



US 20180355038A1

(19) **United States**(12) **Patent Application Publication**
Smith et al.(10) **Pub. No.: US 2018/0355038 A1**(43) **Pub. Date: Dec. 13, 2018**(54) **OPTIMIZED ANTI-CD3 BISPECIFIC
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NY (US)(21) Appl. No.: **15/780,504**(22) PCT Filed: **Sep. 23, 2016**(86) PCT No.: **PCT/US2016/053525**

§ 371 (c)(1),

(2) Date: **May 31, 2018****Related U.S. Application Data**(60) Provisional application No. 62/222,605, filed on Sep.
23, 2015.**Publication Classification**(51) **Int. Cl.**

<i>C07K 16/28</i>	(2006.01)
<i>C07K 16/46</i>	(2006.01)
<i>C07K 16/30</i>	(2006.01)
<i>C07K 16/40</i>	(2006.01)
<i>A61P 35/00</i>	(2006.01)

(52) **U.S. Cl.**CPC *C07K 16/2809* (2013.01); *C07K 16/468*
(2013.01); *C07K 16/3069* (2013.01); *C07K*
16/2863 (2013.01); *A61K 2039/505* (2013.01);
A61P 35/00 (2018.01); *C07K 2317/92*
(2013.01); *C07K 2317/31* (2013.01); *C07K*
16/40 (2013.01)

(57)

ABSTRACT

The present invention provides antibodies that bind to CD3 with weak or no detectable binding affinity and methods of using the same. According to certain embodiments, the antibodies of the invention bind human CD3 with low affinity and induce human T cell proliferation and hence induce T cell-mediated killing of tumor cells with high efficacy. According to certain embodiments, the present invention provides bispecific antigen-binding molecules comprising a first antigen-binding domain that specifically binds human CD3 with weak or no detectable binding affinity in an in vitro assay, and a second antigen-binding molecule that specifically binds human tumor-associated antigen. In certain embodiments, the bispecific antigen-binding molecules of the present invention are capable of inhibiting the growth of tumors expressing target antigen, such as PSMA. The antibodies and bispecific antigen-binding molecules of the invention are useful for the treatment of diseases and disorders in which an upregulated or induced targeted immune response is desired and/or therapeutically beneficial. For example, the antibodies of the invention are useful for the treatment of various cancers or other diseases where immunotherapy, i.e. effector cell immunomodulation is warranted.

Specification includes a Sequence Listing.

	Framework 1	CDR 1	Framework 2	CDR 2
Germline hIgHV	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	AMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-P	EVQLVESGGGLVQPGRSLRLSCVASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3-VH-G	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3-VH-G2	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	AMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-G3	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-G4	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	AMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-G5	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-G8	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-G9	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3-VH-G10	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3-VH-G11	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3-VH-G12	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-G13	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-G14	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-G15	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3-VH-G16	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3-VH-G17	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3-VH-G18	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-G19	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-G20	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3-VH-G21	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		

	Framework 1	CDR 1	Framework 2	CDR 2
Germline highV	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	AMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--P	EVQLVESGGGLVQPPGRSLRLSCVASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3--VH--G	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3--VH--G2	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	AMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--G3	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--G4	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	AMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--G5	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--G8	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--G9	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3--VH--G10	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3--VH--G11	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3--VH--G12	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--G13	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--G14	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--G15	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3--VH--G16	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3--VH--G17	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		
CD3--VH--G18	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--G19	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--G20	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSI		
CD3--VH--G21	EVQLVESGGGLVQPPGRSLRLSCAASGFTFDDY	SMHWVRQAPGKGLEWVSGISWNSGSK		

FIG. 1

	Framework 3	CDR 3	Framework 4
Germline h1gHV	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYGYFYHYGMDVWGQGT	TVTVSS
CD3-VH-P	DYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYG	SGYKGFYHYGLDVGQGT	TVTVSS
CD3-VH-G	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYG	SGYKGFYHYGLDVGQGT	TVTVSS
CD3-VH-G2	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYGYFYHYGMDVWGQGT	TVTVSS
CD3-VH-G3	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYGYFYHYGMDVWGQGT	TVTVSS
CD3-VH-G4	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYKGFYHYGMDVWGQGT	TVTVSS
CD3-VH-G5	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYKGFYHYGMDVWGQGT	TVTVSS
CD3-VH-G8	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYG	SGYKGFYHYGLDVGQGT	TVTVSS
CD3-VH-G9	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYKGFYHYGLDVGQGT	TVTVSS
CD3-VH-G10	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYG	SGYKGFYHYGLDVGQGT	TVTVSS
CD3-VH-G11	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYG	SGYKGFYHYGMDVWGQGT	TVTVSS
CD3-VH-G12	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYKGFYHYGLDVGQGT	TVTVSS
CD3-VH-G13	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYG	SGYKGFYHYGLDVGQGT	TVTVSS
CD3-VH-G14	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYG	SGYKGFYHYGMDVWGQGT	TVTVSS
CD3-VH-G15	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYKGFYHYGLDVGQGT	TVTVSS
CD3-VH-G16	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYKGFYHYGMDVWGQGT	TVTVSS
CD3-VH-G17	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYG	SGYKGFYHYGLDVGQGT	TVTVSS
CD3-VH-G18	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYKGFYHYGLDVGQGT	TVTVSS
CD3-VH-G19	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYKGFYHYGMDVWGQGT	TVTVSS
CD3-VH-G20	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYG	SGYKGFYHYGMDVWGQGT	TVTVSS
CD3-VH-G21	GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG	SGYKGFYHYGMDVWGQGT	TVTVSS

FIG. 1
(Cont.)

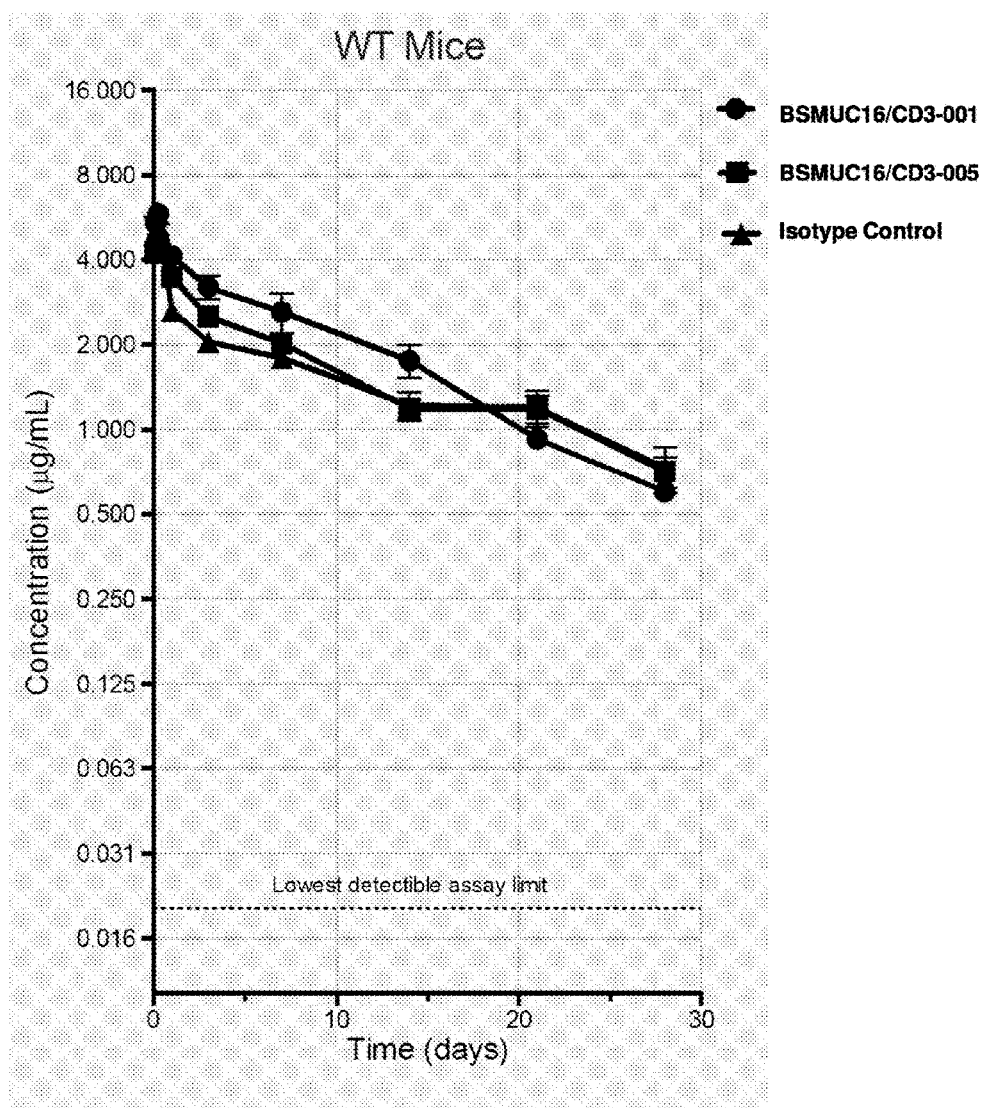


Figure 2A

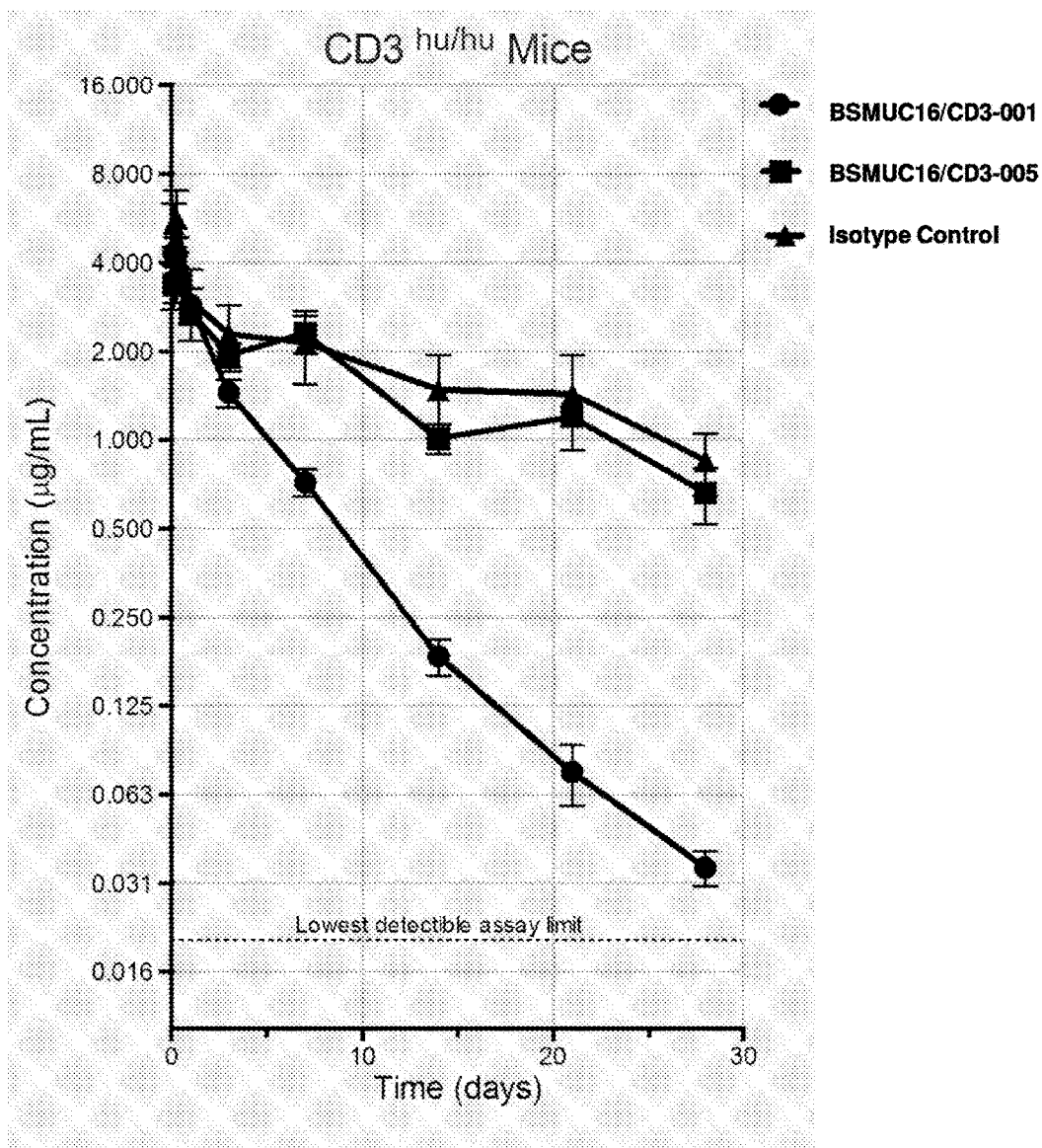


Figure 2B

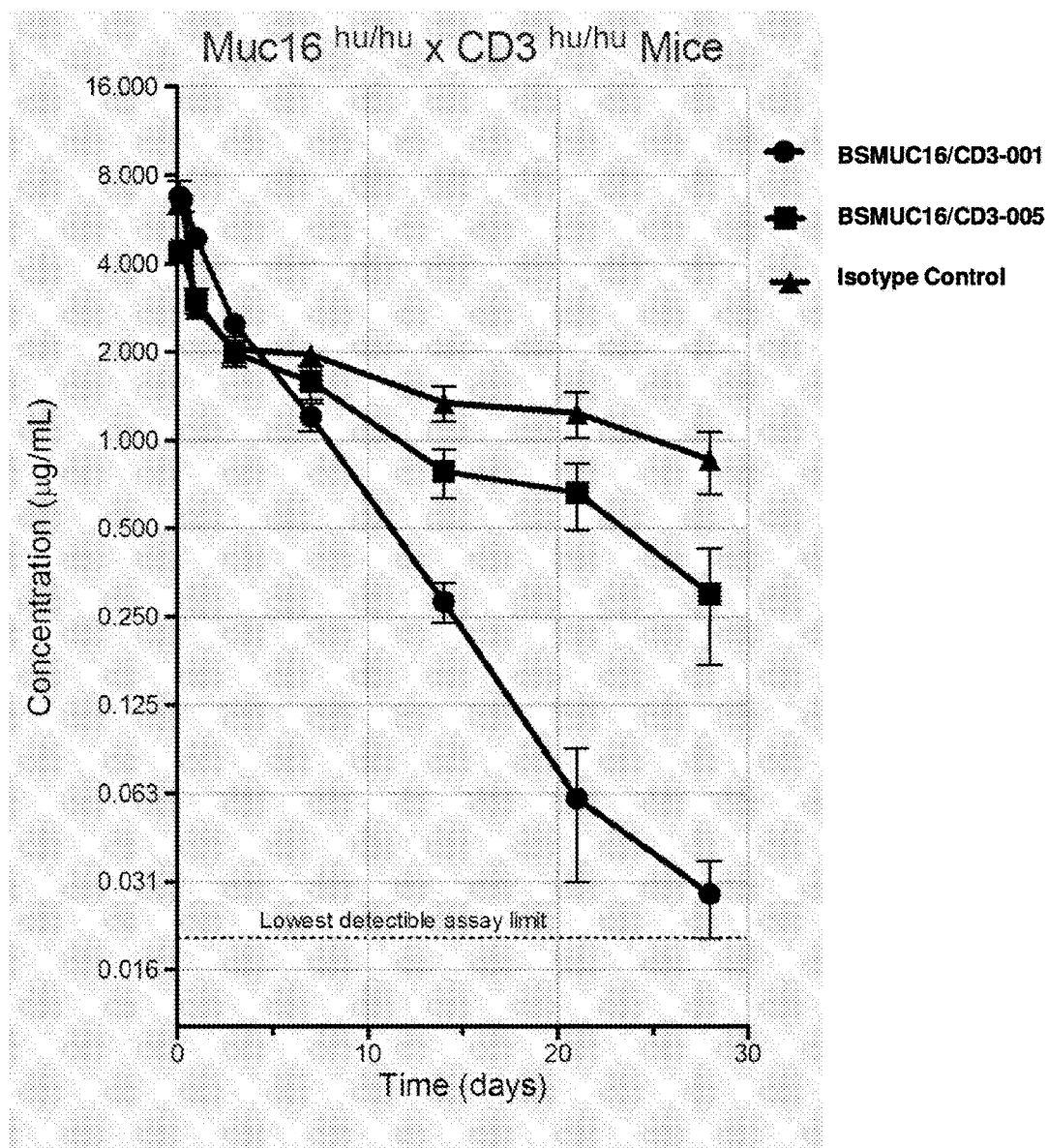


Figure 2C

OPTIMIZED ANTI-CD3 BISPECIFIC ANTIBODIES AND USES THEREOF

REFERENCE TO A SEQUENCE LISTING

[0001] This application incorporates by reference the Sequence Listing submitted in Computer Readable Form as file 10151WO01_ST25.txt, created on Sep. 22, 2016 and containing 264,418 bytes.

FIELD OF THE INVENTION

[0002] The invention related to bispecific antibodies, targeting an effector antigen, such as CD3 antigen, and a tumor associated antigen, and methods of tumor killing. The invention relates to methods of reducing or eliminating tumor burden and controlling the toxic side effects that may be associated with tumor immunotherapy. The present invention provides bispecific antibodies comprising an effector arm which binds to an effector antigen with weak affinity or with no detectable binding affinity, for example, an anti-CD3 antigen-binding arm which binds to CD3 with a K_D of greater than about 500 nM, in an in vitro affinity binding assay.

BACKGROUND

[0003] The promise of therapeutic bispecific antibodies (bsAbs), particularly in cancer immunotherapies, aims to bridge multiple antigen targets in order to elicit a more robust innate immune response to the unwanted target-bearing cells or organism.

[0004] It is now well established that to mediate redirected lysis, a bsAb must cluster a target cell directly to a triggering molecule on an effector cell, such as a T cell. There are many factors to consider in bsAb design, for example, size and composition will affect biodistribution and stability in vivo (Segal, DM, Weiner, G J, and Weiner, LM. *Current Opinion in Immunol* 1999, 11: 558-562; Chames, P. and Baty, D. *MAbs*. 2009, 1(6): 539-547). Differential outcomes are difficult to predict depending on the T cell subset being triggered to respond, as well as the state of the T cell being stimulated. It is well-known that bsAbs do not give consistent results (Manzke O, et al. *Cancer Immunol Immunother*. 1997, 45:198-202). For example, without adequate cytokine production, CD3 crosslinking can induce an apoptotic response in the T cell (Noel P J, Boise L H, Thompson C B: Regulation of T cell activation by CD28 and CTLA4. *Adv Exp Med Biol* 1996, 406:209-217). The subset of T cells and differentiation state of such recruited T cells, e.g. naïve T cells, are important for efficacy, since naïve T cells cannot lyse target cells without preactivation (such as crosslinking with TCR in the presence of IL-2).

[0005] Certain bispecific therapies have been successful, yet, as with many cancer therapies, it comes with a price. Toxicity is the leading cause of failure among cancer therapeutics. It is well known that toxicity of so-called chemotherapeutic drugs is the leading cause of patient side effects and secondary maladies. The act of “cell killing” itself is wrought with trouble for the patient. A plethora of cytotoxic responses can be induced by activation of effector cells e.g. T cells, and a cancer target cell, yet which type of response is most beneficial in tumor immunotherapy remains to be seen. A method of identifying anti-CD3 antibodies for use in a bispecific therapy having reduced side effects while main-

taining efficacy and desirable pharmacokinetic (PK) properties would be advantageous.

[0006] Techniques such as affinity maturation have been described which, based on structure/activity relationship (SAR), utilize mutagenesis to optimize antibodies to have increased and improved binding specificity or affinity for a target antigen compared to the starting antibody (see, e.g. WO2011056997, published May 12, 2011). Modified OKT3 antibodies capable of binding to and interacting with CD3 with varying degrees of affinity while still exhibiting moderate to high T cell activation have been described (U.S. Pat. No. 7,820,166). However, methods of reducing binding affinity of antibody molecules to near or beyond the detectable level of binding have not been described, nor shown to have the requisite efficacy for tumor reduction or suppression.

[0007] Thus, there exists a need for alternative bispecific antigen-binding molecules having controlled cytotoxicity and better PK properties. Such cancer therapies would be quite useful in therapeutic settings.

BRIEF SUMMARY OF THE INVENTION

[0008] In a first aspect, the present invention provides antibodies and antigen-binding fragments thereof that bind human CD3 having weak or no detectable affinity for human and/or cynomolgus CD3. The antibodies according to this aspect of the invention are useful, inter alia, for targeting T cells expressing CD3, and for stimulating T cell activation, e.g., under circumstances where T cell-mediated killing is beneficial or desirable. The anti-CD3 antibodies of the invention, or antigen-binding portions thereof, may be included as part of a bispecific antibody that directs CD3-mediated T cell activation to specific cell types such as tumor cells or infectious agents.

[0009] Exemplary anti-CD3 antibodies of the present invention are listed in Tables 2 and 3 herein. Table 2 sets forth the amino acid sequence identifiers of the heavy chain variable regions (HCVRs), as well as heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3). Table 3 sets forth the sequence identifiers of the nucleic acid molecules encoding the HCVRs, HCDR1, HCDR2 and HCDR3 regions of the exemplary anti-CD3 antibodies. Tables 4 and 5 set forth light chain variable regions (LCVRs), as well as complementarity determining regions (LCDR1, LCDR2 and LCDR3) of the exemplary anti-CD3 antibodies.

[0010] The present invention provides antibodies, or antigen-binding fragments thereof, comprising an HCVR comprising an amino acid sequence selected from any of the HCVR amino acid sequences listed in Table 2, or a substantially similar sequence thereof having having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0011] The present invention also provides antibodies, or antigen-binding fragments thereof, comprising an HCVR and an LCVR amino acid sequence pair (HCVR/LCVR) comprising any of the HCVR amino acid sequences listed in Table 2 paired with any of the LCVR amino acid sequences listed in Table 4, or a common light chain derived from the cognate light chain of the anti-TAA heavy chain, or derived from a known or public domain light chain variable region derived from a light chain exhibiting promiscuity or ability to pair with a wide variety of non-cognate heavy chains, i.e. a universal or common light chain. According to certain

embodiments, the present invention provides antibodies, or antigen-binding fragments thereof, comprising an HCVR/LCVR amino acid sequence pair contained within any of the exemplary anti-CD3 antibodies listed in Table 2 paired with exemplary light chain variable regions listed in Table 4. In certain embodiments, the HCVR/LCVR amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 10/162 (e.g., CD3-VH-G2); 18/162 (e.g., CD3-VH-G3); 26/162 (e.g., CD3-VH-G4); 34/162 (e.g., CD3-VH-G5); 42/162 (e.g., CD3-VH-G8); 50/162 (e.g., CD3-VH-G9); 58/162 (e.g., CD3-VH-G10); 66/162 (e.g., CD3-VH-G11); 74/162 (e.g., CD3-VH-G12); 82/162 (e.g., CD3-VH-G13); 90/162 (e.g., CD3-VH-G14); 98/162 (e.g., CD3-VH-G15); 106/162 (e.g., CD3-VH-G16); 114/162 (e.g., CD3-VH-G17); 122/162 (e.g., CD3-VH-G18); 130/162 (e.g., CD3-VH-G19); 138/162 (e.g., CD3-VH-G20); and 146/162 (e.g., CD3-VH-G21).

[0012] The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR1 (HCDR1) comprising an amino acid sequence selected from any of the HCDR1 amino acid sequences listed in Table 2 or a substantially similar sequence thereof having at least 95%, at least 98% or at least 99% sequence identity. The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR1 (HCDR1) comprising an amino acid sequence set forth in SEQ ID NO: 178.

[0013] The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR2 (HCDR2) comprising an amino acid sequence selected from any of the HCDR2 amino acid sequences listed in Table 2 or a substantially similar sequence thereof having at least 95%, at least 98% or at least 99% sequence identity. The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR2 (HCDR2) comprising an amino acid sequence set forth in SEQ ID NO: 179.

[0014] The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR3 (HCDR3) comprising an amino acid sequence selected from any of the HCDR3 amino acid sequences listed in Table 2 or a substantially similar sequence thereof having at least 95%, at least 98% or at least 99% sequence identity. The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR3 (HCDR3) comprising an amino acid sequence set forth in SEQ ID NO: 180.

[0015] The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR1 (LCDR1) comprising an amino acid sequence selected from any of the LCDR1 amino acid sequences listed in Table 4 or a substantially similar sequence thereof having at least 95%, at least 98% or at least 99% sequence identity. The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR1 (LCDR1) derived from a cognate light chain of the anti-TAA heavy chain, or derived from a light chain exhibiting promiscuity or ability to pair with a wide variety of non-cognate heavy chains, i.e. a universal or common light chain.

[0016] The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR2 (LCDR2) comprising an amino acid sequence selected from any of the LCDR2 amino acid sequences

listed in Table 4 or a substantially similar sequence thereof having at least 95%, at least 98% or at least 99% sequence identity. The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR2 (LCDR2) derived from a cognate light chain of the anti-TAA heavy chain, or derived from a light chain exhibiting promiscuity or ability to pair with a wide variety of non-cognate heavy chains, i.e. a universal or common light chain.

[0017] The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR3 (LCDR3) comprising an amino acid sequence selected from any of the LCDR3 amino acid sequences listed in Table 4 or a substantially similar sequence thereof having at least 95%, at least 98% or at least 99% sequence identity. The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR3 (LCDR3) derived from a cognate light chain of the anti-TAA heavy chain, or derived from a light chain exhibiting promiscuity or ability to pair with a wide variety of non-cognate heavy chains, i.e. a universal or common light chain.

[0018] The present invention also provides antibodies, or antigen-binding fragments thereof, comprising an HCDR3 and an LCDR3 amino acid sequence pair (HCDR3/LCDR3) comprising any of the HCDR3 amino acid sequences listed in Table 2 paired with any of the LCDR3 amino acid sequences listed in Table 4. According to certain embodiments, the present invention provides antibodies, or antigen-binding fragments thereof, comprising an HCDR3/LCDR3 amino acid sequence pair contained within any of the exemplary anti-CD3 antibodies listed in Table 2. In certain embodiments, the HCDR3/LCDR3 amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 16/168 (e.g., CD3-VH-G2); 24/168 (e.g., CD3-VH-G3); 32/168 (e.g., CD3-VH-G4); 40/168 (e.g., CD3-VH-G5); 48/168 (e.g., CD3-VH-G8); 56/168 (e.g., CD3-VH-G9); 64/168 (e.g., CD3-VH-G10); 72/168 (e.g., CD3-VH-G11); 80/168 (e.g., CD3-VH-G12); 88/168 (e.g., CD3-VH-G13); 96/168 (e.g., CD3-VH-G14); 104/168 (e.g., CD3-VH-G15); 112/168 (e.g., CD3-VH-G16); 120/168 (e.g., CD3-VH-G17); 128/168 (e.g., CD3-VH-G18); 136/168 (e.g., CD3-VH-G19); 144/168 (e.g., CD3-VH-G20); and 152/168 (e.g., CD3-VH-G21).

[0019] The present invention also provides antibodies, or antigen-binding fragments thereof, comprising a set of six CDRs (i.e., HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within any of the exemplary anti-CD3 antibodies listed in Tables 2 and 4. In certain embodiments, the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set is selected from the group consisting of SEQ ID NOs: 12-14-16-164-166-168 (e.g., CD3-VH-G2); 20-22-24-164-166-168 (e.g., CD3-VH-G3); 28-30-32-164-166-168 (e.g., CD3-VH-G4); 36-38-40-164-166-168 (e.g., CD3-VH-G5); 44-46-48-164-166-168 (e.g., CD3-VH-G8); 52-54-56-164-166-168 (e.g., CD3-VH-G9); 60-62-64-164-166-168 (e.g., CD3-VH-G10); 68-70-72-164-166-168 (e.g., CD3-VH-G11); 76-78-80-164-166-168 (e.g., CD3-VH-G12); 84-86-88-164-166-168 (e.g., CD3-VH-G13); 92-94-96-164-166-168 (e.g., CD3-VH-G14); 100-102-104-164-166-168 (e.g., CD3-VH-G15); 108-110-112-164-166-168 (e.g., CD3-VH-G16); 116-118-120-164-166-168 (e.g., CD3-VH-G17); 124-126-128-164-166-168 (e.g., CD3-VH-G18); 132-134-136-164-166-168 (e.g., CD3-VH-

G19); 140-142-144-164-166-168 (e.g., CD3-VH-G20); and 148-150-152-164-166-168 (e.g., CD3-VH-G21).

[0020] In a related embodiment, the present invention provides antibodies, or antigen-binding fragments thereof, comprising a set of six CDRs (i.e., HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within an HCVR/LCVR amino acid sequence pair as defined by any of the exemplary anti-CD3 antibodies listed in Tables 2 and 4. For example, the present invention includes antibodies, or antigen-binding fragments thereof, comprising the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 10/162 (e.g., CD3-VH-G2); 18/162 (e.g., CD3-VH-G3); 26/162 (e.g., CD3-VH-G4); 34/162 (e.g., CD3-VH-G5); 42/162 (e.g., CD3-VH-G8); 50/162 (e.g., CD3-VH-G9); 58/162 (e.g., CD3-VH-G10); 66/162 (e.g., CD3-VH-G11); 74/162 (e.g., CD3-VH-G12); 82/162 (e.g., CD3-VH-G13); 90/162 (e.g., CD3-VH-G14); 98/162 (e.g., CD3-VH-G15); 106/162 (e.g., CD3-VH-G16); 114/162 (e.g., CD3-VH-G17); 122/162 (e.g., CD3-VH-G18); 130/162 (e.g., CD3-VH-G19); 138/162 (e.g., CD3-VH-G20); and 146/162 (e.g., CD3-VH-G21).

[0021] Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, e.g., the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. See, e.g., Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani et al., *J. Mol. Biol.* 273:927-948 (1997); and Martin et al., *Proc. Natl. Acad. Sci. USA* 86:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[0022] The present invention also provides nucleic acid molecules encoding anti-CD3 antibodies or portions thereof. For example, the present invention provides nucleic acid molecules encoding any of the HCVR amino acid sequences listed in Table 3; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 3, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0023] The present invention also provides nucleic acid molecules encoding any of the LCVR amino acid sequences listed in Table 4; or an LCVR derived from a cognate light chain of the anti-TAA heavy chain, or derived from a light chain exhibiting promiscuity or ability to pair with a wide variety of non-cognate heavy chains, i.e. a universal or common light chain. In certain embodiments, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 5, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0024] The present invention also provides nucleic acid molecules encoding any of the HCDR1 amino acid

sequences listed in Table 2; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR1 nucleic acid sequences listed in Table 3, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0025] The present invention also provides nucleic acid molecules encoding any of the HCDR2 amino acid sequences listed in Table 2; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR2 nucleic acid sequences listed in Table 3, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0026] The present invention also provides nucleic acid molecules encoding any of the HCDR3 amino acid sequences listed in Table 2; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR3 nucleic acid sequences listed in Table 3, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0027] The present invention also provides nucleic acid molecules encoding any of the LCDR1 amino acid sequences listed in Table 4; or an LCDR1 derived from a cognate light chain of the anti-TAA heavy chain, or derived from a light chain exhibiting promiscuity or ability to pair with a wide variety of non-cognate heavy chains, i.e. a universal or common light chain. In certain embodiments, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR1 nucleic acid sequences listed in Table 5, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0028] The present invention also provides nucleic acid molecules encoding any of the LCDR2 amino acid sequences listed in Table 4; or an LCDR2 derived from a cognate light chain of the anti-TAA heavy chain, or derived from a light chain exhibiting promiscuity or ability to pair with a wide variety of non-cognate heavy chains, i.e. a universal or common light chain. In certain embodiments, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR2 nucleic acid sequences listed in Table 5, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0029] The present invention also provides nucleic acid molecules encoding any of the LCDR3 amino acid sequences listed in Table 4; or an LCDR3 derived from a cognate light chain of the anti-TAA heavy chain, or derived from a light chain exhibiting promiscuity or ability to pair with a wide variety of non-cognate heavy chains, i.e. a universal or common light chain. In certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR3 nucleic acid sequences listed in Table 5, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0030] The present invention also provides nucleic acid molecules encoding an HCVR, wherein the HCVR comprises a set of three CDRs (i.e., HCDR1-HCDR2-HCDR3), wherein the HCDR1-HCDR2-HCDR3 amino acid sequence set is as defined by any of the exemplary anti-CD3 antibodies listed in Table 2.

[0031] The present invention also provides nucleic acid molecules encoding an LCVR, wherein the LCVR comprises a set of three CDRs (i.e., LCDR1-LCDR2-LCDR3), wherein the LCDR1-LCDR2-LCDR3 amino acid sequence set is as defined by any of the exemplary universal light chain antibodies listed in Table 4; or the LCDR1-LCDR2-LCDR3 is derived from a cognate light chain of the anti-TAA heavy chain, or derived from a light chain exhibiting promiscuity or ability to pair with a wide variety of non-cognate heavy chains, i.e. a universal or common light chain.

[0032] The present invention also provides nucleic acid molecules encoding both an HCVR and an LCVR, wherein the HCVR comprises an amino acid sequence of any of the HCVR amino acid sequences listed in Table 2, and wherein the LCVR comprises an amino acid sequence of any of the LCVR amino acid sequences listed in Table 4; or the LCVR is derived from a cognate light chain of the anti-TAA heavy chain, or derived from a light chain exhibiting promiscuity or ability to pair with a wide variety of non-cognate heavy chains, i.e. a universal or common light chain. In certain embodiments, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto, and a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 5, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto. In some embodiments, the nucleic acid molecules encoding both an HCVR and an LCVR are fully human sequences or derived from human germline immunoglobulin sequences.

[0033] The present invention also provides recombinant expression vectors capable of expressing a polypeptide comprising a heavy or light chain variable region of an anti-CD3 antibody. For example, the present invention includes recombinant expression vectors comprising any of the nucleic acid molecules mentioned above, i.e., nucleic acid molecules encoding any of the HCVR, LCVR, and/or CDR sequences as set forth in Table 2 or 4. Also included within the scope of the present invention are host cells into which such vectors have been introduced, as well as methods of producing the antibodies or portions thereof by culturing the host cells under conditions permitting production of the antibodies or antibody fragments, and recovering the antibodies and antibody fragments so produced.

[0034] The present invention includes anti-CD3 antibodies and/or anti-TAA antibodies, as well as bispecific anti-CD3/anti-TAA antibodies having a modified glycosylation pattern. In some embodiments, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0035] In one aspect, the invention provides a cytotoxic composition comprising a bispecific antigen-binding molecule that i) is not capable of specifically binding to an effector cell, and ii) specifically binds a target tumor cell, wherein specific binding is measured in an in vitro FACS binding assay or an in vitro surface plasmon resonance

binding assay. In certain embodiments, the invention provides a cytotoxic composition comprising a bispecific antigen-binding molecule that exhibits no detectable binding to an effector cell, and that specifically binds to a target tumor cell with a measurable binding affinity, wherein the binding affinity value is measured in an in vitro FACS binding assay or an in vitro surface plasmon resonance binding assay.

[0036] In other embodiments, the invention provides a cytotoxic composition comprising a bispecific antigen-binding molecule comprising i) a first antigen-binding fragment (Fab1) that exhibits no detectable binding to CD3, and ii) a second antigen-binding fragment (Fab2) that specifically binds to a target tumor cell with a measurable binding affinity, wherein the binding affinity value is measured in an in vitro FACS binding assay or an in vitro surface plasmon resonance binding assay. In some cases, the binding affinity is monovalent binding affinity (e.g., in a bispecific antibody construct).

[0037] In another aspect the invention provides a cytotoxic composition comprising a bispecific antigen-binding molecule that specifically binds an effector cell with a weak binding affinity, for example exhibiting an EC_{50} value of about or greater than about 100 nM, and that specifically binds a target tumor cell with an appreciable EC_{50} value, or a high affinity EC_{50} value such as less than 50 nM, wherein the EC_{50} binding affinity value is measured in an in vitro FACS binding assay. In certain embodiments, the invention provides a cytotoxic composition comprising a bispecific antigen-binding molecule that specifically binds an effector cell with an EC_{50} value of greater than about 500 nM, and that specifically binds a target tumor cell with an appreciable EC_{50} value, or a high affinity EC_{50} value such as less than 50 nM, wherein the EC_{50} binding affinity value is measured in an in vitro FACS binding assay.

[0038] In some examples, the bispecific antigen-binding molecule includes a Fab1 that specifically binds human CD3 with an EC_{50} value of greater than about 40 nM, or greater than about 100 nM, greater than about 200 nM, greater than about 300 nM, greater than about 400 nM, greater than about 500 nM, or greater than about 1 μ M (e.g. in a monovalent binding context). In some embodiments, the bispecific antigen-binding molecule includes a Fab2 derived from a second antibody that specifically binds the target tumor cell with high affinity, e.g. an EC_{50} value of less than less than about 50 nM, less than about 40 nM, less than about 20 nM, less than about 10 nM or less than about 6 nM (e.g., in a monovalent binding context). In some cases, the Fab1 specifically binds each of human CD3 and cynomolgus CD3 with an EC_{50} value of greater than about 40 nM, or greater than about 100 nM, greater than about 200 nM, or greater than about 1 μ M. In some cases, the Fab1 specifically binds each of human CD3 and cynomolgus CD3 with weak or no measurable affinity.

[0039] In some embodiments, the target tumor cell is a human tumor cell. In some embodiments, the Fab1 (or the bispecific antigen-binding molecule) induces T cell-mediated tumor cell killing with an EC_{50} value of less than about 1.3 nM, as measured in an in vitro T cell-mediated tumor cell killing assay.

[0040] In some applications, the Fab1 or the bispecific antigen-binding molecule specifically binds human CD3 with an K_D value of greater than about 11 nM, as measured in an in vitro surface plasmon resonance binding assay. In other instances, the Fab1 or the bispecific antigen-binding

molecule specifically binds each of human CD3 and cynomolgus CD3 with an K_D value of greater than about 15 nM, or greater than about 30 nM, greater than about 60 nM, greater than about 120 nM, or greater than about 300 nM, as measured in an in vitro surface plasmon resonance binding assay. In still some applications, the Fab1 or the bispecific antigen-binding molecule i) exhibits no detectable binding to human CD3 as measured in each of an in vitro surface plasmon resonance binding assay and a FACS binding assay, and ii) induces T cell-mediated tumor cell killing, as measured in an in vitro T cell-mediated tumor cell killing assay.

[0041] In some applications, the bispecific antigen-binding molecule comprises a first heavy chain comprising a HCDR1 region comprising an amino acid sequence set forth in SEQ ID NO: 12 or 20. In some embodiments, the first heavy chain comprises a HCDR2 region comprising an amino acid sequence set forth in SEQ ID NO: 14 or 54. In other embodiments, the first heavy chain comprises a HCDR3 region comprising an amino acid sequence set forth in SEQ ID NO: 16, SEQ ID NO: 24, SEQ ID NO: 32, SEQ ID NO: 40, SEQ ID NO: 48, SEQ ID NO: 56, SEQ ID NO: 64, SEQ ID NO: 72, SEQ ID NO: 80, SEQ ID NO: 88, SEQ ID NO: 96, SEQ ID NO: 104, SEQ ID NO: 112, SEQ ID NO: 120, SEQ ID NO: 128, SEQ ID NO: 136, SEQ ID NO: 144, or SEQ ID NO: 152. In other applications, the first heavy chain comprises a HCVR comprising HCDR1-HCDR2-HCDR3 having the amino acid sequences of SEQ ID NOs: 178-179-180. In other embodiments, a first heavy chain comprises a CDR1 comprising amino acid residues 1-7 of SEQ ID NO:178, a CDR2 comprising amino acid residues 1-7 of SEQ ID NO:179, a CDR3 comprising amino acid residues 4-11 of SEQ ID NO:180.

[0042] In more embodiments, the first heavy chain comprises variable domain framework regions having an amino acid sequence selected from FR1 (SEQ ID NO: 174), FR2 (SEQ ID NO: 175), FR3 (SEQ ID NO: 176), and FR4 (SEQ ID NO: 177).

[0043] The present invention provides bispecific antigen-binding molecules comprising a Fab1 HCVR and LCVR amino acid sequence pair (HCVR/LCVR) selected from the group consisting of: SEQ ID NOs: 10/162; 18/162; 26/162; 34/162; 42/162; 50/162; 58/162; 66/162; 74/162; 82/162; 90/162; 98/162; 106/162; 114/162; 122/162; 130/162; 138/162; 146/162.

[0044] The antibodies, and antigen-binding fragments and bispecific antibodies thereof were made by replacing amino acid residues of a parental in a stepwise manner based on differences between the germline sequence and the parental antibody sequence. The present invention provides a method of making a cytotoxic composition comprising (a) identifying the amino acid sequence of the first heavy chain derived from a first antibody that specifically binds CD3 with high affinity, for example exhibits a binding affinity EC_{50} value of less than about 40 nM, (b) modifying selected amino acid residues in the heavy chain variable region of the first antibody to produce a modified antibody, (c) pairing the modified antibody with a second heavy chain derived from a second antibody that specifically binds a target tumor antigen to produce a bispecific antibody, (d) testing the bispecific antibody in a binding affinity assay, and if the binding affinity to CD3 has an EC_{50} value of greater than about 40 nM, or greater than 100 nM or greater than 300 nM or greater than 500 nM, or no detectable binding, then (e) preparing a composition comprising the bispecific antibody

and a pharmaceutically acceptable carrier or diluent. In addition to modifying the heavy chain variable region of selected antibodies to engineer antigen-binding arms having weak or no affinity for, yet specifically target an effector cell, the invention provides methods herein for modifying the heavy chain constant region (e.g. C_H3 domain) of each binding arm to prepare and isolate bispecific antibodies.

[0045] An exemplary method provides a method of producing a cytotoxic bispecific antibody, comprising: (a) identifying a first human antibody or antigen-binding fragment thereof that interacts with an effector cell antigen from multiple species; (b) identifying the germline amino acid residues of the heavy chain variable region (HCVR) of the human antibody; (c) comparing the amino acid sequence of the HCVR of the first human antibody to the amino acid sequence of the corresponding germline HCVR; (d) identifying amino acids within a modified region of the HCVR of the first antibody, whereby a modified region in the first antibody displays at least one amino acid modification by substitution, deletion or addition of a single amino acid residue compared to the same region in the germline HCVR; (e) producing a plurality of modified antibodies each comprising at least one modified region of the HCVR; (f) screening each of the plurality of modified antibodies for monovalent affinity to the effector cell antigen; (g) selecting those modified antibodies that exhibit weaker binding affinity or no detectable binding affinity to the effector cell antigen compared to the first antibody; and (h) pairing the selected first antibody with a second antibody that interacts with a tumor-associated antigen to produce a cytotoxic bispecific antibody.

[0046] In another aspect, the invention provides a pharmaceutical composition comprising a recombinant human bispecific antibody or fragment thereof which specifically binds CD3 and a pharmaceutically acceptable carrier. In a related aspect, the invention features a composition which is a combination of an anti-CD3 antibody and a second therapeutic agent. In one embodiment, the second therapeutic agent is any agent that is advantageously combined with an anti-CD3 antibody. Exemplary agents that may be advantageously combined with an anti-CD3 antibody include, without limitation, other agents that bind and/or activate CD3 signaling (including other antibodies or antigen-binding fragments thereof, etc.) and/or agents which do not directly bind CD3 but nonetheless activate or stimulate immune cell activation. Additional combination therapies and co-formulations involving the anti-CD3 antibodies of the present invention are disclosed elsewhere herein.

[0047] In yet another aspect, the invention provides therapeutic methods for stimulating T cell activation using an anti-CD3 antibody or antigen-binding portion of an antibody of the invention, wherein the therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising a bispecific antibody of the invention, or antigen-binding fragment thereof, to a subject in need thereof. The disorder treated is any disease or condition, which is improved, ameliorated, inhibited or prevented by cytotoxic therapy targeted to a tumor-associated antigen, such as cancer.

[0048] According to another aspect, the present invention provides bispecific antigen-binding molecules that bind CD3 and a target antigen, especially a tumor-associated antigen (TAA).

[0049] The present invention also includes the use of an anti-CD3/anti-TAA bispecific antigen-binding molecule of the invention in the manufacture of a medicament for the treatment of a disease or disorder related to or caused by TAA expression. The present invention also provides use of an anti-CD3/anti-TAA bispecific antigen-binding molecule, exhibiting weak affinity to CD3-expressing effector cells and reduced clearance, in the manufacture of a medicament for the treatment of a disease or disorder related to or caused by TAA expression, compared to an anti-CD3/anti-TAA bispecific antigen-binding molecule exhibiting high affinity to CD3-expressing effector cells.

[0050] Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0051] FIG. 1 shows the amino acid alignment of the following antibody heavy chain variable region (HCVR) sequences: germline hIgHV (SEQ ID NO:181); CD3-VH-P (SEQ ID NO:154); CD3-VH-G (SEQ ID NO:2); CD3-VH-G2 (SEQ ID NO:10); CD3-VH-G3 (SEQ ID NO:18); CD3-VH-G4 (SEQ ID NO:26); CD3-VH-G5 (SEQ ID NO: 34); CD3-VH-G8 (SEQ ID NO:42); CD3-VH-G9 (SEQ ID NO:50); CD3-VH-G10 (SEQ ID NO:58); CD3-VH-G11 (SEQ ID NO:66); CD3-VH-G12 (SEQ ID NO:74); CD3-VH-G13 (SEQ ID NO:82); CD3-VH-G14 (SEQ ID NO:90); CD3-VH-G15 (SEQ ID NO:98); CD3-VH-G16 (SEQ ID NO:106); CD3-VH-G17 (SEQ ID NO:114); CD3-VH-G18 (SEQ ID NO:122); CD3-VH-G19 (SEQ ID NO:130); CD3-VH-G20 (SEQ ID NO:138); and CD3-VH-G21 (SEQ ID NO:146). Each derivative HCVR is compared to the parent antibody and germline amino acid residues, with rectangular boxes denoting mutations in the CDRs.

[0052] FIGS. 2A, 2B and 2C illustrate mean concentrations of total IgG in serum following a single 0.4 mg/kg intra-peritoneal injection of BSMUC16/CD3-001, BSMUC16/CD3-005 and isotype control antibodies in wild-type mice (FIG. 2A), humanized CD3 mice (FIG. 2B) and humanized MUC16xCD3 mice (FIG. 2C).

DETAILED DESCRIPTION

[0053] Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0054] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term “about,” when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression “about 100” includes 99 and 101 and all values in between (e.g., 99.1, 99.2, 99.3, 99.4, etc.).

[0055] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

Definitions

[0056] The expression “CD3” refers to an antigen which is expressed on T cells as part of the multimolecular T cell receptor (TCR) and which consists of a homodimer or heterodimer formed from the association of two of four receptor chains: CD3-epsilon, CD3-delta, CD3-zeta, and CD3-gamma. Human CD3-epsilon (hCD3E) comprises the amino acid sequence as set forth in SEQ ID NO:169 (UniProtKB/Swiss-Prot: P07766.2). Human CD3-delta (hCD3δ) comprises the amino acid sequence as set forth in SEQ ID NO:170 (UniProtKB/Swiss-Prot: P04234.1). All references to proteins, polypeptides and protein fragments herein are intended to refer to the human version of the respective protein, polypeptide or protein fragment unless explicitly specified as being from a non-human species. Thus, the expression “CD3” means human CD3 unless specified as being from a non-human species, e.g., “mouse CD3,” “monkey CD3,” etc.

