US 20230110875A1

(19) **United States**

(12) **Patent Application Publication**

Orentas et al.

(10) **Pub. No.: US 2023/0110875 A1**

(43) **Pub. Date: Apr. 13, 2023**

(54) **ANTI-CD276 POLYPEPTIDES, PROTEINS, AND CHIMERIC ANTIGEN RECEPTORS**

(71) Applicants: **The United States of America, as Presented by the Secretary, Department of Health**, Bethesda, MD (US); **BIOMED VALLEY DISCOVERIES, INC.**, Kansas City, MO (US)

(72) Inventors: **Rimas J. Orentas**, Chevy Chase, MD (US); **Zhongyu Zhu**, Frederick, MD (US); **Crystal L. Mackall**, Bethesda, MD (US); **Dimiter S. Dimitrov**, Frederick, MD (US); **Bradley St. Croix**, Frederick, MD (US); **Saurabh Saha**, Leawood, KS (US)

(21) Appl. No.: **18/049,470**

(22) Filed: **Oct. 25, 2022**

Related U.S. Application Data

(63) Continuation of application No. 16/823,218, filed on Mar. 18, 2020, now Pat. No. 11,512,138, which is a continuation of application No. 15/699,419, filed on Sep. 8, 2017, now Pat. No. 10,604,583, which is a continuation of application No. 14/779,586, filed on Sep. 24, 2015, now Pat. No. 9,790,282, filed as application No. PCT/US2014/031543 on Mar. 24, 2014.

(60) Provisional application No. 61/805,001, filed on Mar. 25, 2013.

Publication Classification

(51) **Int. Cl.**

C07K 16/30	(2006.01)
C07K 16/28	(2006.01)
G01N 33/574	(2006.01)

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

CPC ***C07K 16/30*** (2013.01); ***C07K 16/2827*** (2013.01); ***G01N 33/57492*** (2013.01); *C07K 2319/00* (2013.01); *C07K 2317/21* (2013.01); *C07K 2317/33* (2013.01); *C07K 2317/622* (2013.01); *C07K 2317/73* (2013.01); *C07K 2317/92* (2013.01)

(57) **ABSTRACT**

Polypeptides and proteins that specifically bind to and immunologically recognize CD276 are disclosed. Chimeric antigen receptors (CARs), anti-CD276 binding moieties, nucleic acids, recombinant expression vectors, host cells, populations of cells, and pharmaceutical compositions relating to the polypeptides and proteins are also disclosed. Methods of detecting the presence of cancer in a mammal and methods of treating or preventing cancer in a mammal are also disclosed.

Specification includes a Sequence Listing.

