCGAGTGCCGTTCCCTGG ACTTTTCAAGGCCACAACATATGTTTTGGTATCGTCAGTTCCCGAAACAGAGTCTCATGCTGATGGCACT TCCAATGAGGGCTCCAAGGCCACATACGAGCAAGCGCTCGAGAAGGACAAGTTTCTCATCAACCAT GCAAGCCTGACCTTGTCCACTCTGACAGTGACCACTGCCCCATCCTGAAGACAGCAGCTTCTACATCT GCAGTGCTAGATTGGCCCATAGCGGGACCAACACCGGGGAGCTGTTTTTGGAGAAGGCTCTAGGC TGACCGTACTGGAGGACCTGAAAAACGTGTTCCACCCGAGGTGCTGTGTTTGAAGCCATCAGA

295	GGTTTTGATACATCTCAGAAATTAGGAGAAACACACTAATGAGCTCTCTCTGCTAAACTGGTTCTGCA CTTGGCCTCCAGAGGGCGATGCTGCACACACTGGAGCTTTTGTCTGTTGAAGATCAATCCACTGC TCAGTTTCTTCTCCTGCAGCTGGTTGAGTTCTTTCCAGACAAAGACAAGTGACAAGAATTAGAGGTT TAAAAAGCAACCAGATTTCATCTCAGCAGCTTTTGTAGTTTTAAATAAGCAAGGAGTTTCTCCAGCGAA ACTTCCTCACACCTCTTGGTCTTGGTCTCTTCAGACACTTTCTTCCTGTTCTCTGGAGATCTTGCAG AAAAGAGCCTGCAGTGTTCCTTGTTCAGCCATGCTCCTGGAGCTTATCCCACTGCTGGGGATACA TTTTGTCTGAGAACTGCCAGAGCCAGTCAGTGACCCAGCCTGACATCCACATCACTGTCTCTGAA GGAGCCTCACTGGAGTTGAGATGTAATATTCTATGGGGCAACACCTTATCTCTCTGGTATGTCC AGTCCCCCGGCCAAGGCCTCCAGCTGCTCCTGAAGTACTTTTCAGGAGACACTCTGGTTCAAGGCA TTAAAGGCTTTGAGGCTGAATTTAAGAGGAGTCAATCTTCCTTCAATCTGAGGAAACCCTCTGTGCAT TGGAGTGATGCTGCTGAGTACTTCTGTCTGTGGGTGCGTACAGCAGTGCTTCCAAGATAATCTTTG GATCAGGGACCAGACTCAGCATCCGGCCAAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGA GAGACT
296	AAAATGCCCTCTTTCTCCACAGGACCAGATGCCTGAGCTAGGAAAGGCCTCATTCTGCTGTGA TCCTGCCATGGATACCTGGCTCGTATGCTGGGCAATTTTAGTCTCTTGAAGCAGGACTCACAGAA CCTGAAGTCACCCAGACTCCAGCCATCAGGTCACACAGATGGGACAGGAAGTGATCTTGCCTGT GTCCCCATCTCTAATCACTTATACTTCTATTGGTACAGACAAATCTTGGGGCAGAAAGTCGAGTTCT GGTTTCTTTTATAATAATGAAATCTCAGAGAAGTCTGAAATATTGATGATCAATTCTCAGTTGAAAG GCCTGATGGATCAAATTTCACTCTGAAGATCCGGTCCACAAAGCTGGAGGACTCAGCCATGTACTTC TGTGCCAGCAGGGACAGGGGATCTGGGGCCAACGTCCTGACTTTTCGGGGCCGGCAGCAGGCTGAC CGTGCTGGAGGACCTGAAAACGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
297	GTCATCCCTCCTCGCTGGTGAATGGAGGCAAGTGGTCACAACCTCTCCCCAGAGAAGGTGGTGTGAGG CCATCACGGAAGATGCTGCTGCTTCTGCTGCTTCTGGGGCCAGGCTCCGGGCTTGGTGTGCTGCTG TCTCAACATCCGAGCTGGGTATCTGTAAGAGTGGAACCTCTGTGAAGATCGAGTGCCGTTCCCTGG ACTTTACGGCCACAAGTATGTTTGGTATCGTCAGTTCCCGAAACAGAGTCTCACTGAGGCACT TCCAATGAGGGCTCCAAGGCCACATACGAGCAAGGCGTCGAGAAGGACAAGTTTCTCATCAACCAT GCAAGCCTGACCTTGTCCACTCTGACAGTGACCACTGCCCCATCCTGAAGACAGCAGCTTCTACATCT GCACTGGGGGGTGGGGACCTAACACCGGGGAGCTGTTTTTGGAGAAGGCTCTAGGCTGACCGTA CTGGAGGACCTGAAAACGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
298	GGTTGGCTGAATTGCCAAATTGCTATTTCCCTTTTTCTGAGTGTGTGTCTGTGTCCGTGTGTGTGCAT GTGTGTGTGCACGCACGCGCACAGGCAGACGCTAGGGGTAGAGTGTGATGGTTCAAAAAGAAAA GGAAACGCTTAAAGGGAGTGAATCACGTTTTTGCCAGGAAAAACACACTTGATACTGAAGGATGATG AAGTGTCACAGGCTTTACTAGCTATCTTTTGGCTTCTACTGAGCTGGGTGAGCAGTGAAGACAAGG TGGTACAAAGCCCTCTATCTCTGTTGTCCACGAGGGAGACACCGTAACTCTCAATTGCAGTTATGA AGTGACTAACTTTCGAAGCCTACTATGGTACAAGCAGGAAAAGAAAGCTCCACATTTCTATTTATGC TAACTTCAAGTGGAATTGAAAAGAAGTCAGGAAGACTAAGTAGCATATTAGATAAGAAAGAACTTCC AGCATCTGAACATCACAGCCACCCAGACCGGAGACTCGGCCATCTACCTCTGTGCTGTGGGGCAC TTCTCATCTCGGTCTCTGTTCTGCAAGGCAACTGACCTTTTGATCTGGGACACAATTGACTGTTTT ACCTGATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
299	ATGCTCACAGAGGGCCTGGTCTAGAATATTCCACATCTGCTCTCACTCTGCCATGGACTCCTGGACC TTCTGCTGTGTGTCCCTTTGCATCCTGGTAGCGAAGCATACAGATGCTGGAGTTATCCAGTCACCCC GCCATGAGGTGACAGAGATGGGACAAGAAGTGACTCTGAGATGTAAACCAATTTAGGGCCACAAC CCCTTTTCTGGTACAGACAGACCATGATGCGGGGACTGGAGTTGCTCATTACTTTAACAACAACGT TCCGATAGATGATTCAGGGATGCCCGAGGATCGATTCTCAGCTAAGATGCCTAATGCATCAATTCTCC ACTCTGAAGATCCAGCCCTCAGAACCCAGGGACTCAGCTGTGTACTTCTGTGCCAGCAGTTTAAAGG TCGGTGTAGACAGCTCCTACAATGAGCAGTTCTTCGGGCCAGGGACACGGCTCACCGTGCTAGAGG ACCTGAAAACGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
300	GGCCACAAGGTGGCAGAGCTTCTCTGCTCATGTAGAATGTACGAAAGGATCCTTTTGGTTGACTTCT GTGAGTAGGCTGACGACAGAAGCAGATGCCCTCTGTGGACAGTTTAAAGAAACCACAGTGCTTTGGAG GAAAGGAAGAGATACTTGATAATATAGCTCTCTTGGCTGGAGATTGCAGGTCCCAGTGGGGAGAAC ATGAAGACATTTGCTGGATTTTCGTTCTGTTTGTGGCTGCAGCTGGACTGTATGAGTAGAGGAG AGGATGTGGAGCAGAGTCTTTTCTGAGTGTCGAGAGGGAGACAGCTCCGTTATAAACTGCATTA CACAGACAGCTCCTCCACCTACTTATACTGGTATAAGCAAGAACCTGGAGCAGGTCTCCAGTTGCTG ACGTATATTTTTCAAATATGGACATGAAACAAGACCAAAGACTCACTGTTCTATTGAATAAAAGGAT AAACATCTGTCTCTGCGCATTGCAGACACCCAGACTGGGGACTCAGCTATCTACTTCTGTGCAGAGA GCCCTTCAGATGGCCAGAAGCTGCTCTTTGCAAGGGGAACCATGTAAAGGTGGATCTTAATATCCA GAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT

301	ACCTGGAGCCCCAGAACTGGCAGACACCTGCCTGATGCTGCCATGGGCCCCAGCTCCTTGGCTA TGTGGTCCTTTGCCCTTCTAGGAGCAGGCCCCCTGGAAGCCCCAAGTGACCCAGAACCCAAGATACCT CATCACAGTGACTGGAAAGAAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGCCT GGTATCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTTGAGGTGACTGA TAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAAGAGAAGAGGAATTTCCCCCTGATCCTG GAGTCGCCCCAGCCCCAACCCAGACCTCTCTGTACTTCTGTGCCAGCAGTTTGAGACAGGGTATAAGT CCTGAGCAGTTCTCGGGCCAGGGACACGGCTCACCGTGCTAGAGGACCTGAAAAACGTGTTCCCA CCCGAGGTCGCTGTGTTTGAGCCATCAGA
302	GGAAATCGTGTTTCTGTAGAGAAAGAAAACTACCATATTTGGATAGCCCTGGCCAACTTTCAAGGCT CCTAAATCTGAGTTTTAGTGAACTGGACAGAAAAAAAATGAAGAAGCTACTAGCAATGATTCTGT GGCTTCACTAGACCGTTAAGTGAGAGCTGAAAGTGGAACAAAACCTCTGTTCTGAGCATGCA GGAGGGAAAACTATACCATCTACTGCAATTATCAACCACTTCAGACAGACTGATTGGTACAGGC AGGATCCTGGGAAAAAGTCTGGAATCTCTGTTTGTGTTGCTATCAAATGGAGCAGTGAAACAGGAGG GACGATTAATGGCCTCACTTGATACCAAAGCCCGTCTCAGCACCCCTCCACATCACAGCTGCCGTGCA TGACCTCTCTGCCACCTACTTCTGTGCCGTGGAAGAAACCAAGTGCGCTCTAGGTTGACCTTTGGGGAA GGAACACAGCTCACAGTGAATCCTGATATCCAGAACCCCTGACCCTGCCGTGTACCAGCTGAGAGAC T
303	ACCTGGAGCCCCAGAACTGGCAGACACCTGCCTGATGCTGCCATGGGCCCCAGCTCCTTGGCTA TGTGGTCCTTTGCCCTTCTAGGAGCAGGCCCCCTGGAAGCCCCAAGTGACCCAGAACCCAAGATACCT CATCACAGTGACTGGAAAGAAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGCCT GGTATCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTTGAGGTGACTGA TAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAAGAGAAGAGGAATTTCCCCCTGATCCTG GAGTCGCCCCAGCCCCAACCCAGACCTCTCTGTACTTCTGTGCCAGCAGTTTGAGACAGGGTATAAGT CCTGAGCAGTTCTCGGGCCAGGGACACGGCTCACCGTGCTAGAGGACCTGAAAAACGTGTTCCCA CCCGAGGTCGCTGTGTTTGAGCCATCAGA
304	ACCTGGAGCCCCAGAACTGGCAGACACCTGCCTGATGCTGCCATGGGCCCCAGCTCCTTGGCTA TGTGGTCCTTTGCCCTTCTAGGAGCAGGCCCCCTGGAAGCCCCAAGTGACCCAGAACCCAAGATACCT CATCACAGTGACTGGAAAGAAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGCCT GGTATCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTTGAGGTGACTGA TAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAAGAGAAGAGGAATTTCCCCCTGATCCTG GAGTCGCCCCAGCCCCAACCCAGACCTCTCTGTACTTCTGTGCCAGCAGTGAGCGACAGGGGATAACT GAAGCTTTCTTTGGACAAGGCACCCAGACTCACAGTTGTAGAGGACCTGAACAAGGTGTTCCACCC GAGGTCGCTGTGTTTGAGCCATCAGA
305	GTAGCTCGTTGATATCTGTGTGGATAGGGAGCTGTGACGAGAGCAAGAGGTGAGAACATCCAGG CTCCTTAAGGGAAAGCCTCTTTCTGTTTCTGAAACTTTTCAAAGCCAGGGACTTGTCCAATCCAACCT CCTCACAGTTTCTAGCTCCTGAGGCTCAGCGCCCTTGCTTCTGTCCGCCAGCTCAAGGTCTCTGC AGCATTGCCACTGCTCAGCCATGCTCCTGCTGCTCGTCCAGCGTTCCAGGTGATTTTTACCCTGGG AGGAACCAGAGCCCAGTCTGTGACCCAGCTTGACAGCCAAGTCCCTGTCTTTGAAGAAGCCCCGTG GGAGCTGAGGTGCAACTACTCATCGTCTGTTTCAGTGATCTCTTCTGGTATGTGCAATACCCCAAC CAAGGACTCCAGCTTCTCCTGAAGTATTTATCAGGATCCACCCTGGTTAAAGGCATCAACGGTTTTG AGGCTGAATTTAACAAGAGTCAAACCTTCCACTTGAGGAAACCCCTAGTCCATATAAGCGACAC GGCTGAGTACTTCTGTGCTGTGAGTGGTACTGGAGCCAATAGTAAGCTGACATTTGAAAAGGAATA ACTCTGAGTGTTAGACCAGATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
306	ACAGTGATCCTGATCTGGTAAAGCTCCCATCCTGCCCTGACCCTGCCATGGGCACCAAGGCTCCTCTT CTGGGTGGCCTTCTGTCTCCTGGGGGCAGATCACACAGGAGCTGGAGTCTCCCAAGTCCCCCAGTAA CAAGGTCACAGAGAAGGGAAAGGATGTAGAGCTCAGGTGTGATCCAATTTCAAGTCCATACTGCCCTT TACTGGTACCGACAGAGCCTGGGGCAGGGCCTGGAGTTTTTAATTTACTTCCAAGGCAACAGTGCA CCAGACAAATCAGGGCTGCCAGTGATCGCTTCTCTGCAGAGAGGACTGGGGGATCCGTCTCCACT CTGACGATCCAGCGCACACAGCAGGAGGACTCGGCCGTGTATCTCTGTGCCAGCAGCGACCCATT AGCGGGAGAGGGGATGAGCAGTTCTTCGGGCCAGGGACACGGCTCACCGTGCTAGAGGACCTGAA AAACGTGTTCCCAACCCAGGTCGCTGTGTTTGAGCCATCAGA
307	ACAGTGATCCTGATCTGGTAAAGCTCCCATCCTGCCCTGACCCTGCCATGGGCACCAAGGCTCCTCTT CTGGGTGGCCTTCTGTCTCCTGGGGGCAGATCACACAGGAGCTGGAGTCTCCCAAGTCCCCCAGTAA CAAGGTCACAGAGAAGGGAAAGGATGTAGAGCTCAGGTGTGATCCAATTTCAAGTCCATACTGCCCTT TACTGGTACCGACAGAGCCTGGGGCAGGGCCTGGAGTTTTTAATTTACTTCCAAGGCAACAGTGCA CCAGACAAATCAGGGCTGCCAGTGATCGCTTCTCTGCAGAGAGGACTGGGGGATCCGTCTCCACT CTGACGATCCAGCGCACACAGCAGGAGGACTCGGCCGTGTATCTCTGTGCCAGCAGCGACCCATT