[0057] The phrase “an antibody that binds CD3” or an “anti-CD3 antibody” includes antibodies and antigen-binding fragments thereof that specifically recognize and associate with a single CD3 subunit (e.g., epsilon, delta, gamma or zeta), as well as antibodies and antigen-binding fragments thereof that specifically recognize and associate with a dimeric complex of two CD3 subunits (e.g., epsilon/delta, epsilon/gamma, and zeta/zeta CD3 dimers). The antibodies and antigen-binding fragments of the present invention may bind soluble CD3, bound CD3 and/or cell surface expressed CD3. Soluble CD3 includes natural CD3 proteins as well as recombinant CD3 protein variants such as, e.g., monomeric and dimeric CD3 constructs, that lack a transmembrane domain or are otherwise unassociated with a cell membrane. The present invention provides antibodies that bind and activate human and cynomolgus CD3 with weak or no detectable binding affinity. “Binding to CD3 with no detectable binding affinity” means that the antibody and or antigen-binding fragment interaction with the CD3 target may not be measurable or detectable with a known assay for detection, such as a FACS (cell-based) binding assay as described herein or a surface plasmon resonance binding assay as described herein and well-known in the art. Other binding assays are well-known in the art. The antibody and or antigen-binding fragment may recognize the CD3 target by very weak protein-protein biochemical interaction, however a determination of specific KD or EC₅₀ value cannot be measured since the interaction is beyond the detection limit of the assay, e.g. no measurement can be determined. In another instance, “no detectable binding affinity” is determined if the affinity of an antibody corresponding to a K_D value is equal to or less than ten-fold lower than a non-specific antigen such as, BSA, casein, or the like. “Binding to CD3 with weak binding affinity” includes interactions where binding affinity measurement is at or slightly above the detection limit of the assay, or equivalent to the binding affinity to a non-specific antigen.

[0058] The expression “cell surface-expressed CD3” means one or more CD3 protein(s) that is/are expressed on the surface of a cell in vitro or in vivo, such that at least a portion of a CD3 protein is exposed to the extracellular side of the cell membrane and is accessible to an antigen-binding portion of an antibody. “Cell surface-expressed CD3” includes CD3 proteins contained within the context of a functional T cell receptor in the membrane of a cell. The expression “cell surface-expressed CD3” includes CD3 pro-

tein expressed as part of a homodimer or heterodimer on the surface of a cell (e.g., delta/epsilon, gamma/epsilon, and zeta/zeta CD3 dimers). The expression, "cell surface-expressed CD3" also includes a CD3 chain (e.g., CD3-delta, CD3-epsilon or CD3-gamma) that is expressed by itself, without other CD3 chain types, on the surface of a cell. A "cell surface-expressed CD3" can comprise or consist of a CD3 protein expressed on the surface of a cell which normally expresses CD3 protein. Alternatively, "cell surface-expressed CD3" can comprise or consist of CD3 protein expressed on the surface of a cell that normally does not express human CD3 on its surface but has been artificially engineered to express CD3 on its surface.

[0059] Effector cells include effector T cells (T lymphocytes), for example CD4⁺ T cells, CD8⁺ T cells, Th1, Th2 and regulatory T cells (Tregs). Effector cells may also include natural killer (NK) cells, macrophages, granulocytes, plasma cells or B cells (lymphocytes). It is understood that therapies may mediate a plethora of cell-mediated immune responses, or effector functions, through Ig interaction with effector cell surface receptors, such as CD3 (T cell surface receptor), CD28 (T cells), Fcγ receptors (FcγRs) (NK cells, activated macrophages and the like). Effector functions such as cell killing, complement activation, phagocytosis and opsonisation are subsequently triggered through these interactions. Binding to an effector cell and a tumor target cell allows for a valuable and effective immunotherapy design that propagates tumor cell killing and induces endogenous immune functions to fight the tumor or cancer.

[0060] The expression "anti-CD3 antibody" includes both monovalent antibodies with a single specificity, as well as bispecific antibodies comprising a first arm that binds CD3 and a second arm that binds a second (target) antigen, wherein the anti-CD3 arm comprises any of the HCVR/LCVR or CDR sequences as set forth in Tables 2, 3, 4 and/or 5 herein. Examples of anti-CD3 bispecific antibodies are described elsewhere herein. The term "antigen-binding molecule" includes antibodies and antigen-binding fragments of antibodies, including, e.g., bispecific antibodies.

[0061] The term "antibody" includes any antigen-binding molecule or molecular complex comprising at least one complementarity determining region (CDR) that specifically binds to or interacts with a particular antigen (e.g., CD3). The term "antibody" includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (e.g., IgM). Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_H1, C_H2 and C_H3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region comprises one domain (C_L1). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In different embodiments of the invention, the FRs of the anti-CD3 antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An

amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0062] The term "antibody" also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, e.g., commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[0063] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')₂ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (e.g. monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0064] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H-V_H, V_H-V_L or V_L-V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[0065] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or

linker region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in noncovalent association with one another and/or with one or more monomeric V_H or V_L domain (e.g., by disulfide bond(s)).

[0066] As with full antibody molecules, antigen-binding fragments may be monospecific or multispecific (e.g., bispecific). A multispecific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multispecific antibody format, including the exemplary bispecific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present invention using routine techniques available in the art.

[0067] The antibodies of the present invention may function through complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC). “Complement-dependent cytotoxicity” (CDC) refers to lysis of antigen-expressing cells by an antibody of the invention in the presence of complement. “Antibody-dependent cell-mediated cytotoxicity” (ADCC) refers to a cell-mediated reaction in which nonspecific cytotoxic cells that express Fc receptors (FcRs) (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) recognize bound antibody on a target cell and thereby lead to lysis of the target cell. CDC and ADCC can be measured using assays that are well known and available in the art. (See, e.g., U.S. Pat. Nos. 5,500,362 and 5,821,337, and Clynes et al. (1998) *Proc. Natl. Acad. Sci. (USA)* 95:652-656). The constant region of an antibody is important in the ability of an antibody to fix complement and mediate cell-dependent cytotoxicity. Thus, the isotype of an antibody may be selected on the basis of whether it is desirable for the antibody to mediate cytotoxicity.

[0068] In certain embodiments of the invention, the anti-CD3 antibodies of the invention (monospecific or bispecific) are human antibodies. The term “human antibody”, as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term “human antibody”, as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0069] The term “recombinant human antibody” is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic

for human immunoglobulin genes (see e.g., Taylor et al. (1992) *Nucl. Acids Res.* 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, do not necessarily naturally exist within the human antibody germline repertoire *in vivo*.

[0070] Human antibodies can exist in two forms that are associated with hinge heterogeneity. In one form, an immunoglobulin molecule comprises a stable four chain construct of approximately 150-160 kDa in which the dimers are held together by an interchain heavy chain disulfide bond. In a second form, the dimers are not linked via interchain disulfide bonds and a molecule of about 75-80 kDa is formed composed of a covalently coupled light and heavy chain (half-antibody). These forms have been extremely difficult to separate, even after affinity purification.

[0071] The frequency of appearance of the second form in various intact IgG isotypes is due to, but not limited to, structural differences associated with the hinge region isotype of the antibody. A single amino acid substitution in the hinge region of the human IgG4 hinge can significantly reduce the appearance of the second form (Angal et al. (1993) *Molecular Immunology* 30:105) to levels typically observed using a human IgG1 hinge. The instant invention encompasses antibodies having one or more mutations in the hinge, C_H2 or C_H3 region which may be desirable, for example, in production, to improve the yield of the desired antibody form.

[0072] The antibodies of the invention may be isolated antibodies. An “isolated antibody,” as used herein, means an antibody that has been identified and separated and/or recovered from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an organism, or from a tissue or cell in which the antibody naturally exists or is naturally produced, is an “isolated antibody” for purposes of the present invention. An isolated antibody also includes an antibody *in situ* within a recombinant cell. Isolated antibodies are antibodies that have been subjected to at least one purification or isolation step. According to certain embodiments, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0073] The present invention also includes one-arm antibodies that bind CD3. The phrase “one-arm antibody” means an antigen-binding molecule comprising a single antibody heavy chain and a single antibody light chain. The one-arm antibodies of the present invention may comprise any of the HCVR/LCVR or CDR amino acid sequences as set forth in Table 2 herein.

[0074] The term “epitope” refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes

may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

[0075] The term “substantial identity” or “substantially identical,” when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 95%, and more preferably at least about 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[0076] As applied to polypeptides, the term “substantial similarity” or “substantially similar” means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 95% sequence identity, even more preferably at least 98% or 99% sequence identity. Preferably, residue positions which are not identical differ by conservative amino acid substitutions. A “conservative amino acid substitution” is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. See, e.g., Pearson (1994) *Methods Mol. Biol.* 24: 307-331. Examples of groups of amino acids that have side chains with similar chemical properties include (1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; (2) aliphatic-hydroxyl side chains: serine and threonine; (3) amide-containing side chains: asparagine and glutamine; (4) aromatic side chains: phenyl-alanine, tyrosine, and tryptophan; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartate and glutamate, and (7) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenyl-alanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al. (1992) *Science* 256: 1443-1445. A “moderately conservative” replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0077] Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions.

For instance, GCG software contains programs such as Gap and Bestfit which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA using default or recommended parameters, a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) *supra*). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. See, e.g., Altschul et al. (1990) *J. Mol. Biol.* 215:403-410 and Altschul et al. (1997) *Nucleic Acids Res.* 25:3389-402.

Germline Mutations

[0078] The anti-CD3 antibodies disclosed herein comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy chain variable domains as compared to the corresponding germline sequences from which the antibodies were derived.

[0079] The present invention also includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as “germline mutations”), and having weak or no detectable binding to a CD3 antigen. Several such exemplary antibodies that recognize CD3 are described in Table 2 herein.

[0080] Furthermore, the antibodies of the present invention may contain any combination of two or more germline mutations within the framework and/or CDR regions, e.g., wherein certain individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be tested for one or more desired properties such as, improved binding specificity, weak or reduced binding affinity, improved or enhanced pharmacokinetic properties, reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner given the guidance of the present disclosure are encompassed within the present invention.

[0081] The present invention also includes anti-CD3 antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present invention includes anti-CD3 antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences set forth in Table 2 herein. The antibodies and bispecific antigen-

binding molecules of the present invention comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences from which the individual antigen-binding domains were derived, while maintaining or improving the desired weak-to-no detectable binding to CD3 antigen. A “conservative amino acid substitution” is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein, i.e. the amino acid substitution maintains or improves the desired weak to no detectable binding affinity in the case of anti-CD3 binding molecules. Examples of groups of amino acids that have side chains with similar chemical properties include (1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; (2) aliphatic-hydroxyl side chains: serine and threonine; (3) amide-containing side chains: asparagine and glutamine; (4) aromatic side chains: phenyl-alanine, tyrosine, and tryptophan; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartate and glutamate, and (7) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenyl-alanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al. (1992) *Science* 256: 1443-1445. A “moderately conservative” replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0082] The present invention also includes antigen-binding molecules comprising an antigen-binding domain with an HCVR and/or CDR amino acid sequence that is substantially identical to any of the HCVR and/or CDR amino acid sequences disclosed herein, while maintaining or improving the desired weak affinity to CD3 antigen. The term “substantial identity” or “substantially identical,” when referring to an amino acid sequence means that two amino acid sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 95% sequence identity, even more preferably at least 98% or 99% sequence identity. Preferably, residue positions which are not identical differ by conservative amino acid substitutions. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. See, e.g., Pearson (1994) *Methods Mol. Biol.* 24: 307-331.

[0083] Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as Gap and Bestfit which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild

type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA using default or recommended parameters, a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) *supra*). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. See, e.g., Altschul et al. (1990) *J. Mol. Biol.* 215:403-410 and Altschul et al. (1997) *Nucleic Acids Res.* 25:3389-402. **[0084]** Once obtained, antigen-binding domains that contain one or more germline mutations were tested for decreased binding affinity utilizing one or more *in vitro* assays. Although antibodies that recognize a particular antigen are typically screened for their purpose by testing for high (i.e. strong) binding affinity to the antigen, the antibodies of the present invention exhibit weak binding or no detectable binding. Bispecific antigen-binding molecules comprising one or more antigen-binding domains obtained in this general manner are also encompassed within the present invention and were found to be advantageous as avidity-driven tumor therapies.

[0085] Unexpected benefits, for example, improved pharmacokinetic properties and low toxicity to the patient may be realized from the methods described herein.

Binding Properties of the Antibodies

[0086] As used herein, the term “binding” in the context of the binding of an antibody, immunoglobulin, antibody-binding fragment, or Fc-containing protein to either, e.g., a predetermined antigen, such as a cell surface protein or fragment thereof, typically refers to an interaction or association between a minimum of two entities or molecular structures, such as an antibody-antigen interaction.

[0087] For instance, binding affinity typically corresponds to a K_D value of about 10^{-7} M or less, such as about 10^{-8} M or less, such as about 10^{-9} M or less when determined by, for instance, surface plasmon resonance (SPR) technology in a BLAcore 3000 instrument using the antigen as the ligand and the antibody, Ig, antibody-binding fragment, or Fc-containing protein as the analyte (or antiligand). Cell-based binding strategies, such as fluorescent-activated cell sorting (FACS) binding assays, are also routinely used, and FACS data correlates well with other methods such as radioligand competition binding and SPR (Benedict, C A, *J Immunol Methods*. 1997, 201(2):223-31; Geuijen, C A, et al. *J Immunol Methods*. 2005, 302(1-2):68-77).

[0088] Accordingly, the antibody or antigen-binding protein of the invention may bind to the predetermined antigen or cell surface molecule (receptor such as CD3) having an affinity corresponding to a K_D value that is at least ten-fold lower than its affinity for binding to a non-specific antigen (e.g., BSA, casein). According to the present invention, if the affinity of an antibody corresponding to a K_D value is equal to or less than ten-fold lower than a non-specific antigen, this may be considered non-detectable binding, however such an antibody may be paired with a second antigen binding arm for the production of a bispecific antibody of the invention.

[0089] The term “ K_D ” (M) refers to the dissociation equilibrium constant of a particular antibody-antigen inter-

action, or the dissociation equilibrium constant of an antibody or antibody-binding fragment binding to an antigen. There is an inverse relationship between K_D and binding affinity, therefore the smaller the K_D value, the higher, i.e. stronger, the affinity. Thus, the terms “higher affinity” or “stronger affinity” relate to a higher ability to form an interaction and therefore a smaller K_D value, and conversely the terms “lower affinity” or “weaker affinity” relate to a lower ability to form an interaction and therefore a larger K_D value. In some circumstances, a higher binding affinity (or K_D of a particular molecule (e.g. antibody) to its interactive partner molecule (e.g. antigen X) compared to the binding affinity of the molecule (e.g. antibody) to another interactive partner molecule (e.g. antigen Y) may be expressed as a binding ratio determined by dividing the larger K_D value (lower, or weaker, affinity) by the smaller K_D (higher, or stronger, affinity), for example expressed as 5-fold or 10-fold greater binding affinity, as the case may be. For example, “low affinity” refers to less strong binding interaction. In some embodiments, the low binding affinity corresponds to greater than about 1 nM K_D , greater than about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or greater than about 40 nM K_D , wherein such K_D binding affinity value is measured in an in vitro surface plasmon resonance binding assay, or equivalent biomolecular interaction sensing assay. In some embodiments, the low binding affinity corresponds to greater than about 10 nM EC_{50} , greater than about 15 nM EC_{50} , 20 nM EC_{50} , greater than about 25 nM EC_{50} , 30 nM EC_{50} , greater than about 35 nM EC_{50} , or greater than about 40 nM EC_{50} , wherein such EC_{50} binding affinity value is measured in an in vitro FACS binding assay, or equivalent cell-based binding assay. “Weak affinity” refers to weak binding interaction. In some embodiments, the weak binding affinity corresponds to greater than about 100 nM K_D or EC_{50} , greater than about 200, 300, or greater than about 500 nM K_D or EC_{50} , wherein such K_D binding affinity value is measured in an in vitro surface plasmon resonance binding assay, or equivalent biomolecular interaction sensing assay, and such EC_{50} binding affinity value is measured in an in vitro FACS binding assay, or equivalent cell-based interaction detecting assay to detect monovalent binding. No detectable binding means that the affinity between the two biomolecules, for example, especially between the monovalent antibody binding arm and its target antigen, is beyond the detection limit of the assay being used.

[0090] The term “ k_d ” (sec⁻¹ or 1/s) refers to the dissociation rate constant of a particular antibody-antigen interaction, or the dissociation rate constant of an antibody or antibody-binding fragment. Said value is also referred to as the k_{off} value.

[0091] The term “ k_a ” (M⁻¹sec⁻¹ or 1/M) refers to the association rate constant of a particular antibody-antigen interaction, or the association rate constant of an antibody or antibody-binding fragment.

[0092] The term “ K_A ” (M⁻¹ or 1/M) refers to the association equilibrium constant of a particular antibody-antigen interaction, or the association equilibrium constant of an antibody or antibody-binding fragment. The association equilibrium constant is obtained by dividing the k_a by the k_d .

[0093] The term “ EC_{50} ” or “ EC_{50} ” refers to the half maximal effective concentration, which includes the concentration of an antibody which induces a response halfway between the baseline and maximum after a specified expo-

sure time. The EC_{50} essentially represents the concentration of an antibody where 50% of its maximal effect is observed. In certain embodiments, the EC_{50} value equals the concentration of an antibody of the invention that gives half-maximal binding to cells expressing CD3 or tumor-associated antigen, as determined by e.g. a FACS binding assay. Thus, reduced or weaker binding is observed with an increased EC_{50} value, or half maximal effective concentration value such that 500 nM EC_{50} is indicative of a weaker binding affinity than 50 nM EC_{50} .

[0094] In one embodiment, decreased binding can be defined as an increased EC_{50} antibody concentration which enables binding to the half-maximal amount of target cells.

[0095] In other experimental measurements, the EC_{50} value represents the concentration of an antibody of the invention that elicits half-maximal depletion of target cells by T cell cytotoxic activity. Thus, increased cytotoxic activity (e.g. T cell-mediated tumor cell killing) is observed with a decreased EC_{50} , or half maximal effective concentration value.

Bispecific Antigen-Binding Molecules

[0096] The antibodies of the present invention may be bi-specific, or multispecific. Multispecific antibodies may be specific for one effector molecule, such as CD3, in combination with different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, e.g., Tutt et al., 1991, J. Immunol. 147:60-69; Kufer et al., 2004, Trends Biotechnol. 22:238-244. The anti-CD3 antibodies of the present invention can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment to produce a bi-specific or a multispecific antibody with a second binding specificity.

[0097] Use of the expression “anti-CD3 antibody” herein is intended to include both monospecific anti-CD3 antibodies as well as bispecific antibodies comprising a CD3-binding arm and a second arm that binds a target antigen. Thus, the present invention includes bispecific antibodies wherein one arm of an immunoglobulin binds human CD3, and the other arm of the immunoglobulin is specific for a target antigen. The target antigen that the other arm of the CD3 bispecific antibody binds can be any antigen expressed on or in the vicinity of a cell, tissue, organ, microorganism or virus, against which a targeted immune response is desired. The CD3-binding arm can comprise any of the HCVR or CDR amino acid sequences as set forth in Table 2 herein. In certain embodiments, the CD3-binding arm binds weakly to human CD3 and induces human T cell activation. In other embodiments, the CD3-binding arm binds weakly to human CD3 and induces tumor-associated antigen-expressing cell killing in the context of a bispecific or multispecific antibody. In other embodiments, the CD3-binding arm binds or associated weakly with human and cynomolgus (monkey) CD3, yet the binding interaction is not detectable by in vitro assays known in the art. In some embodiments of the invention, the CD3-binding arm does not bind or associate with human and cynomolgus (monkey) CD3, yet the bispecific molecule still elicits tumor-associated cell killing.

[0098] In the context of bispecific antibodies of the present invention wherein one arm of the antibody binds CD3 and the other arm binds a target antigen, the target antigen can be a tumor-associated antigen (TAA). Non-limiting examples of specific tumor-associated antigens include, e.g., AFP, ALK, BAGE proteins, BIRC5 (survivin), BIRC7, β -catenin, bcr-abl, BRCA1, BORIS, CA9, carbonic anhydrase IX, caspase-8, CALR, CCR5, CD19, CD20 (MS4A1), CD22, CD30, CD40, CDK4, CEA, CTLA4, cyclin-B1, CYP1B1, EGFR, EGFRvIII, ErbB2/Her2, ErbB3, ErbB4, ETV6-AML, EpCAM, EphA2, Fra-1, FOLR1, GAGE proteins (e.g., GAGE-1, -2), GD2, GD3, GloboH, glypican-3, GM3, gp100, Her2, HLA/B-raf, HLA/k-ras, HLA/MAGE-A3, hTERT, LMP2, MAGE proteins (e.g., MAGE-1, -2, -3, -4, -6, and -12), MART-1, mesothelin, ML-IAP, Muc1, Muc2, Muc3, Muc4, Muc5, Muc16 (CA-125), MUM1, NA17, NY-BR1, NY-BR62, NY-BR85, NY-ESO1, OX40, p15, p53, PAP, PAX3, PAX5, PCTA-1, PLAC1, PRLR, PRAME, PSMA (FOLH1), RAGE proteins, Ras, RGS5, Rho, SART-1, SART-3, STEAP1, STEAP2, TAG-72, TGF- β , TMPRSS2, Thompson-nouvelle antigen (Tn), TRP-1, TRP-2, tyrosinase, and uroplakin-3.

[0099] The inventors envision that the present invention includes numerous examples of bispecific antibodies having a weak anti-CD3 binding arm made in accordance with the invention.

[0100] According to certain exemplary embodiments, the present invention includes bispecific antigen-binding molecules that specifically bind CD3 and PSMA. Such molecules may be referred to herein as, e.g., “anti-CD3/anti-PSMA,” or “anti-CD3 $\times$ PSMA” or “CD3 $\times$ PSMA” bispecific molecules, and so forth. The term “PSMA,” as used herein, refers to the human PSMA protein unless specified as being from a non-human species (e.g., “mouse PSMA,” “monkey PSMA,” etc.).

[0101] The term “PSMA” refers to prostate-specific membrane antigen, also known as folate hydrolase 1 (FOLH1) (UniProtKB/Swiss-Prot. No. Q04609; SEQ ID NO: 171). PSMA is an integral, non-shed membrane glycoprotein that is highly expressed in prostate epithelial cells and is a cell-surface marker for prostate cancer.

[0102] According to other exemplary embodiments, the present invention includes bispecific antigen-binding molecules that specifically bind CD3 and EGFRvIII. Such molecules may be referred to herein as, e.g., “anti-CD3/anti-EGFRvIII” or “anti-CD3 $\times$ EGFRvIII” or “CD3 $\times$ EGFRvIII” bispecific molecules, and so forth. The term “EGFRvIII” refers to the human EGFRvIII protein unless specified as being from a non-human species (e.g., “mouse EGFRvIII,” “monkey EGFRvIII,” etc.).

[0103] The term “EGFRvIII” refers to the class III variant of the epidermal growth factor receptor (EGFRvIII; SEQ ID NO: 172) which is the most frequently found EGFR variant in glioblastoma (Bigner et al., 1990, *Cancer Res* 50:8017-8022; Humphrey et al., 1990, *Proc Natl Acad Sci USA* 87:4207-4211; Yamazaki et al., 1990, *Jap J Cancer Res* 81:773-779; Ekstrand et al., 1992, *Proc Natl Acad Sci USA* 89:4309-4313; Wikstrand et al., 1995, *Cancer Res* 55:3140-3148; and Frederick et al., 2000, *Cancer Res* 60:1383-1387). EGFRvIII is characterized by a deletion of exons 2-7 of the EGFR gene, resulting in an in-frame deletion of 801 base pairs of the coding region, i.e., deletion of 6-273 amino acid residues (based on the residue numbers of mature EGFR; see UniProtKB/Swiss-Prot. No. P00533), as well as the genera-

tion of a new glycine at the fusion junction (Humphrey et al., 1988, *Cancer Res* 48:2231-2238; Yamazaki et al., 1990, supra). EGFRvIII has been shown to have a ligand-independent, weak but constitutively active kinase activity as well as enhanced tumorigenicity (Nishikawa et al., 1994, *Proc Natl Acad Sci USA* 91:7727-7731; and Batra et al., 1995, *Cell Growth and Differentiation* 6:1251-1259). In addition to gliomas, EGFRvIII has been detected in ductal and intraductal breast carcinoma (Wikstrand et al., 1995, *Cancer Res* 55:3140-3148), non-small cell lung carcinomas (Garcia de Palazzo et al., 1993, *Cancer Res* 53:3217-3220), ovarian carcinomas (Moscatello et al., 1995, *Cancer Res* 55:5536-5539), prostate cancer (Olapade-Olaopa et al., 2000, *British J Cancer* 82:186-194), and squamous cell carcinoma of the head and neck (Tinhofer et al., 2011, *Clin Cancer Res* 17(15):5197-5204).

[0104] In still other exemplary embodiments, the present invention includes bispecific antigen-binding molecules that specifically bind CD3 and MUC16. Such molecules may be referred to herein as, e.g., “anti-CD3/anti-MUC16” or “anti-CD3 $\times$ MUC16” or “CD3 $\times$ MUC16” bispecific molecules, and so forth. The term “MUC16” refers to the human MUC16 protein unless specified as being from a non-human species (e.g., “mouse MUC16,” “monkey MUC16,” etc.).

[0105] Mucin 16 (MUC16; NCBI Reference Sequence: NP_078966.2, SEQ ID NO: 173), otherwise known as cancer antigen 125 (CA-125), is a mucin encoded by MUC16 gene in humans. The family of mucin proteins are known to protect the body from infection by pathogen binding to oligosaccharides in the extracellular domain, preventing the pathogen from reaching the cell surface. For many years, overexpression of MUC16/CA125 has been used as a prognostic and diagnostic marker for ovarian cancer (Yin and Lloyd, 2001, *J. Biol. Chem.* 276 (29), 27371-27375; O'Brien, T J, et al, 2001, *Tumour Biol.* 22 (6), 348-366; Leggieri, C. et al., 2014, *Eur. J. Gynaecol. Oncol.* 35 (4), 438-441). MUC16 has been shown to protect tumor cells from the immune system with its heavily glycosylated tandem repeat domain which can bind to galectin-1 (an immunosuppressive protein) (Seelenmeyer, C., et al., 2003, *J. Cell. Sci.* 116 (Pt 7): 1305-18; O'Brien, T J, et al., 2002, *Tumour Biol.* 23 (3), 154-169). Natural killer cells and monocytes are unable to attack tumor cells expressing high levels of MUC16. In its normal physiologic role, MUC16-galactin interaction serves as a barrier for bacterial and viral infection, however MUC16 is believed to be immunoprotective in the context of tumor cells, thereby preventing cancer cell cytolysis (Felder, M. et al., 2014, *Molecular Cancer*, 13:129). MUC16 is therefore a desirable target for immunotherapeutic bispecific antibody molecules administered to treat ovarian cancer by activating immune effector cells.

[0106] In still other exemplary embodiments, the present invention includes bispecific antigen-binding molecules that specifically bind CD3 and STEAP2. Such molecules may be referred to herein as, e.g., “anti-CD3/anti-STEAP2” or “anti-CD3 $\times$ STEAP2” or “CD3 $\times$ STEAP2” bispecific molecules, and so forth. The term “STEAP2” refers to the human STEAP2 protein unless specified as being from a non-human species (e.g., “mouse STEAP2,” “monkey STEAP2,” etc.). Six transmembrane epithelial antigen of the prostate 2 (STEAP2; UniProtKB/Swiss-Prot: Q8NFT2.3) is a 490-amino acid protein encoded by STEAP2 gene located at the chromosomal region 7q21 in humans.

[0107] The aforementioned bispecific antigen-binding molecules that specifically bind tumor-associated antigen comprise an anti-CD3 antigen-binding molecule which binds to CD3 with a weak or no detectable binding affinity such as exhibiting a K_D of greater than about 100 nM, 300 nM or 500 nM, as measured by an in vitro affinity binding assay.

[0108] As used herein, the expression “antigen-binding molecule” means a protein, polypeptide or molecular complex comprising or consisting of at least one complementing determining region (CDR) that alone, or in combination with one or more additional CDRs and/or framework regions (FRs), specifically binds to a particular antigen. In certain embodiments, an antigen-binding molecule is an antibody or a fragment of an antibody, as those terms are defined elsewhere herein.

[0109] As used herein, the expression “bispecific antigen-binding molecule” means a protein, polypeptide or molecular complex comprising at least a first antigen-binding domain and a second antigen-binding domain. Each antigen-binding domain within the bispecific antigen-binding molecule comprises at least one CDR that alone, or in combination with one or more additional CDRs and/or FRs, specifically binds to a particular antigen. In the context of the present invention, the first antigen-binding domain specifically binds a first antigen (e.g., CD3), and the second antigen-binding domain specifically binds a second, distinct antigen (e.g., PSMA, MUC16, EGFRvIII or STEAP2).

[0110] In certain exemplary embodiments of the present invention, the bispecific antigen-binding molecule is a bispecific antibody. Each antigen-binding domain of a bispecific antibody comprises a heavy chain variable domain (HCVR) and a light chain variable domain (LCVR). In the context of a bispecific antigen-binding molecule comprising a first and a second antigen-binding domain (e.g., a bispecific antibody), the CDRs of the first antigen-binding domain may be designated with the prefix “A1” and the CDRs of the second antigen-binding domain may be designated with the prefix “A2”. Thus, the CDRs of the first antigen-binding domain may be referred to herein as A1-HCDR1, A1-HCDR2, and A1-HCDR3; and the CDRs of the second antigen-binding domain may be referred to herein as A2-HCDR1, A2-HCDR2, and A2-HCDR3.

[0111] The first antigen-binding domain and the second antigen-binding domain may be directly or indirectly connected to one another to form a bispecific antigen-binding molecule of the present invention. Alternatively, the first antigen-binding domain and the second antigen-binding domain may each be connected to a separate multimerizing domain. The association of one multimerizing domain with another multimerizing domain facilitates the association between the two antigen-binding domains, thereby forming a bispecific antigen-binding molecule. As used herein, a “multimerizing domain” is any macromolecule, protein, polypeptide, peptide, or amino acid that has the ability to associate with a second multimerizing domain of the same or similar structure or constitution. For example, a multimerizing domain may be a polypeptide comprising an immunoglobulin C_H3 domain. A non-limiting example of a multimerizing component is an Fc portion of an immunoglobulin (comprising a C_H2 - C_H3 domain), e.g., an Fc domain of an IgG selected from the isotypes IgG1, IgG2, IgG3, and IgG4, as well as any allotype within each isotype group.

[0112] Bispecific antigen-binding molecules of the present invention will typically comprise two multimerizing domains, e.g., two Fc domains that are each individually part of a separate antibody heavy chain. The first and second multimerizing domains may be of the same IgG isotype such as, e.g., IgG1/IgG1, IgG2/IgG2, IgG4/IgG4. Alternatively, the first and second multimerizing domains may be of different IgG isotypes such as, e.g., IgG1/IgG2, IgG1/IgG4, IgG2/IgG4, etc.

[0113] In certain embodiments, the multimerizing domain is an Fc fragment or an amino acid sequence of 1 to about 200 amino acids in length containing at least one cysteine residues. In other embodiments, the multimerizing domain is a cysteine residue, or a short cysteine-containing peptide. Other multimerizing domains include peptides or polypeptides comprising or consisting of a leucine zipper, a helix-loop motif, or a coiled-coil motif.

[0114] Any bispecific antibody format or technology may be used to make the bispecific antigen-binding molecules of the present invention. For example, an antibody or fragment thereof having a first antigen binding specificity can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment having a second antigen-binding specificity to produce a bispecific antigen-binding molecule. Specific exemplary bispecific formats that can be used in the context of the present invention include, without limitation, e.g., scFv-based or diabody bispecific formats, IgG-scFv fusions, dual variable domain (DVD)-Ig, Quadroma, knobs-into-holes, common light chain (e.g., common light chain with knobs-into-holes, etc.), CrossMab, CrossFab, (SEED)body, leucine zipper, Duobody, IgG1/IgG2, dual acting Fab (DAF)-IgG, and Mab² bispecific formats (see, e.g., Klein et al. 2012, mAbs 4:6, 1-11, and references cited therein, for a review of the foregoing formats).

[0115] In the context of bispecific antigen-binding molecules of the present invention, the multimerizing domains, e.g., Fc domains, may comprise one or more amino acid changes (e.g., insertions, deletions or substitutions) as compared to the wild-type, naturally occurring version of the Fc domain. For example, the invention includes bispecific antigen-binding molecules comprising one or more modifications in the Fc domain that results in a modified Fc domain having a modified binding interaction (e.g., enhanced or diminished) between Fc and FcRn. In one embodiment, the bispecific antigen-binding molecule comprises a modification in a C_H2 or a C_H3 region, wherein the modification increases the affinity of the Fc domain to FcRn in an acidic environment (e.g., in an endosome where pH ranges from about 5.5 to about 6.0). Non-limiting examples of such Fc modifications include, e.g., a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., L/Y/F/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., L/R/S/P/Q or K) and/or 434 (e.g., H/F or Y); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (e.g., 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (e.g., M428L) and 434S (e.g., N434S) modification; a 428L, 259I (e.g., V259I), and 308F (e.g., V308F) modification; a 433K (e.g., H433K) and a 434 (e.g., 434Y) modification; a 252, 254, and 256 (e.g., 252Y, 254T, and 256E) modification; a 250Q and 428L

modification (e.g., T250Q and M428L); and a 307 and/or 308 modification (e.g., 308F or 308P).

[0116] The present invention also includes bispecific antigen-binding molecules comprising a first C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_H3 domain binds Protein A and the second Ig C_H3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_H3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V821 (by IMGT; D356E, L358M, N384S, K392N, V397M, and V4221 by EU) in the case of IgG1 antibodies; N44S, K52N, and V821 (IMGT; N384S, K392N, and V4221 by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V821 (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V4221 by EU) in the case of IgG4 antibodies.

[0117] In certain embodiments, the Fc domain may be chimeric, combining Fc sequences derived from more than one immunoglobulin isotype. For example, a chimeric Fc domain can comprise part or all of a C_H2 sequence derived from a human IgG1, human IgG2 or human IgG4 C_H2 region, and part or all of a C_H3 sequence derived from a human IgG1, human IgG2 or human IgG4. A chimeric Fc domain can also contain a chimeric hinge region. For example, a chimeric hinge may comprise an “upper hinge” sequence, derived from a human IgG1, a human IgG2 or a human IgG4 hinge region, combined with a “lower hinge” sequence, derived from a human IgG1, a human IgG2 or a human IgG4 hinge region. A particular example of a chimeric Fc domain that can be included in any of the antigen-binding molecules set forth herein comprises, from N- to C-terminus: [IgG4 C_H1]-[IgG4 upper hinge]-[IgG2 lower hinge]-[IgG4 C_H2]-[IgG4 C_H3]. Another example of a chimeric Fc domain that can be included in any of the antigen-binding molecules set forth herein comprises, from N- to C-terminus: [IgG1 C_H1]-[IgG1 upper hinge]-[IgG2 lower hinge]-[IgG4 C_H2]-[IgG1 C_H3]. These and other examples of chimeric Fc domains that can be included in any of the antigen-binding molecules of the present invention are described in PCT International Publication No. WO2014/121087 A1, published Aug. 7, 2014, which is herein incorporated by reference in its entirety. Chimeric Fc domains having these general structural arrangements, and variants thereof, can have altered Fc receptor binding, which in turn affects Fc effector function.

[0118] In certain embodiments, the invention provides an antibody heavy chain wherein the heavy chain constant region (C_H) region comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to any one of SEQ ID NO: 182, SEQ ID NO: 183, SEQ ID NO: 184, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190 or SEQ ID NO: 191. In some embodiments, the heavy chain constant region (C_H) region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 182, SEQ ID NO: 183, SEQ ID NO: 184, SEQ ID NO:

185, SEQ ID NO: 186, SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190 and SEQ ID NO: 191.

[0119] In other embodiments, the invention provides an antibody heavy chain wherein the Fc domain comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to any one of SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200 or SEQ ID NO: 201. In some embodiments, the Fc domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200 and SEQ ID NO: 201.

Other Fc Variants

[0120] According to certain embodiments of the present invention, anti-CD3 antibodies, and anti-CD3/anti-TAA bispecific antigen-binding molecules, are provided comprising an Fc domain comprising one or more mutations which enhance or diminish antibody binding to the FcRn receptor, e.g., at acidic pH as compared to neutral pH. For example, the present invention includes antibodies comprising a mutation in the C_H2 or a C_H3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (e.g., in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal. Non-limiting examples of such Fc modifications include, e.g., a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., L/Y/F/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (e.g., H/F or Y); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (e.g., 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (e.g., M428L) and 434S (e.g., N434S) modification; a 428L, 259I (e.g., V259I), and 308F (e.g., V308F) modification; a 433K (e.g., H433K) and a 434 (e.g., 434Y) modification; a 252, 254, and 256 (e.g., 252Y, 254T, and 256E) modification; a 250Q and 428L modification (e.g., T250Q and M428L); and a 307 and/or 308 modification (e.g., 308F or 308P).

[0121] For example, the present invention includes anti-CD3 antibodies, and anti-CD3/anti-TAA bispecific antigen-binding molecules, comprising an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of: 250Q and 248L (e.g., T250Q and M248L); 252Y, 254T and 256E (e.g., M252Y, S254T and T256E); 428L and 434S (e.g., M428L and N434S); and 433K and 434F (e.g., H433K and N434F). All possible combinations of the foregoing Fc domain mutations, and other mutations within the antibody variable domains disclosed herein, are contemplated within the scope of the present invention.

Biological Characteristics of the Antibodies and Bispecific Antigen-Binding Molecules

[0122] The present invention includes bispecific antigen-binding molecules (e.g., bispecific antibodies) which are capable of simultaneously binding to human CD3 and a human TAA. According to certain embodiments, the bispecific antigen-binding molecules of the invention specifically

interact with cells that express CD3 and/or TAA, such as PSMA, EGFRvIII or MUC16. The binding arm that interacts with cells that express CD3 may have weak to no detectable binding as measured in a suitable in vitro binding assay. The extent to which a bispecific antigen-binding molecule binds cells that express CD3 and/or TAA can be assessed by fluorescence activated cell sorting (FACS), as illustrated in Example 4 herein.

[0123] For example, the present invention includes antibodies, antigen-binding fragments, and bispecific antibodies thereof which specifically bind human T-cell lines which express CD3 but not the TAA (e.g., Jurkat), primate T-cells (e.g., cynomolgus peripheral blood mononuclear cells [PB-MCs]), and/or TAA-expressing cells. The present invention includes bispecific antigen-binding molecules which bind any of the aforementioned T cells and T cell lines with an EC_{50} value of from about 1.8×10^{-9} (18 nM) to about 2.1×10^{-7} (210 nM), or more (i.e. weaker affinity), and includes bispecific antibodies for which EC_{50} is undetectable, as determined using a FACS binding assay as set forth in Example 4 or a substantially similar assay. In certain embodiments, the antibodies, antigen-binding fragments, and bispecific antibodies of the present invention bind CD3 with an EC_{50} of greater than about 30 nM, greater than about 40 nM, greater than about 45 nM, greater than about 50 nM, greater than about 55 nM, greater than about 60 nM, greater than about 65 nM, greater than about 70 nM, greater than about 75 nM, at least 80 nM, greater than about 90 nM, greater than about 100 nM, at least 120 nM, greater than about 130 nM, greater than about 140 nM, greater than about 150 nM, at least 160 nM, greater than about 170 nM, greater than about 180 nM, greater than about 190 nM, greater than about 200 nM, greater than about 250 nM, greater than about 300 nM, greater than about 500 nM, greater than about 1 μ M, greater than about 2 μ M, or greater than about 3 μ M, or no detectable binding affinity, as measured by FACS binding, e.g., using an assay format as defined in Example 4 herein, or a substantially similar assay.

[0124] The present invention also includes antibodies, antigen-binding fragments, and bispecific antibodies thereof which bind to TAA-expressing cells and cell lines, such as PSMA-, EGFRvIII-, STEAP2- and MUC16-expressing cell lines, with an EC_{50} value of less than about 100 nM, or even less concentration necessary for binding (i.e. stronger affinity) such as less than 5.6 nM (5.6×10^{-9}), as determined using a FACS binding assay as set forth in Example 4 or a substantially similar cell-based assay. The present invention includes bispecific antigen-binding molecules which bind any of the aforementioned tumor cell lines with an EC_{50} value of less than about 50 nM, less than about 45 nM, less than about 40 nM, less than about 35 nM, less than about 30 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 6 nM, less than about 5 nM, or less than about 1 nM, e.g. using the aforementioned assay.

[0125] The present invention includes antibodies, antigen-binding fragments, and bispecific antibodies thereof that bind human CD3 with low, weak or even no detectable affinity. According to certain embodiments, the present invention includes antibodies and antigen-binding fragments of antibodies that bind human CD3 (e.g., at 37° C.) with a K_D of greater than about 11 nM, includes antibodies that bind CD3 with a K_D of greater than about 100 nM or 500 nM, and also includes antibodies having no detectable

binding affinity, as measured by surface plasmon resonance, e.g., using an assay format as defined in Example 5 herein. In certain embodiments, the antibodies or antigen-binding fragments of the present invention bind CD3 with a K_D of greater than about 15 nM, greater than about 20 nM, greater than about 25 nM, greater than about 30 nM, greater than about 35 nM, greater than about 40 nM, greater than about 45 nM, greater than about 50 nM, greater than about 55 nM, greater than about 60 nM, greater than about 65 nM, greater than about 70 nM, greater than about 75 nM, at least 80 nM, greater than about 90 nM, greater than about 100 nM, greater than about 110 nM, at least 120 nM, greater than about 130 nM, greater than about 140 nM, greater than about 150 nM, at least 160 nM, greater than about 170 nM, greater than about 180 nM, greater than about 190 nM, greater than about 200 nM, greater than about 250 nM, greater than about 300 nM, greater than about 1 μ M, greater than about 2 μ M, or greater than about 3 μ M, or no detectable affinity, as measured by surface plasmon resonance, e.g., using an assay format as defined in Example 5 herein (e.g., mAb-capture or antigen-capture format), or a substantially similar assay.

[0126] The present invention includes antibodies, antigen-binding fragments, and bispecific antibodies thereof that bind monkey (i.e. cynomolgus) CD3 with low, weak, or even no detectable affinity. According to certain embodiments, the present invention includes antibodies, antigen-binding fragments, and bispecific antibodies thereof that bind human CD3 (e.g., at 37° C.) with a K_D of greater than about 10 nM, includes antibodies that bind CD3 with a K_D of greater than about 100 nM or 500 nM, and also includes antibodies having no detectable binding affinity, as measured by surface plasmon resonance, e.g., using an assay format as defined in Example 5 herein. In certain embodiments, the antibodies or antigen-binding fragments of the present invention bind CD3 with a K_D of greater than about 15 nM, greater than about 20 nM, greater than about 25 nM, greater than about 30 nM, greater than about 35 nM, greater than about 40 nM, greater than about 45 nM, greater than about 50 nM, greater than about 55 nM, greater than about 60 nM, greater than about 65 nM, greater than about 70 nM, greater than about 75 nM, at least 80 nM, greater than about 90 nM, greater than about 100 nM, greater than about 110 nM, at least 120 nM, greater than about 130 nM, greater than about 140 nM, greater than about 150 nM, at least 160 nM, greater than about 170 nM, greater than about 180 nM, greater than about 190 nM, greater than about 200 nM, greater than about 250 nM, greater than about 300 nM, greater than about 1 μ M, greater than about 2 μ M, or greater than about 3 μ M, or no detectable affinity, as measured by surface plasmon resonance, e.g., using an assay format as defined in Example 5 herein (e.g., mAb-capture or antigen-capture format), or a substantially similar assay.

[0127] The present invention includes antibodies, antigen-binding fragments, and bispecific antibodies thereof that bind human CD3 and induce T cell activation. For example, the present invention includes anti-CD3 antibodies that induce human T cell activation with an EC_{50} value of less than about 113 pM, as measured by an in vitro T cell activation assay, e.g., using the assay format as defined in Example 6 herein [e.g., assessing the percent activated (CD69+) cells out of total T cells (CD2+) in the presence of anti-CD3 antibodies], or a substantially similar assay that assesses T cell in their activated state. In certain embodiments, the antibodies or antigen-binding fragments of the

present invention induce human T cell activation [e.g., percent activated (CD69+) T cells] with an EC_{50} value of less than about 100 pM, less than about 50 pM, less than about 20 pM, less than about 19 pM, less than about 18 pM, less than about 17 pM, less than about 16 pM, less than about 15 pM, less than about 14 pM, less than about 13 pM, less than about 12 pM, less than about 11 pM, less than about 10 pM, less than about 9 pM, less than about 8 pM, less than about 7 pM, less than about 6 pM, less than about 5 pM, less than about 4 pM, less than about 3 pM, less than about 2 pM, or less than about 1 pM, as measured by an in vitro T cell activation assay, e.g., using the assay format as defined in Example 6 herein, or a substantially similar assay. Anti-CD3 antibodies that have weak or no detectable binding to CD3 have the ability to induce T cell activation with high potency (i.e. pM range), despite having weak or no detectable binding affinity to CD3, as exemplified in Example 6 herein.

[0128] The present invention also includes antibodies, antigen-binding fragments, and bispecific antibodies that bind human CD3 and induce T cell-mediated killing of tumor antigen-expressing cells. For example, the present invention includes anti-CD3 antibodies that induce T cell-mediated killing of tumor cells with an EC_{50} of less than about 1.3 nM, as measured in an in vitro T cell-mediated tumor cell killing assay, e.g., using the assay format as defined in Example 6 herein (e.g., assessing the extent of tumor antigen-expressing cells, such as PSMA-expressing, EGFRvIII-expressing or MUC16-expressing cell killing by human PBMCs in the presence of anti-CD3 antibodies), or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present invention induce T cell-mediated tumor cell killing (e.g., PBMC-mediated killing of OVCAR3 cells) with an EC_{50} value of less than about 1 nM, less than about 400 pM, less than about 250 pM, less than about 100 pM, less than about 50 pM, less than about 40 pM, less than about 30 pM, less than about 20 pM, less than about 10 pM, less than about 9 pM, less than about 8 pM, less than about 7 pM, less than about 6 pM, less than about 5 pM, less than about 4 pM, less than about 3 pM, less than about 2 pM, or less than about 1 pM, as measured by an in vitro T cell-mediated tumor cell killing assay, e.g., using the assay format as defined in Example 6 herein, or a substantially similar assay.

[0129] The present invention also includes antibodies, antigen-binding fragments, and bispecific antibodies that bind CD3 with a dissociative half-life ($t_{1/2}$) of less than about 10 minutes as measured by surface plasmon resonance at 25° C. or 37° C., e.g., using an assay format as defined in Example 5 herein, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present invention bind CD3 with a $t_{1/2}$ of less than about 9 minutes, of less than about 8 minutes, of less than about 7 minutes, of less than about 6 minutes, of less than about 5 minutes, of less than about 4 minutes, of less than about 3 minutes, of less than about 2 minutes, of less than about 1.9 minutes, or less than about 1.8 minutes, or exhibit very weak or no detectable binding as measured by surface plasmon resonance at 25° C. or 37° C., e.g., using an assay format as defined in Example 5 herein (e.g., mAb-capture or antigen-capture format), or a substantially similar assay.