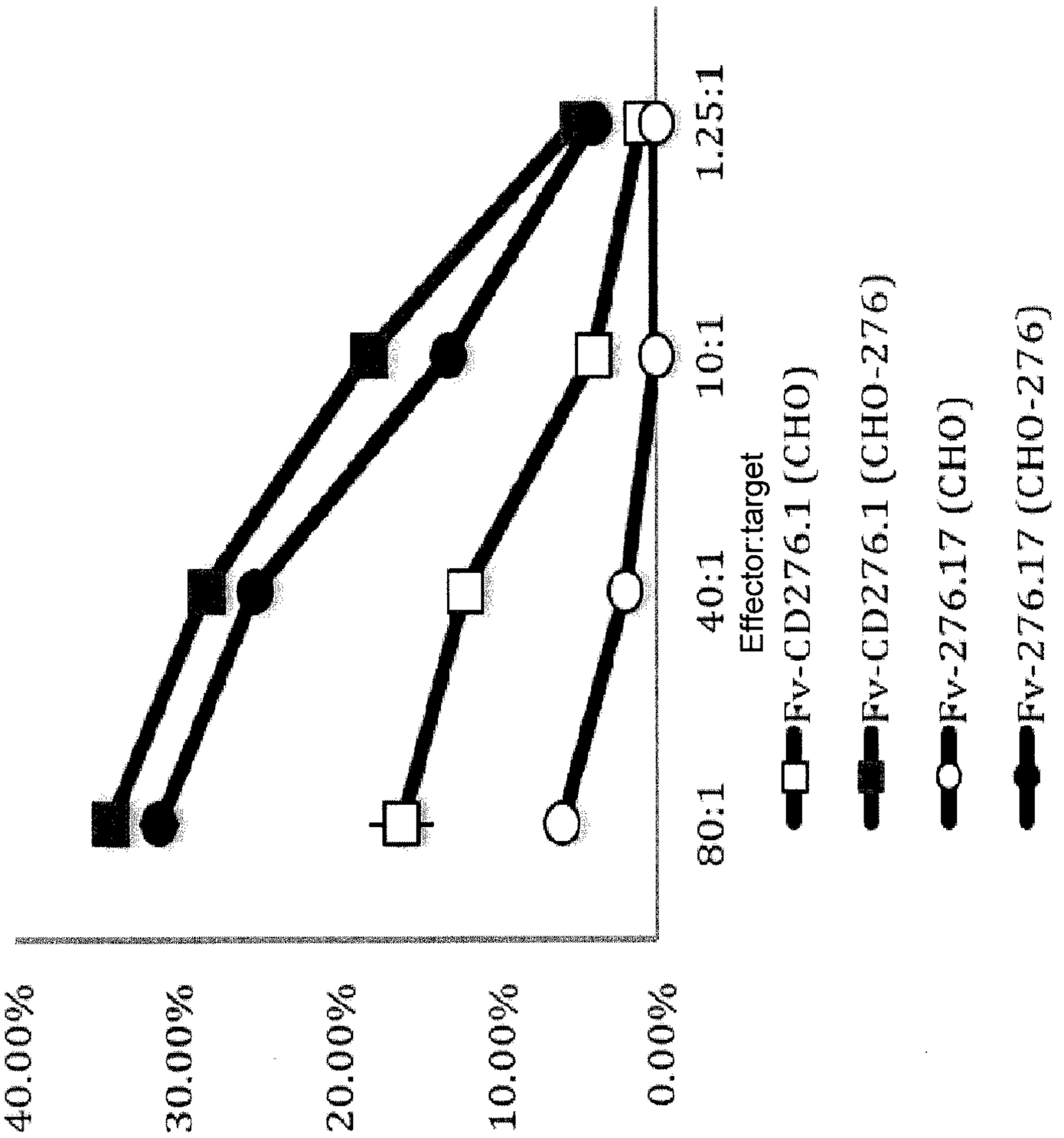
% Lysis
40.00%
30.00%
20.00%
10.00%
0.00%
80:1
40:1
10:1
1.25:1
Effector:target
Fv-CD276.1 (CHO)
Fv-CD276.1 (CHO-276)
Fv-276.17 (CHO)
Fv-276.17 (CHO-276)

FIG. 1

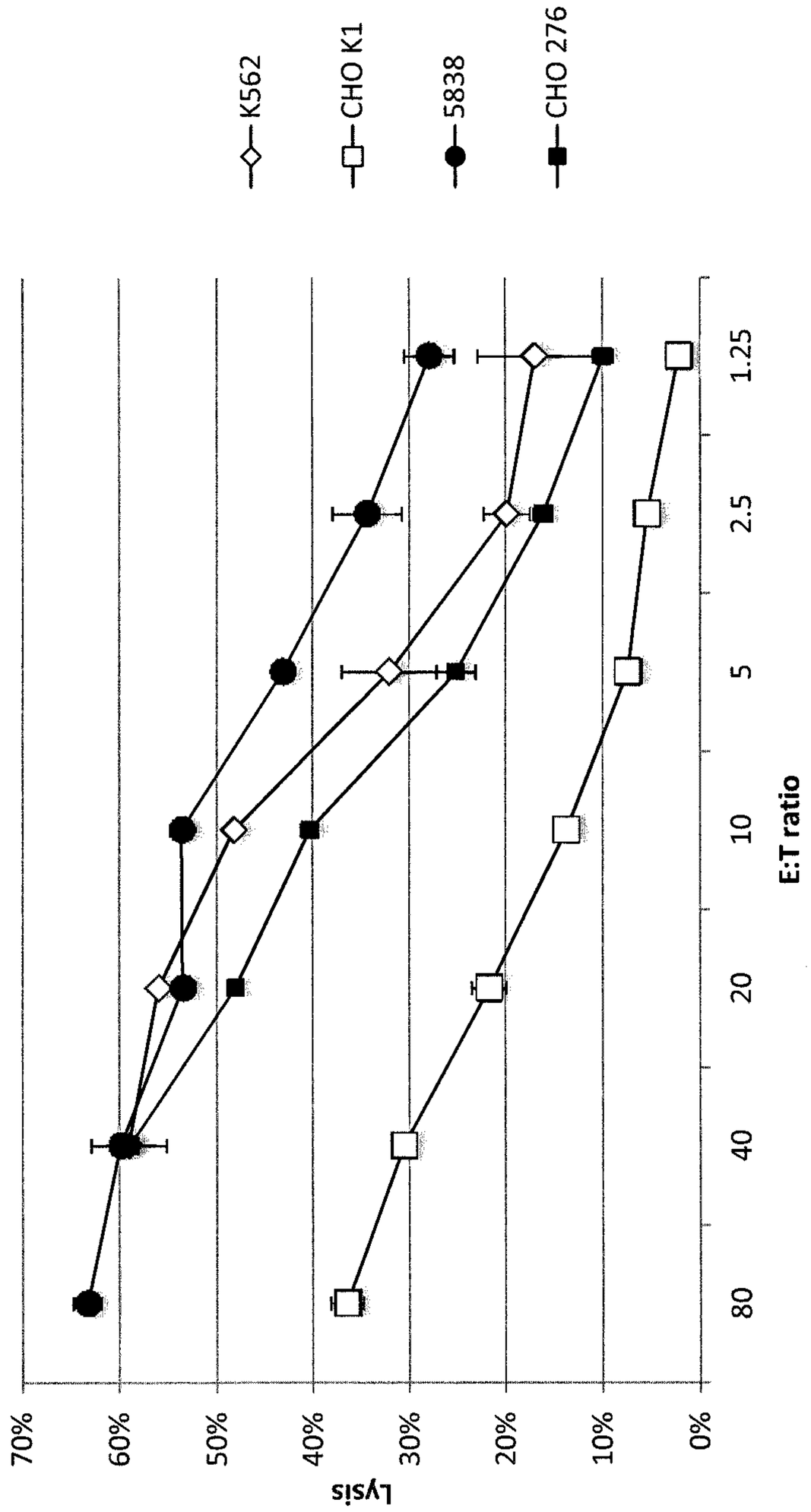
K562
CHO K1
5838
CHO 276
CD276.1
Lysis
70%
60%
50%
40%
30%
20%
10%
0%
E:T ratio
80
40
20
10
5
2.5
1.25