	GGGGGCGTGGAATGAGCAGTTCTTCGGGCCAGGGACACGGCTCACCGTGCTAGAGGACCTGAAAA ACGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
308	GACTGTGATTTCTTCATGTTAAGGATCAAGACCATTATTTGGGTAACACACTAAAGATGAACTATTCTC CAGGCTTAGTATCTCTGATACTCTTACTGCTTGAAGAACCCTGGAAATTAGTGACCCAGATGGA AGGGCCAGTGACTCTCTCAGAAGAGGCCTTCCTGACTATAAACTGCACGTACACAGCCACAGGATA CCCTTCCCTTTTCTGGTATGTCCAATATCCTGGAGAAGGTCTACAGCTCCTCTGAAAGCCACGAAG GCTGATGACAAGGGAAGCAACAAAGGTTTTGAAGCCACATACCGTAAAGAAACCACTCTTTTCCACT TGGAGAAAGGCTCAGTTCAAGTGTGAGACTCAGCGGTGTACTTCTGTGCTCTGAGGCACAAAGCTG CAGGCAACAAGCTAACTTTTGGAGGAGGAACCAGGGTGCTAGTTAAACCAAATATCCAGAACCCTGA CCCTGCCGTGTACCAGCTGAGAGACT
309	CTGGAAGACCACCTGGGCTGTCATTGAGCTCTGGTGCCAGGAGGAATGGACAAGATCTTAGGAGCA TCATTTTTAGTTCTGTGGCTTCAACTATGCTGGGTGAGTGGCCAACAGAAAGGAAAAAGTGACCAGC AGCAGGTGAAACAAAGTCTCAATCTTTGATAGTCCAGAAAGGAGGATTTCAATTATAAACTGTGCT TATGAGAACTGCGTTTGACTACTTTCCATGGTACCAACAATTCCCTGGGAAAGGCCCTGCATTATT GATAGCCATACGTCCAGATGTGAGTGAAGAAAGAAAGGAAGATTACAATCTCCTTCAATAAAAGT GCCAAGCAGTTCTCATTGCATATCATGATTCCAGCCTGGAGACTCAGCCACCTACTTCTGTGCAG CGCTATTTGATGGAGGAAGCCAAGGAAATCTCATCTTTGGAAGGCACTAACTCTCTGTAAACCA AATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
310	GTCATCCCTCCTCGCTGGTGAATGGAGGCAGTGGTCACAACTCTCCCAGAGAAGGTGGTGTGAGG CCATCACGGAAGATGCTGCTGCTTCTGCTGCTTCTGGGGCCAGGCTCCGGGCTTGGTGCTGTCGTC TCTCAACATCCGAGCTGGGTATCTGTAAGAGTGGAACCTCTGTGAAGATCGAGTGCCGTTCCCTGG ACTTTCAGGCCACAACATATGTTTTGGTATCGTCAGTTCGGAACAGAGTCTCATGCTGATGGCAACT TCCAATGAGGGCTCCAAGGCCACATACGAGCAAGGCGTCGAGAAGGACAAGTTTCTCATCAACCAT GCAAGCCTGACCTTGTCCACTCTGACAGTGACCAGTGCCCATCCTGAAGACAGCAGCTTCTACATCT GCAGTGCTAGCGGCCCTGAAAACTGTTTTTGGCAGTGGAACCCAGCTCTCTGTCTTGAGGACCT GAACAAGGTGTTCCACCCGAGGTGCTGTGTTTGAGCCATCAGA
311	AAAGCAGATTCTTTTTATGATTTTTAAAGTAGAAATATCCATTCTAGGTGCATTTTTAAAGGTTTAAAA TTTGAATCCTCAGTGAACCAGGGCAGAGAAGAATGATGAAATCCTTGAGAGTTTTACTAGTGATCCT GTGGCTTCAGTTGAGCTGGGTTTGAGCCAACAGAAAGGAGGTGGAGCAGAATTCTGGACCCCTCAG TGTTCCAGAGGGAGCCATTGCCTCTCTCAACTGCACCTACAGTGACCGAGGTTCCAGTCCCTTCTTC TGGTACAGACAATATTCTGGGAAAAGCCCTGAGTTGATAATGTTTCATATACTCCAATGGTGACAAAGA AGATGGAAGGTTTACAGCACAGCTCAATAAAGCCAGCCAGTATGTTTCTGCTCATCAGAGACTCC CAGCCCAGTGATTAGCCACCTACCTCTGTGCCGTGATCCCGAATTCGGGTATGCACTCAACTTCG GCAAAGGCACCTCGCTGTTGGTCACACCCCATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGA GAGACT
312	GAGAGTCCTGCTCCCCTTTCATCAATGCACAGATACAGAAGACCCCTCCGTCATGCAGCATCTGCCA TGAGCATCGGCCTCCTGTGCTGTGCAGCCTTGTCTCTCCTGTGGGCAGGTCCAGTGAATGCTGGTG TCACTCAGACCCCAAAATCCAGGTCTGAAGACAGGACAGAGCATGACATGCAGTGTGCCCATG ATATGAACCATGAATACATGTCCTGGTATCGACAAGACCCAGGCATGGGGCTGAGGCTGATTCATTA CTCAGTTGGTGCTGGTATCACTGACCAAGGAGAAGTCCCCAATGGCTACAATGTCTCCAGATCAACC ACAGAGGATTTCCGCTCAGGCTGCTGTGGCTGCTCCCTCCAGACATCTGTGTACTTCTGTGCCA GCAGGGGACTAGCGGGAGAGACCCAGTACTTCGGGCCAGGCACGCGGCTCCTGGTGCTCGAGGA CCTGAAAAACGTGTTCCACCCGAGGTGCTGTGTTTGAGCCATCAGA
313	GACTGTGATTTCTTCATGTTAAGGATCAAGACCATTATTTGGGTAACACACTAAAGATGAACTATTCTC CAGGCTTAGTATCTCTGATACTCTTACTGCTTGGAGAACCCTGGAAATTCAGTGACCCAGATGGA AGGGCCAGTGACTCTCTCAGAAGAGGCCTTCCTGACTATAAACTGCACGTACACAGCCACAGGATA CCCTTCCCTTTTCTGGTATGTCCAATATCCTGGAGAAGGTCTACAGCTCCTCTGAAAGCCACGAAG GCTGATGACAAGGGAAGCAACAAAGGTTTTGAAGCCACATACCGTAAAGAAACCACTCTTTTCCACT TGGAGAAAGGCTCAGTTCAAGTGTGAGACTCAGCGGTGTACTTCTGTGCTCTGAGGGGCCGGAACC AGGGAGGAAAGCTTATCTTCGACAGGGAACCGAGTTATCTGTGAAACCAATATCCAGAACCCTGA CCCTGCCGTGTACCAGCTGAGAGACT
314	GTCATCCCTCCTCGCTGGTGAATGGAGGCAGTGGTCACAACTCTCCCAGAGAAGGTGGTGTGAGG CCATCACGGAAGATGCTGCTGCTTCTGCTGCTTCTGGGGCCAGGCTCCGGGCTTGGTGCTGTCGTC TCTCAACATCCGAGCAGGGTTATCTGTAAGAGTGGAACCTCTGTGAAGATCGAGTGCCGTTCCCTGG ACTTTCAGGCCACAACATATGTTTTGGTATCGTCAGTTCGGAACAGAGTCTCATGCTGATGGCAACT TCCAATGAGGGCTCCAAGGCCACATACGAGCAAGGCGTCGAGAAGGACAAGTTTCTCATCAACCAT GCAAGCCTGACCTTGTCCACTCTGACAGTGACCAGTGCCCATCCTGAAGACAGCAGCTTCTACATCT

	GCAGTGCTAGACTTTCTAGCGGGGGGGCTATGAGCAGTTCTTCGGGCCAGGGACACGGCTCACC GTGCTAGAGGACCTGAAAAACGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
315	CTGGGCTCATTGCAGCTCAGACACAGCAAAAGAGCCTAGAACCTGGGTCTAGTTTGACCTAGAAT ATGAGGCAAGTGGCGAGAGTGATCGTGTTCTGACCTGAGTACTTTGAGCCTTGCTAAGACCACC CAGCCCATCTCCATGGACTCATATGAAGGACAAGAAGTGAACATAACCTGTAGCCACAACAACATTG CTCAAAATGATTATATCAGGTGGTACCAACAGTTTCCAGCCAAGGACCAGATTATTATTCAAGGA TACAAGACAAAAGTTACAAACGAAGTGGCCTCCCTGTTTATCCCTGCCGACAGAAAGTCCAGCACTC TGAGCCTGCCCCGGGTTTCCCTGAGCGACACTGCTGTGTAATACTGCTCGTGGTCCCTGTTTATAA CCAGGGAGGAAAGCTTATCTTCGGACAGGGAACGGAGTTATCTGTGAAACCAATATCCAGAACCCT GACCCTGCCGTGTACCAGCTGAGAGACT
316	AGAGGACCAGTATCCCTCACAGGGTGACACCTGACCAGCTCTGTCCACCTGGCCATGGGCTCCAG GTACCTCTGATGGGAAGACCTTTGTCTCTTGGGAACAAGTGAATCCTTGGCACAGGCCAGTGGATT CTGCTGTGCAGAACAGAGAGAGCAGTGGACCTCAGGAGGCCGTGCAAGGGGAGGACATAGGACAGTGA CATCACAGTATGCCCTCCCACCAGGAAAAGCAAGGCTGAGAATTTAGCTCTTCCCAGGAGGACCA AGCCCTGAGCACAGACACAGTGTGCTGCCCTTTGTGCCATGGGCTCCAGGCTGCTCTGTTGGG TGCTGCTTTGTCTCCTGGGAGCAGGCCAGTAAAGGCTGGAGTCACTCAAACCTCAAGATATCTGAT CAAAACGAGAGGACAGCAAGTGACACTGAGCTGCTCCCTATCTCTGGGCATAGGAGTGTATCCTG GTACCAACAGACCCAGGACAGGGCCTTCAGTTCCCTTTGAATACTTCAGTGAGACACAGAGAAAC AAAGGAAAACCTCCCTGGTTCGATTCTCAGGGCGCCAGTTCTCTAACTCTCGCTCTGAGATGAATGTGA GCACCTTGAGCTGGGGGACTCGGCCCTTTATCTTTGCGCCAGCAGCTCGGGGACTAGCGGGATG GGAGAGACCCAGTACTTCGGGCCAGGCACGCGGCTCCTGGTGCTCGAGGACCTGAAAAACGTGTT CCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
317	GGTCTTGTTACATTTGCGTTTGGGTTCTTGGTCATGAAGTCTTTGCCTAAGCCAGTGTCTAGAAGGG TTTTCTGATGGTATCTTCTAGAAATTTTATGGTTTTAGGTGTTTTATTTCTTTTTTTGTTTATGTGGAA GCTGTTCTATCTTTAGCTGACGATTCTCGGGAGTGGGGAATGAACCTGCCTGATGTGGGATGT GCTGTGGCTGCTGCTTTGTTGCTTGGGACCTCCTCTGACCTAGGATCAGACACAGAGTCTGAGTTCT GGGGCCTGGAACCTCAATGTGCACTTGAACAATGAAGTTGGTGACAAGCATTACTGTACTCCTATCT TTGGGTATTATGGGTGATGCTAAGACCACACAGCCAAATCAATGGAGAGTAACGAAGAAGAGCCTG TTCACCTTGCCCTGTAACCACTCCACAATCAGTGGAACCTGATTACATACATTGGTATCGACAGCTTCCC TCCCAGGGTCCAGAGTACGTGATTGCTTACAAGCAATGTGAACAACAGAATGGCCTCTCTGG CAATCGCTGAAGACAGAAAGTCCAGTACCTTGATCCTGCACCGTGCTACCTTGAGAGATGCTGCTGT GTACTACTGCATCCTGAGAGACGTGGGCGGATCTGAAAAGCTGGTCTTTGAAAAGGGAACGAAACT GACAGTAAACCATATATCCAGAACCCTGACCTGCCGTGTACCAGCTGAGAGACT
318	GTCATCCCTCCTCGCTGGTGAATGGAGGCAGTGGTCACAACCTCTCCCAGAGAAGGTGGTGTGAGG CCATCACGAAGATGCTGCTGCTTCTGCTGCTTCTGGGGCCAGGCTCCGGGCTTGGTGCTGTCTGTC TCTCAACATCCGAGCTGGGTATCTGTAAGAGTGGAACCTCTGTGAAGATCGAGTGCCGTTCCCTGG ACTTTACAGGCCACAACATATGTTTTGGTATCGTCAGTTCCCGAAACAGAGTCTCATGCTGATGGCACT TCCAATGAGGGCTCCAAGGCCACATACGAGCAAGGCGTCGAGAAGGACAAGTTTCTCATCAACCAT GCAAGCCTGACCTTGCTCACTCTGACAGTGACCACTGCCATCCTGAAGACAGCAGCTTCTACATCT GCAGTGCCAAAGGCCTCGAAAATCAGCCCCAGCATTTTGGTGATGGGACTCGACTCTCCATCCTAG AGGACCTGAACAAGGTGTTCCACCCGAGGTGCTGTGTTTGAGCCATCAGA
319	CTTCTGCAGACTACAGTGGCTCAGGAACCGGGGATGCAAGTGGCAGGCTCATGGTATCCTGCAGCAG ATGTGGGGAGCTTTCTTCTCTATGTTTCCATGAAGATGGGAGGCACTGCAGGACAAAGCCTTGAGC AGCCCTCTGAAGTGACAGCTGTGGAAGGAGCCATTGTCCAGATAAACTGCACGTACCAGACATCTG GGTTTTATGGGCTGTCTGGTACCAGCAACATGATGGCGGAGCACCCACATTTCTTTCTTACAATGC TCTGGATGGTTTGGAGGAGACAGGTCGTTTTTCTTCTTCTTCTAGTCGCTCTGATAGTTATGGTTACC TCCTTCTACAGGAGCTCCAGATGAAAGACTCTGCCTCTTACTTCTGCGCTGTCTTAAAAAGGGTA TGCACTCAACTTCGGCAAAGGCACCTCGCTGTTGGTCACACCCCATATCCAGAACCCTGACCCTGC CGTGACCAGCTGAGAGACT
320	GAGATTCTGGCTGATGATGTCACTGAGACAAAGGAAAAATGCAAAACAGGTAGTCTTAAAGAAGCA TTCTGGTGAGACGGGGGGCATTGTTGCCATGGCTTTGCAGAGCACTCTGGGGGCGGTGTGGCTAG GGCTTCTCCTCAACTCTCTCTGGAAGGTTGCAGAAAGCAAGGACCAAGTGTTCAGCCTTCCACAGT GGCATCTTCAGAGGGAGCTGTGGTGGAAATCTTCTGTAATCACTCTGTGTCCATGCTTACAACCTTCT TCTGGTACCTTCACTTCCCGGGATGTGCACCAAGACTCCTTGTTAAAGGCTCAAAGCCTTCTCAGCA GGGACGATACAACATGACCTATGAACGGTTCTTCTCATCGCTGCTCATCTCCAGGTGCGGGAGGC AGATGCTGCTGTTTACTACTGTGCTGTGGCTGGTGGCTACAATAAGCTGATTTTTGGAGCAGGGACC AGGCTGGCTGTACACCCATATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT

321	AGTGACCCTGATCTGGCAAAGCTTCCATCCTGCCCTGACCCTGCCATGGGTACCAGGCTCCTCTGC TGGGTGGCCTTCTGTCTCCTGGTGAAGAACTCATAGAAGCTGGAGTGGTTCAGTCTCCCAGATATA AGATTATAGAGAAAAACAGCCTGTGGCTTTTTGGTGCAATCCTATTTCTGGCCACAATACCCTTTAC TGGTACCTGCAGAACTTGGGACAGGGCCCCGGAGCTTCTGATTGATATGAGAATGAGGAAGCAGTA GACGATTCACAGTTGCCTAAGGATCGATTTTCTGCAGAGAGGCTCAAAGGAGTAGACTCCACTCTCA AGATCCAGCCTGCAGAGCTTGGGGACTCGGCCGTGTATCTCTGTGCCAGCAGCTTAGAAGCGGGG GACTCCTACGAGCAGTACTTCGGGCCGGGCCACCAGGCTCACGGTCACAGAGGACCTGAAAAACGT GTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
322	GTCAGTACACAAAGGAAAAAATGCAAAACAGGTAGTATTGGAGAAGCATTCTGGTGTGTTGGGGG GCATTTTGGCCATGGCTTTGCAGAGCACTCTGGGGGCGGTGTGGCTAGGGGCTTCTCCTCAACTCTC TCTGGAAGGTTGCAGAAAGCAAGGACCAAGTGTTCAGCCTTCCACAGTGGCATCTTCAGAGGGAG CTGTGGTGGAAATCTTCTGTAATCACTCTGTGCCAATGCTTACAATCTTCTCTGGTACCTTCACTC CCGGGATGTGCACCAAGACTCCTTGTAAAGGCTCAAAGCCTTCTCAGCAGGGACGATACCAATGA CCTATGAACGGTCTCTTCATCGCTGCTCATCTCCAGGTGCGGGAGGCAGATGCTGCTGTTTACTA CTGTGCTGTGACTGGTGGCTACAATAAGCTGATTTTGGAGCAGGGACCAGGCTGGCTGTACACCC ATATATCCAGAACCTGACCCTGCCGTGTACCAGCTGAGAGACT
323	AGTGACCCTGATCTGGCAAAGCTTCCATCCTGCCCTGACCCTGCCATGGGTACCAGGCTCCTCTGC TGGGTGGCCTTCTGTCTCCTGGTGAAGAACTCATAGAAGCTGGAGTGGTTCAGTCTCCCAGATATA AGATTATAGAGAAAAACAGCCTGTGGCTTTTTGGTGCAATCCTATTTCTGGCCACAATACCCTTTAC TGGTACCTGCAGAACTTGGGACAGGGCCCCGGAGCTTCTGATTGATATGAGAATGAGGAAGCAGTA GACGATTCACAGTTGCCTAAGGATCGATTTTCTGCAGAGAGGCTCAAAGGAGTAGACTCCACTCTCA AGATCCAGCCTGCAGAGCTTGGGGACTCGGCCGTGTATCTCTGTGCCAGCAGCTTAGAAGCGGGG GATTCCTACGAGCAGTACTTCGGGCCGGGCCACCAGGCTCACGGTCACAGAGGACCTGAAAAACGTG TTCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
324	CTGGAACAGAGATTTAAATTTCTGGTAGTGTTTTAGGGGGACTCTAAGCCCAAGAGAGTTTTTTTA AAAAAAAAAAAAAAAAAACCCATTGAGGAAATAATCTTTGCTGATAAGGATGCTCCTTGAACATTTAT TAATAATCTTGTGGATGCAGCTGACATGGGTCACTGGTCAACAGCTGAATCAGAGTCTCAATCTAT GTTTATCCAGGAAGGAGAAGATGTCTCCATGAAGTCACTTCTTCAAGCATATTTAACACCTGGCTAT GGTACAAGCAGGAACCTGGGGAAGGTCTGTCTCTTGATAGCCTTATATAAGGCTGGTGAATTGAC CTCAATGGAAGACTGACTGCTCAGTTTGGTATAACCAGAAAGGACAGCTTCTGAATATCTCAGCA TCCATACCTAGTGATGTAGGCATCTACTTCTGTGCTGGGCACCAAAATTCAGGGAGCCCAAGCTGG TATTTGGCCAAGGAACAGGCTGACTATCAACCCAAATATCCAGAACCTGACCCTGCCGTGTACCA GCTGAGAGACT
325	ATCAATGCACAGATACAGAAGACCCCTCCGTCTGGAGCACCTGCCATGAGCATCAGCCTCCTGTG CTGTGCAGCCTTTCTCTCCTGTGGGCAGGTCCAGTGAATGCTGGTGTCACTCAGACCCCAAAATTC CGCATCCTGAAGATAGGACAGAGCATGACACTGCAGTGTACCCAGGATATGAACCATAACTACATGT ACTGGTATCGACAAGACCCAGGCATGGGGCTGAAGCTGATTTATTATTAGTTGGTGTGGTATCAC TGATAAAGGAGAAGTCCCGAATGGCTACAACGTCTCCAGATCAACCACAGAGGATTTCCCGCTCAG GCTGGAGTTGGCTGCTCCCTCCAGACATCTGTGTAATCTGTGCCAGCAGTTACTCGGGGATGAA CACTGAAGCTTTCTTTGGACAAGGCACCAGACTCACAGTTGTAGAGGACCTGAACAAGGTGTTCCCA CCCGAGGTCGCTGTGTTTGAGCCATCAGA
326	AAGTCTCTCAGCTGGTACACGGCAGGGTCAGGGTTCTGGATATTGGGCTTACCACCAGCTGAGTT CCATCTCCAAACATGAGTCTGGCATTGTTATTCGCCCCAGCACAGAAGTAGATGCCTACATCACTAG GTATGGATGCTGAGATATTCAGGAAGCTGTCTTTCTGGTTATACCAAACTGAGCAGTCACTCTTCCA TTTGAGGTCAATTCACCAGCCTTATATAAGGCTATCAAGAGGACAGGACCTTCCCGAGGGTCTGCT TGTAACCATAGCCAGGTGTTAAATATGCTTGAAGAAGTGCAGTTCATGGAGACATCTTCTCCTTCTGG ATAAACATAGATTGAGGACTCTGATTCAGCTGTTGACCACTGACCCATGTCAGCTGCATCCACAAGA TTATTAATATGAATTCGGATTGGGTGGTTTTTTGTTTTAGTGTCACTCTAAGCCCAATAGAGTTTTT TAAAAAAAAAAAAAAAAAACCCATTGAGGAAATAATCTTTGCTGATAAGGATGCTCCTTGAACATT TATTAATAATCTTGTGGATGCAGCTGACATGGGTCACTGGTCAACAGCTGAATCAGAGTCTCAATCT ATGTTTATCCAGGAAGGAGAAGATGTCTCCATGAAGTCACTTCTTCAAGCATATTTAACACCTGGCT ATGGTACAAGCAGGACCCCTGGGGAAGGTCTGTCTCTTGATAGCCTTATATAAGGCTGGTGAATTG ACCTCAATGGAAGACTGACTGCTCAGTTTGGTATAACCAGAAAGGACAGCTTCTGAATATCTCAG CATCCATACCTAGTGATGTAGGCATCTACTTCTGTGCTGGGGCGAATAACATGCCAGACTCATGTT TGGAGATGGAACCTCAGCTGGTGGTGAAGCCCAATATCCAGAACCTGACCCTGCCGTGTACCAGCT GAGAGACT

327	GAAGGAAAGATGAACTTGAGTTTCACTTCTTAGTGCCTTTTCTCAGGGGAGAGGCCATCACTTGAAG ATGCTGAGTCTTCTGCTCCTTCTCCTGGGACTAGGCTCTGTGTTCAAGTGTGTCATCTCTCAAAAGC CAAGCAGGGATATCTGTCAACGTGGAACCTCCCTGACGATCCAGTGTCAAGTCGATAGCCAAGTCA CCATGATGTTCTGGTACCGTCAGCAACCTGGACAGAGCCTGACACTGATCGAACTGCAAAATCAGG GCTCTGAGGCCACATATGAGAGTGGATTTGTCATTGACAAGTTTCCCATCAGCCGCCAAACCTAAC ATTCTCAACTCTGACTGTGAGCAACATGAGCCCTGAAGACAGCAGCATATATCTCTGCAGCGTCACT CCGGGGGGCGGGGTGAACACTGAAGCTTTCTTTGGACAAGGCACCAGACTCACAGTTGTAGAGGAC CTGAACAAGGTGTTCCACCCGAGGTGCGTGTGTTTGAGCCATCAGA
328	AAAGCAGATTCTTTTTATGATTTTTAAAGTAGAAATATCCATTCCAGGTGCATTTTTTAAGGGTTAAAA TTTGAATCCTCAGTGAACCAGGGCAGAGAAGAATGATGAAATCCTTGAGAGTTTTACTAGTGATCCT GTGGCTTCAGTTGAGCTGGGTTTGAGCCAACAGAAGGAGGTGGAGCAGAATTCTGGACCCCTCAG TGTCCAGAGGGAGCCATTGCCTCTCTCACTGCACTTACAGTGACCGAGGTTCCCGACTCCTTCTTC TGGTACAGACAATATTCTGGGAAAGCCCTGAGTTGATAATGTCCATATACTCCAATGGTGACAAAGA AGATGGAAGGTTTACAGCACAGCTCAATAAAGCCAGCCAGTATGTTTCTGCTCATCAGAGACTCC CAGCCCAGTGATTAGCCACCTACCTCTGTGCCGTGAGCGCTGGTGGTACTAGCTATGGAAGCTG ACATTTGGACAAGGGACCATCTTGACTGTCCATCCAAATATCCAGAACCCTGACCCTGCCGTGTACC AGCTGAGAGACT
329	AGACCAGAATCCTGCCCTGGGCCTTGCCCTGGTCTGCCTCACTCTGCCATGGGCTGCAGGCTCCTCT GCTGTGTGGTCTTCTGCCTCCTCCAAGCAGGTCCCTTGAGACACAGCTGTTTCCAGACTCCAAAATA CCTGGTCACACAGATGGGAAACGACAAGTCCATTAAATGTGAACAAAATCTGGGCCATGATACTATG TATTGGTATAAACAGGACTCTAAGAAATTTCTGAAGATAATGTTTAGCTACAATAAAGGAGCTCATT ATAAATGAAACAGTTCCAAATCGCTTCTCACCTAAATCTCCAGACAAAGCTCACTTAAATCTTACATC AATCCCTGGAGCTTGGTGAATCTGTGCTGTGATTCTGTGCCAGCAGCCAAAGTCTTAGGGGTGAGC AGTACTTCGGGCCGGGCACCAGGCTCAGGTACAGAGGACCTGAAAAACGTGTTCCACCCGAG GTCGCTGTGTTTGAGCCATCAGA
330	GGAGAGACAGGGTCTTGCTCTGTTGCCAGGCTAGAGTGAGTAACATGATCATATCTCACTGTATC CTCAAACTCCTGGGCTCAAGTATTTGACCTGCATAATAAATGTCTACGCCCTCATGCCACTAGGTGGC AATGTGGGTGTTATACTGAAAAGATCACAGATGGTTCAGTTGGGAAGTAAACTGTAATGTTCTTAA GTGTGCATTTCTGCTGCTTCTGATGGGCTGAAAATCCCTTTGATTTCTAAAGTAAATGTAGAGACGT TTTAAAAATAAAGGACTCCTTTGTCCAAGATATATCCGAAATCCTCCAACAGAGACCTGTGTGAGCT TCTGCTGCAGTAATAATGGTGAAGATCCGGCAATTTTGTGGCTATTTGTGGCTTCAGCTAAGCTG TGTAAGTGCCGCCAAAAATGAAGTGGAGCAGAGTCCCTCAGAACCTGACTGCCAGGAAGGAGAATT TATCACAATCACTGCAGTTACTCGGTAGGAATAAGTGCCTTACACTGGCTGCAACAGCATCCAGGA GGAGGCATTGTTTCTTGTGTTATGCTGAGCTCAGGGAAGAAGAAGCATGGAAGATTAATTGCCACAA TAAACATACAGGAAAAGCAGAGCTCCCTGCACATCACAGCCTCCCATCCAGAGACTCTGCCGTCTA CATCTGTGCTGTGAGTACTGGTGGTGTACAACAAGCTCATCTTTGAACTGGCACTCTGCTTGCT GTCCAGCCAAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
331	GGTTGCCAGGCTAGAGTGAGTAACATGATCATATCTCACTGTATCCTCAAACTCCTGGGCTCAAG TATTTGACCTGCATAATAAATGTCTACGCCTCATGCCACTAGGTGGCAATGTGGGTGTTATACTGAAA AGATCACAGATGGTTCAGTTGGGAAGTAAACTGTAAATGTTCTTAAGTGTGATTTCTGCTGCTTCT GATGGGCTGAAAATCCCTTTGATTTCTAAAGTAAATGTAGAGACGTTTTAAAAATAAAGGACTCCTT TGTTCAAGATATATCCGAAATCTCCAACAGAGACCTGTGTGAGCTTCTGCTGCAGTAATAATGGT GAAGATCCGGCAATTTTGTGGCTATTTGTGGCTTCAGCTAAGCTGTGAAGTGCCGCCAAAAAT GAAGTGGAGCAGAGTCCCTCAGAACCTGACTGCCAGGAAGGAGAATTTATCACAATCACTGCAGTT ACTCGGTAGGAATAAGTGCCTTACACTGGCTGCAACAGCATCCAGGAGGAGGCATTGTTTCTTGTGTT TATGCTGAGCTCAGGGAAGAAGAAGCATGGAAGATTAATTGCCACAATAACATACAGGAAAAGCAC AGCTCCCTGCACATCACAGCCTCCATCCAGAGACTCTGCCGTCTACATCTGTGCTGTTTCAGGAG GGAGAAACCAAGTGGCTCTAGGTTGACCTTTGGGGAAGGAACACAGCTCACAGTGAATCCTGATATC CAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
332	GAGAGTCTGCTCCCTTTTCATCAATGCACAGATACAGAAGACCCCTCCGTCATGCAGCCCTGCCA TGAGCATCGGCCCTCCTGTGCTGTGCAGCCTTGTCTCCTGTGGGCAGGTCCAGTGAATGCTGGTG TCACTCAGACCCCAAAATTCAGGTCTGAAGACAGGACAGAGCATGACACTGCAGTGTGCCCAGG ATATGAACCATGAATACATGCTCCTGGTATCGACAAGACCCAGGCATGGGGCTGAGGCTGATTCATTA CTCAGTTGGTGTGTTATCACTGACCAAGGAGAAGTCCCAATGGCTACAATGTCTCCAGATCAACC ACAGAGGATTTCCCGCTCAGGCTGCTGTGCGGCTGCTCCCTCCAGACATCTGTGTAATCTGTGCCA GCAGTCCAGGGTTTAAATGGAACACCATATATTTGGAGAGGGAAGTTGGCTCACTGTTGTAGAGGA CCTGAACAAGGTGTTCCACCCGAGGTGCGTGTGTTTGAGCCATCAGA

