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(54) METHODS OF MAKING AND USING GUIDANCE AND NAVIGATION CONTROL PROTEINS

(71) Applicants: **SYSTIMMUNE, INC.**, Redmond, WA (US); **SICHUAN BAILI PHARMACEUTICAL CO. LTD.**, Chengdu, Sichuan (CN)

(72) Inventors: **Yi ZHU**, Chengdu (CN); **Ole OLSEN**, Everett, WA (US); **Jahan KHALILI**, Everett, WA (US); **Dong XIA**, Redmond, WA (US); **David JELLYMAN**, Duvall, WA (US); **Katrina BYKOVA**, Seattle, WA (US); **Anne-Marie ROUSSEAU**, Seattle, WA (US); **Camilla WANG**, Sammamish, WA (US); **Zeren GAO**, Redmond, WA (US); **Hui HUANG**, Redmond, WA (US); **Steven K. LUNDY**, Woodinville, WA (US)

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C07K 16/28	(2006.01)
A61P 35/00	(2006.01)

(52) **U.S. Cl.**

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(57) **ABSTRACT**

The application provides methods for generating a therapeutic composition. The method includes the steps of providing a cell material comprising a cytotoxic cell, incubating the cell material with a first GNC protein to provide an activated cell composition, wherein the activated cell composition comprises a first therapeutic cell, and formulating the activated cell composition to provide a therapeutic composition, wherein the therapeutic composition is substantially free of exogenous viral and non-viral DNA or RNA. The first GNC protein comprises a first cytotoxic binding moiety and a first cancer targeting moiety, wherein the first cytotoxic binding moiety has a specificity to a first cytotoxic cell receptor and is configured to activate the first cytotoxic cell, and wherein the first cancer targeting moiety has a specificity to a first cancer cell receptor. The first therapeutic cell comprises the first GNC protein bound to the cytotoxic cell through the first cytotoxic cell receptor.

Specification includes a Sequence Listing.

A GNC protein comprising four antigen-specific binding domains in an antibody structure with targeting specificity to CD19 positive cells.

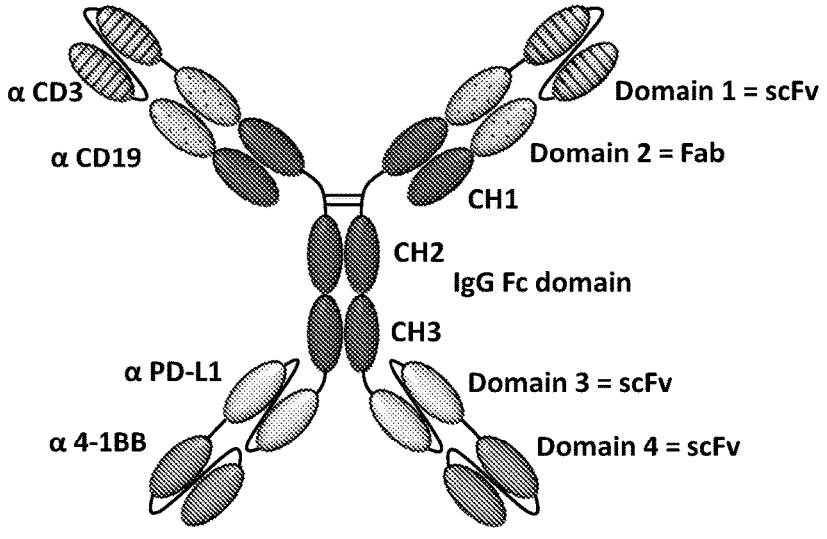


FIGURE 1. A GNC protein comprising four antigen-specific binding domains in an antibody structure with targeting specificity to CD19 positive cells.

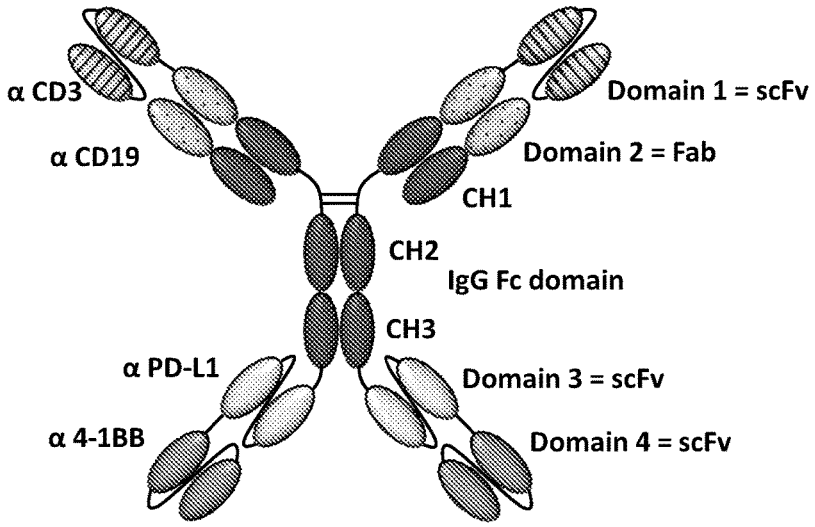


FIGURE 2. An illustration of multi-specific binding mediated by a tetra-specific GNC antibody between a T cell and a tumor cell.

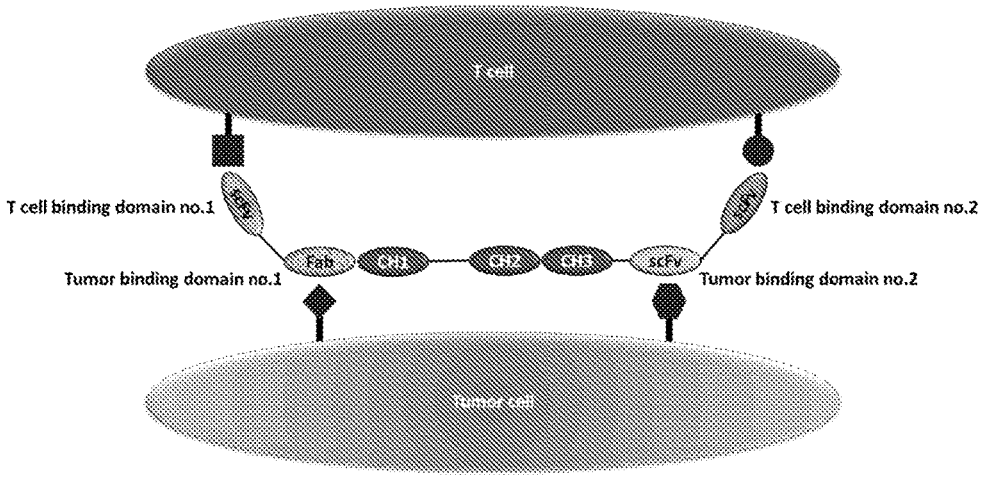


FIGURE 3. A flowchart of manufacturing processes for GNC-T cell therapy (left) and CAR-T cell therapy (right).

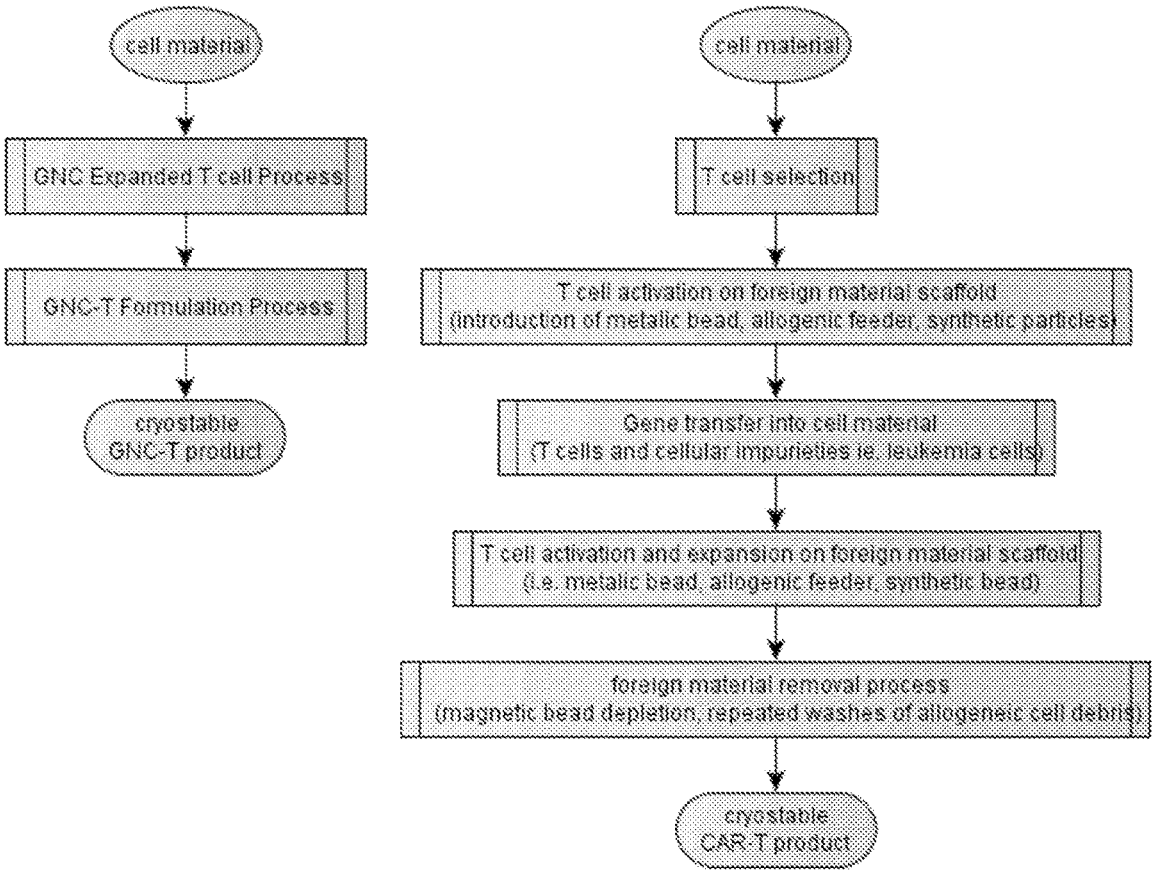


Figure 4. A diagram of sources of cell material for preparing GNC-activated therapeutic cell composition.

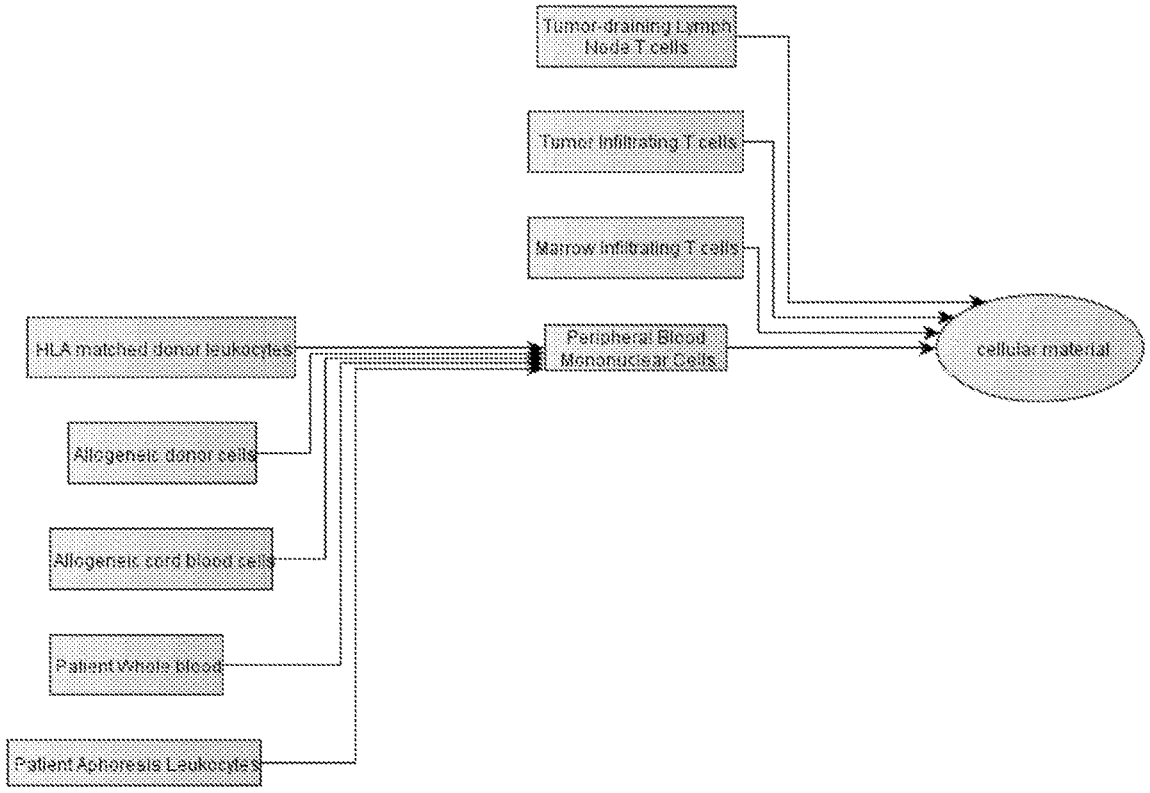


Figure 5. A diagram of sources of selected T cells for preparing GNC-activated therapeutic composition.

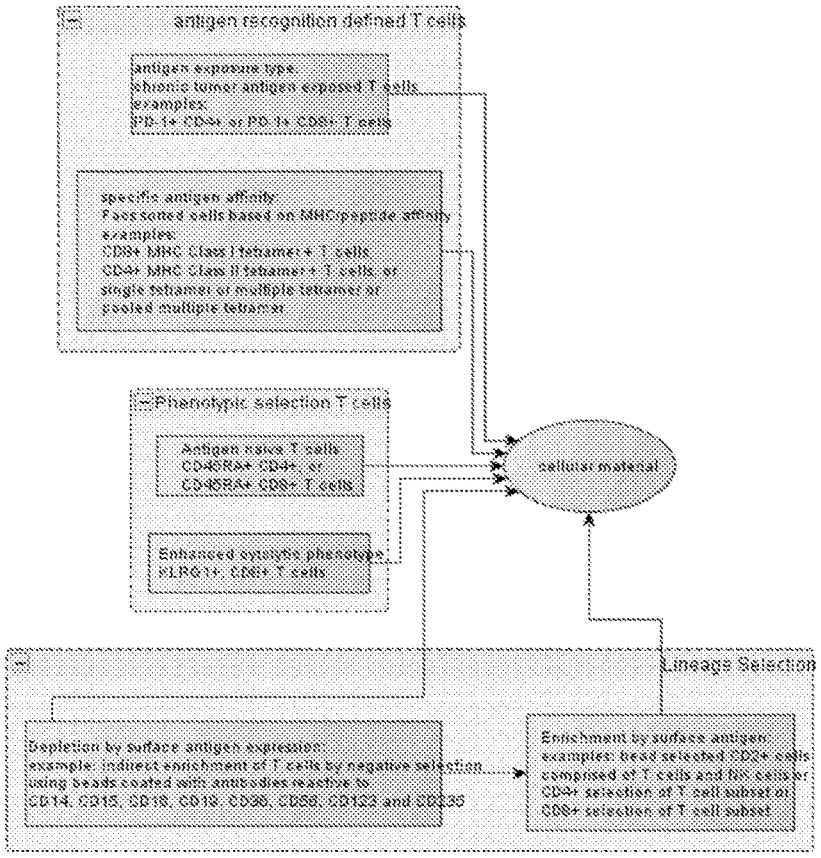


Figure 6. A diagram of preparing GNC-activated therapeutic T cell composition.

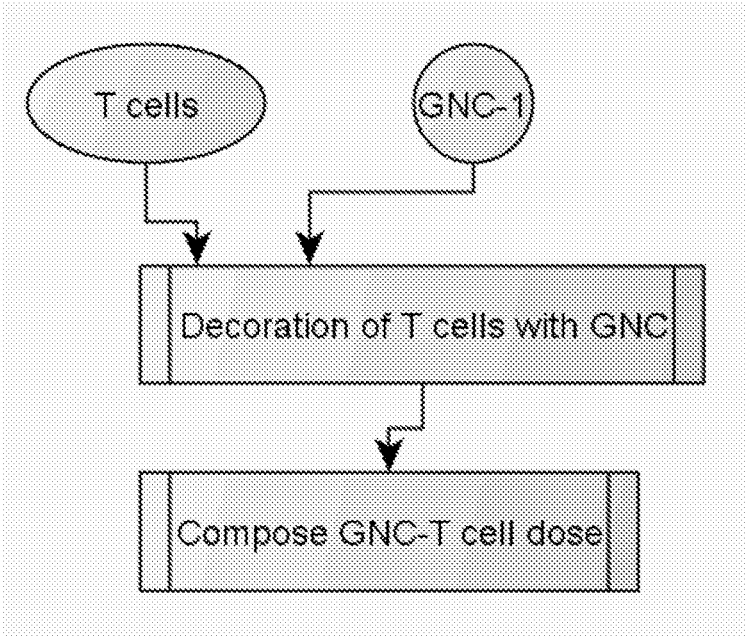


Figure 7. A diagram of incubating and formulating the first GNC-activated T cells for GNC-T cell therapy.

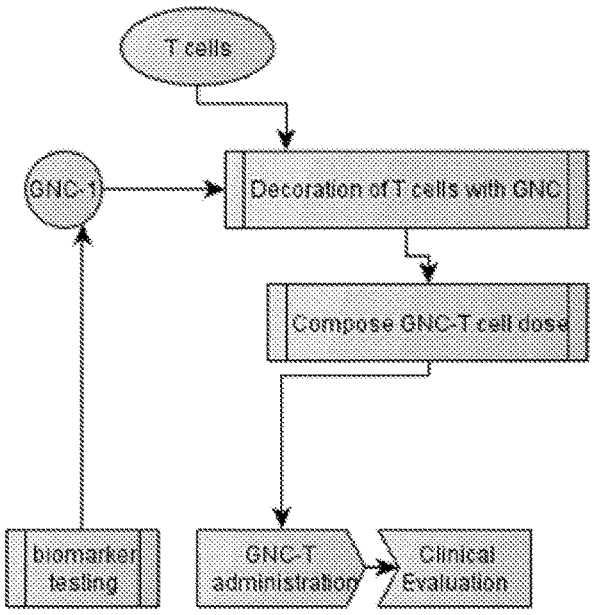


FIGURE 8. GNC proteins induce IL-2 secretion from PBMC.

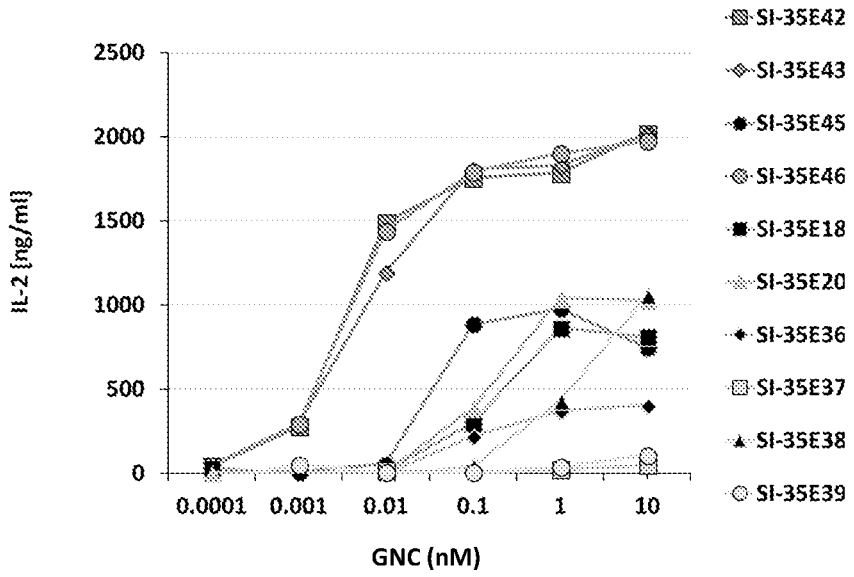


FIGURE 9. GNC proteins induce granzyme B secretion from PBMC.

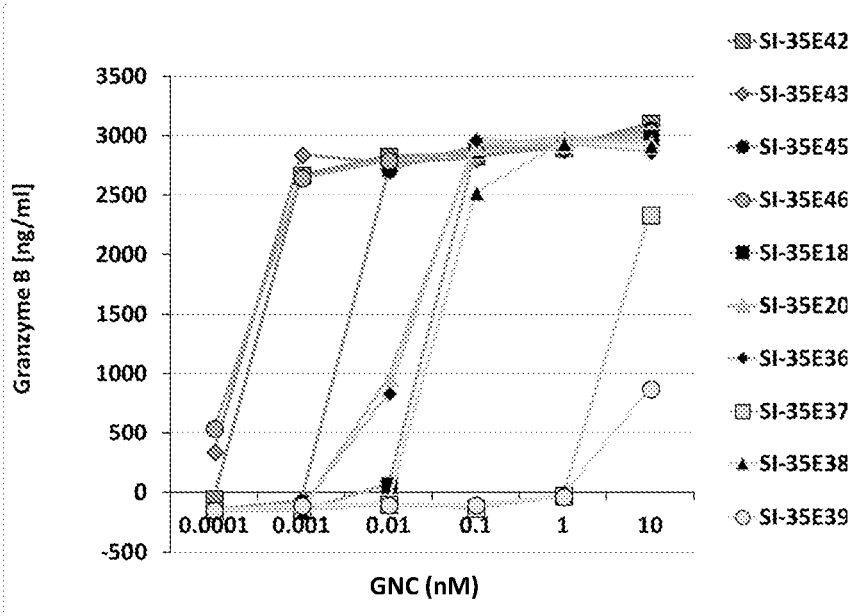


FIGURE 10. GNC proteins induce expression of the activation marker CD69 on CD4+ T cells.

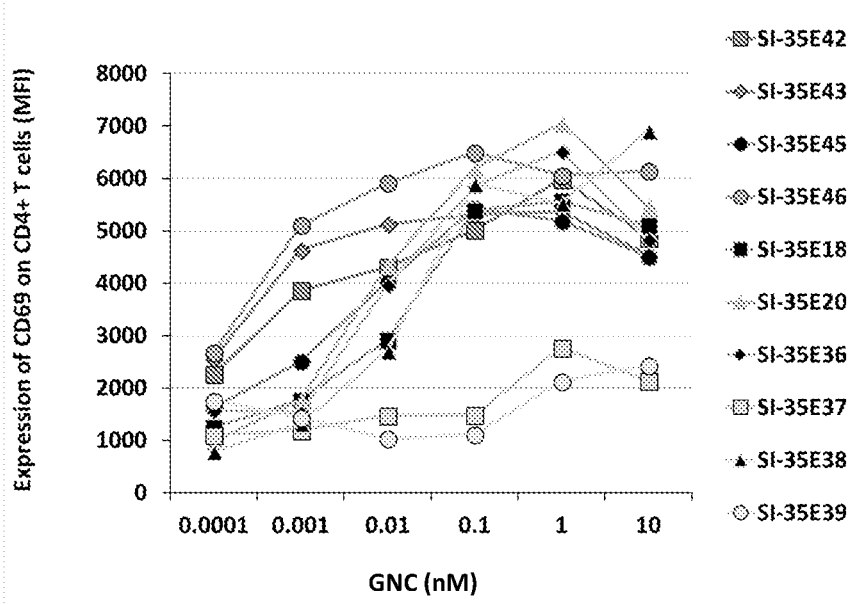


FIGURE 11. GNC proteins induce expression of the activation marker CD69 on CD8+ T cells.

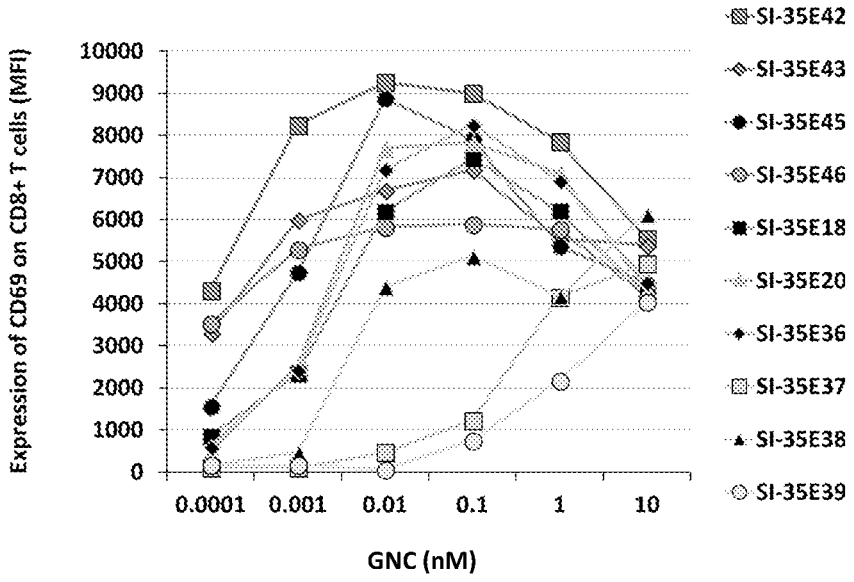


FIGURE 12. GNC proteins induce expression of the activation marker CD69 on CD56+ NK cells.

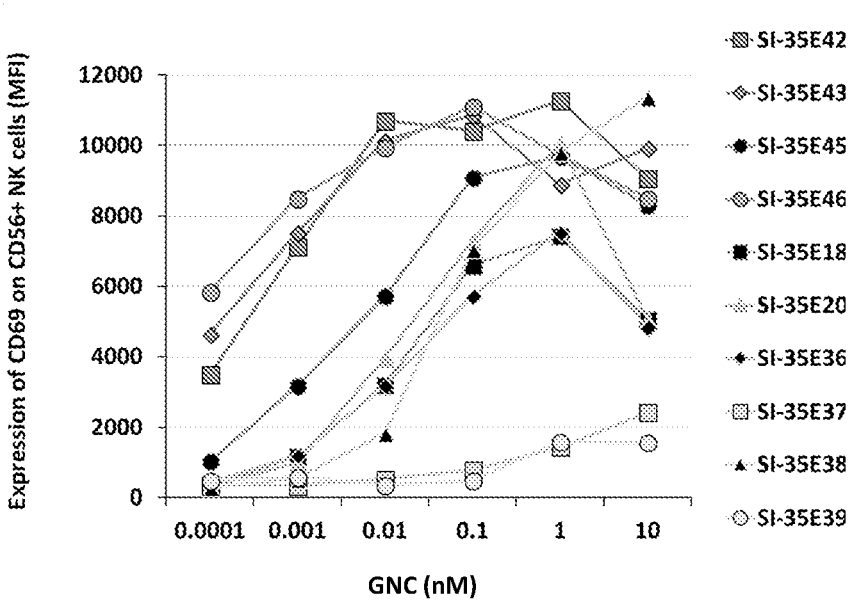


FIGURE 13. GNC proteins induce expression of the marker of cytotoxic degranulation CD107a on CD4+ T cells.

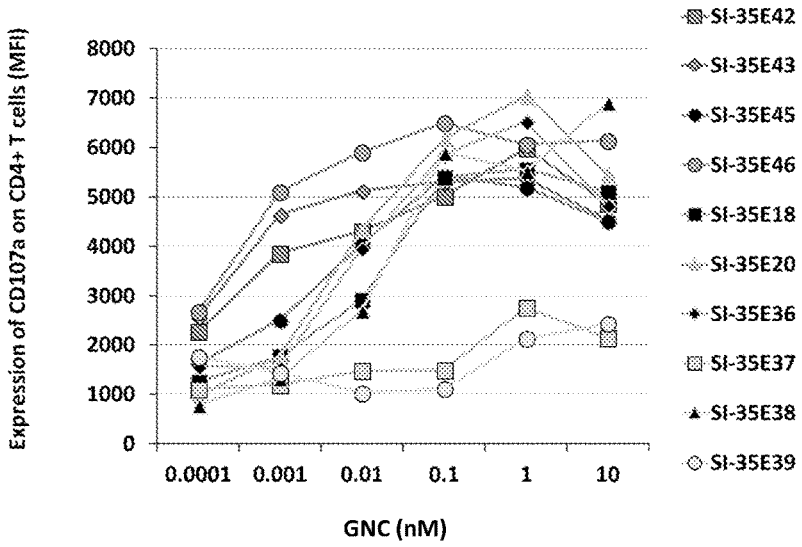


FIGURE 14. GNC proteins induce expression of the marker of cytotoxic degranulation CD107a on CD8+ T cells.

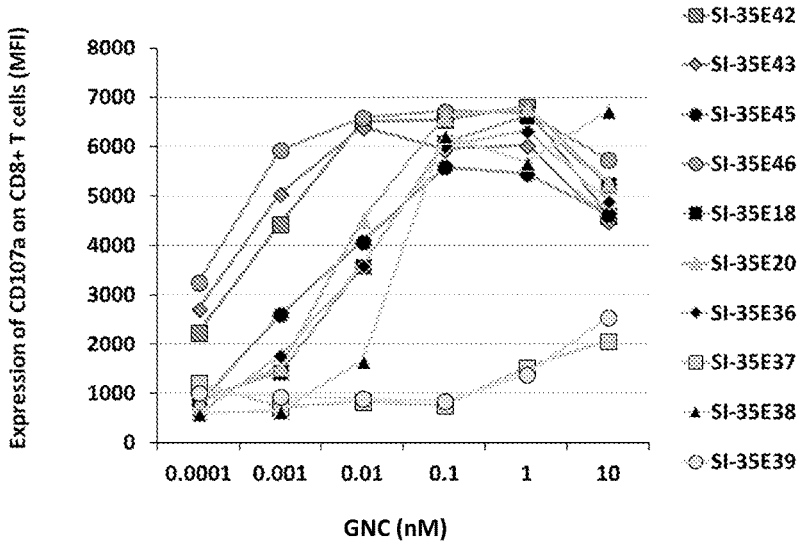


FIGURE 15. GNC proteins induce expression of the marker of cytotoxic degranulation CD107a on CD56+ NK cells.

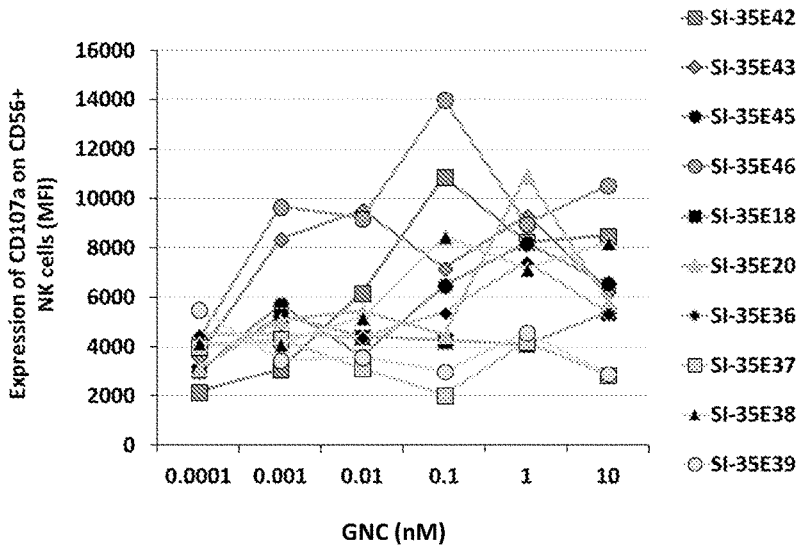


FIGURE 16. GNC proteins activate CD3+ T cells to proliferate.

GNC protein [nM]

GNC protein	0	0.1	0.3	0.6	1.25	2.5	5	10	20	40	80
SI-3SE18 460C3 x PL230C6 x 323H7 x 284A10	7.5	9.8	10.7	10.7	11.0	10.9	5.9	1.7	1.1	1.0	1.0
SI-3SE19 420H5 x PL230C6 x 323H7 x 284A10	7.6	9.7	9.7	9.4	9.5	10.3	7.6	2.2	1.0	1.0	1.0
SI-3SE20 466F6 x PL230C6 x 323H7 x 284A10	8.1	9.5	10.3	10.4	10.1	10.7	9.8	2.4	1.1	1.0	1.0
SI-3SE36 FITC x PL230C6 x 338H4 x 284A10 + 0.5nM 4-1BB mAb 420H5	4.5	10.2	11.4	10.4	11.5	12.2	10.7	6.0	1.8	1.1	1.0
SI-3SE36 FITC x PL230C6 x 338H4 x 284A10	8.0	8.8	9.1	10.0	10.4	10.3	10.8	4.6	1.5	1.0	1.0
SI-3SE37 460C3 x FITC x 338H4 x 284A10	6.2	9.8	9.9	10.1	10.4	10.3	9.6	3.1	1.4	1.1	1.0
SI-3SE38 460C3 x PL230C6 x FITC x 284A10	3.7	2.5	6.6	9.3	8.4	7.5	6.2	2.6	1.2	1.0	1.0
SI-3SE39 460C3 x PL230C6 x 338H4 x FITC	1.1	1.0	1.2	1.0	1.1	1.0	1.0	1.0	1.2	1.0	1.0

Values are for fold-over background proliferation

FIGURE 17. GNC proteins activate CD3+ T cells to secrete gamma interferon.

GNC protein [nM]

GNC protein	10	5	2.5	1.25	0.625	0.313	0.156	0.078	0.039	0.019	0
SI-35E18 460C3 x PL230C6 x 323H7 x 284A10	1.66	1.83	2.12	2.14	2.16	1.91	0.65	0.15	0.06	0.06	0.05
SI-35E19 420H5 x PL230C6 x 323H7 x 284A10	1.17	1.95	2.12	2.38	2.14	1.89	0.80	0.20	0.06	0.05	0.06
SI-35E20 466F6 x PL230C6 x 323H7 x 284A10	1.18	2.26	2.20	2.29	2.11	1.90	1.19	0.25	0.06	0.05	0.05
SI-35E36 FITC x PL230C6 x 338H4 x 284A10 + 0.5nM 4-1BB mAb 420H5	0.98	2.10	2.22	2.34	2.21	2.08	1.83	0.85	0.09	0.05	0.06
SI-35E36 FITC x PL230C6 x 338H4 x 284A10	1.26	1.99	2.04	2.13	2.27	1.76	1.32	0.53	0.09	0.05	0.06
SI-35E37 460C3 x FITC x 338H4 x 284A10	0.89	2.21	2.15	2.16	2.12	2.16	0.63	0.15	0.08	0.06	0.05
SI-35E38 460C3 x PL230C6 x FITC x 284A10	0.50	0.33	0.73	1.65	0.55	0.76	0.60	0.23	0.07	0.05	0.06
SI-35E39 460C3 x PL230C6 x 338H4 x FITC	0.07	0.07	0.08	0.07	0.07	0.05	0.06	0.06	0.05	0.06	0.07

Values are for Gamma interferon OD_{450}

FIGURE 18. GNC proteins activate naïve CD8+/CD45RA+ T cells to proliferate.

GNC protein [nM]

GNC protein	10	3	1.1	0.37	0.12	0.04	0.015	0.005	0.002	0.001	0
SI-35E18 460C3 x PL230C6 x 323H7 x 284A10	3.9	7.8	8.7	9.0	9.8	6.9	1.8	1.0	1.0	1.0	1.0
SI-35E19 420H5 x PL230C6 x 323H7 x 284A10	2.3	10.0	8.7	8.5	9.5	9.1	1.3	1.0	1.0	1.0	1.0
SI-35E20 466F6 x PL230C6 x 323H7 x 284A10	3.1	8.7	8.8	10.0	9.2	10.3	2.3	1.1	1.0	1.0	1.0
SI-35E36 FITC x PL230C6 x 338H4 x 284A10 + 0.5nM 4-1BB mAb 420H5	1.6	8.0	8.5	10.3	11.2	9.5	4.9	1.6	1.1	1.0	1.0
SI-35E36 FITC x PL230C6 x 338H4 x 284A10	1.2	3.6	5.0	6.6	5.0	4.1	1.2	1.1	1.1	1.0	1.0
SI-35E37 460C3 x FITC x 338H4 x 284A10	2.3	7.0	6.7	9.1	10.2	8.1	2.7	1.2	1.0	1.0	1.0
SI-35E38 460C3 x PL230C6 x FITC x 284A10	1.8	2.0	2.6	2.3	3.1	2.2	2.6	1.0	1.0	1.0	1.0
SI-35E39 460C3 x PL230C6 x 338H4 x FITC	0.8	0.9	1.1	1.1	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Values are for fold-over background proliferation

FIGURE 19. GNC proteins activate naïve CD8+/CD45RA+ T cells to secrete gamma interferon.