FIG. 2

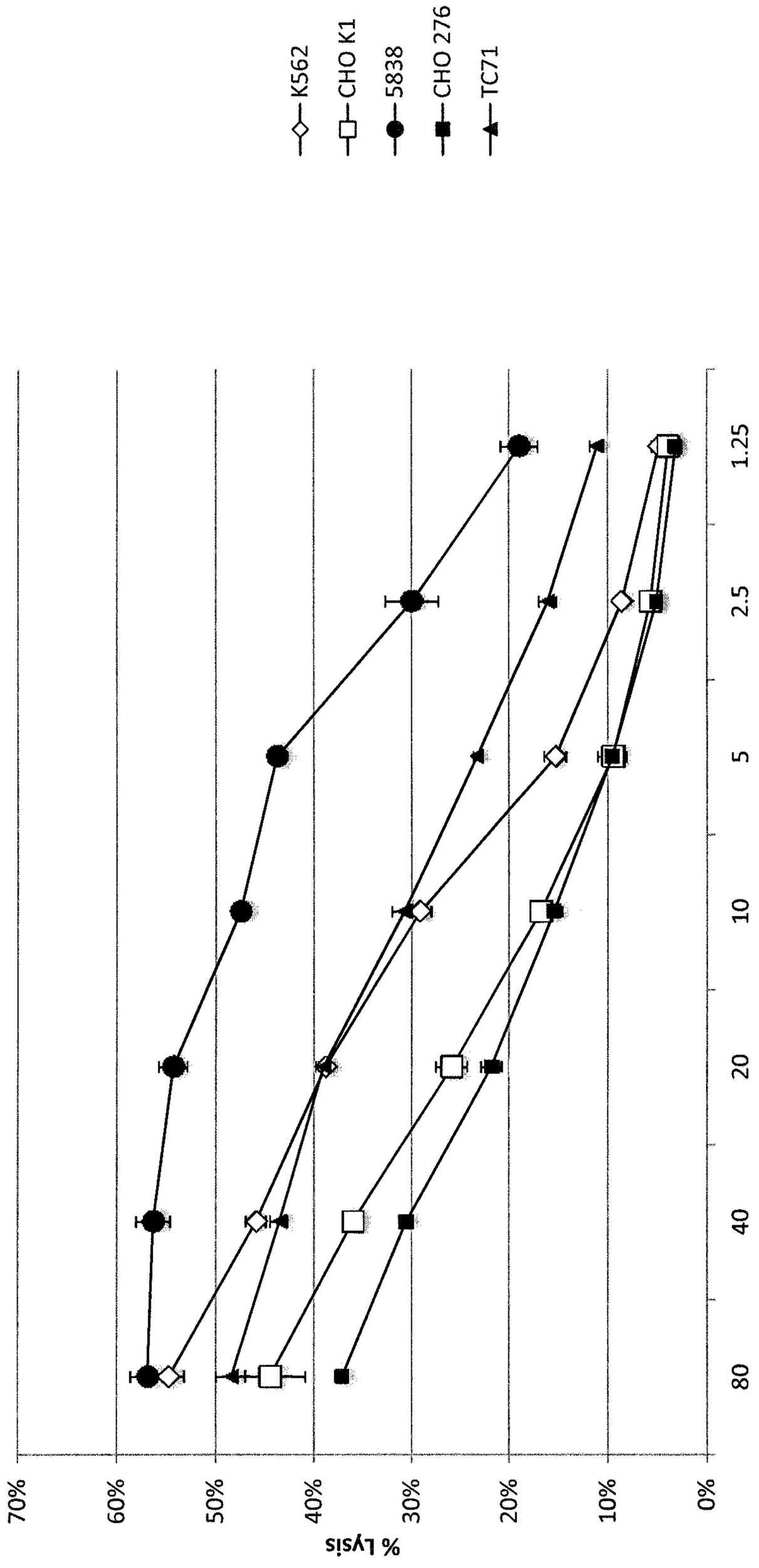
K562
CHO K1
5838
CHO 276
TC71
CD276.6
% Lysis
70%
60%
50%
40%
30%
20%
10%
0%
E:T Ratio
1.25
2.5
5
10
20
40
80