333	GAGAAGCCTCACACAGCCAGTAACCTTTGCTAGTACCTCTTGAGTGCAAGGTGGAGAATTAAGATCTGGATTTGAGACGGAGCACGGAACATTTCACTCAGGGGAAGAGCTATGAACATGCTGACTGCCAGCCGTGTGAGGGCAGTCATAGCCTCCATCTGTGTTGTATCCAGCATGGCTCAGAAGGTAACCTCAAGCGCAGACTGAAATTTCTGTGGTGGAGAAGGAGGATGTGACCTTGGACTGTGTGTATGAAACCCGTGATACTACTTATTACTTATTCTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCTTATTCGTCGGAACCTCTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTTGGAACCTCCAGAAATCCACCAGTTCCCTTCAACTTCACCATCACAGCCTCACAAGTCGTGGACTCAGCAGTATACTTCTGTGCTCTGAGTGAGGCAACATATAACACCGACAAGCTCATCTTTGGGACTGGGACCAGATTACAAGCTTTCCAAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
334	TTCAGCTCTGCAGGACAGGTAGAGACTCCAGGATCATCCACTGAGCACTGGACATAAGGAAGGCTGCATGGGGAGGACACAGGACAGTGACATCACAGGATACCCCTCCTATTAGGAAAAACAAGGCCCAGAACTCACTCGGCTCTTCCCAGGAGGACCAAGCCCTGAATCAGGTGCAGTGCTGCTGCCCTGCCCACTGTGCCATGGGCCCTGGGCTCCTCTGCTGGGCGCTGCTTTGTCTCCTGGGAGCAGGCTCAGTGGAGACTGGAGTCACCCAAAGTCCACACACCTGATCAAAACGAGAGGACAGCAAGTGACTCTGAGATGCTCTTCTCAGTCTGGGCACAACACTGTGTCTGGTACCAACAGGCCCTGGGTGAGGGGCCCCAGTTTATCTTTTCAGTATTATAGGGAGGAAGAGAATGGCAGAGGAACTTCCCTCCTAGATTCTCAGGTCTCCAGTTCCCTAATTATAGCTCTGAGCTGAATGTGAACGCCTTGGAGCTGGACGACTCGGCCCTGTATCTCTGTGCCAGCAGCTCCACCGGGACGGACTATGGCTACACCTTCGGTTCGGGGACCAGGTTAACCGTTGTAGAGGACCTGAACAAGGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
335	AAAGCAGATTCTTTTTATGATTTTTAAAGTAGAAATATCCATTCTAGGTGCATTTTTTAAGGGTTAAAAATTTGAATCCTCAGTGAACCAGGGCAGAGAAGAATGATGAAATCCTTGAGAGTTTTACTAGTGATCCTGTGGCTTCAGTTGAGCTGGGTTTGAGGCCAACAGAAGGAGGTGGAGCAGAATTCTGGACCCCTCAGTGTTCCAGAGGGAGCCATTGCCTCTCTCAACTGCACCTACAGTGACCGAGGTTCCCACTCCTTCTCTGGTACAGACAATATTCTGGGAAAAGCCCTGAGTTGATAATGTTTCATATACTCCAATGGTGACAAAGAAGATGGAAGGTTTACAGCACAGCTCAATAAAGCCAGCCAGTATGTTTCTCTGCTCATCAGAGACTCCAGCCCAGTGATTAGCCACCTACCTCTGTGCCGGGAGGCAAACCTCCTACGACAAGGTGATATTTGGGCCAGGGACAAGCTTATCAGTCATTCCAAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
336	AGAGCTGGAAACACCTCCATCCTGCCTCTTCATGCCATGGCCTCCCTGCTCTTCTTCTGTGGGGCCTTTTATCTCCTGGGAACAGGGTCCATGGATGCTGATGTTACCCAGACCCCAAGGAATAGGATCACAAAACAGAGGAAAGAGGATTATGCTGGAATGTTCTCAGACTAAGGGTCATGATAGAATGTACTGGTATCGACAAGACCCAGGACTGGGCCTACGGTTGATCTATTACTCCTTTGATGTCAAAGATATAAACAAGGAGAGATCTCTGATGGATACAGTGTCTCTCGACAGGCACAGGCTAAATTCTCCCTGTCCCTAGAGTCTGCATCCCCAACCCAGACAGCTCTTACTTCTGTGCCACCACTGATGTGACTGGGCAGGGCGAGATGCGTGCTACACCTTCGGTTCGGGGACCAGGTTAACCGTTGTAGAGGACCTGAACAAGGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
337	GAGAAGCCTCACACAGCCAGTAACCTTTGCTAGTACCTCTTGAGTGCAAGGTGGAGAATTAAGATCTGGATTTGAGACGGAGCACGGAACATTTCACTCAGGGGAAGAGCTATGAACATGCTGACTGCCAGCCGTGTGAGGGCAGTCATAGCCTCCATCTGTGTTGTATCCAGCATGGCTCAGAAGGTAACCTCAAGCGCAGACTGAAATTTCTGTGGTGGAGAAGGAGGATGTGACCTTGGACTGTGTGTATGAAACCCGTGATACTACTTATTACTTATTCTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCTTATTCGTCGGAACCTCTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTTGGAACCTCCAGAAATCCACCAGTTCCCTTCAACTTCACCATCACAGCCTCACAAGTCGTGGACTCAGCAGTATACTTCTGTGCTCTGAGTGAGATGAACAGAGATGACAAGATCATCTTTGAAAAGGGACACGACTTCATATTCTCCCCAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
338	AGCTGTGAGGTCTGGTTCCTCCGACGTGCTGCAGCAAGTGCCTTTGCCCTGCCTGTGGGCTCCCTCCATGGCCAACTCTGCTATGGACACCAGAGTACTCTGCTGTGCGGTCTCTGTCTTCTGGGGGCAGGTCTCTCAAATGCCGGCGTCATGCAGAACCACAGACCTGGTCAGGAGGAGGGGACAGGAGGCAAGACTGAGATGCAGCCCAATGAAAGGACACAGTCATGTTTACTGGTATCGGCAGCTCCCAGAGGAAGGTCTGAAATTCATGGTTTATCTCCAGAAAGAAAATATCATAGATGAGTCAGGAATGCCAAAGGAACGATTTCTGCTGAATTTCCCAAAGAGGGCCCCAGCATCCTGAGGATCCAGCAGGTAGTGCGAGGAGATTGGGCAGCTTATTCTGTGCCAGCTCACCGACAGGGGTCTCTGGAAACACCATATATTTTGGAGAGGGAAGTTGGCTCACTGTTGTAGAGGACCTGAACAAGGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
339	CGGGAAGAGCAGAGATTTAAATTTCTGGTTGTTTTAGTGGGACTCTAAGCCCAAGAGAGTTTCTTGAAAAAATCTTGTGGATGCAGCTGACATGGTCAACAGCTGAATCAGAGTCTCAATCTAT

	GTTATCCAGGAAGGAGAAGATGTCTCCATGAACTGCACTTCTTCAAGCATATTTAACACCTGGCTAT GGTACAAGCAGGACCCTGGGGAAGGTCCTGTCTCTTGATAGCCTTATATAAGGCTGGTGAATTGAC CTCAAATGGAAGACTGACTGCTCAGTTTGGTATAACCAGAAAGGACAGCTTCCTGAATATCTCAGCA TCCATACCTAGTGATGTAGGCATCTACTTCTGTGCTGGGCAGCAAAAACCAAGTGGCTCTAGGTTGA CCTTTGGGGAAGGAACACAGCTCACAGTGAATCCTGATATCCAGAACCCTGACCCTGCCGTGTACC AGCTGAGAGACT
340	GGAGGTGCGAATGACTCTGCTCTGTCTCTCTCATCTGCAAAATTAGGAAGCCTGTCTTGAT TATCTCCAGGAACCTCCCACCTCTTCATTCCAGCCTCTGACAACTCTGCACATTAGGCCAGGAGAA GCCCCGAGCCAAGTCTCTTTCTCATTCTCTTCCAACAAGTGCTTGGAGCTCCAAGAAGGCCCCCT TTGCACTATGAGCAACCAGGTGCTCTGCTGTGTGGTCCTTTGTTCTGGGAGCAAAACACCGTGGAT GGTGGAATCACTCAGTCCCCAAAGTACCTGTTGAGAAAGGAAGGACAGAATGTACCCCTGAGTTGT GAACAGAATTTGAACCACGATGCCATGTACTGGTACCGACAGGACCCAGGGCAAGGGCTGAGATTG ATCTACTACTACAGATAGTAAATGACTTTCAGAAAGGAGATATAGCTGAAGGGTACAGCGTCTCTC GGGAGAAGAAGGAATCCTTCTCTCACTGTGACATCGGCCCAAAAGAACCCGACAGCTTCTATCT CTGTGCCAGTAGTTCCTCCGGGACAGGGTGGTCAGCCCCAGCATTGTTGGTGATGGGACTCGACT CTCCATCCTAGAGGACCTGAACAAGGTGTTCCACCCGAGGTGCTGTGTTGAGCCATCAGA
341	GGCTTTGTGCGGTGGAGCTGATTGGTTGCAGGAGCAGCAACAGTTCCAGAGCCAAGTCATGACACC GACCTCCCCAAGGTTTGTAAATATATCTTATGGTGAAATGCCCGAGCAAGAAGGCCAAAGCATC ATGAAGAGGATATTGGGAGCTCTGCTGGGCTCTTGAGTGCCAGGTTTGTCTGTGAGAGGAATA CAAGTGGAGCAGAGTCTCCAGACCTGATTCTCCAGGAGGGAGCCAATTCACGCTGCGGTGCAAT TTTTCTGACTCTGTGAACAATTTGCAGTGGTTTCATCAAAACCTTGGGGACAGCTCATCAACCTGTT TTACATTCCCTCAGGGACAAAACAGAATGGAAGATTAAAGCGCCACGACTGTGCTACGGAACGCTAC AGCTTATTGTACATTTCTCTTCCAGACCACAGACTCAGGCGTTTATTTCTGTGCTGCCGTGCGGT CGACAATAACAATGACATGCGCTTTGGAGCAGGGACCAAGTACAGTAAACCAATATCCAGAAG CCTGACCCTGCCGTGTACCAGCTGAGAGACT
342	AGCTCCTGTATTGCTGCCCCAAGGGCCTCATCTAGGTGAAGGCTCCACCTGCCCCACCCTGCCAT GGCCACCAGGCTCCTCTGCTGTGTGGTTCTTGTCTCTGGGAGAAGAGCTTATAGATGCTAGAGTC ACCCAGACACCAAGGCACAAGGTGACAGAGATGGGACAAGAAGTAACAATGAGATGTCAGCCAATT TAGGCCACAATACTGTTTTCTGGTACAGACAGACCATGATGCAAGGACTGGAGTTGCTGGCTTACT TCCGCAACCGGGCTCCTCTAGATGATTGCGGGATGCCGAAGGATCGATTCTCAGCAGAGATGCCTG ATGCAACTTTAGCCACTCTGAAGATCCAGCCCTCAGAACCCAGGGACTCAGCTGTGTATTTTGTG TAGTGGTTTAGCTCAGCCCCAGCATTGTTGGTGATGGGACTCGACTCTCATCTAGAGGACCTGAAC AAGGTGTTCCACCCGAGGTGCTGTGTTGAGCCATCAGA
343	AGGAACATGACTAAACCTGGGGAGGAAGACATAGAAAAGCAACTGCTCTATCATTGGCTGACAAGAT CCTGACAACAACACAATGAGAGCTGCACTCCTTGCAAGTCTTTACTAGTAGCTGTTGCTTCTGTTCTC TGGAAATTTCTTAAACCTAGAATCAGACACAAAACTGAACTCTGGGTCCACAATCCTCATTTGCTCT TGAAGTATGAGGCTGGTGGCAAGAGTAAGTGTGTTCTGACCTTTGGAACATAATTGATGCTAAGA CCACCCAGCCCCCTCCATGGATTGCGCTGAAGGAAGAGCTGCAAACTGCTTGTGAATCACTCTA CCATCAGTGGAATGAGTATGTGATTGGTATCGACAGATTCACTCCCAGGGGCCACAGTATATCAT TCATGGTCTAAAAACAATGAAACCAATGAAATGGCCTCTCTGATCATCACAGAAGACAGAAAGTCCA GCACCTTGATCCTGCCCCACGCTACGCTGAGAGACACTGCTGTGTACTATTGCATCGTCAGAGTCG CGGTAACCAATGCAGGCAATCAACCTTTGGGGATGGGACTACGCTCACTGTGAAGCCAAATATCCA GAAGCCTGACCCTGCCGTGTACCAGCTGAGAGACT
344	ACCTGGAGCCCCCAGAACTGGCAGACACCTGCCTGATGCTGCCATGGGCCCCAGCTCCTTGGCTA TGTGGTCTTTGCCCTTCTAGGAGCAGGCCCCCTGGAAGCCCAAGTGACCCAGAACCAGATACCT CATCACAGTGACTGGAAAGAAGTTAACAGTGACTTGTCTCAGAAATATGAACCATGAGTATATGCTCT GGTATCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTTGAGGTGACTGA TAAGGGAGATGTTCTGAAGGTACAAAGTCTCTCGAAAAGAGAAGAGGAATTTCCCCCTGATCCTG GAGTCGCCCAGCCCCAACAGACCTCTCTGTACTTCTGTGCCAGCAGATATTATAGCGCGGATACG CAGTATTTTGGCCAGGCACCCGCTGACAGTGCTCGAGGACCTGAAAAACGTGTTCCACCCGAG GTCGCTGTGTTGAGCCATCAGA
345	GTAGCTCGTTGATATCTGTGTGGATAGGAGCTGTGACGAGAGCAAGAGGTGAGAACATCCAGG CTCCTTAAGGGAAAGCCTCTTTCTGTTTCTGAACTTTTCAAAGCCAGGGACTTGTCCAATCCAACCT CTCACAGTTCTAGCTCCTGAGGCTCAGCGCCCTTGGCTTCTGTCCGCCAGCTCAAGGTCTGCTG AGCATTGCCACTGCTCAGCCATGCTCCTGCTGCTCGTCCCAGCGTTCAGGTGATTTTTACCCTGGG AGGAACCAGAGCCCAGTCTGTGACCCAGCTTGACAGCCAAGTCCCTGTCTTTGAAGAAGCCCTGT GGAGCTGAGGTGCAACTACTCATCGTCTGTTTCACTGTATCTCTTCTGGTATGTGCAATACCCCAAC