GNC protein [nM]

GNC protein	10	5	2.5	1.25	0.63	0.31	0.16	0.08	0.04	0.02	0
SI-35E18 460C3 x PL230C6 x 323H7 x 284A10	0.66	1.66	2.08	2.12	1.69	0.94	0.09	0.06	0.06	0.06	0.05
SI-35E19 420H5 x PL230C6 x 323H7 x 284A10	0.35	1.88	1.97	1.91	1.85	1.28	0.05	0.06	0.05	0.05	0.06
SI-35E20 466F6 x PL230C6 x 323H7 x 284A10	0.30	1.64	1.76	1.74	1.77	1.06	0.08	0.05	0.06	0.05	0.05
SI-35E36 FITC x PL230C6 x 338H4 x 284A10 + 0.5nM 4-1BB mAb 420H5	0.08	2.23	2.06	2.12	1.79	1.41	0.27	0.06	0.05	0.05	0.05
SI-35E36 FITC x PL230C6 x 338H4 x 284A10	0.06	1.12	1.02	1.77	1.30	0.56	0.05	0.05	0.05	0.05	0.05
SI-35E37 460C3 x FITC x 338H4 x 284A10	0.22	1.47	1.09	1.33	1.91	1.32	0.13	0.05	0.05	0.05	0.05
SI-35E38 460C3 x PL230C6 x FITC x 284A10	0.09	0.06	0.10	0.09	0.11	0.08	0.13	0.05	0.05	0.05	0.05
SI-35E39 460C3 x PL230C6 x 338H4 x FITC	0.05	0.06	0.09	0.09	0.06	0.05	0.05	0.05	0.05	0.05	0.07

Values are for Gamma interferon OD_{450}

Figure 20. Images of GET cell growth in 6-well G-Rex plates over time

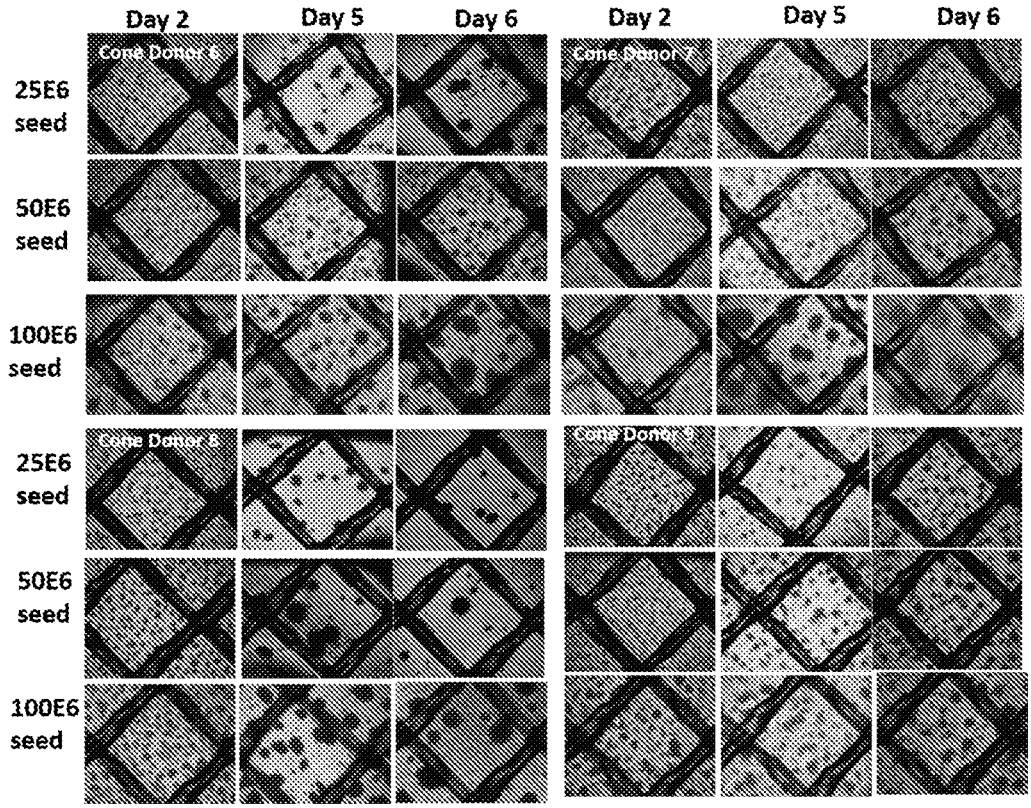
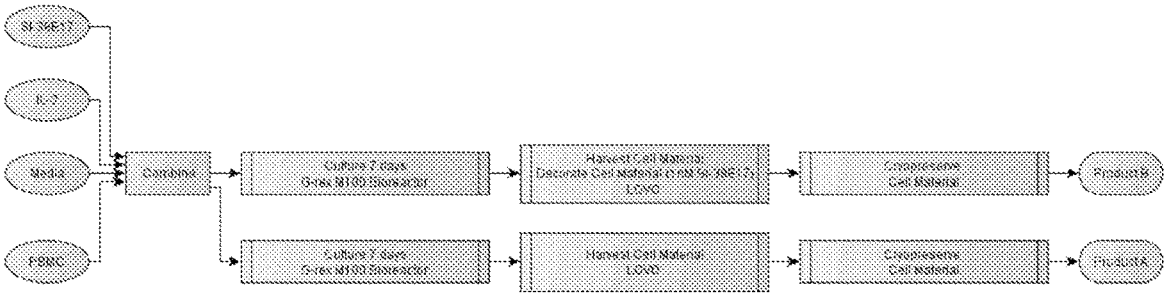


FIGURE 21. A, an example process of making the therapeutic composition as disclosed thereof, and B, cell viability of PBMC, GET, and GNC-T cells after thawing.

A.



B.

Sample ID	Avg. Viability (%)	Avg. Average Diameter (microns)
Donor12 post-thaw PBMC A	86.35	8.58
Donor12 post-thaw PBMC B	88.82	8.89
Donor12 post-thaw GET A	78.43	8.93
Donor12 post-thaw GNC-T B	77.74	9.00

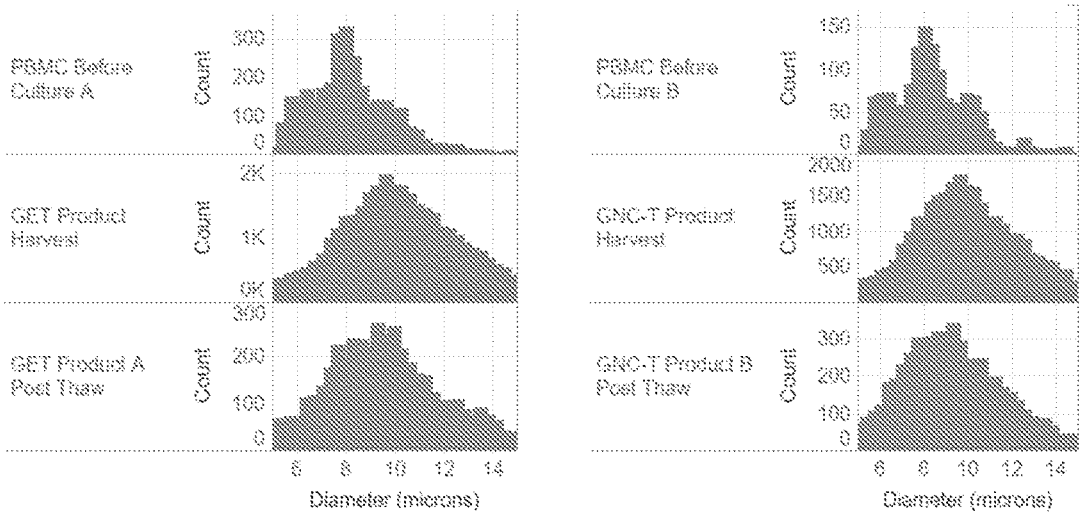


FIGURE 22. A. Flow cytometry analysis of PBMC-derived, the first GNC (SI-38E17)-activated therapeutic cell composition (Product A).

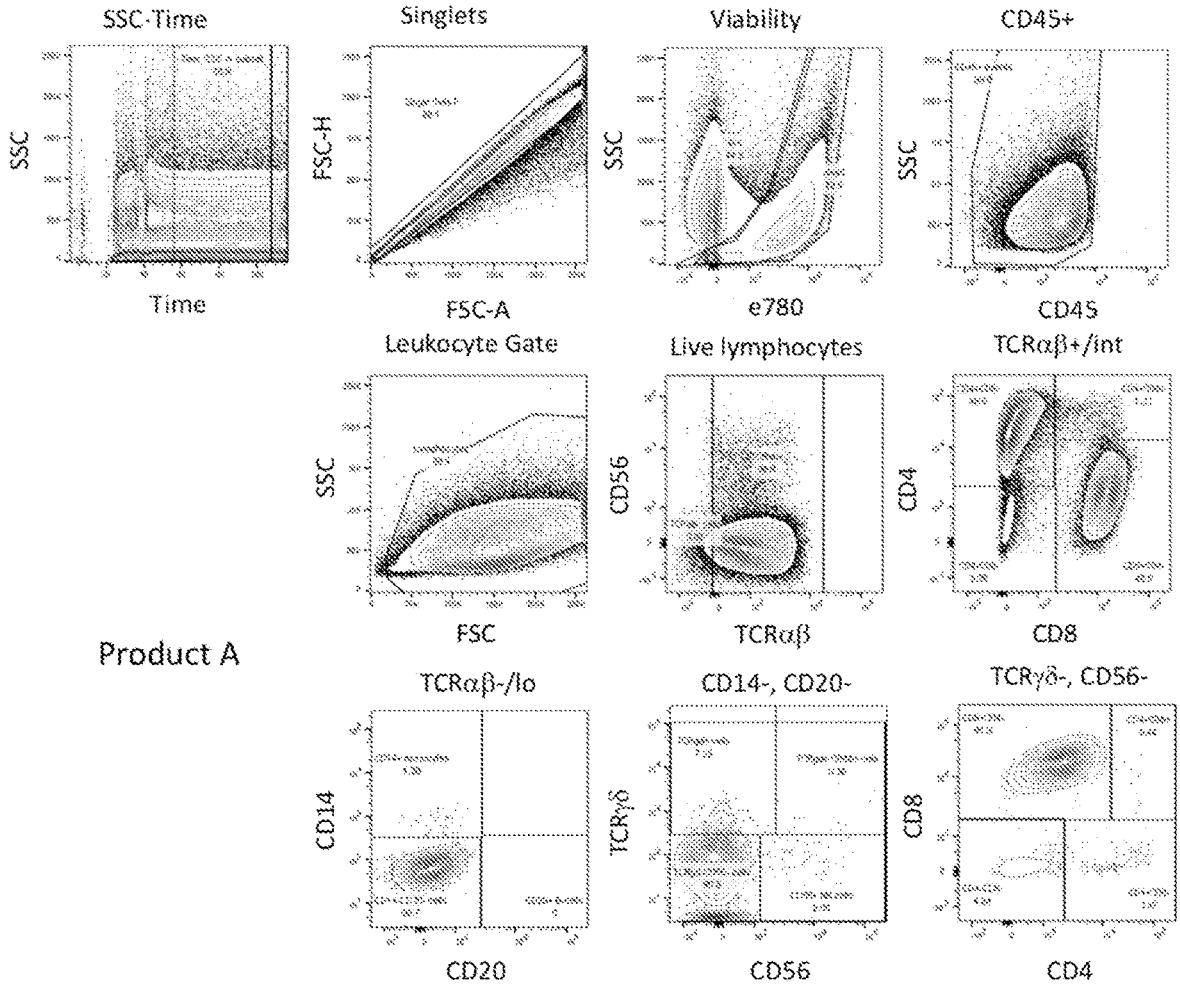


FIGURE 22. B. Flow cytometry analysis of PBMC-derived, the second GNC (SI-38E17)-decorated therapeutic cell composition (Product B).

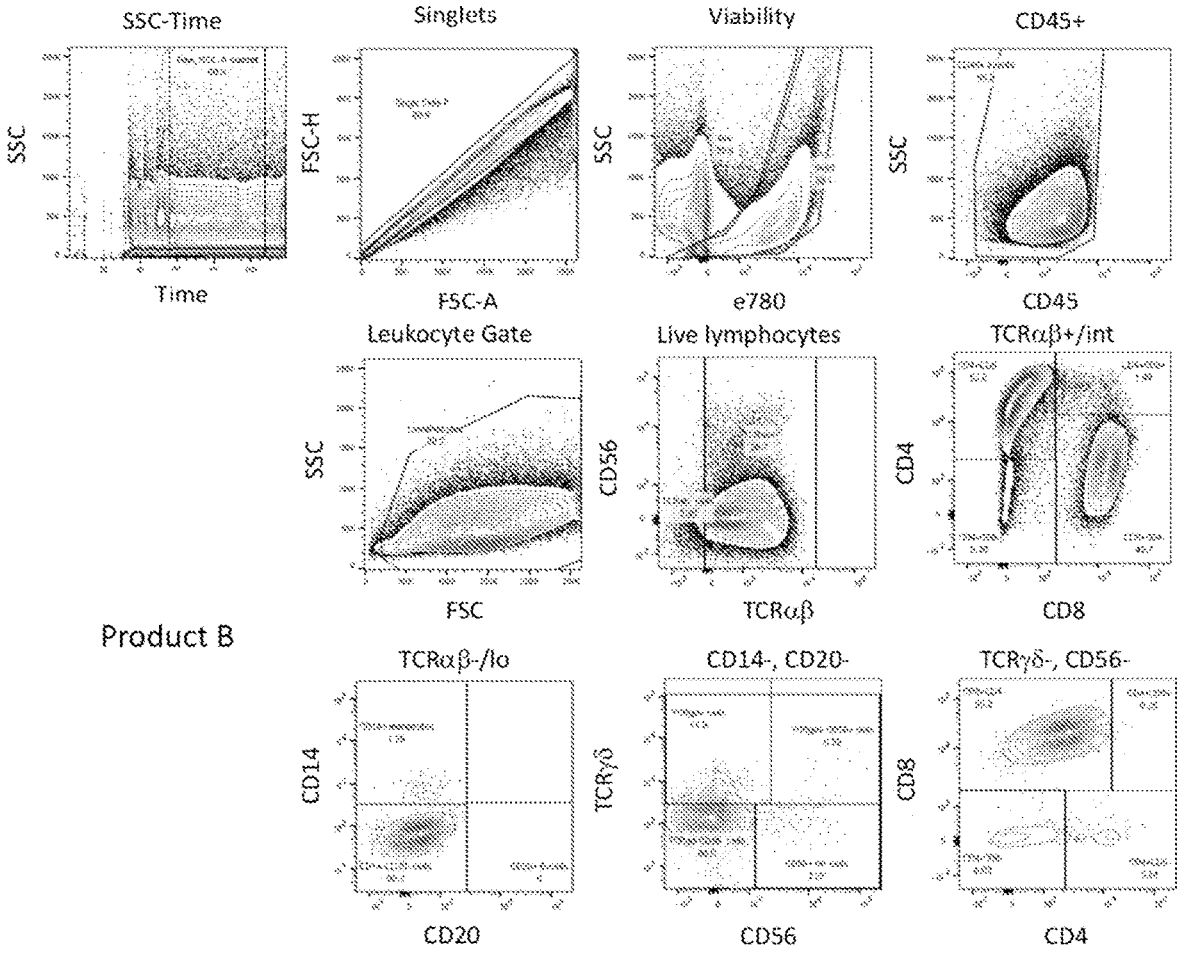


FIGURE 22. C. Flow cytometry analysis of input PBMC cell material.

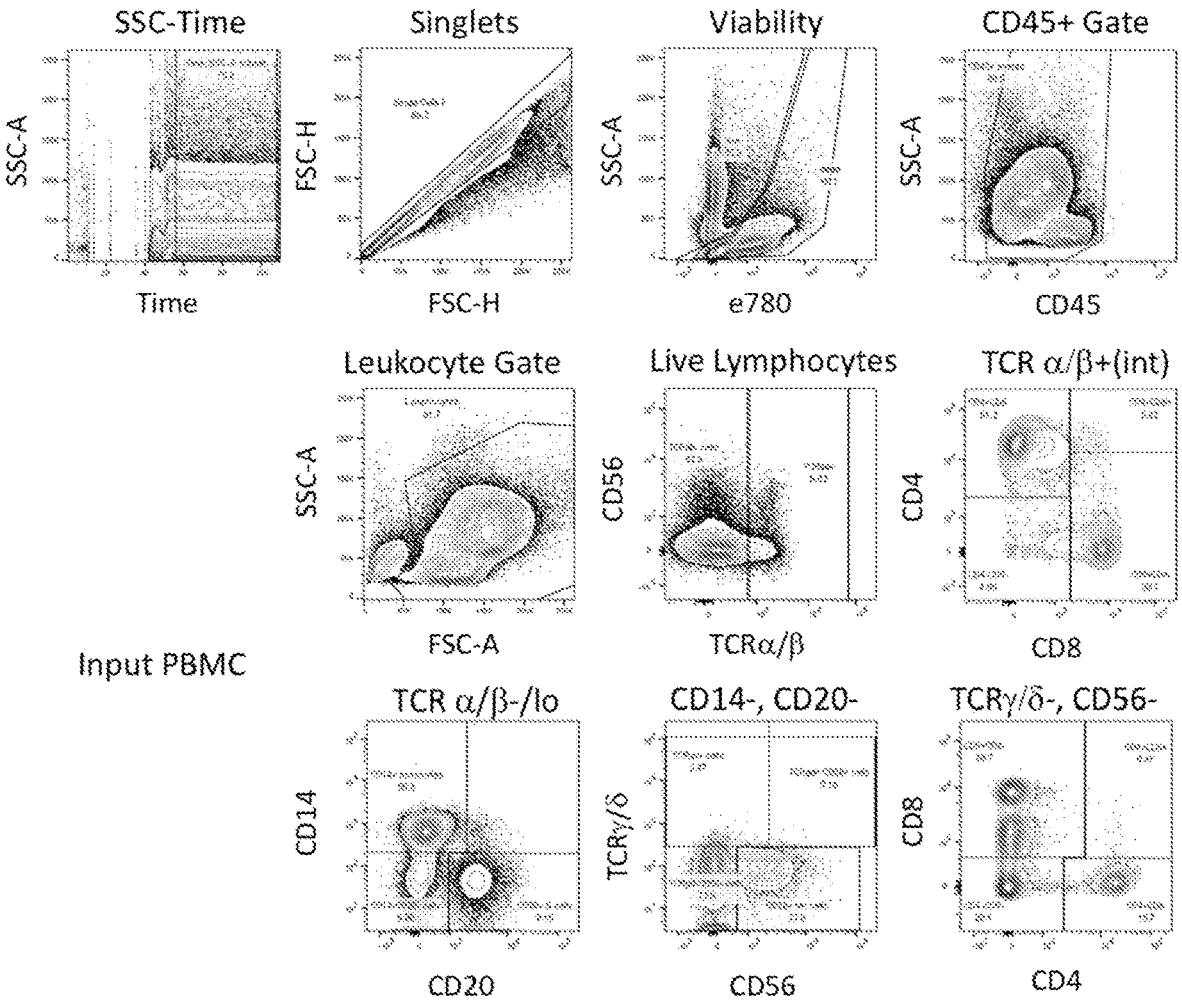


Figure 23. GNC-T therapeutic cell composition of GET cells and formulated GNC-T cells from G-Rex 100M bioreactor after thawing.

Cell Composition	PBMC as input cell material Number of Cells (%)	GNC-activated therapeutic composition-A Number of Cells (%)	GNC-activated therapeutic composition-B Number of Cells (%)
Leukocyte	250,000,000 (100)	1,000,000,000 (100)	1,000,000,000 (100)
TCR α/β T cells	17,375,000 (7)	964,000,000 (96.4)	959,000,000 (95.9)
CD4+ TCR α/β+ T cells	10,225,000 (4.1)	468,000,000 (46.8)	504,000,000 (50.4)
CD8+ TCR α/β+ T cells	5,725,000 (2.3)	451,000,000 (45.1)	409,000,000 (40.9)
TCR α/β-/lo T cells	224,500,000 (89.8)	30,500,000 (3.1)	32,800,000 (3.3)
CD14+ monocytes	179,250,000 (71.7)	380,000 (0)	610,000 (0.1)
CD56+ NK cells	4,825,000 (1.9)	620,000 (0.1)	730,000 (0.1)
TCR γ/δ T cells	450,000 (0.2)	2,200,000 (0.2)	3,800,000 (0.4)
CD20+ B cells	20,350,000 (8.1)	0 (0)	0 (0)

FIGURE 24. RTCC of CHO-ROR1 cells by using GNC (SI-35E class)-treated PBMC cells.

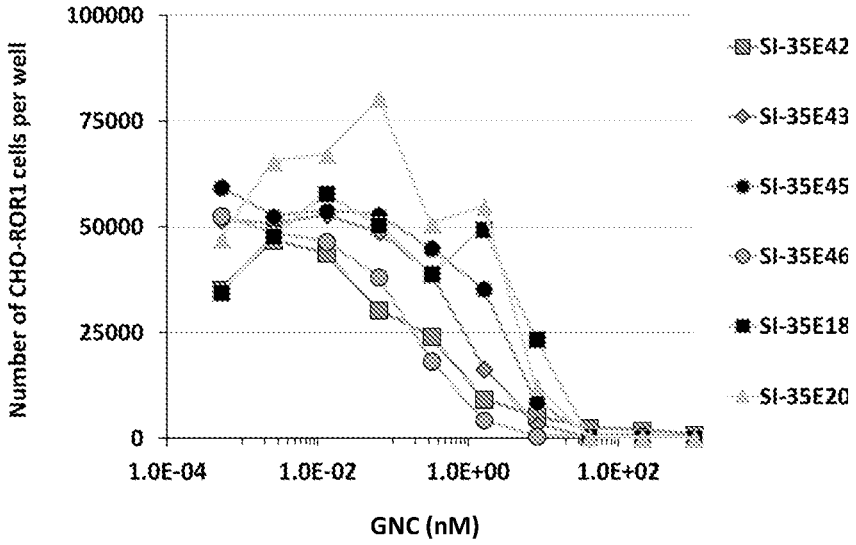


FIGURE 25. Kinetics of PBMC-derived, SI-38E17 GNC-activated therapeutic cells on killing precursor B cell leukemia Kasumi over time.

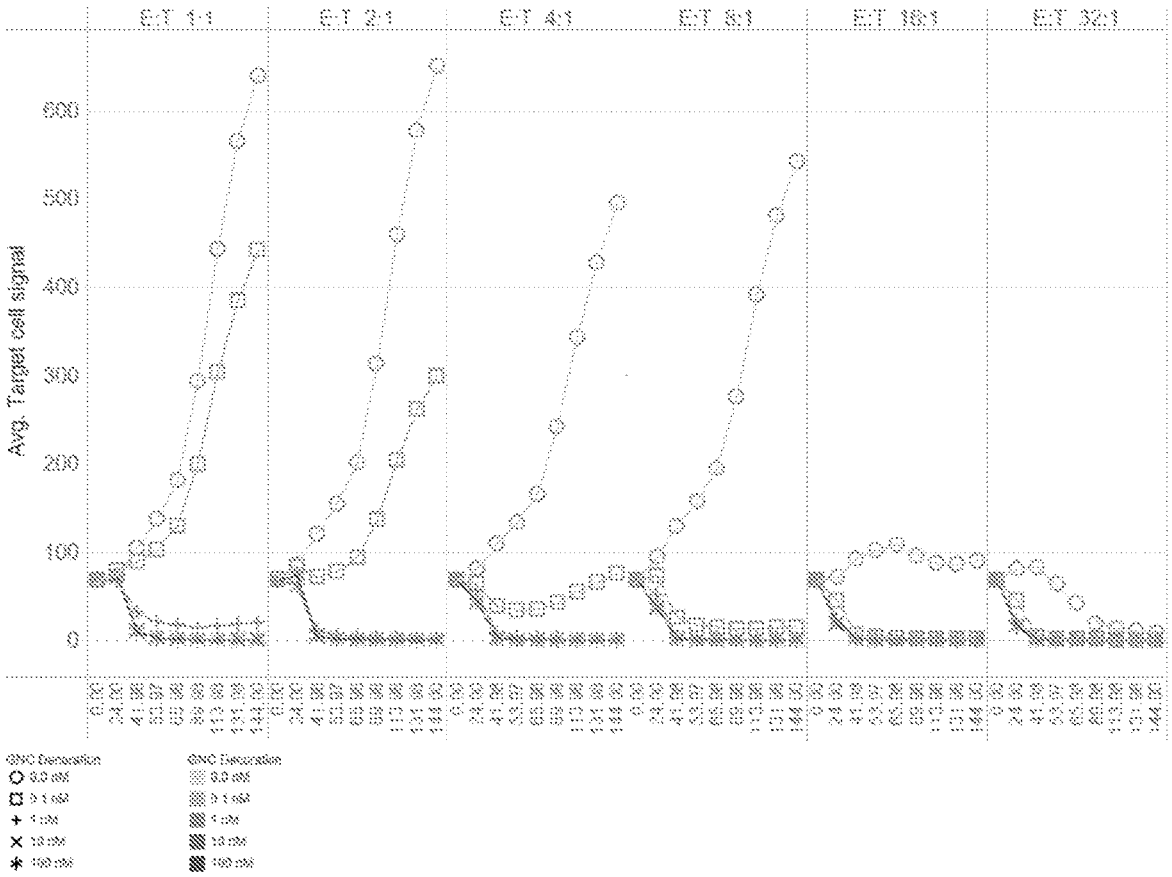


FIGURE 26. Efficacy of killing Nalm-6, MEC-1, Daudi, and Jurkat cells by using PMBC-derived, SI-38E17 GNC-activated therapeutic cells.

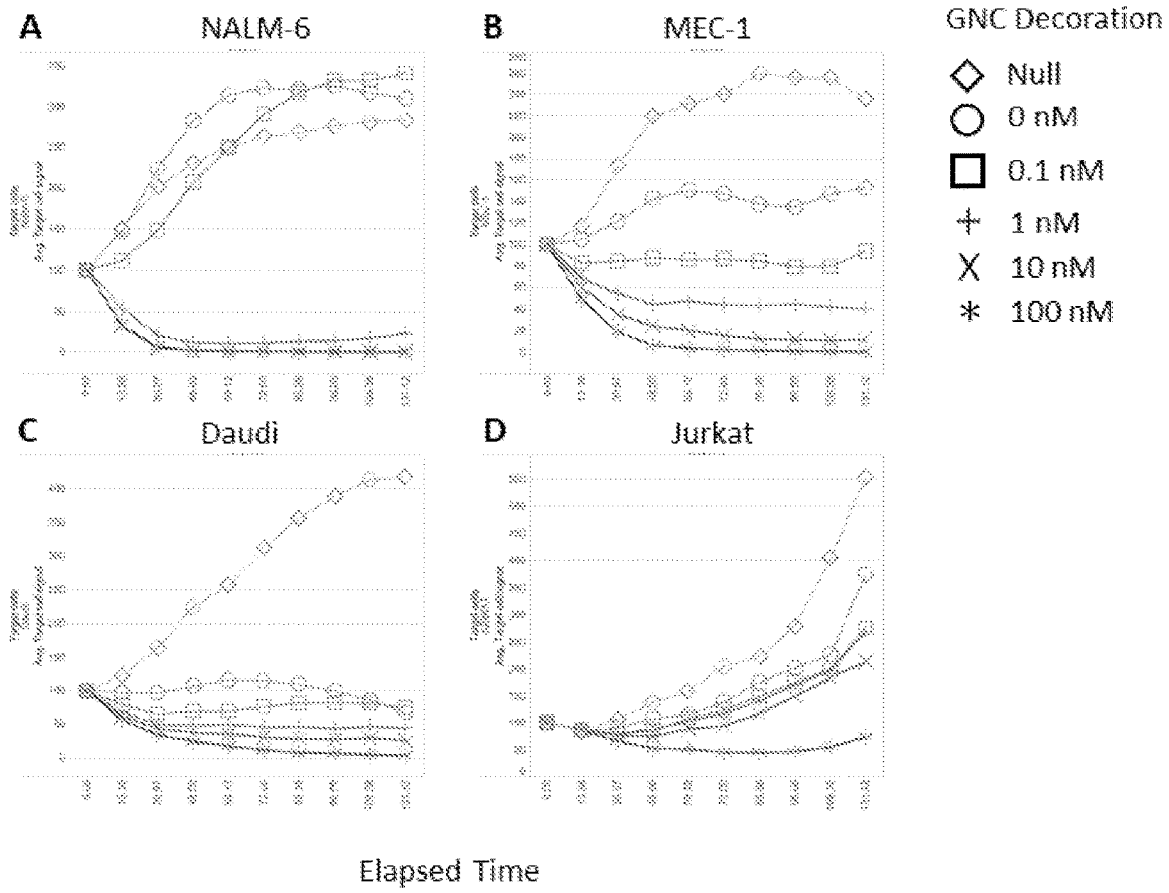
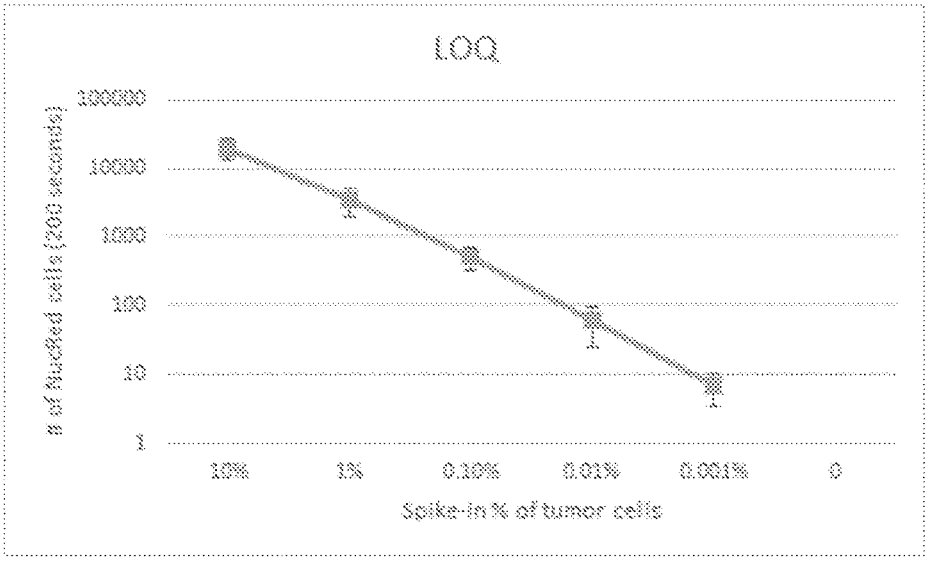


FIGURE 27. Killing of Nalm-6, MEC-1, Daudi, and Jurkat leukemic cells by PBMC-derived, SI-38E17 GNC-activated therapeutic cells in a spike-in model.



Spike-in	Nalm-6	Mec-1	Jurkat	Daudi
10%	1	44	0	0
1%	0	0	0	0
0.10%	1	0	0	0

METHODS OF MAKING AND USING GUIDANCE AND NAVIGATION CONTROL PROTEINS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of filing date of U.S. Provisional Patent Application No. 62/648,888 filed Mar. 27, 2018, and U.S. Provisional Patent Application No. 62/648,880 filed Mar. 27, 2018, the entire disclosures of which are expressly incorporated by reference herein.

TECHNICAL FIELD

[0002] The present application generally relates to the technical field of Guidance and Navigation Control (GNC) proteins with multi-specific binding activities against surface molecules on both immune cells and tumor cells, and more particularly relates to making and using GNC proteins.

BACKGROUND

[0003] Cancer cells develop various strategies to evade the immune system. One of the underlying mechanisms for the immune escape is the reduced recognition of cancer cells by the immune system. Defective presentation of cancer specific antigens or lack of thereof results in immune tolerance and cancer progression. In the presence of effective immune recognition tumors use other mechanisms to avoid elimination by the immune system. Immunocompetent tumors create suppressive microenvironments to downregulate the immune response. Multiple players are involved in shaping the suppressive tumor microenvironment, including tumor cells, regulatory T cells, Myeloid-Derived Suppressor cells, stromal cells, and other cell types. The suppression of immune response can be executed in a cell contact-dependent format as well as in a contact-independent manner, via secretion of immunosuppressive cytokines or elimination of essential survival factors from the local environment. Cell contact-dependent suppression relies on molecules expressed on the cell surface, e.g. Programmed Death Ligand 1 (PD-L1), T-lymphocyte-associated protein 4 (CTLA-4) and others (Dunn, Old et al. 2004, Adachi and Tamada 2015).

[0004] As the mechanisms by which tumors evade recognition by the immune system continue to be better understood, new treatment modalities that target these mechanisms have recently emerged. On Mar. 25, 2011, the U. S. Food and Drug Administration (FDA) approved ipilimumab injection (Yervoy, Bristol-Myers Squibb) for the treatment of unresectable or metastatic melanoma. Yervoy binds to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expressed on activated T cells and blocks the interaction of CTLA-4 with CD80/86 on antigen-presenting cells thereby blocking the negative or inhibitory signal delivered into the T cell through CTLA-4 resulting in re-activation of the antigen-specific T cell leading to, in many patients, eradication of the tumor. A few years later in 2014 the FDA approved Keytruda (Pembrolizumab, Merck) and Opdivo (Nivolumab, Bristol-Myers Squibb) for treatment of advanced melanoma. These monoclonal antibodies bind to PD-1 which is expressed on activated and/or exhausted T cells and block the interaction of PD-1 with PD-L1 expressed on tumors thereby eliminating the inhibitory signal through PD-1 into the T cell resulting in re-activation of the antigen-specific T cell leading to again, in many patients, eradication of the tumor. Since then additional clinical trials have been performed comparing the single monoclonal antibody Yervoy to the combination of the monoclonal antibodies Yervoy and Opdivo in the treatment of advanced melanoma which showed improvement in overall survival and progression-free survival in the patients treated with the combination of antibodies. (Hodi, Chesney et al. 2016, Hellmann, Callahan et al. 2018). However, as many clinical trials have shown a great benefit of treating cancer patients with monoclonal antibodies that are specific for one or more immune checkpoint molecules data has emerged that only those patients with a high mutational burden that generates a novel T cell epitope(s) which is recognized by antigen-specific T cells show a clinical response (Snyder, Makarov et al. 2014). Those patients that have a low tumor mutational load mostly do not show an objective clinical response (Snyder, Makarov et al. 2014, Hellmann, Callahan et al. 2018).

[0005] In recent years other groups have developed an alternate approach that does not require the presence of neoepitope presentation by antigen-presenting cells to activate T cells. One example is the development of a bi-specific antibody where the binding domain of an antibody which is specific for a tumor associated antigen, e.g., CD19, is linked to an antibody binding domain specific for CD3 on T cells thus creating a bi-specific T cell engager or BiTe molecule. In 2014, the FDA approved a bi-specific antibody called Blinatumumab for the treatment of Precursor B-Cell Acute Lymphoblastic Leukemia. Blinatumumab links the single-chain variable fragment (scFv) specific for CD19 expressed on leukemic cells with the scFv specific for CD3 expressed on T cells (Benjamin and Stein 2016). However, despite an initial response rate of >50% in patients with relapsed or refractory ALL many patients are resistant to Blinatumumab therapy or relapse after successful treatment with Blinatumumab. Evidence is emerging that the resistance to Blinatumumab or relapse after Blinatumumab treatment is attributable to the expression of immune checkpoint inhibitory molecules expressed on tumor cells, such as PD-L1 that drives an inhibitory signal through PD-1 expressed on activated T cells (Feucht, Kayser et al. 2016). In a case study of a patient who was resistant to therapy with Blinatumumab, a second round of Blinatumumab therapy was performed but with the addition of a monoclonal antibody, pembrolizumab (Keytruda, Merck). Pembrolizumab specifically binds to PD-1 and blocks the interaction of T cell-expressed PD-1 with tumor cell expressed PD-L1, which resulted in a dramatic response and reduction of tumor cells in the bone marrow from 45% to less than 5% in this one patient (Feucht, Kayser et al. 2016). These results show that combining a bi-specific BiTe molecule with one or more monoclonal antibodies can significantly increase clinical activity compared to either agent alone. Despite the promising outcome, the cost leading to the combined therapy must be high due to multiple clinical trials and the difficulty in recruiting representative populations.

[0006] Adoptive cell therapy with chimeric antigen receptor T cells (CAR-T) is another promising immunotherapy for treating cancer. The clinical success of CAR-T therapy has revealed durable complete remissions and prolonged survival of patients with CD19-positive treatment-refractory B cell malignancies (Gill and June 2015). However, the cost and complexity associated with the manufacture of a per-

sonalized and genetically modified CAR-T immunotherapy has restricted their production and use to specialized centers for treating relatively small numbers of patients. Cytokine release syndrome (CRS), also known as cytokine storm, is considered as the major adverse effect after the infusion of engineered CAR-T cells (Bonifant, Jackson et al. 2016). In many cases, the onset and severity of CRS seems to be personally specific to the patient. Current options of mitigating CRS are mainly focused on rapid response and management care because the option of controlling CRS prior to T cell infusion is limited.

[0007] While the efficacy of CAR-T therapy specific for a CD19-positive B cell malignancy is now clearly established, the efficacy of CAR-T therapy against solid tumors has not been unequivocally demonstrated to date. Currently, many clinical trials are in progress to explore a variety of solid tumor-associated antigens (TAA) for CAR-T therapy. Inefficient T cell trafficking into the tumors, an immunosuppressive tumor micro-environment, suboptimal antigen recognition specificity, and lack of control over treatment-related adverse events are currently considered as the main obstacles in solid tumor CAR-T therapy (Li, Li et al. 2018). The option of managing the therapeutic effect, as well as any adverse effect before and after the CAR-T cell infusion, is limited.

SUMMARY

[0008] The application provides, among others, methods for generating therapeutic compositions containing a guidance and navigation (GNC) proteins, methods for treating cancer conditions using a guidance and navigation control (GNC) proteins, and therapeutic compositions containing GNC proteins or therapeutic cells having cytotoxic cells coated (or bound) with GNC proteins.

[0009] In one aspect, the application provides therapeutic compositions. In one embodiment, the therapeutic composition comprises a cytotoxic cell, a GNC protein, and a therapeutic cell. The therapeutic cell comprises the GNC protein bound to the cytotoxic cell through the binding interaction with the cytotoxic cell receptor, and the therapeutic cell composition is substantially free exogenous of viral and non-viral DNA and RNA.

[0010] In one embodiment, the therapeutic composition may further comprise a second GNC protein, a second therapeutic cell, or a combination thereof, wherein the second therapeutic cell comprises the cytotoxic cells with the second GNC protein bound thereupon or with both the first and the second GNC proteins bound thereupon.

[0011] GNC protein includes a cytotoxic binding moiety and a cancer targeting moiety. The cytotoxic binding moiety has a binding specificity to a cytotoxic cell receptor and is configured to activate the cytotoxic cell through the binding with the cytotoxic cell receptor. The cancer targeting moiety has a binding specificity to a cancer cell receptor.