FIG. 3

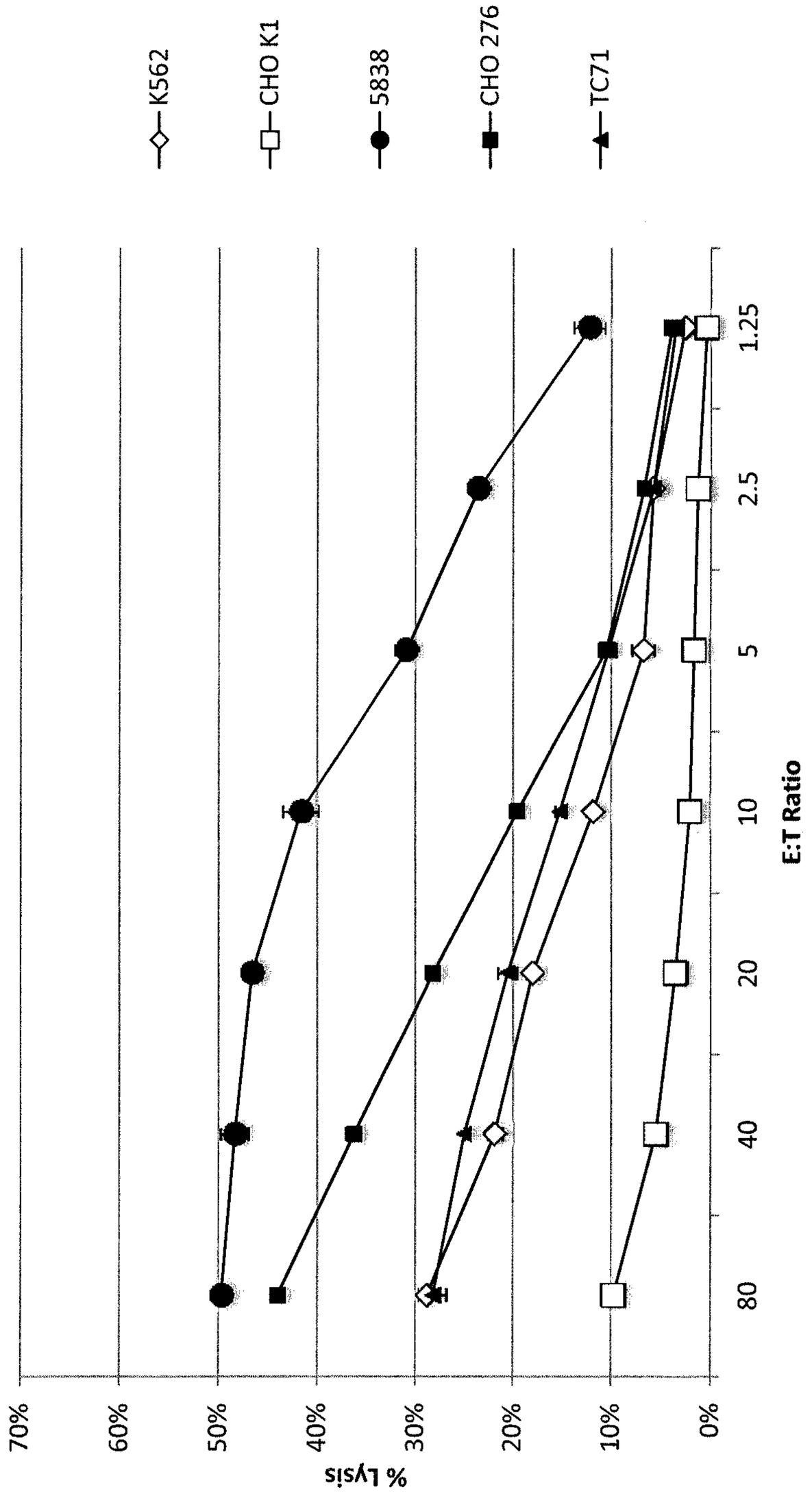
K562
CHO K1
5838
CHO 276
TC71
CD276.17
% Lysis
70%
60%
50%
40%
30%
20%
10%
0%
E:T Ratio
1.25
2.5
5
10
20
40
80