[0130] The anti-CD3/anti-TAA bispecific antigen-binding molecules of the present invention may additionally exhibit one or more characteristics selected from the group consisting of: (a) inducing PBMC proliferation in vitro; (b) acti-

vating T-cells via inducing IFN-gamma release and CD25 up-regulation in human whole blood; and (c) inducing T-cell mediated cytotoxicity on anti-TAA-resistant cell lines.

[0131] The present invention includes anti-CD3/anti-TAA bispecific antigen-binding molecules which are capable of depleting tumor antigen-expressing cells in a subject (see, e.g., Example 7). For example, according to certain embodiments, anti-CD3/anti-PSMA, anti-CD3/anti-MUC16, or anti-CD3/anti-STEAP2 bispecific antigen-binding molecules are provided, wherein a single administration of 1 µg, or 10 µg, or 100 µg of the bispecific antigen-binding molecule to a subject (e.g., at a dose of about 0.1 mg/kg, about 0.08 mg/kg, about 0.06 mg/kg, about 0.04 mg/kg, about 0.03 mg/kg, about 0.02 mg/kg, about 0.01 mg/kg, or less) causes a reduction in the number of tumor antigen-expressing cells in the subject (e.g., tumor growth in the subject is suppressed or inhibited) below detectable levels. In certain embodiments, a single administration of the anti-CD3/anti-PSMA bispecific antigen-binding molecule at a dose of about 0.4 mg/kg causes a reduction in tumor growth in the subject below detectable levels by about day 7, about day 6, about day 5, about day 4, about day 3, about day 2, or about day 1 after administration of the bispecific antigen-binding molecule to the subject. According to certain embodiments, a single administration of an anti-CD3/anti-PSMA bispecific antigen-binding molecule of the invention, at a dose of at least about 0.01 mg/kg, causes the number of PSMA-expressing tumor cells to remain below detectable levels until at least about 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days or more, following the administration. As used herein, the expression “below detectable levels” means that no tumor cells can be directly or indirectly detected growing subcutaneously in a subject using standard caliper measurement methods, e.g., as set forth in Example 7, herein. In certain embodiments, a single administration of the anti-CD3/anti-MUC16 bispecific antigen-binding molecule at a dose of about 10 µg causes a suppression of tumor growth in the subject at about day 6, and maintains tumor suppression until at least day 26 after administration of the bispecific antigen-binding molecule to the subject. In subjects receiving a single administration of the anti-CD3/anti-MUC16 bispecific antigen-binding molecule at a dose of about 10 µg at least 7 days after tumor implantation, the bispecific antigen-binding molecule exhibits efficacy in suppression of established tumors from further growth in the subject at about day 26 after tumor implantation in the subject. According to certain embodiments, a single administration of an anti-CD3/anti-MUC16 bispecific antigen-binding molecule of the invention, at a dose of at least about 0.1 mg/kg, inhibits growth of MUC16-expressing tumor cells for at least about 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days or more, following administration of the bispecific molecule. See, e.g. Example 8.

[0132] In certain embodiments, a single administration of the anti-CD3/anti-STEAP2 bispecific antigen-binding molecule at a dose of about 0.1 mg/kg or 0.01 mg/kg maintains a suppression of tumor growth until at least day 46 after administration of the bispecific antigen-binding molecule and tumor to the subject. According to certain embodiments, a single administration of an anti-CD3/anti-STEAP2 bispecific antigen-binding molecule of the invention, at a dose of at least about 0.1 mg/kg, about 0.08 mg/kg, about 0.06

mg/kg, about 0.05 mg/kg, about 0.04 mg/kg, about 0.03 mg/kg, about 0.02 mg/kg, about 0.01 mg/kg, or less inhibits growth of STEAP2-expressing tumor cells for at least about 20 days, 30 days, 35 days, 40 days, 45 days or more, following administration of the bispecific molecule. See, e.g., Example 10.

[0133] In other embodiments, anti-CD3/anti-TAA bispecific antigen-binding molecules having a CD3 targeted binding arm having weak binding affinity to effector cells exhibit reduced drug elimination rates compared to the bispecific antibodies comprising the same anti-TAA binding arm and a strong CD3 binding arm administered in an in vivo pharmacokinetic study. The results suggest that the bispecific molecules comprising weaker binding of the CD3 targeting arm may exhibit beneficial drug exposure levels (AUC_{last}) and drug elimination profiles (antibody clearance). See, e.g., Example 9.

[0134] The present invention provides anti-CD3/anti-PSMA, anti-CD3/anti-MUC16 and anti-CD3/anti-STEAP2 bispecific antigen-binding molecules (i.e. anti-CD3/anti-TAA bispecific antigen-binding molecules) which exhibit one or more characteristics selected from the group consisting of: (a) inhibiting tumor growth in immunocompromised mice bearing human prostate cancer xenografts; (b) inhibiting tumor growth in immunocompetent mice bearing human prostate cancer xenografts; (c) suppressing tumor growth of established tumors in immunocompromised mice bearing human prostate cancer xenografts; and (d) reducing tumor growth of established tumors in immunocompetent mice bearing human prostate cancer xenografts (see, e.g., Examples 7, 8 and 10). The present invention also provides anti-CD3/anti-PSMA, anti-CD3/anti-MUC16 and anti-CD3/anti-STEAP2 bispecific antibodies (i.e. anti-CD3/anti-TAA bispecific antibodies) comprising a first heavy chain directed to an effector T cell (i.e. CD3), and ii) a second heavy chain directed to a target tumor cell, wherein the bispecific antibodies exhibit weak binding or no detectable binding to the effector cells, and exhibit tumor growth suppression and reduced antibody clearance (i.e. elimination) from the body compared to bispecific antibodies that exhibit strong binding to effector cells.

Epitope Mapping and Related Technologies

[0135] The epitope on CD3 to which the antigen-binding molecules of the present invention bind may consist of a single contiguous sequence of 3 or more (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) amino acids of a CD3 protein. Alternatively, the epitope may consist of a plurality of non-contiguous amino acids (or amino acid sequences) of CD3. The antibodies of the invention may interact with amino acids contained within a single CD3 chain (e.g., CD3-epsilon, CD3-delta or CD3-gamma), or may interact with amino acids on two or more different CD3 chains. The term “epitope,” as used herein, refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide

chain. In certain circumstances, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

[0136] Various techniques known to persons of ordinary skill in the art can be used to determine whether an antigen-binding domain of an antibody “interacts with one or more amino acids” within a polypeptide or protein. Exemplary techniques include, e.g., routine cross-blocking assay such as that described Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY), alanine scanning mutational analysis, peptide blots analysis (Reineke, 2004, *Methods Mol Biol* 248:443-463), and peptide cleavage analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer, 2000, *Protein Science* 9:487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antigen-binding domain of an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water to allow hydrogen-deuterium exchange to occur at all residues except for the residues protected by the antibody (which remain deuterium-labeled). After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues which correspond to the specific amino acids with which the antibody interacts. See, e.g., Ehring (1999) *Analytical Biochemistry* 267(2):252-259; Engen and Smith (2001) *Anal. Chem.* 73:256A-265A. X-ray crystallography of the antigen/antibody complex may also be used for epitope mapping purposes.

[0137] The present invention further includes anti-PSMA antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein (e.g. antibodies comprising any of the amino acid sequences as set forth in Table 6 herein). Likewise, the present invention also includes anti-PSMA antibodies that compete for binding to PSMA with any of the specific exemplary antibodies described herein (e.g. antibodies comprising any of the amino acid sequences as set forth in Table 6 herein). Anti-PSMA antibodies disclosed in U.S. application Ser. No. 15/223,434 are herein incorporated by reference into this application.

[0138] The present invention also includes bispecific antigen-binding molecules comprising a first antigen-binding domain that specifically binds human CD3 and/or cynomolgus CD3 with low or detectable binding affinity, and a second antigen binding domain that specifically binds human tumor-associated antigen (TAA), wherein the first antigen-binding domain binds to the same epitope on CD3 as any of the specific exemplary CD3-specific antigen-binding domains described herein.

[0139] Likewise, the present invention also includes bispecific antigen-binding molecules comprising a first antigen-binding domain that specifically binds human CD3 and/or cynomolgus CD3 with low or detectable binding affinity, and a second antigen binding domain that specifically binds human tumor-associated antigen (TAA), wherein the first antigen-binding domain competes for binding to CD3 with any of the specific exemplary CD3-specific antigen-binding domains described herein.

[0140] One can easily determine whether a particular antigen-binding molecule (e.g., antibody) or antigen-binding domain thereof binds to the same epitope as, or competes for binding with, a reference antigen-binding molecule of the present invention by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope on CD3 (or TAA) as a reference bispecific antigen-binding molecule of the present invention, the reference bispecific molecule is first allowed to bind to a CD3 protein (or TAA protein). Next, the ability of a test antibody to bind to the CD3 molecule is assessed. If the test antibody is able to bind to CD3 (or TAA) following saturation binding with the reference bispecific antigen-binding molecule, it can be concluded that the test antibody binds to a different epitope of CD3 (or TAA) than the reference bispecific antigen-binding molecule. On the other hand, if the test antibody is not able to bind to the CD3 (or TAA) molecule following saturation binding with the reference bispecific antigen-binding molecule, then the test antibody may bind to the same epitope of CD3 (or TAA) as the epitope bound by the reference bispecific antigen-binding molecule of the invention. Additional routine experimentation (e.g., peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference bispecific antigen-binding molecule or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. If the reference antibody is one that has no measurable binding as exemplified herein, then the reference antibody may be mutated back to germline sequence in order to determine binding to the CD3 for purpose of comparing epitope interaction, or comparing its binding properties to the test antibody as described herein. Experiments of this sort can be performed using ELISA, RIA, Biacore, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art. In accordance with certain embodiments of the present invention, two antigen-binding proteins bind to the same (or overlapping) epitope if, e.g., a 1-, 5-, 10-, 20- or 100-fold excess of one antigen-binding protein inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., *Cancer Res.* 1990:50:1495-1502). Alternatively, two antigen-binding proteins are deemed to bind to the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antigen-binding protein reduce or eliminate binding of the other. Two antigen-binding proteins are deemed to have "overlapping epitopes" if only a subset of the amino acid mutations that reduce or eliminate binding of one antigen-binding protein reduce or eliminate binding of the other.

[0141] To determine if an antibody or antigen-binding domain thereof competes for binding with a reference antigen-binding molecule, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antigen-binding molecule is allowed to bind to a CD3 protein (or TAA protein) under saturating conditions followed by assessment of binding of the test antibody to the CD3 (or TAA) molecule. In a second orientation, the test antibody is allowed to bind to a CD3 (or TAA) molecule under saturating conditions followed by assessment of binding of the reference antigen-binding molecule to the CD3 (or TAA) molecule. If, in both orientations, only the first (saturating) antigen-binding molecule

is capable of binding to the CD3 (or TAA) molecule, then it is concluded that the test antibody and the reference antigen-binding molecule compete for binding to CD3 (or TAA). As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antigen-binding molecule may not necessarily bind to the same epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope. If the reference antibody is one that has no measurable binding as exemplified herein, then the reference antibody may be mutated back to germline sequence in order to determine binding to the CD3 for purpose of comparing epitope interaction, or comparing its binding properties or blocking interaction with the test antibody as described herein.

Preparation of Antigen-Binding Domains and Construction of Bispecific Molecules

[0142] Antigen-binding domains specific for particular antigens can be prepared by any antibody generating technology known in the art. Once obtained, two different antigen-binding domains, specific for two different antigens (e.g., CD3 and TAA), can be appropriately arranged relative to one another to produce a bispecific antigen-binding molecule of the present invention using routine methods. (A discussion of exemplary bispecific antibody formats that can be used to construct the bispecific antigen-binding molecules of the present invention is provided elsewhere herein). In certain embodiments, one or more of the individual components (e.g., heavy and light chains) of the multispecific antigen-binding molecules of the invention are derived from chimeric, humanized or fully human antibodies. Methods for making such antibodies are well known in the art. For example, one or more of the heavy and/or light chains of the bispecific antigen-binding molecules of the present invention can be prepared using VELOCIMMUNETM technology. Using VELOCIMMUNETM technology (or any other human antibody generating technology), high affinity chimeric antibodies to a particular antigen (e.g., CD3 or TAA) are initially isolated having a human variable region and a mouse constant region. The antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are replaced with a desired human constant region to generate fully human heavy and/or light chains that can be incorporated into the bispecific antigen-binding molecules of the present invention.

[0143] Genetically engineered animals may be used to make human bispecific antigen-binding molecules. For example, a genetically modified mouse can be used which is incapable of rearranging and expressing an endogenous mouse immunoglobulin light chain variable sequence, wherein the mouse expresses only one or two human light chain variable domains encoded by human immunoglobulin sequences operably linked to the mouse kappa (κ) constant gene at the endogenous mouse kappa (κ) locus. Such genetically modified mice can be used to produce fully human bispecific antigen-binding molecules comprising two different heavy chains that associate with an identical light chain that comprises a variable domain derived from one of two different human light chain variable region gene segments. (See, e.g., US 2011/0195454 for a detailed discussion of such engineered mice and the use thereof to produce bispecific antigen-binding molecules). Antibodies of the inven-

tion may comprise immunoglobulin heavy chains associated with a common light chain. The common light chain may be derived from a cognate light chain of the anti-TAA heavy chain, or derived from a known or public domain light chain variable region derived from a light chain exhibiting promiscuity or ability to pair with a wide variety of non-cognate heavy chains, i.e. a universal or common light chain. Antibodies of the invention may comprise immunoglobulin heavy chains associated with a single rearranged light chain. In some embodiments, the light chain a variable domain derived from a human Vk1-39 gene segment or a Vk3-20 gene segment. In other embodiments, the light chain comprises a variable domain derived from a human Vk1-39 gene segment rearranged with a human Jk5 or a human Jk1 gene segment, or a Vk3-20 gene segment rearranged with a human Jk1 gene segment, or a Vk1-39 gene segment rearranged with a human Jk1 gene segment.

Bioequivalents

[0144] The present invention encompasses antigen-binding molecules having amino acid sequences that vary from those of the exemplary molecules disclosed herein but that retain the ability to bind or interact with CD3 and/or TAA. Such variant molecules may comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described bispecific antigen-binding molecules.

[0145] The present invention includes antigen-binding molecules that are bioequivalent to any of the exemplary antigen-binding molecules set forth herein. Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single dose or multiple dose. Some antigen-binding proteins will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied.

[0146] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0147] In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[0148] In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[0149] Bioequivalence may be demonstrated by in vivo and in vitro methods. Bioequivalence measures include, e.g., (a) an in vivo test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured

in blood, plasma, serum, or other biological fluid as a function of time; (b) an in vitro test that has been correlated with and is reasonably predictive of human in vivo bioavailability data; (c) an in vivo test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antigen-binding protein.

[0150] Bioequivalent variants of the exemplary bispecific antigen-binding molecules set forth herein may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antigen-binding proteins may include variants of the exemplary bispecific antigen-binding molecules set forth herein comprising amino acid changes which modify the glycosylation characteristics of the molecules, e.g., mutations which eliminate or remove glycosylation.

Species Selectivity and Species Cross-Reactivity

[0151] According to certain embodiments of the invention, antigen-binding molecules are provided which display weak or no interaction with human CD3 and weak or no interaction with CD3 from other species, such as cynomolgus monkey CD3. Also provided are antigen-binding molecules which bind to human TAA but not to TAA from other species. The present invention also includes antigen-binding molecules that bind to human CD3 and to CD3 from one or more non-human species; and/or antigen-binding molecules that bind to human TAA and to TAA from one or more non-human species.

[0152] According to certain exemplary embodiments of the invention, antigen-binding molecules are provided which bind weakly to human CD3 and/or human TAA and may bind or not bind, as the case may be, to one or more of mouse, rat, guinea pig, hamster, gerbil, pig, cat, dog, rabbit, goat, sheep, cow, horse, camel, cynomolgus, marmoset, rhesus or chimpanzee CD3 and/or TAA. For example, in certain exemplary embodiments of the present invention bispecific antigen-binding molecules are provided comprising a first antigen-binding domain that weakly binds human CD3 and cynomolgus CD3, and a second antigen-binding domain that specifically binds human PSMA, MUC16, EGFRvIII or STEAP2.

Immunoconjugates

[0153] The present invention encompasses antigen-binding molecules conjugated to a therapeutic moiety ("immunoconjugate"), such as a cytotoxin, a chemotherapeutic drug, an immunosuppressant or a radioisotope. Cytotoxic agents include any agent that is detrimental to cells. Examples of suitable cytotoxic agents and chemotherapeutic agents for forming immunoconjugates are known in the art, (see for example, WO 05/103081).

Therapeutic Formulation and Administration

[0154] The present invention provides pharmaceutical compositions comprising the antigen-binding molecules of

the present invention. The pharmaceutical compositions of the invention are formulated with suitable carriers, excipients, and other agents that provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™, Life Technologies, Carlsbad, Calif.), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

[0155] The dose of antigen-binding molecule administered to a patient may vary depending upon the age and the size of the patient, target disease, conditions, route of administration, and the like. The preferred dose is typically calculated according to body weight or body surface area. When a bispecific antigen-binding molecule of the present invention is used for therapeutic purposes in an adult patient, it may be advantageous to intravenously administer the bispecific antigen-binding molecule of the present invention normally at a single dose of about 0.01 to about 20 mg/kg body weight, more preferably about 0.02 to about 7, about 0.03 to about 5, or about 0.05 to about 3 mg/kg body weight. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. Effective dosages and schedules for administering a bispecific antigen-binding molecule may be determined empirically; for example, patient progress can be monitored by periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (e.g., Mordenti et al., 1991, *Pharmaceut. Res.* 8:1351).

[0156] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al., 1987, *J. Biol. Chem.* 262:4429-4432). Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

[0157] A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be

discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0158] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, Ind.), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, N.J.), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but are not limited to the SOLO-STAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, Calif.), the PEN-LET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park Ill.), to name only a few.

[0159] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201). In another embodiment, polymeric materials can be used; see, *Medical Applications of Controlled Release*, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Fla. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, 1984, in *Medical Applications of Controlled Release*, supra, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, *Science* 249:1527-1533.

[0160] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing

agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[0161] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, it is preferred that the aforesaid antibody is contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

Therapeutic Uses of the Antigen-Binding Molecules

[0162] The present invention includes methods comprising administering to a subject in need thereof a therapeutic composition comprising an anti-tumor antibody or antigen-binding fragment thereof, or a bispecific antigen-binding molecule that specifically binds weakly or has no detectable binding to CD3 and binds a tumor-associated antigen. The therapeutic composition can comprise any of the antibodies or bispecific antigen-binding molecules as disclosed herein and a pharmaceutically acceptable carrier or diluent. As used herein, the expression “a subject in need thereof” means a human or non-human animal that exhibits one or more symptoms or indicia of cancer (e.g., a subject expressing a tumor or suffering from any of the cancers mentioned herein below), or who otherwise would benefit from an inhibition or reduction in tumor activity or a depletion of tumor cells (e.g., PSMA++ prostate cancer cells).

[0163] The antibodies and bispecific antigen-binding molecules of the invention (and therapeutic compositions comprising the same) are useful, inter alia, for treating any disease or disorder in which stimulation, activation and/or targeting of an immune response would be beneficial. In particular, the bispecific antigen-binding molecules of the present invention may be used for the treatment, prevention and/or amelioration of any disease or disorder associated with or mediated by a cell expressing a TAA, e.g. PSMA expression or activity or the proliferation of PSMA+ cells. The mechanism of action by which the therapeutic methods of the invention are achieved include killing of the cells expressing tumor-associated antigens, in the presence of effector cells, for example, by CDC, apoptosis, ADCC, phagocytosis, or by a combination of two or more of these mechanisms. Cells expressing tumor-associated antigens, such as PSMA, MUC16, STEAP2 or EGFRvIII, which can be inhibited or killed using the bispecific antigen-binding molecules of the invention include, for example, prostate tumor cells.

[0164] The antigen-binding molecules of the present invention may be used to treat, e.g., primary and/or metastatic tumors arising in the brain and meninges, head and neck, oropharynx, lung and bronchial tree, gastrointestinal tract, male and female reproductive tract, muscle, bone, skin and appendages, connective tissue, spleen, immune system, blood forming cells and bone marrow, liver and urinary tract, kidney, bladder and/or special sensory organs such as the eye. In certain embodiments, the bispecific antigen-binding molecules of the invention are used to treat one or more of, but not limited to, the following cancers: pancreatic carcinoma, head and neck cancer, prostate cancer, malignant

gliomas, osteosarcoma, colorectal cancer, gastric cancer (e.g., gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, small cell lung cancer, non-small cell lung cancer, synovial sarcoma, thyroid cancer, breast cancer, melanoma, glioma, breast cancer (e.g. ductal or intraductal breast carcinoma, squamous cell carcinoma, esophageal cancer, clear cell renal cell carcinoma, chromophobe renal cell carcinoma, (renal) oncocytoma, (renal) transitional cell carcinoma, urothelial carcinoma, (bladder) adenocarcinoma, or (bladder) small cell carcinoma. According to certain embodiments of the present invention, the bispecific antibodies are useful for treating a patient afflicted with a refractory or treatment-resistant cancer, e.g. castrate-resistant prostate cancer. According to exemplary embodiments of the invention, methods are provided comprising administering an anti-CD3/anti-PSMA bispecific antigen-binding molecule as disclosed herein to a patient who is afflicted with a castrate-resistant prostate cancer. Analytic/diagnostic methods known in the art, such as tumor scanning, etc., may be used to ascertain whether a patient harbors a tumor that is castrate-resistant.

[0165] The present invention also includes methods for treating residual cancer in a subject. As used herein, the term “residual cancer” means the existence or persistence of one or more cancerous cells in a subject following treatment with an anti-cancer therapy, such as a first-line or standard therapy.

[0166] According to certain aspects, the present invention provides methods for treating a cancer associated with TAA expression (e.g., prostate cancer associated with PSMA expression or STEAP2 expression, glioblastoma associated with EGFRvIII expression, or ovarian cancer associated with MUC16 expression) comprising administering one or more of the bispecific antigen-binding molecules described elsewhere herein to a subject after the subject has been determined to have the cancer. For example, the present invention includes methods for treating prostate cancer comprising administering an anti-CD3/anti-TAA bispecific antigen-binding molecule to a patient 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks or 4 weeks, 2 months, 4 months, 6 months, 8 months, 1 year, or more after the subject has received a previous therapy.

Combination Therapies and Formulations

[0167] The present invention provides methods which comprise administering a pharmaceutical composition comprising any of the exemplary antibodies and bispecific antigen-binding molecules described herein in combination with one or more additional therapeutic agents. Exemplary additional therapeutic agents that may be combined with or administered in combination with an antigen-binding molecule of the present invention include, e.g., an anti-Programmed Cell Death 1 antibody (e.g. an anti-PD1 antibody as described in U.S. Pat. Appln. Pub. No. US2015/0203579A1), an anti-Programmed Cell Death Ligand-1 (e.g. an anti-PD-L1 antibody as described in U.S. Pat. Appln. Pub. No. US2015/0203580A1), an EGFR antagonist (e.g., an anti-EGFR antibody [e.g., cetuximab or panitumumab] or small molecule inhibitor of EGFR [e.g., gefitinib or erlotinib]), an antagonist of another EGFR family member such as Her2/ErbB2, ErbB3 or ErbB4 (e.g., anti-ErbB2, anti-ErbB3 or anti-ErbB4 antibody or small molecule inhibitor of ErbB2, ErbB3 or ErbB4 activity), an antagonist of EGFRvIII (e.g., an antibody that specifically binds

EGFRvIII), a cMET antagonist (e.g., an anti-cMET antibody), an IGF1R antagonist (e.g., an anti-IGF1R antibody), a B-raf inhibitor (e.g., vemurafenib, sorafenib, GDC-0879, PLX-4720), a PDGFR- α inhibitor (e.g., an anti-PDGFR- α antibody), a PDGFR- β inhibitor (e.g., an anti-PDGFR- β antibody), a VEGF antagonist (e.g., a VEGF-Trap, see, e.g., U.S. Pat. No. 7,087,411 (also referred to herein as a “VEGF-inhibiting fusion protein”), anti-VEGF antibody (e.g., bevacizumab), a small molecule kinase inhibitor of VEGF receptor (e.g., sunitinib, sorafenib or pazopanib)), a DLL4 antagonist (e.g., an anti-DLL4 antibody disclosed in US 2009/0142354 such as REGN421), an Ang2 antagonist (e.g., an anti-Ang2 antibody disclosed in US 2011/0027286 such as H1H685P), a FOLH1 (PSMA) antagonist, a PRLR antagonist (e.g., an anti-PRLR antibody), a STEAP1 or STEAP2 antagonist (e.g., an anti-STEAP1 antibody or an anti-STEAP2 antibody), a TMRSS2 antagonist (e.g., an anti-TMRSS2 antibody), a MSLN antagonist (e.g., an anti-MSLN antibody), a CA9 antagonist (e.g., an anti-CA9 antibody), a uroplakin antagonist (e.g., an anti-uroplakin antibody), etc. Other agents that may be beneficially administered in combination with the antigen-binding molecules of the invention include cytokine inhibitors, including small-molecule cytokine inhibitors and antibodies that bind to cytokines such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-11, IL-12, IL-13, IL-17, IL-18, or to their respective receptors. The pharmaceutical compositions of the present invention (e.g., pharmaceutical compositions comprising an anti-CD3/anti-PSMA bispecific antigen-binding molecule as disclosed herein) may also be administered as part of a therapeutic regimen comprising one or more therapeutic combinations selected from “ICE”: ifosfamide (e.g., Ifex®), carboplatin (e.g., Paraplatin®), etoposide (e.g., Etopophos®, Toposar®, VePesid®, VP-16); “DHAP”: dexamethasone (e.g., Decadron®), cytarabine (e.g., Cytosar-U®, cytosine arabinoside, ara-C), cisplatin (e.g., Platinol®-AQ); and “ESHAP”: etoposide (e.g., Etopophos®, Toposar®, VePesid®, VP-16), methylprednisolone (e.g., Medrol®), high-dose cytarabine, cisplatin (e.g., Platinol®-AQ).

[0168] The present invention also includes therapeutic combinations comprising any of the antigen-binding molecules mentioned herein and an inhibitor of one or more of VEGF, Ang2, DLL4, EGFR, ErbB2, ErbB3, ErbB4, EGFRvIII, cMet, IGF1R, B-raf, PDGFR- α , PDGFR- β , FOLH1 (PSMA), PRLR, STEAP1, STEAP2, TMRSS2, MSLN, CA9, uroplakin, or any of the aforementioned cytokines, wherein the inhibitor is an aptamer, an antisense molecule, a ribozyme, an siRNA, a peptibody, a nanobody or an antibody fragment (e.g., Fab fragment; F(ab')₂ fragment; Fd fragment; Fv fragment; scFv; dAb fragment; or other engineered molecules, such as diabodies, triabodies, tetrabodies, minibodies and minimal recognition units). The antigen-binding molecules of the invention may also be administered and/or co-formulated in combination with antivirals, antibiotics, analgesics, corticosteroids and/or NSAIDs. The antigen-binding molecules of the invention may also be administered as part of a treatment regimen that also includes radiation treatment and/or conventional chemotherapy.

[0169] The additional therapeutically active component(s) may be administered just prior to, concurrent with, or shortly after the administration of an antigen-binding molecule of the present invention; (for purposes of the present disclosure, such administration regimens are considered the

administration of an antigen-binding molecule “in combination with” an additional therapeutically active component).

[0170] The present invention includes pharmaceutical compositions in which an antigen-binding molecule of the present invention is co-formulated with one or more of the additional therapeutically active component(s) as described elsewhere herein.

Administration Regimens

[0171] According to certain embodiments of the present invention, multiple doses of the bispecific antigen-binding molecule (e.g., an anti-TAA bispecific antigen-binding molecule) may be administered to a subject over a defined time course. The methods according to this aspect of the invention comprise sequentially administering to a subject multiple doses of an antigen-binding molecule of the invention. As used herein, “sequentially administering” means that each dose of an antigen-binding molecule is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of an antigen-binding molecule, followed by one or more secondary doses of the antigen-binding molecule, and optionally followed by one or more tertiary doses of the antigen-binding molecule.

[0172] The terms “initial dose,” “secondary doses,” and “tertiary doses,” refer to the temporal sequence of administration of the antigen-binding molecule of the invention. Thus, the “initial dose” is the dose which is administered at the beginning of the treatment regimen (also referred to as the “baseline dose”); the “secondary doses” are the doses which are administered after the initial dose; and the “tertiary doses” are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of the antigen-binding molecule, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of an antigen-binding molecule contained in the initial, secondary and/or tertiary doses varies from one another (e.g., adjusted up or down as appropriate) during the course of treatment. In certain embodiments, two or more (e.g., 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as “loading doses” followed by subsequent doses that are administered on a less frequent basis (e.g., “maintenance doses”).

[0173] In one exemplary embodiment of the present invention, each secondary and/or tertiary dose is administered 1 to 26 (e.g., 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, 15, 15½, 16, 16½, 17, 17½, 18, 18½, 19, 19½, 20, 20½, 21, 21½, 22, 22½, 23, 23½, 24, 24½, 25, 25½, 26, 26½, or more) weeks after the immediately preceding dose. The phrase “the immediately preceding dose,” as used herein, means, in a sequence of multiple administrations, the dose of antigen-binding molecule which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0174] The methods according to this aspect of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of an antigen-binding molecule (e.g., an anti-TAA bispecific antigen-binding molecule). For example, in certain embodiments, only a single

secondary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0175] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 to 2 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 2 to 4 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

EXAMPLES

[0176] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1: Generation of Anti-CD3 Antibodies

[0177] The following procedures were aimed at identifying antibodies that specifically recognized CD3 (T cell co-receptor) as an antigen.

[0178] A pool of anti-CD3 antibodies were derived by immunizing genetically modified mice. Briefly, mice genetically engineered to express reverse chimeric (human variable, mouse constant) and immunoglobulin heavy chains associated with a single rearranged light chain (e.g., a $V_{K1-39/J}$ or a $V_{K3-20/J}$), were immunized with a CD3 antigen and generated B cells that comprised a diversity of human VH rearrangements in order to express a diverse repertoire of high-affinity antigen-specific antibodies. Certain exemplified antibodies described in the subject application have been made recombinantly and express the same light chain sequence of $V_{K1-39Jk5}$ (LCVR set forth in SEQ ID NO: 162), while other antibodies made recombinantly express a cognate light chain of one of the heavy chain arms (e.g. the tumor target arm).

[0179] Generated antibodies were tested for affinity to human and cynomolgus monkey CD3 antigen in an in vitro binding assay, and e.g. one CD3 antibody: designated CD3-VH-P (HCVR set forth in SEQ ID NO: 154) was identified, amongst a few others, that were found to bind to both human and cyno CD3 having an EC_{50} between 1 and 40 nM affinity

(+++), as determined in a FACS titration of Jurkat cells and cynomolgus T cells, respectively. See, e.g. FACS binding experiments outlined in Example 4 herein below.

[0180] The germline amino acid residues of CD3-VH-P were subsequently identified and an antibody designated “CD3-VH-G” was engineered to contain only germline frameworks. Other antibody derivatives were engineered by well-known molecular cloning techniques to replace amino acid residues in a stepwise manner based on differences between the germline sequence and the CD3-VH-P sequence. Each antibody derivative is given a “CD3-VH-G” number designation. See Table 1 and FIG. 1.

[0181] Bispecific antibodies, comprising a first binding arm derived from the engineered anti-CD3 antibodies with the designations and descriptions shown in Table 1, and a second binding arm derived from anti-TAA antibodies, were prepared and tested for monovalent affinity to CD3-bearing cells in a FACS assay (as described in Example 4). The monovalent binding affinity results of these bispecific antibodies are shown in the two right columns of Table 1. In specific examples, bispecific antibodies having a TAA-binding arm and a CD3-binding arm with designations “CD3-VH-G,” “CD3-VH-G5,” and “CD3-VH-G20,” respectively, bound Jurkat cells with an EC_{50} of 2.7E-08, no detectable binding, and 5.5E-07, respectively.

TABLE 1

Mutations to CDRs Based on the Germline Sequence and Corresponding FACS Binding Affinity for Each Engineered Antibody			
Antibody CD3-VH Designation	Description of Mutations compared to antibody CD3-VH-G*	JURKAT	cyno T cells
CD3-VH-G	Germline (GL) only framework regions (FRs); CD3-VHP CDRs	(+ + +)	(+ + +)
CD3-VH-G2	All GL (FRs and CDRs).	(-)	(-)
CD3-VH-G3	All GL (FRs and CDRs). Add back A33S.	(-)	(-)
CD3-VH-G4	All GL (FRs and CDRs). Add back Y105K	(-)	(-)
CD3-VH-G5	All GL (FRs and CDRs). Add back A33S and Y105K.	(-)	(-)
CD3-VH-G8	Germline frameworks. Add back K58I	(+ + +)	(+)
CD3-VH-G9	Germline frameworks. Add back Y99D	(+)	(-)
CD3-VH-G10	Germline frameworks. Add back H108Y	(+)	(-)
CD3-VH-G11	Germline frameworks. Add back L111M	(+ + +)	(+)
CD3-VH-G12	Germline frameworks. Add back K58I, Y99D	(+ +)	(+/-)
CD3-VH-G13	Germline frameworks. Add back K58I, H108Y	(+ +)	(+)
CD3-VH-G14	Germline frameworks. Add back K58I, L111M	(+ + +)	(+ +)
CD3-VH-G15	Germline frameworks. Add back Y99D, -H108Y	(+)	(-)
CD3-VH-G16	Germline frameworks. Add back Y99D, L111M	(+ +)	(+/-)
CD3-VH-G17	Germline frameworks. Add back H108Y, L111M	(+/-)	(+/-)
CD3-VH-G18	Germline frameworks. Add back K58I, Y99D, H108Y	(+/-)	(-)
CD3-VH-G19	Germline frameworks. Add back K58I, Y99D, L111M	(+/-)	(-)

TABLE 1-continued

Mutations to CDRs Based on the Germline Sequence and Corresponding FACS Binding Affinity for Each Engineered Antibody			
Antibody Designation	Description of Mutations compared to antibody CD3-VH-G*	JURKAT	cyno T cells
CD3-VH-G20	Germline frameworks. Add back K58I, H108Y, L111M	(+/-)	(+/-)
CD3-VH-G21	Germline frameworks. Add back Y99D, H108Y, -L111M	(+/-)	(-)

*Sequential numbering based on 7221G (CD3-VH-G) mature protein

[0182] While CD3-VH-G and some other engineered antibodies retained their binding affinity as seen in the FACS assays, several anti-CD3 antibodies bound to human or cyno CD3 in vitro with weak (+/-) to no (-) measurable affinity. Binding affinities, binding kinetics, and other biological properties to elucidate toxicity and pharmacokinetic (pK) profiles were subsequently investigated for bispecific antibodies comprising the exemplary anti-CD3 antibodies generated in accordance with the methods of this Example, and are described in detail in the Examples set forth below.

Example 2: Heavy and Light Chain Variable Regions (Amino Acid and Nucleic Acid Sequences of the CDRs)

[0183] Amino acid and nucleic acid sequences were determined for each antibody heavy chain sequence. Each antibody heavy chain, as a derivative of the germline sequenceIGHV3-9*01/D5-12*01/J6*02 (SEQ ID NO: 181) was assigned a “G” number designation for consistent nomenclature. Table 2 sets forth the amino acid sequence identifiers of the heavy chain variable regions and CDRs of the engineered anti-CD3 antibodies of the invention. The corresponding nucleic acid sequence identifiers are set forth in Table 3. The amino acid and nucleic acid sequence identifiers of the light chain variable region and CDRs to construct each recombinant antibody are also identified below in Tables 4 and 5, respectively.

TABLE 2

Heavy Chain Amino Acid Sequence Identifiers				
Antibody CD3-VH	SEQ ID NOs:			
Designation	HCVR	CDR1	CDR2	CDR3
CD3-VH-G	2	4	6	8
CD3-VH-G2	10	12	14	16
CD3-VH-G3	18	20	22	24
CD3-VH-G4	26	28	30	32
CD3-VH-G5	34	36	38	40
CD3-VH-G8	42	44	46	48
CD3-VH-G9	50	52	54	56
CD3-VH-G10	58	60	62	64
CD3-VH-G11	66	68	70	72
CD3-VH-G12	74	76	78	80
CD3-VH-G13	82	84	86	88
CD3-VH-G14	90	92	94	96
CD3-VH-G15	98	100	102	104
CD3-VH-G16	106	108	110	112
CD3-VH-G17	114	116	118	120
CD3-VH-G18	122	124	126	128
CD3-VH-G19	130	132	134	136
CD3-VH-G20	138	140	142	144

TABLE 2-continued

Heavy Chain Amino Acid Sequence Identifiers				
Antibody CD3-VH	SEQ ID NOs:			
Designation	HCVR	CDR1	CDR2	CDR3
CD3-VH-G21	146	148	150	152
CD3-VH-P	154	156	158	160

TABLE 3

Heavy Chain Nucleic Acid Sequence Identifiers				
Antibody CD3-VH	SEQ ID NOs:			
Designation	HCVR	CDR1	CDR2	CDR3
CD3-VH-G	1	3	5	7
CD3-VH-G2	9	11	13	15
CD3-VH-G3	17	19	21	23
CD3-VH-G4	25	27	29	31
CD3-VH-G5	33	35	37	39
CD3-VH-G8	41	43	45	47
CD3-VH-G9	49	51	53	55
CD3-VH-G10	57	59	61	63
CD3-VH-G11	65	67	69	71
CD3-VH-G12	73	75	77	79
CD3-VH-G13	81	83	85	87
CD3-VH-G14	89	91	93	95
CD3-VH-G15	97	99	101	103
CD3-VH-G16	105	107	109	111
CD3-VH-G17	113	115	117	119
CD3-VH-G18	121	123	125	127
CD3-VH-G19	129	131	133	135
CD3-VH-G20	137	139	141	143
CD3-VH-G21	145	147	149	151
CD3-VH-P	153	155	157	159

TABLE 4

Light Chain Amino Acid Sequence Identifiers				
Antibody ULC	SEQ ID NOs:			
Designation	LCVR	CDR1	CDR2	CDR3
VK1-39JK5	162	164	166	168

TABLE 5

Light Chain Nucleic Acid Sequence Identifiers				
Antibody ULC	SEQ ID NOs:			
Designation	LCVR	CDR1	CDR2	CDR3
VK1-39JK5	161	163	165	167

[0184] Control 1 antibody designated “CD3-L2K” was constructed based on a known anti-CD3 antibody (i.e., the anti-CD3 antibody “L2K” as set forth in WO2004/106380).

[0185] Isotype Control Antibody, referred to in the Examples hereinbelow, is an isotype matched (modified IgG4) antibody that interacts with an irrelevant antigen, i.e. FelD1 antigen.

Example 3: Generation of ULC Bispecific Antibodies that Bind CD3 and Tumor-Associated Antigens (TAA)

[0186] Bispecific antibodies comprising an anti-CD3-specific binding domain and an anti-TAA-specific binding domain, such as PSMA, EGFRvIII, MUC16, or STEAP2, were constructed using standard molecular biology methodologies utilizing a heavy chain from an anti-CD3 antibody described herein, a heavy chain from an anti-TAA antibody and a common light chain or a universal light chain (ULC). The anti-TAA antibodies used to construct the bispecific antibodies of this invention were obtained by immunizing genetically modified mice.

[0187] A summary of the component parts of the antigen-binding domains of the various bispecific antibodies made in accordance with this Example is set forth below in Tables 6, 7 and 8. All bispecific antibodies were manufactured having a modified (chimeric) IgG4 Fc domain as set forth in US Patent Application Publication No. US20140243504A1, published on Aug. 28, 2014. Exemplary EGFRvIIIxCD3 bispecific antibodies can be prepared using any of the heavy chain and light chain variable regions (or CDRs) of any of the EGFRvIII antibodies discussed in US Patent Application Publication NO. US20150259423, which is hereby incorporated by reference in its entirety, in combination with the variable regions or CDRs of any of the anti-CD3 antibodies discussed herein.

TABLE 6

Construction of PSMAxCD3 Bispecific Antibodies			
Bispecific Antibody Identifier	Anti-PSMA		
	Antigen-Binding Domain	Anti-CD3	Common
	Heavy Chain	Antigen-Binding Domain	Light Chain
	Variable Region	Heavy Chain	Variable Region
BSPSMA/CD3-003	PSMA-VH-B	CD3-VH-G	VK1-39JK5
BSPSMA/CD3-200		CD3-VH-G2	
BSPSMA/CD3-300		CD3-VH-G3	
BSPSMA/CD3-400		CD3-VH-G4	
BSPSMA/CD3-004		CD3-VH-G5	
BSPSMA/CD3-800		CD3-VH-G8	
BSPSMA/CD3-900		CD3-VH-G9	
BSPSMA/CD3-1000		CD3-VH-G10	
BSPSMA/CD3-1100		CD3-VH-G11	
BSPSMA/CD3-1200		CD3-VH-G12	
BSPSMA/CD3-1300		CD3-VH-G13	
BSPSMA/CD3-1400		CD3-VH-G14	
BSPSMA/CD3-1500		CD3-VH-G15	
BSPSMA/CD3-1600		CD3-VH-G16	
BSPSMA/CD3-1700		CD3-VH-G17	
BSPSMA/CD3-1800		CD3-VH-G18	
BSPSMA/CD3-1900		CD3-VH-G19	
BSPSMA/CD3-005		CD3-VH-G20	
BSPSMA/CD3-2100		CD3-VH-G21	

TABLE 7

Construction of EGFRvIII xCD3 Bispecific Antibodies			
Bispecific Antibody Identifier	Anti-EGFRvIII	Anti-CD3	Common Light Chain Variable Region
	Antigen-Binding Domain	Antigen-Binding Domain	
	Heavy Chain	Heavy Chain	
	Variable Region	Variable Region	
BSV3/CD3-001	EGFRvIII-VH-A	CD3-VH-G	EGFRvIII-VL-A
BSV3/CD3-002		CD3-VH-G5	
BSV3/CD3-003		CD3-VH-G9	
BSV3/CD3-004		CD3-VH-G10	

TABLE 8

Construction of MUC16xCD3 Bispecific Antibodies			
Bispecific Antibody Identifier	Anti-MUC16	Anti-CD3	Common
	Antigen-Binding Domain	Antigen-Binding Domain	Light Chain
	Heavy Chain	Heavy Chain	Variable Region
	Variable Region	Variable Region	Region
BSMUC16/CD3-001	MUC16-VH-A	CD3-VH-G	MUC16-VL-A
BSMUC16/CD3-002		CD3-VH-G5	
BSMUC16/CD3-003		CD3-VH-G9	
BSMUC16/CD3-004		CD3-VH-G10	
BSMUC16/CD3-005		CD3-VH-G20	

TABLE 9

Construction of STEAP2xCD3 Bispecific Antibodies			
Bispecific Antibody Identifier	Anti-STEAP2	Anti-CD3	Common
	Antigen-Binding Domain	Antigen-Binding Domain	Light Chain
	Heavy Chain	Heavy Chain	Variable Region
	Variable Region	Variable Region	Region
BSSTEAP2/CD3-001	STEAP2-VH-A	CD3-VH-G	STEAP2-VL-A
BSSTEAP2/CD3-002		CD3-VH-G5	
BSSTEAP2/CD3-003		CD3-VH-G20	

[0188] Each of the exemplary bispecific antibodies were tested in various bioassays as described herein below.

Example 4: Binding Affinities of Exemplified Bispecific Antibodies as Measured by FACS Analysis

[0189] In this example, the ability of CD3×TAA bispecific antibodies to bind to human and cynomolgus CD3-expressing cell lines via FACS was determined. Additionally, the ability of these bispecific antibodies to bind to target-specific (TAA-specific) cell lines was also confirmed. As described above, the various bispecific antibodies of this invention utilized a single TAA-specific binding arm (PSMA, EGFRvIII, MUC16, or STEAP2; see Example 3, Tables 6, 7 and 8) paired with one of a panel of anti-CD3 binding arms (see Examples 1 and 2 hereinabove) and a common light chain. As is also shown in Example 5, the CD3×TAA bispecific antibodies displayed a range of affinities to human soluble heterodimeric hCD3ε/δ.mFc protein via surface plasmon resonance.

[0190] Briefly, 2×10⁵ cells/well of human CD3-expressing Jurkat, cynomolgus T or TAA-specific expressing cells were incubated with a serial dilution of bispecific antibodies for

30 min at 4° C. After incubation, cells were washed and a goat F(ab')₂ anti-human Fcγ PE labeled secondary (Jackson Immunolabs) was added to the cells for an additional 30 min. Next, cells were washed, re-suspended in cold PBS+ 1% BSA and analyzed via flow cytometry on a BD FACS Canto II.

[0191] For FACS analysis, cells were gated by forward scatter height vs. forward scatter area for single events selection, followed by side and forward scatters. The EC₅₀ for cell binding titration was determined using PRISM™ software (GraphPad Software, Inc., La Jolla, Calif.). Values were calculated using 4-parameter non-linear regression analysis.

protein via surface plasmon resonance (see Table 11 hereinbelow) also correlated with weak to no observable binding on Jurkat cells (i.e. CD3-VH-G2, CD3-VH-G3, CD3-VH-G5). Non-detectable binding, or no detectable binding, in the FACS assay or equivalent assay means that the affinity between the antibody and its target antigen is beyond the detection limit of the assay (e.g. >1 μM). Several CD3-binding arms also displayed cross reactivity to cynomolgus T-cells. All tested bispecific antibodies displayed similar cell binding on respective PSMA, EGFRvIII and MUC16-expressing cell lines, confirming that bispecific pairing with individual CD3 arms did not affect or diminish TAA-specific

TABLE 10A

FACS Binding on CD3 and PSMA-Specific Cell lines				
Bispecific Antibody Identifier	Anti-CD3-Binding Arm	Jurkat EC ₅₀ [M]	Cyno T-cells EC ₅₀ [M]	B16F10.9/PSMA EC ₅₀ [M]
BSPSMA/CD3-003	CD3-VH-G	1.65E-08	1.42E-08	2.26E-09
BSPSMA/CD3-200	CD3-VH-G2	NB	NB	1.88E-09
BSPSMA/CD3-300	CD3-VH-G3	NB	NB	1.90E-09
BSPSMA/CD3-400	CD3-VH-G4	NB	NB	1.72E-09
BSPSMA/CD3-004	CD3-VH-G5	Very weak	NB	1.31E-09
BSPSMA/CD3-800	CD3-VH-G8	1.93E-08	1.96E-08	1.31E-09
BSPSMA/CD3-900	CD3-VH-G9	2.74E-07	NB	1.43E-09
BSPSMA/CD3-1000	CD3-VH-G10	2.77E-07	NB	1.19E-09
BSPSMA/CD3-1100	CD3-VH-G11	1.83E-08	8.90E-07	1.03E-09
BSPSMA/CD3-1200	CD3-VH-G12	4.72E-08	NB	1.16E-09
BSPSMA/CD3-1300	CD3-VH-G13	1.02E-07	2.17E-06	1.25E-09
BSPSMA/CD3-1400	CD3-VH-G14	3.19E-08	1.70E-07	1.30E-09
BSPSMA/CD3-1500	CD3-VH-G15	9.30E-08	NB	1.21E-09
BSPSMA/CD3-1600	CD3-VH-G16	5.68E-08	NB	1.03E-09
BSPSMA/CD3-1700	CD3-VH-G17	2.00E-07	3.35E-06	1.34E-09
BSPSMA/CD3-1800	CD3-VH-G18	1.26E-07	NB	2.16E-09
BSPSMA/CD3-1900	CD3-VH-G19	6.07E-08	NB	1.35E-09
BSPSMA/CD3-005	CD3-VH-G20	2.10E-07	6.14E-06	2.09E-09
BSPSMA/CD3-2100	CD3-VH-G21	1.06E-07	NB	1.14E-09

TABLE 10B

FACS Binding on CD3 and EGFRvIII-Specific Cell lines				
Bispecific Antibody Identifier	Anti-CD3 Binding Arm	Jurkat EC ₅₀ [M]	Cyno T-Cells EC ₅₀ [M]	U87/EGFRvIII EC ₅₀ [M]
BSV3/CD3-001	CD3-VH-G	1.46E-09	NT	2.40E-09
BSV3/CD3-002	CD3-VH-G5	Very weak	NT	5.60E-09

TABLE 10C

FACS Binding on CD3 and MUC16-Specific Cell lines				
Bispecific Antibody Identifier	Anti-CD3 Binding Arm	Jurkat EC ₅₀ [M]	Cyno T-cells EC ₅₀ [M]	OVCAR3 (MUC16+) EC ₅₀ [M]
BSMUC16/CD3-001	CD3-VH-G	3.21E-09	NT	1.20E-09
BSMUC16/CD3-002	CD3-VH-G5	Very weak	NT	2.69E-09

[0192] As shown in Table 10A, the CD3 binding arms of each CD3×PSMA bispecific antibody displayed a range of cell binding affinity to human CD3 expressing Jurkat cells (15 to 300 nM EC₅₀ range). Importantly, the CD3 arms that showed weak-to-no binding to human CD3 heterodimeric

binding (TAA-specific binding was less than or equal to 5.6 nM (high affinity) in all examples tested).