[0012] In one embodiment, the GNC protein includes a binding domain for T-cell receptors. Examples T-cell receptor include without limitation CD3, CD28, PDL1, PD1, OX40, 4-1BB, GITR, TIGIT, TIM-3, LAG-3, CTLA4, CD40L, VISTA, ICOS, BTLA, Light, CD30, NKp30, CD28H, CD27, CD226, CD96, CD112R, A2AR, CD160, CD244, CECAM1, CD200R, TNFRSF25 (DR3), or a combination thereof. In one embodiment, the GNC protein is capable of activating a T-cell by binding the T-cell binding moiety to a T-cell receptor on the T-cell. In one embodiment, the GNC protein is capable of activating a T-cell by binding multiple T-cell binding moieties on the T-cell.

[0013] In one embodiment, the GNC protein includes a binding domain for a NK cell receptor. Examples NK cell receptor include, without limitation, receptors for activation of NK cell such as CD16, NKG2D, KIR2DS1, KIR2DS2, KIR2DS4, KIR3DS1, NKG2C, NKG2E, NKG2H; agonist receptors such as NKp30a, NKp30b, NKp46, NKp80, DNAM-1, CD96, CD160, 4-1BB, GITR, CD27, OX-40, CRTAM; and antagonist receptors such as KIR2DL1, KIR2DL2, KIR2DL3, KIR3DL1, KIR3DL2, KIR3DL3, NKG2A, NKp30c, TIGIT, SIGLEC7, SIGLEC9, LILR, LAIR-1, KLRG1, PD-1, CTLA-4, CD161.

[0014] In one embodiment, the GNC protein includes a binding domain for a macrophage receptor. Examples macrophage receptor include, without limitation, agonist receptor on macrophage such as TLR2, TLR4, CD16, CD64, CD40, CD80, CD86, TREM-1, TREM-2, ILT-1, ILT-6a, ILT-7, ILT-8, EMR2, Dectin-1, CD69; antagonist receptors such as CD32b, SIRPa, LAIR-1, VISTA, TIM-3, CD200R, CD300a, CD300f, SIGLEC1, SIGLEC3, SIGLEC5, SIGLEC7, SIGLEC9, ILT-2, ILT-3, ILT-4, ILT-5, LILRB3, LILRB4, DCIR; and other surface receptors such as CSF-1R, LOX-1, CCR2, FRP, CD163, CR3, DC-SIGN, CD206, SR-A, CD36, MARCO.

[0015] In one embodiment, the GNC protein includes a binding domain for a dendritic cell receptor. Examples dendritic cell receptor include, without limitation, agonist receptors on dendritic cell such as TLR, CD16, CD64, CD40, CD80, CD86, HVEM, CD70; antagonist receptors such as VISTA, TIM-3, LAG-3, BTLA; and other surface receptors such as CSF-1R, LOX-1, CCR7, DC-SIGN, GM-CSF-R, IL-4R, IL-10R, CD36, CD206, DCIR, RIG-1, CLEC9A, CXCR4.

[0016] In one embodiment, the GNC protein may include a T-cell binding moiety and a cancer-targeting moiety. In one embodiment, the T-cell binding moiety has a binding specificity to a T-cell receptor comprising CD3, CD28, PDL1, PDL2, PD1, OX40, 4-1BB, GITR, TIGIT, TIM-3, LAG-3, CTLA4, CD40L, VISTA, ICOS, BTLA, Light, CD30, CD27, or a combination thereof. In one embodiment, the cancer targeting moiety has a binding specificity to a cancer cell receptor. In one embodiment, the cancer cell receptor may include BCMA, CD19, CD20, CD33, CD123, CD22, CD30, ROR1, CEA, HER2, EGFR, EGFRvIII, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2, as yet to be discovered tumor associated antigens or a combination thereof.

[0017] In one embodiment, the GNC protein may have multi-specific antigen binding activities to the surface molecules of a T cell and a tumour cell. In one embodiment, the guidance and navigation control (GNC) protein comprises a binding domain for a T cell activating receptor, a binding domain for a tumor associated antigen, a bind domain for an immune checkpoint receptor, and a binding domain for a T cell co-stimulating receptor.

[0018] In one embodiment, the binding domain for the tumor associated antigen is not adjacent to the binding domain for the T cell co-stimulating receptor. In one embodiment, the binding domain for the T cell activating receptor is adjacent to the binding domain for the tumor associated antigen (TAA). The T cell activating receptor may include without limitation CD3. The T cell co-stimulating receptor may include without limitation 4-1BB,

CD28, OX40, GITR, CD40L, ICOS, Light, CD27, CD30, or a combination thereof. The immune checkpoint receptor may include without limitation PD-L1, PD-1, TIGIT, TIM-3, LAG-3, CTLA4, BTLA, VISTA, PDL2, or a combination thereof.

[0019] The tumor associated antigen (TAA) may include without limitation ROR1, CD19, EGFRVIII, BCMA, CD20, CD33, CD123, CD22, CD30, CEA, HER2, EGFR, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2, or a combination thereof. In one embodiment, the tumor associated antigen may be ROR1. In one embodiment, the tumor associated antigen may be CD19. In one embodiment, the tumor associated antigen may be EGFRVIII.

[0020] In one embodiment, the guidance and navigation control (GNC) protein may be an antibody or an antibody monomer or a fragment thereof. In one embodiment, the GNC protein may be a tri-specific antibody. In one embodiment, the GNC protein may be a tetra-specific antibody. In one embodiment, the GNC protein includes Fc domain or a fragment thereof. Any Fc domain from an antibody may be used. Example Fc domains may include Fc domains from IgG, IgA, IgD, IgM, IgE, or a fragment or a combination thereof. Fc domain may be natural or engineered. In one embodiment, the Fc domain may contain an antigen binding site.

[0021] In one embodiment, the GNC protein comprises a bi-specific antibody, a tri-specific antibody, a tetra-specific antibody, or a combination thereof yielding up to eight binding motifs on the GNC protein. Examples of antibodies, antibody monomers, antigen-binding fragment thereof are disclosed herein. In one embodiment, GNC proteins may include an immunoglobulin G (IgG) moiety with two heavy chains and two light chains, and at least two scFv moieties being covalently connected to either C or N terminals of the heavy or light chains. The IgG moiety may provide stability to the scFv moiety, and a tri-specific GNC protein may have two moieties for binding the surface molecules on T cells.

[0022] In one embodiment, the guidance and navigation control (GNC) protein may be an antibody. In one embodiment, the tumor associated antigen comprises ROR1, CD19, or EGRFVIII. In on embodiment, the T cell activating receptor comprises CD3 and the binding domain for CD3 may be linked to the binding domain for the tumor associated (TAA) antigen through a linker to form a CD3-TAA pair. In one embodiment, the IgG Fc domain may intermediate the CD3-TAA pair and the binding domain for the immune checkpoint receptor. In one embodiment, the immune checkpoint receptor may be PD-L1.

[0023] The linker may be a covalent bond or a peptide linker. In one embodiment, the peptide linker may have from about 2 to about 100 amino acid residues.

[0024] In on embodiment, the guidance and navigation control (GNC) protein has a N-terminal and a C-terminal, comprising in tandem from the N-terminal to the C-terminal, the binding domain for CD3, the binding domain for EGFRVI, IgG Fc domain, the bind domain for PD-L1, and the binding domain for 41-BB. In one embodiment, the guidance and navigation control (GNC) protein has a N-terminal and a C-terminal, comprising in tandem from the N-terminal to the C-terminal, the binding domain for 4-1BB, the binding domain for PD-L1, IgG Fc domain, the bind domain for ROR1, and the binding domain for CD3. In one embodiment, the guidance and navigation control (GNC) protein has a N-terminal and a C-terminal, comprising in tandem from the N-terminal to the C-terminal, the binding domain for CD3, the binding domain for CD19, IgG Fc domain, the bind domain for PD-L1, and the binding domain for 4-1BB.

[0025] In one embodiment, the GNC protein comprises an amino acid having a percentage homology to SEQ ID NO. 50, 52, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, and 110. The percentage homology is not less than 70%. 80%, 90%, 95%, 98% or 99%.

[0026] In another aspect, the application provides nucleic acid sequences encoding the GNC protein or its fragments disclosed thereof. In one embodiment, the nucleic acid has a percentage homology to SEQ ID NO. 49, 51, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, and 109. The percentage homology is not less than 70%. 80%, 90%, 95%, 98% or 99%.

[0027] In another aspect, the application provides methods for generating a therapeutic composition. In one embodiment, the method may include the steps of providing a cell material comprising a cytotoxic cell, incubating the cell material with a first GNC protein to provide an activated cell composition, and formulating the activated cell composition to provide a therapeutic composition. The activated cell composition contains a first therapeutic cell. The first therapeutic cell comprises the first GNC protein bound to the cytotoxic cell through the binding interaction with the first cytotoxic cell receptor. The therapeutic composition is substantially free of exogenous viral and non-viral DNA or RNA.

[0028] In one embodiment, the cell material may include or be derived from PBMC.

[0029] The first GNC protein may include a first cytotoxic binding moiety and a first cancer targeting moiety. The first cytotoxic binding moiety has a specificity to a first cytotoxic cell receptor and is configured to activate the first cytotoxic cell through the binding with the first cytotoxic cell receptor. The first cancer targeting moiety has a specificity to a first cancer cell receptor.

[0030] In one embodiment, the method may repeat the incubating step by incubating a second GNC protein with the activated cell composition. The second GNC protein comprising a second cytotoxic binding moiety and a second cancer targeting moiety, the second cytotoxic binding moiety has a specificity to a second cytotoxic cell receptor, and the second cancer targeting moiety has a specificity to a second cancer cell receptor. The activated cell composition comprises a second therapeutic cell, and the second therapeutic cell comprises the second GNC protein bound to the cytotoxic cell or the first therapeutic cell through the binding interaction with the second cytotoxic cell receptor.

[0031] In one embodiment, the first and the second cancer-targeting moiety independently has a specificity for CD19, PDL1, or a combination thereof. In one embodiment, the first and the second cytotoxic binding moiety independently has a specificity for CD3, PDL1, 41BB, or a combination thereof.

[0032] The method may further include the repeated incubating steps by incubating additional GNC proteins with the activated composition. The additional GNC proteins may be a third GNC protein, a fourth GNC protein, etc. to provide addition therapeutic cells, each having the additional protein bound to the cytotoxic cell.

[0033] The first, second, and the additional GNC protein may be the same or may be different. The therapeutic cells may have one GNC protein, multiple same GNC proteins, or multiple different GNC proteins bound thereupon. In one embodiment, the therapeutic cell may have the first GNC protein bound thereupon. In one embodiment, the therapeutic cell may have both the first and the second GNC proteins bound thereupon. In one embodiment, the therapeutic cell may have the first, the second and the additional GNC proteins bound thereupon.

[0034] In one embodiment, the therapeutic cell comprises the cytotoxic cell having at least one bound GNC protein. In one embodiment, the therapeutic cell comprises the cytotoxic cell having at least 10, 20, 50, 100, 200, 300, 400 bound GNC proteins.

[0035] The therapeutic composition may include the first therapeutic cell, the first GNC protein, the cytotoxic cell, or a combination thereof. In one embodiment, the therapeutic composition may include the second therapeutic cell, the second GNC protein, comprises the first therapeutic cell, the first GNC protein, the cytotoxic cell, or a combination thereof. In one embodiment, the therapeutic composition may include additional GNC proteins and additional therapeutic cells.

[0036] In one embodiment, the incubating step may serve to expand the therapeutic cells. In one embodiment, expanding the therapeutic cell may include incubating the therapeutic cells with an additional amount of the GNC protein to provide an expanded cell population. In one embodiment, the expanded cell population comprises at least 10^2, at least 103, at least 10^4, at least 10^5, at least 10^6, at least 10^7, at least 10^8, at least 10^9, at least 10^{10} cells per ml. In one embodiment, the expanded cell population comprises the GNC bound cell, the GNC protein, the cytotoxic cell, or a combination thereof. In one embodiment, in order to deplete PD-1+ T cells, a GNC protein may be added to the expansion culture that redirects killing to PD-1+ T cells therefore resulting in reduction in PD-1+ exhausted T cells. In one embodiment, in order to preferentially support PD-1+ T cells, a GNC protein may be added to the expansion culture that relieves checkpoint signaling through PD-1 on T cells therefore resulting in functional improvement of PD-1+ T cells. In one embodiment, in order to isolate 4-1BB mediated co-stimulation through 3^{rd} gen CAR-T, a GNC protein may be added to the expansion culture that redirects killing to 4-1BB+ T cells or resulting in therapeutic composition with controlling level of 4-1BB stimulation in the therapeutic cells, such as CAR-T cells.

[0037] In one embodiment, the cancer targeting moiety has the specificity against B cell, and the therapeutic composition is substantially free of B cell. Therefore, the methods disclosed herein couple the activation and purification functions for the therapeutic cells, which allows the methods to produce B cell free therapeutic composition without the need to introduce any foreign materials (such as beads) nor any foreign genetic materials (such as viral and non-viral DNA or RNA vectors).

[0038] In one embodiment, the ratio of the GNC protein and the cytotoxic cell is at least 30 to 1 when incubating the cell material with the GNC protein.

[0039] In one embodiment, the therapeutic composition may include at least 10^7 cells per ml.

[0040] In a further aspect, the application provides methods for using guidance and navigation control (GNC) proteins for cancer treatment. In one embodiment, the method of treating a subject having a cancer, comprises providing a cytotoxic cell, combining a GNC protein with the cytotoxic cell to provide a therapeutic cell, optionally expanding the therapeutic cell to provide an expanded cell population, and administering the therapeutic cell or the expanded cell population to the subject.

[0041] In one embodiment, the method include the step of providing a cell material comprising a cytotoxic cell, incubating the cell material with a first GNC protein to provide an activated cell composition, wherein the activated cell composition comprises a first therapeutic cell, formulating the activated cell composition to provide a therapeutic composition, wherein the therapeutic composition is substantially free exogenous of viral and non-viral DNA or RNA, and administering the therapeutic composition to the subject.

[0042] In one embodiment, the method may further include the steps of incubating a second GNC protein with the activated cell composition to provide the activated cell composition further comprising a second therapeutic cell. In one embodiment, the method may further include the step of incubating additional GNC proteins with the activated cell composition to provide the activated cell composition further comprising additional therapeutic cells.

[0043] In one embodiment, the method may further comprise isolating the cytotoxic cell from peripheral blood mononuclear cells (PBMC) before providing the cytotoxic cell. In one embodiment, the method may further comprise isolating the peripheral blood mononuclear cells (PBMC) from a blood. In one embodiment, the blood is from the subject. In one embodiment, the blood is not from the subject. In one embodiment, the cytotoxic cells may be from the patient that is under treatment or a different individual, such as a universal donor.

[0044] In one embodiment, the cytotoxic cell may be an autologous T cell, an alloreactive T cell, or a universal donor T cell. In one embodiment, when autologous donor T cells are used, in order to prevent infusion of contaminating cancer cells, a GNC protein may be added to the expansion culture that redirects killing to tumor antigens, example tumor antigen may include CD19 for B cell malignancies, Epcam for Breast carcinoma, MCP1 for melanoma.

[0045] In one embodiment, the method includes steps of providing a blood from the subject, isolating peripheral blood mononuclear cells (PBMC) from the blood, isolating a cytotoxic cell from the PBMC, combining a GNC protein with the cytotoxic cell to provide a therapeutic cell, optionally expanding the therapeutic cell to provide an expanded cell population, and administering the therapeutic cell or the expanded cell population to the subject.

[0046] In one embodiment, the method further comprises administering additional GNC protein to the subject after administering the therapeutic composition to the subject. In one embodiment, the cytotoxic cell may include CD3+ T cell, NK cell, or a combination thereof.

[0047] In one embodiment, the isolating of the cytotoxic cell comprises isolating at least one subpopulation of cytotoxic cells to provide the therapeutic T cells. In one embodiment, the subpopulation of cytotoxic cells comprises CD4+ cells, CD8+ cells, CD56+ cells, CD69+ cells, CD107a+ cells, CD45RA+ cells, CD45RO+ cells, CD2+ cells, CD178+ cells, Granzyme+ cells, or a combination thereof.

[0048] In one embodiment, the combining of a GNC protein with the cytotoxic cell comprises incubating the GNC protein with the cytotoxic cell for a period of time from about 2 hours to about 14 days, from about 1 day to about 7 days, from about 8 hours to about 24 hours, from about 4 days to about 7 days, or from about 10 days to about 14 days. In one embodiment, the incubating period may be more than 14 days. In one embodiment, the incubating period may be less than 2 hours.

[0049] In one embodiment, the ratio between the GNC protein and the cytotoxic cell is at least 600 to 1, 500 to 1, 400 to 1, 300 to 1, 200 to 1, 100 to 1, or 1 to 1. In one embodiment, the ratio between the GNC protein and the cytotoxic cell is from about 1 to 1, 10 to 1, 100 to 1, or to about 1000 to 1 ratio.

[0050] In one embodiment, the method may further comprise evaluating therapeutic efficacy after the administering step. In one embodiment, the evaluating therapeutic efficacy includes checking one or more biomarkers of the cancer, monitoring the life span of the therapeutic cells, or a combination thereof. In one embodiment, evaluating therapeutic efficacy comprises checking one or more biomarkers of the cancer, monitoring the life span of the therapeutic cells, or a combination thereof. In one embodiment, the biomarker comprises a tumor antigen, release of cytokines e.g., gamma interferon, IL-2, IL-8, and/or chemokines, and/or CD markers on the surface of various cell types e.g., CD69, PD-1, TIGIT, and/or mutated nucleic acid released into the bloodstream by tumors upon death, circulating tumor cells and their associated nucleic acid, or exosome associated nucleic acid, host inflammatory mediators, or tumor derived analytes, or a combination thereof. In one embodiment, the biomarker comprises a tumor antigen, tumor-associated apoptotic bodies, small molecule metabolites, release of cytokines, lymphocyte surface marker expression, phosphorylated/dephosphorylated signaling molecules, transcription factors, or a combination thereof.

[0051] The method disclosed herein is free of the step of transfecting the cytotoxic cell with a DNA vector or a viral vector. In one embodiment, the therapeutic cell or the expanded cell population is substantially free of a DNA vector or a viral vector.

[0052] The method may be used to treat a human subject suffering from cancer. In one embodiment, the cancer comprises cells expressing ROR1, CEA, HER2, EGFR, EGFRvIII, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2, BCMA, CD20, CD33, CD123, CD22, CD30, CD19, as yet to be identified tumor associated antigens, or a combination thereof. In one embodiment, the method may be used to treat mammals.

[0053] Varieties of cancer may be treated using the methods disclosed herein. Example cancers includes without limitation breast cancer, colorectal cancer, anal cancer, pancreatic cancer, gallbladder cancer, bile duct cancer, head and neck cancer, nasopharyngeal cancer, skin cancer, melanoma, ovarian cancer, prostate cancer, urethral cancer, lung cancer, non-small lung cell cancer, small cell lung cancer, brain tumor, glioma, neuroblastoma, esophageal cancer, gastric cancer, liver cancer, kidney cancer, bladder cancer, cervical cancer, endometrial cancer, thyroid cancer, eye cancer, sarcoma, bone cancer, leukemia, myeloma or lymphoma.

[0054] In one embodiment, the method may further include administering an effective amount of a therapeutic agent after the administering the therapeutic cell or the expanded cell population to the subject. In one embodiment, the therapeutic agent comprises a monoclonal antibody, a chemotherapy agent, an enzyme, a protein, a co-stimulator, or a combination thereof. In one embodiment, the co-stimulator is configured to increase the amount of cytotoxic T cells in the subject.

[0055] The application further provides a solution comprising an effective concentration of the GNC protein. In one embodiment, the solution is blood plasma in the subject under treatment. In one embodiment, the solution includes the GNC protein bound cells. In one embodiment, the solution includes a GNC cluster including a GNC protein, a T-cell bound to the T-cell binding moiety of the GNC protein, and a cancer cell is bound to the caner-targeting moiety of the GNC protein.

[0056] The objectives and advantages of the present application will become apparent from the following detailed description of preferred embodiments thereof in connection with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0057] The foregoing and other features of this disclosure will become more fully apparent from the following description and appended claims, taken in conjunction with the accompanying drawings.

[0058] Understanding that these drawings depict only several embodiments arranged in accordance with the disclosure and are, therefore, not to be considered limiting of its scope, the disclosure will be described with additional specificity and detail through use of the accompanying drawings, in which:

[0059] FIG. **1** shows a GNC protein comprising four antigen-specific binding domains in an antibody structure with targeting specificity to CD19 positive cells;

[0060] FIG. **2** illustrates that a tetra-specific GNC antibody mediates multi-specific binding between a T cell and a tumor cell;

[0061] FIG. **3** is a flowchart comparing manufacturing processes for GNC-T cell therapy (left) and CAR-T cell therapy (right);

[0062] FIG. **4** is a diagram showing sources of cell material for preparing GNC-activated therapeutic cell composition;

[0063] FIG. **5** is a diagram showing sources of selected T cells for preparing GNC-activated therapeutic composition;

[0064] FIG. **6** is a diagram showing the preparation of GNC-activated therapeutic T cell composition;

[0065] FIG. **7** is a diagram showing the incubating and formulating steps for preparing the first GNC-activated T cells for GNC-T cell therapy;

[0066] FIG. **8** shows that GNC proteins (SI-35E class) induce IL-2 secretion from PBMC;

[0067] FIG. **9** shows that GNC proteins (SI-35E class) induce granzyme B secretion from PBMC;

[0068] FIG. **10** shows that GNC proteins (SI-35E class) induce expression of the activation marker CD69 on CD4+ T cells;

[0069] FIG. **11** shows that GNC proteins (SI-35E class) induce expression of the activation marker CD69 on CD8+ T cells;

[0070] FIG. **12** shows that GNC proteins (SI-35E class) induce expression of the activation marker CD69 on CD56+ NK cells;

[0071] FIG. **13** shows that GNC proteins (SI-35E class) induce expression of the marker of cytotoxic degranulation CD107a on CD4+ T cells;

[0072] FIG. **14** shows that GNC proteins (SI-35E class) induce expression of the marker of cytotoxic degranulation CD107a on CD8+ T cells;

[0073] FIG. **15** shows that GNC proteins (SI-35E class) induce expression of the marker of cytotoxic degranulation CD107a on CD56+NK cells;

[0074] FIG. **16** shows that GNC proteins (SI-35E class) activate CD3+ T cells to proliferate;

[0075] FIG. **17** shows that GNC proteins (SI-35E class) activate CD3+ T cells to secrete gamma interferon;

[0076] FIG. **18** shows that GNC proteins (SI-35E class) activate naïve CD8+/CD45RA+ T cells to proliferate;

[0077] FIG. **19** shows that GNC proteins (SI-35E class) activate naïve CD8+/CD45RA+ T cells to secrete gamma interferon;

[0078] FIG. **20** shows Images of GNC activated cell growth in 6-well G-Rex plates over time;

[0079] FIG. **21** shows the example process of making the therapeutic composition as disclosed thereof (A), and cell viability of PBMC, GET, and GNC-T cells after thawing (B);

[0080] FIG. **22** shows the result of flow cytometry analyses of PBMC-derived, the first GNC (SI-38E17)-activated therapeutic cell composition (Product A) (**22**A), the second GNC (SI-38E17)-coated therapeutic cell composition (Product B) (**22**B), and input PBMC cell material (22C).

[0081] FIG. **23** shows GNC-T therapeutic cell composition of GET cells and formulated GNC-T cells from G-Rex 100M bioreactor after thawing;

[0082] FIG. **24** shows the result of RTCC of CHO-ROR1 cells by using GNC (SI-35E class)-coated PBMC cells;

[0083] FIG. **25** shows kinetics of PBMC-derived, SI-38E17 GNC-activated therapeutic cells on killing precursor B cell leukemia Kasumi over time;

[0084] FIG. **26** shows efficacy of killing Nalm-6, MEC-1, Daudi, and Jurkat cells by using PMBC-derived, SI-38E17 GNC-activated therapeutic cells; and

[0085] FIG. **27** shows the killing of Nalm-6, MEC-1, Daudi, and Jurkat leukemic cells by using PBMC-derived, SI-38E17 GNC-activated therapeutic cells in a spike-in model.

DETAILED DESCRIPTION

[0086] In the following detailed description, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols typically identify similar components, unless context dictates otherwise. The illustrative embodiments described in the detailed description, drawings, and claims are not meant to be limiting. Other embodiments may be utilized, and other changes may be made, without departing from the spirit or scope of the subject matter presented herein. It will be readily understood that the aspects of the present disclosure, as generally described herein, and illustrated in the Figures, can be arranged, substituted, combined, separated, and designed in a wide variety of different configurations, all of which are explicitly contemplated herein.

[0087] In one embodiment, the guidance navigation control (GNC) proteins are characterized by their composition of multiple antigen-specific binding domains (AgBDs) and by their ability of directing T cells (or other effector cells) to cancer cells (or other target cells such as bystander suppressor cells) through the binding of multiple surface molecules on a T cell and a tumor cell. In one embodiment, GNC proteins are composed of Moiety 1 for binding at least one surface molecule on a T cell and Moiety 2 for binding at least one surface antigen on a cancer cell as shown in TABLE 1. FIG. **1** shows the structure of an example tetra-specific GNC antibody comprising AgBDs for binding to both a T cell expressing CD3, PD-L1, and/or 4-1BB and a target B cell expressing CD19, as illustrated in FIG. **2**.

[0088] In a T cell therapy, the cytotoxic T cells are regulated by T cell receptor complex proteins, as well as co-stimulation signaling proteins via either agonist receptors or antagonist receptors on their surface. To regulate this signaling, as well as the interaction between a T cell and a cancer cell, multiple AgBDs may compose Moiety 1 and Moiety 2, respectively. Examples of molecules that can be targeted by agonistic or antagonistic binding domains in Moiety 1 and 2 are shown in TABLE 1. In one embodiment, the GNC proteins may have at least one linker to link Moiety 1 and Moiety 2. In one example GNC protein, any linker molecule can be used to link two or more AgBDs together either in vitro or in vivo by using complementary linkers of DNA/RNA or protein-protein interactions, including but not limited to, that of biotin-avidin, leucine-zipper, and any two-hybrid positive protein. In some embodiments, the linkers may be an antibody backbone structure or antibody fragments, so that GNC protein and GNC antibody may have the same meaning, e.g. the structure of the example tetra-specific GNC antibody in FIG. **1**.

[0089] GNC proteins or antibodies are capable of directing a T cell to a cancer cell, in vivo or ex vivo, through the binding function of multiple AgBDs (FIG. **2**). The T cells may be derived from the same patient or different individuals, and the cancer cell may exist in vivo, in vitro, or ex vivo. The examples provided in the present application enable GNC proteins as a prime agent in a T cell therapy, i.e. GNC-T cell therapy, for activating and controlling cytotoxic T cells ex vivo, prior to adoptive transfer.

[0090] The present application relates to methods of making GNC-activated therapeutic cell composition. Multiple AgBDs can be divided into Moiety 1 and Moiety 2 due to their interface with a T cell and a cancer cell, respectively (TABLE 1). A GNC protein with two AgBDs may simultaneously bind to a surface molecule, such as CD3 on a T cell, and a tumor antigen, such as ROR1 on a tumor cell, for re-directing the T cell to the tumor cell.

[0091] The addition of a third AgBD, for example, one that specifically binds to 41BB, may help enhance anti-CD3-induced T cell activation because 41BB is a co-stimulation factor and the binding stimulates its agonist activity to activated T cells. The addition of a fourth AgBD to a GNC protein, for example, one that specifically binds to PD-L1 on a tumor cell, may block the inhibitory pathway of PD-L1 on tumor cells or that is mediated through its binding to PD-1 on the T cells.

[0092] In some embodiments, with these basic principles, GNC proteins are constructed to acquire multiple AgBDs specifically for binding unequal numbers of T cell antagonists and agonists, not only to re-direct activated T cells to tumor cells but also to control their activity in vivo (TABLE 2). Therefore, in some embodiments, GNC proteins may be bi-specific, tri-specific, tetra-specific, penta-specific, hexa-specific, hepta-specific, or octa-specific proteins.

[0093] In one embodiment, the application relates to a GNC-T cell therapy where GNC proteins are used to expand the T cells ex vivo prior to adoptive transfer (FIG. **3**). The ex vivo priming of autonomous T cells provides the cytotoxic T cells guidance and navigation control. For example, peripheral blood mononuclear cells (PBMC) or specific types of cell populations within PBMC e.g., CD8+, CD45RO+ memory T cells may be isolated and primed ex vivo by GNC proteins. These expanded cytotoxic T cells can be formulated and infused back to the patient through adoptive transfer. While attacking the cancer in vivo, additional GNC proteins may be infused into the patient for managing the efficacy and lifespan of cytotoxicity. Thus, GNC-T cell therapy is different from GNC protein-based immunotherapy, where GNC proteins are directly administered into patients. However, GNC-T cell therapy does not rule out the direct administration of GNC proteins for managing the efficacy of infused cytotoxic T cells in vivo in a controlled manner. Additional GNC protein can both promote cytolytic activity and encourage T cell proliferation dependent of the configuration of AgBDs.

[0094] In one aspect, the application relates to the production of therapeutic GNC-T cells. In comparison with and to distinguish from the production of therapeutic CAR-T cells, their general processes are shown in FIG. **3**, for comparison purpose. In CAR-T therapy, cell material, for example patient leukocytes, are collected by apheresis, and a subset of CD3+ T cells is selected and activated to facilitate gene transfer to the cellular material, which is then expanded in number by the introduction of foreign material scaffold for support to the T cell populations, for example, by using anti-CD3/anti-CD28 antibody coated beads. Advantageously, GNC-T cell material does not require the introduction of scaffold impurities for T cell expansion from patient leukocytes.

[0095] The CAR-T therapy cellular material must undergo the gene transfer that involves the preparation and transfection of CAR-T vector DNA, which results in genetically modifying the genome of the T cells. Furthermore, these genetically modified T cells may undergo another round of T cell expansion before being transferred back into the patient. The random integration of CAR-T vector DNA carries a risk of transformation of the T cells leading to primary leukemogenesis or introduction of the CAR-T vector to leukemia cells increasing the risk of relapse by mechanism of internal sequestration of the CAR target antigen (Zhang, Liu et al. 2017).

[0096] In contrast, GNC-T cell therapy has the advantages of not involving the transfection of any vector DNA, therefore there is no risk of genetic modification prior to adoptive transfer, which provides one of the significant advantages and technical improvements over the existing CAR-T therapy. Besides the advantage of GNC-T cell therapy being free of exogenous generic material contamination and cancer risk, the efficacy of GNC-T cell therapy may be improved when PBMC or different T cell subsets are being primed and activated ex vivo as shown in FIGS. **5** & **6**. Similar approaches have been explored in the use of CAR-T therapy, where selected specific ratios of some subsets of T cells may be transferred back to the patient (Turtle, Hanafi et al. 2016, Turtle, Hanafi et al. 2016).

[0097] In some embodiments, it may be beneficial to remove leukemia or other cancer cells from the cellular material prior to cell expansion (FIG. **7**). The PBMC of a patient with circulating leukemic cells, in particular from B cell malignancy, may profoundly alter the cellular composition and thus affect the suitability of the final therapeutic cellular products. For example, a high level of circulating leukemic blast cells (greater that 10% of WBC) may require a depletion of leukemic cells prior to GNC mediated cell expansion. The percentage of leukemic cells in the PBMC derived from a patient may be reduced by using cell fractionation methods. These methods may include steps involving density gradient separation, or immunofluorescent cell separation or fluorescent activated cells sorting, immunomagnetic cell separation, or microfluidic flow chambers methods. These methods may be preceded by or follow centrifugation, cell washing, incubation, or temperature modulation. These methods may utilize non-cellular substrates (magnetic beads, Plastic, polymers), modification of non-cellular substrates (protein, antibodies, charge state), antibody treatment, multiple antibody treatments, multispecific antigen binding proteins and cell surface antigen-based cell coupling. These methods may use enzymatic digestion or, ionic chelation, or mechanical agitation or cell vessel rotation. The method for reduction of leukemic blasts may utilize antibody drug conjugates, or leukemia sensitizing agents. The method may consist of a combination of these approaches.

[0098] In one embodiment, to enable the production of therapeutic T cells primed (or coated or bound) with GNC proteins, a tetra-specific antibody is produced and used as the GNC protein. In one embodiment, the tetra-specific antibody/GNC protein comprises 4 different binding domains linked by antibody fragments as its backbone. One binding domain is specific for CD3 on T cells, a second binding domain is specific for a tumor associated antigen, including but not limited to ROR1, CEA, HER2, EGFR, EGFRvIII, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2, BCMA, CD19, CD20, CD33, CD123, CD22, CD30, and a third and fourth binding domains are specific for two distinct immune checkpoint modulators such as PD-L1, PD-L2, PD-1, OX40, 4-1BB, GITR, TIGIT, TIM-3, LAG-3, CTLA4, CD40L, VISTA, ICOS, BTLA, Light, etc.

[0099] Without being bound by theory, the advantages of GNC protein-mediated GNC-T cell therapy over conventional CAR-T therapies include, but are not limited to, first, that inclusion of an IgG Fc domain may confer the characteristic of a longer half-life in serum compared to a bispecific BiTe molecule; second, that inclusion of two binding domains specific for immune checkpoint modulators may inhibit the suppressive pathways and engage the co-stimulatory pathways at the same time; third, that cross-linking CD3 on T cells with tumor associated antigens re-directs and guides T cells to kill the tumor cells without the need of removing T cells from the patient and genetically modifying them to be specific for the tumor cells before re-introducing them back into the patient, also known as chimeric antigen receptor T cells (CAR-T) therapy; and fourth, that GNC protein-mediated antibody therapy or T cell therapy does not involve genetic modification of T cells, the latter of which may carry the risk of transforming modified T cells to clonal expansion, i.e. T cell leukemia.

[0100] The present disclosure may be understood more readily by reference to the following detailed description of specific embodiments and examples included herein. Although the present disclosure has been described with

reference to specific details of certain embodiments thereof, it is not intended that such details should be regarded as limitations upon the scope of the disclosure.

EXAMPLES

[0101] While the following examples are provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of non-critical parameters that could be changed or modified to yield essentially the same or similar results.

Example 1. GNC Proteins and Tetra-Specific GNC Antibodies

[0102] In the present application, the examples of GNC proteins are classes of tetra-specific GNC antibodies, of which 4 AgBDs are covalently linked using an IgG antibody as its backbone (FIG. **1**). From the N-terminal of this protein, the first scFv is linked to the Fab domain of the constant domains C_H1, 2, and 3 of IgG antibody which is then linked to another scFv at the C-terminal. Because each of the scFv domains display independent binding specificity, linking of these AgBDs does not need to be done using the constant domains of an IgG antibody. Structured as a tetra-specific GNC antibody, a GNC protein can directly bind to tumor-associated antigen (TAA) and engage the host endogenous T cells to kill tumor cells independent of tumor antigen presentation by MHC to the antigen specific T cell receptors (FIG. **2**). As shown in FIG. **1**, CD19 is a TAA targeting CD19 positive B cells and tumor cells. In addition, PD-L1 is an example of the immune checkpoint modulating component for tetra-specific GNC antibodies that may overcome the immunosuppressive tumor microenvironment and fully activate the exhausted T cells within the tumor microenvironment.

[0103] Of tetra-specific GNC antibodies, the SI-35E class comprises targets an anti-human CD3 binding domain (SEQ IDs 1-4), an anti-human PD-L1 (SEQ IDs 5-12), an anti-human 4-1BB (SEQ IDs 13-24), and targets a human ROR1 (SEQ IDs 25-32), i.e. a TAA. In this context, the classes of SI-38E and SI-39E target CD19 (SEQ IDs 47-50) and EGFR (SEQ ID 51-54), respectively.

[0104] To construct tetra-specific GNC antibodies, AgBDs were converted to scFv and VLVH for placement at the N-terminal Domain 1 (D1) or scFv and VHVL for placement at the C-terminal Domains 3 (D3) and 4 (D4) of the GNC protein. All scFv molecules described herein contain a 20 amino acid flexible gly-gly-gly-gly-ser (G4S) X4 linker that operably links the VH and VL, regardless of the V-region orientation (LH or HL). The remaining position in the tetra-specific GNC antibody, Domain 2 (D2), consists of an IgG1 heavy chain, VH-CH1-Hinge-CH2-CH3, and its corresponding light chain, VL-CL, which can be either a kappa or lambda chain. D1 and D2 are genetically linked through a 10 amino acid (G4S)×2 linkers, as are D2, D3 and D4 resulting in a contiguous ~150 kDa heavy chain monomer peptide. When co-transfected with the appropriate light chain, the final symmetric tetra-specific GNC peptide can be purified through the IgG1 Fc (Protein A/Protein G) and assayed to assess functional activity. Heavy and light chain gene "cassettes" were previously constructed such that V-regions could be easily cloned using either restriction enzyme sites (HindIII/NheII for the heavy chain and HindIII/BsiWI for the light chain) or "restriction-free cloning" such as Gibson Assembly (SGI-DNA, La Jolla, Calif.), Infusion (Takara Bio USA) or NEBuilder (NEB, Ipswich, Mass.), the latter of which was used here.