FIG. 4

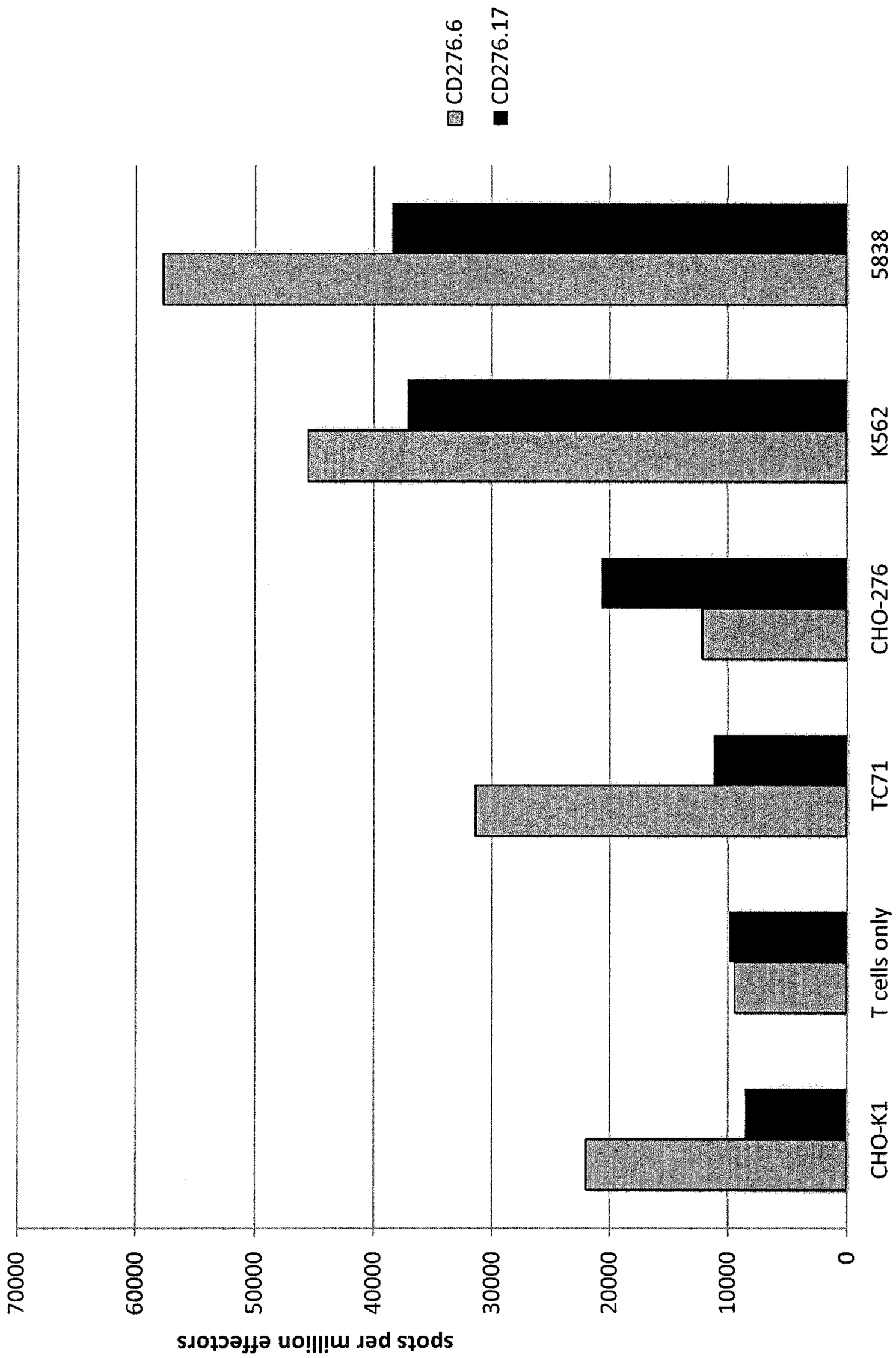
CD276.6
CD276.17
5838
K562
CHO-276
TC71
T cells only
CHO-K1
Target Cell Lnes
spots per million effectors
70000
60000
50000
40000
30000
20000
10000
0