[0193] Antibodies exhibiting weak-to-no detectable binding to human CD3, and also exhibiting weak-to-no binding to cynomolgus CD3, are considered advantageous for avidity-driven bispecific pairing in accordance with the present invention, and were further tested for cytotoxicity in vitro and in vivo assays.

Example 5: Binding Affinities of Exemplified Antibodies as Measured by a Surface Plasmon Resonance Binding Assay

[0194] Binding affinities and kinetic constants of anti-TAAxanti-CD3 bispecific antibodies to soluble heterodimeric hCD3ε/δ.mFc protein (hCD3E=UniProtKB/Swiss-Prot: P07766.2; SEQ_ID NO: 169; hCD3δ=UniProtKB/Swiss-Prot: P04234.1, SEQ ID NO: 170) were determined by surface plasmon resonance at 37° C. using either an antigen-capture format (Table 11) or an antibody-capture format (data not shown). In this example, BSPSMA/CD3 bispecific antibodies were utilized as these pairings represented the use of a wider panel of antibodies for the CD3 binding arm. Measurements were conducted on a Sierra Sensors MASS-1 instrument.

[0195] In the antigen-capture format, the MASS-1 high-density amine sensor surface was derivatized with a goat

anti-mouse IgG2a polyclonal antibody (Southern Biotech). Soluble heterodimeric CD3 protein was captured and the respective antibodies were injected over the captured antigen.

[0196] Kinetic association (k_a) and dissociation (k_d) rate constants were determined by processing and fitting the data to a 1:1 binding model using MASS-1 AnalyserR2 curve fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives ($t_{1/2}$) were calculated from the kinetic rate constants as: K_D (M) = k_d/k_a ; and $t_{1/2}$ (min) = $(\ln 2)/(60 * k_d)$.

antibodies displayed a range of affinity to CD3 protein and CD3-expressing cell lines (i.e. weak, moderate and strong binding). This same panel of bispecific antibodies was tested for the ability to induce naïve human T-cells to re-direct killing toward target-expressing cells.

[0200] Briefly, PSMA-expressing (C4-2, 22Rv1 and TRAMPC2_PSMA), EGFRvIII-expressing (U87/EGFRvIII) or MUC16-expressing (OVCAR3) cell lines were labeled with 1 μ M of the fluorescent tracking dye Violet Cell Tracker. After labeling, cells were plated overnight at 37° C. Separately, human PBMCs were plated in

TABLE 11

Affinities of anti-CD3 Bispecific Antibodies to Soluble Human CD3					
Bispecific Antibody Identifier	Corresponding anti-CD3 Antigen-Binding HCVR Identifier	Binding at 37° C./Antigen-Capture Format			
		k_a (M ⁻¹ s ⁻¹)	k_d (s ⁻¹)	K_D (M)	$T_{1/2}$ (min)
BSPSMA/CD3-003	CD3-VH-G	1.32E+05	7.62E-04	5.78E-09	15.2
BSPSMA/CD3-200	CD3-VH-G2	NB	NB	NB	NB
BSPSMA/CD3-300	CD3-VH-G3	NB	NB	NB	NB
BSPSMA/CD3-400	CD3-VH-G4	NB	NB	NB	NB
BSPSMA/CD3-004	CD3-VH-G5	NB	NB	NB	NB
BSPSMA/CD3-800	CD3-VH-G8	5.95E+04	1.15E-03	1.94E-08	10.0
BSPSMA/CD3-900	CD3-VH-G9	4.38E+04	4.95E-03	1.13E-07	2.3
BSPSMA/CD3-1000	CD3-VH-G10	3.44E+04	6.37E-03	1.85E-07	1.8
BSPSMA/CD3-1100	CD3-VH-G11	9.21E+04	1.02E-03	1.11E-08	11.3
BSPSMA/CD3-1200	CD3-VH-G12	3.85E+04	2.47E-03	6.42E-08	4.7
BSPSMA/CD3-1300	CD3-VH-G13	2.03E+04	2.48E-03	1.22E-07	4.7
BSPSMA/CD3-1400	CD3-VH-G14	6.21E+04	3.31E-03	5.33E-08	3.5
BSPSMA/CD3-1500	CD3-VH-G15	7.36E+04	6.11E-03	8.29E-08	1.9
BSPSMA/CD3-1600	CD3-VH-G16	6.43E+04	2.43E-03	3.78E-08	4.7
BSPSMA/CD3-1700	CD3-VH-G17	4.70E+04	3.07E-03	6.52E-08	3.8
BSPSMA/CD3-1800	CD3-VH-G18	NB	NB	NB	NB
BSPSMA/CD3-1900	CD3-VH-G19	4.43E+04	5.09E-03	1.15E-07	2.3
BSPSMA/CD3-005	CD3-VH-G20	1.73E+04	5.77E-03	3.34E-07	2.0
BSPSMA/CD3-2100	CD3-VH-G21	3.02E+04	2.34E-03	7.75E-08	4.9
Control 1	CD3-L2K	3.68E+05	2.66E-03	7.22E-09	4.3

NB: No binding detected

[0197] As shown in Table 11, all of the derived anti-CD3× anti-PSMA bispecific antibodies maintained very weak binding to soluble CD3 in the surface plasmon resonance binding assay, e.g. having a K_D value greater than 11 nM up to 334 nM which is weaker than that of the bispecific anti-CD3 arm derived from germline frameworks, CD3-VH-G.

[0198] Several bispecific antibodies exhibited greater than 50 nM K_D values, and some were greater than 100 nM ($>1 \times 10^{-7}$) K_D values (i.e. BSPSMA/CD3-900, BSPSMA/CD3-1000, BSPSMA/CD3-1900), greater than 300 nM ($>3 \times 10^{-7}$) K_D values (i.e. BSPSMA/CD3-005) and even beyond the detection limit of the assay (>500 nM; $>5 \times 10^{-7}$), i.e. showed no detectable binding to soluble human CD3 (i.e. BSPSMA/CD3-200, BSPSMA/CD3-300, BSPSMA/CD3-400, BSPSMA/CD3-004 and BSPSMA/CD3-1800).

Example 6: T Cell Activation and Tumor-Specific Cytotoxicity Exhibited by Bispecific Antibodies of the Invention as Measured In Vitro

[0199] In this example, the specific killing of PSMA, EGFRvIII or MUC16-expressing TAA target cells in the presence of CD3-based bispecific antibodies was monitored via flow cytometry. As reported previously, the bispecific

supplemented RPMI media at 1×10^6 cells/mL and incubated overnight at 37° C. in order to enrich for lymphocytes by depleting adherent macrophages, dendritic cells, and some monocytes. The next day, target cells were co-incubated with adherent cell-depleted naïve PBMC (Effector/Target cell 4:1 ratio) and a serial dilution of relevant bispecific antibodies or Isotype control (concentration range: 66.7 nM to 0.25 pM) for 48 hours at 37° C. Cells were removed from cell culture plates using an enzyme-free cell dissociation buffer, and analyzed by FACS.

[0201] For FACS analysis, cells were stained with a dead/live far red cell tracker (Invitrogen). 5×10^5 counting beads were added to each well immediately before FACS analysis. 1×10^4 beads were collected for each sample. For the assessment of specificity of killing, cells were gated on live Violet labeled populations. Percent of live population was recorded and used for the calculation of normalized survival.

[0202] T cell activation was assessed by incubating cells with directly conjugated antibodies to CD2 and CD69, and by reporting the percent of activated (CD69+) T cells out of total T cells (CD2+).

[0203] As the results in Tables 12A-12C show, depletion of TAA-expressing cells was observed with anti-PSMA, EGFRvIII or MUC16×CD3 bispecifics. Most of the tested

bispecific antibodies activated and directed human T cells to deplete the target cells with EC₅₀s in picomolar range. Additionally, the observed target-cell lysis (depletion) was associated with an up-regulation of CD69 cells on CD2+ T cells, with picomolar (pM) EC₅₀s.

[0204] Importantly, the results of this example demonstrate that several bispecifics which utilized a CD3 binding arm that displayed weak-to-non-observable binding to CD3 protein or CD3-expressing cells (i.e. CD3-VH-G5) still retained the ability to activate T-cells and exhibited potent cytotoxicity of tumor antigen-expressing cells.

Example 7: Anti-PSMA/Anti-CD3 Bispecific Antibodies Display Potent Anti-Tumor Efficacy In Vivo

[0205] To determine the in vivo efficacy of exemplary anti-PSMA/anti-CD3 bispecific antibodies identified as having weak or no detectable binding affinity to human and cynomolgus CD3, studies were performed in immunocompromised mice bearing human prostate cancer xenografts. Additional studies were also carried out in immunocompetent mice bearing mouse prostate cancer xenografts engineered to express human PSMA.

TABLE 12A

Cytotoxicity and T-cell activation properties of selected PSMAxCD3 Bispecific Antibodies					
Bispecific Antibody Identifier	Anti-CD3 Binding Arm	C4-2 Cell depletion EC ₅₀ [M]	22RV1 Cell depletion EC ₅₀ [M]	TrampC2.PSMA Cell depletion EC ₅₀ [M]	T cell activation EC ₅₀ [M]
BSPSMA/CD3-003	CD3-VH-G	1.03E-11	NT	6.43E-12	1.23E-12
BSPSMA/CD3-200	CD3-VH-G2	NT	No activity	NT	No activity
BSPSMA/CD3-300	CD3-VH-G3	NT	Very weak	NT	1.85E-11
BSPSMA/CD3-400	CD3-VH-G4	NT	Very weak	NT	Very weak
BSPSMA/CD3-004	CD3-VH-G5	2.15E-11	6.31E-12	1.15E-11	1.34E-11
BSPSMA/CD3-800	CD3-VH-G8	NT	NT	9.27E-12	1.76E-12
BSPSMA/CD3-900	CD3-VH-G9	NT	NT	3.50E-12	1.12E-12
BSPSMA/CD3-1000	CD3-VH-G10	NT	NT	5.97E-12	1.28E-12
BSPSMA/CD3-1100	CD3-VH-G11	NT	NT	3.86E-12	1.11E-12
BSPSMA/CD3-1300	CD3-VH-G13	8.74E-12	NT	NT	2.31E-12
BSPSMA/CD3-1700	CD3-VH-G17	7.37E-12	2.07E-12	NT	3.89E-12
BSPSMA/CD3-005	CD3-VH-G20	1.39E-11	8.32E-12	NT	6.11E-12

NT = not tested

TABLE 12B

Cytotoxicity and T-cell activation properties of selected EGFRvIIIxCD3 Bispecific Antibodies			
Bispecific Antibody Identifier	Anti-CD3 Binding Arm	U87__EGFRvIII cell depletion EC ₅₀ [M]	T cell activation EC ₅₀ [M]
BSV3/CD3-001	CD3-VH-G	3.64E-10	3.33E-11
BSV3/CD3-002	CD3-VH-G5	1.30E-09	1.13E-10

TABLE 12C

Cytotoxicity and T-cell activation properties of selected MUC16xCD3 Bispecific Antibodies			
Bispecific Antibody Identifier	Anti-CD3 Binding Arm	OVCAR3 cell depletion EC ₅₀ [M]	T cell activation EC ₅₀ [M]
BSV3/CD3-001	CD3-VH-G	2.24E-11	5.88E-12
BSV3/CD3-002	CD3-VH-G5	3.06E-11	1.01E-11

Efficacy of Anti-PSMA/Anti-CD3 Bispecific Antibodies in Human Tumor Xenograft Models

[0206] To assess the in vivo efficacy of the anti-PSMA/anti-CD3 bispecifics in human tumor xenograft studies, NOD scid gamma (NSG) mice (Jackson Laboratories, Bar Harbor, Me.) were co-implanted with human peripheral blood mononuclear cells (PBMCs) along with 22Rv1 or C4-2 human prostate tumor cells which endogenously express PSMA.

[0207] Briefly, 4×10⁶ 22 Rv1 or 5×10⁶ C4-2 cells (MD Anderson, TX) cells were co-implanted s.c. with 1×10⁶ human PBMCs (ReachBio, LLC., Seattle, Wash.) in a 50:50 mix of matrigel matrix (BD Biosciences) into the right flank of male NSG mice. In the C4-2 study, mice were treated i.p. on days 0, 4, and 7 post tumor implantation with 0.1 mg/kg BSPSMA/CD3-003 or BSPSMA/CD3-005.

[0208] In an additional xenogenic model, anti-PSMA/anti-CD3 bispecifics were tested in mice engrafted with human hematopoietic CD34+ stem cells. Briefly, newborn SIRPα BALB/c-Rag2-IL2rγ-(BRG) pups were engrafted with hCD34+ fetal liver cells. 3-6 months later hCD34-engrafted SIRPα BRG mice were then implanted with C4-2 cells

(5×10^6 s.c. in matrigel), 8 days later, mice were treated with 10 μ g of BSPSMA/CD3-004 or an isotype control antibody, followed by 2 $\times$ /week doses throughout the study.

[0209] In all studies, tumor size was measured 2 $\times$ /week using calipers and tumor volume calculated as $\text{Volume} = (\text{length} \times \text{width}^2)/2$.

[0210] As the results in Table 13 show, the bispecific antibodies tested in the xenogenic models described above were all effective at suppressing tumor growth compared to treatment with the isotype control.

Table 13: Suppression of Tumor Growth by Administering Anti-PSMA/Anti-CD3 Bispecific Antibodies to Xenogenic Mouse Models

Xenogenic model: suppression of tumor growth				
Tumor Model/ Mouse Strain	N # mice/ treatment group	Bispecific Antibody Identifier	Dose	Final Tumor Volume (mm ³) Mean $\pm$ SD
C4-/2 NSG	5	BSPSMA/CD3-003	0.1 mg/kg on day 0,4 & 7	0 $\pm$ 0
	5	BSPSMA/CD3-005		0 $\pm$ 0
	5	Isotype Control		960 $\pm$ 660
C4-2/ SIRP α Balb/c-Rag2- IL2 γ - BRG engrafted with hCD34+ HSC	5	BSPSMA/CD3-004	1.0 μ g/mouse 2x/week	70 $\pm$ 60
	5	Isotype Control		260 $\pm$ 180

Efficacy of Anti-PSMA/Anti-CD3 Bispecific Antibodies in Immune-Competent Tumor Model

[0211] Additionally, anti-PSMA/anti-CD3 bispecifics were assessed for anti-tumor activity in an immune-competent model (U.S. Provisional Application No. 62/083,653, filed Nov. 24, 2014). Mice humanized for the three chains (Sys) of CD3 were also humanized for PSMA and implanted with a variant murine prostate cancer cell line TRAMP-C2 transfected with human PSMA.

[0212] Prior to study initiation, the tumorigenic cell line variant TRAMP-C2_hPSMAv#1 was generated. Briefly, 7.5×10^6 TRAMP-C2_hPSMA cells were implanted s.c. into the right flank of male mice humanized for CD3 and PSMA. A tumor was excised and cut into 3 mm fragments and subsequently implanted into the right flank of new male humanized mice. A tumor arising from the implanted tumor fragments was then harvested and disaggregated into a single cell suspension. These cells (TRAMP-C2_hPS-

MAv#1) were then cultured in vitro under G418 selection. 4×10^6 cells of this variant cell line were then implanted into the right flank of male PSMA/CD3 humanized mice for the bispecific antibody efficacy studies.

[0213] Humanized PSMA/CD3 mice implanted with TRAMPC2_hPSMAv#1 were treated with 100 μ g or 10 μ g of anti-PSMA/anti-CD3 bispecific antibody BSPSMA/CD3-004 or an isotype control 2 $\times$ /week starting from the day of tumor implantation. Serum cytokine levels 4 h post-injection were also examined, as well as spleen T-cell levels. Study was terminated at Day 27.

[0214] As the results in Table 14 show, the anti-PSMA/anti-CD3 bispecific molecule tested, BSPSMA/CD3-004, showed efficacy in significantly delaying tumor growth across treatment groups. Minimal cytokine release was observed after administration of BSPSMA/CD3-004, possibly due to the weak binding of the anti-CD3. Both antibodies tested showed anti-tumor efficacy without depleting T cells in the spleen.

Table 14: Efficacy of anti-PSMA/anti-CD3 Bispecific antibodies in immune-competent syngeneic model

Tumor Model/ Mouse Strain	Bispecific Antibody Identifier	Dose ($\mu\text{g}/\text{mouse}$) 2x/ week*	N # mice/ treatment group	Tumor Volume (mm^3) at Day 27 (Mean $\pm$ SD)	Mean Serum Cytokine Concentrations, (pg/mL)					Spleen T-cell level %, (mean $\pm$ SD)#	
					IFNg	TNF α	IL-2	IL-12p70	IL-6	CD4+	CD8+
TRAMP-C2/ PSMA ^{Hum/Hum} CD3 ^{Hum}											
	BSPSMA/CD3- 004	100	4	50 $\pm$ 60	30	60	60	40	370	8.0 $\pm$ 1.0	12.0 $\pm$ 2.0
		10	5	380 $\pm$ 650	10	50	50	10	330	8.0 $\pm$ 3.0	14.0 $\pm$ 4.0
	Isotype Control	100	5	1740 $\pm$ 560	4	30	30	10	230	5.0 $\pm$ 1.0	8.0 $\pm$ 2.0

* Mice were dosed with antibody or isotype control 2x/week starting on the day of tumor implantation

Measured as the percentage of CD4+ or CD8+ cells in spleen out of live mCD45+ cells

[0215] In summary, the anti-PSMA/anti-CD3 bispecific antibodies of this invention display potent anti-tumor efficacy in both immune-compromised and immune-competent tumor models, despite having low to no detectable binding to CD3 antigen.

Example 8: Anti-MUC16/Anti-CD3 Bispecific
Antibodies Display Potent Anti-Tumor Efficacy In
Vivo

[0216] To determine the in vivo efficacy of exemplary anti-MUC16/anti-CD3 bispecific antibodies identified as having weak or no detectable binding affinity to human and cynomolgus CD3, studies were performed in immunocompromised mice bearing human prostate cancer xenografts. The efficacy of selected bispecific antibodies was tested in both immediate treatment and therapeutic treatment dosing models.

Efficacy of Anti-MUC16/Anti-CD3 Bispecific Antibodies in
Human Tumor Xenograft Models

[0217] To assess the in vivo efficacy of the anti-MUC16/anti-CD3 bispecifics in human tumor xenograft studies, NOD scid gamma (NSG) mice (Jackson Laboratories, Bar Harbor, Me.) were pre-implanted with human peripheral blood mononuclear cells (PBMCs; ReachBio LLC., Seattle, Wash.) and then given ascites cells from the human ovarian cancer cell line OVCAR-3 (American Type Tissue Culture, Manassas, Va.) transduced with luciferase (OVCAR-3/Luc). OVCAR-3 cells endogenously express MUC-16.

[0218] Briefly, NSG mice were injected intraperitoneally (i.p.) with 5.0×10^6 human PBMCs. 8d later, 1.5×10^6 ascites cells from the OVCAR-3/Luc cell line, previously passaged in vivo, were administered i.p. to the NSG mice engrafted with PBMCs. In the immediate treatment group, mice were treated i.p. on the day of OVCAR-3/Luc cell implantation with MUC16/CD3 Bispecific antibodies BSMUC16/CD3-001 or BSMUC16/CD3-005, or an isotype control, at a dose of 10 ug/mouse (N=5 mice/treatment group). In the therapeutic dose model, mice were treated i.p. 7d post tumor implantation with the MUC16/CD3 Bispecific or control antibodies described above, at a dose of 10 ug/mouse (N=5/treatment group).

[0219] In all studies, tumor growth was monitored via bioluminescent imaging (BLI). Mice were injected i.p. with the luciferase substrate D-luciferin suspended in PBS (150 mg/kg) and imaged under isoflurane anesthesia after 10 min. BLI was performed using the Xenogen IVIS system (Perkin Elmer, Hopkinton, Mass.) and BLI signals were extracted using Living Image software (Xenogen/Perkin Elmer). Regions of interest were drawn around each cell mass and photon intensities were recorded as photons(p)/sec(s)/cm²/steradian(sr). For the immediate-treatment group, data is shown as BLI levels 26d post tumor implantation (Table 15). For the therapeutic-treatment group, data is shown as fold-change in BLI between day 6 (1 d before treatment) and at study endpoint (26d post tumor implantation; Table 16).

[0220] As the results show, both BSMUC16/CD3-001 and BSMUC16/CD3-005 showed similar efficacy in suppressing tumor growth compared to the isotype control when BLI was measured at Day 26 in the immediate dosing model. Both anti-MUC16/anti-CD3 bispecific antibodies also suppressed the growth of established tumors when administered 7d post tumor implantation, compared to the control. In

summary, the bispecific anti-MUC16/anti-CD3 antibodies of this invention display potent anti-tumor efficacy in several models.

TABLE 15

Efficacy of anti-MUC16/anti-CD3 Bispecific Antibodies in Immune-Compromised Xenograft Model: Immediate Dosing			
Tumor Model/ Mouse Strain/ Dose	Bispecific Antibody Identifier	N	Avg Bioluminescent Radiance (photons/sec/cm ² / steradian) Day 26 (mean $\pm$ SD)
OVCAR-3/Luc/ NSG/ 10 ug/mouse	BSMUC16/CD3-001	5	$1.4 \times 10^3 \pm 3.5 \times 10^2$
	BSMUC16/CD3-005	5	$1.5 \times 10^3 \pm 9.7 \times 10^2$
	Isotype Control	5	$2.0 \times 10^7 \pm 1.0 \times 10^6$

TABLE 16

Efficacy of anti-Muc16/anti-CD3 Bispecific Antibodies in Immune-Compromised Xenograft Model: Therapeutic Treatment			
Tumor Model/ Mouse Strain/ Dose	Bispecific Antibody Identifier	N	Fold change in Avg Bioluminescent Radiance [p/s/cm ² /sr] at Day 26 relative to Day 6 (mean $\pm$ SD)
OVCAR-3/ Luc/NSG/ 10 ug/mouse	BSMUC16/CD3-001	5	2.0 ± 5.0
	BSMUC16/CD3-005	5	0.01 ± 0.02
	Isotype Control	5	21.0 ± 8.0

Example 9: Pharmacokinetic Assessment of
Anti-MUC16 $\times$ CD3 Bispecific Antibodies

[0221] Assessment of the pharmacokinetics of anti-MUC16 $\times$ CD3 bispecific antibodies BSMUC16/CD3-001 and BSMUC16/CD3-005 and an isotype control were conducted in humanized MUC16 $\times$ CD3 mice (mice homozygous for human MUC16 and CD3 expression, MUC16^{hu/hu} $\times$ CD3^{hu/hu}), CD3 humanized mice (mice homozygous for human CD3 expression, C_{D3} hu/hu) and strain-matched (75% C57BL, 25%129Sv) wild-type (WT) mice. Cohorts contained 4-5 mice per tested antibody and per mouse strain. All mice received a single intra-peritoneal (i.p.) 0.4 mg/kg dose. Blood samples were collected at 3 and 6 hours, 1, 3, 7, 14 and 28 days post dosing. Blood was processed into serum and frozen at -80° C. until analyzed.

[0222] Circulating antibody concentrations were determined by total human IgG antibody analysis using the GyroLab xPlore™ (Gyros, Uppsala, Sweden). Briefly, a biotinylated goat anti-human IgG polyclonal antibody (Jackson ImmunoResearch, West Grove, Pa.) was captured onto streptavidin coated beads on a Gyrolab Bioaffly 200 CD (Gyros) in order to capture the human IgG present in the sera. After affinity column capture, bound human IgG antibody in samples was detected with Alexa-647 labeled goat anti-human IgG (Jackson ImmunoResearch). Fluorescent signal on the column allowed for the detection of bound IgG and response units (RU) were read by the instrument. Sample concentrations were determined by interpolation from a standard curve that was fit using a 5-parameter logistic curve fit using the Gyrolab Evaluator Software.

[0223] PK parameters were determined by non-compartmental analysis (NCA) using Phoenix®WinNonlin® soft-

ware Version 6.3 (Certara, L. P., Princeton, N.J.) and an extravascular dosing model. Using the respective mean concentration values for each antibody, all PK parameters including observed maximum concentration in serum (C_{max}), estimated half-life observed ($t_{1/2}$), and area under the concentration curve versus time up to the last measureable concentration (AUC_{last}) were determined using a linear trapezoidal rule with linear interpolation and uniform weighting

[0224] Following i.p. administration of antibodies in WT mice, the total IgG concentration-time profiles of BSMUC16/CD3-001, BSMUC16/CD3-005 and the isotype control were all similar, characterized first by a brief drug distribution followed by a single drug elimination phase throughout the remainder of the study. Maximum serum concentrations (C_{max}) and calculated drug exposure (AUC_{last}) of the three antibodies were comparable (within 1.3-fold of each other). Following i.p. administration of antibodies in $CD3^{hu/hu}$ mice, BSMUC16/CD3-001, BSMUC16/CD3-005 and isotype control had comparable C_{max} concentrations (4.6, 3.6 and 4.1 $\mu\text{g/mL}$, respectively). BSMUC16/CD3-005 and the isotype control exhibited similar drug elimination curves, while BSMUC16/CD3-001 exhibited steeper drug elimination than both, suggesting that human CD3 target binding drives clearance. Terminal antibody concentration for BSMUC16/CD3-001 was 0.03 $\mu\text{g/mL}$, which is about 28-fold less than terminal antibody concentrations determined for the isotype control (0.85

$\mu\text{g/mL}$) and 22-fold less than BSMUC16/CD3-005 (0.66 $\mu\text{g/mL}$) serum concentrations.

[0225] In $MUC16^{hu/hu} \times CD3^{hu/hu}$ double-humanized mice, the $Muc16 \times CD3$ bispecific and isotype control antibodies had comparable C_{max} concentrations (C_{max} range: 4.5-6.9 $\mu\text{g/mL}$). Both bispecific antibodies exhibited steeper drug elimination than the isotype control suggesting a target-mediated effect. Terminal antibody concentrations for BSMUC16/CD3-001 and BSMUC16/CD3-005 were about 29-fold and 2.9-fold less, respectively, than terminal antibody concentrations determined for the isotype control (0.86 $\mu\text{g/mL}$).

[0226] A summary of the data for total anti- $MUC16 \times CD3$ bispecific antibodies and isotype control antibody concentrations are summarized in Table 17. Mean PK parameters are described in Tables 18A and 18B. Mean total antibody concentrations versus time are shown in FIGS. 2A, 2B and 2C. In conclusion, $MUC16 \times CD3$ bispecific antibodies exhibited similar C_{max} and drug elimination curves in WT mice, but BSMUC16/CD3-001 displayed steeper elimination rates than BSMUC16/CD3-005 and the isotype control in $CD3$ single-humanized mice and $MUC16/CD3$ double humanized mice. Since the bispecific antibodies administered in this PK study are comprised of the same anti- $MUC16$ binding arm, the results suggest that the strength of binding of the $CD3$ targeting arm may play a role in drug exposure levels (AUC_{last}) and drug elimination rates. Neither BSMUC16/CD3-001 or BSMUC16/CD3-005 bind mouse $MUC16$ or mouse $CD3$.

TABLE 17

Mean Concentrations of Total IgG in Serum Following a Single 0.4 mg/kg Intraperitoneal Injection of BSMUC16/CD3-001, BSMUC16/CD3-005 and Isotype Control Antibodies in WT Mice, Humanized CD3 Mice and Humanized $MUC16 \times CD3$ mice							
Total mAb Concentration In Mouse Serum							
Antibody	Time (d)	WT		$CD3^{hu/hu}$		$MUC16^{hu/hu} \times CD3^{hu/hu}$	
		Mean ($\mu\text{g/mL}$)	+/-SD	Mean ($\mu\text{g/mL}$)	+/-SD	Mean ($\mu\text{g/mL}$)	+/-SD
BSMUC16/CD3-001	0.13	5.39	0.34	4.30	0.29	6.77	1.52
	0.25	5.80	0.36	4.26	1.07	6.63	1.06
	1.00	4.13	0.43	2.87	0.71	4.89	0.53
	3.00	3.19	0.53	1.44	0.27	2.50	0.22
	7.00	2.61	0.73	0.72	0.13	1.20	0.22
	14.00	1.44	0.69	0.18	0.05	0.28	0.08
	21.00	0.93	ND	0.07	0.02	0.06	0.05
	28.00	0.60	ND	0.04	0.01	0.03	0.02
BSMUC16/CD3-005	0.13	4.23	0.62	3.35	1.15	4.35	0.24
	0.25	4.53	0.55	3.40	0.96	4.45	0.49
	1.00	3.47	0.32	2.72	0.42	3.00	0.61
	3.00	2.51	0.13	1.95	0.37	1.98	0.41
	7.00	2.02	0.24	2.31	0.67	1.58	0.36
	14.00	1.19	0.17	1.01	0.23	0.78	0.26
	21.00	1.19	0.29	1.19	0.11	0.66	0.29
	28.00	0.71	0.20	0.66	0.28	0.30	0.22
Isotype Control	0.13	5.07	1.16	5.43	1.30	6.56	0.70
	0.25	5.91	1.10	5.67	1.91	6.48	0.90
	1.00	2.64	0.24	2.98	1.14	2.82	0.30
	3.00	2.05	0.06	2.29	0.83	1.57	0.37
	7.00	1.80	0.25	2.14	0.85	1.96	0.37

TABLE 17-continued

Mean Concentrations of Total IgG in Serum Following a Single 0.4 mg/kg Intra-peritoneal Injection of BSMUC16/CD3-001, BSMUC16/CD3-005 and Isotype Control Antibodies in WT Mice, Humanized CD3 Mice and Humanized MUC16 × CD3 mice							
Total mAb Concentration In Mouse Serum							
Antibody	Time (d)	WT		CD3 ^{hu/hu}		MUC16 ^{hu/hu} × CD3 ^{hu/hu}	
		Mean (μg/mL)	+/-SD	Mean (μg/mL)	+/-SD	Mean (μg/mL)	+/-SD
	14.00	1.22	0.28	1.48	0.66	1.34	0.37
	21.00	1.20	0.58	1.43	0.72	1.24	0.44
	28.00	0.73	0.24	0.85	0.29	0.86	0.41

Time: (h, when noted) = time in hours post single-dose injection;

D = Day of study;

SD = Standard deviation;

ND = Not determined due to exclusion of mice with drug clearing anti-drug titers

TABLE 18A

Summary of Pharmacokinetic Parameters: CD3 ^{hu/hu} humanized mice							
Parameter	Units	WT mice			CD3 ^{hu/hu} mice		
		Isotype Control	BSMUC16/CD3-001	BSMUC16/CD3-005	Isotype Control	BSMUC16/CD3-001	BSMUC16/CD3-005
C _{max}	μg/mL	5 ± 3	6 ± 0.4	5 ± 0.5	4.1 ± 3	4.6 ± 0.8	3.5 ± 1
T _{1/2}	d	11 ± 4	7 ± 3	12 ± 2	14 ± 0.5	3.9 ± 0.6	11 ± 5
AUC _{last}	d · μg/mL	35 ± 18	40 ± 11	45 ± 5	49 ± 20	16 ± 3	36 ± 13

C_{max} = Peak concentration;

AUC = Area under the concentration-time curve;

AUC_{last} = AUC computed from time zero to the time of the last positive concentration;

T_{1/2} = Estimated half-life observed;

d = day

TABLE 18B

Summary of Pharmacokinetic Parameters: MUC16 ^{hu/hu} × CD3 ^{hu/hu} double-humanized mice							
Parameter	Units	WT mice			MUC16 ^{hu/hu} × CD3 ^{hu/hu} mice		
		Isotype Control	BSMUC16/CD3-001	BSMUC16/CD3-005	Isotype Control	BSMUC16/CD3-001	BSMUC16/CD3-005
C _{max}	μg/mL	5 ± 3	6 ± 0.4	5 ± 0.5	6.7 ± 0.7	6.9 ± 1	4.5 ± 4
T _{1/2}	d	11 ± 4	7 ± 3	12 ± 2	12.9 ± 4	3.3 ± 0.8	8.2 ± 4
AUC _{last}	d · μg/mL	35 ± 18	40 ± 11	45 ± 5	46 ± 10	27 ± 3	34 ± 11

C_{max} = Peak concentration;

AUC = Area under the concentration-time curve;

AUC_{last} = AUC computed from time zero to the time of the last positive concentration;

T_{1/2} = Estimated half-life observed;

d = day

Example 10: Anti-STEAP2/Anti-CD3 Bispecific
Antibodies Display Potent Anti-Tumor Efficacy In
Vivo

[0227] To determine the in vivo efficacy of exemplary anti-STEAP2/anti-CD3 bispecific antibodies identified as having weak or no detectable binding affinity to human and cynomolgus CD3, studies were performed in immunocompromised mice bearing human prostate cancer xenografts.

[0228] To assess the in vivo efficacy of the anti-STEAP2/anti-CD3 bispecifics in human tumor xenograft studies, NOD scid gamma (NSG) mice (Jackson Laboratories, Bar Harbor, Me.) were co-implanted with human peripheral blood mononuclear cells (PBMCs; ReachBio LLC., Seattle, Wash.) along with human prostate cancer C4-2 cells (MD Anderson Cancer Center, Houston Tex.) which endogenously express STEAP2.

[0229] Briefly, 5.0×10^6 C4-2 cells were co-implanted subcutaneously (s.c.) with 1.25×10^6 human PBMCs in a 50:50 mix of matrigel matrix (BD Biosciences, San Jose, Calif.) into the right flank of male NSG mice. Mice were treated intraperitoneally (i.p.) on the day of implantation (immediate treatment model) with anti-STEAP2/anti-CD3 bispecifics BSSTEAP2/CD3-001, BSSTEAP2/CD3-002 or BSSTEAP2/CD3-003, or an isotype control (that does not bind C4-2 tumor cells), at a dose of 0.1 or 0.01 mg/kg (N=5 mice/group).

[0230] Tumor size was measured 2x/week using calipers and tumor volume calculated as $\text{Volume} = (\text{length} \times \text{width}^2)/2$. Data is shown as tumor size (mm^3) at study endpoint, 46d post-tumor implantation (Table 19).

[0231] As the results in Table 19 show, BSSTEAP2/CD3-001, BSSTEAP2/CD3-002 and BSSTEAP2/CD3-003 significantly suppressed tumor growth compared to an isotype control when tumor sizes were measured at study endpoint. Importantly, the anti-STEAP2/anti-CD3 bispecific antibodies were efficacious in inhibiting C4-2 tumor growth even at the lowest dose of 0.1 mg/kg.

TABLE 19

Efficacy of anti-STEAP2/anti-CD3 Bispecific Antibodies in Immune-Compromised Xenograft Model: Immediate Dosing				
Tumor Model/ Mouse Strain	Bispecific Antibody Identifier	Dose (mg/kg)	N	Tumor Size (mm^3) 46 d post-tumor implantation (mean $\pm$ SD)
C4-2/ NSG	BSSTEAP2/CD3-001	0.1	5	18.0 $\pm$ 14.0
		0.01	5	23.0 $\pm$ 22.0
	BSSTEAP2/CD3-002	0.1	5	15.0 $\pm$ 12.0
		0.01	5	17.0 $\pm$ 8.0
	BSSTEAP2/CD3-003	0.1	5	19.0 $\pm$ 12.0
		0.01	5	25.0 $\pm$ 21.0
	Control Bispecific	0.1	5	1020.0 $\pm$ 922.0

The present invention is not to be limited in scope by the specific embodiments

[0232] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

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 Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Gly Ile Ser Trp Asn Ser Gly Ser Lys Gly Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
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Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
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Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
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Val

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Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
          50          55          60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
          65          70          75          80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
          85          90          95
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35 40 45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
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1 5

<210> SEQ ID NO 37
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 37

atatcttgga actcaggcag tatt

24

<210> SEQ ID NO 38
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

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<400> SEQUENCE: 38

Ile Ser Trp Asn Ser Gly Ser Ile
1 5

<210> SEQ ID NO 39

<211> LENGTH: 51

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 39

gcaaaagatg gaagcgggta tgggaaattt tattattatg gtatggatgt a 51

<210> SEQ ID NO 40

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 40

Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 41

<211> LENGTH: 372

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 41

gaagtacagc ttgtagaatc cgcgaggagga ctggtacaac ctggaagaag tcttagactg 60

agttgcgag ctagtgggtt tacattcgac gattacagca tgcattgggt gaggcaagct 120

cctggtaaag gattggaatg ggtagcggg atatcatgga actcaggaag catcggatac 180

gccgacagcg tgaaggccg atttacaata tctagggaca acgcaaaaaa ctctctctac 240

cttcaaatga actctcttag gccagaagac acagcattgt attattgcgc aaaatacggc 300

agtgggtatg gcaagtttta tcattatgga ctggacgtgt ggggacaagg gacaacagtg 360

acagtgaagta gc 372

<210> SEQ ID NO 42

<211> LENGTH: 124

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 42

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

-continued

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Leu Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 43
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 43

gggtttacat tcgacgatta cagc

24

<210> SEQ ID NO 44
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 44

Gly Phe Thr Phe Asp Asp Tyr Ser
1 5

<210> SEQ ID NO 45
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 45

atatcatgga actcaggaag catc

24

<210> SEQ ID NO 46
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 46

Ile Ser Trp Asn Ser Gly Ser Ile
1 5

<210> SEQ ID NO 47
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 47

gcaaaatacg gcagtgggta tggcaagttt taccattatg gactggacgt g

51

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<210> SEQ ID NO 48
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 48

Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Leu Asp
1 5 10 15

Val

<210> SEQ ID NO 49
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 49

gaagtacagc ttgtagaatc cgccggagga ctggtacaac ctggaagaag tcttagactg 60
agttgcgcag ctagtgggtt tacattcgac gattacagca tgcattgggt gaggcaagct 120
cctggtaaag gattggaatg ggtagcggg atatcatgga actcaggaag caagggatac 180
gccgacagcg tgaagggccg atttacaata tctagggaca acgcaaaaaa ctctctctac 240
cttcaaatga actctcttag ggcagaagac acagcattgt attattgcgc aaaagacggc 300
agtggttatg gcaagtttta tcattatgga ctggacgtgt ggggacaagg gacaacagtg 360
acagtga gta gc 372

<210> SEQ ID NO 50
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 50

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Lys Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Leu Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 51

-continued

<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 51

gggtttacat tcgacgatta cagc

24

<210> SEQ ID NO 52
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 52

Gly Phe Thr Phe Asp Asp Tyr Ser
1 5

<210> SEQ ID NO 53
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 53

atatcatgga actcaggaag caag

24

<210> SEQ ID NO 54
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 54

Ile Ser Trp Asn Ser Gly Ser Lys
1 5

<210> SEQ ID NO 55
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 55

gcaaaagacg gcagtgggta tggcaagttt tatcattatg gactggacgt g

51

<210> SEQ ID NO 56
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 56

Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Leu Asp
1 5 10 15

Val

-continued

<210> SEQ ID NO 57
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 57

gaagtacagc ttgtagaatc cggcggagga ctggtacaac ctggaagaag tcttagactg	60
agttgcgcag ctagtgggtt tacattcgac gattacagca tgcattgggt gagggcaagct	120
cctggtaaag gattggaatg ggtagcggg atatcatgga actcaggaag caagggatac	180
gccgacagcg tgaaaggccg atttacaata tctagggaca acgcaaaaaa ctctctctac	240
cttcaaatga actctcttag ggcagaagac acagcattgt attattgcgc aaaatacggc	300
agtggttatg gcaagtttta ttattatgga ctggacgtgt ggggacaagg gacaacagtg	360
acagtgaagta gc	372

<210> SEQ ID NO 58
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 58

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg	1	5	10	15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr	20	25	30	
Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	35	40	45	
Ser Gly Ile Ser Trp Asn Ser Gly Ser Lys Gly Tyr Ala Asp Ser Val	50	55	60	
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr	65	70	75	80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys	85	90	95	
Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Leu Asp	100	105	110	
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser	115	120		

<210> SEQ ID NO 59
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 59

gggtttacat tcgacgatta cagc	24
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<210> SEQ ID NO 60
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

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<400> SEQUENCE: 60

Gly Phe Thr Phe Asp Asp Tyr Ser
1 5

<210> SEQ ID NO 61

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 61

atatcatgga actcaggaag caag 24

<210> SEQ ID NO 62

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 62

Ile Ser Trp Asn Ser Gly Ser Lys
1 5

<210> SEQ ID NO 63

<211> LENGTH: 51

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 63

gcaaaatacgc gcagtggtta tggcaagttt tattattatg gactggacgt g 51

<210> SEQ ID NO 64

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 64

Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Leu Asp
1 5 10 15

Val

<210> SEQ ID NO 65

<211> LENGTH: 372

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 65

gaagtacagc ttgtagaatc cggcggagga ctggtacaac ctggaagaag tcttagactg 60

agttgcgag ctagtgggtt tacattcgac gattacagca tgcattgggt gaggaagct 120

cctggtaaag gattggaatg gggttagcggg atatcatgga actcaggaag caagggatac 180

gccgacagcg tgaaaggccg atttacaata tctagggaca acgcaaaaaa ctctctctac 240

-continued

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cttcaaatga actctcttag ggcagaagac acagcattgt attattgcgc aaaatacggc 300
agtgggttatg gcaagtttta tcattatgga atggacgtgt ggggacaagg gacaacagtg 360
acagtgaagta gc 372

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<210> SEQ ID NO 66
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

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<400> SEQUENCE: 66

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1           5           10           15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
          20           25           30
Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35           40           45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Lys Gly Tyr Ala Asp Ser Val
          50           55           60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
          65           70           75           80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
          85           90           95
Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Met Asp
          100          105          110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
          115          120

```

```

<210> SEQ ID NO 67
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

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<400> SEQUENCE: 67

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```

gggtttacat tcgacgatta cagc 24

```

```

<210> SEQ ID NO 68
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

```

```

<400> SEQUENCE: 68

```

```

Gly Phe Thr Phe Asp Asp Tyr Ser
1           5

```

```

<210> SEQ ID NO 69
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

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```

<400> SEQUENCE: 69

```

```

atatcatgga actcaggaag caag 24

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-continued

<210> SEQ ID NO 70
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 70

Ile Ser Trp Asn Ser Gly Ser Lys
1 5

<210> SEQ ID NO 71
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 71

gcaaaatacg gcagtgggta tggcaagttt taccattatg gaatggacgt g 51

<210> SEQ ID NO 72
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 72

Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 73
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 73

gaagtacagc ttgtagaatc cggcggagga ctggtacaac ctggaagaag tcttagactg 60
agttgcgcag ctagtgggtt tacattcgac gattacagca tgcattgggt gagggcaagct 120
cctggtaaag gattggaatg ggtagcggg atatcatgga actcaggaag catcggatac 180
gccgacagcg tgaaaggccg atttacaata tctagggaca acgcaaaaaa ctctctctac 240
cttcaaatga actctcttag gccagaagac acagcattgt attattgcgc aaaagacggc 300
agtggttatg gcaagtttta tcattatgga ctggacgtgt ggggacaagg gacaacagtg 360
acagtga gta gc 372

<210> SEQ ID NO 74
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 74

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg

-continued

1	5	10	15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr	20	25	30
Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	35	40	45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val	50	55	60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr	65	70	75
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys	85	90	95
Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Leu Asp	100	105	110
Val Trp Gly Gln Gly Thr Thr Val Ser Ser	115	120	

<210> SEQ ID NO 75
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 75

gggtttacat tcgacgatta cagc

24

<210> SEQ ID NO 76
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 76

Gly Phe Thr Phe Asp Asp Tyr Ser
1 5

<210> SEQ ID NO 77
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 77

atatcatgga actcaggaag catc

24

<210> SEQ ID NO 78
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 78

Ile Ser Trp Asn Ser Gly Ser Ile
1 5

<210> SEQ ID NO 79
 <211> LENGTH: 51

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 79

gcaaaagacg gcagtgggta tggcaagttt tatcattatg gactggacgt g 51

<210> SEQ ID NO 80
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 80

Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Leu Asp
1 5 10 15

Val

<210> SEQ ID NO 81
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 81

gaagtacagc ttgtagaatc cgccggagga ctggtacaac ctggaagaag tcttagactg 60
agttgcgag ctagtgggtt tacattcgac gattacagca tgcattgggt gaggaagct 120
cctggtaaag gattggaatg ggtagcggg atatcatgga actcaggaag catcggatac 180
gccgacagcg tgaaggccg atttacaata tctagggaca acgcaaaaaa ctctctctac 240
cttcaaatga actctcttag gccagaagac acagcattgt attattgcgc aaaatacggc 300
agtgggtatg gcaagtttta ttattatgga ctggacgtgt ggggacaagg gacaacagtg 360
acagtga gta gc 372

<210> SEQ ID NO 82
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 82

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

-continued

Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Leu Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 83
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 83

gggtttacat tcgacgatta cagc

24

<210> SEQ ID NO 84
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 84

Gly Phe Thr Phe Asp Asp Tyr Ser
1 5

<210> SEQ ID NO 85
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 85

atatcatgga actcaggaag catc

24

<210> SEQ ID NO 86
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 86

Ile Ser Trp Asn Ser Gly Ser Ile
1 5

<210> SEQ ID NO 87
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 87

gcaaaatacg gcagtggtta tggcaagttt tattattatg gactggacgt g

51

<210> SEQ ID NO 88
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

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<400> SEQUENCE: 88

Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Leu Asp
 1 5 10 15

Val

<210> SEQ ID NO 89

<211> LENGTH: 372

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 89

gaagtacagc ttgtagaatc cggcggagga ctggtacaac ctggaagaag tcttagactg 60
 agttgcgcag ctagtgggtt tacattcgac gattacagca tgcattgggt gaggcaagct 120
 cctggtaaag gattggaatg ggtagcggg atatcatgga actcaggaag catcgatac 180
 gccgacagcg tgaagggccg atttacaata tctagggaca acgcaaaaaa ctctctctac 240
 cttcaaatga actctcttag ggcagaagac acagcattgt attattgcgc aaaatacggc 300
 agtggttatg gcaagtttta tcattatgga atggacgtgt ggggacaagg gacaacagtg 360
 acagtga gta gc 372