[0105] The tetra-specific GNC antibodies can be produced through a process that involves design of the intact molecule, synthesis and cloning of the nucleotide sequences for each domain, expression in mammalian cells and purification of the final product. Herein, nucleotide sequences were assembled using the Geneious 10.2.3 software package (Biomatters, Auckland, NZ) and broken up into their component domains for gene synthesis (Genewiz, South Plainsfield, N.J.). In this example, SI-35E18 (SEQ ID 65 and 67) was split into its component domains where the anti-41BB scFv, VL-VH, occupies D1, anti-human PD-L1 clone PL230C6 occupies D2 (Fab position), anti-human ROR1 Ig domain-specific clone 323H7 VHVL scFv occupies D3, and anti-human CD3 scFv, VHVL, occupies the C-terminal D4. Using NEBuilder web-based tools, 5' and 3' nucleotides were appended to each of the domains depending on their position in the larger protein so that each domain overlaps its flanking domains by 20-30 nucleotides which direct site-specific recombination, thus genetically fusing each domain in a single gene assembly step. Due to the high number of homologous regions in the tetra-specific nucleotide sequence, the N-terminal domains 1 and 2 are assembled separately from the C-terminal D3 and D4. The N- and C-terminal fragments were then assembled together in a second NEBuilder reaction. A small aliquot was transformed into *E. coli* DH10b (Invitrogen, Carlsbad, Calif.) and plated on TB+carbenicillin 100 ug/ml plates (Teknova, Hollister, Calif.) and incubated at 37° C. overnight. Resultant colonies were selected and 2 mL overnight cultures inoculated in TB+carbenicillin. DNA was prepared (Thermo-Fisher, Carlsbad, Calif.) from overnight cultures and subsequently sequenced (Genewiz, South Plainsfield, N.J.) using sequencing primers (Sigma, St. Louis, Mo.) flanking each domain. All DNA sequences were assembled and analyzed in Geneious.

[0106] In another tetra-specific GNC protein, SI-38E17 targeting human CD19 (SEQ IDs 47-50), multiple AgBDs carry an anti-human 4-1BB (scFv 466F6, SEQ IDs 17-20) as well as an anti-human PD-L1 (scFv PL221G5 SEQ IDs 9-13), and an anti-human CD3 binding domain (SEQ IDs 1-4). The methods and procedures for producing this tetra-specific antibody were the same.

[0107] GNC proteins are composed of Moiety 1 for binding at least one surface molecule on a T cell and Moiety 2 for binding at least one surface antigen on a cancer cell (TABLE 1A). The tetra-specific GNC antibodies can be used to directly engage the body's endogenous T cells to kill tumor cells independent of tumor antigen presentation by MHC to the antigen specific T cell receptors. This is in contrast to therapies based solely on immune checkpoint blockade, which have been limited by antigen recognition. In context, the immune checkpoint modulating component may be constructed as a part of tetra-specific GNC antibodies, which may provide benefits similar to that in a standard checkpoint blockade therapy.

[0108] In addition to T cells, other cytotoxic cells may also be targeted by GNC proteins for cancer killing or preventing purposes. TABLE 1B shows the example compositions of functional moieties (Moiety 1 and Moiety 2) and antigen binding domain in GNC proteins with NK cell binding domains. TABLE 1C shows the example compositions of

functional moieties (Moiety 1 and Moiety 2) and antigen binding domain in GNC proteins with macrophage binding domains. TABLE 1D shows the example compositions of functional moieties (Moiety 1 and Moiety 2) and antigen binding domain in GNC proteins with dendritic cell binding domains.

[0109] GNC proteins are constructed to acquire multiple AgBDs specifically for binding unequal numbers of T cell antagonists and agonists. In this way, GNC proteins may re-direct activated T cells to tumor cells with certain levels of control of their activity in vivo (TABLE 2). Therefore, GNC proteins may be bi-specific, tri-specific, tetra-specific, penta-specific, hexa-specific, hepta-specific, or even octa-specific proteins. In the present invention, three classes of tetra-specific GNC antibodies, i.e. SI-39E, SI-35E, and SI-38E, were created to enable GNC-T cell therapy, of which antibody domains and its specificity is listed in TABLE 3. The structures of tetra-specific GNC antibodies targeting EGFRvIII (SI-39E), ROR1 (SI-35E), and CD19 (SI-38E) are listed in TABLE 4.

Example 2: GNC-Activated, PBMS-Derived Cell Composition

[0110] The SI-35 class listed in Table 4 were tested for their ability to activate and induce proliferation of different cell types, such as CD4+ and/or CD8+ T cells and/or CD56+ natural killer cells (NK) within PBMC. The tetra-specific GNC antibodies were prepared at 2× final concentration and titrated in 1:10 serial dilutions across 6 wells of a 96 well plate in 200 ul of RPMI+10% FBS. Human PBMC were purified by standard Ficoll density gradient from a "leuko-pak" which is an enriched leukapheresis product collected from normal human peripheral blood. In the final destination 96 well plate, the PBMC and serially titrated GNC proteins were combined by adding 100 μL of PBMC (100,000), and 100 μL of each antibody dilution to each well of the assay. The assay plate was incubated at 37° C. for approximately 72 hours and then the contents of each assay well were harvested and analyzed by FACS for the number of CD4+ T cells, CD8+ T cells, and CD56+NK cells. Cells were harvested from each well and transferred to a new 96 well V-bottom plate then centrifuged at 400×g for 3 minutes. Supernatant was transferred to a 96 well plate for analysis of IL-2 and Granzyme B. Cells were re-suspended in 200 μL of 2% FBS/PBS of FACS antibodies and incubated on ice for 30 minutes. The plate was centrifuged at 400×g for 3 minutes and the supernatant was aspirated. This wash step was repeated once more and then the cells were re-suspended in 100 μL 2% FBS/PBS and analyzed on a BD LSR FORTESSA.

[0111] As shown in FIG. **8**, all SI-35E tetra-specific GNC antibodies, with the exception of those that had the scFv binding domain replaced with FITC at positions 2 (SI-35E37) and 4 (SI-35E39), induced production of IL-2 from PBMC. These two proteins lacked the binding domains for PD-L1 or CD3 respectively. The secretion of Granzyme B into the culture supernatant followed a similar pattern as that for IL-2 production as shown in FIG. **9**. Both SI-35E37 and SI-35E3 were also much less potent at inducing cell-surface expression of the activation marker CD69 on CD4+(FIG. **10**), CD8+(FIG. **11**), and CD56+(FIG. **12**) cells in the PBMC culture. Surface expression of the cytotoxic degranulation marker CD107a (LAMP-1) was induced by all GNC proteins tested except those lacking binding at positions 2 and 4 on CD4+(FIG. **13**), CD8+(FIG. **14**), but less consistently on CD56+(FIG. **15**) in the culture. At lower concentrations, 3 of the GNC proteins (SI-35E42, SI-35E43, and SI-35E46) induced expression of CD69 on CD4+ T cells, CD8+ T cells, and CD56+NK cells, which correlated well with the level of IL-2 and granzyme B secretion (FIGS. **8** and **9**) induced by these GNC.

[0112] Proliferation and production of gamma interferon was measured from cultures of CD3+ or naïve CD8+ T cells (70,000 cells/well) stimulated for 5 days with a panel of SI-35 class antibodies. Human CD3+ or CD8+CD45RA+ naïve T cells were enriched from peripheral blood mononuclear cells from a normal donor using the EasySep™ Human CD3+ or Naïve CD8+ T Cell Isolation Kits (Stem-Cell Technologies) as per the manufacturer protocols. The final cell populations were determined to be >98% CD3+ or CD8+CD45RA+ T cells by flow cytometry. Proliferation in the culture was measured after stain with Alamar blue (ThermoFisher Cat. No. DAL1100) for 1 hour at 37° C., and then read on a Spectramax plus 384 well reader (Molecular Devices). Proliferation of GNC-expanded CD3+ T cells was expressed as a fold increase in cell number over background of CD3+ T cells in cell culture without GNC (FIG. **16**). Proliferation was induced by all constructs tested except the one lacking CD3 binding domain. Culture supernatants were also collected from these cultures and analyzed for the presence of gamma interferon by ELISA. Secretion of gamma interferon (FIG. **17**) was high unless CD3 or ROR1 binding domains were changed to FITC in the GNC constructs. Proliferation of naïve CD8+CD45RA+ T cells (FIG. **18**) was more sensitive to the presence or absence of 4-1BB binding domain compared to total CD3+ T cells as shown by addition of soluble anti-4-1BB monoclonal antibody to the culture in which 4-1BB binding on the GNC was absent. A similar pattern was found for secretion of gamma interferon from the naïve CD8+ T cells (FIG. **19**).

Example 3. Scale Up and Formulation of a First GNC-Activated Therapeutic Cell Composition

[0113] The manufacture of GNC-activated and -coated T cells at clinically significant dosage of 10E9 was achieved after 7 days culture. Human PBMC were isolated from LRS cone leukocytes by standard Ficoll density gradient from leukopaks which are enriched leukapheresis product collected from normal human peripheral blood. After collection the cells were frozen at −80° C. and then later thawed before putting in culture. Using the G-Rex plate and bioreactor culture systems, the growth of SI-38E17 GNC-stimulated PBMC cultures was monitored for up to 14 days. The culture medium consisted of RPMI 1640, 10% fetal calf serum, 1% non-essential amino acids, 1% GlutaMax, 0.6% glutamine-alanine supplement, 15 ng/mL human IL-2, and 1 nM GNC protein. The 6-well G-Rex cultures tolerated seeding densities of 25-100 million PBMC/well for six days, which greatly exceeded recommended amounts, but was tolerated by the cells in the system with a single 50% medium change on day 7. Clustering of cells was indicative of their activation in the culture (FIG. **20**). At least 250 million cells from one leukapheresis donor were seeded into two G-Rex 100M bioreactors and cultured in 1 liter of culture medium for seven days. The larger volume of medium allowed the culture to continue without needing to exchange the culture medium. Cell yield in each of the 100M bioreactors was between 1.2-1.4 billion cells with greater than 88% viability.

Example 4. A Second GNC-Activated Therapeutic Cell Composition

[0114] The cells from the bioreactor were harvested as the first GNC-activated therapeutic cell composition, which were optionally concentrated using LOVO Automated Cell Processing System (Fresenius Kabi). One sample (Product B) was exposed to 1 nM SI-38E17, which is identical to the first GNC in this case for preparing a second GNC-activated therapeutic cell composition, potential for being used to target treat patients harboring CD19 positive malignancies (FIG. **21**A).

[0115] After the second concentration step (100 mL volume) during the processing in the LOVO system, the second GNC-activated therapeutic cells were washed twice before eluting to a final volume of 54 mL in a sterile processing bag. The other sample (Product A) was only exposed to the first GNC protein during the culture phase and not re-exposed during processing in the LOVO system (FIG. **21**A). Cells were removed from bags, mixed 1:1 with CryoStor CS10 reagent, and frozen to −80° C. The processed cells were thawed and compared to the thawed unstimulated PBMC from the same donor before culture.

[0116] Cell viability from the GNC-expanded T cell (GET) culture was >75% and was not affected by exposure to additional GNC reagent (GNC-T, Product B) during processing (FIG. **21**B). The mean diameter of the cells increased during culture, indicative of cell activation. Flow cytometry was performed on the input PBMC cell material and the two formulations after thawing using a multi-color panel of antibodies to stain for: live/dead (e780), CD45, TCRα/β, CD56, CD4, CD8, CD14, TCRγ/δ, and CD20. Gating for quantification of the different cell subsets is shown on the GNC-activated T cells (Product A) and the additional GNC-coated GNC-T cells (Product B) (FIGS. **22**A and **22**B). The percentages of each subpopulation of cells were similar between Product A and Product B, but very different from those of input PBMC (FIG. **22**C). FIG. **23** summaries the total number and percentage of each subpopulation of cells. Compared to the input PBMC cell material, while the total number of leukocytes increased from 250 to 1000 millions or four-fold, the total number of each subpopulation of T cells was vastly increased by 55-fold for α/β T cells, 45-fold for CD4+ T cells, and 78-fold for CD8+ T cells. In this context, the increase of γ/δ T cells was modest at 5-fold, and TCRα/β−/lo, γ/δ+, CD8+ T cells seemed to the most abundant. Finally, the characteristic feature of both Product A and Product B cell compositions is the fact that there were no detectable B cells.

[0117] This example illustrates a number of advantages of GNC-T cells in comparison to CAR-T cell preparations. First, the cell composition of the starting material was fresh PBMC from the donor and did not need to be pre-selected for particular subsets of cells or require addition of feeder cells or synthetic beads. The GNC protein was 100% non-nucleotide biological material, and did not require the transfer of RNA or DNA into the cells, or transfection with a viral vector. The GNC-induced expansion yielded a therapeutic dose in 9 days, compared to the average of 40 days for CAR-T cell expansion. The resulting cells were devoid of B cells and highly enriched for activated CD4+ and CD8+ T cells that had potent killing potential against their specific targets. The GNC therapeutic composition was viable and bioactive upon thaw from −80° C. Together these advantages are expected to significantly lower waiting times, costs and issues related to infrastructure and training related to CAR-T cell therapy. Improvements in the purity, safety and quantity of the end product will be of significant benefit to the patient.

Example 5. PBMC Pre-Activated with GNC Proteins are Redirected to Potently Kill Tumor Cells

[0118] Six of the GNC SI-35 class proteins listed in Table 4 were tested for the ability to activate PBMC for redirected T cell cytotoxicity (RTCC) activity against a human ROR1-transduced CHO cell line (FIG. **24**). GNC proteins were prepared at 2× final concentration and titrated 1:3 across 10 wells of a 96 well plate in 200 ul of RPMI+10% FBS. In the final destination 96 well plate, the PBMC and serially titrated antibodies were combined by adding 100 μL of PBMC (200,000), and 100 μL of each antibody dilution to each well of the assay. The assay plate was incubated at 37° C. for approximately 72 hours before the addition of CFSE-labeled CHO-ROR1 cells. CHO-ROR1 target cells, 5×10e6, were labeled with CFSE (Invitrogen, #C34554) at 0.5 μM in 10 mL of culture media for 20 minutes at 37° C. The CHO-ROR1 cells were washed 3 times with 50 mL of culture media before resuspending in 10 mL, counted again and then 5,000 CFSE-labeled CHO-ROR1 cells were added to each well of GNC-activated PBMC. Cells were incubated for another 72 hours and then the contents of each assay well were harvested and analyzed for the number of CFSE-labeled target cells remaining. As shown on FIG. **24**, all of the GNC proteins tested directed RTCC activity with SI-35E42, SI-35E43, and SI-35E46 being the most potent in reducing the number of CHO-ROR1 cells in the well.

[0119] To further demonstrate the killing effects of GNC-labeled PBMC against human tumor cells, a GNC-dose and effector:target ratio escalation experiment was performed using an IncuCyte S3 Live Cell Analysis System (Sartorius/Essen Biosciences) to monitor the cells over time. PBMC from a healthy donor were labeled with GNC protein SI-38E17 at 10-fold serial doses ranging from 0.01 to 100 nM for 30 minutes at 37° C. and then washed prior to culture. The GNC SI-38E17 targets the CD19 antigen expressed on B cell surfaces, and therefore, the Kasumi-2 precursor B cell leukemia line was chosen as a target cell. The Kasumi-2 cell used was transduced to express green fluorescence protein (GFP) and therefore the presence of tumor cells was tracked by measuring the average green fluorescence in 4 images/well collected 9 times over a six-day period. The effector:target (E:T) ratios were escalated by adding GNC-labeled PBMC in a serial 2-fold dilution of 5,000 (1:1) to 160,000 (32:1) cells to duplicate wells. As shown in FIG. **25**, Kasumi-2 cells increased in number in the wells that had from 1:1 to 8:1 E:T ratios of unlabeled PBMC. Exposure to as little as 0.1 nM GNC led to decreased growth of Kasumi-2 in the 1:1 culture with suppression increasing at each 2-fold increase in the E:T ratio. Coating of PBMC with 1 nM or greater concentrations

of GNC led to nearly complete elimination of Kasumi-2 cells after 42 hours of culture at all E:T ratios.

[0120] As a follow up experiment, three other transformed B cell lines: NALM-6, MEC-1, and Daudi and the acute T cell leukemia line, Jurkat, were used as target cells. These target cells were previously transduced by lentivirus to constitutively express the NucRed 647 molecule. In this assay, PBMC were exposed to 10-fold doses of GNC protein SI-38E17 for 30 minutes at 37° C. and then washed as before. PBMC were plated at 1.2×10^6 cells/well and 50,000 target tumor cells were added. Cells were placed in IncuCyte S3 set to collect red fluorescence images (4 images/well) collected at 10 time points over a 5.5-day period (FIG. **26**). Growth curves were established for all four tumor cell lines in the absence of PBMC (null). Labeling of PBMC with 1 nM or more of GNC protein SI-38E17 led to arrested growth of all three B cell lines but not Jurkat T cell leukemia. The B cell lines varied in their susceptibility to PBMC cells pre-exposed to 0.1 nM of GNC protein.

[0121] As a different method of quantifying the outcome of cultures of GNC-T cells with tumor cells, we established a limit of quantification (LOQ) curve for detection by flow cytometry. Daudi-Red cells were serially diluted 10-fold in a range from 200,000 to 20 cells and then mixed 1:1 with 1 million PBMC to create samples of 10%, 1.0%, 0.1%, 0.01% and 0.001% tumor cells, which were then analyzed by flow cytometry (FIG. **27**). Next, cells were harvested from a 15 day 6-well G-Rex culture of 1 nM GNC-expanded T cells that had been spiked with 10%, 1% or 0.1% of NALM-6, MEC-1, Daudi, or Jurkat (all NucRed-transduced) tumor cells at time 0 and analyzed using the same flow cytometry settings as above. Tumor cells were reduced to less than 0.001% in all conditions with the exception of the culture in which the MEC-1 tumor line was spiked in at 10% were 44 cells were detected. In this condition the MEC-1 cells were reduced to <0.01% in the culture.

[0122] While the present disclosure has been described with reference to particular embodiments or examples, it may be understood that the embodiments are illustrative and that the disclosure scope is not so limited. Alternative embodiments of the present disclosure may become apparent to those having ordinary skill in the art to which the present disclosure pertains. Such alternate embodiments are considered to be encompassed within the scope of the present disclosure. Accordingly, the scope of the present disclosure is defined by the appended claims and is supported by the foregoing description. All references cited or referred to in this disclosure are hereby incorporated by reference in their entireties.

Tables

[0123]

TABLE 1A

Composition of example GNC proteins with T cell binding domains.

Moiety 1			
Activation of T cells	Agonist receptor	Antagonist receptor	Moiety 2 Tumor Antigen
CD3	CD28, 41BB, OX40, GITR, CD40L, ICOS, Light, CD27, CD30	PDL1, PD1, TIGIT, TIM-3, LAG-3, CTLA4, BTLA, VISTA, PDL2	BCMA, CD19, CD20, CD33, CD123, CD22, CD30, ROR1, CEA, HER2, EGFR, EGFRvIII, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2

TABLE 2

Examples of possible combinations of T cell activation, T cell agonist, T cell antagonist, and tumor antigen binding domains in a single GNC protein.

GNC protein	T cell activation	Tumor antigen	T cell antagonist	T cell agonist	T cell antagonist	T cell antagonist	T cell antagonist	T cell agonist
Bi-specific	CD3	ROR1						
Tri-specific	CD3	ROR1	PD1					
Tetra-specific	CD3	ROR1	PD1	41BB				
Penta-specific	CD3	ROR1	PD1	41BB	LAG3			
Hexa-specific	CD3	ROR1	PD1	41BB	LAG3	TIM3		
Hepta-specific	CD3	ROR1	PD1	41BB	LAG3	TIM3	TIGIT	
Octa-specific	CD3	ROR1	PD1	41BB	LAG3	TIM3	TIGIT	CD28

TABLE 3

Specificity of antibody binding domains used in GNC proteins.

AgBD Specificity	Antibody Name
CD3ε	284A10
	480C8
4-1BB	460C3
	420H5
	466F6
FITC	4420
PD-L1	PL230C6
CD19	21D4
ROR1	323H7
IgD Domain	330F11
Kringle Domain	338H4
Frizzled Domain	324C6
EGFRvIII	806

TABLE 4

Classes of tetra-specific GNC antibodies targeting EGFRvIII (SI-39E), ROR1 (SI-35E), and CD19 (SI-38E).

GNC ID	AgBD 1 (LH-scFv)	Humanized Variant	AgBD 2 (Fab)	Humanized Variant	IgG1 Fc	AgBD 3 (HL-scFv)	Humanized Variant	AgBD 4 (HL-ScFv)	Humanized Variant
SI-39E18	284A10	L1H1	806	—	n2	PL221G5	H1L1	420H5	H3L3
SI-39E29	806	—	284A10	H1L1	n2	PL221G5	H1L1	420H5	H3L3
SI-35E20	466F6	L5H2	PL230C6	H3L2	n2	323H7	H4L1	284A10	H1L1
SI-35E58	284A10	L1H1	PL230C6	H3L2	n2	323H7	H4L1	466F6	H2L5
SI-35E88	284A10	L1H1	323H7	H4L1	n2	PL230C6	H3L2	466F6	H2L5
SI-35E99	284A10	L1H1	323H7	H4L1	n2	PL221G5	H1L1	466F6	H2L5
SI-35E18	460C3	L1H1	PL230C6	H3L2	n2	323H7	H4L1	284A10	H1L1
SI-35E19	420H5	L3H3	PL230C6	H3L2	n2	323H7	H4L1	284A10	H1L1
SI-35E36	4420	—	PL230C6	H3L2	n2	338H4	H3L4	284A10	H1L1
SI-35E37	460C3	L1H1	4420	—	n2	338H4	H3L4	284A10	H1L1
SI-35E38	460C3	L1H1	PL230C6	H3L2	n2	4420	—	284A10	H1L1
SI-35E39	460C3	L1H1	PL230C6	H3L2	n2	338H4	H3L4	4420	—
SI-38E17	284A10	H1L1	21D4	—	n2	PL221G5	H1L1	466F6	H2L5
SI-38E33	21D4	—	284A10	H1L1	n2	PL221G5	H1L1	466F6	H2L5

SEQ ID	Description
1	anti-CD3 284A10 VHv1 nt
2	anti-CD3 284A10 VHv1 aa
3	anti-CD3 284A10 VLv1 nt
4	anti-CD3 284A10 VLv1 aa
5	anti-PD-L1 PL23006 VHv3 nt
6	anti-PD-L1 PL23006 VHv3 aa
7	anti-PD-L1 PL23006 VLv2 nt
8	anti-PD-L1 PL23006 VLv2 aa
9	anti-PD-L1 PL221G5 VHv1 nt
10	anti-PD-L1 PL221G5 VHv1 aa
11	anti-PD-L1 PL221G5 VLv1 nt
12	anti-PD-L1 PL221G5 VLv1 aa
13	anti-4-1BB 420H5 VHv3 nt
14	anti-4-1BB 420H5 VHv3 aa
15	anti-4-1BB 420H5 VLv3 nt
16	anti-4-1BB 420H5 VHLv3 aa
17	anti-4-1BB 466F6 VHv2 nt
18	anti-4-1BB 466F6 VHv2 aa
19	anti-4-1BB 466F6 VLv5 nt
20	anti-4-1BB 466F6 VLv5 aa
21	anti-4-1BB 460C3 VHv1 nt
22	anti-4-1BB 460C3 VHv1 aa
23	anti-4-1BB 460C3 VLv1 nt
24	anti-4-1BB 460C3 VLv1 aa
25	anti-ROR1 323H7 VHv4 nt
26	anti-ROR1 323H7 VHv4 aa
27	anti-ROR1 323H7 VLv1 nt
28	anti-ROR1 323H7 VLv1 aa
29	anti-ROR1 338H4 VHv3 nt
30	anti-ROR1 338H4 VHv3 aa
31	anti-ROR1 338H4 VLv4 nt
32	anti-ROR1 338H4 VLv4 aa
33	anti-FITC 4-4-20 VH nt
34	anti-FITC 4-4-20 VH aa
35	anti-FITC 4-4-20 VL nt
36	anti-FITC 4-4-20 VL aa
37	human IgG1 null2 (G1m-fa with ADCC/CDC null mutations) nt
38	human IgG1 null2 (G1m-fa with ADCC/CDC null mutations) aa
39	human Ig Kappa nt
40	human Ig Kappa aa
41	SI-35E18 (460C3-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) heavy chain nt
42	SI-35E18 (460C3-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) heavy chain aa
43	SI-35E18 (460C3-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) light chain nt
44	SI-35E18 (460C3-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) light chain aa

-continued

SEQ ID	Description
45	anti-CD3 284A10 VHv1b nt
46	anti-CD3 284A10 VHv1b aa
47	anti-huCD19 21D4 VH nt
48	anti-huCD19 21D4 VH aa
49	anti-huCD19 21D4 VL nt
50	anti-huCD19 21D4 VL aa
51	anti-huEGFRvIII 806 VH nt
52	anti-huEGFRvIII 806 VH aa
53	anti-huEGFRvIII 806 VL nt
54	anti-huEGFRvIII 806 VL aa
55	GGGGSGGGGSG linker nt
56	GGGGSGGGGSG linker aa
57	GGGSGGGGS linker 01 nt
58	GGGSGGGGS linker 01 aa
59	GGGSGGGGS linker 02 nt
60	GGGSGGGGS linker 02 aa
61	GGGSGGGGSGGGSGGGGS linker nt
62	GGGSGGGGSGGGSGGGGS linker aa
63	SI-39E18 (284A10-L1H1-scFv × 806-Fab × PL221G5-H1L1-sc Fv × 420H5-H3L3-scFv) heavy chain nt
64	SI-39E18 (284A10-L1H1-scFv × 806-Fab × PL221G5-H1L1-sc Fv × 420H5-H3L3-scFv) heavy chain aa
65	SI-39E18 (284A10-L1H1-scFv × 806-Fab × PL221G5-H1L1-sc Fv × 420H5-H3L3-scFv) light chain nt
66	SI-39E18 (284A10-L1H1-scFv × 806-Fab × PL221G5-H1L1-sc Fv × 420H5-H3L3-scFv) light chain aa
67	SI-39E29 (806-LH-scFv × 284A10-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) heavy chain nt
68	SI-39E29 (806-LH-scFv × 284A10-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) heavy chain aa
69	SI-39E29 (806-LH-scFv × 284A10-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) light chain nt
70	SI-39E29 (806-LH-scFv × 284A10-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) light chain aa
71	SI-35E20 (466F6-L5H2-scFv × PL230C6-Fab × 3 23H7-H4L1-scFv × 284A10-H1L1-scFv) heavy chain nt
72	SI-35E20 (466F6-L5H2-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) heavy chain aa
73	SI-35E20 (466F6-L5H2-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) light chain nt
74	SI-35E20 (466F6-L5H2-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) light chain aa
75	SI-35E58 (284A10-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-sc Fv × 466F6-H2L5-scFv) heavy chain nt
76	SI-35E58 (284A10-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-sc Fv × 466F6-H2L5-scFv) heavy chain aa
77	SI-35E58 (284A10-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-sc Fv × 466F6-H2L5-scFv) light chain nt

-continued

SEQ ID	Description
78	SI-35E58 (284A10-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-sc Fv × 466F6-H2L5-scFv) light chain aa
79	SI-35E88 (284A10-L1H1-scFv × 323H7-Fab × PL230C6-H3L2-sc Fv × 466F6-H2L5-scFv) heavy chain nt
80	SI-35E88 (284A10-L1H1-scFv × 323H7-Fab × PL230C6-H3L2-sc Fv × 466F6-H2L5-scFv) heavy chain aa
81	SI-35E88 (284A10-L1H1-scFv × 323H7-Fab × PL230C6-H3L2-sc Fv × 466F6-H2L5-scFv) light chain nt
82	SI-35E88 (284A10-L1H1-scFv × 323H7-Fab × PL230C6-H3L2-sc Fv × 466F6-H2L5-scFv) light chain aa
83	SI-35E99 (284A10-L1H1-scFv × 323H7-Fab × PL221G5-H1L1-sc Fv × 466F6-H2L5-scFv) heavy chain nt
84	SI-35E99 (284A10-L1H1-scFv × 323H7-Fab × PL221G5-H1L1-sc Fv × 466F6-H2L5-scFv) heavy chain aa
85	SI-35E99 (284A10-L1H1-scFv × 323H7-Fab × PL221G5-H1L1-sc Fv × 466F6-H2L5-scFv) light chain nt
86	SI-35E99 (284A10-L1H1-scFv × 323H7-Fab × PL221G5-H1L1-sc Fv × 466F6-H2L5-scFv) light chain aa

-continued

SEQ ID	Description
87	SI-38E17 (284A10-L1H1-scFv × 21D4-Fab × PL221G5-H1L1-scFv × 466F6-H2L5-scFv) heavy chain nt
88	SI-38E17 (284A10-L1H1-scFv × 21D4-Fab × PL221G5-H1L1-scFv × 466F6-H2L5-scFv) heavy chain aa
89	SI-38E17 (284A10-L1H1-scFv × 21D4-Fab × PL221G5-H1L1-scFv × 466F6-H2L5-scFv) light chain nt
90	SI-38E17 (284A10-L1H1-scFv × 21D4-Fab × PL221G5-H1L1-scFv × 466F6-H2L5-scFv) light chain aa
91	SI-38E33 (21D4-LH-scFv × 284A10-Fab × PL221G5-H1L1-sc Fv × 466F6-H2L5-scFv) heavy chain nt
92	SI-38E33 (21D4-LH-scFv × 284A10-Fab × PL221G5-H1L1-sc Fv × 466F6-H2L5-scFv) heavy chain aa
93	SI-38E33 (21D4-LH-scFv × 284A10-Fab × PL221G5-H1L1-sc Fv × 466F6-H2L5-scFv) light chain nt
94	SI-38E33 (21D4-LH-scFv × 284A10-Fab × PL221G5-H1L1-sc Fv × 466F6-H2L5-scFv) light chain aa

GNC-T Sequence Listing of Tetra-Specific GNC Antibodies

[0124]

>SEQ ID 01 anti-CD3 284A10 VHv1 nt
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG

ATTCACCATCAGTACCAATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAGTCATTA

CTGGTCGTGATATCACATACTACGCGAGCTGGGCGAAAGGCAGATTCACCATCTCCAGAGACAATTCCAAGAACACG

CTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGCGCGACGGTGGATCATCTGC

TATTACTAGTAACAACATTTGGGGCCAAGGAACTCTGGTCACCGTTTCTTCA

>SEQ ID 02 anti-CD3 284A10 VHv1 aa
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LYLQMNSLRAEDTAVYYCARDGGSSAITSNNIWGQGTLVTVSS

>SEQ ID 03 anti-CD3 284A10 VLv1 nt
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TGAGAGCATTAGCAGTTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGAAGCAT

CCAAACTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCAGC

CTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAGGCTATTTTTATTTTATTAGTCGTACTTATGTAAATTCTTT

CGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 04 anti-CD3 284A10 VLv1 aa
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LQPDDFATYYCQGYFYFISRTYVNSFGGGTKVEIK

>SEQ ID 05 anti-PD-L1 PL230C6 VHv3 nt
CAGTCGGTGGAGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTCTGGAAT

CGACCTTAATACCTACGACATGATCTGGGTCCGCCAGGCTCCAGGCAAGGGGCTAGAGTGGGTTGGAATCATTACTT

ATAGTGGTAGTAGATACTACGCGAACTGGGCGAAAGGCCGATTCACCATCTCCAAAGACAATACCAAGAACACGGTG

TATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCCAGAGATTATATGAGTGGTTCCCA

CTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCTAGT

>SEQ ID 06 anti-PD-L1 PL230C6 VHv3 aa
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YLQMNSLRAEDTAVYYCARDYMSGSHLWGQGTLVTVSS

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>SEQ ID 07 anti-PD-L1 PL230C6 VLv2 nt
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TGAGGACATTTATAGCTTCTTGGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCATTCTGCAT

CCTCTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGC

CTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGGGTTATGGTAAAAATAATGTTGATAATGCTTTCGGCGG

AGGGACCAAGGTGGAGATCAAA

>SEQ ID 08 anti-PD-L1 PL230C6 VLv2 aa
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LQPEDFATYYCQQGYGKNNVDNAFGGGTKVEIK

>SEQ ID 09 anti-PD-L1 PL221G5 VHv1 nt
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ATTCTCCTTCAGTAGCGGGTACGACATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGCATGCA

TTGCTGCTGGTAGTGCTGGTATCACTTACGACGCGAACTGGGCGAAAGGCCGGTTCACCATCTCCAGAGACAATTCC

AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAGATCGGCGTT

TTCGTTCGACTACGCCATGGACCTCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

>SEQ ID 10 anti-PD-L1 PL221G5 VHv1 aa
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KNTLYLQMNSLRAEDTAVYYCARSAFSFDYAMDLWGQGTLVTVSS

>SEQ ID 11 anti-PD-L1 PL221G5 VLv1 nt
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TCAGAGCATTAGTTCCCACTTAAACTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATAAGGCAT

CCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTTACTCTCACCATCAGCAGC

CTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGGGTTATAGTTGGGGTAATGTTGATAATGTTTTCGGCGG

AGGGACCAAGGTGGAGATCAAA

>SEQ ID 12 anti-PD-L1 PL221G5 VLv1 aa
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LQPDDFATYYCQQGYSWGNVDNVFGGGTKVEIK

>SEQ ID 13 anti-4-1BB 420H5 VHv3 nt
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CTCCTTCAGTAGCAACTACTGGATATGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGCATGCATTT

ATGTTGGTAGTAGTGGTGACACTTACTACGCGAGCTCCGCGAAAGGCCGGTTCACCATCTCCAGAGACAATTCCAAG

AACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAGAGATAGTAGTAG

TTATTATATGTTTAACTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

>SEQ ID 14 anti-4-1BB 420H5 VHv3 aa
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NTLYLQMNSLRAEDTAVYYCARDSSSYYMFNLWGQGTLVTVSS

>SEQ ID 15 anti-4-1BB 420H5 VLv3 nt
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TGAGGACATTGATACCTATTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTTTTATGCAT

CCGATCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACCATCAGCAGC

CTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAGGCGGTTACTATACTAGTAGTGCTGATACGAGGGGTGCTTT

CGGCGGAGGGACCAAGGTGGAGATCAAA

-continued

>SEQ ID 16 anti-4-1BB 420H5 VLv3 aa
ALVMTQSPSTLSASVGDRVTINCQASEDIDTYLAWYQQKPGKAPKLLIFYASDLASGVPSRFSGSGSGTEFTLTISS

LQPDDFATYYCQGGYYTSSADTRGAFGGGTKVEIK

>SEQ ID 17 anti-4-1BB 466F6 VHv2 nt
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CACCATCAGTAGCTACCACATGCAGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTACATCGGAACCATTAGTA

GTGGTGGTAATGTATACTACGCGAGCTCCGCGAGAGGCAGATTCACCATCTCCAGACCCTCGTCCAAGAACACGGTG

GATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGACTCTGGTTATAGTGATCC

TATGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

>SEQ ID 18 anti-4-1BB 466F6 VHv2 aa
RSLVESGGGLVQPGGSLRLSCTASGFTISSYHMQWVRQAPGKGLEYIGTISSGGNVYYASSARGRFTISRPSSKNTV

DLQMNSLRAEDTAVYYCARDSGYSDPMWGQGTLVTVSS

>SEQ ID 19 anti-4-1BB 466F6 VLv5 nt
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TCAGAACATTAGGACTTACTTATCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCAG

CCAATCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCGAC

CTGGAGCCTGGCGATGCTGCAACTTACTATTGTCAGTCTACCTATCTTGGTACTGATTATGTTGGCGGTGCTTTCGG

CGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 20 anti-4-1BB 466F6 VLv5 aa
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LEPGDAATYYCQSTYLGTDYVGGAFGGGTKVEIK

>SEQ ID 21 anti-4-1BB 460C3 VHv1 nt
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TATATACTGGTAGCCGCGATACTCCTCACTACGCGAGCTCCGCGAAAGGCCGGTTCACCATCTCCAGAGACAATTCC

AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAGAGAAGGTAG

CCTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

>SEQ ID 22 anti-4-1BB 460C3 VHv1 aa
EVQLLESGGGLVQPGGSLRLSCAASGIDFSRRYYMCWVRQAPGKGLEWIACIYTGSRDTPHYASSAKGRFTISRDNS

KNTLYLQMNSLRAEDTAVYYCAREGSLWGQGTLVTVSS

>SEQ ID 23 anti-4-1BB 460C3 VLv1 nt
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CATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACCATCAGC

AGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCGCAGGCGGTTACAATACTGTTATTGATACTTTTGCTTTCGG

CGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 24 anti-4-1BB 460C3 VLv1 aa
DIQMTQSPSTLSASVGDRVTITCQSSQSVYSNWFSWYQQKPGKAPKLLIYSASTLASGVPSRFSGSGSGTEFTLTIS

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>SEQ ID 25 anti-ROR1 323H7 VHv4 nt
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ATGTTAATAATGATGACACAGACTACGCGAGCTCCGCGAAAGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAAC

ACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCACCTATTTCTGTGCGAGATTGGATGTTGGTGG

TGGTGGTGCTTATATTGGGGACATCTGGGGCCAGGGAACTCTGGTTACCGTCTCTTCA

>SEQ ID 26 anti-ROR1 323H7 VHv4 aa
EVQLLESGGGLVQPGGSLRLSCAASGETISRYHMTWVRQAPGKGLEWIGHIYVNNDDTDYASSAKGRFTISRDNSKN

TLYLQMNSLRAEDTATYFCARLDVGGGGAYIGDIWGQGTLVTVSS

>SEQ ID 27 anti-ROR1 323H7 VLv1 nt
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TCAGAGTGTTTATAACAACAACGACTTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATT

ATGCTTCCACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATC

AGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTGCAGGCGGTTATGATACGGATGGTCTTGATACGTTTGC

TTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 28 anti-ROR1 323H7 VLv1 aa
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SSLQPEDVATYYCAGGYDTDGLDTFAFGGGTKVEIK

>SEQ ID 29 anti-ROR1 338H4 VHv3 nt
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ATTCTCCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAGGGGGCTGGAGTGGATCGGAATCATTT