	CAAGGACTCCAGCTTCTCCTGAAGTATTTATCAGGATCCACCCTGGTTAAAGGCATCAACGGTTTTG AGGCTGAATTTAAACAAGAGTCAAACCTTCTTCCACTTGAGGAAACCCTCAGTCCATATAAGCGACAC GGCTGAGTACTTCTGTGCTGTGAGTGGGGTACTCACGGGAGGAGGAAACAACTCAGCTTTGGGAC AGGCACTCAGCTAAAAGTGGAACTCAATATCCAGAAGCCTGACCCTGCCGTGTACCAGCTGAGAGA CT
346	AATTTGCCACAGCAGGGCTGGGAGACACAAGATCCTGCCCTGGAGCTGAAATGGGCACCAGGCTC TTCTTCTATGTGGCCCTTTGTCTGCTGTGGGCAGGACACAGGGATGCTGGAATACCCAGAGCCCA AGATAACAAGATCACAGAGACAGGAAGGCAGGTGACCTTGATGTGCACCAGACTTGGAGCCACAGC TATATGTTCTGGTATCGACAAGACCTGGGACATGGGCTGAGGCTGATCTATTACTCAGCAGCTGCTG ATATTACAGATAAAGGAGAAGTCCCCGATGGCTATGTTGTCTCCAGATCCAAGACAGAGAATTTCCC CCTCACTCTGGAGTCAGCTACCCGCTCCCAGACATCTGTGATTTCTGCCCCAGCAGTGAGGGGAC AGTTAGCAATCAGCCCCAGCATTTTGGTGATGGGACTCGACTCTCCATCCTAGAGGACCTGAACAAG GTGTTCCCAACCGAGGTGCTGTGTTTGAGCCATCAGA
347	CGATGATGGAAGTAGCTCTTATGGCTGGAGATTGCAGGTTTATGACTGATCCTATTTGGGAAGAACA ATGATGGCAGGCATTTCGAGCTTTATTTATGTACTTGTGGCTGCAGCTGGACTGGGTGAGCAGAGGA GAGAGTGTGGGGCTGCATCTTCTACCCTGAGTGTCCAGGAGGGTGACAACCTCTATTATCAACTGTG CTTATTTCAAACAGCGCCTCAGACTACTTCATTTGGTACAAGCAAGAATCTGGAAGGTCCTCAATTC ATTATAGACATTCGTTCAAATATGGACAAAAGGCCAAGGCCAAAGAGTCACCGTTTTATTGAATAAGAC AGTGAAACATCTCTCTGCAAAATTCAGCTACTCAACCTGGAGACTCAGCTGTCTACTTTTGTGCAG AGATCGGGTCTGGGGCTGGGAGTTACCAACTCACTTTCGGGAAGGGGACCAAACTCTCGGTCATAC CAAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
348	CGATGATGGAAGTAGCTCTTATGGCTGGAGATTGCAGGTTTATGACTGATCCTATTTGGGAAGAACA ATGATGGCAGGCATTTCGAGCTTTATTTATGTACTTGTGGCTGCAGCTGGACTGGGTGAGCAGAGGA GAGAGTGTGGGGCTGCATCTTCTACCCTGAGTGTCCAGGAGGGTGACAACCTCTATTATCAACTGTG CTTATTTCAAACAGCGCCTCAGACTACTTCATTTGGTACAAGCAAGAATCTGGAAGGTCCTCAATTC ATTATAGACATTCGTTCAAATATGGACAAAAGGCCAAGGCCAAAGAGTCACCGTTTTATTGAATAAGAC AGTGAAACATCTCTCTGCAAAATTCAGCTACTCAACCTGGAGACTCAGCTGTCTACTTTTGTGCAG AGAATCAGGGAGGCAGCAGCTATAAATTGATCTTCGGGAGTGGGACCAGACTGCTGGTCAGGCCTG ATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
349	GTGGAAACCCACTTCTGACTTATCACTTGTCTGATGAATTCATGCTTCATGGTGTACACCGTTTATTGT TTCTGATGAGTGACAGTAATTTTCTTTCTTCTGCTGGTACATAATAAAGTGGTGACATCAGAGTTG CTGCCATCTTAGACTTAACTCATCAGTATCAGGTGATCCTGAGGCTCAGTGATGTGACTGTGGGAAC TGCTCTGTGGCGACAAGGACGTCCTCATCCTCTGCTCCTGGTGACAGTGACCCTGATCTGGTAA GCTCCCATCCTGCCCTGACCCTGCCATGGGCACCAGCCTCCTCTGCTGGATGGCCCTGTGTCTCCT GGGGGCAGATCAGCAGATACTGGAGTCTCCAGAACCCAGACACAAGATCACAAGAGGGGAC AGAATGTAACCTTCAGGTGTGATCCAATTTCTGAACACAACCGCCTTTATTGGTACCGACAGACCCTG GGGCAGGGCCAGAGTTTCTGACTTACTCCAGAATGAAGCTCAACTAGAAAAATCAAGGCTGCTCA GTGATCGGTTCTCTGCAGAGAGCCCTAAGGGATCTTTCTCCACCTTGAGAGTCCAGCGCACAGAGC AGGGGGACTCGCCATGTATCTCTGTGCCAGCAGCTCTCAGTCGGGTGTGGACACTGAAGCTTCT TTGGACAAGGCACCAGACTCACAGTTGTAGAGGACCTGAACAAGGTGTTCCACCCGAGGTCGCTG GTTTGAGCCATCAGA
350	TTTTGAAACCCCTTCAAAGGCAGAGACTTGTCCAGCCTAACCTGCCTGCTGCTCCTAGCTCCTGAGGC TCAGGGCCCTTGGCTTCTGTCCGCTCTGCTCAGGGCCCTCCAGCGTGGCCACTGCTCAGCCATGCT CCTGCTGCTCGTCCAGTGCTCGAGGTGATTTTTACCCTGGGAGGAACCAGAGCCAGTCGGTGAC CCAGCTTGGCAGCCACGTCCTGTCTGTGAGGGAGCCCTGGTTCTGCTGAGGTGCAACTACTCATC GTCTGTTCCACCATATCTCTTCTGGTATGTGCAATACCCCAACCAAGGACTCCAGCTTCTCCTGAAGT ACACAACAGGGGCCACCCTGGTTAAAGGCATCAACGGTTTTGAGGCTGAATTTAAGAAGAGTGAAC CTCCTTCCACCTGACGAAACCTCAGCCCATATGAGCGACGCGGCTGAGTACTTCTGTGCTGTGAG TCCCCCGCGCAGAACTTGATTTGGAAGTGGCACCCGACTTCTGGTCAGTCCAAATATCCAGAAC CCTGACCCTGCCGTGTACCAGCTGAGAGACT
351	GAGAGTCTGCTCCCCTTTCATCAATGCACAGATACAGAAGACCCCTCCGTCATGCAGCATCTGCCA TGAGCATCGGCCTCCTGTGCTGTGCAGCCTTGTCTCTCCTGTGGGCAGGTCCAGTGAATGCTGGTG TCACTCAGACCCCAAAATTCAGGTCCTGAAGACAGGACAGAGCATGACACTGCAGTGTGCCCAGG ATATGAACCATGAATACATGTCCTGGTATCGACAAGACCCAGGCATGGGGCTGAGGCTGATTCTTA CTCAGTTGGTGCTGGTATCACTGACCAAGGAGAAGTCCCCAATGGCTACAATGTCTCCAGATCAACC ACAGAGGATTTCCCGCTCAGGCTGCTGTGCGCTGCTCCCTCCAGACATCTGTGTAATCTGTGCCA

	GCCAAGAGACAGGGGTTGCGGGGAGCTGTTTTTGGAGAAGGCTCTAGGCTGACCGTACTGGAG GACCTGAAAAACGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
352	GAGAGTCCTGCTCCCCTTTTCATCAATGCACAGATACAGAAGACCCCTCCGTCATGCAGCATCTGCCA TGAGCATCGGCCTCCTGTGCTGTGCAGCCTTGTCTCTCCTGTGGGCAGGTCCAGTGAATGCTGGTG TCACTCAGACCCCCAAAATTCCAGGTCCTGAAGACAGGACAGAGCATGACACTGCAGTGTGCCCAGG ATATGAACCATGAATACATGTCCTGGTATCGACAAGACCCAGGCATGGGGTGAGGCTGATTCATTA CTCAGTTGGTGCTGGTATCACTGACCAAGGAGAAGTCCCCAATGGCTACAATGTCTCCAGATCAACC ACAGAGGATTTCCCGCTCAGGCTGCTGTCGGCTGCTCCCTCCAGACATCTGTGTACTTCTGTGCCA GCAGTACGACAGCCGTGGTTTACCCCTCCACTTTGGGAATGGGACCAGGCTCACTGTGACAGAGG ACCTGAACAAGGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
353	AGAATCTCCACAGATACAGGATAATTGGTTTAGCGTTTGGGGATCTGGCCACAAGGTGGCAGAGCT TCTCTGCTCATGTAGAATGTACGAAAGGATCCTTTTGGTTGACTTCTGTGAGTAGGCTGACGGCAGA AGCAGATGCCTCTGTGGACAGTTTAAGAAACACAGTGCTTTGGAGGAAAGGAAGATACCTTGATA ATATAGCTCTCTTGGCTGGAGATTGCAGGTCCAGTGCGGAGAACAAATGAAGACATTTGCTGGATTT TCGTTCCCTGTTTTGTGGCTGCAGCTGGACTGTATGAGTAGAGGAGAGGATGTGGAGCAGAGTCTTT TCCTGAGTGTCGAGAGGGGAGACAGCTCCGTTATAAACTGCACCTACACAGACAGCTCCTCCACCTA CTTATACTGGTATAAGCAAGAACCCTGGAGCAGGTCTCCAGTTGCTGACGTATATTTTTCAAATATGG ACATGAAACAAGACCAAGACTCACTGTTCTATTGAATAAAAAGGATAAACATCTGTCTCTGCGCATT GCAGACACCCAGACTGGGGACTCAGCTATCTACTTCTGTGCAGAGAAGAAGGAAGGCTTCAAACT ATCTTTGGAGCAGGAACAAGACTATTTGTTAAAGCAATATCCAGAACCCTGACCCTGCCGTGTACC AGCTGAGAGACT
354	GAGAGTCCTGCTCCCCTTTTCATCAATGCACAGATACAGAAGACCCCTCCGTCATGCAGCATCTGCCA TGAGCATCGGCCTCCTGTGCTGTGCAGCCTTGTCTCTCCTGTGGGCAGGTCCAGTGAATGCTGGTG TCACTCAGACCCCCAAAATTCCAGGTCCTGAAGACAGGACAGAGCATGACACTGCAGTGTGCCCAGG ATATGAACCATGAATACATGTCCTGGTATCGACAAGACCCAGGCATGGGGTGAGGCTGATTCATTA CTCAGTTGGTGCTGGTATCACTGACCAAGGAGAAGTCCCCAATGGCTACAATGTCTCCAGATCAACC ACAGAGGATTTCCCGCTCAGGCTGCTGTCGGCTGCTCCCTCCAGACATCTGTGTACTTCTGTGCCA GCCAAGAGACAGGGGTTGCGGGGAGCTGTTTTTGGAGAAGGCTCTAGGCTGACCGTACTGGAG GACCTGAAAAACGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
355	AGGACTGAGCTTGCCGTGTGACTGGCTAGGGAGGAACCTGAGACTAGGGGACAGAAAGACTAGGGA TTCACCCAGTAAAGAGAGCTCATCTGTGACTGAGGAGCCTTGCTCCATTTTCAGGTCTTCTGTGATTTT AATAAGGAAGAAGAATGGAACCTCTCTGGGAGTGCTTTGGTGATTCTATGGCTTCAACTGGCTAG GGTGAACAGTCAACAGGGAGAAGAGGATCCTCAGGCCTTGAGCATCCAGGAGGGTGAAATGCCAC CATGAATGCAGTTACAAAAGTAGTATAAACAATTTACAGTGGTATAGACAAAATTCAGGTAGAGGCC TTGTCCACCTAATTTTAATACGTTCAAATGAAAGAGAGAAACACAGTGGAAGATTAAGAGTCACGCTT GACACTTCCAAGAAAAGCAGTTCTTGTGATCACGGCTTCCCGGGCAGCAGACACTGCTTCTTACT TCTGTGCTACGGACGAGGCTGCAGGCAACAAGCTAACTTTTGGAGGAGGAACCAGGGTGCTAGTTA AACCAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
356	AAAATGCCCTCCTTTCTCCACAGGACCAGATGCCTGAGCTAGGAAAGGCCTCATTCTGCTGTGA TCCTGCCATGGATACCTGGCTCGTATGCTGGGCAATTTTGTCTCTTGAAAGCAGGACTCACAGAA CCTGAAGTCAACCCAGACTCCAGCCATCAGGTACACAGATGGGACAGGAAGTGATCTTGCCTGT GTCCCCATCTCTAATCACTTATACTTCTATTGGTACAGACAAATCTTGGGGCAGAAAGTCGAGTTTCT GGTTTCTTTTATAAATGAAATCTCAGAGAAGTCTGAAATATTCGATGATCAATTCTCAGTTGAAAG GCCTGATGGATCAAATTTCACTCTGAAGATCCGCTCCACAAAGCTGGAGGACTCAGCCATGTACTTC TGTGCCAGCAAAAGGGAATCACTAGCCACCGGGGAGCTGTTTTTGGAGAAGGCTCTAGGCTGACC GTACTGGAGGACCTGAAAAACGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
357	AGGACTGAGCTTGCCGTGTGACTGGCTAGGGAGGAACCTGAGACTAGGGGACAGAAAGACTAGGGA TTCACCCAGTAAAGAGAGCTCATCTGTGACTGAGGAGCCTTGCTCCATTTTCAGGTCTTCTGTGATTTT AATAAGGAAGAAGAATGGAACCTCTCTGGGAGTGCTTTGGTGATTCTATGGCTTCAACTGGCTAG GGTGAACAGTCAACAGGGAGAAGAGGATCCTCAGGCCTTGAGCATCCAGGAGGGTGAAATGCCAC CATGAAGTGCAGTTACAAAAGTAGTATAAACAATTTACAGTGGTATAGACAAAATTCAGGTAGAGGCC TTGTCCACCTAATTTTAATACGTTCAAATGAAAGAGAGAAACACAGTGGAAGATTAAGAGTCACGCTT GACACTTCCAAGAAAAGCAGTTCTTGTGATCACGGCTTCCCGGGCAGCAGACACTGCTTCTTACT TCTGTGCTGCCATGTATTAGGAGGAGGTGCTGACGGAATCACTTTTGGCAAAGGACTCATCTAAT CATCCAGCCCTATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
358	AAAATGCCCTCCTTTCTCCACAGGACCAGATGCCTGAGCTAGGAAAGGCCTCATTCTGCTGTGA TCCTGCCATGGATACCTGGCTCGTATGCTGGGCAATTTTGTCTCTTGAAAGCAGGACTCACAGAA