<210> SEQ ID NO 90

<211> LENGTH: 124

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 90

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
 20 25 30
 Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
 85 90 95
 Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Met Asp
 100 105 110
 Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> SEQ ID NO 91

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 91

gggtttacat tcgacgatta cagc

24

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<210> SEQ ID NO 92
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 92

Gly Phe Thr Phe Asp Asp Tyr Ser
1 5

<210> SEQ ID NO 93
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 93

atatcatgga actcaggaag catc 24

<210> SEQ ID NO 94
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 94

Ile Ser Trp Asn Ser Gly Ser Ile
1 5

<210> SEQ ID NO 95
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 95

gcaaaatacgc gcagtgggta tggcaagttt tatcattatg gaatggacgt g 51

<210> SEQ ID NO 96
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 96

Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 97
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 97

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gaagtacagc ttgtagaatc cggcggagga ctggtacaac ctggaagaag tcttagactg      60
agttgcgcag ctagtgggtt tacattcgac gattacagca tgcattgggt gaggcaagct      120
cctggtaaag gattggaatg ggtagcggg atatcatgga actcaggaag caagggatac      180
gccgacagcg tgaaggccg atttacaata tctagggaca acgcaaaaaa ctctctctac      240
cttcaaatga actctcttag ggcagaagac acagcattgt attattgcgc aaaagacggc      300
agtggttatg gcaagtttta ttattatgga ctggacgtgt ggggacaagg gacaacagtg      360
acagtgahta gc                                                              372

```

```

<210> SEQ ID NO 98
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

```

```

<400> SEQUENCE: 98

```

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1          5          10          15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20          25          30
Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35          40          45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Lys Gly Tyr Ala Asp Ser Val
50          55          60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65          70          75          80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85          90          95
Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Leu Asp
100         105         110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115         120

```

```

<210> SEQ ID NO 99
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

```

```

<400> SEQUENCE: 99

```

```

gggtttacat tcgacgatta cagc                                          24

```

```

<210> SEQ ID NO 100
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

```

```

<400> SEQUENCE: 100

```

```

Gly Phe Thr Phe Asp Asp Tyr Ser
1          5

```

```

<210> SEQ ID NO 101
<211> LENGTH: 24

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```

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 101

atatcatgga actcaggaag caag                                24

<210> SEQ ID NO 102
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 102

Ile Ser Trp Asn Ser Gly Ser Lys
1             5

<210> SEQ ID NO 103
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 103

gcaaaagacg gcagtgggta tggcaagttt tattattatg gactggacgt g      51

<210> SEQ ID NO 104
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 104

Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Leu Asp
1             5             10             15

Val

<210> SEQ ID NO 105
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 105

gaagtacagc ttgtagaatc cggcggagga ctggtacaac ctggaagaag tcttagactg      60
agttgcgcag ctagtggggt tacattcgac gattacagca tgcattgggt gaggcaagct      120
cctggtaaag gattggaatg ggtagcggg atatcatgga actcaggaag caagggatac      180
gccgacagcg tgaagggccg atttacaata tctagggaca acgcaaaaaa ctctctctac      240
cttcaaatga actctcttag ggcagaagac acagcattgt attattgcgc aaaagacggc      300
agtggttatg gcaagtttta tcattatgga atggacgtgt ggggacaagg gacaacagtg      360
acagtgagta gc                                              372

<210> SEQ ID NO 106
<211> LENGTH: 124

```

-continued

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 106

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Lys Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 107
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 107

gggtttacat tcgacgatta cagc

24

<210> SEQ ID NO 108
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 108

Gly Phe Thr Phe Asp Asp Tyr Ser
1 5

<210> SEQ ID NO 109
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 109

atatcatgga actcaggaag caag

24

<210> SEQ ID NO 110
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

-continued

<400> SEQUENCE: 110

Ile Ser Trp Asn Ser Gly Ser Lys
1 5

<210> SEQ ID NO 111
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 111

gcaaaagacg gcagtgggta tggcaagttt tatcattatg gaatggacgt g 51

<210> SEQ ID NO 112
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 112

Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 113
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 113

gaagtacagc ttgtagaatc cggcggagga ctggtacaac ctggaagaag tcttagactg 60
agttgcgcag ctagtgggtt tacattcgac gattacagca tgcattgggt gagggcaagct 120
cctggtaaag gattggaatg ggtagcggg atatcatgga actcaggaag caagggatac 180
gccgacagcg tgaaaggccg atttacaata tctagggaca acgcaaaaaa ctctctctac 240
cttcaaatga actctcttag ggcagaagac acagcattgt attattgcgc aaaatacggc 300
agtggttatg gcaagtttta ttattatgga atggacgtgt ggggacaagg gacaacagtg 360
acagtga gta gc 372

<210> SEQ ID NO 114
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 114

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Lys Gly Tyr Ala Asp Ser Val

-continued

50	55	60	
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala	Lys Asn Ser Leu Tyr		
65	70	75	80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr	Ala Leu Tyr Tyr Cys		
	85	90	95
Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr	Tyr Tyr Gly Met Asp		
	100	105	110
Val Trp Gly Gln Gly Thr Thr Val Ser Ser			
	115	120	

<210> SEQ ID NO 115
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

 <400> SEQUENCE: 115

 ggggtttacat tcgacgatta cagc 24

<210> SEQ ID NO 116
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

 <400> SEQUENCE: 116

 Gly Phe Thr Phe Asp Asp Tyr Ser
 1 5

<210> SEQ ID NO 117
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

 <400> SEQUENCE: 117

 atatcatgga actcaggaag caag 24

<210> SEQ ID NO 118
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

 <400> SEQUENCE: 118

 Ile Ser Trp Asn Ser Gly Ser Lys
 1 5

<210> SEQ ID NO 119
 <211> LENGTH: 51
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

 <400> SEQUENCE: 119

 gcaaaatacg gcagtgggta tggcaagttt tattattatg gaatggacgt g 51

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<210> SEQ ID NO 120
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 120

Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 121
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 121

gaagtacagc ttgtagaatc cgccggagga ctggtacaac ctggaagaag tcttagactg 60
agttgcgag ctagtgggtt tacattcgac gattacagca tgcattgggt gaggaagct 120
cctggtaaag gattggaatg ggtagcggg atatcatgga actcaggaag catcgatac 180
gccgacagcg tgaaggccg atttacaata tctagggaca acgcaaaaaa ctctctctac 240
cttcaaatga actctcttag gccagaagac acagcattgt attattgcgc aaaagacggc 300
agtgggtatg gcaagtttta ttattatgga ctggacgtgt ggggacaagg gacaacagt 360
acagtgaagta gc 372

<210> SEQ ID NO 122
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 122

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Leu Asp
100 105 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 123
<211> LENGTH: 24