ATGCTAGTGGTAGCACATACTACGCGAGCTCGGCGAAAGGCAGATTCACCATCTCCAAAGACAATACCAAGAACACG

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CCTCTGGGGCCAGGGAACTCTGGTTACCGTCTCTTCA

>SEQ ID 30 anti-ROR1 338H4 VHv3 aa
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VDLQMNSLRAEDTAVYYCARIYDGMDLWGQGTLVTVSS

>SEQ ID 31 anti-ROR1 338H4 VLv4 nt
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TCAGAACATTTACAGCTACTTATCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCGCCTGATCTATCTGGCAT

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CTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAAAGCAATTATAACGGTAATTATGGTTTCGGCGGAGGGACCAA

GGTGGAGATCAAA

>SEQ ID 32 anti-ROR1 338H4 VLv4 aa
DIQMTQSPSSLSASVGDRVTINCQASQNIYSYLSWYQQKPGKVPKRLIYLASTLASGVPSRFSGSGSGTDYTLTISS

LQPEDVATYYCQSNYNGNYGFGGGTKVEIK

>SEQ ID 33 anti-FITC 4420 VH nt
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>SEQ ID 34 anti-FITC 4420 VH aa
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>SEQ ID 35 anti-FITC 4420 VL nt
GATGTCGTGATGACCCAAACTCCACTCTCCCTGCCTGTCAGTCTTGGAGATCAAGCCTCCATCTCTTGCAGATCTAG

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TGATCTACAAAGTTTCCAACCGATTTTCTGGGGTCCCAGACAGGTTCAGTGGCAGTGGATCAGGGACAGATTTCACA

CTCAAGATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTTATTTCTGCTCTCAAAGTACACATGTTCCGTGGACGTT

CGGTGGAGGCACCAAGCTGGAAATCAAA

>SEQ ID 36 anti-FITC 4420 VL aa
DVVMTQTPLSLPVSLGDQASISCRSSQSLVHSNGNTYLRWYLQKPGQSPKVLIYKVSNRFSGVPDRFSGSGSGTDFT

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>SEQ ID 37 human IgG1 null (G1m-fa with ADCC/CDC null mutations) nt
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CCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGC

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TGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAA

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TCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTG

TACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCC

CAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACT

CCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGC

TCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

>SEQ ID 38 human IgG1 null (G1m-fa with ADCC/CDC null mutations) aa
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TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLEPPKPKDTLMISRTPEVTCVVVDVSHEDP

EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQV

YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC

SVMHEALHNHYTQKSLSLSPG

>SEQ ID 39 human Ig Kappa nt
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CCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCA

GACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAA

CAGGGGAGAGTGT

>SEQ ID 40 human Ig Kappa aa
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA

DYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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>SEQ ID 41 SI-35E18 (460C3-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) heavy chain nt

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TCAGAGTGTTTATAGTAACTGGTTCTCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATTCTG

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ACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAGA

GAAGGTAGCCTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGGCGGTGGAGGGTCCGGCGGTGGTGGATCCCA

GTCGGTGGAGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTCTGGAATCG

ACCTTAATACCTACGACATGATCTGGGTCCGCCAGGCTCCAGGCAAGGGGCTAGAGTGGGTTGGAATCATTACTTAT

AGTGGTAGTAGATACTACGCGAACTGGGCGAAAGGCCGATTCACCATCTCCAAAGACAATACCAAGAACACGGTGTA

TCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCCAGAGATTATATGAGTGGTTCCCACT

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ACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGC

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GGGAAAGCCCCTAAGCTCCTGATCTATGAAGCATCCAAACTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGG

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>SEQ ID 42 SI-35E18 (460C3-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) heavy chain aa

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ASGIDFSRRYYMCWVRQAPGKGLEWIACIYTGSRDTPHYASSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR

EGSLWGQGTLVTVSSGGGGSGGGGSQSVEESGGGLVQPGGSLRLSCTASGIDLNTYDMIWVRQAPGKGLEWVGIITY

SGSRYYANWAKGRFTISKDNTKNTVYLQMNSLRAEDTAVYYCARDYMSGSHLWGQGTLVTVSSASTKGPSVFPLAPS

SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN

TKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH

NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ

VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK

SLSLSPGGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGETISRYHMTWVRQAPGKGLEWIGHIYVNNDDTDY

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FTISTNAMSWVRQAPGKGLEWIGVITGRDITYYASWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGGSSA

ITSNNIWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPSTLSASVGDRVTINCQASESISSWLAWYQQKP

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>SEQ ID 43 SI-35E18 (460C3-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) light chain nt

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CCTCTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGC

CTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGGGTTATGGTAAAAATAATGTTGATAATGCTTTCGGCGG

AGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGA

AATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGAT

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>SEQ ID 44 SI-35E18 (460C3-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) light chain aa
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LQPEDFATYYCQQGYGKNNVDNAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNEYPREAKVQWKVD

NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>SEQ ID 45 anti-CD3 284A10 VHv1b nt
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG

ATTCACCATCAGTACCAATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAGTCATTA

CTGGTCGTGATATCACATACTACGCGAGCTGGGCGAAAGGCAGATTCACCATCTCCAGAGACAATTCCAAGAACACG

CTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGACGGTGGTTCTTCTGC

TATTACTAGTAACAACATTTGGGGCCAGGGAACCCTGGTCACCGTGTCGACA

>SEQ ID 46 anti-CD3 284A10 VHv1b aa
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LYLQMNSLRAEDTAVYYCARDGGSSAITSNNIWGQGTLVTVST

>SEQ ID 47 anti-huCD19 21D4 VH nt
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>SEQ ID 48 anti-huCD19 21D4 VH aa
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>SEQ ID 49 anti-huCD19 21D4 VL nt
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>SEQ ID 50 anti-huCD19 21D4 VL aa
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>SEQ ID 51 anti-huEGFRvIII 806 VH nt
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>SEQ ID 52 anti-huEGFRvIII 806 VH aa
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>SEQ ID 53 anti-huEGFRvIII 806 VL nt
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>SEQ ID 54 anti-huEGFRvIII 806 VL aa
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>SEQ ID 55 GGGGSGGGGSG linker nt
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>SEQ ID 56 GGGGSGGGGSG linker aa
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>SEQ ID 57 GGGGSGGGGS linker 01 nt
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>SEQ ID 58 GGGGSGGGGS linker 01 aa
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>SEQ ID 59 GGGGSGGGGS linker 02 nt
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>SEQ ID 60 GGGGSGGGGS linker 02 aa
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>SEQ ID 61 GGGGSGGGGSGGGGSGGGGS linker nt
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>SEQ ID 62 GGGGSGGGGSGGGGSGGGGS linker aa
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>SEQ ID 63 SI-39E18 (284A10-L1H1-scFv × 806-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) heavy chain nt
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CGGCGGAGGGACCAAGGTGGAGATCAAAGGCGGTGGCGGTAGTGGGGGAGGCGGTTCTGGCGGCGGAGGGTCCGGCG

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CGGAGTCATTACTGGTCGTGATATCACATACTACGCGAGCTGGGCGAAAGGCAGATTCACCATCTCCAGAGACAATT

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>SEQ ID 64 SI-39E18 (284A10-L1H1-scFv × 806-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) heavy chain aa

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AASGFTISTNAMSWVRQAPGKGLEWIGVITGRDITYYASWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDG

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EWMGYISYSGNTRYNPSLKSRISITRDTSKNQFFLQLNSVTIEDTATYYCVTAGRGFPYWGQGTLVTVSAASTKGPS

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VNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY

VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR

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HNHYTQKSLSLSPGGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFSFSSGYDMCWVRQAPGKGLEWIACIA

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ASGFSFSSNYWICWVRQAPGKGLEWIACIYVGSSGDTYYASSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR

DSSSYYMFNLWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSALVMTQSPSTLSASVGDRVTINCQASEDIDTYLAWY

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>SEQ ID 65 SI-39E18 (284A10-L1H1-scFv × 806-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) light chain nt
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TCAGGACATTAACAGTAATATAGGGTGGTTGCAGCAGAGACCAGGGAAATCATTTAAGGGCCTGATCTATCATGGAA

CCAACTTGGACGATGAAGTTCCATCAAGGTTCAGTGGCAGTGGATCTGGAGCCGATTATTCTCTCACCATCAGCAGC

CTGGAATCTGAAGATTTTGCAGACTATTACTGTGTACAGTATGCTCAGTTTCCGTGGACGTTCGGTGGAGGCACCAA

GCTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA

CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTC

CAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGAC

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>SEQ ID 66 SI-39E18 (284A10-L1H1-scFv × 806-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) light chain aa
DILMTQSPSSMSVSLGDTVSITCHSSQDINSNIGWLQQRPGKSFKGLIYHGTNLDDEVPSRFSGSGSGADYSLTISS

LESEDFADYYCVQYAQFPWTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL

QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>SEQ ID 67 SI-39E29 (806-LH-scFv × 284A10-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) heavy chain nt
GACATCCTGATGACCCAATCTCCATCCTCCATGTCTGTATCTCTGGGAGACACAGTCAGCATCA

CTTGCCATTCAAGTCAGGACATTAACAGTAATATAGGGTGGTTGCAGCAGAGACCAGGGAAATC

ATTTAAGGGCCTGATCTATCATGGAACCAACTTGGACGATGAAGTTCCATCAAGGTTCAGTGGC

AGTGGATCTGGAGCCGATTATTCTCTCACCATCAGCAGCCTGGAATCTGAAGATTTTGCAGACT

ATTACTGTGTACAGTATGCTCAGTTTCCGTGGACGTTCGGTGGAGGCACCAAGCTGGAAATCAA

AGGCGGTGGCGGTAGTGGGGGAGGCGGTTCTGGCGGCGGAGGGTCCGGCGGTGGAGGATCAGAT

GTGCAGCTTCAGGAGTCGGGACCTAGCCTGGTGAAACCTTCTCAGTCTCTGTCCCTCACCTGCA

CTGTCACTGGCTACTCAATCACCAGTGATTTTGCCTGGAACTGGATTCGGCAGTTTCCAGGAAA

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CTATTGAGGACACAGCCACATATTACTGTGTAACGGCGGGACGCGGGTTTCCTTATTGGGGCCA

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CTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCT

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ACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGG

ACACGGCTGTGTATTACTGTGCGCGCGACGGTGGATCATCTGCTATTACTAGTAACAACATTTG

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GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACT

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TCGAGCGGCGGTGGCGGTAGTGGGGGAGGCGGTTCTGGCGGCGGAGGGTCCGGCGGTGGAGGAT

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CACTTGCCAGGCCAGTCAGAGCATTAGTTCCCACTTAAACTGGTATCAGCAGAAACCAGGGAAA

GCCCCTAAGCTCCTGATCTATAAGGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCG

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GAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTCCTTCAG

TAGCAACTACTGGATATGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGCATGT

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CCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGC

CGTATATTACTGTGCGAGAGATAGTAGTAGTTATTATATGTTTAACTTGTGGGGCCAGGGAACC

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CAGAGTCACCATCAATTGCCAGGCCAGTGAGGACATTGATACCTATTTAGCCTGGTATCAGCAG

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TTCGGCGGAGGGACCAAGGTGGAGATCAAA

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>SEQ ID 68 SI-39E29 (806-LH-scFv × 284A10-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) heavy chain aa
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SGSGADYSLTISSLESEDFADYYCVQYAQFPWTFGGGTKLEIKGGGGSGGGGSGGGGSGGGGSD

VQLQESGPSLVKPSQSLSLTCTVTGYSITSDFAWNWIRQFPGNKLEWMGYISYSGNTRYNPSLK

SRISITRDTSKNQFFLQLNSVTIEDTATYYCVTAGRGFPYWGQGTLVTVSAGGGGSGGGGSEVQ

LVESGGGLVQPGGSLRLSCAASGFTISTNAMSWVRQAPGKGLEWIGVITGRDITYYASWAKGRF

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LGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRT

PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK

CAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN

GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG

GGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFSFSSGYDMCWVRQAPGKGLEWIACIAAGS

AGITYDANWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSAFSFDYAMDLWGQGTLVTV

SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTITCQASQSISSHLNWYQQKPGK

APKLLIYKASTLASGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQGYSWGNVDNVFGGGTK

VEIKGGGGSGGGGSQSLVESGGGLVQPGGSLRLSCAASGFSFSSNYWICWVRQAPGKGLEWIAC

IYVGSSGDTYYASSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDSSSYYMFNLWGQGT

LVTVSSGGGGSGGGGSGGGGSGGGGSALVMTQSPSTLSASVGDRVTINCQASEDIDTYLAWYQQ

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FGGGTKVEIK

>SEQ ID 69 SI-39E29 (806-LH-scFv × 284A10-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) light chain nt
GACGTCGTGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA

ATTGCCAAGCCAGTGAGAGCATTAGCAGTTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGC

CCCTAAGCTCCTGATCTATGAAGCATCCAAACTGGCATCTGGGGTCCCATCAAGGTTCAGCGGC

AGTGGATCTGGGACAGAATTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTT

ATTACTGCCAAGGCTATTTTTATTTTATTAGTCGTACTTATGTAAATTCTTTCGGCGGAGGGAC

CAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG

CAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCA

AAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCA

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>SEQ ID 70 SI-39E29 (806-LH-scFv × 284A10-Fab × PL221G5-H1L1-scFv × 420H5-H3L3-scFv) light chain aa
DVVMTQSPSTLSASVGDRVTINCQASESISSWLAWYQQKPGKAPKLLIYEASKLASGVPSRFSG

SGSGTEFTLTISSLQPDDFATYYCQGYFYFISRTYVNSFGGGTKVEIKRTVAAPSVFIFPPSDE

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>SEQ ID 71 SI-35E20 (466F6-L5H2-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) heavy chain nt

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AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCGACCTGGAGCCTGGCGATGCTGCAACTT

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ACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTG

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>SEQ ID 72 SI-35E20 (466F6-L5H2-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) heavy chain aa

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GGSRSLVESGGGLVQPGGSLRLSCTASGFTISSYHMQWVRQAPGKGLEYIGTISSGGNVYYASS

ARGRFTISRPSSKNTVDLQMNSLRAEDTAVYYCARDSGYSDPMWGQGTLVTVSSGGGGSGGGGS

QSVEESGGGLVQPGGSLRLSCTASGIDLNTYDMIWVRQAPGKGLEWVGIITYSGSRYYANWAKG

RFTISKDNTKNTVYLQMNSLRAEDTAVYYCARDYMSGSHLWGQGTLVTVSSASTKGPSVFPLAP

SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG

TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE

VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCA

VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ

PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGG

SGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTISRYHMTWVRQAPGKGLEWIGHIYVNNDDT

DYASSAKGRFTISRDNSKNTLYLQMNSLRAEDTATYFCARLDVGGGGAYIGDIWGQGTLVTVSS

GGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCQSSQSVYNNNDLAWYQQKPGK

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SFGGGTKVEIK

>SEQ ID 73 SI-35E20 (466F6-L5H2-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) light chain nt
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AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTT

ACTATTGTCAACAGGGTTATGGTAAAAATAATGTTGATAATGCTTTCGGCGGAGGGACCAAGGT

GGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG

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>SEQ ID 74 SI-35E20 (466F6-L5H2-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 284A10-H1L1-scFv) light chain aa
AYDMTQSPSSVSASVGDRVTIKCQASEDIYSFLAWYQQKPGKAPKLLIHSASSLASGVPSRFSG

SGSGTDFTLTISSLQPEDFATYYCQQGYGKNNVDNAFGGGTKVEIKRTVAAPSVFIFPPSDEQL

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>SEQ ID 75 SI-35E58 (284A10-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 466F6-H2L5-scFv) heavy chain nt
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ATTACTGCCAAGGCTATTTTTATTTTATTAGTCGTACTTATGTAAATTCTTTCGGCGGAGGGAC

CAAGGTGGAGATCAAAGGCGGTGGCGGTAGTGGGGGAGGCGGTTCTGGCGGCGGAGGGTCCGGC

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>SEQ ID 76 SI-35E58 (284A10-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 466F6-H2L5-scFv) heavy chain aa

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SGSGTEFTLTISSLQPDDFATYYCQGYFYFISRTYVNSFGGGTKVEIKGGGGSGGGGSGGGGSG

GGGSEVQLVESGGGLVQPGGSLRLSCAASGFTISTNAMSWVRQAPGKGLEWIGVITGRDITYYA

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PSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLM

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YVNNDDTDYASSAKGRFTISRDNSKNTLYLQMNSLRAEDTATYFCARLDVGGGGAYIGDIWGQG

TLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCQSSQSVYNNNDLAW

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FAFGGGTKVEIKGGGGSGGGGSGRSLVESGGGLVQPGGSLRLSCTASGFTISSYHMQWVRQAPG

KGLEYIGTISSGGNVYYASSARGRFTISRPSSKNTVDLQMNSLRAEDTAVYYCARDSGYSDPMW

GQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPSSVSASVGDRVTITCQASQNIRTYLS

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GGAFGGGTKVEIK

>SEQ ID 77 SI-35E58 (284A10-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 466F6-H2L5-scFv) light chain nt

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CAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACAC

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>SEQ ID 78 SI-35E58 (284A10-L1H1-scFv × PL230C6-Fab × 323H7-H4L1-scFv × 466F6-H2L5-scFv) light chain aa

AYDMTQSPSSVSASVGDRVTIKCQASEDIYSFLAWYQQKPGKAPKLLIHSASSLASGVPSRFSG

SGSGTDFTLTISSLQPEDFATYYCQQGYGKNNVDNAFGGGTKVEIKRTVAAPSVFIFPPSDEQL

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>SEQ ID 79 SI-35E88 (284A10-L1H1-scFv x 323H7-Fab x PL230C6-H3L2-scFv x 466F6-H2L5-scFv) heavy chain nt

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>SEQ ID 80 SI-35E88 (284A10-L1H1-scFv × 323H7-Fab × PL230C6-H3L2-scFv × 466F6-H2L5-scFv) heavy chain aa

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>SEQ ID 81 SI-35E88 (284A10-L1H1-scFv x 323H7-Fab x PL230C6-H3L2-scFv x 466F6-H2L5-scFv) light chain nt

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GCTTCAACAGGGGAGAGTGT

>SEQ ID 82 SI-35E88 (284A10-L1H1-scFv x 323H7-Fab x PL230C6-H3L2-scFv x 466F6-H2L5-scFv) light chain aa

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SGSGSGTDFTLTISSLQPEDVATYYCAGGYDTDGLDTFAFGGGTKVEIKRTVAAPSVFIFPPSD

EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVIEQDSKDSTYSLSSTLTLSKADY

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>SEQ ID 83 SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain nt

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>SEQ ID 84 SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain aa

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>SEQ ID 85 SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain nt

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>SEQ ID 86 SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain aa

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>SEQ ID 87 SI-38E17 (284A10-L1H1-scFv x 21D4-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain nt

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>SEQ ID 88 SI-38E17 (284A10-L1H1-scFv × 21D4-Fab × PL221G5-H1L1-scFv × 466F6-H2L5-scFv) heavy chain aa

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>SEQ ID 89 SI-38E17 (284A10-L1H1-scFv x 21D4-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain nt
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>SEQ ID 90 SI-38E17 (284A10-L1H1-scFv x 21D4-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain aa
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>SEQ ID 91 SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain nt
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>SEQ ID 92 SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain aa
AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSG

SGSGTDFTLTISSLQPEDFATYYCQQFNSYPFTFGPGTKVDIKGGGGSGGGGSGGGGSGGGGSE

VQLVQSGAEVKKPGESLKISCKGSGYSFSSSWIGWVRQAPGKGLEWMGIIYPDDSDTRYSPSFQ

GQVTISADKSIRTAYLQWSSLKASDTAMYYCARHVTMIWGVIIDFWGQGTLVTVSSGGGGSGGG

GSEVQLVESGGGLVQPGGSLRLSCAASGFTISTNAMSWVRQAPGKGLEWIGVITGRDITYYASW

AKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGGSSAITSNNIWGQGTLVTVSSASTKGP

SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT

VPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTL

MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN

GKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV

EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL

SPGGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFSFSSGYDMCWVRQAPGKGLEWIAC

IAAGSAGITYDANWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSAFSFDYAMDLWGQG

TLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTITCQASQSISSHLNWYQ

QKPGKAPKLLIYKASTLASGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQGYSWGNVDNVF

GGGTKVEIKGGGGSGGGGSRSLVESGGGLVQPGGSLRLSCTASGFTISSYHMQWVRQAPGKGLE

YIGTISSGGNVYYASSARGRFTISRPSSKNTVDLQMNSLRAEDTAVYYCARDSGYSDPMWGQGT

LVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPSSVSASVGDRVTITCQASQNIRTYLSWYQQ

KPGKAPKLLIYAAANLASGVPSRFSGSGSGTDFTLTISDLEPGDAATYYCQSTYLGTDYVGGAF

GGGTKVEIK

SEQ ID 93 SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain nt
GACGTCGTGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA

ATTGCCAAGCCAGTGAGAGCATTAGCAGTTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGC

CCCTAAGCTCCTGATCTATGAAGCATCCAAACTGGCATCTGGGGTCCCATCAAGGTTCAGCGGC

AGTGGATCTGGGACAGAATTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTT

ATTACTGCCAAGGCTATTTTTATTTTATTAGTCGTACTTATGTAAATTCTTTCGGCGGAGGGAC

CAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG

CAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCA

AAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCA

GGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAG

AAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCT

TCAACAGGGGAGAGTGT

SEQ ID 94 SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain aa
DVVMTQSPSTLSASVGDRVTINCQASESISSWLAWYQQKPGKAPKLLIYEASKLASGVPSRFSG

SGSGTEFTLTISSLQPDDFATYYCQGYFYFISRTYVNSFGGGTKVEIKRTVAAPSVFIFPPSDE

QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE

KHKVYACEVTHQGLSSPVTKSFNRGEC

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 94

<210> SEQ ID NO 1
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 1

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt caccatcagt accaatgcaa tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg gatcggagtc attactggtc gtgatatcac atactacgcg 180

agctgggcga aaggcagatt caccatctcc agagacaatt ccaagaacac gctgtatctt 240

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgcg cgacggtgga 300

tcatctgcta ttactagtaa caacatttgg ggccaaggaa ctctggtcac cgtttcttca 360

<210> SEQ ID NO 2
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 2

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Thr Asn
20 25 30

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

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

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

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

Arg Asp Gly Gly Ser Ser Ala Ile Thr Ser Asn Asn Ile Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 3
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 3

gacgtcgtga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcaattgcc aagccagtga gagcattagc agttggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgaa gcatccaaac tggcatctgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagag ttcactctca ccatcagcag cctgcagcct 240

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gatgattttg caacttatta ctgccaaggc tatttttatt ttattagtcg tacttatgta 300

aattctttcg gcggagggac caaggtggag atcaaa 336

<210> SEQ ID NO 4
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 4

Asp Val Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Gln Ala Ser Glu Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Glu Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Tyr Phe Tyr Phe Ile Ser
85 90 95

Arg Thr Tyr Val Asn Ser Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> SEQ ID NO 5
<211> LENGTH: 345
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 5

cagtcggtgg aggagtctgg gggaggcttg gtccagcctg gggggtccct gagactctcc 60

tgtacagcct ctggaatcga ccttaatacc tacgacatga tctgggtccg ccaggctcca 120

ggcaaggggc tagagtgggt tggaatcatt acttatagtg gtagtagata ctacgcgaac 180

tgggcgaaag gccgattcac catctccaaa gacaatacca agaacacggt gtatctgcaa 240

atgaacagcc tgagagctga ggacacggct gtgtattact gtgccagaga ttatatgagt 300

ggttcccact tgtggggcca gggaaccctg gtcaccgtct ctagt 345

<210> SEQ ID NO 6
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 6

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

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

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

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Ile Ile Thr Tyr Ser Gly Ser Arg Tyr Tyr Ala Asn Trp Ala Lys Gly
    50                  55                  60

Arg Phe Thr Ile Ser Lys Asp Asn Thr Lys Asn Thr Val Tyr Leu Gln
65                  70                  75                  80

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

Asp Tyr Met Ser Gly Ser His Leu Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115


<210> SEQ ID NO 7
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 7

gcctatgata tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc     60

atcaagtgtc aggccagtga ggacatttat agcttcttgg cctggtatca gcagaaacca    120

gggaaagccc ctaagctcct gatccattct gcatcctctc tggcatctgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct    240

gaagattttg caacttacta ttgtcaacag ggttatggta aaaataatgt tgataatgct    300

ttcggcggag ggaccaaggt ggagatcaaa                                     330


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

<400> SEQUENCE: 8

Ala Tyr Asp Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Lys Cys Gln Ala Ser Glu Asp Ile Tyr Ser Phe
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

His Ser Ala Ser Ser Leu Ala 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 Gly Tyr Gly Lys Asn Asn
                85                  90                  95

Val Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 9
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized
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<400> SEQUENCE: 9

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgagactc 60

tcctgtgcag cctctggatt ctccttcagt agcgggtacg acatgtgctg ggtccgccag 120

gctccaggga aggggctgga gtggatcgca tgcattgctg ctggtagtgc tggtatcact 180

tacgacgcga actgggcgaa aggccggttc accatctcca gagacaattc caagaacacg 240

ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ccgtatatta ctgtgcgaga 300

tcggcgtttt cgttcgacta cgccatggac ctctggggcc agggaaccct ggtcaccgtc 360

tcgagc 366

<210> SEQ ID NO 10
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 10

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Gly
20 25 30

Tyr Asp Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Ala Cys Ile Ala Ala Gly Ser Ala Gly Ile Thr Tyr Asp Ala Asn
50 55 60

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

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

Tyr Cys Ala Arg Ser Ala Phe Ser Phe Asp Tyr Ala Met Asp Leu Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 11
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 11

gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc aggccagtca gagcattagt tcccacttaa actggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctataag gcatccactc tggcatctgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa tttactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacag ggttatagtt ggggtaatgt tgataatgtt 300

ttcggcggag ggaccaaggt ggagatcaaa 330

<210> SEQ ID NO 12
<211> LENGTH: 110
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 12

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Ser Ser His
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Trp Gly Asn
85 90 95

Val Asp Asn Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> SEQ ID NO 13
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 13

cagtcgctgg tggagtctgg gggaggcttg gtacagcctg gggggtccct gagactctcc 60

tgtgcagcct ctggattctc cttcagtagc aactactgga tatgctgggt ccgccaggct 120

ccagggaagg ggctggagtg gatcgcatgc atttatgttg gtagtagtgg tgacacttac 180

tacgcgagct ccgcgaaagg ccggttcacc atctccagag acaattccaa gaacacgctg 240

tatctgcaaa tgaacagcct gagagccgag gacacggccg tatattactg tgcgagagat 300

agtagtagtt attatatgtt taacttgtgg ggccagggaa ccctggtcac cgtctcgagc 360

<210> SEQ ID NO 14
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 14

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

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Asn Tyr
20 25 30

Trp Ile Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Ala Cys Ile Tyr Val Gly Ser Ser Gly Asp Thr Tyr Tyr Ala Ser Ser
50 55 60

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

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

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Cys Ala Arg Asp Ser Ser Ser Tyr Tyr Met Phe Asn Leu Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 15
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 15

gcccttgtga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc     60

atcaattgcc aggccagtga ggacattgat acctatttag cctggtatca gcagaaacca    120

gggaaagccc ctaagctcct gatcttttat gcatccgatc tggcatctgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct    240

gatgattttg caacttatta ctgccaaggc ggttactata ctagtagtgc tgatacgagg    300

ggtgctttcg gcggagggac caaggtggag atcaaa                               336


<210> SEQ ID NO 16
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 16

Ala Leu Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Asn Cys Gln Ala Ser Glu Asp Ile Asp Thr Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Phe Tyr Ala Ser Asp Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Gly Tyr Tyr Thr Ser Ser
                85                  90                  95

Ala Asp Thr Arg Gly Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 17
<211> LENGTH: 345
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 17

cggtcgctgg tggagtctgg gggaggcttg gtccagcctg gggggtccct gagactctcc     60

tgtacagcct ctggattcac catcagtagc taccacatgc agtgggtccg ccaggctcca    120

gggaaggggc tggagtacat cggaaccatt agtagtggtg gtaatgtata ctacgcgagc    180
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-continued

tccgcgagag gcagattcac catctccaga ccctcgtcca agaacacggt ggatcttcaa 240

atgaacagcc tgagagccga ggacacggct gtgtattact gtgcgagaga ctctggttat 300

agtgatccta tgtggggcca gggaaccctg gtcaccgtct cgagc 345

<210> SEQ ID NO 18
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 18

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

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

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

Thr Ile Ser Ser Gly Gly Asn Val Tyr Tyr Ala Ser Ser Ala Arg Gly
50 55 60

Arg Phe Thr Ile Ser Arg Pro Ser Ser Lys Asn Thr Val Asp Leu Gln
65 70 75 80

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

Asp Ser Gly Tyr Ser Asp Pro Met Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> SEQ ID NO 19
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 19

gacgttgtga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacctgtc aggccagtca gaacattagg acttacttat cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcagccaatc tggcatctgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcga cctggagcct 240

ggcgatgctg caacttacta ttgtcagtct acctatcttg gtactgatta tgttggcggt 300

gctttcggcg gagggaccaa ggtggagatc aaa 333

<210> SEQ ID NO 20
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 20

Asp Val Val Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asn Ile Arg Thr Tyr

-continued

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            20                  25                  30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ala Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asp Leu Glu Pro
65                  70                  75                  80

Gly Asp Ala Ala Thr Tyr Tyr Cys Gln Ser Thr Tyr Leu Gly Thr Asp
                85                  90                  95

Tyr Val Gly Gly Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 21
<211> LENGTH: 345
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 21

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc     60

tcctgtgcag cctctggaat cgacttcagt aggagatact acatgtgctg ggtccgccag    120

gctccaggga aggggctgga gtggatcgca tgcatatata ctggtagccg cgatactcct    180

cactacgcga gctccgcgaa aggccggttc accatctcca gagacaattc caagaacacg    240

ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ccgtatatta ctgtgcgaga    300

gaaggtagcc tgtggggcca gggaaccctg gtcaccgtct cgagc                    345


<210> SEQ ID NO 22
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 22

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Asp Phe Ser Arg Arg
            20                  25                  30

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

Ile Ala Cys Ile Tyr Thr Gly Ser Arg Asp Thr Pro His Tyr Ala Ser
    50                  55                  60

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

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

Tyr Cys Ala Arg Glu Gly Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115


<210> SEQ ID NO 23
<211> LENGTH: 333
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 23

gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc agtccagtca gagtgtttat agtaactggt tctcctggta tcagcagaaa 120

ccagggaaag cccctaagct cctgatctat tctgcatcca ctctggcatc tggggtccca 180

tcaaggttca gcggcagtgg atctgggaca gaattcactc tcaccatcag cagcctgcag 240

cctgatgatt ttgcaactta ttactgcgca ggcggttaca atactgttat tgatactttt 300

gctttcggcg gagggaccaa ggtggagatc aaa 333

<210> SEQ ID NO 24
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 24

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser Val Tyr Ser Asn
20 25 30

Trp Phe Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Asn Thr Val
85 90 95

Ile Asp Thr Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> SEQ ID NO 25
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 25

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt caccatcagt cgctaccaca tgacttgggt ccgccaggct 120

ccagggaagg ggctggagtg gatcggacat atttatgtta ataatgatga cacagactac 180

gcgagctccg cgaaaggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccacct atttctgtgc gagattggat 300

gttggtggtg gtggtgctta tattggggac atctggggcc agggaactct ggttaccgtc 360

tcttca 366

<210> SEQ ID NO 26

-continued

<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 26

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

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

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

Gly His Ile Tyr Val Asn Asn Asp Asp Thr Asp Tyr Ala Ser Ser Ala
50 55 60

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

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

Ala Arg Leu Asp Val Gly Gly Gly Gly Ala Tyr Ile Gly Asp Ile Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 27
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 27

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc agtccagtca gagtgtttat aacaacaacg acttagcctg gtatcagcag 120

aaaccaggga aagttcctaa gctcctgatc tattatgctt ccactctggc atctggggtc 180

ccatctcggt tcagtggcag tggatctggg acagatttca ctctcaccat cagcagcctg 240

cagcctgaag atgttgcaac ttattactgt gcaggcggtt atgatacgga tggtcttgat 300

acgtttgctt tcggcggagg gaccaaggtg gagatcaaa 339

<210> SEQ ID NO 28
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 28

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 Gln Ser Ser Gln Ser Val Tyr Asn Asn
20 25 30

Asn Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu
35 40 45

Leu Ile Tyr Tyr Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe
50 55 60

-continued

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65 70 75 80

Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Asp Thr
85 90 95

Asp Gly Leu Asp Thr Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> SEQ ID NO 29
<211> LENGTH: 345
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 29

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtactg cctctggatt ctccctcagt agctatgcaa tgagctgggt ccgccaggct 120

ccagggaggg ggctggagtg gatcggaatc atttatgcta gtggtagcac atactacgcg 180

agctcggcga aaggcagatt caccatctcc aaagacaata ccaagaacac ggtggatctt 240

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag aatttatgac 300

ggcatggacc tctggggcca gggaactctg gttaccgtct cttca 345

<210> SEQ ID NO 30
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 30

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

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

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

Gly Ile Ile Tyr Ala Ser Gly Ser Thr Tyr Tyr Ala Ser Ser Ala Lys
50 55 60

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

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

Arg Ile Tyr Asp Gly Met Asp Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> SEQ ID NO 31
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 31

-continued

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcaattgcc aggccagtca gaacatttac agctacttat cctggtatca gcagaaacca 120

gggaaagttc ctaagcgcct gatctatctg gcatctactc tggcatctgg ggtcccatct 180

cggttcagtg gcagtggatc tgggacagat tacactctca ccatcagcag cctgcagcct 240

gaagatgttg caacttatta ctgtcaaagc aattataacg gtaattatgg tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 32
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 32

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 Asn Cys Gln Ala Ser Gln Asn Ile Tyr Ser Tyr
20 25 30

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

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

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Ser Asn Tyr Asn Gly Asn Tyr
85 90 95

Gly Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 33
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 33

gaggtgaagc tggatgagac tggaggaggc ttggtgcaac ctgggaggcc catgaaactc 60

tcctgtgttg cctctggatt cacttttagt gactactgga tgaactgggt ccgccagtct 120

ccagagaaag gactggagtg ggtagcacaa attagaaaca aaccttataa ttatgaaaca 180

tattattcag attctgtgaa aggcagattc accatctcaa gagatgattc caaaagtagt 240

gtctacctgc aaatgaacaa cttaagagtt gaagacatgg gtatctatta ctgtacgggt 300

tcttactatg gtatggacta ctggggtcaa ggaacctcag tcaccgtctc ctca 354

<210> SEQ ID NO 34
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 34

-continued

```
Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15

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

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

Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp
    50                  55                  60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
65                  70                  75                  80

Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr
                85                  90                  95

Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Ser Val Thr Val Ser Ser
        115


<210> SEQ ID NO 35
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 35

gatgtcgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc     60

atctcttgca gatctagtca gagccttgta cacagtaatg gaaacaccta tttacgttgg    120

tacctgcaga agccaggcca gtctccaaag gtcctgatct acaaagtttc caaccgattt    180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc    240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccg    300

tggacgttcg gtggaggcac caagctggaa atcaaa                              336


<210> SEQ ID NO 36
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 36

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1               5                   10                  15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
            20                  25                  30

Asn Gly Asn Thr Tyr Leu Arg Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Lys Val Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

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

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
                85                  90                  95

Thr His Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
```

-continued

<210> SEQ ID NO 37
<211> LENGTH: 987
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 37

gctagcacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg 60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc 240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc 300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaagc cgcgggggca 360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccccct 420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 600

gagtacaagt gcgcggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggatgag 720

ctgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 840

ctggactccg acggctcctt cttcctctat agcaagctca ccgtggacaa gagcaggtgg 900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 960

cagaagagcc tctccctgtc tccgggt 987

<210> SEQ ID NO 38
<211> LENGTH: 329
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 38

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

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

-continued

```
Pro Ala Pro Glu Ala Ala Gly Ala 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 Ala 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 His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
```

<210> SEQ ID NO 39
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 39

```
cgtacggtgg ctgcaccatc tgtcttcatc ttcccgccat ctgatgagca gttgaaatct     60

ggaactgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag    120

tggaaggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggac    180

agcaaggaca gcacctacag cctcagcagc accctgacgc tgagcaaagc agactacgag    240

aaacacaaag tctacgcctg cgaagtcacc catcagggcc tgagctcgcc cgtcacaaag    300

agcttcaaca ggggagagtg t                                              321
```

<210> SEQ ID NO 40
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 40

```
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15
```