FIG. 5

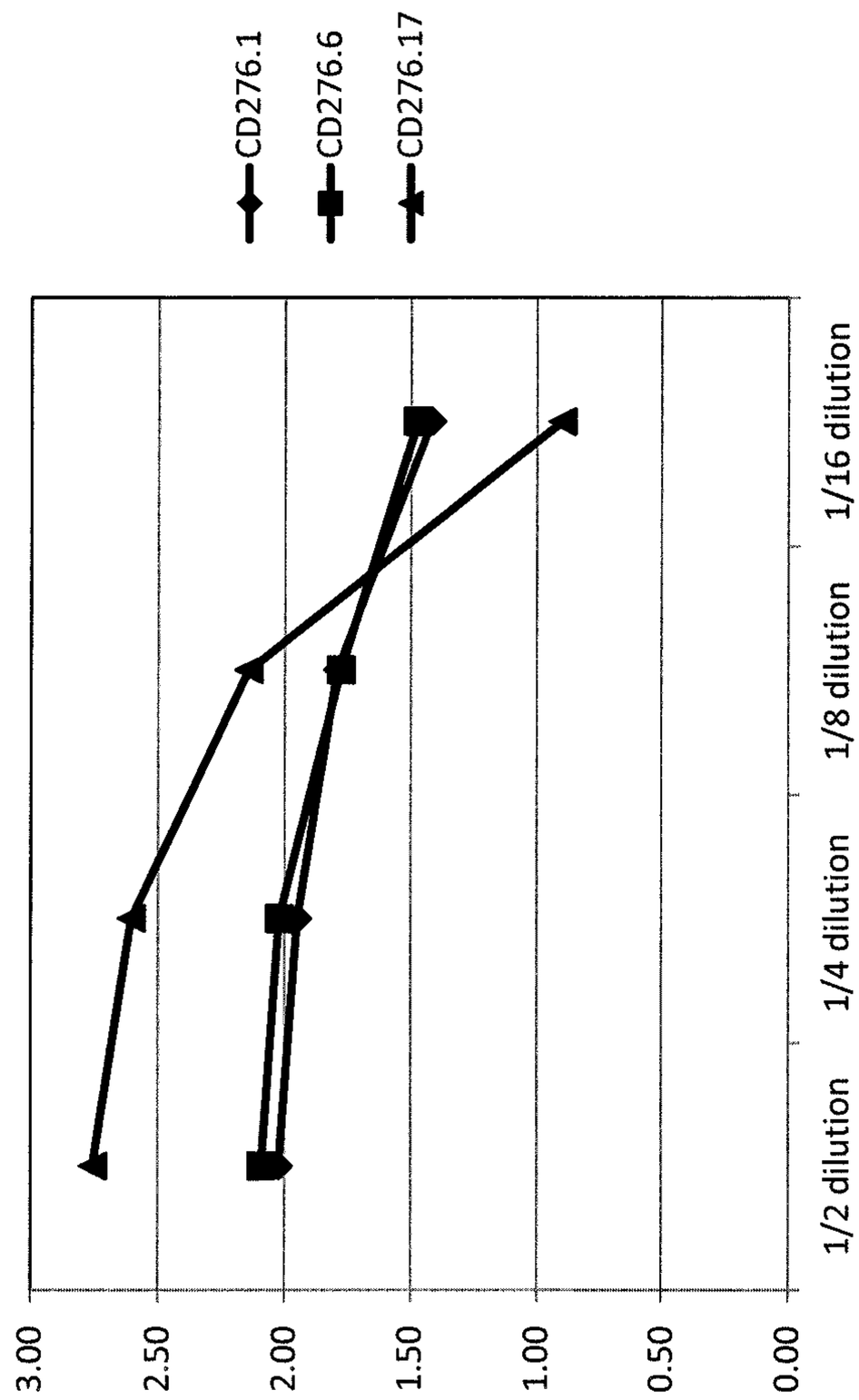
CD276.1
CD276.6
CD276.17
3.00
2.50
2.00
1.50
1.00
0.50
0.00
1/2 dilution
1/4 dilution
1/8 dilution
1/16 dilution
Culture medium antibody dilutions