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 123

gggtttacat tgcagatta cagc

24

<210> SEQ ID NO 124
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 124

Gly Phe Thr Phe Asp Asp Tyr Ser
1 5

<210> SEQ ID NO 125
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 125

atatcatgga actcaggaag catc

24

<210> SEQ ID NO 126
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 126

Ile Ser Trp Asn Ser Gly Ser Ile
1 5

<210> SEQ ID NO 127
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 127

gcaaaagacg gcagtgggta tggcaagttt tattattatg gactggacgt g

51

<210> SEQ ID NO 128
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 128

Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Leu Asp
1 5 10 15

Val

<210> SEQ ID NO 129

```

<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 129

gaagtacagc ttgtagaatc cggcggagga ctggtacaac ctggaagaag tcttagactg      60
agttgcgcag ctagtgggtt tacattcgac gattacagca tgcattgggt gaggcaagct      120
cctggtaaag gattggaatg ggtagcgagg atatcatgga actcaggaag catcggatac      180
gccgacagcg tgaaaggccg atttacaata tctagggaca acgcaaaaaa ctctctctac      240
cttcaaatga actctcttag ggcagaagac acagcattgt attattgcgc aaaagacggc      300
agtggttatg gcaagtttta tcattatgga atggacgtgt ggggacaagg gacaacagtg      360
acagtgagta gc                                                    372


<210> SEQ ID NO 130
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 130

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1             5             10             15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20            25            30
Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35            40            45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50            55            60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65            70            75            80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85            90            95
Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Met Asp
100           105           110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115            120


<210> SEQ ID NO 131
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 131

gggtttacat tcgacgatta cagc

24


<210> SEQ ID NO 132
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

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<400> SEQUENCE: 132

Gly Phe Thr Phe Asp Tyr Ser
1 5

<210> SEQ ID NO 133

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 133

atatcatgga actcaggaag catc 24

<210> SEQ ID NO 134

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 134

Ile Ser Trp Asn Ser Gly Ser Ile
1 5

<210> SEQ ID NO 135

<211> LENGTH: 51

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 135

gcaaaagacg gcagtgggta tggcaagttt tatcattatg gaatggacgt g 51

<210> SEQ ID NO 136

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 136

Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 137

<211> LENGTH: 372

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 137

gaagtacagc ttgtagaatc cggcggagga ctggtacaac ctggaagaag tcttagactg 60

agttgcgcag ctagtgggtt tacattcgac gattacagca tgcattgggt gagggcaagct 120

cctggtaaag gattggaatg gggttagcggg atatcatgga actcaggaag catcggatac 180

gccgacagcg tgaaaggccg atttacaata tctagggaca acgcaaaaaa ctctctctac 240

cttcaaatga actctcttag ggcagaagac acagcattgt attattgcgc aaaatacggc 300

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agtggttatg gcaagtttta ttattatgga atggacgtgt ggggacaagg gacaacagtg 360

acagtgagta gc 372

<210> SEQ ID NO 138

<211> LENGTH: 124

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 138

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Met Asp
100 105 110Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 139

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 139

gggtttacat tcgacgatta cagg 24

<210> SEQ ID NO 140

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 140

Gly Phe Thr Phe Asp Asp Tyr Ser
1 5

<210> SEQ ID NO 141

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 141

atatcatgga actcaggaag catc 24

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<210> SEQ ID NO 142
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 142

Ile Ser Trp Asn Ser Gly Ser Ile
1 5

<210> SEQ ID NO 143
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 143

gcaaaatacgcgcagtgggttatggcaagttttattattatggaatggacgtg 51

<210> SEQ ID NO 144
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 144

Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 145
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 145

gaagtacagc ttgtagaatc cggcggagga ctggtacaac ctggaagaag tcttagactg 60
agtgtgcgcag ctagtgggtt tacattcgac gattacagca tgcattgggt gaggaagct 120
cctggtaaag gattggaatg ggtagcggg atatcatgga actcaggaag caagggatac 180
gccgacagcg tgaaggccg attacaata tctagggaca acgcaaaaaa ctctctctac 240
cttcaaatga actctcttag gccagaagac acagcattgt attattgcgc aaaagacggc 300
agtggttatg gcaagtttta ttattatgga atggacgtgt ggggacaagg gacaacagtg 360
acagtgaagta gc 372

<210> SEQ ID NO 146
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 146

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

-continued

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Lys Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Met Asp
100 105 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 147
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 147

gggtttacat tcgacgatta cagc

24

<210> SEQ ID NO 148
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 148

Gly Phe Thr Phe Asp Asp Tyr Ser
1 5

<210> SEQ ID NO 149
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 149

atatcatgga actcaggaag caag

24

<210> SEQ ID NO 150
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 150

Ile Ser Trp Asn Ser Gly Ser Lys
1 5

<210> SEQ ID NO 151
<211> LENGTH: 51
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 151

gcaaaagacg gcagtgggta tggcaagttt tattattatg gaatggacgt g 51

<210> SEQ ID NO 152

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 152

Ala Lys Asp Gly Ser Gly Tyr Gly Lys Phe Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 153

<211> LENGTH: 372

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 153

gaagtgcagc tgggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60

tcctgtgtag cctctggatt cacctttgat gattattcca tgcactgggt ccggcgaagct 120

ccagggaagg gcctggagtg ggtctcaggt attagtgtga atagtgttag caaagactat 180

gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agctgaagac acggccttgt attactgtgc aaaatatgga 300

agtggctacg ggaagttcta ccactacggt ttggacgtct ggggcccaagg gaccacggtc 360

accgtctcct ca 372

<210> SEQ ID NO 154

<211> LENGTH: 124

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 154

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Lys Asp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Leu Asp

-continued

100	105	110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser		
115	120	
 <210> SEQ ID NO 155 <211> LENGTH: 24 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: synthetic <400> SEQUENCE: 155 ggattcacct ttgatgatta ttcc 24		
 <210> SEQ ID NO 156 <211> LENGTH: 8 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: synthetic <400> SEQUENCE: 156 Gly Phe Thr Phe Asp Asp Tyr Ser 1 5		
 <210> SEQ ID NO 157 <211> LENGTH: 24 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: synthetic <400> SEQUENCE: 157 attagttgga atagtggtag caaa 24		
 <210> SEQ ID NO 158 <211> LENGTH: 8 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: synthetic <400> SEQUENCE: 158 Ile Ser Trp Asn Ser Gly Ser Lys 1 5		
 <210> SEQ ID NO 159 <211> LENGTH: 51 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: synthetic <400> SEQUENCE: 159 gcaaaaatag gaagtggcta cggaaggttc taccactacg gtttggacgt c 51		
 <210> SEQ ID NO 160 <211> LENGTH: 17 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: synthetic <400> SEQUENCE: 160		

-continued

Ala Lys Tyr Gly Ser Gly Tyr Gly Lys Phe Tyr His Tyr Gly Leu Asp
 1 5 10 15

Val

<210> SEQ ID NO 161
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 161

gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccgta 180
 aggttcagtg gcagtggatc tgggacagat ttcactetca ccacagcag tctgcaacct 240
 gaagattttg caacttacta ctgtcaacag agttacagta cccctccgat caccttcggc 300
 caagggacac gactggagat taaa 324

<210> SEQ ID NO 162
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 162

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
 85 90 95
 Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
 100 105

<210> SEQ ID NO 163
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 163

cagagcatta gcagctat 18

<210> SEQ ID NO 164
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 164

Gln Ser Ile Ser Ser Tyr
1 5

<210> SEQ ID NO 165
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 165

gctgcatcc

9

<210> SEQ ID NO 166
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 166

Ala Ala Ser
1

<210> SEQ ID NO 167
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 167

caacagagtt acagtacccc tccgatcacc

30

<210> SEQ ID NO 168
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 168

Gln Gln Ser Tyr Ser Thr Pro Pro Ile Thr
1 5 10

<210> SEQ ID NO 169
<211> LENGTH: 207
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 169

Met Gln Ser Gly Thr His Trp Arg Val Leu Gly Leu Cys Leu Leu Ser
1 5 10 15

Val Gly Val Trp Gly Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr
20 25 30

Gln Thr Pro Tyr Lys Val Ser Ile Ser Gly Thr Thr Val Ile Leu Thr
35 40 45

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Cys Pro Gln Tyr Pro Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys
 50 55 60
 Asn Ile Gly Gly Asp Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp
 65 70 75 80
 His Leu Ser Leu Lys Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr
 85 90 95
 Val Cys Tyr Pro Arg Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu
 100 105 110
 Tyr Leu Arg Ala Arg Val Cys Glu Asn Cys Met Glu Met Asp Val Met
 115 120 125
 Ser Val Ala Thr Ile Val Ile Val Asp Ile Cys Ile Thr Gly Gly Leu
 130 135 140
 Leu Leu Leu Val Tyr Tyr Trp Ser Lys Asn Arg Lys Ala Lys Ala Lys
 145 150 155 160
 Pro Val Thr Arg Gly Ala Gly Ala Gly Gly Arg Gln Arg Gly Gln Asn
 165 170 175
 Lys Glu Arg Pro Pro Pro Val Pro Asn Pro Asp Tyr Glu Pro Ile Arg
 180 185 190
 Lys Gly Gln Arg Asp Leu Tyr Ser Gly Leu Asn Gln Arg Arg Ile
 195 200 205

<210> SEQ ID NO 170
 <211> LENGTH: 171
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 170

Met Glu His Ser Thr Phe Leu Ser Gly Leu Val Leu Ala Thr Leu Leu
 1 5 10 15
 Ser Gln Val Ser Pro Phe Lys Ile Pro Ile Glu Glu Leu Glu Asp Arg
 20 25 30
 Val Phe Val Asn Cys Asn Thr Ser Ile Thr Trp Val Glu Gly Thr Val
 35 40 45
 Gly Thr Leu Leu Ser Asp Ile Thr Arg Leu Asp Leu Gly Lys Arg Ile
 50 55 60
 Leu Asp Pro Arg Gly Ile Tyr Arg Cys Asn Gly Thr Asp Ile Tyr Lys
 65 70 75 80
 Asp Lys Glu Ser Thr Val Gln Val His Tyr Arg Met Cys Gln Ser Cys
 85 90 95
 Val Glu Leu Asp Pro Ala Thr Val Ala Gly Ile Ile Val Thr Asp Val
 100 105 110
 Ile Ala Thr Leu Leu Leu Ala Leu Gly Val Phe Cys Phe Ala Gly His
 115 120 125
 Glu Thr Gly Arg Leu Ser Gly Ala Ala Asp Thr Gln Ala Leu Leu Arg
 130 135 140
 Asn Asp Gln Val Tyr Gln Pro Leu Arg Asp Arg Asp Asp Ala Gln Tyr
 145 150 155 160
 Ser His Leu Gly Gly Asn Trp Ala Arg Asn Lys
 165 170

<210> SEQ ID NO 171

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<211> LENGTH: 750
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 171

Met Trp Asn Leu Leu His Glu Thr Asp Ser Ala Val Ala Thr Ala Arg
1      5      10      15
Arg Pro Arg Trp Leu Cys Ala Gly Ala Leu Val Leu Ala Gly Gly Phe
      20      25      30
Phe Leu Leu Gly Phe Leu Phe Gly Trp Phe Ile Lys Ser Ser Asn Glu
      35      40      45
Ala Thr Asn Ile Thr Pro Lys His Asn Met Lys Ala Phe Leu Asp Glu
      50      55      60
Leu Lys Ala Glu Asn Ile Lys Lys Phe Leu Tyr Asn Phe Thr Gln Ile
      65      70      75      80
Pro His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala Lys Gln Ile
      85      90      95
Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Ala His
      100     105     110
Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn Tyr Ile
      115     120     125
Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr Ser Leu Phe
      130     135     140
Glu Pro Pro Pro Pro Gly Tyr Glu Asn Val Ser Asp Ile Val Pro Pro
      145     150     155     160
Phe Ser Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp Leu Val Tyr
      165     170     175
Val Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg Asp Met
      180     185     190
Lys Ile Asn Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr Gly Lys Val
      195     200     205
Phe Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly Ala Lys Gly
      210     215     220
Val Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Ala Pro Gly Val Lys
      225     230     235     240
Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln Arg Gly
      245     250     255
Asn Ile Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr Pro Gly Tyr
      260     265     270
Pro Ala Asn Glu Tyr Ala Tyr Arg Arg Gly Ile Ala Glu Ala Val Gly
      275     280     285
Leu Pro Ser Ile Pro Val His Pro Ile Gly Tyr Tyr Asp Ala Gln Lys
      290     295     300
Leu Leu Glu Lys Met Gly Gly Ser Ala Pro Pro Asp Ser Ser Trp Arg
      305     310     315     320
Gly Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Thr Gly Asn
      325     330     335
Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr Asn Glu Val
      340     345     350
Thr Arg Ile Tyr Asn Val Ile Gly Thr Leu Arg Gly Ala Val Glu Pro
      355     360     365

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Asp	Arg	Tyr	Val	Ile	Leu	Gly	Gly	His	Arg	Asp	Ser	Trp	Val	Phe	Gly
370						375				380					
Gly	Ile	Asp	Pro	Gln	Ser	Gly	Ala	Ala	Val	Val	His	Glu	Ile	Val	Arg
385					390					395					400
Ser	Phe	Gly	Thr	Leu	Lys	Lys	Glu	Gly	Trp	Arg	Pro	Arg	Arg	Thr	Ile
				405					410					415	
Leu	Phe	Ala	Ser	Trp	Asp	Ala	Glu	Glu	Phe	Gly	Leu	Leu	Gly	Ser	Thr
			420					425					430		
Glu	Trp	Ala	Glu	Glu	Asn	Ser	Arg	Leu	Leu	Gln	Glu	Arg	Gly	Val	Ala
		435					440					445			
Tyr	Ile	Asn	Ala	Asp	Ser	Ser	Ile	Glu	Gly	Asn	Tyr	Thr	Leu	Arg	Val
450						455					460				
Asp	Cys	Thr	Pro	Leu	Met	Tyr	Ser	Leu	Val	His	Asn	Leu	Thr	Lys	Glu
465					470					475					480
Leu	Lys	Ser	Pro	Asp	Glu	Gly	Phe	Glu	Gly	Lys	Ser	Leu	Tyr	Glu	Ser
				485					490					495	
Trp	Thr	Lys	Lys	Ser	Pro	Ser	Pro	Glu	Phe	Ser	Gly	Met	Pro	Arg	Ile
			500					505					510		
Ser	Lys	Leu	Gly	Ser	Gly	Asn	Asp	Phe	Glu	Val	Phe	Phe	Gln	Arg	Leu
		515					520					525			
Gly	Ile	Ala	Ser	Gly	Arg	Ala	Arg	Tyr	Thr	Lys	Asn	Trp	Glu	Thr	Asn
530						535					540				
Lys	Phe	Ser	Gly	Tyr	Pro	Leu	Tyr	His	Ser	Val	Tyr	Glu	Thr	Tyr	Glu
545					550					555					560
Leu	Val	Glu	Lys	Phe	Tyr	Asp	Pro	Met	Phe	Lys	Tyr	His	Leu	Thr	Val
				565					570					575	
Ala	Gln	Val	Arg	Gly	Gly	Met	Val	Phe	Glu	Leu	Ala	Asn	Ser	Ile	Val
			580					585					590		
Leu	Pro	Phe	Asp	Cys	Arg	Asp	Tyr	Ala	Val	Val	Leu	Arg	Lys	Tyr	Ala
		595				600						605			
Asp	Lys	Ile	Tyr	Ser	Ile	Ser	Met	Lys	His	Pro	Gln	Glu	Met	Lys	Thr
610						615					620				
Tyr	Ser	Val	Ser	Phe	Asp	Ser	Leu	Phe	Ser	Ala	Val	Lys	Asn	Phe	Thr
625					630					635					640
Glu	Ile	Ala	Ser	Lys	Phe	Ser	Glu	Arg	Leu	Gln	Asp	Phe	Asp	Lys	Ser
				645					650					655	
Asn	Pro	Ile	Val	Leu	Arg	Met	Met	Asn	Asp	Gln	Leu	Met	Phe	Leu	Glu
			660					665					670		
Arg	Ala	Phe	Ile	Asp	Pro	Leu	Gly	Leu	Pro	Asp	Arg	Pro	Phe	Tyr	Arg
		675					680					685			
His	Val	Ile	Tyr	Ala	Pro	Ser	Ser	His	Asn	Lys	Tyr	Ala	Gly	Glu	Ser
690						695					700				
Phe	Pro	Gly	Ile	Tyr	Asp	Ala	Leu	Phe	Asp	Ile	Glu	Ser	Lys	Val	Asp
705					710					715					720
Pro	Ser	Lys	Ala	Trp	Gly	Glu	Val	Lys	Arg	Gln	Ile	Tyr	Val	Ala	Ala
				725					730					735	
Phe	Thr	Val	Gln	Ala	Ala	Ala	Glu	Thr	Leu	Ser	Glu	Val	Ala		
			740					745				750			

<210> SEQ ID NO 172

<211> LENGTH: 943

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<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 172

Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu Leu Ala
1 5 10 15
Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Gly Asn Tyr
20 25 30
Val Val Thr Asp His Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser
35 40 45
Tyr Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly
50 55 60
Pro Cys Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp
65 70 75 80
Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr
85 90 95
Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp
100 105 110
Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu
115 120 125
Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro
130 135 140
Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg
145 150 155 160
Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu
165 170 175
Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly
180 185 190
Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile
195 200 205
Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile
210 215 220
Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His
225 230 235 240
Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys
245 250 255
Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys
260 265 270
Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys
275 280 285
Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys
290 295 300
Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp
305 310 315 320
Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn
325 330 335
Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys His Leu
340 345 350
Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly
355 360 365

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Cys	Pro	Thr	Asn	Gly	Pro	Lys	Ile	Pro	Ser	Ile	Ala	Thr	Gly	Met	Val
370						375					380				
Gly	Ala	Leu	Leu	Leu	Leu	Leu	Val	Val	Ala	Leu	Gly	Ile	Gly	Leu	Phe
385					390					395					400
Met	Arg	Arg	Arg	His	Ile	Val	Arg	Lys	Arg	Thr	Leu	Arg	Arg	Leu	Leu
				405					410					415	
Gln	Glu	Arg	Glu	Leu	Val	Glu	Pro	Leu	Thr	Pro	Ser	Gly	Glu	Ala	Pro
			420					425					430		
Asn	Gln	Ala	Leu	Leu	Arg	Ile	Leu	Lys	Glu	Thr	Glu	Phe	Lys	Lys	Ile
		435					440					445			
Lys	Val	Leu	Gly	Ser	Gly	Ala	Phe	Gly	Thr	Val	Tyr	Lys	Gly	Leu	Trp
450						455					460				
Ile	Pro	Glu	Gly	Glu	Lys	Val	Lys	Ile	Pro	Val	Ala	Ile	Lys	Glu	Leu
465					470					475					480
Arg	Glu	Ala	Thr	Ser	Pro	Lys	Ala	Asn	Lys	Glu	Ile	Leu	Asp	Glu	Ala
				485					490					495	
Tyr	Val	Met	Ala	Ser	Val	Asp	Asn	Pro	His	Val	Cys	Arg	Leu	Leu	Gly
			500					505					510		
Ile	Cys	Leu	Thr	Ser	Thr	Val	Gln	Leu	Ile	Thr	Gln	Leu	Met	Pro	Phe
		515					520					525			
Gly	Cys	Leu	Leu	Asp	Tyr	Val	Arg	Glu	His	Lys	Asp	Asn	Ile	Gly	Ser
530						535					540				
Gln	Tyr	Leu	Leu	Asn	Trp	Cys	Val	Gln	Ile	Ala	Lys	Gly	Met	Asn	Tyr
545					550					555					560
Leu	Glu	Asp	Arg	Arg	Leu	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val
				565					570					575	
Leu	Val	Lys	Thr	Pro	Gln	His	Val	Lys	Ile	Thr	Asp	Phe	Gly	Leu	Ala
			580					585					590		
Lys	Leu	Leu	Gly	Ala	Glu	Glu	Lys	Glu	Tyr	His	Ala	Glu	Gly	Gly	Lys
		595					600					605			
Val	Pro	Ile	Lys	Trp	Met	Ala	Leu	Glu	Ser	Ile	Leu	His	Arg	Ile	Tyr
610						615					620				
Thr	His	Gln	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Val	Thr	Val	Trp	Glu	Leu
625					630					635					640
Met	Thr	Phe	Gly	Ser	Lys	Pro	Tyr	Asp	Gly	Ile	Pro	Ala	Ser	Glu	Ile
				645					650					655	
Ser	Ser	Ile	Leu	Glu	Lys	Gly	Glu	Arg	Leu	Pro	Gln	Pro	Pro	Ile	Cys
			660					665					670		
Thr	Ile	Asp	Val	Tyr	Met	Ile	Met	Val	Lys	Cys	Trp	Met	Ile	Asp	Ala
		675					680					685			
Asp	Ser	Arg	Pro	Lys	Phe	Arg	Glu	Leu	Ile	Ile	Glu	Phe	Ser	Lys	Met
690						695					700				
Ala	Arg	Asp	Pro	Gln	Arg	Tyr	Leu	Val	Ile	Gln	Gly	Asp	Glu	Arg	Met
705					710					715					720
His	Leu	Pro	Ser	Pro	Thr	Asp	Ser	Asn	Phe	Tyr	Arg	Ala	Leu	Met	Asp
				725					730					735	
Glu	Glu	Asp	Met	Asp	Asp	Val	Val	Asp	Ala	Asp	Glu	Tyr	Leu	Ile	Pro
			740					745					750		
Gln	Gln	Gly	Phe	Phe	Ser	Ser	Pro	Ser	Thr	Ser	Arg	Thr	Pro	Leu	Leu
		755					760					765			
Ser	Ser	Leu	Ser	Ala	Thr	Ser	Asn	Asn	Ser	Thr	Val	Ala	Cys	Ile	Asp

-continued

770	775	780
Arg Asn Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln		
785	790	795 800
Arg Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp		
	805	810 815
Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val Pro Lys		
	820	825 830
Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln Pro Leu		
	835	840 845
Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro His Ser Thr		
	850	855 860
Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln Pro Thr Cys Val		
	865	870 875 880
Asn Ser Thr Phe Asp Ser Pro Ala His Trp Ala Gln Lys Gly Ser His		
	885	890 895
Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln Gln Asp Phe Phe Pro Lys		
	900	905 910
Glu Ala Lys Pro Asn Gly Ile Phe Lys Gly Ser Thr Ala Glu Asn Ala		
	915	920 925
Glu Tyr Leu Arg Val Ala Pro Gln Ser Ser Glu Phe Ile Gly Ala		
	930	935 940

<210> SEQ ID NO 173

<211> LENGTH: 14507

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 173

Met Leu Lys Pro Ser Gly Leu Pro Gly Ser Ser Ser Pro Thr Arg Ser		
1	5	10 15
Leu Met Thr Gly Ser Arg Ser Thr Lys Ala Thr Pro Glu Met Asp Ser		
	20	25 30
Gly Leu Thr Gly Ala Thr Leu Ser Pro Lys Thr Ser Thr Gly Ala Ile		
	35	40 45
Val Val Thr Glu His Thr Leu Pro Phe Thr Ser Pro Asp Lys Thr Leu		
	50	55 60
Ala Ser Pro Thr Ser Ser Val Val Gly Arg Thr Thr Gln Ser Leu Gly		
	65	70 75 80
Val Met Ser Ser Ala Leu Pro Glu Ser Thr Ser Arg Gly Met Thr His		
	85	90 95
Ser Glu Gln Arg Thr Ser Pro Ser Leu Ser Pro Gln Val Asn Gly Thr		
	100	105 110
Pro Ser Arg Asn Tyr Pro Ala Thr Ser Met Val Ser Gly Leu Ser Ser		
	115	120 125
Pro Arg Thr Arg Thr Ser Ser Thr Glu Gly Asn Phe Thr Lys Glu Ala		
	130	135 140
Ser Thr Tyr Thr Leu Thr Val Glu Thr Thr Ser Gly Pro Val Thr Glu		
	145	150 155 160
Lys Tyr Thr Val Pro Thr Glu Thr Ser Thr Thr Glu Gly Asp Ser Thr		
	165	170 175
Glu Thr Pro Trp Asp Thr Arg Tyr Ile Pro Val Lys Ile Thr Ser Pro		

-continued

180							185					190				
Met	Lys	Thr	Phe	Ala	Asp	Ser	Thr	Ala	Ser	Lys	Glu	Asn	Ala	Pro	Val	
	195						200					205				
Ser	Met	Thr	Pro	Ala	Glu	Thr	Thr	Val	Thr	Asp	Ser	His	Thr	Pro	Gly	
	210					215					220					
Arg	Thr	Asn	Pro	Ser	Phe	Gly	Thr	Leu	Tyr	Ser	Ser	Phe	Leu	Asp	Leu	
225					230					235					240	
Ser	Pro	Lys	Gly	Thr	Pro	Asn	Ser	Arg	Gly	Glu	Thr	Ser	Leu	Glu	Leu	
				245					250					255		
Ile	Leu	Ser	Thr	Thr	Gly	Tyr	Pro	Phe	Ser	Ser	Pro	Glu	Pro	Gly	Ser	
			260					265					270			
Ala	Gly	His	Ser	Arg	Ile	Ser	Thr	Ser	Ala	Pro	Leu	Ser	Ser	Ser	Ala	
		275					280					285				
Ser	Val	Leu	Asp	Asn	Lys	Ile	Ser	Glu	Thr	Ser	Ile	Phe	Ser	Gly	Gln	
	290					295					300					
Ser	Leu	Thr	Ser	Pro	Leu	Ser	Pro	Gly	Val	Pro	Glu	Ala	Arg	Ala	Ser	
305					310					315					320	
Thr	Met	Pro	Asn	Ser	Ala	Ile	Pro	Phe	Ser	Met	Thr	Leu	Ser	Asn	Ala	
				325					330					335		
Glu	Thr	Ser	Ala	Glu	Arg	Val	Arg	Ser	Thr	Ile	Ser	Ser	Leu	Gly	Thr	
			340					345					350			
Pro	Ser	Ile	Ser	Thr	Lys	Gln	Thr	Ala	Glu	Thr	Ile	Leu	Thr	Phe	His	
		355					360					365				
Ala	Phe	Ala	Glu	Thr	Met	Asp	Ile	Pro	Ser	Thr	His	Ile	Ala	Lys	Thr	
	370					375					380					
Leu	Ala	Ser	Glu	Trp	Leu	Gly	Ser	Pro	Gly	Thr	Leu	Gly	Gly	Thr	Ser	
385					390					395					400	
Thr	Ser	Ala	Leu	Thr	Thr	Thr	Ser	Pro	Ser	Thr	Thr	Leu	Val	Ser	Glu	
			405						410					415		
Glu	Thr	Asn	Thr	His	His	Ser	Thr	Ser	Gly	Lys	Glu	Thr	Glu	Gly	Thr	
		420						425					430			
Leu	Asn	Thr	Ser	Met	Thr	Pro	Leu	Glu	Thr	Ser	Ala	Pro	Gly	Glu	Glu	
		435					440					445				
Ser	Glu	Met	Thr	Ala	Thr	Leu	Val	Pro	Thr	Leu	Gly	Phe	Thr	Thr	Leu	
	450					455					460					
Asp	Ser	Lys	Ile	Arg	Ser	Pro	Ser	Gln	Val	Ser	Ser	Ser	His	Pro	Thr	
465					470					475					480	
Arg	Glu	Leu	Arg	Thr	Thr	Gly	Ser	Thr	Ser	Gly	Arg	Gln	Ser	Ser	Ser	
			485						490				495			
Thr	Ala	Ala	His	Gly	Ser	Ser	Asp	Ile	Leu	Arg	Ala	Thr	Thr	Ser	Ser	
			500					505					510			
Thr	Ser	Lys	Ala	Ser	Ser	Trp	Thr	Ser	Glu	Ser	Thr	Ala	Gln	Gln	Phe	
		515					520					525				
Ser	Glu	Pro	Gln	His	Thr	Gln	Trp	Val	Glu	Thr	Ser	Pro	Ser	Met	Lys	
	530					535					540					
Thr	Glu	Arg	Pro	Pro	Ala	Ser	Thr	Ser	Val	Ala	Ala	Pro	Ile	Thr	Thr	
	545				550					555					560	
Ser	Val	Pro	Ser	Val	Val	Ser	Gly	Phe	Thr	Thr	Leu	Lys	Thr	Ser	Ser	
				565					570					575		
Thr	Lys	Gly	Ile	Trp	Leu	Glu	Glu	Thr	Ser	Ala	Asp	Thr	Leu	Ile	Gly	
			580					585					590			

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Glu	Ser	Thr	Ala	Gly	Pro	Thr	Thr	His	Gln	Phe	Ala	Val	Pro	Thr	Gly	595	600	605
Ile	Ser	Met	Thr	Gly	Gly	Ser	Ser	Thr	Arg	Gly	Ser	Gln	Gly	Thr	Thr	610	615	620
His	Leu	Leu	Thr	Arg	Ala	Thr	Ala	Ser	Ser	Glu	Thr	Ser	Ala	Asp	Leu	625	630	635
Thr	Leu	Ala	Thr	Asn	Gly	Val	Pro	Val	Ser	Val	Ser	Pro	Ala	Val	Ser	645	650	655
Lys	Thr	Ala	Ala	Gly	Ser	Ser	Pro	Pro	Gly	Gly	Thr	Lys	Pro	Ser	Tyr	660	665	670
Thr	Met	Val	Ser	Ser	Val	Ile	Pro	Glu	Thr	Ser	Ser	Leu	Gln	Ser	Ser	675	680	685
Ala	Phe	Arg	Glu	Gly	Thr	Ser	Leu	Gly	Leu	Thr	Pro	Leu	Asn	Thr	Arg	690	695	700
His	Pro	Phe	Ser	Ser	Pro	Glu	Pro	Asp	Ser	Ala	Gly	His	Thr	Lys	Ile	705	710	715
Ser	Thr	Ser	Ile	Pro	Leu	Leu	Ser	Ser	Ala	Ser	Val	Leu	Glu	Asp	Lys	725	730	735
Val	Ser	Ala	Thr	Ser	Thr	Phe	Ser	His	His	Lys	Ala	Thr	Ser	Ser	Ile	740	745	750
Thr	Thr	Gly	Thr	Pro	Glu	Ile	Ser	Thr	Lys	Thr	Lys	Pro	Ser	Ser	Ala	755	760	765
Val	Leu	Ser	Ser	Met	Thr	Leu	Ser	Asn	Ala	Ala	Thr	Ser	Pro	Glu	Arg	770	775	780
Val	Arg	Asn	Ala	Thr	Ser	Pro	Leu	Thr	His	Pro	Ser	Pro	Ser	Gly	Glu	785	790	795
Glu	Thr	Ala	Gly	Ser	Val	Leu	Thr	Leu	Ser	Thr	Ser	Ala	Glu	Thr	Thr	805	810	815
Asp	Ser	Pro	Asn	Ile	His	Pro	Thr	Gly	Thr	Leu	Thr	Ser	Glu	Ser	Ser	820	825	830
Glu	Ser	Pro	Ser	Thr	Leu	Ser	Leu	Pro	Ser	Val	Ser	Gly	Val	Lys	Thr	835	840	845
Thr	Phe	Ser	Ser	Ser	Thr	Pro	Ser	Thr	His	Leu	Phe	Thr	Ser	Gly	Glu	850	855	860
Glu	Thr	Glu	Glu	Thr	Ser	Asn	Pro	Ser	Val	Ser	Gln	Pro	Glu	Thr	Ser	865	870	875
Val	Ser	Arg	Val	Arg	Thr	Thr	Leu	Ala	Ser	Thr	Ser	Val	Pro	Thr	Pro	885	890	895
Val	Phe	Pro	Thr	Met	Asp	Thr	Trp	Pro	Thr	Arg	Ser	Ala	Gln	Phe	Ser	900	905	910
Ser	Ser	His	Leu	Val	Ser	Glu	Leu	Arg	Ala	Thr	Ser	Ser	Thr	Ser	Val	915	920	925
Thr	Asn	Ser	Thr	Gly	Ser	Ala	Leu	Pro	Lys	Ile	Ser	His	Leu	Thr	Gly	930	935	940
Thr	Ala	Thr	Met	Ser	Gln	Thr	Asn	Arg	Asp	Thr	Phe	Asn	Asp	Ser	Ala	945	950	955
Ala	Pro	Gln	Ser	Thr	Thr	Trp	Pro	Glu	Thr	Ser	Pro	Arg	Phe	Lys	Thr	965	970	975
Gly	Leu	Pro	Ser	Ala	Thr	Thr	Thr	Val	Ser	Thr	Ser	Ala	Thr	Ser	Leu	980	985	990

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Ser	Ala	Thr	Val	Met	Val	Ser	Lys	Phe	Thr	Ser	Pro	Ala	Thr	Ser	Ser	995	1000	1005
Met	Glu	Ala	Thr	Ser	Ile	Arg	Glu	Pro	Ser	Thr	Thr	Ile	Leu	Thr		1010	1015	1020
Thr	Glu	Thr	Thr	Asn	Gly	Pro	Gly	Ser	Met	Ala	Val	Ala	Ser	Thr		1025	1030	1035
Asn	Ile	Pro	Ile	Gly	Lys	Gly	Tyr	Ile	Thr	Glu	Gly	Arg	Leu	Asp		1040	1045	1050
Thr	Ser	His	Leu	Pro	Ile	Gly	Thr	Thr	Ala	Ser	Ser	Glu	Thr	Ser		1055	1060	1065
Met	Asp	Phe	Thr	Met	Ala	Lys	Glu	Ser	Val	Ser	Met	Ser	Val	Ser		1070	1075	1080
Pro	Ser	Gln	Ser	Met	Asp	Ala	Ala	Gly	Ser	Ser	Thr	Pro	Gly	Arg		1085	1090	1095
Thr	Ser	Gln	Phe	Val	Asp	Thr	Phe	Ser	Asp	Asp	Val	Tyr	His	Leu		1100	1105	1110
Thr	Ser	Arg	Glu	Ile	Thr	Ile	Pro	Arg	Asp	Gly	Thr	Ser	Ser	Ala		1115	1120	1125
Leu	Thr	Pro	Gln	Met	Thr	Ala	Thr	His	Pro	Pro	Ser	Pro	Asp	Pro		1130	1135	1140
Gly	Ser	Ala	Arg	Ser	Thr	Trp	Leu	Gly	Ile	Leu	Ser	Ser	Ser	Pro		1145	1150	1155
Ser	Ser	Pro	Thr	Pro	Lys	Val	Thr	Met	Ser	Ser	Thr	Phe	Ser	Thr		1160	1165	1170
Gln	Arg	Val	Thr	Thr	Ser	Met	Ile	Met	Asp	Thr	Val	Glu	Thr	Ser		1175	1180	1185
Arg	Trp	Asn	Met	Pro	Asn	Leu	Pro	Ser	Thr	Thr	Ser	Leu	Thr	Pro		1190	1195	1200
Ser	Asn	Ile	Pro	Thr	Ser	Gly	Ala	Ile	Gly	Lys	Ser	Thr	Leu	Val		1205	1210	1215
Pro	Leu	Asp	Thr	Pro	Ser	Pro	Ala	Thr	Ser	Leu	Glu	Ala	Ser	Glu		1220	1225	1230
Gly	Gly	Leu	Pro	Thr	Leu	Ser	Thr	Tyr	Pro	Glu	Ser	Thr	Asn	Thr		1235	1240	1245
Pro	Ser	Ile	His	Leu	Gly	Ala	His	Ala	Ser	Ser	Glu	Ser	Pro	Ser		1250	1255	1260
Thr	Ile	Lys	Leu	Thr	Met	Ala	Ser	Val	Val	Lys	Pro	Gly	Ser	Tyr		1265	1270	1275
Thr	Pro	Leu	Thr	Phe	Pro	Ser	Ile	Glu	Thr	His	Ile	His	Val	Ser		1280	1285	1290
Thr	Ala	Arg	Met	Ala	Tyr	Ser	Ser	Gly	Ser	Ser	Pro	Glu	Met	Thr		1295	1300	1305
Ala	Pro	Gly	Glu	Thr	Asn	Thr	Gly	Ser	Thr	Trp	Asp	Pro	Thr	Thr		1310	1315	1320
Tyr	Ile	Thr	Thr	Thr	Asp	Pro	Lys	Asp	Thr	Ser	Ser	Ala	Gln	Val		1325	1330	1335
Ser	Thr	Pro	His	Ser	Val	Arg	Thr	Leu	Arg	Thr	Thr	Glu	Asn	His		1340	1345	1350
Pro	Lys	Thr	Glu	Ser	Ala	Thr	Pro	Ala	Ala	Tyr	Ser	Gly	Ser	Pro		1355	1360	1365
Lys	Ile	Ser	Ser	Ser	Pro	Asn	Leu	Thr	Ser	Pro	Ala	Thr	Lys	Ala				

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1370	1375	1380
Trp Thr Ile Thr Asp Thr Thr Glu His Ser Thr Gln Leu His Tyr		
1385	1390	1395
Thr Lys Leu Ala Glu Lys Ser Ser Gly Phe Glu Thr Gln Ser Ala		
1400	1405	1410
Pro Gly Pro Val Ser Val Val Ile Pro Thr Ser Pro Thr Ile Gly		
1415	1420	1425
Ser Ser Thr Leu Glu Leu Thr Ser Asp Val Pro Gly Glu Pro Leu		
1430	1435	1440
Val Leu Ala Pro Ser Glu Gln Thr Thr Ile Thr Leu Pro Met Ala		
1445	1450	1455
Thr Trp Leu Ser Thr Ser Leu Thr Glu Glu Met Ala Ser Thr Asp		
1460	1465	1470
Leu Asp Ile Ser Ser Pro Ser Ser Pro Met Ser Thr Phe Ala Ile		
1475	1480	1485
Phe Pro Pro Met Ser Thr Pro Ser His Glu Leu Ser Lys Ser Glu		
1490	1495	1500
Ala Asp Thr Ser Ala Ile Arg Asn Thr Asp Ser Thr Thr Leu Asp		
1505	1510	1515
Gln His Leu Gly Ile Arg Ser Leu Gly Arg Thr Gly Asp Leu Thr		
1520	1525	1530
Thr Val Pro Ile Thr Pro Leu Thr Thr Thr Trp Thr Ser Val Ile		
1535	1540	1545
Glu His Ser Thr Gln Ala Gln Asp Thr Leu Ser Ala Thr Met Ser		
1550	1555	1560
Pro Thr His Val Thr Gln Ser Leu Lys Asp Gln Thr Ser Ile Pro		
1565	1570	1575
Ala Ser Ala Ser Pro Ser His Leu Thr Glu Val Tyr Pro Glu Leu		
1580	1585	1590
Gly Thr Gln Gly Arg Ser Ser Ser Glu Ala Thr Thr Phe Trp Lys		
1595	1600	1605
Pro Ser Thr Asp Thr Leu Ser Arg Glu Ile Glu Thr Gly Pro Thr		
1610	1615	1620
Asn Ile Gln Ser Thr Pro Pro Met Asp Asn Thr Thr Thr Gly Ser		
1625	1630	1635
Ser Ser Ser Gly Val Thr Leu Gly Ile Ala His Leu Pro Ile Gly		
1640	1645	1650
Thr Ser Ser Pro Ala Glu Thr Ser Thr Asn Met Ala Leu Glu Arg		
1655	1660	1665
Arg Ser Ser Thr Ala Thr Val Ser Met Ala Gly Thr Met Gly Leu		
1670	1675	1680
Leu Val Thr Ser Ala Pro Gly Arg Ser Ile Ser Gln Ser Leu Gly		
1685	1690	1695
Arg Val Ser Ser Val Leu Ser Glu Ser Thr Thr Glu Gly Val Thr		
1700	1705	1710
Asp Ser Ser Lys Gly Ser Ser Pro Arg Leu Asn Thr Gln Gly Asn		
1715	1720	1725
Thr Ala Leu Ser Ser Ser Leu Glu Pro Ser Tyr Ala Glu Gly Ser		
1730	1735	1740
Gln Met Ser Thr Ser Ile Pro Leu Thr Ser Ser Pro Thr Thr Pro		
1745	1750	1755

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Asp	Val	Glu	Phe	Ile	Gly	Gly	Ser	Thr	Phe	Trp	Thr	Lys	Glu	Val
1760						1765					1770			
Thr	Thr	Val	Met	Thr	Ser	Asp	Ile	Ser	Lys	Ser	Ser	Ala	Arg	Thr
1775						1780					1785			
Glu	Ser	Ser	Ser	Ala	Thr	Leu	Met	Ser	Thr	Ala	Leu	Gly	Ser	Thr
1790						1795					1800			
Glu	Asn	Thr	Gly	Lys	Glu	Lys	Leu	Arg	Thr	Ala	Ser	Met	Asp	Leu
1805						1810					1815			
Pro	Ser	Pro	Thr	Pro	Ser	Met	Glu	Val	Thr	Pro	Trp	Ile	Ser	Leu
1820						1825					1830			
Thr	Leu	Ser	Asn	Ala	Pro	Asn	Thr	Thr	Asp	Ser	Leu	Asp	Leu	Ser
1835						1840					1845			
His	Gly	Val	His	Thr	Ser	Ser	Ala	Gly	Thr	Leu	Ala	Thr	Asp	Arg
1850						1855					1860			
Ser	Leu	Asn	Thr	Gly	Val	Thr	Arg	Ala	Ser	Arg	Leu	Glu	Asn	Gly
1865						1870					1875			
Ser	Asp	Thr	Ser	Ser	Lys	Ser	Leu	Ser	Met	Gly	Asn	Ser	Thr	His
1880						1885					1890			
Thr	Ser	Met	Thr	Tyr	Thr	Glu	Lys	Ser	Glu	Val	Ser	Ser	Ser	Ile
1895						1900					1905			
His	Pro	Arg	Pro	Glu	Thr	Ser	Ala	Pro	Gly	Ala	Glu	Thr	Thr	Leu
1910						1915					1920			
Thr	Ser	Thr	Pro	Gly	Asn	Arg	Ala	Ile	Ser	Leu	Thr	Leu	Pro	Phe
1925						1930					1935			
Ser	Ser	Ile	Pro	Val	Glu	Glu	Val	Ile	Ser	Thr	Gly	Ile	Thr	Ser
1940						1945					1950			
Gly	Pro	Asp	Ile	Asn	Ser	Ala	Pro	Met	Thr	His	Ser	Pro	Ile	Thr
1955						1960					1965			
Pro	Pro	Thr	Ile	Val	Trp	Thr	Ser	Thr	Gly	Thr	Ile	Glu	Gln	Ser
1970						1975					1980			
Thr	Gln	Pro	Leu	His	Ala	Val	Ser	Ser	Glu	Lys	Val	Ser	Val	Gln
1985						1990					1995			
Thr	Gln	Ser	Thr	Pro	Tyr	Val	Asn	Ser	Val	Ala	Val	Ser	Ala	Ser
2000						2005					2010			
Pro	Thr	His	Glu	Asn	Ser	Val	Ser	Ser	Gly	Ser	Ser	Thr	Ser	Ser
2015						2020					2025			
Pro	Tyr	Ser	Ser	Ala	Ser	Leu	Glu	Ser	Leu	Asp	Ser	Thr	Ile	Ser
2030						2035					2040			
Arg	Arg	Asn	Ala	Ile	Thr	Ser	Trp	Leu	Trp	Asp	Leu	Thr	Thr	Ser
2045						2050					2055			
Leu	Pro	Thr	Thr	Thr	Trp	Pro	Ser	Thr	Ser	Leu	Ser	Glu	Ala	Leu
2060						2065					2070			
Ser	Ser	Gly	His	Ser	Gly	Val	Ser	Asn	Pro	Ser	Ser	Thr	Thr	Thr
2075						2080					2085			
Glu	Phe	Pro	Leu	Phe	Ser	Ala	Ala	Ser	Thr	Ser	Ala	Ala	Lys	Gln
2090						2095					2100			
Arg	Asn	Pro	Glu	Thr	Glu	Thr	His	Gly	Pro	Gln	Asn	Thr	Ala	Ala
2105						2110					2115			
Ser	Thr	Leu	Asn	Thr	Asp	Ala	Ser	Ser	Val	Thr	Gly	Leu	Ser	Glu
2120						2125					2130			

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Thr 2135	Pro	Val	Gly	Ala	Ser	Ile 2140	Ser	Ser	Glu	Val	Pro 2145	Leu	Pro	Met
Ala 2150	Ile	Thr	Ser	Arg	Ser	Asp 2155	Val	Ser	Gly	Leu	Thr 2160	Ser	Glu	Ser
Thr 2165	Ala	Asn	Pro	Ser	Leu	Gly 2170	Thr	Ala	Ser	Ser	Ala 2175	Gly	Thr	Lys
Leu 2180	Thr	Arg	Thr	Ile	Ser	Leu 2185	Pro	Thr	Ser	Glu	Ser 2190	Leu	Val	Ser
Phe 2195	Arg	Met	Asn	Lys	Asp	Pro 2200	Trp	Thr	Val	Ser	Ile 2205	Pro	Leu	Gly
Ser 2210	His	Pro	Thr	Thr	Asn	Thr 2215	Glu	Thr	Ser	Ile	Pro 2220	Val	Asn	Ser
Ala 2225	Gly	Pro	Pro	Gly	Leu	Ser 2230	Thr	Val	Ala	Ser	Asp 2235	Val	Ile	Asp
Thr 2240	Pro	Ser	Asp	Gly	Ala	Glu 2245	Ser	Ile	Pro	Thr	Val 2250	Ser	Phe	Ser
Pro 2255	Ser	Pro	Asp	Thr	Glu	Val 2260	Thr	Thr	Ile	Ser	His 2265	Phe	Pro	Glu
Lys 2270	Thr	Thr	His	Ser	Phe	Arg 2275	Thr	Ile	Ser	Ser	Leu 2280	Thr	His	Glu
Leu 2285	Thr	Ser	Arg	Val	Thr	Pro 2290	Ile	Pro	Gly	Asp	Trp 2295	Met	Ser	Ser
Ala 2300	Met	Ser	Thr	Lys	Pro	Thr 2305	Gly	Ala	Ser	Pro	Ser 2310	Ile	Thr	Leu
Gly 2315	Glu	Arg	Arg	Thr	Ile	Thr 2320	Ser	Ala	Ala	Pro	Thr 2325	Thr	Ser	Pro
Ile 2330	Val	Leu	Thr	Ala	Ser	Phe 2335	Thr	Glu	Thr	Ser	Thr 2340	Val	Ser	Leu
Asp 2345	Asn	Glu	Thr	Thr	Val	Lys 2350	Thr	Ser	Asp	Ile	Leu 2355	Asp	Ala	Arg
Lys 2360	Thr	Asn	Glu	Leu	Pro	Ser 2365	Asp	Ser	Ser	Ser	Ser 2370	Ser	Asp	Leu
Ile 2375	Asn	Thr	Ser	Ile	Ala	Ser 2380	Ser	Thr	Met	Asp	Val 2385	Thr	Lys	Thr
Ala 2390	Ser	Ile	Ser	Pro	Thr	Ser 2395	Ile	Ser	Gly	Met	Thr 2400	Ala	Ser	Ser
Ser 2405	Pro	Ser	Leu	Phe	Ser	Ser 2410	Asp	Arg	Pro	Gln	Val 2415	Pro	Thr	Ser
Thr 2420	Thr	Glu	Thr	Asn	Thr	Ala 2425	Thr	Ser	Pro	Ser	Val 2430	Ser	Ser	Asn
Thr 2435	Tyr	Ser	Leu	Asp	Gly	Gly 2440	Ser	Asn	Val	Gly	Gly 2445	Thr	Pro	Ser
Thr 2450	Leu	Pro	Pro	Phe	Thr	Ile 2455	Thr	His	Pro	Val	Glu 2460	Thr	Ser	Ser
Ala 2465	Leu	Leu	Ala	Trp	Ser	Arg 2470	Pro	Val	Arg	Thr	Phe 2475	Ser	Thr	Met
Val 2480	Ser	Thr	Asp	Thr	Ala	Ser 2485	Gly	Glu	Asn	Pro	Thr 2490	Ser	Ser	Asn
Ser 2495	Val	Val	Thr	Ser	Val	Pro 2500	Ala	Pro	Gly	Thr	Trp 2505	Thr	Ser	Val
Gly	Ser	Thr	Thr	Asp	Leu	Pro	Ala	Met	Gly	Phe	Leu	Lys	Thr	Ser

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2510	2515	2520
Pro Ala Gly Glu Ala His Ser Leu Leu Ala Ser Thr Ile Glu Pro		
2525	2530	2535
Ala Thr Ala Phe Thr Pro His Leu Ser Ala Ala Val Val Thr Gly		
2540	2545	2550
Ser Ser Ala Thr Ser Glu Ala Ser Leu Leu Thr Thr Ser Glu Ser		
2555	2560	2565
Lys Ala Ile His Ser Ser Pro Gln Thr Pro Thr Thr Pro Thr Ser		
2570	2575	2580
Gly Ala Asn Trp Glu Thr Ser Ala Thr Pro Glu Ser Leu Leu Val		
2585	2590	2595
Val Thr Glu Thr Ser Asp Thr Thr Leu Thr Ser Lys Ile Leu Val		
2600	2605	2610
Thr Asp Thr Ile Leu Phe Ser Thr Val Ser Thr Pro Pro Ser Lys		
2615	2620	2625
Phe Pro Ser Thr Gly Thr Leu Ser Gly Ala Ser Phe Pro Thr Leu		
2630	2635	2640
Leu Pro Asp Thr Pro Ala Ile Pro Leu Thr Ala Thr Glu Pro Thr		
2645	2650	2655
Ser Ser Leu Ala Thr Ser Phe Asp Ser Thr Pro Leu Val Thr Ile		
2660	2665	2670
Ala Ser Asp Ser Leu Gly Thr Val Pro Glu Thr Thr Leu Thr Met		
2675	2680	2685
Ser Glu Thr Ser Asn Gly Asp Ala Leu Val Leu Lys Thr Val Ser		
2690	2695	2700
Asn Pro Asp Arg Ser Ile Pro Gly Ile Thr Ile Gln Gly Val Thr		
2705	2710	2715
Glu Ser Pro Leu His Pro Ser Ser Thr Ser Pro Ser Lys Ile Val		
2720	2725	2730
Ala Pro Arg Asn Thr Thr Tyr Glu Gly Ser Ile Thr Val Ala Leu		
2735	2740	2745
Ser Thr Leu Pro Ala Gly Thr Thr Gly Ser Leu Val Phe Ser Gln		
2750	2755	2760
Ser Ser Glu Asn Ser Glu Thr Thr Ala Leu Val Asp Ser Ser Ala		
2765	2770	2775
Gly Leu Glu Arg Ala Ser Val Met Pro Leu Thr Thr Gly Ser Gln		
2780	2785	2790
Gly Met Ala Ser Ser Gly Gly Ile Arg Ser Gly Ser Thr His Ser		
2795	2800	2805
Thr Gly Thr Lys Thr Phe Ser Ser Leu Pro Leu Thr Met Asn Pro		
2810	2815	2820
Gly Glu Val Thr Ala Met Ser Glu Ile Thr Thr Asn Arg Leu Thr		
2825	2830	2835
Ala Thr Gln Ser Thr Ala Pro Lys Gly Ile Pro Val Lys Pro Thr		
2840	2845	2850
Ser Ala Glu Ser Gly Leu Leu Thr Pro Val Ser Ala Ser Ser Ser		
2855	2860	2865
Pro Ser Lys Ala Phe Ala Ser Leu Thr Thr Ala Pro Pro Thr Trp		
2870	2875	2880
Gly Ile Pro Gln Ser Thr Leu Thr Phe Glu Phe Ser Glu Val Pro		
2885	2890	2895

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Ser Leu Asp Thr Lys Ser Ala	Ser Leu Pro Thr Pro Gly Gln Ser
2900	2905 2910
Leu Asn Thr Ile Pro Asp Ser	Asp Ala Ser Thr Ala Ser Ser Ser
2915	2920 2925
Leu Ser Lys Ser Pro Glu Lys	Asn Pro Arg Ala Arg Met Met Thr
2930	2935 2940
Ser Thr Lys Ala Ile Ser Ala	Ser Ser Phe Gln Ser Thr Gly Phe
2945	2950 2955
Thr Glu Thr Pro Glu Gly Ser	Ala Ser Pro Ser Met Ala Gly His
2960	2965 2970
Glu Pro Arg Val Pro Thr Ser	Gly Thr Gly Asp Pro Arg Tyr Ala
2975	2980 2985
Ser Glu Ser Met Ser Tyr Pro	Asp Pro Ser Lys Ala Ser Ser Ala
2990	2995 3000
Met Thr Ser Thr Ser Leu Ala	Ser Lys Leu Thr Thr Leu Phe Ser
3005	3010 3015
Thr Gly Gln Ala Ala Arg Ser	Gly Ser Ser Ser Ser Pro Ile Ser
3020	3025 3030
Leu Ser Thr Glu Lys Glu Thr	Ser Phe Leu Ser Pro Thr Ala Ser
3035	3040 3045
Thr Ser Arg Lys Thr Ser Leu	Phe Leu Gly Pro Ser Met Ala Arg
3050	3055 3060
Gln Pro Asn Ile Leu Val His	Leu Gln Thr Ser Ala Leu Thr Leu
3065	3070 3075
Ser Pro Thr Ser Thr Leu Asn	Met Ser Gln Glu Glu Pro Pro Glu
3080	3085 3090
Leu Thr Ser Ser Gln Thr Ile	Ala Glu Glu Glu Gly Thr Thr Ala
3095	3100 3105
Glu Thr Gln Thr Leu Thr Phe	Thr Pro Ser Glu Thr Pro Thr Ser
3110	3115 3120
Leu Leu Pro Val Ser Ser Pro	Thr Glu Pro Thr Ala Arg Arg Lys
3125	3130 3135
Ser Ser Pro Glu Thr Trp Ala	Ser Ser Ile Ser Val Pro Ala Lys
3140	3145 3150
Thr Ser Leu Val Glu Thr Thr	Asp Gly Thr Leu Val Thr Thr Ile
3155	3160 3165
Lys Met Ser Ser Gln Ala Ala	Gln Gly Asn Ser Thr Trp Pro Ala
3170	3175 3180
Pro Ala Glu Glu Thr Gly Ser	Ser Pro Ala Gly Thr Ser Pro Gly
3185	3190 3195
Ser Pro Glu Met Ser Thr Thr	Leu Lys Ile Met Ser Ser Lys Glu
3200	3205 3210
Pro Ser Ile Ser Pro Glu Ile	Arg Ser Thr Val Arg Asn Ser Pro
3215	3220 3225
Trp Lys Thr Pro Glu Thr Thr	Val Pro Met Glu Thr Thr Val Glu
3230	3235 3240
Pro Val Thr Leu Gln Ser Thr	Ala Leu Gly Ser Gly Ser Thr Ser
3245	3250 3255
Ile Ser His Leu Pro Thr Gly	Thr Thr Ser Pro Thr Lys Ser Pro
3260	3265 3270

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Thr	Glu	Asn	Met	Leu	Ala	Thr	Glu	Arg	Val	Ser	Leu	Ser	Pro	Ser
3275						3280					3285			
Pro	Pro	Glu	Ala	Trp	Thr	Asn	Leu	Tyr	Ser	Gly	Thr	Pro	Gly	Gly
3290						3295					3300			
Thr	Arg	Gln	Ser	Leu	Ala	Thr	Met	Ser	Ser	Val	Ser	Leu	Glu	Ser
3305						3310					3315			
Pro	Thr	Ala	Arg	Ser	Ile	Thr	Gly	Thr	Gly	Gln	Gln	Ser	Ser	Pro
3320						3325					3330			
Glu	Leu	Val	Ser	Lys	Thr	Thr	Gly	Met	Glu	Phe	Ser	Met	Trp	His
3335						3340					3345			
Gly	Ser	Thr	Gly	Gly	Thr	Thr	Gly	Asp	Thr	His	Val	Ser	Leu	Ser
3350						3355					3360			
Thr	Ser	Ser	Asn	Ile	Leu	Glu	Asp	Pro	Val	Thr	Ser	Pro	Asn	Ser
3365						3370					3375			
Val	Ser	Ser	Leu	Thr	Asp	Lys	Ser	Lys	His	Lys	Thr	Glu	Thr	Trp
3380						3385					3390			
Val	Ser	Thr	Thr	Ala	Ile	Pro	Ser	Thr	Val	Leu	Asn	Asn	Lys	Ile
3395						3400					3405			
Met	Ala	Ala	Glu	Gln	Gln	Thr	Ser	Arg	Ser	Val	Asp	Glu	Ala	Tyr
3410						3415					3420			
Ser	Ser	Thr	Ser	Ser	Trp	Ser	Asp	Gln	Thr	Ser	Gly	Ser	Asp	Ile
3425						3430					3435			
Thr	Leu	Gly	Ala	Ser	Pro	Asp	Val	Thr	Asn	Thr	Leu	Tyr	Ile	Thr
3440						3445					3450			
Ser	Thr	Ala	Gln	Thr	Thr	Ser	Leu	Val	Ser	Leu	Pro	Ser	Gly	Asp
3455						3460					3465			
Gln	Gly	Ile	Thr	Ser	Leu	Thr	Asn	Pro	Ser	Gly	Gly	Lys	Thr	Ser
3470						3475					3480			
Ser	Ala	Ser	Ser	Val	Thr	Ser	Pro	Ser	Ile	Gly	Leu	Glu	Thr	Leu
3485						3490					3495			
Arg	Ala	Asn	Val	Ser	Ala	Val	Lys	Ser	Asp	Ile	Ala	Pro	Thr	Ala
3500						3505					3510			
Gly	His	Leu	Ser	Gln	Thr	Ser	Ser	Pro	Ala	Glu	Val	Ser	Ile	Leu
3515						3520					3525			
Asp	Val	Thr	Thr	Ala	Pro	Thr	Pro	Gly	Ile	Ser	Thr	Thr	Ile	Thr
3530						3535					3540			
Thr	Met	Gly	Thr	Asn	Ser	Ile	Ser	Thr	Thr	Thr	Pro	Asn	Pro	Glu
3545						3550					3555			
Val	Gly	Met	Ser	Thr	Met	Asp	Ser	Thr	Pro	Ala	Thr	Glu	Arg	Arg
3560						3565					3570			
Thr	Thr	Ser	Thr	Glu	His	Pro	Ser	Thr	Trp	Ser	Ser	Thr	Ala	Ala
3575						3580					3585			
Ser	Asp	Ser	Trp	Thr	Val	Thr	Asp	Met	Thr	Ser	Asn	Leu	Lys	Val
3590						3595					3600			
Ala	Arg	Ser	Pro	Gly	Thr	Ile	Ser	Thr	Met	His	Thr	Thr	Ser	Phe
3605						3610					3615			
Leu	Ala	Ser	Ser	Thr	Glu	Leu	Asp	Ser	Met	Ser	Thr	Pro	His	Gly
3620						3625					3630			
Arg	Ile	Thr	Val	Ile	Gly	Thr	Ser	Leu	Val	Thr	Pro	Ser	Ser	Asp
3635						3640					3645			
Ala	Ser	Ala	Val	Lys	Thr	Glu	Thr	Ser	Thr	Ser	Glu	Arg	Thr	Leu

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3650	3655	3660
Ser Pro Ser Asp Thr Thr Ala	Ser Thr Pro Ile Ser Thr Phe Ser	
3665	3670	3675
Arg Val Gln Arg Met Ser Ile	Ser Val Pro Asp Ile Leu Ser Thr	
3680	3685	3690
Ser Trp Thr Pro Ser Ser Thr	Glu Ala Glu Asp Val Pro Val Ser	
3695	3700	3705
Met Val Ser Thr Asp His Ala	Ser Thr Lys Thr Asp Pro Asn Thr	
3710	3715	3720
Pro Leu Ser Thr Phe Leu Phe	Asp Ser Leu Ser Thr Leu Asp Trp	
3725	3730	3735
Asp Thr Gly Arg Ser Leu Ser	Ser Ala Thr Ala Thr Thr Ser Ala	
3740	3745	3750
Pro Gln Gly Ala Thr Thr Pro	Gln Glu Leu Thr Leu Glu Thr Met	
3755	3760	3765
Ile Ser Pro Ala Thr Ser Gln	Leu Pro Phe Ser Ile Gly His Ile	
3770	3775	3780
Thr Ser Ala Val Thr Pro Ala	Ala Met Ala Arg Ser Ser Gly Val	
3785	3790	3795
Thr Phe Ser Arg Pro Asp Pro	Thr Ser Lys Lys Ala Glu Gln Thr	
3800	3805	3810
Ser Thr Gln Leu Pro Thr Thr	Thr Ser Ala His Pro Gly Gln Val	
3815	3820	3825
Pro Arg Ser Ala Ala Thr Thr	Leu Asp Val Ile Pro His Thr Ala	
3830	3835	3840
Lys Thr Pro Asp Ala Thr Phe	Gln Arg Gln Gly Gln Thr Ala Leu	
3845	3850	3855
Thr Thr Glu Ala Arg Ala Thr	Ser Asp Ser Trp Asn Glu Lys Glu	
3860	3865	3870
Lys Ser Thr Pro Ser Ala Pro	Trp Ile Thr Glu Met Met Asn Ser	
3875	3880	3885
Val Ser Glu Asp Thr Ile Lys	Glu Val Thr Ser Ser Ser Ser Val	
3890	3895	3900
Leu Arg Thr Leu Asn Thr Leu	Asp Ile Asn Leu Glu Ser Gly Thr	
3905	3910	3915
Thr Ser Ser Pro Ser Trp Lys	Ser Ser Pro Tyr Glu Arg Ile Ala	
3920	3925	3930
Pro Ser Glu Ser Thr Thr Asp	Lys Glu Ala Ile His Pro Ser Thr	
3935	3940	3945
Asn Thr Val Glu Thr Thr Gly	Trp Val Thr Ser Ser Glu His Ala	
3950	3955	3960
Ser His Ser Thr Ile Pro Ala	His Ser Ala Ser Ser Lys Leu Thr	
3965	3970	3975
Ser Pro Val Val Thr Thr Ser	Thr Arg Glu Gln Ala Ile Val Ser	
3980	3985	3990
Met Ser Thr Thr Thr Trp Pro	Glu Ser Thr Arg Ala Arg Thr Glu	
3995	4000	4005
Pro Asn Ser Phe Leu Thr Ile	Glu Leu Arg Asp Val Ser Pro Tyr	
4010	4015	4020
Met Asp Thr Ser Ser Thr Thr	Gln Thr Ser Ile Ile Ser Ser Pro	
4025	4030	4035

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Gly Ser Thr Ala Ile Thr Lys Gly Pro Arg Thr Glu Ile Thr Ser	4040	4045	4050
Ser Lys Arg Ile Ser Ser Ser Phe Leu Ala Gln Ser Met Arg Ser	4055	4060	4065
Ser Asp Ser Pro Ser Glu Ala Ile Thr Arg Leu Ser Asn Phe Pro	4070	4075	4080
Ala Met Thr Glu Ser Gly Gly Met Ile Leu Ala Met Gln Thr Ser	4085	4090	4095
Pro Pro Gly Ala Thr Ser Leu Ser Ala Pro Thr Leu Asp Thr Ser	4100	4105	4110
Ala Thr Ala Ser Trp Thr Gly Thr Pro Leu Ala Thr Thr Gln Arg	4115	4120	4125
Phe Thr Tyr Ser Glu Lys Thr Thr Leu Phe Ser Lys Gly Pro Glu	4130	4135	4140
Asp Thr Ser Gln Pro Ser Pro Pro Ser Val Glu Glu Thr Ser Ser	4145	4150	4155
Ser Ser Ser Leu Val Pro Ile His Ala Thr Thr Ser Pro Ser Asn	4160	4165	4170
Ile Leu Leu Thr Ser Gln Gly His Ser Pro Ser Ser Thr Pro Pro	4175	4180	4185
Val Thr Ser Val Phe Leu Ser Glu Thr Ser Gly Leu Gly Lys Thr	4190	4195	4200
Thr Asp Met Ser Arg Ile Ser Leu Glu Pro Gly Thr Ser Leu Pro	4205	4210	4215
Pro Asn Leu Ser Ser Thr Ala Gly Glu Ala Leu Ser Thr Tyr Glu	4220	4225	4230
Ala Ser Arg Asp Thr Lys Ala Ile His His Ser Ala Asp Thr Ala	4235	4240	4245
Val Thr Asn Met Glu Ala Thr Ser Ser Glu Tyr Ser Pro Ile Pro	4250	4255	4260
Gly His Thr Lys Pro Ser Lys Ala Thr Ser Pro Leu Val Thr Ser	4265	4270	4275
His Ile Met Gly Asp Ile Thr Ser Ser Thr Ser Val Phe Gly Ser	4280	4285	4290
Ser Glu Thr Thr Glu Ile Glu Thr Val Ser Ser Val Asn Gln Gly	4295	4300	4305
Leu Gln Glu Arg Ser Thr Ser Gln Val Ala Ser Ser Ala Thr Glu	4310	4315	4320
Thr Ser Thr Val Ile Thr His Val Ser Ser Gly Asp Ala Thr Thr	4325	4330	4335
His Val Thr Lys Thr Gln Ala Thr Phe Ser Ser Gly Thr Ser Ile	4340	4345	4350
Ser Ser Pro His Gln Phe Ile Thr Ser Thr Asn Thr Phe Thr Asp	4355	4360	4365
Val Ser Thr Asn Pro Ser Thr Ser Leu Ile Met Thr Glu Ser Ser	4370	4375	4380
Gly Val Thr Ile Thr Thr Gln Thr Gly Pro Thr Gly Ala Ala Thr	4385	4390	4395
Gln Gly Pro Tyr Leu Leu Asp Thr Ser Thr Met Pro Tyr Leu Thr	4400	4405	4410

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Glu Thr	Pro Leu Ala Val	Thr	Pro Asp Phe Met	Gln	Ser Glu Lys
4415		4420		4425	
Thr Thr	Leu Ile Ser Lys	Gly	Pro Lys Asp Val Ser	Trp Thr Ser	
4430		4435		4440	
Pro Pro	Ser Val Ala Glu Thr	Ser Tyr Pro Ser	Ser	Leu Thr Pro	
4445		4450		4455	
Phe Leu	Val Thr Thr Ile	Pro	Pro Ala Thr Ser	Thr	Leu Gln Gly
4460		4465		4470	
Gln His	Thr Ser Ser Pro	Val	Ser Ala Thr Ser	Val	Leu Thr Ser
4475		4480		4485	
Gly Leu	Val Lys Thr Thr	Asp	Met Leu Asn Thr	Ser	Met Glu Pro
4490		4495		4500	