-continued

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> SEQ ID NO 41
<211> LENGTH: 3681
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 41

gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc agtccagtca gagtgtttat agtaactggt tctcctggta tcagcagaaa 120

ccagggaaag cccctaagct cctgatctat tctgcatcca ctctggcatc tggggtccca 180

tcaaggttca gcggcagtgg atctgggaca gaattcactc tcaccatcag cagcctgcag 240

cctgatgatt ttgcaactta ttactgcgca ggcggttaca atactgttat tgatactttt 300

gctttcggcg gagggaccaa ggtggagatc aaaggcggtg gcggtagtgg gggaggcggt 360

tctggcggcg gagggtccgg cggtggagga tcagaggtgc agctgttgga gtctgggga 420

ggcttggtac agcctgggg gtccctgaga ctctcctgtg cagcctctgg aatcgacttc 480

agtaggagat actacatgtg ctgggtccgc caggctccag ggaaggggct ggagtggatc 540

gcatgcatat atactggtag ccgcgatact cctcactacg cgagctccgc gaaaggccgg 600

ttcaccatct ccagagacaa ttccaagaac acgctgtatc tgcaaatgaa cagcctgaga 660

gccgaggaca cggccgtata ttactgtgcg agagaaggta gcctgtgggg ccagggaacc 720

ctggtcaccg tctcgagcgg cggtggaggg tccggcggtg gtggatccca gtcggtggag 780

gagtctgggg gaggcttggt ccagcctggg gggtccctga gactctcctg tacagcctct 840

ggaatcgacc ttaataccta cgacatgatc tgggtccgcc aggctccagg caaggggcta 900

gagtgggttg gaatcattac ttatagtggt agtagatact acgcgaactg ggcgaaaggc 960

cgattcacca tctccaaaga caataccaag aacacggtgt atctgcaaat gaacagcctg 1020

agagctgagg acacggctgt gtattactgt gccagagatt atatgagtgg ttcccacttg 1080

tggggccagg gaaccctggt caccgtctct agtgctagca ccaagggccc atcggtcttc 1140

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc 1200

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc 1260

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg 1320

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc 1380

agcaacacca aggtggacaa gagagttgag cccaaatctt gtgacaaaac tcacacatgc 1440

-continued

```
ccaccgtgcc cagcacctga agccgcgggg gcaccgtcag tcttcctctt ccccccaaaa   1500

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg   1560

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat   1620

gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc   1680

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcgcggt ctccaacaaa   1740

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca   1800

caggtgtata ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc   1860

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag   1920

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc   1980

tatagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc   2040

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt   2100

ggcggtggag ggtccggcgg tggtggatcc gaggtgcagc tgttggagtc tgggggaggc   2160

ttggtacagc ctgggggggtc cctgagactc tcctgtgcag cctctggatt caccatcagt   2220

cgctaccaca tgacttgggt ccgccaggct ccagggaagg ggctggagtg gatcggacat   2280

atttatgtta ataatgatga cacagactac gcgagctccg cgaaaggccg gttcaccatc   2340

tccagagaca attccaagaa cacgctgtat ctgcaaatga acagcctgag agccgaggac   2400

acggccacct atttctgtgc gagattggat gttggtggtg gtggtgctta tattggggac   2460

atctggggcc agggaactct ggttaccgtc tcttcaggcg gtggcggtag tgggggaggc   2520

ggttctggcg gcggagggtc cggcggtgga ggatcagaca tccagatgac ccagtctcca   2580

tcctccctgt ctgcatctgt aggagacaga gtcaccatca cttgccagtc cagtcagagt   2640

gtttataaca acaacgactt agcctggtat cagcagaaac cagggaaagt tcctaagctc   2700

ctgatctatt atgcttccac tctggcatct ggggtcccat ctcggttcag tggcagtgga   2760

tctgggacag atttcactct caccatcagc agcctgcagc ctgaagatgt tgcaacttat   2820

tactgtgcag gcggttatga tacggatggt cttgatacgt ttgctttcgg cggagggacc   2880

aaggtggaga tcaaaggcgg tggagggtcc ggcggtggtg gatccgaggt gcagctggtg   2940

gagtctgggg gaggcttggt ccagcctggg gggtccctga gactctcctg tgcagcctct   3000

ggattcacca tcagtaccaa tgcaatgagc tgggtccgcc aggctccagg gaaggggctg   3060

gagtggatcg gagtcattac tggtcgtgat atcacatact acgcgagctg ggcgaaaggc   3120

agattcacca tctccagaga caattccaag aacacgctgt atcttcaaat gaacagcctg   3180

agagccgagg acacggctgt gtattactgt gcgcgcgacg gtggatcatc tgctattact   3240

agtaacaaca tttggggcca aggaactctg gtcaccgttt cttcaggcgg tggcggtagt   3300

gggggaggcg gttctggcgg cggagggtcc ggcggtggag gatcagacgt cgtgatgacc   3360

cagtctcctt ccaccctgtc tgcatctgta ggagacagag tcaccatcaa ttgccaagcc   3420

agtgagagca ttagcagttg gttagcctgg tatcagcaga aaccagggaa agcccctaag   3480

ctcctgatct atgaagcatc caaactggca tctggggtcc catcaaggtt cagcggcagt   3540

ggatctggga cagagttcac tctcaccatc agcagcctgc agcctgatga ttttgcaact   3600

tattactgcc aaggctattt ttattttatt agtcgtactt atgtaaattc tttcggcgga   3660

gggaccaagg tggagatcaa a                                             3681
```

-continued

<210> SEQ ID NO 42
<211> LENGTH: 1227
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 42

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser Val Tyr Ser Asn
            20                  25                  30

Trp Phe Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Ser Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80

Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Asn Thr Val
                85                  90                  95

Ile Asp Thr Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly
            100                 105                 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
    130                 135                 140

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Asp Phe
145                 150                 155                 160

Ser Arg Arg Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Ala Cys Ile Tyr Thr Gly Ser Arg Asp Thr Pro His
            180                 185                 190

Tyr Ala Ser Ser Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
        195                 200                 205

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

Ala Val Tyr Tyr Cys Ala Arg Glu Gly Ser Leu Trp Gly Gln Gly Thr
225                 230                 235                 240

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
                245                 250                 255

Gln Ser Val Glu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
            260                 265                 270

Leu Arg Leu Ser Cys Thr Ala Ser Gly Ile Asp Leu Asn Thr Tyr Asp
        275                 280                 285

Met Ile Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
    290                 295                 300

Ile Ile Thr Tyr Ser Gly Ser Arg Tyr Tyr Ala Asn Trp Ala Lys Gly
305                 310                 315                 320

Arg Phe Thr Ile Ser Lys Asp Asn Thr Lys Asn Thr Val Tyr Leu Gln
                325                 330                 335

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
            340                 345                 350
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Asp Tyr Met Ser Gly Ser His Leu Trp Gly Gln Gly Thr Leu Val Thr
        355                 360                 365

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
    370                 375                 380

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
385                 390                 395                 400

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
                405                 410                 415

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
            420                 425                 430

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
        435                 440                 445

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
    450                 455                 460

Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
465                 470                 475                 480

Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu
                485                 490                 495

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            500                 505                 510

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
        515                 520                 525

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    530                 535                 540

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
545                 550                 555                 560

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala
                565                 570                 575

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            580                 585                 590

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
        595                 600                 605

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    610                 615                 620

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
625                 630                 635                 640

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
                645                 650                 655

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            660                 665                 670

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        675                 680                 685

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly
    690                 695                 700

Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
705                 710                 715                 720

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
                725                 730                 735

Phe Thr Ile Ser Arg Tyr His Met Thr Trp Val Arg Gln Ala Pro Gly
            740                 745                 750
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Lys Gly Leu Glu Trp Ile Gly His Ile Tyr Val Asn Asn Asp Asp Thr
        755                 760                 765

Asp Tyr Ala Ser Ser Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
    770                 775                 780

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
785                 790                 795                 800

Thr Ala Thr Tyr Phe Cys Ala Arg Leu Asp Val Gly Gly Gly Gly Ala
                805                 810                 815

Tyr Ile Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            820                 825                 830

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        835                 840                 845

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
    850                 855                 860

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser
865                 870                 875                 880

Val Tyr Asn Asn Asn Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
                885                 890                 895

Val Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Thr Leu Ala Ser Gly Val
            900                 905                 910

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        915                 920                 925

Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Ala Gly
    930                 935                 940

Gly Tyr Asp Thr Asp Gly Leu Asp Thr Phe Ala Phe Gly Gly Gly Thr
945                 950                 955                 960

Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
                965                 970                 975

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
            980                 985                 990

Leu Arg Leu Ser Cys Ala Ala Ser  Gly Phe Thr Ile Ser  Thr Asn Ala
        995                 1000                1005

Met Ser  Trp Val Arg Gln Ala  Pro Gly Lys Gly Leu  Glu Trp Ile
    1010                1015                1020

Gly Val  Ile Thr Gly Arg Asp  Ile Thr Tyr Tyr Ala  Ser Trp Ala
    1025                1030                1035

Lys Gly  Arg Phe Thr Ile Ser  Arg Asp Asn Ser Lys  Asn Thr Leu
    1040                1045                1050

Tyr Leu  Gln Met Asn Ser Leu  Arg Ala Glu Asp Thr  Ala Val Tyr
    1055                1060                1065

Tyr Cys  Ala Arg Asp Gly Gly  Ser Ser Ala Ile Thr  Ser Asn Asn
    1070                1075                1080

Ile Trp  Gly Gln Gly Thr Leu  Val Thr Val Ser Ser  Gly Gly Gly
    1085                1090                1095

Gly Ser  Gly Gly Gly Gly Ser  Gly Gly Gly Gly Ser  Gly Gly Gly
    1100                1105                1110

Gly Ser  Asp Val Val Met Thr  Gln Ser Pro Ser Thr  Leu Ser Ala
    1115                1120                1125

Ser Val  Gly Asp Arg Val Thr  Ile Asn Cys Gln Ala  Ser Glu Ser
    1130                1135                1140

Ile Ser  Ser Trp Leu Ala Trp  Tyr Gln Gln Lys Pro  Gly Lys Ala
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    1145                1150                1155

Pro Lys  Leu Leu Ile Tyr Glu  Ala Ser Lys Leu Ala  Ser Gly Val
    1160                1165                1170

Pro Ser  Arg Phe Ser Gly Ser  Gly Ser Gly Thr Glu  Phe Thr Leu
    1175                1180                1185

Thr Ile  Ser Ser Leu Gln Pro  Asp Asp Phe Ala Thr  Tyr Tyr Cys
    1190                1195                1200

Gln Gly  Tyr Phe Tyr Phe Ile  Ser Arg Thr Tyr Val  Asn Ser Phe
    1205                1210                1215

Gly Gly  Gly Thr Lys Val Glu  Ile Lys
    1220                1225


<210> SEQ ID NO 43
<211> LENGTH: 651
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 43

gcctatgata tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc     60

atcaagtgtc aggccagtga ggacatttat agcttcttgg cctggtatca gcagaaacca    120

gggaaagccc ctaagctcct gatccattct gcatcctctc tggcatctgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct    240

gaagattttg caacttacta ttgtcaacag ggttatggta aaaataatgt tgataatgct    300

ttcggcggag ggaccaaggt ggagatcaaa cgtacggtgg ctgcaccatc tgtcttcatc    360

ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgttgtgtg cctgctgaat    420

aacttctatc ccagagaggc caaagtacag tggaaggtgg ataacgccct ccaatcgggt    480

aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc    540

accctgacgc tgagcaaagc agactacgag aaacacaaag tctacgcctg cgaagtcacc    600

catcagggcc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtg t              651


<210> SEQ ID NO 44
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 44

Ala Tyr Asp Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Lys Cys Gln Ala Ser Glu Asp Ile Tyr Ser Phe
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

His Ser Ala Ser Ser Leu Ala 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 Gly Tyr Gly Lys Asn Asn
                85                  90                  95
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Val Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
        115                 120                 125

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
    130                 135                 140

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
145                 150                 155                 160

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
                165                 170                 175

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
            180                 185                 190

Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
        195                 200                 205

Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 45
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 45

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc     60

tcctgtgcag cctctggatt caccatcagt accaatgcaa tgagctgggt ccgccaggct    120

ccagggaagg ggctggagtg gatcggagtc attactggtc gtgatatcac atactacgcg    180

agctgggcga aaggcagatt caccatctcc agagacaatt ccaagaacac gctgtatctt    240

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agacggtggt    300

tcttctgcta ttactagtaa caacatttgg ggccagggaa ccctggtcac cgtgtcgaca    360


<210> SEQ ID NO 46
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 46

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Thr Asn
            20                  25                  30

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

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

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

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

Arg Asp Gly Gly Ser Ser Ala Ile Thr Ser Asn Asn Ile Trp Gly Gln
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            100                 105                 110

Gly Thr Leu Val Thr Val Ser Thr
        115                 120


<210> SEQ ID NO 47
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 47

gaggtgcagc tggtgcagtc tggagcagag gtgaagaaac caggagagtc tctgaagatc     60

tcctgtaagg gttctggata cagctttagc agttcatgga tcggctgggt gcgccaggca    120

cctgggaaag gcctggaatg gatggggatc atctatcctg atgactctga taccagatac    180

agtccatcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag gactgcctac    240

ctgcagtgga gtagcctgaa ggcctcggac accgctatgt attactgtgc gagacatgtt    300

actatgattt ggggagttat tattgacttc tggggccagg gaaccctggt caccgtctcc    360

tca                                                                  363


<210> SEQ ID NO 48
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 48

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Ser Ser
            20                  25                  30

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

Gly Ile Ile Tyr Pro Asp Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Arg Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg His Val Thr Met Ile Trp Gly Val Ile Ile Asp Phe Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 49
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 49

gccatccagt tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc     60

atcacttgcc gggcaagtca gggcattagc agtgctttag cctggtatca gcagaaacca    120
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gggaaagctc ctaagctcct gatctatgat gcctccagtt tggaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtcaacag tttaatagtt acccattcac tttcggccct 300

gggaccaaag tggatatcaa a 321

<210> SEQ ID NO 50
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 50

Ala Ile Gln Leu 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 Gly Ile Ser Ser Ala
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu 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 Phe Asn Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 51
<211> LENGTH: 348
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 51

gatgtgcagc ttcaggagtc gggacctagc ctggtgaaac cttctcagtc tctgtccctc 60

acctgcactg tcactggcta ctcaatcacc agtgattttg cctggaactg gattcggcag 120

tttccaggaa acaagctgga gtggatgggc tacataagtt atagtggtaa cactaggtac 180

aacccatctc tcaaaagtcg aatctctatc actcgcgaca catccaagaa ccaattcttc 240

ctgcagttga actctgtgac tattgaggac acagccacat attactgtgt aacggcggga 300

cgcgggtttc cttattgggg ccaagggact ctggtcactg tctctgca 348

<210> SEQ ID NO 52
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 52

Asp Val Gln Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1 5 10 15

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp

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            20                  25                  30

Phe Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35                  40                  45

Met Gly Tyr Ile Ser Tyr Ser Gly Asn Thr Arg Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80

Leu Gln Leu Asn Ser Val Thr Ile Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Val Thr Ala Gly Arg Gly Phe Pro Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ala
        115


<210> SEQ ID NO 53
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 53

gacatcctga tgacccaatc tccatcctcc atgtctgtat ctctgggaga cacagtcagc     60

atcacttgcc attcaagtca ggacattaac agtaatatag ggtggttgca gcagagacca    120

gggaaatcat ttaagggcct gatctatcat ggaaccaact tggacgatga agttccatca    180

aggttcagtg gcagtggatc tggagccgat tattctctca ccatcagcag cctggaatct    240

gaagattttg cagactatta ctgtgtacag tatgctcagt ttccgtggac gttcggtgga    300

ggcaccaagc tggaaatcaa a                                               321


<210> SEQ ID NO 54
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 54

Asp Ile Leu Met Thr Gln Ser Pro Ser Ser Met Ser Val Ser Leu Gly
1               5                   10                  15

Asp Thr Val Ser Ile Thr Cys His Ser Ser Gln Asp Ile Asn Ser Asn
            20                  25                  30

Ile Gly Trp Leu Gln Gln Arg Pro Gly Lys Ser Phe Lys Gly Leu Ile
        35                  40                  45

Tyr His Gly Thr Asn Leu Asp Asp Glu Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Ala Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65                  70                  75                  80

Glu Asp Phe Ala Asp Tyr Tyr Cys Val Gln Tyr Ala Gln Phe Pro Trp
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 55
<211> LENGTH: 33
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-continued

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

<400> SEQUENCE: 55

ggcggtggag ggtccggcgg tggtggctcc gga 33

<210> SEQ ID NO 56
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 56

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10

<210> SEQ ID NO 57
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 57

ggcggtggag ggtccggcgg tggtggatca 30

<210> SEQ ID NO 58
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 58

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> SEQ ID NO 59
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 59

ggcggtggag ggtccggcgg tggtggatcc 30

<210> SEQ ID NO 60
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 60

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> SEQ ID NO 61
<211> LENGTH: 60
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 61

ggcggtggcg gtagtggggg aggcggttct ggcggcggag ggtccggcgg tggaggatca 60

<210> SEQ ID NO 62
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 62

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> SEQ ID NO 63
<211> LENGTH: 3693
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 63

gacgtcgtga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcaattgcc aagccagtga gagcattagc agttggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgaa gcatccaaac tggcatctgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagag ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaaggc tatttttatt ttattagtcg tacttatgta 300

aattctttcg gcggagggac caaggtggag atcaaaggcg gtggcggtag tgggggaggc 360

ggttctggcg gcggagggtc cggcggtgga ggatcagagg tgcagctggt ggagtctggg 420

ggaggcttgg tccagcctgg ggggtccctg agactctcct gtgcagcctc tggattcacc 480

atcagtacca atgcaatgag ctgggtccgc caggctccag ggaaggggct ggagtggatc 540

ggagtcatta ctggtcgtga tatcacatac tacgcgagct gggcgaaagg cagattcacc 600

atctccagag acaattccaa gaacacgctg tatcttcaaa tgaacagcct gagagccgag 660

gacacggctg tgtattactg tgcgcgcgac ggtggatcat ctgctattac tagtaacaac 720

atttggggcc aaggaactct ggtcaccgtt tcttcaggcg gtggagggtc cggcggtggt 780

ggatccgatg tgcagcttca ggagtcggga cctagcctgg tgaaaccttc tcagtctctg 840

tccctcacct gcactgtcac tggctactca atcaccagtg attttgcctg gaactggatt 900

cggcagtttc caggaaacaa gctggagtgg atgggctaca taagttatag tggtaacact 960

aggtacaacc catctctcaa aagtcgaatc tctatcactc gcgacacatc caagaaccaa 1020

ttcttcctgc agttgaactc tgtgactatt gaggacacag ccacatatta ctgtgtaacg 1080

gcgggacgcg ggtttcctta ttggggccaa gggactctgg tcactgtctc tgcagctagc 1140

accaagggcc catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca 1200

gcggccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac 1260

-continued

tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc 1320

tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc 1380

tgcaacgtga atcacaagcc cagcaacacc aaggtggaca agagagttga gcccaaatct 1440

tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg aagccgcggg ggcaccgtca 1500

gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc 1560

acatgcgtgg tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg 1620

gacggcgtgg aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg 1680

taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac 1740

aagtgcgcgg tctccaacaa agccctccca gcccccatcg agaaaaccat ctccaaagcc 1800

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga tgagctgacc 1860

aagaaccagg tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg 1920

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac 1980

tccgacggct ccttcttcct ctatagcaag ctcaccgtgg acaagagcag gtggcagcag 2040

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag 2100

agcctctccc tgtctccggg tggcggtgga gggtccggcg gtggtggatc cgaggtgcag 2160

ctgttggagt ctgggggagg cttggtacag cctgggggggt ccctgagact ctcctgtgca 2220

gcctctggat tctccttcag tagcgggtac gacatgtgct gggtccgcca ggctccaggg 2280

aaggggctgg agtggatcgc atgcattgct gctggtagtg ctggtatcac ttacgacgcg 2340

aactgggcga aaggccggtt caccatctcc agagacaatt ccaagaacac gctgtatctg 2400

caaatgaaca gcctgagagc cgaggacacg gccgtatatt actgtgcgag atcggcgttt 2460

tcgttcgact acgccatgga cctctggggc cagggaaccc tggtcaccgt ctcgagcggc 2520

ggtggcggta gtgggggagg cggttctggc ggcggagggt ccggcggtgg aggatcagac 2580

atccagatga cccagtctcc ttccaccctg tctgcatctg taggagacag agtcaccatc 2640

acttgccagg ccagtcagag cattagttcc cacttaaact ggtatcagca gaaaccaggg 2700

aaagccccta agctcctgat ctataaggca tccactctgg catctggggt cccatcaagg 2760

ttcagcggca gtggatctgg gacagaattt actctcacca tcagcagcct gcagcctgat 2820

gattttgcaa cttattactg ccaacagggt tatagttggg gtaatgttga taatgttttc 2880

ggcggaggga ccaaggtgga gatcaaaggc ggtggagggt ccggcggtgg tggatcccag 2940

tcgctggtgg agtctggggg aggcttggta cagcctgggg ggtccctgag actctcctgt 3000

gcagcctctg gattctcctt cagtagcaac tactggatat gctgggtccg ccaggctcca 3060

gggaaggggc tggagtggat cgcatgtatt tatgttggta gtagtggtga cacttactac 3120

gcgagctccg cgaaaggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 3180

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gagagatagt 3240

agtagttatt atatgtttaa cttgtggggc cagggaaccc tggtcaccgt ctcttcaggc 3300

ggtggcggta gtgggggagg cggttctggc ggcggagggt ccggcggtgg aggatcagcc 3360

cttgtgatga cccagtctcc ttccaccctg tctgcatctg taggagacag agtcaccatc 3420

aattgccagg ccagtgagga cattgatacc tatttagcct ggtatcagca gaaaccaggg 3480

aaagccccta agctcctgat cttttacgca tccgatctgg catctggggt cccatcaagg 3540

-continued

ttcagcggca gtggatctgg gacagaattt actctcacca tcagcagcct gcagcctgat 3600

gattttgcaa cttattactg ccaaggcggt tactatacta gtagtgctga tacgaggggt 3660

gctttcggcg gagggaccaa ggtggagatc aaa 3693

<210> SEQ ID NO 64
<211> LENGTH: 1231
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 64

Asp Val Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Gln Ala Ser Glu Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Glu Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Tyr Phe Tyr Phe Ile Ser
85 90 95

Arg Thr Tyr Val Asn Ser Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
130 135 140

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
145 150 155 160

Ile Ser Thr Asn Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly
165 170 175

Leu Glu Trp Ile Gly Val Ile Thr Gly Arg Asp Ile Thr Tyr Tyr Ala
180 185 190

Ser Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
195 200 205

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
210 215 220

Tyr Tyr Cys Ala Arg Asp Gly Gly Ser Ser Ala Ile Thr Ser Asn Asn
225 230 235 240

Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
245 250 255

Ser Gly Gly Gly Gly Ser Asp Val Gln Leu Gln Glu Ser Gly Pro Ser
260 265 270

Leu Val Lys Pro Ser Gln Ser Leu Ser Leu Thr Cys Thr Val Thr Gly
275 280 285

Tyr Ser Ile Thr Ser Asp Phe Ala Trp Asn Trp Ile Arg Gln Phe Pro
290 295 300

Gly Asn Lys Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Asn Thr
305 310 315 320

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Arg Tyr Asn Pro Ser Leu Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr
                325                 330                 335

Ser Lys Asn Gln Phe Phe Leu Gln Leu Asn Ser Val Thr Ile Glu Asp
            340                 345                 350

Thr Ala Thr Tyr Tyr Cys Val Thr Ala Gly Arg Gly Phe Pro Tyr Trp
        355                 360                 365

Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro
    370                 375                 380

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
385                 390                 395                 400

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                405                 410                 415

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            420                 425                 430

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        435                 440                 445

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
    450                 455                 460

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
465                 470                 475                 480

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
                485                 490                 495

Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            500                 505                 510

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        515                 520                 525

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    530                 535                 540

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
545                 550                 555                 560

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                565                 570                 575

Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
            580                 585                 590

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        595                 600                 605

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
    610                 615                 620

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
625                 630                 635                 640

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                645                 650                 655

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            660                 665                 670

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        675                 680                 685

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    690                 695                 700

Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln
705                 710                 715                 720

Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg
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               725                 730                 735

Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Gly Tyr Asp Met
            740                 745                 750

Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Ala Cys
        755                 760                 765

Ile Ala Ala Gly Ser Ala Gly Ile Thr Tyr Asp Ala Asn Trp Ala Lys
    770                 775                 780

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
785                 790                 795                 800

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                805                 810                 815

Arg Ser Ala Phe Ser Phe Asp Tyr Ala Met Asp Leu Trp Gly Gln Gly
            820                 825                 830

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        835                 840                 845

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
    850                 855                 860

Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
865                 870                 875                 880

Thr Cys Gln Ala Ser Gln Ser Ile Ser Ser His Leu Asn Trp Tyr Gln
                885                 890                 895

Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Thr
            900                 905                 910

Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
        915                 920                 925

Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr
    930                 935                 940

Tyr Tyr Cys Gln Gln Gly Tyr Ser Trp Gly Asn Val Asp Asn Val Phe
945                 950                 955                 960

Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly
                965                 970                 975

Gly Gly Ser Gln Ser Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
            980                 985                 990

Gly Gly Ser Leu Arg Leu Ser Cys  Ala Ala Ser Gly Phe  Ser Phe Ser
        995                 1000                1005

Ser Asn  Tyr Trp Ile Cys Trp  Val Arg Gln Ala Pro  Gly Lys Gly
    1010                1015                1020

Leu Glu  Trp Ile Ala Cys Ile  Tyr Val Gly Ser Ser  Gly Asp Thr
    1025                1030                1035

Tyr Tyr  Ala Ser Ser Ala Lys  Gly Arg Phe Thr Ile  Ser Arg Asp
    1040                1045                1050

Asn Ser  Lys Asn Thr Leu Tyr  Leu Gln Met Asn Ser  Leu Arg Ala
    1055                1060                1065

Glu Asp  Thr Ala Val Tyr Tyr  Cys Ala Arg Asp Ser  Ser Ser Tyr
    1070                1075                1080

Tyr Met  Phe Asn Leu Trp Gly  Gln Gly Thr Leu Val  Thr Val Ser
    1085                1090                1095

Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Gly
    1100                1105                1110

Ser Gly  Gly Gly Gly Ser Ala  Leu Val Met Thr Gln  Ser Pro Ser
    1115                1120                1125
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```
Thr Leu  Ser Ala Ser Val Gly  Asp Arg Val Thr Ile  Asn Cys Gln
    1130                1135                1140

Ala Ser  Glu Asp Ile Asp Thr  Tyr Leu Ala Trp Tyr  Gln Gln Lys
    1145                1150                1155

Pro Gly  Lys Ala Pro Lys Leu  Leu Ile Phe Tyr Ala  Ser Asp Leu
    1160                1165                1170

Ala Ser  Gly Val Pro Ser Arg  Phe Ser Gly Ser Gly  Ser Gly Thr
    1175                1180                1185

Glu Phe  Thr Leu Thr Ile Ser  Ser Leu Gln Pro Asp  Asp Phe Ala
    1190                1195                1200

Thr Tyr  Tyr Cys Gln Gly Gly  Tyr Tyr Thr Ser Ser  Ala Asp Thr
    1205                1210                1215

Arg Gly  Ala Phe Gly Gly Gly  Thr Lys Val Glu Ile  Lys
    1220                1225                1230
```

<210> SEQ ID NO 65
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 65

```
gacatcctga tgacccaatc tccatcctcc atgtctgtat ctctgggaga cacagtcagc     60

atcacttgcc attcaagtca ggacattaac agtaatatag ggtggttgca gcagagacca    120

gggaaatcat ttaagggcct gatctatcat ggaaccaact tggacgatga agttccatca    180

aggttcagtg gcagtggatc tggagccgat tattctctca ccatcagcag cctggaatct    240

gaagattttg cagactatta ctgtgtacag tatgctcagt ttccgtggac gttcggtgga    300

ggcaccaagc tggaaatcaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca    360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat    420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag    480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg    540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc    600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt                       642
```

<210> SEQ ID NO 66
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 66

```
Asp Ile Leu Met Thr Gln Ser Pro Ser Ser Met Ser Val Ser Leu Gly
1               5                  10                  15

Asp Thr Val Ser Ile Thr Cys His Ser Ser Gln Asp Ile Asn Ser Asn
            20                  25                  30

Ile Gly Trp Leu Gln Gln Arg Pro Gly Lys Ser Phe Lys Gly Leu Ile
        35                  40                  45

Tyr His Gly Thr Asn Leu Asp Asp Glu Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

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```
Ser Gly Ser Gly Ala Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65                  70                  75                  80

Glu Asp Phe Ala Asp Tyr Tyr Cys Val Gln Tyr Ala Gln Phe Pro Trp
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> SEQ ID NO 67
<211> LENGTH: 3678
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 67

```
gacatcctga tgacccaatc tccatcctcc atgtctgtat ctctgggaga cacagtcagc     60

atcacttgcc attcaagtca ggacattaac agtaatatag ggtggttgca gcagagacca    120

gggaaatcat ttaagggcct gatctatcat ggaaccaact tggacgatga agttccatca    180

aggttcagtg gcagtggatc tggagccgat tattctctca ccatcagcag cctggaatct    240

gaagattttg cagactatta ctgtgtacag tatgctcagt ttccgtggac gttcggtgga    300

ggcaccaagc tggaaatcaa aggcggtggc ggtagtgggg gaggcggttc tggcggcgga    360

gggtccggcg gtggaggatc agatgtgcag cttcaggagt cgggacctag cctggtgaaa    420

ccttctcagt ctctgtccct cacctgcact gtcactggct actcaatcac cagtgatttt    480

gcctggaact ggattcggca gtttccagga aacaagctgg agtggatggg ctacataagt    540

tatagtggta acactaggta caacccatct ctcaaaagtc gaatctctat cactcgcgac    600

acatccaaga accaattctt cctgcagttg aactctgtga ctattgagga cacagccaca    660

tattactgtg taacggcggg acgcgggttt ccttattggg gccaagggac tctggtcact    720

gtctctgcag gcggtggagg gtccggcggt ggtggatccg aggtgcagct ggtggagtct    780

gggggaggct tggtccagcc tgggggggtcc ctgagactct cctgtgcagc ctctggattc    840

accatcagta ccaatgcaat gagctgggtc cgccaggctc cagggaaggg gctggagtgg    900

atcggagtca ttactggtcg tgatatcaca tactacgcga gctgggcgaa aggcagattc    960

accatctcca gagacaattc caagaacacg ctgtatcttc aaatgaacag cctgagagcc   1020

gaggacacgg ctgtgtatta ctgtgcgcgc gacggtggat catctgctat tactagtaac   1080
```

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aacatttggg gccaaggaac tctggtcacc gtttcttcag ctagcaccaa gggcccatcg 1140

gtcttccccc tggcaccctc ctccaagagc acctctgggg gcacagcggc cctgggctgc 1200

ctggtcaagg actacttccc cgaaccggtg acggtgtcgt ggaactcagg cgccctgacc 1260

agcggcgtgc acaccttccc ggctgtccta cagtcctcag gactctactc cctcagcagc 1320

gtggtgaccg tgccctccag cagcttgggc acccagacct acatctgcaa cgtgaatcac 1380

aagcccagca acaccaaggt ggacaagaga gttgagccca aatcttgtga caaaactcac 1440

acatgcccac cgtgcccagc acctgaagcc gcgggggcac cgtcagtctt cctcttcccc 1500

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg 1560

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg 1620

cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 1680

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg cgcggtctcc 1740

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 1800

gaaccacagg tgtacaccct gcccccatcc cgggatgagc tgaccaagaa ccaggtcagc 1860

ctgacctgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat 1920

gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc 1980

ttcctctata gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 2040

tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 2100

ccgggtggcg gtggagggtc cggcggtggt ggatccgagg tgcagctgtt ggagtctggg 2160

ggaggcttgg tacagcctgg ggggtccctg agactctcct gtgcagcctc tggattctcc 2220

ttcagtagcg ggtacgacat gtgctgggtc cgccaggctc cagggaaggg gctggagtgg 2280

atcgcatgca ttgctgctgg tagtgctggt atcacttacg acgcgaactg ggcgaaaggc 2340

cggttcacca tctccagaga caattccaag aacacgctgt atctgcaaat gaacagcctg 2400

agagccgagg acacggccgt atattactgt gcgagatcgg cgttttcgtt cgactacgcc 2460

atggacctct ggggccaggg aaccctggtc accgtctcga gcggcggtgg cggtagtggg 2520

ggaggcggtt ctggcggcgg agggtccggc ggtggaggat cagacatcca gatgacccag 2580

tctccttcca ccctgtctgc atctgtagga gacagagtca ccatcacttg ccaggccagt 2640

cagagcatta gttcccactt aaactggtat cagcagaaac cagggaaagc ccctaagctc 2700

ctgatctata aggcatccac tctggcatct ggggtcccat caaggttcag cggcagtgga 2760

tctgggacag aatttactct caccatcagc agcctgcagc ctgatgattt tgcaacttat 2820

tactgccaac agggttatag ttggggtaat gttgataatg ttttcggcgg agggaccaag 2880

gtggagatca aaggcggtgg agggtccggc ggtggtggat cccagtcgct ggtggagtct 2940

gggggaggct tggtacagcc tgggggggtcc ctgagactct cctgtgcagc ctctggattc 3000

tccttcagta gcaactactg gatatgctgg gtccgccagg ctccagggaa ggggctggag 3060

tggatcgcat gtatttatgt tggtagtagt ggtgacactt actacgcgag ctccgcgaaa 3120

ggccggttca ccatctccag agacaattcc aagaacacgc tgtatctgca aatgaacagc 3180

ctgagagccg aggacacggc cgtatattac tgtgcgagag atagtagtag ttattatatg 3240

tttaacttgt ggggccaggg aaccctggtc accgtctctt caggcggtgg cggtagtggg 3300

ggaggcggtt ctggcggcgg agggtccggc ggtggaggat cagcccttgt gatgacccag 3360

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tctccttcca ccctgtctgc atctgtagga gacagagtca ccatcaattg ccaggccagt 3420

gaggacattg atacctattt agcctggtat cagcagaaac cagggaaagc ccctaagctc 3480

ctgatctttt acgcatccga tctggcatct ggggtcccat caaggttcag cggcagtgga 3540

tctgggacag aatttactct caccatcagc agcctgcagc ctgatgattt tgcaacttat 3600

tactgccaag gcggttacta tactagtagt gctgatacga ggggtgcttt cggcggaggg 3660

accaaggtgg agatcaaa 3678

<210> SEQ ID NO 68
<211> LENGTH: 1226
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 68

Asp Ile Leu Met Thr Gln Ser Pro Ser Ser Met Ser Val Ser Leu Gly
1 5 10 15

Asp Thr Val Ser Ile Thr Cys His Ser Ser Gln Asp Ile Asn Ser Asn
20 25 30

Ile Gly Trp Leu Gln Gln Arg Pro Gly Lys Ser Phe Lys Gly Leu Ile
35 40 45

Tyr His Gly Thr Asn Leu Asp Asp Glu Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Ala Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Val Gln Tyr Ala Gln Phe Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
115 120 125

Val Gln Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln Ser
130 135 140

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

Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp Met
165 170 175

Gly Tyr Ile Ser Tyr Ser Gly Asn Thr Arg Tyr Asn Pro Ser Leu Lys
180 185 190

Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe Leu
195 200 205

Gln Leu Asn Ser Val Thr Ile Glu Asp Thr Ala Thr Tyr Tyr Cys Val
210 215 220

Thr Ala Gly Arg Gly Phe Pro Tyr Trp Gly Gln Gly Thr Leu Val Thr
225 230 235 240

Val Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln
245 250 255

Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg
260 265 270

Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Thr Asn Ala Met Ser
275 280 285

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```
Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile
    290                 295                 300

Thr Gly Arg Asp Ile Thr Tyr Tyr Ala Ser Trp Ala Lys Gly Arg Phe
305                 310                 315                 320

Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn
                325                 330                 335

Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Gly
            340                 345                 350

Gly Ser Ser Ala Ile Thr Ser Asn Asn Ile Trp Gly Gln Gly Thr Leu
        355                 360                 365

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
    370                 375                 380

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
385                 390                 395                 400

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
                405                 410                 415

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
            420                 425                 430

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
        435                 440                 445

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
    450                 455                 460

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
465                 470                 475                 480

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
                485                 490                 495

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            500                 505                 510

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        515                 520                 525

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    530                 535                 540

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
545                 550                 555                 560

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                565                 570                 575

Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
            580                 585                 590

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
        595                 600                 605

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    610                 615                 620

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
625                 630                 635                 640

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
                645                 650                 655

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            660                 665                 670

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        675                 680                 685

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly
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    690                 695                 700

Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly
705                 710                 715                 720

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
                725                 730                 735

Ser Gly Phe Ser Phe Ser Ser Gly Tyr Asp Met Cys Trp Val Arg Gln
            740                 745                 750

Ala Pro Gly Lys Gly Leu Glu Trp Ile Ala Cys Ile Ala Ala Gly Ser
        755                 760                 765

Ala Gly Ile Thr Tyr Asp Ala Asn Trp Ala Lys Gly Arg Phe Thr Ile
    770                 775                 780

Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu
785                 790                 795                 800

Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ser Ala Phe Ser
                805                 810                 815

Phe Asp Tyr Ala Met Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val
            820                 825                 830

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        835                 840                 845

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr
    850                 855                 860

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser
865                 870                 875                 880

Gln Ser Ile Ser Ser His Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
                885                 890                 895

Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Thr Leu Ala Ser Gly Val
            900                 905                 910

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
        915                 920                 925

Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
    930                 935                 940

Gly Tyr Ser Trp Gly Asn Val Asp Asn Val Phe Gly Gly Gly Thr Lys
945                 950                 955                 960

Val Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
                965                 970                 975

Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg
            980                 985                 990

Leu Ser Cys Ala Ala Ser Gly Phe  Ser Phe Ser Ser Asn  Tyr Trp Ile
        995                 1000                1005

Cys Trp  Val Arg Gln Ala Pro  Gly Lys Gly Leu Glu  Trp Ile Ala
    1010                1015                1020

Cys Ile  Tyr Val Gly Ser Ser  Gly Asp Thr Tyr Tyr  Ala Ser Ser
    1025                1030                1035

Ala Lys  Gly Arg Phe Thr Ile  Ser Arg Asp Asn Ser  Lys Asn Thr
    1040                1045                1050

Leu Tyr  Leu Gln Met Asn Ser  Leu Arg Ala Glu Asp  Thr Ala Val
    1055                1060                1065

Tyr Tyr  Cys Ala Arg Asp Ser  Ser Ser Tyr Tyr Met  Phe Asn Leu
    1070                1075                1080