FIG. 6

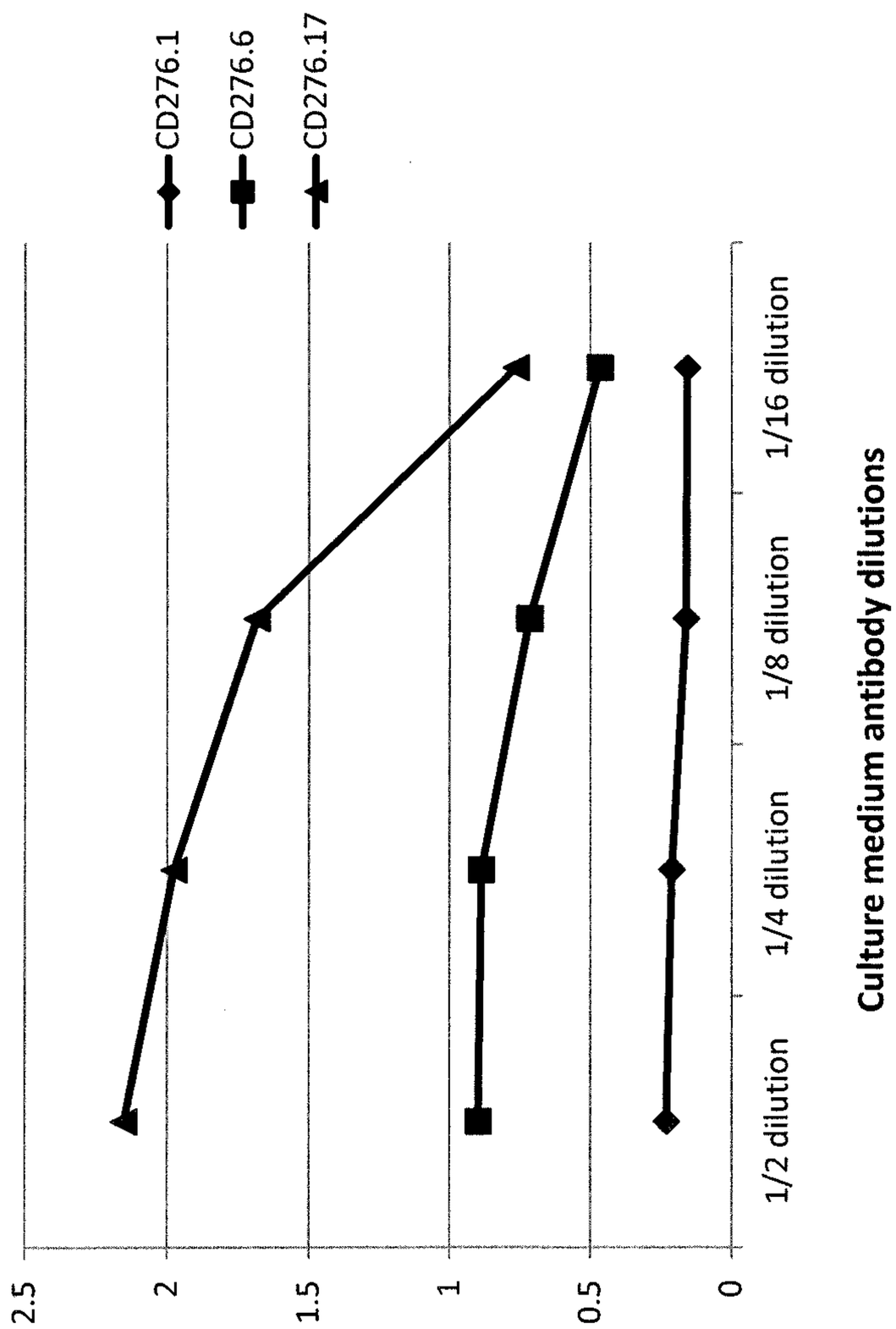
CD276.1
CD276.6
CD276.17
1/2 dilution
1/4 dilution
1/8 dilution
1/16 dilution
Culture medium antibody dilutions
2.5
2
1.5
1
0.5
0
OD Reading at 450nm