	CCTGAAGTCACCCAGACTCCCAGCCATCAGGTCACACAGATGGGACAGGAAGTGATCTTGCGCTGT GTCCCCATCTCTAATCACTTATACTTCTATTGGTACAGACAAATCTTGGGGCAGAAAGTCGAGTTTCT GGTTTCCTTTTATAATAATGAAATCTCAGAGAAGTCTGAAATATTCGATGATCAATTCTCAGTTGAAAG GCCTGATGGATCAAATTTCACTCTGAAGATCCGGTCCACAAAGCTGGAGGACTCAGCCATGTACTTC TGTGCCAGCAGTACCCAGGGACAGGCCTACGAGCAGTACTTCGGGCCGGGCACCAGGCTCACGGT CACAGAGGACCTGAAAAACGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
359	GATCTTAATTGGGAAGAACAAGGATGACATCCATTCGAGCTGTATTTATTCCTGTGGCTGCAGCTG GACTTGGTGAATGGAGAGAATGTGGAGCAGCATCCTTCAACCCTGAGTGTCAGGAGGGAGACAGC GCTGTTATCAAGTGACTTATTAGACAGTGCCTCAAACCTACTTCCCTTGGTATAAGCAAGAACTTGG AAAAAGACCTCAGCTTATTATAGACATTGTTCAAATGTGGGCGAAAAAGACCAACGAATTGCTG TTACATTGAACAAGACAGCCAAACATTTCTCCCTGCACATCACAGAGACCCAACTGGAAGACTCGGC TGTCTACTTCTGTGCAGCAAGAGGAGGTAGCAACTATAAATGACATTTGGAAAAGGAACTCTCTTAA CCGTGAATCCAAATATCCAGAACCTGACCCTGCCGTGTACCAGCTGAGAGACT
360	TATGGGGATGTTTACAGAGGGCCTGGTCTGGAATATTCACATCTGCTCTCACTCTGCCATGGGCTC CTGGACCCTCTGCTGTGTGTCCCTTTGCATCCTGGTAGCAAAGCACACAGATGCTGGAGTTATCCAG TCACCCCGGCACGAGGTGACAGAGATGGGACAAGAAGTACTCTGAGATGTAAACCAATTCAGGA CACGACTACCTTTTCTGGTACAGACAGACCATGATGCGGGGACTGGAGTTGCTCATTACTTTAACA ACAACGTTCCGATAGATGATTGAGGGATGCCGAGGATCGATTCTCAGCTAAGATGCCTAATGCATC ATTCTCCACTCTGAAGATCCAGCCCTCAGAACCCAGGGACTCAGCTGTGTACTTCTGTGCCAGCAGC ACAGGGGGCGAGCAGTACTTCGGGCCGGGCACCAGGCTCACGGTCACAGAGGACCTGAAAAACGT GTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
361	AGGACTGAGCTTGCCTGTGACTGGCTAGGGAGGAACCTGAGACTAGGGGACAGAAAGACTAGGGA TTCACCCAGTAAAGAGAGCTCATCTGTGACTGAGGAGCCTTGCTCCATTCAGGTCTTCTGTGATTC AATAAGGAAGAAGAAATGAAACTCTCCTGGGAGTGCTTTGGTGATTCTATGGCTTCAACTGGCTAG GGTGAACAGTCAACAGGGAGAAGAGGATCCTCAGGCCTTGAGCATCCAGGAGGTGAAAATGCCAC CATGAACCTGCAGTTACAAAACCTAGTATAACAATTTACAGTGGTATAGACAAAATTCAGGTAGAGGCC TTGTCCACCTAATTTAATACGTTCAAATGAAAGAGAGAAACACAGTGGAAGATTAAGAGTCACGCTT GACACTTCCAAGAAAAGCAGTTCCTTGTGATCACGGCTTCCCGGGCAGCAGACACTGCTTCTTACT TCTGTGCTACAAAGGGTGGGAACAACAGACTCGCTTTTGGGAAGGGGAACCAAGTGGTGGTCATAC CAATATCCAGAACCTGACCCTGCCGTGTACCAGCTGAGAGACT
362	AAAATGCCCTCCTTTCTCCACAGGACCAGATGCCTGAGCTAGGAAAGCCTCATTCTGCTGTGA TCCTGCCATGGATACCTGGCTCGTATGCTGGCAATTTTATGCTCTTGAAGCAGGACTCACAGAA CCTGAAGTCACCCAGACTCCCAGCCATCAGGTCACACAGATGGGACAGGAAGTGATCTTGCGCTGT GTCCCCATCTCTAATCACTTATACTTCTATTGGTACAGACAAATCTTGGGGCAGAAAGTCGAGTTTCT GGTTTCCTTTTATAATAATGAAATCTCAGAGAAGTCTGAAATATTCGATGATCAATTCTCAGTTGAAAG GCCTGATGGATCAAATTTCACTCTGAAGATCCGGTCCACAAAGCTGGAGGACTCAGCCATGTACTTC TGTGCCAGCAGTGCCTGGACAGGGGAGACGGGCTACACCTTCGGTTCGGGGACCAGGTTAACCGT TGATAGGACCTGAACAAGGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
363	ATATGTAAAATGAAGGGTCTGTGGAAGGACATGAATAAAGCACAGGAGGTTGAAGTCAGATTTGCAG CTTTCTAGGCAGGAGACAAGACAATCTGCATCTTCACAGGAGGGATGGCCATGCTCCTGGGGGCAT CAGTGCTGATTCTGTGGCTTCAGCCAGACTGGGTAAACAGTCAACAGAAGAATGATGACCAGCAAGT TAAGCAAAATTCACCATCCCTGAGCGTCCAGGAAGGAAGAATTTCTATTCTGAAGTGTGACTATACTA ACAGCATGTTTGATTATTTCTATGGTACAAAAAATACCCTGCTGAAGGTCCTACATTCCTGATATCTA TAAGTTCCATTAAGGATAAAAAATGAAGATGGAAGATTCAGTGTCTTCTTAAACAAAAGTGCCAAAGCAC CTCTCTCTGCACATTGTGCCCTCCCAGCCTGGAGACTCTGCAGTGTACTTCTGTGCAGCAACCCGC GCTGGTGGTACTAGCTATGGAAGCTGACATTTGGACAAGGGACCATCTTACTGTCCATCCAAATA TCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
364	TTCCTCTGCTCTGGCAGCAGATCTCCAGAGGGAGCAGCCTGACCACATCACTGGCCCAGAAGAGG AGGCGTCTGTCCCCAGACTAGCTGAAGGAAAGGCTGGCTTGGATGATGCTCTGCTCTCTCCTTGC CCTTCTCCTGGGCACTTTCTTTGGGGTCAGATCTCAGACTATTCATCAATGGCCAGCGACCCCTGGTG CAGCCTGTGGGCAGCCCGCTCTCTCTGGAGTGCAGTGTGGAGGGAACATCAACCCCAACCTATAC TGGTACCAGCAGGCTGCAGGCAGGGGCTCCAGCTGCTCTTCTACTCCGTTGGTATTGGCCAGATC AGCTCTGAGGTGCCCCAGAATCTCTCAGCCTCCAGACCCAGGACCGGCAGTTCATCCTGAGTTCT AAGAAGCTCCTTCTCAGTACTCTGGCTTCTATCTCTGTGCCTGGAGTGTACTAGCAGGGGTTTCCC AGTACTTCGGGCCAGGCACGCGGCTCCTGGTGTCTGAGGACCTGAAAAACGTGTTCCACCCGAG GTCGCTGTGTTTGAGCCATCAGA