Trp Gly  Gln Gly Thr Leu Val  Thr Val Ser Ser Gly  Gly Gly Gly
    1085                1090                1095
```

-continued

```
Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Gly
    1100                1105                1110

Ser Ala  Leu Val Met Thr Gln  Ser Pro Ser Thr Leu  Ser Ala Ser
    1115                1120                1125

Val Gly  Asp Arg Val Thr Ile  Asn Cys Gln Ala Ser  Glu Asp Ile
    1130                1135                1140

Asp Thr  Tyr Leu Ala Trp Tyr  Gln Gln Lys Pro Gly  Lys Ala Pro
    1145                1150                1155

Lys Leu  Leu Ile Phe Tyr Ala  Ser Asp Leu Ala Ser  Gly Val Pro
    1160                1165                1170

Ser Arg  Phe Ser Gly Ser Gly  Ser Gly Thr Glu Phe  Thr Leu Thr
    1175                1180                1185

Ile Ser  Ser Leu Gln Pro Asp  Asp Phe Ala Thr Tyr  Tyr Cys Gln
    1190                1195                1200

Gly Gly  Tyr Tyr Thr Ser Ser  Ala Asp Thr Arg Gly  Ala Phe Gly
    1205                1210                1215

Gly Gly  Thr Lys Val Glu Ile  Lys
    1220                1225
```

<210> SEQ ID NO 69
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 69

```
gacgtcgtga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc     60

atcaattgcc aagccagtga gagcattagc agttggttag cctggtatca gcagaaacca    120

gggaaagccc ctaagctcct gatctatgaa gcatccaaac tggcatctgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct    240

gatgattttg caacttatta ctgccaaggc tatttttatt ttattagtcg tacttatgta    300

aattctttcg gcggagggac caaggtggag atcaaacgta cggtggctgc accatctgtc    360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg    420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa    480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc    540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa    600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt       657
```

<210> SEQ ID NO 70
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 70

```
Asp Val Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Asn Cys Gln Ala Ser Glu Ser Ile Ser Ser Trp
            20                  25                  30
```

-continued

```
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Glu Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Tyr Phe Tyr Phe Ile Ser
                85                  90                  95

Arg Thr Tyr Val Asn Ser Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 71
<211> LENGTH: 3681
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 71

gacgttgtga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc     60

atcacctgtc aggccagtca gaacattagg acttacttat cctggtatca gcagaaacca    120

gggaaagccc ctaagctcct gatctatgct gcagccaatc tggcatctgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcga cctggagcct    240

ggcgatgctg caacttacta ttgtcagtct acctatcttg gtactgatta tgttggcggt    300

gctttcggcg gagggaccaa ggtggagatc aaaggcggtg gcggtagtgg gggaggcggt    360

tctggcggcg gagggtccgg cggtggagga tcacggtcgc tggtggagtc tgggggaggc    420

ttggtccagc ctgggggtc cctgagactc tcctgtacag cctctggatt caccatcagt    480

agctaccaca tgcagtgggt ccgccaggct ccagggaagg ggctggagta catcggaacc    540

attagtagtg gtggtaatgt atactacgcg agctccgcga gaggcagatt caccatctcc    600

agaccctcgt ccaagaacac ggtggatctt caaatgaaca gcctgagagc cgaggacacg    660

gctgtgtatt actgtgcgag agactctggt tatagtgatc ctatgtgggg ccagggaacc    720

ctggtcaccg tctcgagcgg cggtggaggg tccggcggtg gtggatccca gtcggtggag    780

gagtctgggg gaggcttggt ccagcctggg gggtccctga gactctcctg tacagcctct    840

ggaatcgacc ttaataccta cgacatgatc tgggtccgcc aggctccagg caaggggcta    900
```

-continued

gagtgggttg gaatcattac ttatagtggt agtagatact acgcgaactg ggcgaaaggc 960

cgattcacca tctccaaaga caataccaag aacacggtgt atctgcaaat gaacagcctg 1020

agagctgagg acacggctgt gtattactgt gccagagatt atatgagtgg ttcccacttg 1080

tggggccagg gaaccctggt caccgtctct agtgctagca ccaagggccc atcggtcttc 1140

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc 1200

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc 1260

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg 1320

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc 1380

agcaacacca aggtggacaa gagagttgag cccaaatctt gtgacaaaac tcacacatgc 1440

ccaccgtgcc cagcacctga agccgcgggg gcaccgtcag tcttcctctt cccccaaaa 1500

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 1560

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 1620

gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 1680

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcgcggt ctccaacaaa 1740

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 1800

caggtgtata ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 1860

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag 1920

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1980

tatagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 2040

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 2100

ggcggtggag ggtccggcgg tggtggatcc gaggtgcagc tgttggagtc tgggggaggc 2160

ttggtacagc ctgggggtc cctgagactc tcctgtgcag cctctggatt caccatcagt 2220

cgctaccaca tgacttgggt ccgccaggct ccagggaagg ggctggagtg gatcggacat 2280

atttatgtta ataatgatga cacagactac gcgagctccg cgaaaggccg gttcaccatc 2340

tccagagaca attccaagaa cacgctgtat ctgcaaatga acagcctgag agccgaggac 2400

acggccacct atttctgtgc gagattggat gttggtggtg gtggtgctta tattggggac 2460

atctggggcc agggaactct ggttaccgtc tcttcaggcg gtggcggtag tgggggaggc 2520

ggttctggcg gcggagggtc cggcggtgga ggatcagaca tccagatgac ccagtctcca 2580

tcctccctgt ctgcatctgt aggagacaga gtcaccatca cttgccagtc cagtcagagt 2640

gtttataaca acaacgactt agcctggtat cagcagaaac cagggaaagt tcctaagctc 2700

ctgatctatt atgcttccac tctggcatct ggggtcccat ctcggttcag tggcagtgga 2760

tctgggacag atttcactct caccatcagc agcctgcagc ctgaagatgt tgcaacttat 2820

tactgtgcag gcggttatga tacggatggt cttgatacgt ttgctttcgg cggagggacc 2880

aaggtggaga tcaaaggcgg tggagggtcc ggcggtggtg gatccgaggt gcagctggtg 2940

gagtctgggg gaggcttggt ccagcctggg gggtccctga gactctcctg tgcagcctct 3000

ggattcacca tcagtaccaa tgcaatgagc tgggtccgcc aggctccagg gaaggggctg 3060

gagtggatcg gagtcattac tggtcgtgat atcacatact acgcgagctg ggcgaaaggc 3120

agattcacca tctccagaga caattccaag aacacgctgt atcttcaaat gaacagcctg 3180

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agagccgagg acacggctgt gtattactgt gcgcgcgacg gtggatcatc tgctattact 3240

agtaacaaca tttggggcca aggaactctg gtcaccgttt cttcaggcgg tggcggtagt 3300

gggggaggcg gttctggcgg cggagggtcc ggcggtggag gatcagacgt cgtgatgacc 3360

cagtctcctt ccaccctgtc tgcatctgta ggagacagag tcaccatcaa ttgccaagcc 3420

agtgagagca ttagcagttg gttagcctgg tatcagcaga aaccagggaa agcccctaag 3480

ctcctgatct atgaagcatc caaactggca tctggggtcc catcaaggtt cagcggcagt 3540

ggatctggga cagagttcac tctcaccatc agcagcctgc agcctgatga ttttgcaact 3600

tattactgcc aaggctattt ttattttatt agtcgtactt atgtaaattc tttcggcgga 3660

gggaccaagg tggagatcaa a 3681

<210> SEQ ID NO 72
<211> LENGTH: 1227
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 72

Asp Val Val Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asn Ile Arg Thr Tyr
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ala Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asp Leu Glu Pro
65 70 75 80

Gly Asp Ala Ala Thr Tyr Tyr Cys Gln Ser Thr Tyr Leu Gly Thr Asp
85 90 95

Tyr Val Gly Gly Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Arg Ser Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
130 135 140

Gly Gly Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Ile Ser
145 150 155 160

Ser Tyr His Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
165 170 175

Tyr Ile Gly Thr Ile Ser Ser Gly Gly Asn Val Tyr Tyr Ala Ser Ser
180 185 190

Ala Arg Gly Arg Phe Thr Ile Ser Arg Pro Ser Ser Lys Asn Thr Val
195 200 205

Asp Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
210 215 220

Cys Ala Arg Asp Ser Gly Tyr Ser Asp Pro Met Trp Gly Gln Gly Thr
225 230 235 240

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
245 250 255

-continued

```
Gln Ser Val Glu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
            260                 265                 270

Leu Arg Leu Ser Cys Thr Ala Ser Gly Ile Asp Leu Asn Thr Tyr Asp
        275                 280                 285

Met Ile Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
    290                 295                 300

Ile Ile Thr Tyr Ser Gly Ser Arg Tyr Tyr Ala Asn Trp Ala Lys Gly
305                 310                 315                 320

Arg Phe Thr Ile Ser Lys Asp Asn Thr Lys Asn Thr Val Tyr Leu Gln
                325                 330                 335

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
            340                 345                 350

Asp Tyr Met Ser Gly Ser His Leu Trp Gly Gln Gly Thr Leu Val Thr
        355                 360                 365

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
    370                 375                 380

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
385                 390                 395                 400

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
                405                 410                 415

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
            420                 425                 430

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
        435                 440                 445

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
    450                 455                 460

Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
465                 470                 475                 480

Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu
                485                 490                 495

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            500                 505                 510

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
        515                 520                 525

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    530                 535                 540

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
545                 550                 555                 560

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala
                565                 570                 575

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            580                 585                 590

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
        595                 600                 605

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    610                 615                 620

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
625                 630                 635                 640

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
                645                 650                 655

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
```

-continued

```
           660                 665                 670

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
       675                 680                 685

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly
   690                 695                 700

Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
705                 710                 715                 720

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
               725                 730                 735

Phe Thr Ile Ser Arg Tyr His Met Thr Trp Val Arg Gln Ala Pro Gly
           740                 745                 750

Lys Gly Leu Glu Trp Ile Gly His Ile Tyr Val Asn Asn Asp Asp Thr
       755                 760                 765

Asp Tyr Ala Ser Ser Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
   770                 775                 780

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
785                 790                 795                 800

Thr Ala Thr Tyr Phe Cys Ala Arg Leu Asp Val Gly Gly Gly Gly Ala
               805                 810                 815

Tyr Ile Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
           820                 825                 830

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
       835                 840                 845

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
   850                 855                 860

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser
865                 870                 875                 880

Val Tyr Asn Asn Asn Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
               885                 890                 895

Val Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Thr Leu Ala Ser Gly Val
           900                 905                 910

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
       915                 920                 925

Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Ala Gly
   930                 935                 940

Gly Tyr Asp Thr Asp Gly Leu Asp Thr Phe Ala Phe Gly Gly Gly Thr
945                 950                 955                 960

Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
               965                 970                 975

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
           980                 985                 990

Leu Arg Leu Ser Cys Ala Ala Ser  Gly Phe Thr Ile Ser  Thr Asn Ala
       995                 1000                1005

Met Ser  Trp Val Arg Gln Ala  Pro Gly Lys Gly Leu  Glu Trp Ile
   1010                1015                1020

Gly Val  Ile Thr Gly Arg Asp  Ile Thr Tyr Tyr Ala  Ser Trp Ala
   1025                1030                1035

Lys Gly  Arg Phe Thr Ile Ser  Arg Asp Asn Ser Lys  Asn Thr Leu
   1040                1045                1050

Tyr Leu  Gln Met Asn Ser Leu  Arg Ala Glu Asp Thr  Ala Val Tyr
   1055                1060                1065
```

-continued

```
Tyr Cys  Ala Arg Asp Gly Gly  Ser Ser Ala Ile Thr  Ser Asn Asn
    1070                1075                1080

Ile Trp  Gly Gln Gly Thr Leu  Val Thr Val Ser Ser  Gly Gly Gly
    1085                1090                1095

Gly Ser  Gly Gly Gly Gly Ser  Gly Gly Gly Gly Ser  Gly Gly Gly
    1100                1105                1110

Gly Ser  Asp Val Val Met Thr  Gln Ser Pro Ser Thr  Leu Ser Ala
    1115                1120                1125

Ser Val  Gly Asp Arg Val Thr  Ile Asn Cys Gln Ala  Ser Glu Ser
    1130                1135                1140

Ile Ser  Ser Trp Leu Ala Trp  Tyr Gln Gln Lys Pro  Gly Lys Ala
    1145                1150                1155

Pro Lys  Leu Leu Ile Tyr Glu  Ala Ser Lys Leu Ala  Ser Gly Val
    1160                1165                1170

Pro Ser  Arg Phe Ser Gly Ser  Gly Ser Gly Thr Glu  Phe Thr Leu
    1175                1180                1185

Thr Ile  Ser Ser Leu Gln Pro  Asp Asp Phe Ala Thr  Tyr Tyr Cys
    1190                1195                1200

Gln Gly  Tyr Phe Tyr Phe Ile  Ser Arg Thr Tyr Val  Asn Ser Phe
    1205                1210                1215

Gly Gly  Gly Thr Lys Val Glu  Ile Lys
    1220                1225
```

<210> SEQ ID NO 73
<211> LENGTH: 651
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 73

```
gcctatgata tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc     60

atcaagtgtc aggccagtga ggacatttat agcttcttgg cctggtatca gcagaaacca    120

gggaaagccc ctaagctcct gatccattct gcatcctctc tggcatctgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct    240

gaagattttg caacttacta ttgtcaacag ggttatggta aaaataatgt tgataatgct    300

ttcggcggag ggaccaaggt ggagatcaaa cgtacggtgg ctgcaccatc tgtcttcatc    360

ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgttgtgtg cctgctgaat    420

aacttctatc ccagagaggc caaagtacag tggaaggtgg ataacgccct ccaatcgggt    480

aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc    540

accctgacgc tgagcaaagc agactacgag aaacacaaag tctacgcctg cgaagtcacc    600

catcagggcc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtg t              651
```

<210> SEQ ID NO 74
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 74

-continued

```
Ala Tyr Asp Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Lys Cys Gln Ala Ser Glu Asp Ile Tyr Ser Phe
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

His Ser Ala Ser Ser Leu Ala 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 Gly Tyr Gly Lys Asn Asn
                85                  90                  95

Val Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
        115                 120                 125

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
    130                 135                 140

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
145                 150                 155                 160

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
                165                 170                 175

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
            180                 185                 190

Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
        195                 200                 205

Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 75
<211> LENGTH: 3687
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 75

gacgtcgtga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc     60

atcaattgcc aagccagtga gagcattagc agttggttag cctggtatca gcagaaacca    120

gggaaagccc ctaagctcct gatctatgaa gcatccaaac tggcatctgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagaa tttactctca ccatcagcag cctgcagcct    240

gatgattttg caacttatta ctgccaaggc tatttttatt ttattagtcg tacttatgta    300

aattctttcg gcggagggac caaggtggag atcaaaggcg gtggcggtag tgggggaggc    360

ggttctggcg gcggagggtc cggcggtgga ggatcagagg tgcagctggt ggagtctggg    420

ggaggcttgg tccagcctgg ggggtccctg agactctcct gtgcagcctc tggattcacc    480

atcagtacca atgcaatgag ctgggtccgc caggctccag ggaaggggct ggagtggatc    540

ggagtcatta ctggtcgtga tatcacatac tacgcgagct gggcgaaagg cagattcacc    600

atctccagag acaattccaa gaacacgctg tatcttcaaa tgaacagcct gagagccgag    660

gacacggctg tgtattactg tgcgagagac ggtggttctt ctgctattac tagtaacaac    720
```

-continued

atttggggcc agggaaccct ggtcaccgtg tcgacaggcg gtggagggtc cggcggtggt 780

ggatcccagt cggtggagga gtctgggggga ggcttggtcc agcctggggg gtccctgaga 840

ctctcctgta ccgcctctgg aatcgacctt aatacctacg acatgatctg ggtccgccag 900

gctccaggca aggggctaga gtgggttgga atcattactt atagtggtag tagatactac 960

gcgaactggg cgaaaggccg attcaccatc tccaaagaca ataccaagaa cacggtgtat 1020

ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagagattat 1080

atgagtggtt cccacttgtg gggccaggga accctggtca ccgtctcttc agctagcacc 1140

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 1200

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 1260

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 1320

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 1380

aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 1440

gacaaaactc acacatgccc accgtgccca gcacctgaag ccgcgggggc accgtcagtc 1500

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 1560

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 1620

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 1680

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 1740

tgcgcggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1800

gggcagcccc gagaaccaca ggtgtatacc ctgcccccat cccgggatga gctgaccaag 1860

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1920

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1980

gacggctcct tcttcctcta tagcaagctc accgtggaca agagcaggtg gcagcagggg 2040

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 2100

ctctccctgt ctccgggtgg cggtggaggg tccggcggtg gtgggtccgg agaggtgcag 2160

ctgttggagt ctgggggagg cttggtacag cctgggggggt ccctgagact ctcctgtgca 2220

gcctctggat tcaccatcag tcgctaccac atgacttggg tccgccaggc tccagggaag 2280

gggctggagt ggatcggaca tatttatgtt aataatgatg acacagacta cgcgagctcc 2340

gcgaaaggcc ggttcaccat ctccagagac aattccaaga acacgctgta tctgcaaatg 2400

aacagcctga gagccgagga cacggccacc tatttctgtg cgagattgga tgttggtggt 2460

ggtggtgctt atattgggga catctggggc cagggaactc tggttaccgt ctcttcaggc 2520

ggtggcggta gtgggggagg cggttctggc ggcggagggt ccggcggtgg aggatcagac 2580

atccagatga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 2640

acttgccagt ccagtcagag tgtttataac aacaacgact tagcctggta tcagcagaaa 2700

ccagggaaag ttcctaagct cctgatctat tatgcttcca ctctggcatc tggggtccca 2760

tctcggttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 2820

cctgaagatg ttgcaactta ttactgtgca ggcggttatg atacggatgg tcttgatacg 2880

tttgctttcg gcggagggac caaggtggag atcaaaggcg gtggagggtc cggcggtggt 2940

gggtccggac ggtcgctggt ggagtctggg ggaggcttgg tccagcctgg ggggtccctg 3000

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agactctcct gtactgcctc tggattcacc atcagtagct accacatgca gtgggtccgc 3060

caggctccag ggaaggggct ggagtacatc ggaaccatta gtagtggtgg taatgtatac 3120

tacgcaagct ccgctagagg cagattcacc atctccagac cctcgtccaa gaacacggtg 3180

gatcttcaaa tgaacagcct gagagccgag gacacggctg tgtattactg tgcgagagac 3240

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gtgatgaccc agtctccatc ttccgtgtct gcatctgtag gagacagagt caccatcacc 3420

tgtcaggcca gtcagaacat taggacttac ttatcctggt atcagcagaa accagggaaa 3480

gcccctaagc tcctgatcta tgctgcagcc aatctggcat ctggggtccc atcaaggttc 3540

agcggcagtg gatctgggac agatttcact ctcaccatca gcgacctgga gcctggcgat 3600

gctgcaactt actattgtca gtctacctat cttggtactg attatgttgg cggtgctttc 3660

ggcggaggga ccaaggtgga gatcaaa 3687

<210> SEQ ID NO 76
<211> LENGTH: 1229
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 76

Asp Val Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Gln Ala Ser Glu Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Glu Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Tyr Phe Tyr Phe Ile Ser
85 90 95

Arg Thr Tyr Val Asn Ser Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
130 135 140

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
145 150 155 160

Ile Ser Thr Asn Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly
165 170 175

Leu Glu Trp Ile Gly Val Ile Thr Gly Arg Asp Ile Thr Tyr Tyr Ala
180 185 190

Ser Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
195 200 205

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
210 215 220

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Tyr Tyr Cys Ala Arg Asp Gly Gly Ser Ser Ala Ile Thr Ser Asn Asn
225                 230                 235                 240

Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Thr Gly Gly Gly Gly
                245                 250                 255

Ser Gly Gly Gly Gly Ser Gln Ser Val Glu Glu Ser Gly Gly Gly Leu
            260                 265                 270

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Ile
        275                 280                 285

Asp Leu Asn Thr Tyr Asp Met Ile Trp Val Arg Gln Ala Pro Gly Lys
    290                 295                 300

Gly Leu Glu Trp Val Gly Ile Ile Thr Tyr Ser Gly Ser Arg Tyr Tyr
305                 310                 315                 320

Ala Asn Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Asp Asn Thr Lys
                325                 330                 335

Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
            340                 345                 350

Val Tyr Tyr Cys Ala Arg Asp Tyr Met Ser Gly Ser His Leu Trp Gly
        355                 360                 365

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
    370                 375                 380

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
385                 390                 395                 400

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                405                 410                 415

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            420                 425                 430

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        435                 440                 445

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
    450                 455                 460

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
465                 470                 475                 480

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
                485                 490                 495

Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            500                 505                 510

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        515                 520                 525

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    530                 535                 540

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
545                 550                 555                 560

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                565                 570                 575

Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            580                 585                 590

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        595                 600                 605

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    610                 615                 620

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
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625                 630                 635                 640

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                645                 650                 655

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            660                 665                 670

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        675                 680                 685

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    690                 695                 700

Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Glu Val Gln
705                 710                 715                 720

Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg
                725                 730                 735

Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Arg Tyr His Met Thr
            740                 745                 750

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly His Ile
        755                 760                 765

Tyr Val Asn Asn Asp Asp Thr Asp Tyr Ala Ser Ser Ala Lys Gly Arg
    770                 775                 780

Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met
785                 790                 795                 800

Asn Ser Leu Arg Ala Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Leu
                805                 810                 815

Asp Val Gly Gly Gly Gly Ala Tyr Ile Gly Asp Ile Trp Gly Gln Gly
            820                 825                 830

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        835                 840                 845

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
    850                 855                 860

Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
865                 870                 875                 880

Thr Cys Gln Ser Ser Gln Ser Val Tyr Asn Asn Asn Asp Leu Ala Trp
                885                 890                 895

Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile Tyr Tyr Ala
            900                 905                 910

Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
        915                 920                 925

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val
    930                 935                 940

Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Asp Thr Asp Gly Leu Asp Thr
945                 950                 955                 960

Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly
                965                 970                 975

Ser Gly Gly Gly Gly Ser Gly Arg Ser Leu Val Glu Ser Gly Gly Gly
            980                 985                 990

Leu Val Gln Pro Gly Gly Ser Leu  Arg Leu Ser Cys Thr  Ala Ser Gly
        995                 1000                1005

Phe Thr  Ile Ser Ser Tyr His  Met Gln Trp Val Arg  Gln Ala Pro
    1010                1015                1020

Gly Lys  Gly Leu Glu Tyr Ile  Gly Thr Ile Ser Ser  Gly Gly Asn
    1025                1030                1035
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Val Tyr  Tyr Ala Ser Ser Ala  Arg Gly Arg Phe Thr  Ile Ser Arg
    1040                1045                1050

Pro Ser  Ser Lys Asn Thr Val  Asp Leu Gln Met Asn  Ser Leu Arg
    1055                1060                1065

Ala Glu  Asp Thr Ala Val Tyr  Tyr Cys Ala Arg Asp  Ser Gly Tyr
    1070                1075                1080

Ser Asp  Pro Met Trp Gly Gln  Gly Thr Leu Val Thr  Val Ser Ser
    1085                1090                1095

Gly Gly  Gly Gly Ser Gly Gly  Gly Gly Ser Gly Gly  Gly Gly Ser
    1100                1105                1110

Gly Gly  Gly Gly Ser Asp Val  Val Met Thr Gln Ser  Pro Ser Ser
    1115                1120                1125

Val Ser  Ala Ser Val Gly Asp  Arg Val Thr Ile Thr  Cys Gln Ala
    1130                1135                1140

Ser Gln  Asn Ile Arg Thr Tyr  Leu Ser Trp Tyr Gln  Gln Lys Pro
    1145                1150                1155

Gly Lys  Ala Pro Lys Leu Leu  Ile Tyr Ala Ala Ala  Asn Leu Ala
    1160                1165                1170

Ser Gly  Val Pro Ser Arg Phe  Ser Gly Ser Gly Ser  Gly Thr Asp
    1175                1180                1185

Phe Thr  Leu Thr Ile Ser Asp  Leu Glu Pro Gly Asp  Ala Ala Thr
    1190                1195                1200

Tyr Tyr  Cys Gln Ser Thr Tyr  Leu Gly Thr Asp Tyr  Val Gly Gly
    1205                1210                1215

Ala Phe  Gly Gly Gly Thr Lys  Val Glu Ile Lys
    1220                1225
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<210> SEQ ID NO 77
<211> LENGTH: 651
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 77

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gcctatgata tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc     60

atcaagtgtc aggccagtga ggacatttat agcttcttgg cctggtatca gcagaaacca    120

gggaaagccc ctaagctcct gatccattct gcatcctctc tggcatctgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct    240

gaagattttg caacttacta ttgtcaacag ggttatggta aaaataatgt tgataatgct    300

ttcggcggag ggaccaaggt ggagatcaaa cgtacggtgg ctgcaccatc tgtcttcatc    360

ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgttgtgtg cctgctgaat    420

aacttctatc ccagagaggc caaagtacag tggaaggtgg ataacgccct ccaatcgggt    480

aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc    540

accctgacgc tgagcaaagc agactacgag aaacacaaag tctacgcctg cgaagtcacc    600

catcagggcc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtg t              651
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<210> SEQ ID NO 78
<211> LENGTH: 217
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 78

Ala Tyr Asp Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Lys Cys Gln Ala Ser Glu Asp Ile Tyr Ser Phe
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

His Ser Ala Ser Ser Leu Ala 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 Gly Tyr Gly Lys Asn Asn
85 90 95

Val Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
115 120 125

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
130 135 140

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
145 150 155 160

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
165 170 175

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
180 185 190

Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
195 200 205

Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> SEQ ID NO 79
<211> LENGTH: 3675
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 79

gacgtcgtga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcaattgcc aagccagtga gagcattagc agttggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgaa gcatccaaac tggcatctgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa tttactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaaggc tatttttatt ttattagtcg tacttatgta 300

aattctttcg gcggagggac caaggtggag atcaaaggcg gtggcggtag tgggggaggc 360

ggttctggcg gcggagggtc cggcggtgga ggatcagagg tgcagctggt ggagtctggg 420

ggaggcttgg tccagcctgg ggggtccctg agactctcct gtgcagcctc tggattcacc 480

atcagtacca atgcaatgag ctgggtccgc caggctccag ggaaggggct ggagtggatc 540

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ggagtcatta ctggtcgtga tatcacatac tacgcgagct gggcgaaagg cagattcacc 600

atctccagag acaattccaa gaacacgctg tatcttcaaa tgaacagcct gagagccgag 660

gacacggctg tgtattactg tgcgagagac ggtggttctt ctgctattac tagtaacaac 720

atttggggcc agggaaccct ggtcaccgtg tcgacaggcg gtggagggtc cggcggtggt 780

ggatccgagg tgcagctgtt ggagtctggg ggaggcttgg tacagcctgg ggggtccctg 840

agactctcct gtgcagcctc tggattcacc atcagtcgct accacatgac ttgggtccgc 900

caggctccag ggaaggggct ggagtggatc ggacatattt atgttaataa tgatgacaca 960

gactacgcga gctccgcgaa aggccggttc accatctcca gagacaattc caagaacacg 1020

ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ccacctattt ctgtgcgaga 1080

ttggatgttg gtggtggtgg tgcttatatt ggggacatct ggggccaggg aaccctggtc 1140

accgtctcga gcgctagcac caagggccca tcggtcttcc ccctggcacc ctcctccaag 1200

agcacctctg ggggcacagc ggccctgggc tgcctggtca aggactactt ccccgaaccg 1260

gtgacggtgt cgtggaactc aggcgccctg accagcggcg tgcacacctt cccggctgtc 1320

ctacagtcct caggactcta ctccctcagc agcgtggtga ccgtgccctc cagcagcttg 1380

ggcacccaga cctacatctg caacgtgaat cacaagccca gcaacaccaa ggtggacaag 1440

agagttgagc ccaaatcttg tgacaaaact cacacatgcc caccgtgccc agcacctgaa 1500

gccgcggggg caccgtcagt cttcctcttc cccccaaaac ccaaggacac cctcatgatc 1560

tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga gccacgaaga ccctgaggtc 1620

aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag 1680

gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg 1740

ctgaatggca aggagtacaa gtgcgcggtc tccaacaaag ccctcccagc ccccatcgag 1800

aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtatac cctgccccca 1860

tcccgggatg agctgaccaa gaaccaggtc agcctgacct gcctggtcaa aggcttctat 1920

cccagcgaca tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc 1980

acgcctcccg tgctggactc cgacggctcc ttcttcctct atagcaagct caccgtggac 2040

aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg tgatgcatga ggctctgcac 2100

aaccactaca cgcagaagag cctctccctg tctccgggtg gcggtggagg gtccggcggt 2160

ggtggatccc agtcggtgga ggagtctggg ggaggcttgg tccagcctgg ggggtccctg 2220

agactctcct gtaccgcctc tggaatcgac cttaatacct acgacatgat ctgggtccgc 2280

caggctccag gcaaggggct agagtgggtt ggaatcatta cttatagtgg tagtagatac 2340

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tatctgcaaa tgaacagcct gagagctgag gacacggctg tgtattactg tgcgagagat 2460

tatatgagtg gttcccactt gtggggccag ggaaccctgg tcaccgtctc ttccggtgga 2520

ggcggttcag gcggaggtgg aagtggtggt ggcggctctg gaggcggcgg atctgcctat 2580

gatatgaccc agtctccatc ttccgtgtct gcatctgtag gagacagagt caccatcaag 2640

tgtcaggcca gtgaggacat ttatagcttc ttggcctggt atcagcagaa accagggaaa 2700

gcccctaagc tcctgatcca ttctgcatcc tctctggcat ctggggtccc atcaaggttc 2760

agcggcagtg gatctgggac agatttcact ctcaccatca gcagcctgca gcctgaagat 2820

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tttgcaactt actattgtca acagggttat ggtaaaaata atgttgataa tgctttcggc 2880

ggagggacca aggtggagat caaaggcggt ggagggtccg gcggtggtgg gtccggacgg 2940

tcgctggtgg agtctggggg aggcttggtc cagcctgggg ggtccctgag actctcctgt 3000

actgcctctg gattcaccat cagtagctac cacatgcagt gggtccgcca ggctccaggg 3060

aaggggctgg agtacatcgg aaccattagt agtggtggta atgtatacta cgcaagctcc 3120

gctagaggca gattcaccat ctccagaccc tcgtccaaga acacggtgga tcttcaaatg 3180

aacagcctga gagccgagga cacggctgtg tattactgtg cgagagactc tggttatagt 3240

gatcctatgt ggggccaggg aaccctggtc accgtctctt caggcggtgg cggtagtggg 3300

ggaggcggtt ctggcggcgg agggtccggc ggtggaggat cagacgttgt gatgacccag 3360

tctccatctt ccgtgtctgc atctgtagga gacagagtca ccatcacctg tcaggccagt 3420

cagaacatta ggacttactt atcctggtat cagcagaaac cagggaaagc ccctaagctc 3480

ctgatctatg ctgcagccaa tctggcatct ggggtcccat caaggttcag cggcagtgga 3540

tctgggacag atttcactct caccatcagc gacctggagc ctggcgatgc tgcaacttac 3600

tattgtcagt ctacctatct tggtactgat tatgttggcg gtgctttcgg cggagggacc 3660

aaggtggaga tcaaa 3675

<210> SEQ ID NO 80
<211> LENGTH: 1225
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 80

Asp Val Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Gln Ala Ser Glu Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Glu Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Tyr Phe Tyr Phe Ile Ser
85 90 95

Arg Thr Tyr Val Asn Ser Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
130 135 140

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
145 150 155 160

Ile Ser Thr Asn Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly
165 170 175

Leu Glu Trp Ile Gly Val Ile Thr Gly Arg Asp Ile Thr Tyr Tyr Ala
180 185 190

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Ser Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
        195                 200                 205

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Arg Asp Gly Gly Ser Ser Ala Ile Thr Ser Asn Asn
225                 230                 235                 240

Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Thr Gly Gly Gly Gly
                245                 250                 255

Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
            260                 265                 270

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        275                 280                 285

Phe Thr Ile Ser Arg Tyr His Met Thr Trp Val Arg Gln Ala Pro Gly
    290                 295                 300

Lys Gly Leu Glu Trp Ile Gly His Ile Tyr Val Asn Asn Asp Asp Thr
305                 310                 315                 320

Asp Tyr Ala Ser Ser Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                325                 330                 335

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            340                 345                 350

Thr Ala Thr Tyr Phe Cys Ala Arg Leu Asp Val Gly Gly Gly Gly Ala
        355                 360                 365

Tyr Ile Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    370                 375                 380

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
385                 390                 395                 400

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
                405                 410                 415

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
            420                 425                 430

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
        435                 440                 445

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
    450                 455                 460

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
465                 470                 475                 480

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
                485                 490                 495

Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
            500                 505                 510

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
        515                 520                 525

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
    530                 535                 540

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
545                 550                 555                 560

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
                565                 570                 575

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn
            580                 585                 590

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
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        595                 600                 605

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
    610                 615                 620

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
625                 630                 635                 640

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
                645                 650                 655

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
            660                 665                 670

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
        675                 680                 685

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
    690                 695                 700

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly
705                 710                 715                 720

Gly Gly Ser Gln Ser Val Glu Glu Ser Gly Gly Gly Leu Val Gln Pro
                725                 730                 735

Gly Gly Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Ile Asp Leu Asn
            740                 745                 750

Thr Tyr Asp Met Ile Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
        755                 760                 765

Trp Val Gly Ile Ile Thr Tyr Ser Gly Ser Arg Tyr Tyr Ala Asn Trp
    770                 775                 780

Ala Lys Gly Arg Phe Thr Ile Ser Lys Asp Asn Thr Lys Asn Thr Val
785                 790                 795                 800

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                805                 810                 815

Cys Ala Arg Asp Tyr Met Ser Gly Ser His Leu Trp Gly Gln Gly Thr
            820                 825                 830

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        835                 840                 845

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Tyr Asp Met Thr Gln
    850                 855                 860

Ser Pro Ser Ser Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Lys
865                 870                 875                 880

Cys Gln Ala Ser Glu Asp Ile Tyr Ser Phe Leu Ala Trp Tyr Gln Gln
                885                 890                 895

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile His Ser Ala Ser Ser Leu
            900                 905                 910

Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        915                 920                 925

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
    930                 935                 940

Tyr Cys Gln Gln Gly Tyr Gly Lys Asn Asn Val Asp Asn Ala Phe Gly
945                 950                 955                 960

Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly
                965                 970                 975

Gly Ser Gly Arg Ser Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
            980                 985                 990

Gly Gly Ser Leu Arg Leu Ser Cys  Thr Ala Ser Gly Phe  Thr Ile Ser
        995                 1000                1005
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Ser Tyr  His Met Gln Trp Val  Arg Gln Ala Pro Gly  Lys Gly Leu
    1010                1015                1020

Glu Tyr  Ile Gly Thr Ile Ser  Ser Gly Gly Asn Val  Tyr Tyr Ala
    1025                1030                1035

Ser Ser  Ala Arg Gly Arg Phe  Thr Ile Ser Arg Pro  Ser Ser Lys
    1040                1045                1050

Asn Thr  Val Asp Leu Gln Met  Asn Ser Leu Arg Ala  Glu Asp Thr
    1055                1060                1065

Ala Val  Tyr Tyr Cys Ala Arg  Asp Ser Gly Tyr Ser  Asp Pro Met
    1070                1075                1080

Trp Gly  Gln Gly Thr Leu Val  Thr Val Ser Ser Gly  Gly Gly Gly
    1085                1090                1095

Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Gly
    1100                1105                1110

Ser Asp  Val Val Met Thr Gln  Ser Pro Ser Ser Val  Ser Ala Ser
    1115                1120                1125

Val Gly  Asp Arg Val Thr Ile  Thr Cys Gln Ala Ser  Gln Asn Ile
    1130                1135                1140

Arg Thr  Tyr Leu Ser Trp Tyr  Gln Gln Lys Pro Gly  Lys Ala Pro
    1145                1150                1155

Lys Leu  Leu Ile Tyr Ala Ala  Ala Asn Leu Ala Ser  Gly Val Pro
    1160                1165                1170

Ser Arg  Phe Ser Gly Ser Gly  Ser Gly Thr Asp Phe  Thr Leu Thr
    1175                1180                1185

Ile Ser  Asp Leu Glu Pro Gly  Asp Ala Ala Thr Tyr  Tyr Cys Gln
    1190                1195                1200

Ser Thr  Tyr Leu Gly Thr Asp  Tyr Val Gly Gly Ala  Phe Gly Gly
    1205                1210                1215

Gly Thr  Lys Val Glu Ile Lys
    1220                1225


<210> SEQ ID NO 81
<211> LENGTH: 660
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 81

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc     60

atcacttgcc agtccagtca gagtgtttat aacaacaacg acttagcctg gtatcagcag    120

aaaccaggga aagttcctaa gctcctgatc tattatgcat ccactctggc atctggggtc    180

ccatctcggt tcagtggcag tggatctggg acagatttca ctctcaccat cagcagcctg    240

cagcctgaag atgttgcaac ttattactgt gcaggcggtt atgatacgga tggtcttgat    300

acgtttgctt tcggcggagg gaccaaggtg gagatcaaac gtacggtggc tgcaccatct    360

gtcttcatct tcccgccatc tgatgagcag ttgaaatctg gaactgcctc tgttgtgtgc    420

ctgctgaata acttctatcc cagagaggcc aaagtacagt ggaaggtgga taacgccctc    480

caatcgggta actcccagga gagtgtcaca gagcaggaca gcaaggacag cacctacagc    540

ctcagcagca ccctgacgct gagcaaagca gactacgaga aacacaaagt ctacgcctgc    600
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gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gcttcaacag gggagagtgt 660

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

<400> SEQUENCE: 82

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 Gln Ser Ser Gln Ser Val Tyr Asn Asn
20 25 30

Asn Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu
35 40 45

Leu Ile Tyr Tyr Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe
50 55 60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65 70 75 80

Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Asp Thr
85 90 95

Asp Gly Leu Asp Thr Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile
100 105 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
115 120 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
130 135 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145 150 155 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
165 170 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> SEQ ID NO 83
<211> LENGTH: 3696
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 83

gacgtcgtga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcaattgcc aagccagtga gagcattagc agttggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgaa gcatccaaac tggcatctgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa tttactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaaggc tatttttatt ttattagtcg tacttatgta 300

aattctttcg gcggagggac caaggtggag atcaaaggcg gtggcggtag tgggggaggc 360

-continued

ggttctggcg gcggagggtc cggcggtgga ggatcagagg tgcagctggt ggagtctggg 420

ggaggcttgg tccagcctgg ggggtccctg agactctcct gtgcagcctc tggattcacc 480

atcagtacca atgcaatgag ctgggtccgc caggctccag ggaaggggct ggagtggatc 540

ggagtcatta ctggtcgtga tatcacatac tacgcgagct gggcgaaagg cagattcacc 600

atctccagag acaattccaa gaacacgctg tatcttcaaa tgaacagcct gagagccgag 660

gacacggctg tgtattactg tgcgagagac ggtggttctt ctgctattac tagtaacaac 720

atttggggcc agggaaccct ggtcaccgtg tcgacaggcg gtggagggtc cggcggtggt 780

ggatcagagg tgcagctgtt ggagtctggg ggaggcttgg tacagcctgg ggggtccctg 840

agactctcct gtgcagcctc tggattcacc atcagtcgct accacatgac ttgggtccgc 900

caggctccag ggaaggggct ggagtggatc ggacatattt atgttaataa tgatgacaca 960

gactacgcga gctccgcgaa aggccggttc accatctcca gagacaattc caagaacacg 1020

ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ccacctattt ctgtgcgaga 1080

ttggatgttg gtggtggtgg tgcttatatt ggggacatct ggggccaggg aactctggtt 1140

accgtctctt cagctagcac caagggccca tcggtcttcc ccctggcacc ctcctccaag 1200

agcacctctg ggggcacagc ggccctgggc tgcctggtca aggactactt ccccgaaccg 1260

gtgacggtgt cgtggaactc aggcgccctg accagcggcg tgcacacctt cccggctgtc 1320

ctacagtcct caggactcta ctccctcagc agcgtggtga ccgtgccctc cagcagcttg 1380

ggcacccaga cctacatctg caacgtgaat cacaagccca gcaacaccaa ggtggacaag 1440

agagttgagc ccaaatcttg tgacaaaact cacacatgcc caccgtgccc agcacctgaa 1500

gccgcggggg caccgtcagt cttcctcttc cccccaaaac ccaaggacac cctcatgatc 1560

tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga gccacgaaga ccctgaggtc 1620

aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag 1680

gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg 1740

ctgaatggca aggagtacaa gtgcgcggtc tccaacaaag ccctcccagc ccccatcgag 1800

aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtacac cctgccccca 1860

tcccgggatg agctgaccaa gaaccaggtc agcctgacct gcctggtcaa aggcttctat 1920

cccagcgaca tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc 1980

acgcctcccg tgctggactc cgacggctcc ttcttcctct atagcaagct caccgtggac 2040

aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg tgatgcatga ggctctgcac 2100

aaccactaca cgcagaagag cctctccctg tctccgggtg gcggtggagg gtccggcggt 2160

ggtggatccg aggtgcagct gttggagtct gggggaggct tggtacagcc tgggggggtcc 2220

ctgagactct cctgtgcagc ctctggattc tccttcagta gcgggtacga catgtgctgg 2280

gtccgccagg ctccagggaa ggggctggag tggatcgcat gcattgctgc tggtagtgct 2340

ggtatcactt acgacgcgaa ctgggcgaaa ggccggttca ccatctccag agacaattcc 2400

aagaacacgc tgtatctgca aatgaacagc ctgagagccg aggacacggc cgtatattac 2460

tgtgcgagat cggcgttttc gttcgactac gccatggacc tctggggcca gggaaccctg 2520

gtcaccgtct cgagcggtgg aggcggatct ggcggaggtg gttccggcgg tggcggctcc 2580

ggtggaggcg gctctgacat ccagatgacc cagtctcctt ccaccctgtc tgcatctgta 2640

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ggagacagag tcaccatcac ttgccaggcc agtcagagca ttagttccca cttaaactgg 2700

tatcagcaga aaccagggaa agcccctaag ctcctgatct ataaggcatc cactctggca 2760

tctggggtcc catcaaggtt cagcggcagt ggatctggga cagaatttac tctcaccatc 2820

agcagcctgc agcctgatga ttttgcaact tattactgcc aacagggtta tagttggggt 2880

aatgttgata atgttttcgg cggagggacc aaggtggaga tcaaaggcgg tggagggtcc 2940

ggcggtggtg gctccggacg gtcgctggtg gagtctgggg gaggcttggt ccagcctggg 3000

gggtccctga gactctcctg tactgcctct ggattcacca tcagtagcta ccacatgcag 3060

tgggtccgcc aggctccagg gaaggggctg gagtacatcg gaaccattag tagtggtggt 3120

aatgtatact acgcaagctc cgctagaggc agattcacca tctccagacc ctcgtccaag 3180

aacacggtgg atcttcaaat gaacagcctg agagccgagg acacggctgt gtattactgt 3240

gcgagagact ctggttatag tgatcctatg tggggccagg gaaccctggt caccgtctct 3300

tcaggcggtg gcggtagtgg gggaggcggt tctggcggcg gagggtccgg cggtggagga 3360

tcagacgttg tgatgaccca gtctccatct tccgtgtctg catctgtagg agacagagtc 3420

accatcacct gtcaggccag tcagaacatt aggacttact tatcctggta tcagcagaaa 3480

ccagggaaag cccctaagct cctgatctat gctgcagcca atctggcatc tggggtccca 3540

tcaaggttca gcggcagtgg atctgggaca gatttcactc tcaccatcag cgacctggag 3600

cctggcgatg ctgcaactta ctattgtcag tctacctatc ttggtactga ttatgttggc 3660

ggtgctttcg gcggagggac caaggtggag atcaaa 3696

<210> SEQ ID NO 84
<211> LENGTH: 1232
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 84

Asp Val Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Gln Ala Ser Glu Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Glu Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Tyr Phe Tyr Phe Ile Ser
85 90 95

Arg Thr Tyr Val Asn Ser Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
130 135 140

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
145 150 155 160

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Ile Ser Thr Asn Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Val Ile Thr Gly Arg Asp Ile Thr Tyr Tyr Ala
            180                 185                 190

Ser Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
        195                 200                 205

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Arg Asp Gly Gly Ser Ser Ala Ile Thr Ser Asn Asn
225                 230                 235                 240

Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Thr Gly Gly Gly Gly
                245                 250                 255

Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
            260                 265                 270

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        275                 280                 285

Phe Thr Ile Ser Arg Tyr His Met Thr Trp Val Arg Gln Ala Pro Gly
    290                 295                 300

Lys Gly Leu Glu Trp Ile Gly His Ile Tyr Val Asn Asn Asp Asp Thr
305                 310                 315                 320

Asp Tyr Ala Ser Ser Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                325                 330                 335

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            340                 345                 350

Thr Ala Thr Tyr Phe Cys Ala Arg Leu Asp Val Gly Gly Gly Gly Ala
        355                 360                 365

Tyr Ile Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    370                 375                 380

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
385                 390                 395                 400

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
                405                 410                 415

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
            420                 425                 430

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
        435                 440                 445

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
    450                 455                 460

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
465                 470                 475                 480

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
                485                 490                 495

Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
            500                 505                 510

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
        515                 520                 525

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
    530                 535                 540

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
545                 550                 555                 560

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
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               565                 570                 575

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn
            580                 585                 590

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
        595                 600                 605

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
    610                 615                 620

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
625                 630                 635                 640

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
                645                 650                 655

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
            660                 665                 670

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
        675                 680                 685

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
    690                 695                 700

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly
705                 710                 715                 720

Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
                725                 730                 735

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe
            740                 745                 750

Ser Ser Gly Tyr Asp Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly
        755                 760                 765

Leu Glu Trp Ile Ala Cys Ile Ala Ala Gly Ser Ala Gly Ile Thr Tyr
    770                 775                 780

Asp Ala Asn Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
785                 790                 795                 800

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
                805                 810                 815

Ala Val Tyr Tyr Cys Ala Arg Ser Ala Phe Ser Phe Asp Tyr Ala Met
            820                 825                 830

Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        835                 840                 845

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    850                 855                 860

Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val
865                 870                 875                 880

Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Ser Ser
                885                 890                 895

His Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
            900                 905                 910

Ile Tyr Lys Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
        915                 920                 925

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
    930                 935                 940

Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Trp Gly
945                 950                 955                 960

Asn Val Asp Asn Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly
                965                 970                 975
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Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Arg Ser Leu Val Glu Ser
            980                 985                 990

Gly Gly Gly Leu Val Gln Pro Gly  Gly Ser Leu Arg Leu  Ser Cys Thr
        995                 1000                1005

Ala Ser  Gly Phe Thr Ile Ser  Ser Tyr His Met Gln  Trp Val Arg
    1010                1015                1020

Gln Ala  Pro Gly Lys Gly Leu  Glu Tyr Ile Gly Thr  Ile Ser Ser
    1025                1030                1035

Gly Gly  Asn Val Tyr Tyr Ala  Ser Ser Ala Arg Gly  Arg Phe Thr
    1040                1045                1050

Ile Ser  Arg Pro Ser Ser Lys  Asn Thr Val Asp Leu  Gln Met Asn
    1055                1060                1065

Ser Leu  Arg Ala Glu Asp Thr  Ala Val Tyr Tyr Cys  Ala Arg Asp
    1070                1075                1080

Ser Gly  Tyr Ser Asp Pro Met  Trp Gly Gln Gly Thr  Leu Val Thr
    1085                1090                1095

Val Ser  Ser Gly Gly Gly Gly  Ser Gly Gly Gly Gly  Ser Gly Gly
    1100                1105                1110

Gly Gly  Ser Gly Gly Gly Gly  Ser Asp Val Val Met  Thr Gln Ser
    1115                1120                1125

Pro Ser  Ser Val Ser Ala Ser  Val Gly Asp Arg Val  Thr Ile Thr
    1130                1135                1140

Cys Gln  Ala Ser Gln Asn Ile  Arg Thr Tyr Leu Ser  Trp Tyr Gln
    1145                1150                1155

Gln Lys  Pro Gly Lys Ala Pro  Lys Leu Leu Ile Tyr  Ala Ala Ala
    1160                1165                1170

Asn Leu  Ala Ser Gly Val Pro  Ser Arg Phe Ser Gly  Ser Gly Ser
    1175                1180                1185

Gly Thr  Asp Phe Thr Leu Thr  Ile Ser Asp Leu Glu  Pro Gly Asp
    1190                1195                1200

Ala Ala  Thr Tyr Tyr Cys Gln  Ser Thr Tyr Leu Gly  Thr Asp Tyr
    1205                1210                1215

Val Gly  Gly Ala Phe Gly Gly  Gly Thr Lys Val Glu  Ile Lys
    1220                1225                1230
```