Val Thr	Asn Ser Pro Gln	Asn	Leu Asn Asn Pro	Ser	Asn Glu Ile
4505		4510		4515	
Leu Ala	Thr Leu Ala Ala	Thr	Thr Asp Ile Glu Thr	Ile His Pro	
4520		4525		4530	
Ser Ile	Asn Lys Ala Val	Thr	Asn Met Gly Thr	Ala	Ser Ser Ala
4535		4540		4545	
His Val	Leu His Ser Thr	Leu	Pro Val Ser Ser	Glu	Pro Ser Thr
4550		4555		4560	
Ala Thr	Ser Pro Met Val	Pro	Ala Ser Ser Met	Gly	Asp Ala Leu
4565		4570		4575	
Ala Ser	Ile Ser Ile Pro	Gly	Ser Glu Thr Thr	Asp	Ile Glu Gly
4580		4585		4590	
Glu Pro	Thr Ser Ser Leu	Thr	Ala Gly Arg Lys	Glu	Asn Ser Thr
4595		4600		4605	
Leu Gln	Glu Met Asn Ser	Thr	Thr Glu Ser Asn	Ile	Ile Leu Ser
4610		4615		4620	
Asn Val	Ser Val Gly Ala	Ile	Thr Glu Ala Thr	Lys	Met Glu Val
4625		4630		4635	
Pro Ser	Phe Asp Ala Thr	Phe	Ile Pro Thr Pro	Ala	Gln Ser Thr
4640		4645		4650	
Lys Phe	Pro Asp Ile Phe	Ser	Val Ala Ser Ser	Arg	Leu Ser Asn
4655		4660		4665	
Ser Pro	Pro Met Thr Ile	Ser	Thr His Met Thr	Thr	Thr Gln Thr
4670		4675		4680	
Gly Ser	Ser Gly Ala Thr	Ser	Lys Ile Pro Leu	Ala	Leu Asp Thr
4685		4690		4695	
Ser Thr	Leu Glu Thr Ser	Ala	Gly Thr Pro Ser	Val	Val Thr Glu
4700		4705		4710	
Gly Phe	Ala His Ser Lys	Ile	Thr Thr Ala Met	Asn	Asn Asp Val
4715		4720		4725	
Lys Asp	Val Ser Gln Thr	Asn	Pro Pro Phe Gln	Asp	Glu Ala Ser
4730		4735		4740	
Ser Pro	Ser Ser Gln Ala	Pro	Val Leu Val Thr	Thr	Leu Pro Ser
4745		4750		4755	
Ser Val	Ala Phe Thr Pro	Gln	Trp His Ser Thr	Ser	Ser Pro Val
4760		4765		4770	
Ser Met	Ser Ser Val Leu	Thr	Ser Ser Leu Val	Lys	Thr Ala Gly
4775		4780		4785	
Lys Val	Asp Thr Ser Leu	Glu	Thr Val Thr Ser	Ser	Pro Gln Ser

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4790	4795	4800
Met Ser Asn Thr Leu Asp Asp Ile Ser Val Thr Ser Ala Ala Thr		
4805	4810	4815
Thr Asp Ile Glu Thr Thr His Pro Ser Ile Asn Thr Val Val Thr		
4820	4825	4830
Asn Val Gly Thr Thr Gly Ser Ala Phe Glu Ser His Ser Thr Val		
4835	4840	4845
Ser Ala Tyr Pro Glu Pro Ser Lys Val Thr Ser Pro Asn Val Thr		
4850	4855	4860
Thr Ser Thr Met Glu Asp Thr Thr Ile Ser Arg Ser Ile Pro Lys		
4865	4870	4875
Ser Ser Lys Thr Thr Arg Thr Glu Thr Glu Thr Thr Ser Ser Leu		
4880	4885	4890
Thr Pro Lys Leu Arg Glu Thr Ser Ile Ser Gln Glu Ile Thr Ser		
4895	4900	4905
Ser Thr Glu Thr Ser Thr Val Pro Tyr Lys Glu Leu Thr Gly Ala		
4910	4915	4920
Thr Thr Glu Val Ser Arg Thr Asp Val Thr Ser Ser Ser Ser Thr		
4925	4930	4935
Ser Phe Pro Gly Pro Asp Gln Ser Thr Val Ser Leu Asp Ile Ser		
4940	4945	4950
Thr Glu Thr Asn Thr Arg Leu Ser Thr Ser Pro Ile Met Thr Glu		
4955	4960	4965
Ser Ala Glu Ile Thr Ile Thr Thr Gln Thr Gly Pro His Gly Ala		
4970	4975	4980
Thr Ser Gln Asp Thr Phe Thr Met Asp Pro Ser Asn Thr Thr Pro		
4985	4990	4995
Gln Ala Gly Ile His Ser Ala Met Thr His Gly Phe Ser Gln Leu		
5000	5005	5010
Asp Val Thr Thr Leu Met Ser Arg Ile Pro Gln Asp Val Ser Trp		
5015	5020	5025
Thr Ser Pro Pro Ser Val Asp Lys Thr Ser Ser Pro Ser Ser Phe		
5030	5035	5040
Leu Ser Ser Pro Ala Met Thr Thr Pro Ser Leu Ile Ser Ser Thr		
5045	5050	5055
Leu Pro Glu Asp Lys Leu Ser Ser Pro Met Thr Ser Leu Leu Thr		
5060	5065	5070
Ser Gly Leu Val Lys Ile Thr Asp Ile Leu Arg Thr Arg Leu Glu		
5075	5080	5085
Pro Val Thr Ser Ser Leu Pro Asn Phe Ser Ser Thr Ser Asp Lys		
5090	5095	5100
Ile Leu Ala Thr Ser Lys Asp Ser Lys Asp Thr Lys Glu Ile Phe		
5105	5110	5115
Pro Ser Ile Asn Thr Glu Glu Thr Asn Val Lys Ala Asn Asn Ser		
5120	5125	5130
Gly His Glu Ser His Ser Pro Ala Leu Ala Asp Ser Glu Thr Pro		
5135	5140	5145
Lys Ala Thr Thr Gln Met Val Ile Thr Thr Thr Val Gly Asp Pro		
5150	5155	5160
Ala Pro Ser Thr Ser Met Pro Val His Gly Ser Ser Glu Thr Thr		
5165	5170	5175

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Asn Ile	Lys Arg	Glu Pro	Thr	Tyr Phe	Leu Thr	Pro	Arg Leu	Arg
5180			5185			5190		
Glu Thr	Ser Thr	Ser Gln	Glu	Ser Ser	Phe Pro	Thr	Asp Thr	Ser
5195			5200			5205		
Phe Leu	Leu Ser	Lys Val	Pro	Thr Gly	Thr Ile	Thr	Glu Val	Ser
5210			5215			5220		
Ser Thr	Gly Val	Asn Ser	Ser	Ser Lys	Ile Ser	Thr	Pro Asp	His
5225			5230			5235		
Asp Lys	Ser Thr	Val Pro	Pro	Asp Thr	Phe Thr	Gly	Glu Ile	Pro
5240			5245			5250		
Arg Val	Phe Thr	Ser Ser	Ile	Lys Thr	Lys Ser	Ala	Glu Met	Thr
5255			5260			5265		
Ile Thr	Thr Gln	Ala Ser	Pro	Pro Glu	Ser Ala	Ser	His Ser	Thr
5270			5275			5280		
Leu Pro	Leu Asp	Thr Ser	Thr	Thr Leu	Ser Gln	Gly	Gly Thr	His
5285			5290			5295		
Ser Thr	Val Thr	Gln Gly	Phe	Pro Tyr	Ser Glu	Val	Thr Thr	Leu
5300			5305			5310		
Met Gly	Met Gly	Pro Gly	Asn	Val Ser	Trp Met	Thr	Thr Pro	Pro
5315			5320			5325		
Val Glu	Glu Thr	Ser Ser	Val	Ser Ser	Leu Met	Ser	Ser Pro	Ala
5330			5335			5340		
Met Thr	Ser Pro	Ser Pro	Val	Ser Ser	Thr Ser	Pro	Gln Ser	Ile
5345			5350			5355		
Pro Ser	Ser Pro	Leu Pro	Val	Thr Ala	Leu Pro	Thr	Ser Val	Leu
5360			5365			5370		
Val Thr	Thr Thr	Asp Val	Leu	Gly Thr	Thr Ser	Pro	Glu Ser	Val
5375			5380			5385		
Thr Ser	Ser Pro	Pro Asn	Leu	Ser Ser	Ile Thr	His	Glu Arg	Pro
5390			5395			5400		
Ala Thr	Tyr Lys	Asp Thr	Ala	His Thr	Glu Ala	Ala	Met His	His
5405			5410			5415		
Ser Thr	Asn Thr	Ala Val	Thr	Asn Val	Gly Thr	Ser	Gly Ser	Gly
5420			5425			5430		
His Lys	Ser Gln	Ser Ser	Val	Leu Ala	Asp Ser	Glu	Thr Ser	Lys
5435			5440			5445		
Ala Thr	Pro Leu	Met Ser	Thr	Thr Ser	Thr Leu	Gly	Asp Thr	Ser
5450			5455			5460		
Val Ser	Thr Ser	Thr Pro	Asn	Ile Ser	Gln Thr	Asn	Gln Ile	Gln
5465			5470			5475		
Thr Glu	Pro Thr	Ala Ser	Leu	Ser Pro	Arg Leu	Arg	Glu Ser	Ser
5480			5485			5490		
Thr Ser	Glu Lys	Thr Ser	Ser	Thr Thr	Glu Thr	Asn	Thr Ala	Phe
5495			5500			5505		
Ser Tyr	Val Pro	Thr Gly	Ala	Ile Thr	Gln Ala	Ser	Arg Thr	Glu
5510			5515			5520		
Ile Ser	Ser Ser	Arg Thr	Ser	Ile Ser	Asp Leu	Asp	Arg Pro	Thr
5525			5530			5535		
Ile Ala	Pro Asp	Ile Ser	Thr	Gly Met	Ile Thr	Arg	Leu Phe	Thr
5540			5545			5550		

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Ser	Pro	Ile	Met	Thr	Lys	Ser	Ala	Glu	Met	Thr	Val	Thr	Thr	Gln
5555						5560					5565			
Thr	Thr	Thr	Pro	Gly	Ala	Thr	Ser	Gln	Gly	Ile	Leu	Pro	Trp	Asp
5570						5575					5580			
Thr	Ser	Thr	Thr	Leu	Phe	Gln	Gly	Gly	Thr	His	Ser	Thr	Val	Ser
5585						5590					5595			
Gln	Gly	Phe	Pro	His	Ser	Glu	Ile	Thr	Thr	Leu	Arg	Ser	Arg	Thr
5600						5605					5610			
Pro	Gly	Asp	Val	Ser	Trp	Met	Thr	Thr	Pro	Pro	Val	Glu	Glu	Thr
5615						5620					5625			
Ser	Ser	Gly	Phe	Ser	Leu	Met	Ser	Pro	Ser	Met	Thr	Ser	Pro	Ser
5630						5635					5640			
Pro	Val	Ser	Ser	Thr	Ser	Pro	Glu	Ser	Ile	Pro	Ser	Ser	Pro	Leu
5645						5650					5655			
Pro	Val	Thr	Ala	Leu	Leu	Thr	Ser	Val	Leu	Val	Thr	Thr	Thr	Asn
5660						5665					5670			
Val	Leu	Gly	Thr	Thr	Ser	Pro	Glu	Pro	Val	Thr	Ser	Ser	Pro	Pro
5675						5680					5685			
Asn	Leu	Ser	Ser	Pro	Thr	Gln	Glu	Arg	Leu	Thr	Thr	Tyr	Lys	Asp
5690						5695					5700			
Thr	Ala	His	Thr	Glu	Ala	Met	His	Ala	Ser	Met	His	Thr	Asn	Thr
5705						5710					5715			
Ala	Val	Ala	Asn	Val	Gly	Thr	Ser	Ile	Ser	Gly	His	Glu	Ser	Gln
5720						5725					5730			
Ser	Ser	Val	Pro	Ala	Asp	Ser	His	Thr	Ser	Lys	Ala	Thr	Ser	Pro
5735						5740					5745			
Met	Gly	Ile	Thr	Phe	Ala	Met	Gly	Asp	Thr	Ser	Val	Ser	Thr	Ser
5750						5755					5760			
Thr	Pro	Ala	Phe	Phe	Glu	Thr	Arg	Ile	Gln	Thr	Glu	Ser	Thr	Ser
5765						5770					5775			
Ser	Leu	Ile	Pro	Gly	Leu	Arg	Asp	Thr	Arg	Thr	Ser	Glu	Glu	Ile
5780						5785					5790			
Asn	Thr	Val	Thr	Glu	Thr	Ser	Thr	Val	Leu	Ser	Glu	Val	Pro	Thr
5795						5800					5805			
Thr	Thr	Thr	Thr	Glu	Val	Ser	Arg	Thr	Glu	Val	Ile	Thr	Ser	Ser
5810						5815					5820			
Arg	Thr	Thr	Ile	Ser	Gly	Pro	Asp	His	Ser	Lys	Met	Ser	Pro	Tyr
5825						5830					5835			
Ile	Ser	Thr	Glu	Thr	Ile	Thr	Arg	Leu	Ser	Thr	Phe	Pro	Phe	Val
5840						5845					5850			
Thr	Gly	Ser	Thr	Glu	Met	Ala	Ile	Thr	Asn	Gln	Thr	Gly	Pro	Ile
5855						5860					5865			
Gly	Thr	Ile	Ser	Gln	Ala	Thr	Leu	Thr	Leu	Asp	Thr	Ser	Ser	Thr
5870						5875					5880			
Ala	Ser	Trp	Glu	Gly	Thr	His	Ser	Pro	Val	Thr	Gln	Arg	Phe	Pro
5885						5890					5895			
His	Ser	Glu	Glu	Thr	Thr	Thr	Met	Ser	Arg	Ser	Thr	Lys	Gly	Val
5900						5905					5910			
Ser	Trp	Gln	Ser	Pro	Pro	Ser	Val	Glu	Glu	Thr	Ser	Ser	Pro	Ser
5915						5920					5925			
Ser	Pro	Val	Pro	Leu	Pro	Ala	Ile	Thr	Ser	His	Ser	Ser	Leu	Tyr

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5930	5935	5940
Ser Ala Val Ser Gly Ser Ser Pro Thr Ser Ala Leu Pro Val Thr		
5945	5950	5955
Ser Leu Leu Thr Ser Gly Arg Arg Lys Thr Ile Asp Met Leu Asp		
5960	5965	5970
Thr His Ser Glu Leu Val Thr Ser Ser Leu Pro Ser Ala Ser Ser		
5975	5980	5985
Phe Ser Gly Glu Ile Leu Thr Ser Glu Ala Ser Thr Asn Thr Glu		
5990	5995	6000
Thr Ile His Phe Ser Glu Asn Thr Ala Glu Thr Asn Met Gly Thr		
6005	6010	6015
Thr Asn Ser Met His Lys Leu His Ser Ser Val Ser Ile His Ser		
6020	6025	6030
Gln Pro Ser Gly His Thr Pro Pro Lys Val Thr Gly Ser Met Met		
6035	6040	6045
Glu Asp Ala Ile Val Ser Thr Ser Thr Pro Gly Ser Pro Glu Thr		
6050	6055	6060
Lys Asn Val Asp Arg Asp Ser Thr Ser Pro Leu Thr Pro Glu Leu		
6065	6070	6075
Lys Glu Asp Ser Thr Ala Leu Val Met Asn Ser Thr Thr Glu Ser		
6080	6085	6090
Asn Thr Val Phe Ser Ser Val Ser Leu Asp Ala Ala Thr Glu Val		
6095	6100	6105
Ser Arg Ala Glu Val Thr Tyr Tyr Asp Pro Thr Phe Met Pro Ala		
6110	6115	6120
Ser Ala Gln Ser Thr Lys Ser Pro Asp Ile Ser Pro Glu Ala Ser		
6125	6130	6135
Ser Ser His Ser Asn Ser Pro Pro Leu Thr Ile Ser Thr His Lys		
6140	6145	6150
Thr Ile Ala Thr Gln Thr Gly Pro Ser Gly Val Thr Ser Leu Gly		
6155	6160	6165
Gln Leu Thr Leu Asp Thr Ser Thr Ile Ala Thr Ser Ala Gly Thr		
6170	6175	6180
Pro Ser Ala Arg Thr Gln Asp Phe Val Asp Ser Glu Thr Thr Ser		
6185	6190	6195
Val Met Asn Asn Asp Leu Asn Asp Val Leu Lys Thr Ser Pro Phe		
6200	6205	6210
Ser Ala Glu Glu Ala Asn Ser Leu Ser Ser Gln Ala Pro Leu Leu		
6215	6220	6225
Val Thr Thr Ser Pro Ser Pro Val Thr Ser Thr Leu Gln Glu His		
6230	6235	6240
Ser Thr Ser Ser Leu Val Ser Val Thr Ser Val Pro Thr Pro Thr		
6245	6250	6255
Leu Ala Lys Ile Thr Asp Met Asp Thr Asn Leu Glu Pro Val Thr		
6260	6265	6270
Arg Ser Pro Gln Asn Leu Arg Asn Thr Leu Ala Thr Ser Glu Ala		
6275	6280	6285
Thr Thr Asp Thr His Thr Met His Pro Ser Ile Asn Thr Ala Val		
6290	6295	6300
Ala Asn Val Gly Thr Thr Ser Ser Pro Asn Glu Phe Tyr Phe Thr		
6305	6310	6315

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Val Ser	Pro Asp Ser Asp	Pro Tyr Lys Ala Thr	Ser Ala Val Val
6320		6325	6330
Ile Thr	Ser Thr Ser Gly Asp	Ser Ile Val Ser Thr	Ser Met Pro
6335		6340	6345
Arg Ser	Ser Ala Met Lys Lys	Ile Glu Ser Glu Thr	Thr Phe Ser
6350		6355	6360
Leu Ile	Phe Arg Leu Arg Glu	Thr Ser Thr Ser Gln	Lys Ile Gly
6365		6370	6375
Ser Ser	Ser Asp Thr Ser Thr	Val Phe Asp Lys Ala	Phe Thr Ala
6380		6385	6390
Ala Thr	Thr Glu Val Ser Arg	Thr Glu Leu Thr Ser	Ser Ser Arg
6395		6400	6405
Thr Ser	Ile Gln Gly Thr Glu	Lys Pro Thr Met Ser	Pro Asp Thr
6410		6415	6420
Ser Thr	Arg Ser Val Thr Met	Leu Ser Thr Phe Ala	Gly Leu Thr
6425		6430	6435
Lys Ser	Glu Glu Arg Thr Ile	Ala Thr Gln Thr Gly	Pro His Arg
6440		6445	6450
Ala Thr	Ser Gln Gly Thr Leu	Thr Trp Asp Thr Ser	Ile Thr Thr
6455		6460	6465
Ser Gln	Ala Gly Thr His Ser	Ala Met Thr His Gly	Phe Ser Gln
6470		6475	6480
Leu Asp	Leu Ser Thr Leu Thr	Ser Arg Val Pro Glu	Tyr Ile Ser
6485		6490	6495
Gly Thr	Ser Pro Pro Ser Val	Glu Lys Thr Ser Ser	Ser Ser Ser
6500		6505	6510
Leu Leu	Ser Leu Pro Ala Ile	Thr Ser Pro Ser Pro	Val Pro Thr
6515		6520	6525
Thr Leu	Pro Glu Ser Arg Pro	Ser Ser Pro Val His	Leu Thr Ser
6530		6535	6540
Leu Pro	Thr Ser Gly Leu Val	Lys Thr Thr Asp Met	Leu Ala Ser
6545		6550	6555
Val Ala	Ser Leu Pro Pro Asn	Leu Gly Ser Thr Ser	His Lys Ile
6560		6565	6570
Pro Thr	Thr Ser Glu Asp Ile	Lys Asp Thr Glu Lys	Met Tyr Pro
6575		6580	6585
Ser Thr	Asn Ile Ala Val Thr	Asn Val Gly Thr Thr	Thr Ser Glu
6590		6595	6600
Lys Glu	Ser Tyr Ser Ser Val	Pro Ala Tyr Ser Glu	Pro Pro Lys
6605		6610	6615
Val Thr	Ser Pro Met Val Thr	Ser Phe Asn Ile Arg	Asp Thr Ile
6620		6625	6630
Val Ser	Thr Ser Met Pro Gly	Ser Ser Glu Ile Thr	Arg Ile Glu
6635		6640	6645
Met Glu	Ser Thr Phe Ser Leu	Ala His Gly Leu Lys	Gly Thr Ser
6650		6655	6660
Thr Ser	Gln Asp Pro Ile Val	Ser Thr Glu Lys Ser	Ala Val Leu
6665		6670	6675
His Lys	Leu Thr Thr Gly Ala	Thr Glu Thr Ser Arg	Thr Glu Val
6680		6685	6690

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Ala 6695	Ser	Ser	Arg	Arg	Thr	Ser 6700	Ile	Pro	Gly	Pro	Asp 6705	His	Ser	Thr
Glu 6710	Ser	Pro	Asp	Ile	Ser	Thr 6715	Glu	Val	Ile	Pro	Ser 6720	Leu	Pro	Ile
Ser 6725	Leu	Gly	Ile	Thr	Glu	Ser 6730	Ser	Asn	Met	Thr	Ile 6735	Ile	Thr	Arg
Thr 6740	Gly	Pro	Pro	Leu	Gly	Ser 6745	Thr	Ser	Gln	Gly	Thr 6750	Phe	Thr	Leu
Asp 6755	Thr	Pro	Thr	Thr	Ser	Ser 6760	Arg	Ala	Gly	Thr	His 6765	Ser	Met	Ala
Thr 6770	Gln	Glu	Phe	Pro	His	Ser 6775	Glu	Met	Thr	Thr	Val 6780	Met	Asn	Lys
Asp 6785	Pro	Glu	Ile	Leu	Ser	Trp 6790	Thr	Ile	Pro	Pro	Ser 6795	Ile	Glu	Lys
Thr 6800	Ser	Phe	Ser	Ser	Ser	Leu 6805	Met	Pro	Ser	Pro	Ala 6810	Met	Thr	Ser
Pro 6815	Pro	Val	Ser	Ser	Thr	Leu 6820	Pro	Lys	Thr	Ile	His 6825	Thr	Thr	Pro
Ser 6830	Pro	Met	Thr	Ser	Leu	Leu 6835	Thr	Pro	Ser	Leu	Val 6840	Met	Thr	Thr
Asp 6845	Thr	Leu	Gly	Thr	Ser	Pro 6850	Glu	Pro	Thr	Thr	Ser 6855	Ser	Pro	Pro
Asn 6860	Leu	Ser	Ser	Thr	Ser	His 6865	Glu	Ile	Leu	Thr	Thr 6870	Asp	Glu	Asp
Thr 6875	Thr	Ala	Ile	Glu	Ala	Met 6880	His	Pro	Ser	Thr	Ser 6885	Thr	Ala	Ala
Thr 6890	Asn	Val	Glu	Thr	Thr	Ser 6895	Ser	Gly	His	Gly	Ser 6900	Gln	Ser	Ser
Val 6905	Leu	Ala	Asp	Ser	Glu	Lys 6910	Thr	Lys	Ala	Thr	Ala 6915	Pro	Met	Asp
Thr 6920	Thr	Ser	Thr	Met	Gly	His 6925	Thr	Thr	Val	Ser	Thr 6930	Ser	Met	Ser
Val 6935	Ser	Ser	Glu	Thr	Thr	Lys 6940	Ile	Lys	Arg	Glu	Ser 6945	Thr	Tyr	Ser
Leu 6950	Thr	Pro	Gly	Leu	Arg	Glu 6955	Thr	Ser	Ile	Ser	Gln 6960	Asn	Ala	Ser
Phe 6965	Ser	Thr	Asp	Thr	Ser	Ile 6970	Val	Leu	Ser	Glu	Val 6975	Pro	Thr	Gly
Thr 6980	Thr	Ala	Glu	Val	Ser	Arg 6985	Thr	Glu	Val	Thr	Ser 6990	Ser	Gly	Arg
Thr 6995	Ser	Ile	Pro	Gly	Pro	Ser 7000	Gln	Ser	Thr	Val	Leu 7005	Pro	Glu	Ile
Ser 7010	Thr	Arg	Thr	Met	Thr	Arg 7015	Leu	Phe	Ala	Ser	Pro 7020	Thr	Met	Thr
Glu 7025	Ser	Ala	Glu	Met	Thr	Ile 7030	Pro	Thr	Gln	Thr	Gly 7035	Pro	Ser	Gly
Ser 7040	Thr	Ser	Gln	Asp	Thr	Leu 7045	Thr	Leu	Asp	Thr	Ser 7050	Thr	Thr	Lys
Ser 7055	Gln	Ala	Lys	Thr	His	Ser 7060	Thr	Leu	Thr	Gln	Arg 7065	Phe	Pro	His
Ser 7065	Glu	Met	Thr	Thr	Leu	Met	Ser	Arg	Gly	Pro	Gly	Asp	Met	Ser

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7070	7075	7080
Trp Gln Ser Ser Pro Ser Leu Glu Asn Pro Ser Ser Leu Pro Ser		
7085	7090	7095
Leu Leu Ser Leu Pro Ala Thr Thr Ser Pro Pro Pro Ile Ser Ser		
7100	7105	7110
Thr Leu Pro Val Thr Ile Ser Ser Ser Pro Leu Pro Val Thr Ser		
7115	7120	7125
Leu Leu Thr Ser Ser Pro Val Thr Thr Thr Asp Met Leu His Thr		
7130	7135	7140
Ser Pro Glu Leu Val Thr Ser Ser Pro Pro Lys Leu Ser His Thr		
7145	7150	7155
Ser Asp Glu Arg Leu Thr Thr Gly Lys Asp Thr Thr Asn Thr Glu		
7160	7165	7170
Ala Val His Pro Ser Thr Asn Thr Ala Ala Ser Asn Val Glu Ile		
7175	7180	7185
Pro Ser Ser Gly His Glu Ser Pro Ser Ser Ala Leu Ala Asp Ser		
7190	7195	7200
Glu Thr Ser Lys Ala Thr Ser Pro Met Phe Ile Thr Ser Thr Gln		
7205	7210	7215
Glu Asp Thr Thr Val Ala Ile Ser Thr Pro His Phe Leu Glu Thr		
7220	7225	7230
Ser Arg Ile Gln Lys Glu Ser Ile Ser Ser Leu Ser Pro Lys Leu		
7235	7240	7245
Arg Glu Thr Gly Ser Ser Val Glu Thr Ser Ser Ala Ile Glu Thr		
7250	7255	7260
Ser Ala Val Leu Ser Glu Val Ser Ile Gly Ala Thr Thr Glu Ile		
7265	7270	7275
Ser Arg Thr Glu Val Thr Ser Ser Ser Arg Thr Ser Ile Ser Gly		
7280	7285	7290
Ser Ala Glu Ser Thr Met Leu Pro Glu Ile Ser Thr Thr Arg Lys		
7295	7300	7305
Ile Ile Lys Phe Pro Thr Ser Pro Ile Leu Ala Glu Ser Ser Glu		
7310	7315	7320
Met Thr Ile Lys Thr Gln Thr Ser Pro Pro Gly Ser Thr Ser Glu		
7325	7330	7335
Ser Thr Phe Thr Leu Asp Thr Ser Thr Thr Pro Ser Leu Val Ile		
7340	7345	7350
Thr His Ser Thr Met Thr Gln Arg Leu Pro His Ser Glu Ile Thr		
7355	7360	7365
Thr Leu Val Ser Arg Gly Ala Gly Asp Val Pro Arg Pro Ser Ser		
7370	7375	7380
Leu Pro Val Glu Glu Thr Ser Pro Pro Ser Ser Gln Leu Ser Leu		
7385	7390	7395
Ser Ala Met Ile Ser Pro Ser Pro Val Ser Ser Thr Leu Pro Ala		
7400	7405	7410
Ser Ser His Ser Ser Ser Ala Ser Val Thr Ser Leu Leu Thr Pro		
7415	7420	7425
Gly Gln Val Lys Thr Thr Glu Val Leu Asp Ala Ser Ala Glu Pro		
7430	7435	7440
Glu Thr Ser Ser Pro Pro Ser Leu Ser Ser Thr Ser Val Glu Ile		
7445	7450	7455

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Leu Ala Thr Ser Glu Val Thr Thr Asp Thr Glu Lys Ile His Pro 7460 7465 7470
Phe Ser Asn Thr Ala Val Thr Lys Val Gly Thr Ser Ser Ser Gly 7475 7480 7485
His Glu Ser Pro Ser Ser Val Leu Pro Asp Ser Glu Thr Thr Lys 7490 7495 7500
Ala Thr Ser Ala Met Gly Thr Ile Ser Ile Met Gly Asp Thr Ser 7505 7510 7515
Val Ser Thr Leu Thr Pro Ala Leu Ser Asn Thr Arg Lys Ile Gln 7520 7525 7530
Ser Glu Pro Ala Ser Ser Leu Thr Thr Arg Leu Arg Glu Thr Ser 7535 7540 7545
Thr Ser Glu Glu Thr Ser Leu Ala Thr Glu Ala Asn Thr Val Leu 7550 7555 7560
Ser Lys Val Ser Thr Gly Ala Thr Thr Glu Val Ser Arg Thr Glu 7565 7570 7575
Ala Ile Ser Phe Ser Arg Thr Ser Met Ser Gly Pro Glu Gln Ser 7580 7585 7590
Thr Met Ser Gln Asp Ile Ser Ile Gly Thr Ile Pro Arg Ile Ser 7595 7600 7605
Ala Ser Ser Val Leu Thr Glu Ser Ala Lys Met Thr Ile Thr Thr 7610 7615 7620
Gln Thr Gly Pro Ser Glu Ser Thr Leu Glu Ser Thr Leu Asn Leu 7625 7630 7635
Asn Thr Ala Thr Thr Pro Ser Trp Val Glu Thr His Ser Ile Val 7640 7645 7650
Ile Gln Gly Phe Pro His Pro Glu Met Thr Thr Ser Met Gly Arg 7655 7660 7665
Gly Pro Gly Gly Val Ser Trp Pro Ser Pro Pro Phe Val Lys Glu 7670 7675 7680
Thr Ser Pro Pro Ser Ser Pro Leu Ser Leu Pro Ala Val Thr Ser 7685 7690 7695
Pro His Pro Val Ser Thr Thr Phe Leu Ala His Ile Pro Pro Ser 7700 7705 7710
Pro Leu Pro Val Thr Ser Leu Leu Thr Ser Gly Pro Ala Thr Thr 7715 7720 7725
Thr Asp Ile Leu Gly Thr Ser Thr Glu Pro Gly Thr Ser Ser Ser 7730 7735 7740
Ser Ser Leu Ser Thr Thr Ser His Glu Arg Leu Thr Thr Tyr Lys 7745 7750 7755
Asp Thr Ala His Thr Glu Ala Val His Pro Ser Thr Asn Thr Gly 7760 7765 7770
Gly Thr Asn Val Ala Thr Thr Ser Ser Gly Tyr Lys Ser Gln Ser 7775 7780 7785
Ser Val Leu Ala Asp Ser Ser Pro Met Cys Thr Thr Ser Thr Met 7790 7795 7800
Gly Asp Thr Ser Val Leu Thr Ser Thr Pro Ala Phe Leu Glu Thr 7805 7810 7815
Arg Arg Ile Gln Thr Glu Leu Ala Ser Ser Leu Thr Pro Gly Leu 7820 7825 7830

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Arg 7835	Glu	Ser	Ser	Gly	Ser	Glu 7840	Gly	Thr	Ser	Ser	Gly 7845	Thr	Lys	Met
Ser 7850	Thr	Val	Leu	Ser	Lys	Val 7855	Pro	Thr	Gly	Ala	Thr 7860	Thr	Glu	Ile
Ser 7865	Lys	Glu	Asp	Val	Thr	Ser 7870	Ile	Pro	Gly	Pro	Ala 7875	Gln	Ser	Thr
Ile 7880	Ser	Pro	Asp	Ile	Ser	Thr 7885	Arg	Thr	Val	Ser	Trp 7890	Phe	Ser	Thr
Ser 7895	Pro	Val	Met	Thr	Glu	Ser 7900	Ala	Glu	Ile	Thr	Met 7905	Asn	Thr	His
Thr 7910	Ser	Pro	Leu	Gly	Ala	Thr 7915	Thr	Gln	Gly	Thr	Ser 7920	Thr	Leu	Asp
Thr 7925	Ser	Ser	Thr	Thr	Ser	Leu 7930	Thr	Met	Thr	His	Ser 7935	Thr	Ile	Ser
Gln 7940	Gly	Phe	Ser	His	Ser	Gln 7945	Met	Ser	Thr	Leu	Met 7950	Arg	Arg	Gly
Pro 7955	Glu	Asp	Val	Ser	Trp	Met 7960	Ser	Pro	Pro	Leu	Leu 7965	Glu	Lys	Thr
Arg 7970	Pro	Ser	Phe	Ser	Leu	Met 7975	Ser	Ser	Pro	Ala	Thr 7980	Thr	Ser	Pro
Ser 7985	Pro	Val	Ser	Ser	Thr	Leu 7990	Pro	Glu	Ser	Ile	Ser 7995	Ser	Ser	Pro
Leu 8000	Pro	Val	Thr	Ser	Leu	Leu 8005	Thr	Ser	Gly	Leu	Ala 8010	Lys	Thr	Thr
Asp 8015	Met	Leu	His	Lys	Ser	Ser 8020	Glu	Pro	Val	Thr	Asn 8025	Ser	Pro	Ala
Asn 8030	Leu	Ser	Ser	Thr	Ser	Val 8035	Glu	Ile	Leu	Ala	Thr 8040	Ser	Glu	Val
Thr 8045	Thr	Asp	Thr	Glu	Lys	Thr 8050	His	Pro	Ser	Ser	Asn 8055	Arg	Thr	Val
Thr 8060	Asp	Val	Gly	Thr	Ser	Ser 8065	Ser	Gly	His	Glu	Ser 8070	Thr	Ser	Phe
Val 8075	Leu	Ala	Asp	Ser	Gln	Thr 8080	Ser	Lys	Val	Thr	Ser 8085	Pro	Met	Val
Ile 8090	Thr	Ser	Thr	Met	Glu	Asp 8095	Thr	Ser	Val	Ser	Thr 8100	Ser	Thr	Pro
Gly 8105	Phe	Phe	Glu	Thr	Ser	Arg 8110	Ile	Gln	Thr	Glu	Pro 8115	Thr	Ser	Ser
Leu 8120	Thr	Leu	Gly	Leu	Arg	Lys 8125	Thr	Ser	Ser	Ser	Glu 8130	Gly	Thr	Ser
Leu 8135	Ala	Thr	Glu	Met	Ser	Thr 8140	Val	Leu	Ser	Gly	Val 8145	Pro	Thr	Gly
Ala 8150	Thr	Ala	Glu	Val	Ser	Arg 8155	Thr	Glu	Val	Thr	Ser 8160	Ser	Ser	Arg
Thr 8165	Ser	Ile	Ser	Gly	Phe	Ala 8170	Gln	Leu	Thr	Val	Ser 8175	Pro	Glu	Thr
Ser 8180	Thr	Glu	Thr	Ile	Thr	Arg 8185	Leu	Pro	Thr	Ser	Ser 8190	Ile	Met	Thr
Glu 8195	Ser	Ala	Glu	Met	Met	Ile 8200	Lys	Thr	Gln	Thr	Asp 8205	Pro	Pro	Gly
Ser 8210	Thr	Pro	Glu	Ser	Thr	His 8215	Thr	Val	Asp	Ile	Ser 8220	Thr	Thr	Pro

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8210	8215	8220
Asn Trp Val Glu Thr His Ser Thr Val Thr Gln Arg Phe Ser His		
8225	8230	8235
Ser Glu Met Thr Thr Leu Val Ser Arg Ser Pro Gly Asp Met Leu		
8240	8245	8250
Trp Pro Ser Gln Ser Ser Val Glu Glu Thr Ser Ser Ala Ser Ser		
8255	8260	8265
Leu Leu Ser Leu Pro Ala Thr Thr Ser Pro Ser Pro Val Ser Ser		
8270	8275	8280
Thr Leu Val Glu Asp Phe Pro Ser Ala Ser Leu Pro Val Thr Ser		
8285	8290	8295
Leu Leu Asn Pro Gly Leu Val Ile Thr Thr Asp Arg Met Gly Ile		
8300	8305	8310
Ser Arg Glu Pro Gly Thr Ser Ser Thr Ser Asn Leu Ser Ser Thr		
8315	8320	8325
Ser His Glu Arg Leu Thr Thr Leu Glu Asp Thr Val Asp Thr Glu		
8330	8335	8340
Asp Met Gln Pro Ser Thr His Thr Ala Val Thr Asn Val Arg Thr		
8345	8350	8355
Ser Ile Ser Gly His Glu Ser Gln Ser Ser Val Leu Ser Asp Ser		
8360	8365	8370
Glu Thr Pro Lys Ala Thr Ser Pro Met Gly Thr Thr Tyr Thr Met		
8375	8380	8385
Gly Glu Thr Ser Val Ser Ile Ser Thr Ser Asp Phe Phe Glu Thr		
8390	8395	8400
Ser Arg Ile Gln Ile Glu Pro Thr Ser Ser Leu Thr Ser Gly Leu		
8405	8410	8415
Arg Glu Thr Ser Ser Ser Glu Arg Ile Ser Ser Ala Thr Glu Gly		
8420	8425	8430
Ser Thr Val Leu Ser Glu Val Pro Ser Gly Ala Thr Thr Glu Val		
8435	8440	8445
Ser Arg Thr Glu Val Ile Ser Ser Arg Gly Thr Ser Met Ser Gly		
8450	8455	8460
Pro Asp Gln Phe Thr Ile Ser Pro Asp Ile Ser Thr Glu Ala Ile		
8465	8470	8475
Thr Arg Leu Ser Thr Ser Pro Ile Met Thr Glu Ser Ala Glu Ser		
8480	8485	8490
Ala Ile Thr Ile Glu Thr Gly Ser Pro Gly Ala Thr Ser Glu Gly		
8495	8500	8505
Thr Leu Thr Leu Asp Thr Ser Thr Thr Thr Phe Trp Ser Gly Thr		
8510	8515	8520
His Ser Thr Ala Ser Pro Gly Phe Ser His Ser Glu Met Thr Thr		
8525	8530	8535
Leu Met Ser Arg Thr Pro Gly Asp Val Pro Trp Pro Ser Leu Pro		
8540	8545	8550
Ser Val Glu Glu Ala Ser Ser Val Ser Ser Ser Leu Ser Ser Pro		
8555	8560	8565
Ala Met Thr Ser Thr Ser Phe Phe Ser Thr Leu Pro Glu Ser Ile		
8570	8575	8580
Ser Ser Ser Pro His Pro Val Thr Ala Leu Leu Thr Leu Gly Pro		
8585	8590	8595

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Val Lys	Thr Thr	Asp Met	Leu	Arg Thr	Ser Ser	Glu	Pro Glu	Thr	
8600			8605			8610			
Ser Ser	Pro Pro	Asn Leu	Ser	Ser Thr	Ser Ala	Glu	Ile Leu	Ala	
8615			8620			8625			
Thr Ser	Glu Val	Thr Lys	Asp	Arg Glu	Lys Ile	His	Pro Ser	Ser	
8630			8635			8640			
Asn Thr	Pro Val	Val Asn	Val	Gly Thr	Val Ile	Tyr	Lys His	Leu	
8645			8650			8655			
Ser Pro	Ser Ser	Val Leu	Ala	Asp Leu	Val Thr	Thr	Lys Pro	Thr	
8660			8665			8670			
Ser Pro	Met Ala	Thr Thr	Ser	Thr Leu	Gly Asn	Thr	Ser Val	Ser	
8675			8680			8685			
Thr Ser	Thr Pro	Ala Phe	Pro	Glu Thr	Met Met	Thr	Gln Pro	Thr	
8690			8695			8700			
Ser Ser	Leu Thr	Ser Gly	Leu	Arg Glu	Ile Ser	Thr	Ser Gln	Glu	
8705			8710			8715			
Thr Ser	Ser Ala	Thr Glu	Arg	Ser Ala	Ser Leu	Ser	Gly Met	Pro	
8720			8725			8730			
Thr Gly	Ala Thr	Thr Lys	Val	Ser Arg	Thr Glu	Ala	Leu Ser	Leu	
8735			8740			8745			
Gly Arg	Thr Ser	Thr Pro	Gly	Pro Ala	Gln Ser	Thr	Ile Ser	Pro	
8750			8755			8760			
Glu Ile	Ser Thr	Glu Thr	Ile	Thr Arg	Ile Ser	Thr	Pro Leu	Thr	
8765			8770			8775			
Thr Thr	Gly Ser	Ala Glu	Met	Thr Ile	Thr Pro	Lys	Thr Gly	His	
8780			8785			8790			
Ser Gly	Ala Ser	Ser Gln	Gly	Thr Phe	Thr Leu	Asp	Thr Ser	Ser	
8795			8800			8805			
Arg Ala	Ser Trp	Pro Gly	Thr	His Ser	Ala Ala	Thr	His Arg	Ser	
8810			8815			8820			
Pro His	Ser Gly	Met Thr	Thr	Pro Met	Ser Arg	Gly	Pro Glu	Asp	
8825			8830			8835			
Val Ser	Trp Pro	Ser Arg	Pro	Ser Val	Glu Lys	Thr	Ser Pro	Pro	
8840			8845			8850			
Ser Ser	Leu Val	Ser Leu	Ser	Ala Val	Thr Ser	Pro	Ser Pro	Leu	
8855			8860			8865			
Tyr Ser	Thr Pro	Ser Glu	Ser	Ser His	Ser Ser	Pro	Leu Arg	Val	
8870			8875			8880			
Thr Ser	Leu Phe	Thr Pro	Val	Met Met	Lys Thr	Thr	Asp Met	Leu	
8885			8890			8895			
Asp Thr	Ser Leu	Glu Pro	Val	Thr Thr	Ser Pro	Pro	Ser Met	Asn	
8900			8905			8910			
Ile Thr	Ser Asp	Glu Ser	Leu	Ala Thr	Ser Lys	Ala	Thr Met	Glu	
8915			8920			8925			
Thr Glu	Ala Ile	Gln Leu	Ser	Glu Asn	Thr Ala	Val	Thr Gln	Met	
8930			8935			8940			
Gly Thr	Ile Ser	Ala Arg	Gln	Glu Phe	Tyr Ser	Ser	Tyr Pro	Gly	
8945			8950			8955			
Leu Pro	Glu Pro	Ser Lys	Val	Thr Ser	Pro Val	Val	Thr Ser	Ser	
8960			8965			8970			

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Thr	Ile	Lys	Asp	Ile	Val	Ser	Thr	Thr	Ile	Pro	Ala	Ser	Ser	Glu
8975						8980					8985			
Ile	Thr	Arg	Ile	Glu	Met	Glu	Ser	Thr	Ser	Thr	Leu	Thr	Pro	Thr
8990						8995					9000			
Pro	Arg	Glu	Thr	Ser	Thr	Ser	Gln	Glu	Ile	His	Ser	Ala	Thr	Lys
9005						9010					9015			
Pro	Ser	Thr	Val	Pro	Tyr	Lys	Ala	Leu	Thr	Ser	Ala	Thr	Ile	Glu
9020						9025					9030			
Asp	Ser	Met	Thr	Gln	Val	Met	Ser	Ser	Ser	Arg	Gly	Pro	Ser	Pro
9035						9040					9045			
Asp	Gln	Ser	Thr	Met	Ser	Gln	Asp	Ile	Ser	Thr	Glu	Val	Ile	Thr
9050						9055					9060			
Arg	Leu	Ser	Thr	Ser	Pro	Ile	Lys	Thr	Glu	Ser	Thr	Glu	Met	Thr
9065						9070					9075			
Ile	Thr	Thr	Gln	Thr	Gly	Ser	Pro	Gly	Ala	Thr	Ser	Arg	Gly	Thr
9080						9085					9090			
Leu	Thr	Leu	Asp	Thr	Ser	Thr	Thr	Phe	Met	Ser	Gly	Thr	His	Ser
9095						9100					9105			
Thr	Ala	Ser	Gln	Gly	Phe	Ser	His	Ser	Gln	Met	Thr	Ala	Leu	Met
9110						9115					9120			
Ser	Arg	Thr	Pro	Gly	Asp	Val	Pro	Trp	Leu	Ser	His	Pro	Ser	Val
9125						9130					9135			
Glu	Glu	Ala	Ser	Ser	Ala	Ser	Phe	Ser	Leu	Ser	Ser	Pro	Val	Met
9140						9145					9150			
Thr	Ser	Ser	Ser	Pro	Val	Ser	Ser	Thr	Leu	Pro	Asp	Ser	Ile	His
9155						9160					9165			
Ser	Ser	Ser	Leu	Pro	Val	Thr	Ser	Leu	Leu	Thr	Ser	Gly	Leu	Val
9170						9175					9180			
Lys	Thr	Thr	Glu	Leu	Leu	Gly	Thr	Ser	Ser	Glu	Pro	Glu	Thr	Ser
9185						9190					9195			
Ser	Pro	Pro	Asn	Leu	Ser	Ser	Thr	Ser	Ala	Glu	Ile	Leu	Ala	Ile
9200						9205					9210			
Thr	Glu	Val	Thr	Thr	Asp	Thr	Glu	Lys	Leu	Glu	Met	Thr	Asn	Val
9215						9220					9225			
Val	Thr	Ser	Gly	Tyr	Thr	His	Glu	Ser	Pro	Ser	Ser	Val	Leu	Ala
9230						9235					9240			
Asp	Ser	Val	Thr	Thr	Lys	Ala	Thr	Ser	Ser	Met	Gly	Ile	Thr	Tyr
9245						9250					9255			
Pro	Thr	Gly	Asp	Thr	Asn	Val	Leu	Thr	Ser	Thr	Pro	Ala	Phe	Ser
9260						9265					9270			
Asp	Thr	Ser	Arg	Ile	Gln	Thr	Lys	Ser	Lys	Leu	Ser	Leu	Thr	Pro
9275						9280					9285			
Gly	Leu	Met	Glu	Thr	Ser	Ile	Ser	Glu	Glu	Thr	Ser	Ser	Ala	Thr
9290						9295					9300			
Glu	Lys	Ser	Thr	Val	Leu	Ser	Ser	Val	Pro	Thr	Gly	Ala	Thr	Thr
9305						9310					9315			
Glu	Val	Ser	Arg	Thr	Glu	Ala	Ile	Ser	Ser	Ser	Arg	Thr	Ser	Ile
9320						9325					9330			
Pro	Gly	Pro	Ala	Gln	Ser	Thr	Met	Ser	Ser	Asp	Thr	Ser	Met	Glu
9335						9340					9345			
Thr	Ile	Thr	Arg	Ile	Ser	Thr	Pro	Leu	Thr	Arg	Lys	Glu	Ser	Thr

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9350	9355	9360
Asp Met Ala Ile Thr Pro Lys Thr Gly Pro Ser Gly Ala Thr Ser		
9365	9370	9375
Gln Gly Thr Phe Thr Leu Asp Ser Ser Ser Thr Ala Ser Trp Pro		
9380	9385	9390
Gly Thr His Ser Ala Thr Thr Gln Arg Phe Pro Gln Ser Val Val		
9395	9400	9405
Thr Thr Pro Met Ser Arg Gly Pro Glu Asp Val Ser Trp Pro Ser		
9410	9415	9420
Pro Leu Ser Val Glu Lys Asn Ser Pro Pro Ser Ser Leu Val Ser		
9425	9430	9435
Ser Ser Ser Val Thr Ser Pro Ser Pro Leu Tyr Ser Thr Pro Ser		
9440	9445	9450
Gly Ser Ser His Ser Ser Pro Val Pro Val Thr Ser Leu Phe Thr		
9455	9460	9465
Ser Ile Met Met Lys Ala Thr Asp Met Leu Asp Ala Ser Leu Glu		
9470	9475	9480
Pro Glu Thr Thr Ser Ala Pro Asn Met Asn Ile Thr Ser Asp Glu		
9485	9490	9495
Ser Leu Ala Ala Ser Lys Ala Thr Thr Glu Thr Glu Ala Ile His		
9500	9505	9510
Val Phe Glu Asn Thr Ala Ala Ser His Val Glu Thr Thr Ser Ala		
9515	9520	9525
Thr Glu Glu Leu Tyr Ser Ser Ser Pro Gly Phe Ser Glu Pro Thr		
9530	9535	9540
Lys Val Ile Ser Pro Val Val Thr Ser Ser Ser Ile Arg Asp Asn		
9545	9550	9555
Met Val Ser Thr Thr Met Pro Gly Ser Ser Gly Ile Thr Arg Ile		
9560	9565	9570
Glu Ile Glu Ser Met Ser Ser Leu Thr Pro Gly Leu Arg Glu Thr		
9575	9580	9585
Arg Thr Ser Gln Asp Ile Thr Ser Ser Thr Glu Thr Ser Thr Val		
9590	9595	9600
Leu Tyr Lys Met Pro Ser Gly Ala Thr Pro Glu Val Ser Arg Thr		
9605	9610	9615
Glu Val Met Pro Ser Ser Arg Thr Ser Ile Pro Gly Pro Ala Gln		
9620	9625	9630
Ser Thr Met Ser Leu Asp Ile Ser Asp Glu Val Val Thr Arg Leu		
9635	9640	9645
Ser Thr Ser Pro Ile Met Thr Glu Ser Ala Glu Ile Thr Ile Thr		
9650	9655	9660
Thr Gln Thr Gly Tyr Ser Leu Ala Thr Ser Gln Val Thr Leu Pro		
9665	9670	9675
Leu Gly Thr Ser Met Thr Phe Leu Ser Gly Thr His Ser Thr Met		
9680	9685	9690
Ser Gln Gly Leu Ser His Ser Glu Met Thr Asn Leu Met Ser Arg		
9695	9700	9705
Gly Pro Glu Ser Leu Ser Trp Thr Ser Pro Arg Phe Val Glu Thr		
9710	9715	9720
Thr Arg Ser Ser Ser Ser Leu Thr Ser Leu Pro Leu Thr Thr Ser		
9725	9730	9735

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Leu Ser	Pro Val Ser Ser Thr	Leu Leu Asp Ser Ser	Pro Ser Ser
9740	9745	9750	
Pro Leu	Pro Val Thr Ser Leu	Ile Leu Pro Gly Leu	Val Lys Thr
9755	9760	9765	
Thr Glu	Val Leu Asp Thr Ser	Ser Glu Pro Lys Thr	Ser Ser Ser
9770	9775	9780	
Pro Asn	Leu Ser Ser Thr Ser	Val Glu Ile Pro Ala	Thr Ser Glu
9785	9790	9795	
Ile Met	Thr Asp Thr Glu Lys	Ile His Pro Ser Ser	Asn Thr Ala
9800	9805	9810	
Val Ala	Lys Val Arg Thr Ser	Ser Ser Val His Glu	Ser His Ser
9815	9820	9825	
Ser Val	Leu Ala Asp Ser Glu	Thr Thr Ile Thr Ile	Pro Ser Met
9830	9835	9840	
Gly Ile	Thr Ser Ala Val Asp	Asp Thr Thr Val Phe	Thr Ser Asn
9845	9850	9855	
Pro Ala	Phe Ser Glu Thr Arg	Arg Ile Pro Thr Glu	Pro Thr Phe
9860	9865	9870	
Ser Leu	Thr Pro Gly Phe Arg	Glu Thr Ser Thr Ser	Glu Glu Thr
9875	9880	9885	
Thr Ser	Ile Thr Glu Thr Ser	Ala Val Leu Tyr Gly	Val Pro Thr
9890	9895	9900	
Ser Ala	Thr Thr Glu Val Ser	Met Thr Glu Ile Met	Ser Ser Asn
9905	9910	9915	
Arg Ile	His Ile Pro Asp Ser	Asp Gln Ser Thr Met	Ser Pro Asp
9920	9925	9930	
Ile Ile	Thr Glu Val Ile Thr	Arg Leu Ser Ser Ser	Ser Met Met
9935	9940	9945	
Ser Glu	Ser Thr Gln Met Thr	Ile Thr Thr Gln Lys	Ser Ser Pro
9950	9955	9960	
Gly Ala	Thr Ala Gln Ser Thr	Leu Thr Leu Ala Thr	Thr Thr Ala
9965	9970	9975	
Pro Leu	Ala Arg Thr His Ser	Thr Val Pro Pro Arg	Phe Leu His
9980	9985	9990	
Ser Glu	Met Thr Thr Leu Met	Ser Arg Ser Pro Glu	Asn Pro Ser
9995	10000	10005	
Trp Lys	Ser Ser Leu Phe Val	Glu Lys Thr Ser Ser	Ser Ser Ser
10010	10015	10020	
Leu Leu	Ser Leu Pro Val Thr	Thr Ser Pro Ser Val	Ser Ser Thr
10025	10030	10035	
Leu Pro	Gln Ser Ile Pro Ser	Ser Ser Phe Ser Val	Thr Ser Leu
10040	10045	10050	
Leu Thr	Pro Gly Met Val Lys	Thr Thr Asp Thr Ser	Thr Glu Pro
10055	10060	10065	
Gly Thr	Ser Leu Ser Pro Asn	Leu Ser Gly Thr Ser	Val Glu Ile
10070	10075	10080	
Leu Ala	Ala Ser Glu Val Thr	Thr Asp Thr Glu Lys	Ile His Pro
10085	10090	10095	
Ser Ser	Ser Met Ala Val Thr	Asn Val Gly Thr Thr	Ser Ser Gly
10100	10105	10110	

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His 10115	Glu	Leu	Tyr	Ser	Ser	Val 10120	Ser	Ile	His	Ser	Glu 10125	Pro	Ser	Lys
Ala 10130	Thr	Tyr	Pro	Val	Gly	Thr 10135	Pro	Ser	Ser	Met	Ala 10140	Glu	Thr	Ser
Ile 10145	Ser	Thr	Ser	Met	Pro	Ala 10150	Asn	Phe	Glu	Thr	Thr 10155	Gly	Phe	Glu
Ala 10160	Glu	Pro	Phe	Ser	His	Leu 10165	Thr	Ser	Gly	Phe	Arg 10170	Lys	Thr	Asn
Met 10175	Ser	Leu	Asp	Thr	Ser	Ser 10180	Val	Thr	Pro	Thr	Asn 10185	Thr	Pro	Ser
Ser 10190	Pro	Gly	Ser	Thr	His	Leu 10195	Leu	Gln	Ser	Ser	Lys 10200	Thr	Asp	Phe
Thr 10205	Ser	Ser	Ala	Lys	Thr	Ser 10210	Ser	Pro	Asp	Trp	Pro 10215	Pro	Ala	Ser
Gln 10220	Tyr	Thr	Glu	Ile	Pro	Val 10225	Asp	Ile	Ile	Thr	Pro 10230	Phe	Asn	Ala
Ser 10235	Pro	Ser	Ile	Thr	Glu	Ser 10240	Thr	Gly	Ile	Thr	Ser 10245	Phe	Pro	Glu
Ser 10250	Arg	Phe	Thr	Met	Ser	Val 10255	Thr	Glu	Ser	Thr	His 10260	His	Leu	Ser
Thr 10265	Asp	Leu	Leu	Pro	Ser	Ala 10270	Glu	Thr	Ile	Ser	Thr 10275	Gly	Thr	Val
Met 10280	Pro	Ser	Leu	Ser	Glu	Ala 10285	Met	Thr	Ser	Phe	Ala 10290	Thr	Thr	Gly
Val 10295	Pro	Arg	Ala	Ile	Ser	Gly 10300	Ser	Gly	Ser	Pro	Phe 10305	Ser	Arg	Thr
Glu 10310	Ser	Gly	Pro	Gly	Asp	Ala 10315	Thr	Leu	Ser	Thr	Ile 10320	Ala	Glu	Ser
Leu 10325	Pro	Ser	Ser	Thr	Pro	Val 10330	Pro	Phe	Ser	Ser	Ser 10335	Thr	Phe	Thr
Thr 10340	Thr	Asp	Ser	Ser	Thr	Ile 10345	Pro	Ala	Leu	His	Glu 10350	Ile	Thr	Ser
Ser 10355	Ser	Ala	Thr	Pro	Tyr	Arg 10360	Val	Asp	Thr	Ser	Leu 10365	Gly	Thr	Glu
Ser 10370	Ser	Thr	Thr	Glu	Gly	Arg 10375	Leu	Val	Met	Val	Ser 10380	Thr	Leu	Asp
Thr 10385	Ser	Ser	Gln	Pro	Gly	Arg 10390	Thr	Ser	Ser	Ser	Pro 10395	Ile	Leu	Asp
Thr 10400	Arg	Met	Thr	Glu	Ser	Val 10405	Glu	Leu	Gly	Thr	Val 10410	Thr	Ser	Ala
Tyr 10415	Gln	Val	Pro	Ser	Leu	Ser 10420	Thr	Arg	Leu	Thr	Arg 10425	Thr	Asp	Gly
Ile 10430	Met	Glu	His	Ile	Thr	Lys 10435	Ile	Pro	Asn	Glu	Ala 10440	Ala	His	Arg
Gly 10445	Thr	Ile	Arg	Pro	Val	Lys 10450	Gly	Pro	Gln	Thr	Ser 10455	Thr	Ser	Pro
Ala 10460	Ser	Pro	Lys	Gly	Leu	His 10465	Thr	Gly	Gly	Thr	Lys 10470	Arg	Met	Glu
Thr 10475	Thr	Thr	Thr	Ala	Leu	Lys 10480	Thr	Thr	Thr	Thr	Ala 10485	Leu	Lys	Thr
Thr 10490	Ser	Arg	Ala	Thr	Leu	Thr	Thr	Ser	Val	Tyr	Thr	Pro	Thr	Leu

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10490	10495	10500
Gly Thr Leu Thr Pro Leu Asn Ala Ser Met Gln Met Ala Ser Thr		
10505	10510	10515
Ile Pro Thr Glu Met Met Ile Thr Thr Pro Tyr Val Phe Pro Asp		
10520	10525	10530
Val Pro Glu Thr Thr Ser Ser Leu Ala Thr Ser Leu Gly Ala Glu		
10535	10540	10545
Thr Ser Thr Ala Leu Pro Arg Thr Thr Pro Ser Val Phe Asn Arg		
10550	10555	10560
Glu Ser Glu Thr Thr Ala Ser Leu Val Ser Arg Ser Gly Ala Glu		
10565	10570	10575
Arg Ser Pro Val Ile Gln Thr Leu Asp Val Ser Ser Ser Glu Pro		
10580	10585	10590
Asp Thr Thr Ala Ser Trp Val Ile His Pro Ala Glu Thr Ile Pro		
10595	10600	10605
Thr Val Ser Lys Thr Thr Pro Asn Phe Phe His Ser Glu Leu Asp		
10610	10615	10620
Thr Val Ser Ser Thr Ala Thr Ser His Gly Ala Asp Val Ser Ser		
10625	10630	10635
Ala Ile Pro Thr Asn Ile Ser Pro Ser Glu Leu Asp Ala Leu Thr		
10640	10645	10650
Pro Leu Val Thr Ile Ser Gly Thr Asp Thr Ser Thr Thr Phe Pro		
10655	10660	10665
Thr Leu Thr Lys Ser Pro His Glu Thr Glu Thr Arg Thr Thr Trp		
10670	10675	10680
Leu Thr His Pro Ala Glu Thr Ser Ser Thr Ile Pro Arg Thr Ile		
10685	10690	10695
Pro Asn Phe Ser His His Glu Ser Asp Ala Thr Pro Ser Ile Ala		
10700	10705	10710
Thr Ser Pro Gly Ala Glu Thr Ser Ser Ala Ile Pro Ile Met Thr		
10715	10720	10725
Val Ser Pro Gly Ala Glu Asp Leu Val Thr Ser Gln Val Thr Ser		
10730	10735	10740
Ser Gly Thr Asp Arg Asn Met Thr Ile Pro Thr Leu Thr Leu Ser		
10745	10750	10755
Pro Gly Glu Pro Lys Thr Ile Ala Ser Leu Val Thr His Pro Glu		
10760	10765	10770
Ala Gln Thr Ser Ser Ala Ile Pro Thr Ser Thr Ile Ser Pro Ala		
10775	10780	10785
Val Ser Arg Leu Val Thr Ser Met Val Thr Ser Leu Ala Ala Lys		
10790	10795	10800
Thr Ser Thr Thr Asn Arg Ala Leu Thr Asn Ser Pro Gly Glu Pro		
10805	10810	10815
Ala Thr Thr Val Ser Leu Val Thr His Pro Ala Gln Thr Ser Pro		
10820	10825	10830
Thr Val Pro Trp Thr Thr Ser Ile Phe Phe His Ser Lys Ser Asp		
10835	10840	10845
Thr Thr Pro Ser Met Thr Thr Ser His Gly Ala Glu Ser Ser Ser		
10850	10855	10860
Ala Val Pro Thr Pro Thr Val Ser Thr Glu Val Pro Gly Val Val		
10865	10870	10875

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Thr Pro	Leu Val Thr Ser	Ser	Arg Ala Val Ile	Ser	Thr Thr Ile
10880		10885		10890	
Pro Ile	Leu Thr Leu Ser	Pro	Gly Glu Pro Glu Thr	Thr Pro Ser	
10895		10900		10905	
Met Ala	Thr Ser His Gly	Glu	Glu Ala Ser Ser Ala	Ile Pro Thr	
10910		10915		10920	
Pro Thr	Val Ser Pro Gly	Val	Pro Gly Val Val Thr	Ser Leu Val	
10925		10930		10935	
Thr Ser	Ser Arg Ala Val	Thr	Ser Thr Thr Ile Pro	Ile Leu Thr	
10940		10945		10950	
Phe Ser	Leu Gly Glu Pro	Glu	Thr Thr Pro Ser Met	Ala Thr Ser	
10955		10960		10965	
His Gly	Thr Glu Ala Gly	Ser	Ala Val Pro Thr Val	Leu Pro Glu	
10970		10975		10980	
Val Pro	Gly Met Val Thr	Ser	Leu Val Ala Ser Ser	Arg Ala Val	
10985		10990		10995	
Thr Ser	Thr Thr Leu Pro	Thr	Leu Thr Leu Ser Pro	Gly Glu Pro	
11000		11005		11010	
Glu Thr	Thr Pro Ser Met	Ala	Thr Ser His Gly Ala	Glu Ala Ser	
11015		11020		11025	
Ser Thr	Val Pro Thr Val	Ser	Pro Glu Val Pro Gly	Val Val Thr	
11030		11035		11040	
Ser Leu	Val Thr Ser Ser	Ser	Gly Val Asn Ser Thr	Ser Ile Pro	
11045		11050		11055	
Thr Leu	Ile Leu Ser Pro	Gly	Glu Leu Glu Thr Thr	Pro Ser Met	
11060		11065		11070	
Ala Thr	Ser His Gly Ala	Glu	Ala Ser Ser Ala Val	Pro Thr Pro	
11075		11080		11085	
Thr Val	Ser Pro Gly Val	Ser	Gly Val Val Thr Pro	Leu Val Thr	
11090		11095		11100	
Ser Ser	Arg Ala Val Thr	Ser	Thr Thr Ile Pro Ile	Leu Thr Leu	
11105		11110		11115	
Ser Ser	Ser Glu Pro Glu	Thr	Thr Pro Ser Met Ala	Thr Ser His	
11120		11125		11130	
Gly Val	Glu Ala Ser Ser	Ala	Val Leu Thr Val Ser	Pro Glu Val	
11135		11140		11145	
Pro Gly	Met Val Thr Ser	Leu	Val Thr Ser Ser Arg	Ala Val Thr	
11150		11155		11160	
Ser Thr	Thr Ile Pro Thr	Leu	Thr Ile Ser Ser Asp	Glu Pro Glu	
11165		11170		11175	
Thr Thr	Thr Ser Leu Val	Thr	His Ser Glu Ala Lys	Met Ile Ser	
11180		11185		11190	
Ala Ile	Pro Thr Leu Ala	Val	Ser Pro Thr Val Gln	Gly Leu Val	
11195		11200		11205	
Thr Ser	Leu Val Thr Ser	Ser	Gly Ser Glu Thr Ser	Ala Phe Ser	
11210		11215		11220	
Asn Leu	Thr Val Ala Ser	Ser	Gln Pro Glu Thr Ile	Asp Ser Trp	
11225		11230		11235	
Val Ala	His Pro Gly Thr	Glu	Ala Ser Ser Val Val	Pro Thr Leu	
11240		11245		11250	

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Thr Val 11255	Ser Thr Gly Glu Pro 11260	Phe Thr Asn Ile Ser 11265	Leu Val Thr
His Pro 11270	Ala Glu Ser Ser Ser 11275	Thr Leu Pro Arg Thr 11280	Thr Ser Arg
Phe Ser 11285	His Ser Glu Leu Asp 11290	Thr Met Pro Ser Thr 11295	Val Thr Ser
Pro Glu 11300	Ala Glu Ser Ser Ser 11305	Ala Ile Ser Thr Thr 11310	Ile Ser Pro
Gly Ile 11315	Pro Gly Val Leu Thr 11320	Ser Leu Val Thr Ser 11325	Ser Gly Arg
Asp Ile 11330	Ser Ala Thr Phe Pro 11335	Thr Val Pro Glu Ser 11340	Pro His Glu
Ser Glu 11345	Ala Thr Ala Ser Trp 11350	Val Thr His Pro Ala 11355	Val Thr Ser
Thr Thr 11360	Val Pro Arg Thr Thr 11365	Pro Asn Tyr Ser His 11370	Ser Glu Pro
Asp Thr 11375	Thr Pro Ser Ile Ala 11380	Thr Ser Pro Gly Ala 11385	Glu Ala Thr
Ser Asp 11390	Phe Pro Thr Ile Thr 11395	Val Ser Pro Asp Val 11400	Pro Asp Met
Val Thr 11405	Ser Gln Val Thr Ser 11410	Ser Gly Thr Asp Thr 11415	Ser Ile Thr
Ile Pro 11420	Thr Leu Thr Leu Ser 11425	Ser Gly Glu Pro Glu 11430	Thr Thr Thr
Ser Phe 11435	Ile Thr Tyr Ser Glu 11440	Thr His Thr Ser Ser 11445	Ala Ile Pro
Thr Leu 11450	Pro Val Ser Pro Gly 11455	Ala Ser Lys Met Leu 11460	Thr Ser Leu
Val Ile 11465	Ser Ser Gly Thr Asp 11470	Ser Thr Thr Thr Phe 11475	Pro Thr Leu
Thr Glu 11480	Thr Pro Tyr Glu Pro 11485	Glu Thr Thr Ala Ile 11490	Gln Leu Ile
His Pro 11495	Ala Glu Thr Asn Thr 11500	Met Val Pro Arg Thr 11505	Thr Pro Lys
Phe Ser 11510	His Ser Lys Ser Asp 11515	Thr Thr Leu Pro Val 11520	Ala Ile Thr
Ser Pro 11525	Gly Pro Glu Ala Ser 11530	Ser Ala Val Ser Thr 11535	Thr Thr Ile
Ser Pro 11540	Asp Met Ser Asp Leu 11545	Val Thr Ser Leu Val 11550	Pro Ser Ser
Gly Thr 11555	Asp Thr Ser Thr Thr 11560	Phe Pro Thr Leu Ser 11565	Glu Thr Pro
Tyr Glu 11570	Pro Glu Thr Thr Ala 11575	Thr Trp Leu Thr His 11580	Pro Ala Glu
Thr Ser 11585	Thr Thr Val Ser Gly 11590	Thr Ile Pro Asn Phe 11595	Ser His Arg
Gly Ser 11600	Asp Thr Ala Pro Ser 11605	Met Val Thr Ser Pro 11610	Gly Val Asp
Thr Arg 11615	Ser Gly Val Pro Thr 11620	Thr Thr Ile Pro Pro 11625	Ser Ile Pro
Gly Val	Val Thr Ser Gln Val	Thr Ser Ser Ala Thr	Asp Thr Ser

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11630	11635	11640
Thr Ala Ile Pro Thr Leu Thr Pro Ser Pro Gly Glu Pro Glu Thr		
11645	11650	11655
Thr Ala Ser Ser Ala Thr His Pro Gly Thr Gln Thr Gly Phe Thr		
11660	11665	11670
Val Pro Ile Arg Thr Val Pro Ser Ser Glu Pro Asp Thr Met Ala		
11675	11680	11685
Ser Trp Val Thr His Pro Pro Gln Thr Ser Thr Pro Val Ser Arg		
11690	11695	11700
Thr Thr Ser Ser Phe Ser His Ser Ser Pro Asp Ala Thr Pro Val		
11705	11710	11715
Met Ala Thr Ser Pro Arg Thr Glu Ala Ser Ser Ala Val Leu Thr		
11720	11725	11730
Thr Ile Ser Pro Gly Ala Pro Glu Met Val Thr Ser Gln Ile Thr		
11735	11740	11745
Ser Ser Gly Ala Ala Thr Ser Thr Thr Val Pro Thr Leu Thr His		
11750	11755	11760
Ser Pro Gly Met Pro Glu Thr Thr Ala Leu Leu Ser Thr His Pro		
11765	11770	11775
Arg Thr Glu Thr Ser Lys Thr Phe Pro Ala Ser Thr Val Phe Pro		
11780	11785	11790
Gln Val Ser Glu Thr Thr Ala Ser Leu Thr Ile Arg Pro Gly Ala		
11795	11800	11805
Glu Thr Ser Thr Ala Leu Pro Thr Gln Thr Thr Ser Ser Leu Phe		
11810	11815	11820
Thr Leu Leu Val Thr Gly Thr Ser Arg Val Asp Leu Ser Pro Thr		
11825	11830	11835
Ala Ser Pro Gly Val Ser Ala Lys Thr Ala Pro Leu Ser Thr His		
11840	11845	11850
Pro Gly Thr Glu Thr Ser Thr Met Ile Pro Thr Ser Thr Leu Ser		
11855	11860	11865
Leu Gly Leu Leu Glu Thr Thr Gly Leu Leu Ala Thr Ser Ser Ser		
11870	11875	11880
Ala Glu Thr Ser Thr Ser Thr Leu Thr Leu Thr Val Ser Pro Ala		
11885	11890	11895
Val Ser Gly Leu Ser Ser Ala Ser Ile Thr Thr Asp Lys Pro Gln		
11900	11905	11910
Thr Val Thr Ser Trp Asn Thr Glu Thr Ser Pro Ser Val Thr Ser		
11915	11920	11925
Val Gly Pro Pro Glu Phe Ser Arg Thr Val Thr Gly Thr Thr Met		
11930	11935	11940
Thr Leu Ile Pro Ser Glu Met Pro Thr Pro Pro Lys Thr Ser His		
11945	11950	11955
Gly Glu Gly Val Ser Pro Thr Thr Ile Leu Arg Thr Thr Met Val		
11960	11965	11970
Glu Ala Thr Asn Leu Ala Thr Thr Gly Ser Ser Pro Thr Val Ala		
11975	11980	11985
Lys Thr Thr Thr Thr Phe Asn Thr Leu Ala Gly Ser Leu Phe Thr		
11990	11995	12000
Pro Leu Thr Thr Pro Gly Met Ser Thr Leu Ala Ser Glu Ser Val		
12005	12010	12015

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Thr Ser	Arg Thr Ser Tyr Asn	His Arg Ser Trp Ile	Ser Thr Thr
12020	12025	12030	
Ser Ser	Tyr Asn Arg Arg Tyr	Trp Thr Pro Ala Thr	Ser Thr Pro
12035	12040	12045	
Val Thr	Ser Thr Phe Ser Pro	Gly Ile Ser Thr Ser	Ser Ile Pro
12050	12055	12060	
Ser Ser	Thr Ala Ala Thr Val	Pro Phe Met Val Pro	Phe Thr Leu
12065	12070	12075	
Asn Phe	Thr Ile Thr Asn Leu	Gln Tyr Glu Glu Asp	Met Arg His
12080	12085	12090	
Pro Gly	Ser Arg Lys Phe Asn	Ala Thr Glu Arg Glu	Leu Gln Gly
12095	12100	12105	
Leu Leu	Lys Pro Leu Phe Arg	Asn Ser Ser Leu Glu	Tyr Leu Tyr
12110	12115	12120	
Ser Gly	Cys Arg Leu Ala Ser	Leu Arg Pro Glu Lys	Asp Ser Ser
12125	12130	12135	
Ala Thr	Ala Val Asp Ala Ile	Cys Thr His Arg Pro	Asp Pro Glu
12140	12145	12150	
Asp Leu	Gly Leu Asp Arg Glu	Arg Leu Tyr Trp Glu	Leu Ser Asn
12155	12160	12165	
Leu Thr	Asn Gly Ile Gln Glu	Leu Gly Pro Tyr Thr	Leu Asp Arg
12170	12175	12180	
Asn Ser	Leu Tyr Val Asn Gly	Phe Thr His Arg Ser	Ser Met Pro
12185	12190	12195	
Thr Thr	Ser Thr Pro Gly Thr	Ser Thr Val Asp Val	Gly Thr Ser
12200	12205	12210	
Gly Thr	Pro Ser Ser Ser Pro	Ser Pro Thr Thr Ala	Gly Pro Leu
12215	12220	12225	
Leu Met	Pro Phe Thr Leu Asn	Phe Thr Ile Thr Asn	Leu Gln Tyr
12230	12235	12240	
Glu Glu	Asp Met Arg Arg Thr	Gly Ser Arg Lys Phe	Asn Thr Met
12245	12250	12255	
Glu Ser	Val Leu Gln Gly Leu	Leu Lys Pro Leu Phe	Lys Asn Thr
12260	12265	12270	
Ser Val	Gly Pro Leu Tyr Ser	Gly Cys Arg Leu Thr	Leu Leu Arg
12275	12280	12285	
Pro Glu	Lys Asp Gly Ala Ala	Thr Gly Val Asp Ala	Ile Cys Thr
12290	12295	12300	
His Arg	Leu Asp Pro Lys Ser	Pro Gly Leu Asn Arg	Glu Gln Leu
12305	12310	12315	
Tyr Trp	Glu Leu Ser Lys Leu	Thr Asn Asp Ile Glu	Glu Leu Gly
12320	12325	12330	
Pro Tyr	Thr Leu Asp Arg Asn	Ser Leu Tyr Val Asn	Gly Phe Thr
12335	12340	12345	
His Gln	Ser Ser Val Ser Thr	Thr Ser Thr Pro Gly	Thr Ser Thr
12350	12355	12360	
Val Asp	Leu Arg Thr Ser Gly	Thr Pro Ser Ser Leu	Ser Ser Pro
12365	12370	12375	
Thr Ile	Met Ala Ala Gly Pro	Leu Leu Val Pro Phe	Thr Leu Asn
12380	12385	12390	

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Phe Thr 12395	Ile Thr Asn Leu Gln 12400	Tyr Gly Glu Asp Met 12405	Gly His Pro
Gly Ser 12410	Arg Lys Phe Asn Thr 12415	Thr Glu Arg Val Leu 12420	Gln Gly Leu
Leu Gly 12425	Pro Ile Phe Lys Asn 12430	Thr Ser Val Gly Pro 12435	Leu Tyr Ser
Gly Cys 12440	Arg Leu Thr Ser Leu 12445	Arg Ser Glu Lys Asp 12450	Gly Ala Ala
Thr Gly 12455	Val Asp Ala Ile Cys 12460	Ile His His Leu Asp 12465	Pro Lys Ser
Pro Gly 12470	Leu Asn Arg Glu Arg 12475	Leu Tyr Trp Glu Leu 12480	Ser Gln Leu
Thr Asn 12485	Gly Ile Lys Glu Leu 12490	Gly Pro Tyr Thr Leu 12495	Asp Arg Asn
Ser Leu 12500	Tyr Val Asn Gly Phe 12505	Thr His Arg Thr Ser 12510	Val Pro Thr
Ser Ser 12515	Thr Pro Gly Thr Ser 12520	Thr Val Asp Leu Gly 12525	Thr Ser Gly
Thr Pro 12530	Phe Ser Leu Pro Ser 12535	Pro Ala Thr Ala Gly 12540	Pro Leu Leu
Val Leu 12545	Phe Thr Leu Asn Phe 12550	Thr Ile Thr Asn Leu 12555	Lys Tyr Glu
Glu Asp 12560	Met His Arg Pro Gly 12565	Ser Arg Lys Phe Asn 12570	Thr Thr Glu
Arg Val 12575	Leu Gln Thr Leu Leu 12580	Gly Pro Met Phe Lys 12585	Asn Thr Ser
Val Gly 12590	Leu Leu Tyr Ser Gly 12595	Cys Arg Leu Thr Leu 12600	Leu Arg Ser
Glu Lys 12605	Asp Gly Ala Ala Thr 12610	Gly Val Asp Ala Ile 12615	Cys Thr His
Arg Leu 12620	Asp Pro Lys Ser Pro 12625	Gly Val Asp Arg Glu 12630	Gln Leu Tyr
Trp Glu 12635	Leu Ser Gln Leu Thr 12640	Asn Gly Ile Lys Glu 12645	Leu Gly Pro
Tyr Thr 12650	Leu Asp Arg Asn Ser 12655	Leu Tyr Val Asn Gly 12660	Phe Thr His
Trp Ile 12665	Pro Val Pro Thr Ser 12670	Ser Thr Pro Gly Thr 12675	Ser Thr Val
Asp Leu 12680	Gly Ser Gly Thr Pro 12685	Ser Ser Leu Pro Ser 12690	Pro Thr Thr
Ala Gly 12695	Pro Leu Leu Val Pro 12700	Phe Thr Leu Asn Phe 12705	Thr Ile Thr
Asn Leu 12710	Lys Tyr Glu Glu Asp 12715	Met His Cys Pro Gly 12720	Ser Arg Lys
Phe Asn 12725	Thr Thr Glu Arg Val 12730	Leu Gln Ser Leu Leu 12735	Gly Pro Met
Phe Lys 12740	Asn Thr Ser Val Gly 12745	Pro Leu Tyr Ser Gly 12750	Cys Arg Leu
Thr Leu 12755	Leu Arg Ser Glu Lys 12760	Asp Gly Ala Ala Thr 12765	Gly Val Asp
Ala Ile	Cys Thr His Arg Leu	Asp Pro Lys Ser Pro	Gly Val Asp

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12770	12775	12780
Arg Glu Gln Leu Tyr Trp	Glu Leu Ser Gln Leu Thr	Asn Gly Ile
12785	12790	12795
Lys Glu Leu Gly Pro Tyr Thr	Leu Asp Arg Asn Ser	Leu Tyr Val
12800	12805	12810
Asn Gly Phe Thr His Gln Thr	Ser Ala Pro Asn Thr	Ser Thr Pro