365	GATCTTAATTGGGAAGAACAAGGATGACATCCATTCGAGCTGTATTTATTCCTGTGGCTGCAGCTG GACTTGGTGAATGGAGAGAATGTGGAGCAGCATCCTTCAACCCTGAGTGTCCAGGAGGGAGACAGC GCTGTTATCAAGTGACTTATTAGACAGTGCCTCAAACCTACTTCCCTTGGTATAAGCAAGAACTTGG AAAAAGACCTCAGCTTATTATAGACATTCTGTTCAAATGTGGGCGAAAAAGACCAACGAATTGCTG TTACATTGAACAAGACAGCCAAACATTTCTCCCTGCACATCACAGAGACCCAACCTGAAGACTCGGC TGCTACTTCTGTGCAGCAAGTATAGCCACCGACAAGCTCATCTTTGGGACTGGGACCAGATTACAA GTCTTTCCAAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
366	AGAGGACCAGTATCCCTCACAGGGTGACACCTGACCAGCTCTGTCCCACCTGGCCATGGGCTCCAG GTACCTCTGATGGGAAGACCTTTGTCTCTTGGGAACAAGTGAATCCTTGGCACAGGCCAGTGGATT CTGCTGTGCAGAACAGAGAGCAGTGGACCTCAGGAGGCCCTGCAAGGGGAGGACATAGGACAGTGA CATCACAGTATGCCCTCCCACCAGGAAAAGCAAGGCTGAGAATTTAGCTCTTTCCAGGAGGACCA AGCCCTGAGCACAGACAGTGTGCTGCCCTTTGTGCCATGGGCTCCAGGCTGCTCTGTTGGG TGCTGCTTTGTCTGCTGGGAGCAGGCCAGTAAAGGCTGGAGTCACTCAAACCTCAAGATATCTGAT CAAAACGAGAGGACAGCAAGTGACACTGAGCTGCTCCCTATCTCTGGGCATAGGAGTGTATCCTG GTACCAACAGACCCCAGGACAGGGCCTTCAGTTCCCTTTGAATACTTCAGTGAGACACAGAGAAAC AAAGGAACTTCCCTGGTTCGATTCTCAGGGCGCCAGTTCTCTAACTCTCGCTCTGAGATGAATGTGA GCACCTTGAGCTGGGGGACTCGGCCCTTTATCTTTGCGCCAGCAGCTGGAGGGGACAGGGGGAA GGCTACACCTTCGGTTCGGGGACCAGGTTAACCCTGTAGAGGACCTGAACAAGGTGTTCCACCC GAGGTCGCTGTGTTTGAGCCATCAGA
367	AGTCAACTTCTGGGAGCAGATCTCTGCAGAATAAAAAAGCAATCTGACGACCTTCTTGGTGA TTTTGTGGCTTTATTTTATAGGGGAATGGCAAAAACCAAGTGGAGCAGAGTCTCAGTCCCTGAT CATCCTGGAGGGAAAGAACTGCACTCTTCAATGCAATTATACAGTGAGCCCCCTCAGCAACTTAAGG TGGTATAAGCAAGATACTGGGAGAGGTCTGTTTCCCTGACAATCATGACTTTCAGTGAGAACACAA AGTGAACGGAAGATATACAGCAACTCTGGATGCAGACACAAAGCAAAGCTCTCTGCACATCACAGC CTCCAGCTCAGCGATTACAGCTCTACATCTGTGTGGTGACCGGGGGGCAACCAACTCTTCTTT GGGACTGGAACGAGACTACCGTTATTCCCTATATCCAGAACCCTGACCCTGCCGTGTACCAGCTG AGAGACT
368	CTCAGAGGACCAGTATCCCTCACAGGGTGACACCTGACCAGCTCTGTCCCACCTGGCCATGGGCTC CAGGTACCTCTGATGGGAAGACCTTTGTCTCTTGGGAACAAGTGAATCCTTGGCACAGGCCAGTG GATTCTGCTGTGCAGAACAGAGAGCAGTGGACCTCAGGAGGCCCTGCAAGGGGAGGACATAGGACA GTGACATCACAGTATGCCCTCCCACCAGGAAAAGCAAGGCTGAGAATTTAGCTCTTTCCAGGAG GACCAAGCCCTGAGCACAGACACAGTGTGCTGCCCTTTGTGCCATGGGCTCCAGGCTGCTCTG TTGGGTGCTGCTTTGTCTCCTGGGAGCAGGCCAGTAAAGGCTGGAGTCACTCAAACCTCAAGATAT CTGATCAAAACGAGAGGACAGCAAGTGACACTGAGCTGCTCCCTATCTCTGGGCATAGGAGTGTA TCCTGGTACCAACAGACCCCAGGACAGGGCCTTCAGTTCCCTTTGAATACTTCAGTGAGACACAGA GAAACAAAGGAACTTCCCTGGTTCGATTCTCAGGGCGCCAGTTCTCTAACTCTCGCTCTGAGATGAA TGTGAGCACCTTGAGCTGGGGGACTCGGCCCTTTATCTTTGCGCCAGCAGTGAGGCTGGGGAGT GGACGCAGTATTTTGGCCAGGCACCCGGCTGACAGTGCTCGAGGACCTGAAAAACGTGTTCCAC CCGAGGTGCTGTGTTTGAGCCATCAGA
369	AGGGGGGAAATTGAAACCTGCCTGATGTGGGATGTGCTGTGGCTGCTGCTTTGTTGCTTGGGACCT CCTCTGACCTAGGATCAGACACAGAGTCTGAGTTCTGGGGCCTGGAACCTCAATGTGCACTTGAACA ATGAAGTTGGTGACAAGCATTACTGTACTCTATCTTTGGGTATTATGGGTGATGCTAAGACCACACA GCCAAATTCAATGGAGAGTAACGAAGAAGAGCCTGTTCACTTGCCTTGTAACCACTCCACAATCAGT GGAAGTGATTACATACATTGGTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTTCATGGTC TTACAAGCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTCCAGTACCTT GATCCTGCACCGTGCTACCTTGAGAGATGCTGCTGTGTAATACTGCTGCTGGTGAAGGAAATGAG AAATTAACCTTTGGGACTGGAACAAGACTCACCATCATACCCAATATCCAGAACCCTGACCTGCCG TGTACCAGCTGAGAGACT
370	GAATCCAGGTATGGCTTCTGATTGGTGCAATCTCCTGCACCAATGAGCAAAGTAACTTCTGCTGGG AAGCTCATTCAGTAAAACTGATTGAAGTGTGTTTTCTAAATAGCTAAGGGATGGAGACTGTTCTGCA AGTACTCCTAGGGATATTGGGGTCCAAAGCAGCCTGGGTGAGTACCAAGAACTGGAGCAGAGTCC TCAGTCTTGATCGTCCAAGAGGGAAAGAATCTCACCATAAACTGCACGTATCAAGACGTTATAT GGCTTAACTGGTATAAGCAAAAGTATGGTGAAGGTCTTATCTTCTGATGATGCTACAGAAAGGTGG GGAGAGAAAAGTCATGAAAAGATAACTGCCAAGTTGGATGAGAAAAAGCAGCAAAGTTCCCTGCAT ATCACAGCCTCCCAGCCCAGCCATGCAGGCATCTACCTCTGTGGAGCAGACGTACAAGGAAGCCAA GGAAATCTCATCTTTGAAAAGGCACTAACTCTCTGTTAAACCAATATCCAGAACCCTGACCTGCG CGTGATACCAGCTGAGAGACT

371	AAAATGCCCTCCTTTCTCCACAGGACCATGCTGAGCTAGGAAAGCCTCATTCTCGTGTGA TCCTGCCATGGATACCTGGCTCGTATGCTGGGCAATTTTGTAGTCTCTTGAAGCAGGACTCACAGAA CCTGAAGTACCCAGACTCCCAGCCATCAGGTCACACAGATGGGACAGGAAGTGATCTTGCCTGT GTCCCCATCTCTAATCACTTATACTTCTATTGGTACAGACAATCTTTGGGGCAGAAAGTCGAGTTTCT GGTTTCCTTTTATAATAATGAAATCTCAGAGAAGTCTGAAATATTCGATGATCAATTCTCAGTTGAAAG GCCTGATGGATCAAAATTTCACTCTGAAGATCCGGTCCCAAAGCTGGAGGACTCAGCCATGTACTTC TGTGCCAGCAGGCTGGGGGGAAGCACTGAAGCTTTCTTTGGACAGGACCACTCACAGTTCAGAGTT GTAGAGGACCTGAACAAGGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
372	GAGGGCGATAAGAGGAGGGGGTAGTGATATACCAGGGGTTGTGAAAATAACCTCTTTTTTCTAATTG GTAGGACAGATTCTTTTTATGATTCTCTAAAGTGGAAAGAAATAAGTATCTCTGCTATGTTCAATTCCTT TTGGATTGAAAATTTAATCCTCAGTGAACCAGGGCAGAAAAGAATGATGATATCCTTGAGAGTTTAA CTGGTGATCTGTGGCTTCAGTTAAGCTGGGTTTGGAGCACAACGGAAGGAGGTTGGAGCAGGATCCT GGACCCCTCAATGTTCCAGAGGGAGCCACTGTGCTGTTCAACTGTACTTACAGCAACAGTGCCTTCTC AGTCTTTCTTCTGGTACAGACAGGATTGCAGGAAAGAACCTAAGTTGCTGATGTCCGTATACTCCAG TGGTAATGAAGATGGAAGGTTTACAGCACAGCTCAATAGAGCCAGCCAGTATATTTCCCTGCTCATC AGAGACTCCAAGCTCAGTGATTACAGCCACCTACCTCTGTGTGGTGGATTTTATACCTCAGGAACCT ACAAATACATCTTTGGAACAGGCACCAGGCTGAAGGTTTTAGCAAATATCCAGAACCCTGACCCTGC CGTGACCAGCTGAGAGACT
373	GTATCCCTCCTCGCTGGTGAATGGAGGCAGTGGTCACAACCTCTCCCAGAGAAGGTGGTGTGAGG CCATCCCGAAGATGCTGCTGCTTCTGCTGCTTCTGGGGCCAGGCTCCGGGCTTGGTGCTGTCTGTC TCTCAACATCCGAGCAGGGTTATCTGTAAGAGTGGAACCTCTGTGAAGATCGAGTGCCGTTCCCTGG ACTTTCAGGCCACAACCTATGTTTTGGTATCGTCAGTCCCGAACAGAGTCTCATGCTGATGGCAACT TCCAATGAGGGCTCCAAGGCCACATACGAGCAAGGCGTGCAGAAAGGACAAGTTTCTCATCAACCAT GCAAGCCTGACCTTGCCACTCTGACAGTGACCAAGTGCCCATCCTGAAGACAGCAGCTTCTACATCT GCAGTGCTAGAGATCGGGAGGCGCGGCTATGGCTACACCTTCGGTTCGGGGACCAAGGTTAACC GTTGTAGAGGACCTGAACAAGGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
374	AAGCACTCTTCTAGCCCAGAGAAGTCTGTTCCAGGACGGGCTCTTTCAGGAGCAGCTAAAGTCAGG GGCCATGTCCACCATGTGATAGAAAGACAAGATGGTCTGAAATTCTCCGTGTCCATTCTTTGGATT CAGTTGGCATGGGTGAGCACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGA GAAAATCTCACTGTGTAAGTCAACTCCTCAAGTGTGTTTTCCAGCTTACAATGGTACAGACAGGAGCC TGGGGAAGGTCTGCTCTGCTGGTAGACAGTAGTTACGGGTGGAGAAGTGAAGAAGCTGAAGAGACT AACCTTTTCAGTTTGGTGTGACAAGAAAGACAGTCTCTCCACACTGACAGCAAGCCAGCCTGGTGAT ACAGGCCTCTACCTCTGTGACAGGTTAGATGACAAGATCATCTTTGAAAAGGGACACGACTTCATA TTCTCCCAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACT
375	GGCTTTGTGCGGTGGAGCTGATTGGTTGCAGGAGCAGCAACAGTCCAGAGCCAAGTCATGACACC GACCTCCCCAAGGTTTAGTTAAATATATCTTATGGTGAAAATGCCCGGAGCAGAAGGCAAGGATC ATGAAGAGGATATTTGGAGCTCTGCTGGGCTCTTGAGTCCCGAGGTTTGTGCTGTGAGAGGAATA CAAGTGGAGCAGAGTCTCTCAGACTGATTCTCCAGAGGAGGCAACTTCCACGCTCGCGTGCAAT TTTTCTGACTCTGTGAACAATTTGCAAGTGGTTTCATCAAAACCCTTGGGGACAGCTCATCAACCTGTT TTACATTCCCTCAGGGACAAAACAGAATGGAAGATTAAGCGCCACGACTGTCGCTACGGAACGCTAC AGCTTATTGTACATTTCTCTTCCAGACCACAGACTCAGGCGTTTATTCTGTGCTGTGGCGGGTA GCAACTATCAGTTAATCTGGGGCGCTGGGACCAAGCTAATTATAAGCCAGATATCCAGAACCCTGA CCCTGCCGTGTACCAGCTGAGAGACT
376	ACTAAGTATATCTCTGTTTCGAGTTGCCTTCAACTCGAAACATCCAGCAGAGGATGGGCTAGAGA TGGAGTAGGAGATCCAGTCCCCAAGCCCTAGAGATGCATTTGTGGAGGCAATGATGTCACTGTGGG AACTGCCATGAGAGGACAGGGACGTCCTCCTTGGGGGCTGTTGCTCACAGTGACCTGATTGGGC AAAGCTCCCATCCTTCCCTGACCCTGCCATGGGCACCAGGCTCCTCTGCTGGCGGCCCTCTGTCT CCTGGGAGCAGAACTCACAGAAGCTGGAGTTGCCAGTCTCCAGATATAAGATTATAGAGAAAAG GCAGAGTGTTGGCTTTTGGTGAATCCTATATCTGGCCATGCTACCCCTTACTGGTACCAGCAGATC CTGGGACAGGGCCAAAGCTTGATTGAGTTTCAAGTAAACGCTGTAGTGATGATTACAGTTGCTG CTAAGGATGCAATTTCTGCAGAGAGGCTCAAAGGATAGACTCCACTCTCAAGATCCAACTGCAAA GCTTGAGGACTCGGCCGTGTATCTGTGCCAGCAGCGACCCATTAGCGGGAGAGGGGATGAGC AGTTCTTCGGGCCAGGGACACGGCTCACCGTGCTAGAGGACCTGAAAACGTTTCCACCCGAGG TCGCTGTGTTTGAGCCATCAGA
377	GGCTCGTGTGTGTGTGTGTGTGTGTGTGTGTGCTTGAGAGAGAGAGAAGGAGAGAAAGAG AGAGAATGGGAAGGCGATAAGAGGAGGGGTTAGTGATATACCAGGGGTTGTGAAAATAACCTCTT TTTTCTAATTTGGGAGGACAGATCTTTTTTACGATTCTCTAAGTGGAAAGAAATAAAGTATCTCTGCTATG

	TTCATTTCTTTTGGATTGAAAATTTAATCCTCAGTGAACCAAGGCAGAAAAGAATGATGATATCCTT GAGAGTTTTACTGGTGATCCTGTGGCTTCAGTTAAGCTGGGTTTGGAGCCAACGGAAGGAGGTGGA GCAGGATCCTGGACCCTTCAATGTTCCAGAGGGAGCCACTGTCGCTTTCAACTGTACTTACAGCAAC AGTGCTTCTCAGTCTTTCTTCTGGTACAGACAGGATTGCAGGAAAAGAACCTAAGTTGCTGATGTCCG TATACTCCAGTGGTAATGAAGATGGAAGGTTTACAGCACAGCTCAATAGAGCCAGCCAGTATATTTT CCTGCTCATCAGAGACTCCAAGCTCAGTGATTACAGCCACCTACCTCTGTGTGGTGAACAAAGCCACC TCAGGAACCTACAAATACATCTTTGGAACAGGCACCAGGCTGAAGGTTTTAGCAAATATCCAGAACC CTGACCCTGCCGTGTACCAGCTGAGAGACT
378	GTCATCCCTCCTCGCTGGTGAATGGAGGCAGTGGTCACAACCTCTCCCCAGAGAAGGTGGTGTGAGG CCATCACGGAAGATGCTGCTGCTTCTGCTGCTTCTGGGGCCAGGCTCCGGGCTTGGTGCTGTCGTC TCTCAACATCCGAGCTGGGTATCTGTAAGAGTGGAACCTCTGTGAAGATCGAGTGCCGTTCCCTGG ACTTTCAGGCCACAACATATGTTTTGGTATCGTCAGTTCCCGAAACAGAGTCTCATGTGATGGCAACT TCCAATGAGGGCTCCAAGGCCACATACGAGCAAGGCGTCGAGAAGGACAAGTTTCTCATCAACCAT GCAAGCCTGACCTTGCCACTCTGACAGTGACCAGTGCCCATCCTGAAGACAGCAGCTTCTACATCT GCAGTGCTAGAGATCGGGAGGCGGCCGCTATGGCTACACCTTCGGTTCGGGGACCAGGTTAACC GTTGTAGAGGACCTGAACAAGGTGTTCCACCCGAGGTCGCTGTGTTTGAGCCATCAGA
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383	KVVGARGVGKSAFLQAFLGR
384	GQKSPRFRVSCFLRLGRST
385	RFRRVSCFLRLGRSTLLELE
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387	EVQDCLKQLMMSLLQLYRFS
388	GYSPLHILAIGTRSGAIKL
389	VATFPVYTMVAIPVCKD
390	PPLYRQRYQFIKNLVDQHEP
391	PLYRQRYQFIKNLVDQHEPK
392	VSRPELLRESISAFVPMPT
393	TDRALQNKISAFVPMPTP
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399	LGLIFALTNRHKYPLNLYL
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404	LHRDKALLKRLKGMQKKRP
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407	QTVYVQHILITFLDRPIQMCC
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414	ISLLDTSNLELPEAVVFQDS
415	AASCEPLASVLRAKPTSRS
416	GAGPDPLRLRGHLPVRTSCP
417	TQRSVLLCKVVGACGVGKSA
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419	GQKSPRFRRTCFRLRGRST
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421	ALAFLLLISTAANLSLLSR
422	EVQDCLKQLMMSLLRLYRFS
423	GYSPLRILAIATRSGAIKL
424	VATFPVYTMGAIPVCKD
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426	PLYRQRYQFVKNLVDQHEPK
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428	TDRALQNKGISAFVPMPTP
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434	LGLIFALILNRHKYPLNLYL
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437	AGTGLTSIIATMARTVYCT
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441	ITVQTVYVQHPITFLDRPIQ
442	QTVYVQHPITFLDRPIQMCC
443	PGLISVFSSSQELGAALAQL
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445	VRIALALKGIDYKTPINLI
446	DRAEKFNRGIRKLGVTPPEGQ
447	EKFNRGIRKLGVTPPEGQSYL
448	ATGYPS
449	DFQATT
450	YGATPY
451	SNHLY
452	DFQATT
453	VTNFRS
454	SGHNS
455	DSSSTY
456	MNHEY
457	TTSDR
458	MNHEY
459	MNHEY
460	SSVSVY
461	SGHTA
462	SGHTA
463	ATGYPS
464	NTAFDY
465	DFQATT