<210> SEQ ID NO 85
<211> LENGTH: 660
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 85

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gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc     60

atcacttgcc agtccagtca gagtgtttat aacaacaacg acttagcctg gtatcagcag    120

aaaccaggga aagttcctaa gctcctgatc tattatgcat ccactctggc atctggggtc    180

ccatctcggt tcagtggcag tggatctggg acagatttca ctctcaccat cagcagcctg    240

cagcctgaag atgttgcaac ttattactgt gcaggcggtt atgatacgga tggtcttgat    300

acgtttgctt tcggcggagg gaccaaggtg gagatcaaac gtacggtggc tgcaccatct    360

gtcttcatct tcccgccatc tgatgagcag ttgaaatctg gaactgcctc tgttgtgtgc    420
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ctgctgaata acttctatcc cagagaggcc aaagtacagt ggaaggtgga taacgccctc 480

caatcgggta actcccagga gagtgtcaca gagcaggaca gcaaggacag cacctacagc 540

ctcagcagca ccctgacgct gagcaaagca gactacgaga aacacaaagt ctacgcctgc 600

gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gcttcaacag gggagagtgt 660

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

<400> SEQUENCE: 86

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 Gln Ser Ser Gln Ser Val Tyr Asn Asn
20 25 30

Asn Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu
35 40 45

Leu Ile Tyr Tyr Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe
50 55 60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65 70 75 80

Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Asp Thr
85 90 95

Asp Gly Leu Asp Thr Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile
100 105 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
115 120 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
130 135 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145 150 155 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
165 170 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> SEQ ID NO 87
<211> LENGTH: 3690
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 87

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atcaattgcc aagccagtga gagcattagc agttggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgaa gcatccaaac tggcatctgg ggtcccatca 180

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aggttcagcg gcagtggatc tgggacagag ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaaggc tatttttatt ttattagtcg tacttatgta 300

aattctttcg gcggagggac caaggtggag atcaaaggcg gtggcggtag tgggggaggc 360

ggttctggcg gcggagggtc cggcggtgga ggatcagagg tgcagctggt ggagtctggg 420

ggaggcttgg tccagcctgg ggggtccctg agactctcct gtgcagcctc tggattcacc 480

atcagtacca atgcaatgag ctgggtccgc caggctccag ggaaggggct ggagtggatc 540

ggagtcatta ctggtcgtga tatcacatac tacgcgagct gggcgaaagg cagattcacc 600

atctccagag acaattccaa gaacacgctg tatcttcaaa tgaacagcct gagagccgag 660

gacacggctg tgtattactg tgcgcgcgac ggtggatcat ctgctattac tagtaacaac 720

atttggggcc aaggaactct ggtcaccgtt tcttcaggcg gtggagggtc cggcggtggt 780

ggatccgagg tgcagctggt gcagtctgga gcagaggtga agaaaccagg agagtctctg 840

aagatctcct gtaagggttc tggatacagc tttagcagtt catggatcgg ctgggtgcgc 900

caggcacctg ggaaaggcct ggaatggatg gggatcatct atcctgatga ctctgatacc 960

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gcctacctgc agtggagtag cctgaaggcc tcggacaccg ctatgtatta ctgtgcgaga 1080

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cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc 1380

acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaga 1440

gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaagcc 1500

gcgggggcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 1560

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 1620

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cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1740

aatggcaagg agtacaagtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 1800

accatctcca aagccaaagg gcagccccga gaaccacagg tgtataccct gcccccatcc 1860

cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 1920

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1980

cctcccgtgc tggactccga cggctccttc ttcctctata gcaagctcac cgtggacaag 2040

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aacacgctgt atctgcaaat gaacagcctg agagccgagg acacggccgt atattactgt 2460

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accgtctcga gcggtggagg cggatctggc ggaggtggtt ccggcggtgg cggctccggt 2580

ggaggcggct ctgacatcca gatgacccag tctccttcca ccctgtctgc atctgtagga 2640

gacagagtca ccatcacttg ccaggccagt cagagcatta gttcccactt aaactggtat 2700

cagcagaaac cagggaaagc ccctaagctc ctgatctata aggcatccac tctggcatct 2760

ggggtcccat caaggttcag cggcagtgga tctgggacag aatttactct caccatcagc 2820

agcctgcagc ctgatgattt tgcaacttat tactgccaac agggttatag ttggggtaat 2880

gttgataatg ttttcggcgg agggaccaag gtggagatca aaggcggtgg agggtccggc 2940

ggtggtggat cccggtcgct ggtggagtct gggggaggct tggtccagcc tgggggggtcc 3000

ctgagactct cctgtacagc ctctggattc accatcagta gctaccacat gcagtgggtc 3060

cgccaggctc cagggaaggg gctggagtac atcggaacca ttagtagtgg tggtaatgta 3120

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gactctggtt atagtgatcc tatgtggggc cagggaaccc tggtcaccgt ctcgagcggc 3300

ggtggcggta gtgggggagg cggttctggc ggcggagggt ccggcggtgg aggatcagac 3360

gttgtgatga cccagtctcc atcttccgtg tctgcatctg taggagacag agtcaccatc 3420

acctgtcagg ccagtcagaa cattaggact tacttatcct ggtatcagca gaaaccaggg 3480

aaagccccta agctcctgat ctatgctgca gccaatctgg catctggggt cccatcaagg 3540

ttcagcggca gtggatctgg gacagatttc actctcacca tcagcgacct ggagcctggc 3600

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ttcggcggag ggaccaaggt ggagatcaaa 3690

<210> SEQ ID NO 88
<211> LENGTH: 1230
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 88

Asp Val Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Gln Ala Ser Glu Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Glu Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Tyr Phe Tyr Phe Ile Ser
85 90 95

Arg Thr Tyr Val Asn Ser Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

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Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
    130                 135                 140

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
145                 150                 155                 160

Ile Ser Thr Asn Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Val Ile Thr Gly Arg Asp Ile Thr Tyr Tyr Ala
            180                 185                 190

Ser Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
        195                 200                 205

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Arg Asp Gly Gly Ser Ser Ala Ile Thr Ser Asn Asn
225                 230                 235                 240

Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
                245                 250                 255

Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu
            260                 265                 270

Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly
        275                 280                 285

Tyr Ser Phe Ser Ser Ser Trp Ile Gly Trp Val Arg Gln Ala Pro Gly
    290                 295                 300

Lys Gly Leu Glu Trp Met Gly Ile Ile Tyr Pro Asp Asp Ser Asp Thr
305                 310                 315                 320

Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys
                325                 330                 335

Ser Ile Arg Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp
            340                 345                 350

Thr Ala Met Tyr Tyr Cys Ala Arg His Val Thr Met Ile Trp Gly Val
        355                 360                 365

Ile Ile Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
    370                 375                 380

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
385                 390                 395                 400

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                405                 410                 415

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            420                 425                 430

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
        435                 440                 445

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
    450                 455                 460

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
465                 470                 475                 480

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                485                 490                 495

Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
            500                 505                 510

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        515                 520                 525

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
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    530                 535                 540

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
545                 550                 555                 560

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                565                 570                 575

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys
            580                 585                 590

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        595                 600                 605

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    610                 615                 620

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
625                 630                 635                 640

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                645                 650                 655

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            660                 665                 670

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        675                 680                 685

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    690                 695                 700

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly
705                 710                 715                 720

Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro
                725                 730                 735

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser
            740                 745                 750

Ser Gly Tyr Asp Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
        755                 760                 765

Glu Trp Ile Ala Cys Ile Ala Ala Gly Ser Ala Gly Ile Thr Tyr Asp
    770                 775                 780

Ala Asn Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
785                 790                 795                 800

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
                805                 810                 815

Val Tyr Tyr Cys Ala Arg Ser Ala Phe Ser Phe Asp Tyr Ala Met Asp
            820                 825                 830

Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
        835                 840                 845

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    850                 855                 860

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
865                 870                 875                 880

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Ser Ser His
                885                 890                 895

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
            900                 905                 910

Tyr Lys Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
        915                 920                 925

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
    930                 935                 940
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Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Trp Gly Asn
945                 950                 955                 960

Val Asp Asn Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly
                965                 970                 975

Gly Gly Ser Gly Gly Gly Gly Ser Arg Ser Leu Val Glu Ser Gly Gly
            980                 985                 990

Gly Leu Val Gln Pro Gly Gly Ser  Leu Arg Leu Ser Cys  Thr Ala Ser
        995                 1000                1005

Gly Phe  Thr Ile Ser Ser Tyr  His Met Gln Trp Val  Arg Gln Ala
    1010                1015                1020

Pro Gly  Lys Gly Leu Glu Tyr  Ile Gly Thr Ile Ser  Ser Gly Gly
    1025                1030                1035

Asn Val  Tyr Tyr Ala Ser Ser  Ala Arg Gly Arg Phe  Thr Ile Ser
    1040                1045                1050

Arg Pro  Ser Ser Lys Asn Thr  Val Asp Leu Gln Met  Asn Ser Leu
    1055                1060                1065

Arg Ala  Glu Asp Thr Ala Val  Tyr Tyr Cys Ala Arg  Asp Ser Gly
    1070                1075                1080

Tyr Ser  Asp Pro Met Trp Gly  Gln Gly Thr Leu Val  Thr Val Ser
    1085                1090                1095

Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Gly
    1100                1105                1110

Ser Gly  Gly Gly Gly Ser Asp  Val Val Met Thr Gln  Ser Pro Ser
    1115                1120                1125

Ser Val  Ser Ala Ser Val Gly  Asp Arg Val Thr Ile  Thr Cys Gln
    1130                1135                1140

Ala Ser  Gln Asn Ile Arg Thr  Tyr Leu Ser Trp Tyr  Gln Gln Lys
    1145                1150                1155

Pro Gly  Lys Ala Pro Lys Leu  Leu Ile Tyr Ala Ala  Ala Asn Leu
    1160                1165                1170

Ala Ser  Gly Val Pro Ser Arg  Phe Ser Gly Ser Gly  Ser Gly Thr
    1175                1180                1185

Asp Phe  Thr Leu Thr Ile Ser  Asp Leu Glu Pro Gly  Asp Ala Ala
    1190                1195                1200

Thr Tyr  Tyr Cys Gln Ser Thr  Tyr Leu Gly Thr Asp  Tyr Val Gly
    1205                1210                1215

Gly Ala  Phe Gly Gly Gly Thr  Lys Val Glu Ile Lys
    1220                1225                1230


<210> SEQ ID NO 89
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 89

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atcacttgcc gggcaagtca gggcattagc agtgctttag cctggtatca gcagaaacca    120

gggaaagctc ctaagctcct gatctatgat gcctccagtt tggaaagtgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct    240
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gaagattttg caacttatta ctgtcaacag tttaatagtt acccattcac tttcggccct 300

gggaccaaag tggatatcaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> SEQ ID NO 90
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 90

Ala Ile Gln Leu 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 Gly Ile Ser Ser Ala
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu 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 Phe Asn Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 91
<211> LENGTH: 3675
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 91

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gggaaagctc ctaagctcct gatctatgat gcctccagtt tggaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtcaacag tttaatagtt acccattcac tttcggccct 300

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atcggctggg tgcgccaggc acctgggaaa ggcctggaat ggatggggat catctatcct 540

gatgactctg ataccagata cagtccatcc ttccaaggcc aggtcaccat ctcagccgac 600

aagtccatca ggactgccta cctgcagtgg agtagcctga aggcctcgga caccgctatg 660

tattactgtg cgagacatgt tactatgatt tggggagtta ttattgactt ctggggccag 720

ggaaccctgg tcaccgtctc ctcaggcggt ggagggtccg gcggtggtgg atccgaggtg 780

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gcagcctctg gattcaccat cagtaccaat gcaatgagct gggtccgcca ggctccaggg 900

aaggggctgg agtggatcgg agtcattact ggtcgtgata tcacatacta cgcgagctgg 960

gcgaaaggca gattcaccat ctccagagac aattccaaga acacgctgta tcttcaaatg 1020

aacagcctga gagccgagga cacggctgtg tattactgtg cgcgcgacgg tggatcatct 1080

gctattacta gtaacaacat ttggggccaa ggaactctgg tcaccgtttc ttcagctagc 1140

accaagggcc catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca 1200

gcggccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac 1260

tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc 1320

tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc 1380

tgcaacgtga atcacaagcc cagcaacacc aaggtggaca agagagttga gcccaaatct 1440

tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg aagccgcggg ggcaccgtca 1500

gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc 1560

acatgcgtgg tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg 1620

gacggcgtgg aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg 1680

taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac 1740

aagtgcgcgg tctccaacaa agccctccca gcccccatcg agaaaaccat ctccaaagcc 1800

aaagggcagc cccgagaacc acaggtgtat accctgcccc catcccggga tgagctgacc 1860

aagaaccagg tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg 1920

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac 1980

tccgacggct ccttcttcct ctatagcaag ctcaccgtgg acaagagcag gtggcagcag 2040

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag 2100

agcctctccc tgtctccggg tggcggtgga gggtccggcg gtggtggatc cgaggtgcag 2160

ctgttggagt ctgggggagg cttggtacag cctgggggggt ccctgagact ctcctgtgca 2220

gcctctggat tctccttcag tagcgggtac gacatgtgct gggtccgcca ggctccaggg 2280

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aaggggctgg agtggatcgc atgcattgct gctggtagtg ctggtatcac ttacgacgcg 2340

aactgggcga aaggccggtt caccatctcc agagacaatt ccaagaacac gctgtatctg 2400

caaatgaaca gcctgagagc cgaggacacg gccgtatatt actgtgcgag atcggcgttt 2460

tcgttcgact acgccatgga cctctggggc cagggaaccc tggtcaccgt ctcgagcggt 2520

ggaggcggat ctggcggagg tggttccggc ggtggcggct ccggtggagg cggctctgac 2580

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acttgccagg ccagtcagag cattagttcc cacttaaact ggtatcagca gaaaccaggg 2700

aaagccccta agctcctgat ctataaggca tccactctgg catctggggt cccatcaagg 2760

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gattttgcaa cttattactg ccaacagggt tatagttggg gtaatgttga taatgttttc 2880

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tcgctggtgg agtctggggg aggcttggtc cagcctgggg ggtccctgag actctcctgt 3000

acagcctctg gattcaccat cagtagctac cacatgcagt gggtccgcca ggctccaggg 3060

aaggggctgg agtacatcgg aaccattagt agtggtggta atgtatacta cgcgagctcc 3120

gcgagaggca gattcaccat ctccagaccc tcgtccaaga acacggtgga tcttcaaatg 3180

aacagcctga gagccgagga cacggctgtg tattactgtg cgagagactc tggttatagt 3240

gatcctatgt ggggccaggg aaccctggtc accgtctcga gcggcggtgg cggtagtggg 3300

ggaggcggtt ctggcggcgg agggtccggc ggtggaggat cagacgttgt gatgacccag 3360

tctccatctt ccgtgtctgc atctgtagga gacagagtca ccatcacctg tcaggccagt 3420

cagaacatta ggacttactt atcctggtat cagcagaaac cagggaaagc ccctaagctc 3480

ctgatctatg ctgcagccaa tctggcatct ggggtcccat caaggttcag cggcagtgga 3540

tctgggacag atttcactct caccatcagc gacctggagc ctggcgatgc tgcaacttac 3600

tattgtcagt ctacctatct tggtactgat tatgttggcg gtgctttcgg cggagggacc 3660

aaggtggaga tcaaa 3675

<210> SEQ ID NO 92
<211> LENGTH: 1225
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 92

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
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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 Phe Asn Ser Tyr Pro Phe
85 90 95

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Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
    130                 135                 140

Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Ser Ser Trp
145                 150                 155                 160

Ile Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met Gly
                165                 170                 175

Ile Ile Tyr Pro Asp Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
            180                 185                 190

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Arg Thr Ala Tyr Leu
        195                 200                 205

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
    210                 215                 220

Arg His Val Thr Met Ile Trp Gly Val Ile Ile Asp Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
                245                 250                 255

Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
            260                 265                 270

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser
        275                 280                 285

Thr Asn Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    290                 295                 300

Trp Ile Gly Val Ile Thr Gly Arg Asp Ile Thr Tyr Tyr Ala Ser Trp
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Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
                325                 330                 335

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
            340                 345                 350

Cys Ala Arg Asp Gly Gly Ser Ser Ala Ile Thr Ser Asn Asn Ile Trp
        355                 360                 365

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
    370                 375                 380

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
385                 390                 395                 400

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                405                 410                 415

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            420                 425                 430

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        435                 440                 445

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
    450                 455                 460

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
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Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
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Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
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His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
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Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
545                 550                 555                 560

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                565                 570                 575

Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
            580                 585                 590

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        595                 600                 605

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
    610                 615                 620

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
625                 630                 635                 640

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                645                 650                 655

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            660                 665                 670

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        675                 680                 685

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    690                 695                 700

Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln
705                 710                 715                 720

Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg
                725                 730                 735

Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Gly Tyr Asp Met
            740                 745                 750

Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Ala Cys
        755                 760                 765

Ile Ala Ala Gly Ser Ala Gly Ile Thr Tyr Asp Ala Asn Trp Ala Lys
    770                 775                 780

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
785                 790                 795                 800

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                805                 810                 815

Arg Ser Ala Phe Ser Phe Asp Tyr Ala Met Asp Leu Trp Gly Gln Gly
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Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
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Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
    850                 855                 860

Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
865                 870                 875                 880

Thr Cys Gln Ala Ser Gln Ser Ile Ser Ser His Leu Asn Trp Tyr Gln
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Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Thr
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Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr
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Tyr Tyr Cys Gln Gln Gly Tyr Ser Trp Gly Asn Val Asp Asn Val Phe
945                 950                 955                 960

Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly
                965                 970                 975

Gly Gly Ser Arg Ser Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
            980                 985                 990

Gly Gly Ser Leu Arg Leu Ser Cys  Thr Ala Ser Gly Phe  Thr Ile Ser
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Ser Tyr  His Met Gln Trp Val  Arg Gln Ala Pro Gly  Lys Gly Leu
    1010                1015                1020

Glu Tyr  Ile Gly Thr Ile Ser  Ser Gly Gly Asn Val  Tyr Tyr Ala
    1025                1030                1035

Ser Ser  Ala Arg Gly Arg Phe  Thr Ile Ser Arg Pro  Ser Ser Lys
    1040                1045                1050

Asn Thr  Val Asp Leu Gln Met  Asn Ser Leu Arg Ala  Glu Asp Thr
    1055                1060                1065

Ala Val  Tyr Tyr Cys Ala Arg  Asp Ser Gly Tyr Ser  Asp Pro Met
    1070                1075                1080

Trp Gly  Gln Gly Thr Leu Val  Thr Val Ser Ser Gly  Gly Gly Gly
    1085                1090                1095

Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Gly
    1100                1105                1110

Ser Asp  Val Val Met Thr Gln  Ser Pro Ser Ser Val  Ser Ala Ser
    1115                1120                1125

Val Gly  Asp Arg Val Thr Ile  Thr Cys Gln Ala Ser  Gln Asn Ile
    1130                1135                1140

Arg Thr  Tyr Leu Ser Trp Tyr  Gln Gln Lys Pro Gly  Lys Ala Pro
    1145                1150                1155

Lys Leu  Leu Ile Tyr Ala Ala  Ala Asn Leu Ala Ser  Gly Val Pro
    1160                1165                1170

Ser Arg  Phe Ser Gly Ser Gly  Ser Gly Thr Asp Phe  Thr Leu Thr
    1175                1180                1185

Ile Ser  Asp Leu Glu Pro Gly  Asp Ala Ala Thr Tyr  Tyr Cys Gln
    1190                1195                1200

Ser Thr  Tyr Leu Gly Thr Asp  Tyr Val Gly Gly Ala  Phe Gly Gly
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Gly Thr  Lys Val Glu Ile Lys
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gggaaagccc ctaagctcct gatctatgaa gcatccaaac tggcatctgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaaggc tatttttatt ttattagtcg tacttatgta 300

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ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

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35 40 45

Tyr Glu Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Tyr Phe Tyr Phe Ile Ser
85 90 95

Arg Thr Tyr Val Asn Ser Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

What we claim is:

1. A method for generating a therapeutic composition, comprising

providing a cell material comprising a cytotoxic cell,

incubating the cell material with a first GNC protein to provide an activated cell composition, wherein the activated cell composition comprises a first therapeutic cell,

wherein the first GNC protein comprising a first cytotoxic binding moiety and a first cancer targeting moiety, wherein the first cytotoxic binding moiety has a specificity to a first cytotoxic cell receptor and is configured to activate the first cytotoxic cell through the binding with the first cytotoxic cell receptor, and wherein the first cancer targeting moiety has a specificity to a first cancer cell receptor, and

wherein the first therapeutic cell comprises the first GNC protein bound to the cytotoxic cell through the binding interaction with the first cytotoxic cell receptor, and

formulating the activated cell composition to provide a therapeutic composition, wherein the therapeutic composition is substantially free of exogenous viral and non-viral DNA or RNA.

2. The method of claim 1, wherein the incubating step is repeated by incubating a second GNC protein with the activated cell composition,

wherein the second GNC protein comprising a second cytotoxic binding moiety and a second cancer targeting moiety, wherein the second cytotoxic binding moiety has a specificity to a second cytotoxic cell receptor, and wherein the second cancer targeting moiety has a specificity to a second cancer cell receptor,

wherein the activated cell composition further comprises a second therapeutic cell, and

wherein the second therapeutic cell comprises the second GNC protein bound to the cytotoxic cell or the first therapeutic cell through the binding interaction with the second cytotoxic cell receptor.

3. The method of claim 2, wherein the second GNC protein is the same as the first GNC protein.

4. The method of claim 2, wherein the second GNC protein is different from the first GNC protein.

5. The method of claim 1, wherein the first or the second cancer targeting moiety has the specificity against B cell, and wherein the therapeutic composition is substantially free of B cell.

6. The method of claim 1, wherein the cytotoxic cell receptor comprises a T-cell receptor, a NK cell receptor, a macrophage receptor, a dendritic cell receptor, or a combination thereof.

7. The method of claim 1, wherein the molar to cell ratio between the first GNC protein and the cytotoxic cell is at least 30 to 1 when incubating the cell material with the first GNC protein.

8. The method of claim 1, wherein the therapeutic composition comprises at least 10^6 cells per ml.

9. The method of claim 1, wherein the therapeutic composition comprises the first therapeutic cell, the first GNC protein, the cytotoxic cell, or a combination thereof.

10. The method of claim 2, wherein the therapeutic composition comprises the second therapeutic cell, the second GNC protein, comprises the first therapeutic cell, the first GNC protein, the cytotoxic cell, or a combination thereof.

11. The method of claim 1, wherein the cell material comprises PBMC.

12. The method of claim 1, wherein the first and the second cancer-targeting moiety independently has a specificity for CD19, PDL1, or a combination thereof.

13. The method of claim 1, wherein the first and the second cytotoxic binding moiety independently has a specificity for CD3, PDL1, 41BB, or a combination thereof.

14. A method of treating a subject having a cancer, comprising

providing a cell material comprising a cytotoxic cell,

incubating the cell material with a first GNC protein to provide an activated cell composition, wherein the activated cell composition comprises a first therapeutic cell,

wherein the first GNC protein comprising a first cytotoxic binding moiety and a first cancer targeting moiety, wherein the first cytotoxic binding moiety has a specificity to a first cytotoxic cell receptor and is configured to activate the first cytotoxic cell through the binding with the first cytotoxic cell receptor, and wherein the first cancer targeting moiety has a specificity to a first cancer cell receptor, and

wherein the first therapeutic cell comprises the first GNC protein bound to the cytotoxic cell through the binding interaction with the first cytotoxic cell receptor, and

formulating the activated cell composition to provide a therapeutic composition, wherein the therapeutic composition is substantially free of exogenous viral and non-viral DNA or RNA, and

administering the therapeutic composition to the subject.

15. The method of claim 14, wherein the incubating step is repeated by incubating a second GNC protein with the activated cell composition,

wherein the second GNC protein comprising a second cytotoxic binding moiety and a second cancer targeting moiety, wherein the second cytotoxic binding moiety has a specificity to a second cytotoxic cell receptor, and wherein the second cancer targeting moiety has a specificity to a second cancer cell receptor,

wherein the activated cell composition further comprises a second therapeutic cell, and

wherein the second therapeutic cell comprises the second GNC protein bound to the cytotoxic cell or the first therapeutic cell through the binding interaction with the second cytotoxic cell receptor.

16. The method of claim 14, wherein the second GNC protein is the same as the first GNC protein.

17. The method of claim 14, wherein the second GNC protein is different from the first GNC protein.

18. The method of claim 14, wherein the first or the second cancer targeting moiety has the specificity against B cell, and wherein the therapeutic composition is substantially free of B cell.

19. The method of claim 14, further comprising isolating the cytotoxic cell from peripheral blood mononuclear cells (PBMC) before providing the cell material.

20. The method of claim 19, further comprising isolating the peripheral blood mononuclear cells (PBMC) from a blood.

21-22. (canceled)

23. The method of claim **14**, further comprising administering an additional GNC protein to the subject after the administering the therapeutic composition to the subject.

24. The method of claim **14**, wherein the cytotoxic cell comprises T cell, NK cell, or a combination thereof.

25. The method of claim **19**, wherein the isolating the cytotoxic cell comprising isolating at least one subpopulation of cytotoxic cell to provide therapeutic T cells, wherein the subpopulation of cytotoxic cell comprises CD3+ cells, CD4+ cells, CD8+ cells, CD56+ cells, CD28+ cells, CD69+ cells, CD107a+ cells, CD45RA+ cells, CD45RO+ cells, γδ TCR+ cells, αβ TCR+ cells, CD25+ cells, $CD127^{lo/-}$ cells, CCR7+ cells, PD-1+ cells or a combination thereof.

26. (canceled)

27. The method of claim **14**, further comprising evaluating therapeutic efficacy after the administering step, wherein the evaluating therapeutic efficacy comprises checking one or more biomarkers of the cancer, monitoring the life span of the therapeutic cells, or a combination thereof.

28-29. (canceled)

30. The method of claim **14**, wherein the subject is a human.

31. The method of claim **14**, wherein the cancer comprises cells expressing ROR1, CEA, HER2, EGFR, EGFR VIII, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2, BCMA, CD19, CD20, CD33, CD123, CD22, CD30, or a combination thereof.

32. (canceled)

33. The method of claim **14**, wherein the cancer is CD19 positive.

34. The method of claim **14**, further comprising administering an effective amount of a therapeutic agent after the administering the therapeutic composition to the subject.

35. The method of claim **34**, wherein the therapeutic agent comprises a monoclonal antibody, a multi-specific antibody, a chemotherapy agent, an enzyme, a protein, a co-stimulator, an apoptosis sensitizer, a tumor vascular disruptor, or a combination thereof, wherein the co-stimulator is configured to increase the amount of cytotoxic T cells in the subject.

36-39. (canceled)

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