12815	12820	12825
Gly Thr Ser Thr Val Asp Leu	Gly Thr Ser Gly Thr	Pro Ser Ser
12830	12835	12840
Leu Pro Ser Pro Thr Ser Ala	Gly Pro Leu Leu Val	Pro Phe Thr
12845	12850	12855
Leu Asn Phe Thr Ile Thr Asn	Leu Gln Tyr Glu Glu	Asp Met His
12860	12865	12870
His Pro Gly Ser Arg Lys Phe	Asn Thr Thr Glu Arg	Val Leu Gln
12875	12880	12885
Gly Leu Leu Gly Pro Met Phe	Lys Asn Thr Ser Val	Gly Leu Leu
12890	12895	12900
Tyr Ser Gly Cys Arg Leu Thr	Leu Leu Arg Pro Glu	Lys Asn Gly
12905	12910	12915
Ala Ala Thr Gly Met Asp Ala	Ile Cys Ser His Arg	Leu Asp Pro
12920	12925	12930
Lys Ser Pro Gly Leu Asn Arg	Glu Gln Leu Tyr Trp	Glu Leu Ser
12935	12940	12945
Gln Leu Thr His Gly Ile Lys	Glu Leu Gly Pro Tyr	Thr Leu Asp
12950	12955	12960
Arg Asn Ser Leu Tyr Val Asn	Gly Phe Thr His Arg	Ser Ser Val
12965	12970	12975
Ala Pro Thr Ser Thr Pro Gly	Thr Ser Thr Val Asp	Leu Gly Thr
12980	12985	12990
Ser Gly Thr Pro Ser Ser Leu	Pro Ser Pro Thr Thr	Ala Val Pro
12995	13000	13005
Leu Leu Val Pro Phe Thr Leu	Asn Phe Thr Ile Thr	Asn Leu Gln
13010	13015	13020
Tyr Gly Glu Asp Met Arg His	Pro Gly Ser Arg Lys	Phe Asn Thr
13025	13030	13035
Thr Glu Arg Val Leu Gln Gly	Leu Leu Gly Pro Leu	Phe Lys Asn
13040	13045	13050
Ser Ser Val Gly Pro Leu Tyr	Ser Gly Cys Arg Leu	Ile Ser Leu
13055	13060	13065
Arg Ser Glu Lys Asp Gly Ala	Ala Thr Gly Val Asp	Ala Ile Cys
13070	13075	13080
Thr His His Leu Asn Pro Gln	Ser Pro Gly Leu Asp	Arg Glu Gln
13085	13090	13095
Leu Tyr Trp Gln Leu Ser Gln	Met Thr Asn Gly Ile	Lys Glu Leu
13100	13105	13110
Gly Pro Tyr Thr Leu Asp Arg	Asn Ser Leu Tyr Val	Asn Gly Phe
13115	13120	13125
Thr His Arg Ser Ser Gly Leu	Thr Thr Ser Thr Pro	Trp Thr Ser
13130	13135	13140
Thr Val Asp Leu Gly Thr Ser	Gly Thr Pro Ser Pro	Val Pro Ser
13145	13150	13155

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Pro Thr	Thr Thr Gly Pro	Leu	Leu Val Pro Phe Thr	Leu Asn Phe
13160		13165		13170
Thr Ile	Thr Asn Leu Gln Tyr	Glu Glu Asn Met Gly	His Pro Gly	
13175		13180	13185	
Ser Arg	Lys Phe Asn Ile Thr	Glu Ser Val Leu Gln	Gly Leu Leu	
13190		13195	13200	
Lys Pro	Leu Phe Lys Ser Thr	Ser Val Gly Pro Leu	Tyr Ser Gly	
13205		13210	13215	
Cys Arg	Leu Thr Leu Leu Arg	Pro Glu Lys Asp Gly	Val Ala Thr	
13220		13225	13230	
Arg Val	Asp Ala Ile Cys Thr	His Arg Pro Asp Pro	Lys Ile Pro	
13235		13240	13245	
Gly Leu	Asp Arg Gln Gln Leu	Tyr Trp Glu Leu Ser	Gln Leu Thr	
13250		13255	13260	
His Ser	Ile Thr Glu Leu Gly	Pro Tyr Thr Leu Asp	Arg Asp Ser	
13265		13270	13275	
Leu Tyr	Val Asn Gly Phe Thr	Gln Arg Ser Ser Val	Pro Thr Thr	
13280		13285	13290	
Ser Thr	Pro Gly Thr Phe Thr	Val Gln Pro Glu Thr	Ser Glu Thr	
13295		13300	13305	
Pro Ser	Ser Leu Pro Gly Pro	Thr Ala Thr Gly Pro	Val Leu Leu	
13310		13315	13320	
Pro Phe	Thr Leu Asn Phe Thr	Ile Thr Asn Leu Gln	Tyr Glu Glu	
13325		13330	13335	
Asp Met	Arg Arg Pro Gly Ser	Arg Lys Phe Asn Thr	Thr Glu Arg	
13340		13345	13350	
Val Leu	Gln Gly Leu Leu Met	Pro Leu Phe Lys Asn	Thr Ser Val	
13355		13360	13365	
Ser Ser	Leu Tyr Ser Gly Cys	Arg Leu Thr Leu Leu	Arg Pro Glu	
13370		13375	13380	
Lys Asp	Gly Ala Ala Thr Arg	Val Asp Ala Val Cys	Thr His Arg	
13385		13390	13395	
Pro Asp	Pro Lys Ser Pro Gly	Leu Asp Arg Glu Arg	Leu Tyr Trp	
13400		13405	13410	
Lys Leu	Ser Gln Leu Thr His	Gly Ile Thr Glu Leu	Gly Pro Tyr	
13415		13420	13425	
Thr Leu	Asp Arg His Ser Leu	Tyr Val Asn Gly Phe	Thr His Gln	
13430		13435	13440	
Ser Ser	Met Thr Thr Thr Arg	Thr Pro Asp Thr Ser	Thr Met His	
13445		13450	13455	
Leu Ala	Thr Ser Arg Thr Pro	Ala Ser Leu Ser Gly	Pro Met Thr	
13460		13465	13470	
Ala Ser	Pro Leu Leu Val Leu	Phe Thr Ile Asn Phe	Thr Ile Thr	
13475		13480	13485	
Asn Leu	Arg Tyr Glu Glu Asn	Met His His Pro Gly	Ser Arg Lys	
13490		13495	13500	
Phe Asn	Thr Thr Glu Arg Val	Leu Gln Gly Leu Leu	Arg Pro Val	
13505		13510	13515	
Phe Lys	Asn Thr Ser Val Gly	Pro Leu Tyr Ser Gly	Cys Arg Leu	
13520		13525	13530	

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Thr 13535	Leu	Arg	Pro	Lys	Lys 13540	Asp	Gly	Ala	Ala	Thr 13545	Lys	Val	Asp
Ala 13550	Ile	Cys	Thr	Tyr	Arg 13555	Asp	Pro	Lys	Ser	Pro 13560	Gly	Leu	Asp
Arg 13565	Glu	Gln	Leu	Tyr	Trp 13570	Leu	Ser	Gln	Leu	Thr 13575	His	Ser	Ile
Thr 13580	Glu	Leu	Gly	Pro	Tyr 13585	Leu	Asp	Arg	Asp	Ser 13590	Leu	Tyr	Val
Asn 13595	Gly	Phe	Thr	Gln	Arg 13600	Ser	Val	Pro	Thr	Thr 13605	Ser	Ile	Pro
Gly 13610	Thr	Pro	Thr	Val	Asp 13615	Gly	Thr	Ser	Gly	Thr 13620	Pro	Val	Ser
Lys 13625	Pro	Gly	Pro	Ser	Ala 13630	Ser	Pro	Leu	Leu	Val 13635	Leu	Phe	Thr
Leu 13640	Asn	Phe	Thr	Ile	Thr 13645	Leu	Arg	Tyr	Glu	Glu 13650	Asn	Met	Gln
His 13655	Pro	Gly	Ser	Arg	Lys 13660	Asn	Thr	Thr	Glu	Arg 13665	Val	Leu	Gln
Gly 13670	Leu	Leu	Arg	Ser	Leu 13675	Lys	Ser	Thr	Ser	Val 13680	Gly	Pro	Leu
Tyr 13685	Ser	Gly	Cys	Arg	Leu 13690	Leu	Leu	Arg	Pro	Glu 13695	Lys	Asp	Gly
Thr 13700	Ala	Thr	Gly	Val	Asp 13705	Ile	Cys	Thr	His	His 13710	Pro	Asp	Pro
Lys 13715	Ser	Pro	Arg	Leu	Asp 13720	Glu	Gln	Leu	Tyr	Trp 13725	Glu	Leu	Ser
Gln 13730	Leu	Thr	His	Asn	Ile 13735	Glu	Leu	Gly	Pro	Tyr 13740	Ala	Leu	Asp
Asn 13745	Asp	Ser	Leu	Phe	Val 13750	Gly	Phe	Thr	His	Arg 13755	Ser	Ser	Val
Ser 13760	Thr	Thr	Ser	Thr	Pro 13765	Thr	Pro	Thr	Val	Tyr 13770	Leu	Gly	Ala
Ser 13775	Lys	Thr	Pro	Ala	Ser 13780	Phe	Gly	Pro	Ser	Ala 13785	Ala	Ser	His
Leu 13790	Leu	Ile	Leu	Phe	Thr 13795	Asn	Phe	Thr	Ile	Thr 13800	Asn	Leu	Arg
Tyr 13805	Glu	Glu	Asn	Met	Trp 13810	Gly	Ser	Arg	Lys	Phe 13815	Asn	Thr	Thr
Glu 13820	Arg	Val	Leu	Gln	Gly 13825	Leu	Arg	Pro	Leu	Phe 13830	Lys	Asn	Thr
Ser 13835	Val	Gly	Pro	Leu	Tyr 13840	Gly	Cys	Arg	Leu	Thr 13845	Leu	Leu	Arg
Pro 13850	Glu	Lys	Asp	Gly	Glu 13855	Thr	Gly	Val	Asp	Ala 13860	Ile	Cys	Thr
His 13865	Arg	Pro	Asp	Pro	Thr 13870	Pro	Gly	Leu	Asp	Arg 13875	Glu	Gln	Leu
Tyr 13880	Leu	Glu	Leu	Ser	Gln 13885	Thr	His	Ser	Ile	Thr 13890	Glu	Leu	Gly
Pro 13895	Tyr	Thr	Leu	Asp	Arg 13900	Ser	Leu	Tyr	Val	Asn 13905	Gly	Phe	Thr
His 13910	Arg	Ser	Ser	Val	Pro 13915	Thr	Ser	Thr	Gly	Val 13920	Val	Ser	Gln

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13910	13915	13920
Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr Met		
13925	13930	13935
Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp		
13940	13945	13950
Asn Val Met Gln His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser		
13955	13960	13965
Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser		
13970	13975	13980
Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr		
13985	13990	13995
Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe		
14000	14005	14010
His Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro		
14015	14020	14025
Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu		
14030	14035	14040
Pro Gly Pro Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr		
14045	14050	14055
Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His		
14060	14065	14070
Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr		
14075	14080	14085
Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu		
14090	14095	14100
Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser		
14105	14110	14115
Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro		
14120	14125	14130
Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr		
14135	14140	14145
His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr		
14150	14155	14160
Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe		
14165	14170	14175
Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro		
14180	14185	14190
Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile		
14195	14200	14205
Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr		
14210	14215	14220
Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr		
14225	14230	14235
Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr		
14240	14245	14250
Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe		
14255	14260	14265
Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp		
14270	14275	14280
Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln		
14285	14290	14295

<210> SEQ ID NO 176

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<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 176

Gly Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
1 5 10 15

Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Leu Tyr Tyr Cys
35

<210> SEQ ID NO 177
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 177

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
1 5 10

<210> SEQ ID NO 178
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa = Ala or Ser

<400> SEQUENCE: 178

Gly Phe Thr Phe Asp Asp Tyr Xaa
1 5

<210> SEQ ID NO 179
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa = Lys or Ile

<400> SEQUENCE: 179

Ile Ser Trp Asn Ser Gly Ser Xaa
1 5

<210> SEQ ID NO 180
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa = Tyr or Asp
<220> FEATURE:

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<221> NAME/KEY: VARIANT
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa = Tyr or His
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa = Met or Leu
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa = Met or Leu

<400> SEQUENCE: 180

Ala Lys Xaa Gly Ser Gly Tyr Gly Lys Phe Tyr Xaa Tyr Gly Xaa Asp
1 5 10 15

Val

<210> SEQ ID NO 181
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 181

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Asp Gly Tyr Ser Gly Tyr Gly Tyr Phe Tyr Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 182
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 182

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr

-continued

65	70	75	80
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys	85	90	95
Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys	100	105	110
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro	115	120	125
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys	130	135	140
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp	145	150	155
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu	165	170	175
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu	180	185	190
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn	195	200	205
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly	210	215	220
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu	225	230	235
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr	245	250	255
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn	260	265	270
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe	275	280	285
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn	290	295	300
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr	305	310	315
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys	325	330	

<210> SEQ ID NO 183

<211> LENGTH: 330

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 183

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys	1	5	10	15
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr	20	25	30	
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser	35	40	45	
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser	50	55	60	
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr	65	70	75	80
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys				

-continued

85					90					95					
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys
			100					105					110		
Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
			115				120					125			
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
			130				135					140			
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp
			145				150					155			160
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
			165						170					175	
Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu
			180					185					190		
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn
			195				200					205			
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
			210				215					220			
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu
			225				230					235			240
Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr
			245						250					255	
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn
			260					265					270		
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe
			275				280					285			
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn
			290				295					300			
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	Arg	Phe	Thr
			305				310					315			320
Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys						
			325					330							

<210> SEQ ID NO 184

<211> LENGTH: 326

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 184

Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
1				5					10					15	
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
			20					25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
			35				40					45			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
			50			55						60			
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr	Gln	Thr
			65			70			75					80	
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85					90						95	
Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro

-continued

100					105					110					
Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp
	115						120					125			
Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp
	130					135					140				
Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly
	145					150					155				160
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn
			165						170					175	
Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp
			180					185					190		
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro
		195					200					205			
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu
	210					215					220				
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn
	225					230					235				240
Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile
			245						250					255	
Ser	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr
		260						265					270		
Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys
		275					280					285			
Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys
	290					295					300				
Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu
	305					310					315				320
Ser	Leu	Ser	Pro	Gly	Lys										
			325												

<210> SEQ ID NO 185
 <211> LENGTH: 326
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 185

Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
1			5						10				15		
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
		20						25				30			
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
	35						40				45				
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55					60				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr	Gln	Thr
	65				70						75			80	
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85					90					95		
Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro
		100						105					110		
Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp

-continued

115					120					125					
Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp
130						135					140				
Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly
145					150					155					160
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn
				165					170						175
Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp
			180					185					190		
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro
		195					200					205			
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu
	210						215					220			
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn
225					230					235					240
Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile
			245						250						255
Ser	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr
		260						265					270		
Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys
		275					280					285			
Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys
	290						295					300			
Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	Arg	Phe	Thr	Gln	Lys	Ser	Leu
305					310					315					320
Ser	Leu	Ser	Pro	Gly	Lys										
				325											

<210> SEQ ID NO 186

<211> LENGTH: 327

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 186

Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
1			5						10					15	
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
		20						25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
	35						40					45			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55					60				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr
65					70					75					80
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85						90					95	
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Ser	Cys	Pro	Ala	Pro
			100					105					110		
Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys
	115						120					125			
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val

-continued

130	135	140
Asp Val Ser Gln Glu Asp	Pro Glu Val Gln Phe	Asn Trp Tyr Val Asp
145	150	155 160
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe		
	165	170 175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
	180	185 190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu		
	195	200 205
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg		
	210	215 220
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys		
	225	230 235 240
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp		
	245	250 255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys		
	260	265 270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser		
	275	280 285
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser		
	290	295 300
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser		
	305	310 315 320
Leu Ser Leu Ser Leu Gly Lys		
	325	
<210> SEQ ID NO 187		
<211> LENGTH: 327		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: synthetic		
<400> SEQUENCE: 187		
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg		
1	5	10 15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr		
	20	25 30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser		
	35	40 45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser		
	50	55 60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr		
	65	70 75 80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys		
	85	90 95
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro		
	100	105 110
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys		
	115	120 125
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val		
	130	135 140
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp		

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145	150	155	160
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe	165	170	175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp	180	185	190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu	195	200	205
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg	210	215	220
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys	225	230	235
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp	245	250	255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys	260	265	270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser	275	280	285
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser	290	295	300
Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln Lys Ser	305	310	315
Leu Ser Leu Ser Leu Gly Lys	325		

<210> SEQ ID NO 188

<211> LENGTH: 329

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 188

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys	1	5	10	15
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr	20	25	30	
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser	35	40	45	
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser	50	55	60	
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr	65	70	75	80
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys	85	90	95	
Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys	100	105	110	
Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys	115	120	125	
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val	130	135	140	
Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr	145	150	155	160
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu				

<400> SEQUENCE: 189

Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys
1			5						10					15	
Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
			20					25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35					40					45			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55					60				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr
65					70				75						80
Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85					90						95	
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys
			100					105					110		
Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
			115				120					125			
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
		130				135					140				
Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr
145					150					155					160
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
				165					170					175	
Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His

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180					185					190					
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
	195						200					205			
Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln
	210					215					220				
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu
	225				230					235				240	
Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro
			245						250					255	
Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn
		260						265					270		
Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu
		275						280					285		
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val
	290					295					300				
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	Arg	Phe	Thr	Gln
	305				310					315					320
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys							
					325										
<210> SEQ ID NO 190															
<211> LENGTH: 326															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: synthetic															
<400> SEQUENCE: 190															
Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
1				5					10					15	
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
		20						25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
	35					40						45			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55					60				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr
	65				70					75				80	
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85					90						95	
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro
		100						105						110	
Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp
		115					120					125			
Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp
	130					135					140				
Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly
	145				150					155				160	
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn
			165					170						175	
Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp
		180						185					190		
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro

-continued

195					200					205					
Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu
210						215					220				
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn
225					230					235					240
Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile
				245					250					255	
Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr
			260					265					270		
Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg
		275					280					285			
Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys
290						295					300				
Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu
305					310					315					320
Ser	Leu	Ser	Leu	Gly	Lys										
				325											

<210> SEQ ID NO 191

<211> LENGTH: 326

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 191

Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
1				5					10					15	
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
		20						25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35				40					45				
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55					60				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr
65					70					75					80
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85					90						95	
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro
			100					105						110	
Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp
		115					120					125			
Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp
	130					135					140				
Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly
145				150					155						160
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn
			165					170						175	
Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp
			180					185						190	
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro
	195						200					205			
Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu

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<210> SEQ ID NO 192
<211> LENGTH: 232
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 192

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1          5          10          15
Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20          25          30
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35          40          45
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50          55          60
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65          70          75          80
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85          90          95
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
100         105         110
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115         120         125
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130         135         140
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145         150         155         160
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165         170         175
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180         185         190
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195         200         205
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210         215         220
Ser Leu Ser Leu Ser Pro Gly Lys

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225 230

<210> SEQ ID NO 193
<211> LENGTH: 232
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 193

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 115 120 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 165 170 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 180 185 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> SEQ ID NO 194
<211> LENGTH: 228
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 194

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
1 5 10 15

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

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His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu
50						55					60				
Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr
65					70					75					80
Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp	Leu	Asn
				85					90					95	
Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro
			100						105				110		
Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln
		115					120					125			
Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val
	130					135					140				
Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ser	Val
145					150					155					160
Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro
				165					170					175	
Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr
			180					185					190		
Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val
		195					200					205			
Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu
	210					215					220				
Ser	Pro	Gly	Lys												
225															

<210> SEQ ID NO 195
 <211> LENGTH: 228
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 195

Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val
1				5					10				15		
Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
			20					25					30		
Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser
	35						40					45			
His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu
	50					55					60				
Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr
65					70					75					80
Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp	Leu	Asn
				85					90					95	
Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro
			100						105				110		
Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln
		115					120					125			
Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val
	130					135					140				
Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ser	Val
145					150					155					160

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<210> SEQ ID NO 196
<211> LENGTH: 229
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic
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[illegible]

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<210> SEQ ID NO 197
<211> LENGTH: 229
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 197

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
1 5 10 15
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45
Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
130 135 140
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145 150 155 160
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
165 170 175
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
180 185 190
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
195 200 205
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
210 215 220
Leu Ser Leu Gly Lys
225

<210> SEQ ID NO 198

<211> LENGTH: 231

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 198

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15
Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
50 55 60
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65 70 75 80
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
85 90 95

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Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
 100 105 110
 Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 115 120 125
 Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
 130 135 140
 Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 145 150 155 160
 Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 165 170 175
 Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 180 185 190
 Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
 195 200 205
 Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 210 215 220
 Leu Ser Leu Ser Pro Gly Lys
 225 230

<210> SEQ ID NO 199
 <211> LENGTH: 231
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 199

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 1 5 10 15
 Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 20 25 30
 Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 35 40 45
 Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
 50 55 60
 Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
 65 70 75 80
 Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
 85 90 95
 Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
 100 105 110
 Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 115 120 125
 Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
 130 135 140
 Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 145 150 155 160
 Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 165 170 175
 Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 180 185 190
 Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
 195 200 205

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Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Pro Gly Lys
225 230

<210> SEQ ID NO 200
<211> LENGTH: 228
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic

<400> SEQUENCE: 200

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Pro Val
1 5 10 15

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser
100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val
130 135 140

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
145 150 155 160

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr
180 185 190

Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val
195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
210 215 220

Ser Leu Gly Lys
225

<210> SEQ ID NO 201
<211> LENGTH: 228
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[illegible]

7. The composition of any one of claims 1-6, wherein the target tumor cell is a human tumor cell.

8. The composition of any one of claims 1-7, wherein the bispecific antigen-binding molecule induces T cell-mediated tumor cell killing with an EC₅₀ value of less than about 1.3 nM, as measured in an in vitro T cell-mediated tumor cell killing assay.

9. The composition of any one of claims **1-8**, wherein the target tumor cell expresses a tumor-associated antigen selected from the group consisting of AFP, ALK, BAGE proteins, BIRC5 (survivin), BIRC7, β -catenin, bcr-abl, BRCA1, BORIS, CA9, carbonic anhydrase IX, caspase-8, CALR, CCR5, CD19, CD20 (MSA41), CD22, CD30, CD40, CDK4, CEA, CTLA4, cyclin-B1, CYP1B1, EGFR, EGFRvIII, ErbB2/Her2, ErbB3, ErbB4, ETV6-AML, EpCAM, EphA2, Fra-1, FOLR1, GAGE proteins (e.g., GAGE-1, -2), GD2, GD3, GloboH, glypican-3, GM3, gp100, Her2, HLA/B-raf, HLA/k-ras, HLA/MAGE-A3, hTERT, LMP2, MAGE proteins (e.g., MAGE-1, -2, -3, -4, -6, and -12), MART-1, mesothelin, ML-IAP, Muc1, Muc2, Muc3, Muc4, Muc5, Muc16 (CA-125), MUM1, NA17, NY-BR1, NY-BR62, NY-BR85, NY-ESO1, OX40, p15, p53, PAP, PAX3, PAX5, PCTA-1, PLAC1, PRLR, PRAME, PSMA (FOLH1), RAGE proteins, Ras, RGS5, Rho, SART-1, SART-3, STEAP1, STEAP2, TAG-72, TGF- β , TMRPSS2, Thompson-nouvelle antigen (Tn), TRP-1, TRP-2, tyrosinase, and uroplakin-3.

9. The composition of any one of claims **1-8**, wherein the target tumor cell expresses a tumor-associated antigen selected from the group consisting of AFP, ALK, BAGE proteins, BIRC5 (survivin), BIRC7, β -catenin, bcr-abl, BRCA1, BORIS, CA9, carbonic anhydrase IX, caspase-8, CALR, CCR5, CD19, CD20 (MSA41), CD22, CD30, CD40, CDK4, CEA, CTLA4, cyclin-B1, CYP1B1, EGFR, EGFRvIII, ErbB2/Her2, ErbB3, ErbB4, ETV6-AML, EpCAM, EphA2, Fra-1, FOLR1, GAGE proteins (e.g., GAGE-1, -2), GD2, GD3, GloboH, glypican-3, GM3, gp100, Her2, HLA/B-raf, HLA/k-ras, HLA/MAGE-A3, hTERT, LMP2, MAGE proteins (e.g., MAGE-1, -2, -3, -4, -6, and -12), MART-1, mesothelin, ML-IAP, Muc1, Muc2, Muc3, Muc4, Muc5, Muc16 (CA-125), MUM1, NA17, NY-BR1, NY-BR62, NY-BR85, NY-ESO1, OX40, p15, p53, PAP, PAX3, PAX5, PCTA-1, PLAC1, PRLR, PRAME, PSMA (FOLH1), RAGE proteins, Ras, RGS5, Rho, SART-1, SART-3, STEAP1, STEAP2, TAG-72, TGF- β , TMPPRSS2, Thompson-nouvelle antigen (Tn), TRP-1, TRP-2, tyrosinase, and uroplakin-3.

9. The composition of any one of claims **1-8**, wherein the target tumor cell expresses a tumor-associated antigen selected from the group consisting of AFP, ALK, BAGE proteins, BIRC5 (survivin), BIRC7, β -catenin, bcr-abl, BRCA1, BORIS, CA9, carbonic anhydrase IX, caspase-8, CALR, CCR5, CD19, CD20 (MSA41), CD22, CD30, CD40, CDK4, CEA, CTLA4, cyclin-B1, CYP1B1, EGFR, EGFRvIII, ErbB2/Her2, ErbB3, ErbB4, ETV6-AML, EpCAM, EphA2, Fra-1, FOLR1, GAGE proteins (e.g., GAGE-1, -2), GD2, GD3, GloboH, glypican-3, GM3, gp100, Her2, HLA/B-raf, HLA/k-ras, HLA/MAGE-A3, hTERT, LMP2, MAGE proteins (e.g., MAGE-1, -2, -3, -4, -6, and -12), MART-1, mesothelin, ML-IAP, Muc1, Muc2, Muc3, Muc4, Muc5, Muc16 (CA-125), MUM1, NA17, NY-BR1, NY-BR62, NY-BR85, NY-ESO1, OX40, p15, p53, PAP, PAX3, PAX5, PCTA-1, PLAC1, PRLR, PRAME, PSMA (FOLH1), RAGE proteins, Ras, RGS5, Rho, SART-1, SART-3, STEAP1, STEAP2, TAG-72, TGF- β , TMPPRSS2, Thompson-nouvelle antigen (Tn), TRP-1, TRP-2, tyrosinase, and uroplakin-3.

9. The composition of any one of claims **1-8**, wherein the target tumor cell expresses a tumor-associated antigen selected from the group consisting of AFP, ALK, BAGE proteins, BIRC5 (survivin), BIRC7, β -catenin, bcr-abl, BRCA1, BORIS, CA9, carbonic anhydrase IX, caspase-8, CALR, CCR5, CD19, CD20 (MSA41), CD22, CD30, CD40, CDK4, CEA, CTLA4, cyclin-B1, CYP1B1, EGFR, EGFRvIII, ErbB2/Her2, ErbB3, ErbB4, ETV6-AML, EpCAM, EphA2, Fra-1, FOLR1, GAGE proteins (e.g., GAGE-1, -2), GD2, GD3, GloboH, glypican-3, GM3, gp100, Her2, HLA/B-raf, HLA/k-ras, HLA/MAGE-A3, hTERT, LMP2, MAGE proteins (e.g., MAGE-1, -2, -3, -4, -6, and -12), MART-1, mesothelin, ML-IAP, Muc1, Muc2, Muc3, Muc4, Muc5, Muc16 (CA-125), MUM1, NA17, NY-BR1, NY-BR62, NY-BR85, NY-ESO1, OX40, p15, p53, PAP, PAX3, PAX5, PCTA-1, PLAC1, PRLR, PRAME, PSMA (FOLH1), RAGE proteins, Ras, RGS5, Rho, SART-1, SART-3, STEAP1, STEAP2, TAG-72, TGF- β , TMRPSS2, Thompson-nouvelle antigen (Tn), TRP-1, TRP-2, tyrosinase, and uroplakin-3.

9. The composition of any one of claims **1-8**, wherein the target tumor cell expresses a tumor-associated antigen selected from the group consisting of AFP, ALK, BAGE proteins, BIRC5 (survivin), BIRC7, β -catenin, bcr-abl, BRCA1, BORIS, CA9, carbonic anhydrase IX, caspase-8, CALR, CCR5, CD19, CD20 (MSA41), CD22, CD30, CD40, CDK4, CEA, CTLA4, cyclin-B1, CYP1B1, EGFR, EGFRvIII, ErbB2/Her2, ErbB3, ErbB4, ETV6-AML, EpCAM, EphA2, Fra-1, FOLR1, GAGE proteins (e.g., GAGE-1, -2), GD2, GD3, GloboH, glypican-3, GM3, gp100, Her2, HLA/B-raf, HLA/k-ras, HLA/MAGE-A3, hTERT, LMP2, MAGE proteins (e.g., MAGE-1, -2, -3, -4, -6, and -12), MART-1, mesothelin, ML-IAP, Muc1, Muc2, Muc3, Muc4, Muc5, Muc16 (CA-125), MUM1, NA17, NY-BR1, NY-BR62, NY-BR85, NY-ESO1, OX40, p15, p53, PAP, PAX3, PAX5, PCTA-1, PLAC1, PRLR, PRAME, PSMA (FOLH1), RAGE proteins, Ras, RGS5, Rho, SART-1, SART-3, STEAP1, STEAP2, TAG-72, TGF- β , TMPPRSS2, Thompson-nouvelle antigen (Tn), TRP-1, TRP-2, tyrosinase, and uroplakin-3.

10. The composition of any one of claims **1-9**, wherein the tumor-associated antigen is CD20, EGFRvIII, PSMA (FOLH1), STEAP2, or MUC16.

11. The composition of any one of claims **1-10**, wherein the bispecific antigen-binding molecule comprises a first heavy chain comprising: a CDR1 comprising amino acid residues 1-7 of SEQ ID NO:178, a CDR2 comprising amino acid residues 1-7 of SEQ ID NO:179, and/or a CDR3 comprising amino acid residues 4-11 of SEQ ID NO:180.

12. The composition of claim **11**, wherein the first heavy chain comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 12 or 20.

13. The composition of any one of claim **11** or **12**, wherein the first heavy chain comprises a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 14 or 54.

14. The composition of any one of claims **11** to **13**, wherein the first heavy chain comprises a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 16, SEQ ID NO: 24, SEQ ID NO: 32, SEQ ID NO: 40, SEQ ID NO: 48, SEQ ID NO: 56, SEQ ID NO: 64, SEQ ID NO: 72, SEQ ID NO: 80, SEQ ID NO: 88, SEQ ID NO: 96, SEQ ID NO: 104, SEQ ID NO: 112, SEQ ID NO: 120, SEQ ID NO: 128, SEQ ID NO: 136, SEQ ID NO: 144, or SEQ ID NO: 152.

15. The composition of any one of claims **11** to **14**, wherein the first heavy chain comprises variable domain framework regions having an amino acid sequence selected from FR1 (SEQ ID NO: 174), FR2 (SEQ ID NO: 175), FR3 (SEQ ID NO: 176), and FR4 (SEQ ID NO: 177).

16. The composition of any one of claims **1-11**, wherein the bispecific antigen-binding molecule comprises a HCVR and LCVR amino acid sequence pair (HCVR/LCVR) selected from the group consisting of: SEQ ID NOs: 2/162; 10/162; 18/162; 26/162; 34/162; 42/162; 50/162; 58/162; 66/162; 74/162; 82/162; 90/162; 98/162; 106/162; 114/162; 122/162; 130/162; 138/162; 146/162.

17. The composition of any one of claims **1-11**, wherein the bispecific antigen binding molecule comprises a first heavy chain comprising a HCVR comprising HCDR1-HCDR2-HCDR3 domains having the amino acid sequences of SEQ ID NOs: 178-179-180, respectively.

18. A method of making the composition of any one of claims **1-17**, the method comprising:

- identifying the amino acid sequence of a first heavy chain derived from a first antibody that specifically binds CD3 with an EC_{50} value of less than about 40 nM,
- modifying selected amino acid residues in the heavy chain variable region of the first antibody to produce a modified antibody,
- pairing the modified antibody with a second heavy chain derived from a second antibody that specifically binds a target tumor antigen to produce a bispecific antibody,
- testing the bispecific antibody in a binding affinity assay, and if the binding affinity to CD3 has an EC_{50} value of greater than about 500 nM, then
- preparing a composition comprising the bispecific antibody and a pharmaceutically acceptable carrier or diluent.

19. The method of claim **18**, wherein the first antibody heavy chain comprises a first C_H3 domain and the second antibody comprises a second C_H3 domain suitable for bispecific pairing and isolation.

20. The method of claim **19**, wherein the first and second C_H3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference.

21. A pharmaceutical composition comprising the composition of any one of claims **1-17** or made by the method of any one of claims **18-20**, comprising a pharmaceutically acceptable carrier or diluent.

22. A method for treating cancer in a subject, the method comprising administering to the subject the pharmaceutical composition of claim **21**.

23. The method of claim **22**, wherein the cancer is selected from the group consisting of: pancreatic cancer, melanoma, glioblastoma, head and neck cancer, prostate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, malignant mesothelioma, multiple myeloma, ovarian cancer, small cell lung cancer, non-small cell lung cancer, synovial sarcoma, thyroid cancer, breast cancer, melanomaglioma, breast cancer, squamous cell carcinoma, esophageal cancer, clear cell renal cell carcinoma, chromophobe renal cell carcinoma, renal oncocytoma, renal transitional cell carcinoma, urothelial carcinoma, adenocarcinoma, or small cell carcinoma.

24. The method of claim **22** or **23**, wherein the subject is afflicted with a tumor that is resistant to, or incompletely responsive to monospecific therapy alone.

25. A method for mediating tumor cell lysis, or suppressing tumor growth in a subject, the method comprising administering to the subject a therapeutic amount of the composition of claim **21**.

26. The method of claim **25**, wherein the amount is sufficient to reduce tumor burden, produce tumor regression, inhibit tumor growth or reduce tumor development in the subject.

27. The method of claim **26**, wherein subject is afflicted with a tumor expressing a tumor-associated antigen selected from the group consisting of AFP, ALK, BAGE proteins, BIRC5 (survivin), BIRC7, β -catenin, bcr-abl, BRCA1, BORIS, CA9, carbonic anhydrase IX, caspase-8, CALR, CCR5, CD19, CD20 (MS4A1), CD22, CD30, CD40, CDK4, CEA, CTLA4, cyclin-B1, CYP1B1, EGFR, EGFRvIII, ErbB2/Her2, ErbB3, ErbB4, ETV6-AML, EpCAM, EphA2, Fra-1, FOLR1, GAGE proteins (e.g., GAGE-1, -2), GD2, GD3, GloboH, glypican-3, GM3, gp100, Her2, HLA/B-raf, HLA/k-ras, HLA/MAGE-A3, hTERT, LMP2, MAGE proteins (e.g., MAGE-1, -2, -3, -4, -6, and -12), MART-1, mesothelin, ML-IAP, Muc1, Muc2, Muc3, Muc4, Muc5, Muc16 (CA-125), MUM1, NA17, NY-BR1, NY-BR62, NY-BR85, NY-ESO1, OX40, p15, p53, PAP, PAX3, PAX5, PCTA-1, PLAC1, PRLR, PRAME, PSMA (FOLH1), RAGE proteins, Ras, RGS5, Rho, SART-1, SART-3, STEAP1, STEAP2, TGS-72, TGF- β , TMPRSS2, Thompson-nouvelle antigen (Tn), TRP-1, TRP-2, tyrosinase, and uroplakin-3.

28. Use of a cytotoxic bispecific antibody having reduced clearance for suppression of tumor growth in a subject, wherein the bispecific antibody comprises no detectable binding affinity to an effector cell or weak binding affinity to an effector cell at least greater than 200 EC_{50} or K_D , and specifically binds with high affinity to a target tumor cell, wherein binding affinity is measured in an in vitro FACS binding assay or in vitro surface plasmon resonance assay.

29. A method of producing a cytotoxic bispecific antibody, comprising:

- a. identifying a first human antibody or antigen-binding fragment thereof that interacts with an effector cell antigen from multiple species;
- b. identifying the germline amino acid residues of the heavy chain variable region (HCVR) of the first human antibody;
- c. comparing the amino acid sequence of the HCVR of the first human antibody to the amino acid sequence of the corresponding germline HCVR;
- d. identifying amino acids within a modified region of the HCVR of the first human antibody; whereby a modified region in the first human antibody displays at least one amino acid modification by substitution, deletion or addition of a single amino acid residue compared to the same region in the germline HCVR;
- e. producing a plurality of modified antibodies each comprising at least one modified region of the HCVR;
- f. screening each of the plurality of modified antibodies for monovalent affinity to the effector cell antigen;
- g. selecting those modified antibodies that exhibit weaker binding affinity for the effector cell antigen compared to the first human antibody; and
- h. pairing a selected antibody with a second antibody that interacts with a tumor-associated antigen to produce a cytotoxic bispecific antibody.

* * * * *