466	DRGSQS
467	MNHEY
468	ATGYPS
469	DFQATT
470	NIATNDY
471	SGHRS
472	TISGTDY
473	DFQATT
474	TSGFYG
475	VSNAYN
476	SGHNT
477	VSNAYN
478	SGHNT
479	SIFNT
480	MNHNY
481	SIFNT
482	SQVTM
483	DRGSQS
484	LGHDT
485	VGISA
486	VGISA
487	MNHEY
488	TRDTTTY
489	SGHNT
490	DRGSQS
491	KGHDR
492	TRDTTTY
493	KGHSH
494	SIFNT
495	LNHDA
496	DSVNN
497	LGHNT
498	TISGNEY
499	MNHEY
500	SSVSVY
501	WSHSY
502	NSASDY
503	NSASDY
504	SEHNR
505	SSVPPY
506	MNHEY
507	MNHEY
508	DSSSTY
509	MNHEY
510	TSINN
511	SNHLY
512	TSINN
513	SNHLY
514	DSASNY
515	SGHDY
516	TSINN
517	SNHLY
518	NSMFDY
519	GTSNPN
520	DSASNY

521	SGHRS
522	VSPFSN
523	SGHRS
524	TISGTDY
525	KTLYG
526	SNHLY
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624	YFSGDTLV
625	FYNNEI
626	SNEGSKA
627	LTSSGIE
628	FNNNVP
629	IFSNMDM
630	SMNVEV

631	LLSNGAV
632	SMNVEV
633	SMNVEV
634	YLSGSTLV
635	FQGNSA
636	FQGNSA
637	ATKADDK
638	IRPDVSE
639	SNEGSKA
640	IYSNGD
641	SVGAGI
642	ATKADDK
643	SNEGSKA
644	GYKTK
645	YFSETQ
646	GLTSN
647	SNEGSKA
648	NALDGL
649	GSKP
650	YENEEA
651	GSKP
652	YENEEA
653	LYKAGEL
654	SVGAGI
655	LYKAGEL
656	ANQGSEA
657	IYSNGD
658	YNNKEL
659	LSSGK
660	LSSGK
661	SVGAGI
662	RNSFDEQN
663	YYREEE
664	IYSNGD
665	SFDVKD
666	RNSFDEQN
667	LQKENI
668	LYKAGEL
669	SQIVND
670	IPSGT
671	FRNRAP
672	GLKNN
673	SMNVEV
674	YLSGSTLV
675	SAAADI
676	IRSNMDK
677	IRSNMDK
678	FQNEAQ
679	YTTGATLV
680	SVGAGI
681	SVGAGI
682	IFSNMDM
683	SVGAGI
684	IRSNERE
685	FYNNEI

686	IRSNERE
687	FYNNEI
688	IRSNVGE
689	FNNNVP
690	IRSNERE
691	FYNNEI
692	ISSIKDK
693	SVGIG
694	IRSNVGE
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696	MTFSENT
697	YFSETQ
698	GLTSN
699	LQKGEE
700	FYNNEI
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702	SNEGSKA
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724	GCCACGAAGGCTGATGACAAG
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727	ATATACTCCAATGGTGAC
728	TCAGTTGGTGCTGGTATC
729	GCCACGAAGGCTGATGACAAG
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773	ATACGTTCAAATGAAAGAGAG
774	TTTTATAATAATGAAATC
775	ATTCGTTCAAATGTGGGCGAA
776	TTTAAACAACAAGTTCCG
777	ATACGTTCAAATGAAAGAGAG
778	TTTTATAATAATGAAATC
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785	GGTCTTACAAGCAAT
786	CTACAGAAAGGTGGGGAAGAG
787	TTTTATAATAATGAAATC
788	GTATACTCCAGTGGT
789	TCCAATGAGGGCTCCAAGGCC
790	GTAGTTACGGGTGGAGAAGTG
791	ATTCCCTCAGGGACA
792	TTTCAGAATAACGGTGTA
793	GTATACTCCAGTGGT
794	TCCAATGAGGGCTCCAAGGCC
795	TCCAATGAGGGCTCCAAGGCC

Claims

1. A method of selecting an immunotherapeutic agent for treating a disease in an individual, the method comprising
- 5
- (a) identifying a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual; and
- 10
- (b) selecting an immunotherapeutic agent that comprises an antigen binding molecule that binds to the peptide antigen.
2. A method of treating a disease in an individual, the method comprising
- 15 administering to the individual an immunotherapeutic agent that comprises an antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual.
- 20
3. A method of treating a disease in an individual, the method comprising administering a composition comprising a peptide antigen to the individual and thereby inducing an immune response specific for the peptide antigen, wherein the peptide antigen is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC
- 25 molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual.
4. An immunotherapeutic agent for use in a method of treating a disease in an individual, wherein the method comprises administering the immunotherapeutic agent to
- 30 the individual, and the immunotherapeutic agent comprises an antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in the individual,

(ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual.

5. A composition comprising a peptide antigen for use in a method of treating a disease in an individual, the method comprising administering the composition to the individual and thereby inducing an immune response specific for the peptide antigen, wherein the peptide antigen is (i) encoded by a germline variation in the individual, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual.

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6. An antigen binding molecule that binds to a peptide antigen that is (i) encoded by a germline variation in an individual having a disease, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the individual.

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7. The method of any one of claims 1 to 3, immunotherapeutic agent for use of claim 4, composition for use of claim 5, or antigen binding molecule of claim 6, wherein the MHC molecule is a MHC class I molecule or a MHC Class II molecule.

8. The method of any one of claims 1 to 3 and 7, immunotherapeutic agent for use of claim 4 or 7, composition for use of claim 5 or 7, or antigen binding molecule of claim 6 or 7, wherein the peptide antigen binds to an antigen binding domain that is expressed by an immune cell from a donor whose genome does not comprise the germline variation.

9. The method, immunotherapeutic agent for use, composition for use, or antigen binding molecule of claim 8, wherein the donor does not have the disease.

10. The method, immunotherapeutic agent for use, composition for use, or antigen binding molecule of claim 8 or 9, wherein the germline variation comprises one or more nucleotide substitutions, insertions and/or deletions relative to the donor genome.

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11. The method of any one of claims 1 to 3 and 7 to 10, immunotherapeutic agent for use of any one of claims 4 and 7 to 10, composition for use of any one of claims 5 and 7 to 10, or antigen binding molecule of any one of claims 6 to 10, wherein the disease is cancer and the target cell is a cancer cell.
- 5
12. The method, immunotherapeutic agent for use, composition for use, or antigen binding molecule of claim 11, wherein the cancer is acute myeloid leukaemia (AML) and the cancer cell is an AML cell.
- 10
13. The method of any one of claims 1 to 3 and 7 to 12, immunotherapeutic agent for use of any one of claims 4 and 7 to 12, composition for use of claims 5 and 7 to 12, or antigen binding molecule of any one of claims 6 to 15, wherein the antigen binding molecule is a T cell receptor (TCR), a chimeric antigen receptor (CAR), an antibody, antibody fragment or bi-specific T cell engager (BiTE).
- 15
14. The method, immunotherapeutic agent for use, composition for use, or antigen binding molecule of claim 13, wherein the antibody fragment comprises a fragment antigen-binding (Fab) fragment, a F(ab')₂ fragment, a single chain variable fragment (scFv), a scFv-Fc, or a single domain antibody.
- 20
15. The method of any one of claims 1, to 3 and 7 to 14, immunotherapeutic agent for use of any one of claims 4 and 7 to 14, composition for use of any one of claims 5 and 7 to 14, or antigen binding molecule of any one of claims 6 to 14, wherein the antigen binding molecule comprises the antigen binding domain defined in claim 8 or a variant thereof.
- 25
16. The method of any one of claims 1 to 3 and 7 to 15, or immunotherapeutic agent for use of any one of claims 4 and 7 to 15, wherein the immunotherapeutic agent further comprises an immune cell that expresses the antigen binding molecule on its surface, and optionally wherein the immune cell is a T cell.
- 30

17. The method or immunotherapeutic agent for use of claim 16, wherein the immune cell is derived from a donor whose genome does not comprise the germline variation.
18. The method or immunotherapeutic agent for use of claim 16 or 17, wherein the
5 donor does not have the disease.
19. The method or immunotherapeutic agent for use of claim 17, wherein the antigen binding molecule is a TCR.
- 10 20. The method or immunotherapeutic agent for use of claim 16, wherein the antigen binding molecule is a CAR, optionally wherein the immune cell is autologous or allogeneic with respect to the individual.
21. The method of claim 3, or composition for use of claim 5, wherein the immune
15 response is a T cell response, optionally wherein the T cell response comprises a CD4+ T cell response or a CD8+ T cell response.
22. The method of claim 3 or 21, or composition for use of claim 5 or 21, wherein the method further comprises administering to the individual immune cells specific for the
20 peptide antigen.
23. A peptide antigen that is (i) encoded by a germline variation in an individual having a disease, (ii) capable of binding to a MHC molecule, and (iii) present on the surface of a target cell in the individual and optionally absent on the surface of non-target cells in the
25 individual.
24. A polynucleotide encoding the antigen binding molecule of any one of claims 6 to 15 or the peptide antigen of claim 23.
- 30 25. A vector comprising the polynucleotide of claim 24.

26. The method of any one of claims 1 to 3 and 7 to 22, immunotherapeutic agent for use of any one of claims 4 and 7 to 20, composition for use of any one of claims 5, 7 to 15, 21 and 22, antigen binding molecule of any one of claims 6 to 15, peptide antigen of claim 23, polynucleotide of claim 24, or vector of claim 25, wherein the peptide antigen
5 comprises or consists of one or more of SEQ ID NOs: 1 to 4 and 380 to 412.

27. The method of any one of claims 1, 2, 7 to 22, and 26, immunotherapeutic agent for use of any one of claims 4, 7 to 20 and 26, composition for use of any one of claims 5, 7 to 15, 21, 22 and 26, or antigen binding molecule of any one of claims 6 to 15 and 26,
10 wherein the antigen binding molecule comprises:

(a) a CDR3 from one or more of SEQ ID NOs: 6, 10, 12 16, 20, 206, 208, 211, 213, 215, 218, 221, 222, 224, 226, 228, 230, 232, 233, 235, 237, 239, 241, 243, 244, 246, 248, 250, 252, 254, 256, 258, 260, 261, 263, 266, 268, 270, 272, 274, 276, 278, 280, 282, 283, 285,
15 287, 288, and 290; and/or

(b) a CDR3 from one or more of SEQ ID NOs: 8, 14, 18, 22, 207, 209, 210, 212, 214, 216, 217, 219, 220, 223, 225, 227, 229, 231, 234, 236, 238, 240, 242, 245, 247, 249, 251, 253, 255, 257, 259, 262, 264, 265, 267, 269, 271, 273, 275, 277, 279, 281, 284, 286, 289, 291,
20 and 292.

28. The method, immunotherapeutic agent for use, composition for use, or antigen binding molecule of claim 27, wherein the antigen binding molecule comprises:

25 (a) CDR1, CDR2 and CDR3 from one or more of SEQ ID NOs: 6, 10, 12 16, 20, 206, 208, 211, 213, 215, 218, 221, 222, 224, 226, 228, 230, 232, 233, 235, 237, 239, 241, 243, 244, 246, 248, 250, 252, 254, 256, 258, 260, 261, 263, 266, 268, 270, 272, 274, 276, 278, 280, 282, 283, 285, 287, 288, and 290; and/or

30 (b) CDR1, CDR2 and CDR3 from one or more of SEQ ID NOs: 8, 14, 18, 22, 207, 209, 210, 212, 214, 216, 217, 219, 220, 223, 225, 227, 229, 231, 234, 236, 238, 240, 242, 245,

247, 249, 251, 253, 255, 257, 259, 262, 264, 265, 267, 269, 271, 273, 275, 277, 279, 281, 284, 286, 289, 291, and 292.

29. The method, immunotherapeutic agent for use, composition for use, or antigen
5 binding molecule of claim 28, wherein the antigen binding molecule comprises:

(a) one or more of SEQ ID NOs: 6, 10, 12 16, 20, 206, 208, 211, 213, 215, 218, 221, 222,
224, 226, 228, 230, 232, 233, 235, 237, 239, 241, 243, 244, 246, 248, 250, 252, 254, 256,
258, 260, 261, 263, 266, 268, 270, 272, 274, 276, 278, 280, 282, 283, 285, 287, 288, and
10 290; and/or

(b) one or more of SEQ ID NOs: 8, 14, 18, 22, 207, 209, 210, 212, 214, 216, 217, 219,
220, 223, 225, 227, 229, 231, 234, 236, 238, 240, 242, 245, 247, 249, 251, 253, 255, 257,
259, 262, 264, 265, 267, 269, 271, 273, 275, 277, 279, 281, 284, 286, 289, 291, and 292.
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