FIG. 7

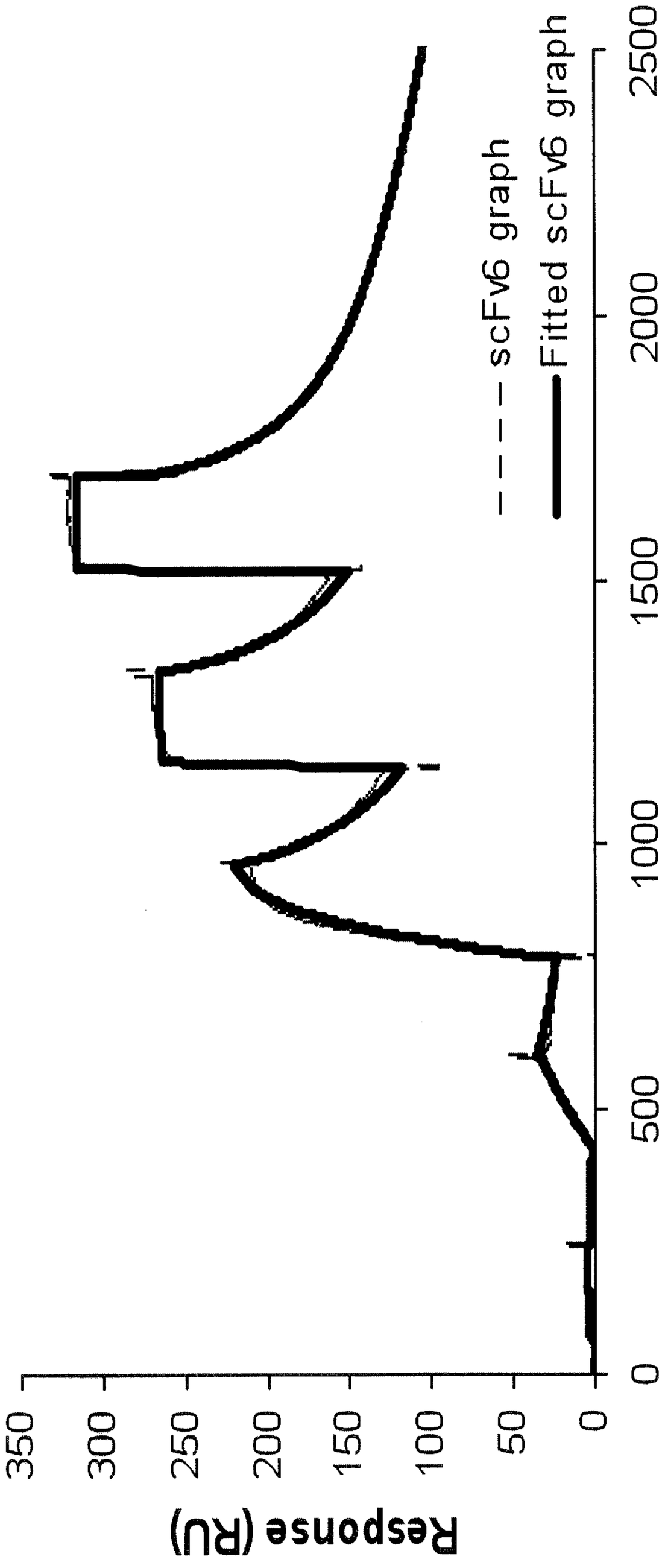
Response (RU)
350
300
250
200
150
100
50
0
Time (S)
0
500
1000
1500
2000
2500
Fitted scFv6 graph
scFv6 graph

FIG. 8

ANTI-CD276 POLYPEPTIDES, PROTEINS, AND CHIMERIC ANTIGEN RECEPTORS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 61/805,001, filed Mar. 25, 2013, which is incorporated by reference herein in its entirety.

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: one 210,944 Byte ASCII (Text) file named "716393_ST25.txt," dated Mar. 17, 2014.

BACKGROUND OF THE INVENTION

[0003] Cancer is a public health concern. Despite advances in treatments such as chemotherapy, the prognosis for many cancers, including solid tumors, may be poor. It is estimated that about 559,650 Americans will die from cancer, corresponding to 1,500 deaths per day (Jemal et al., *CA Cancer J Clin.,* 57:43-66 (2007)). Accordingly, there exists an unmet need for additional treatments for cancer, particularly solid tumors.

BRIEF SUMMARY OF THE INVENTION

[0004] An embodiment of the invention provides a polypeptide comprising (i) SEQ ID NOs: 1-6, (ii) SEQ ID NOs: 11-16, or (iii) SEQ ID NOs: 20-25.

[0005] Another embodiment of the invention provides a protein comprising a first polypeptide chain comprising (i) SEQ ID NOs: 1-3, (ii) SEQ ID NOs: 11-13, or (iii) SEQ ID NOs: 20-22 and a second polypeptide chain comprising (i) SEQ ID NOs: 4-6, (ii) SEQ ID NOs: 14-16, or (iii) SEQ ID NOs: 23-25.

[0006] Further embodiments of the invention provide related chimeric antigen receptors (CARs), anti-CD276 binding moieties, nucleic acids, recombinant expression vectors, host cells, populations of cells, conjugates, and pharmaceutical compositions relating to the polypeptides and proteins of the invention.

[0007] Additional embodiments of the invention provide methods of detecting the presence of cancer in a mammal and methods of treating or preventing cancer in a mammal.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0008] FIG. **1** is a graph showing percent lysis of target ^{51}Cr labeled CHO or CHO-276 cells by effector human T cells transduced with a nucleotide sequence encoding a CAR comprising SEQ ID NO: 42 (CD276.1 second generation, version 1) or a CAR comprising SEQ ID NO: 45 (CD276.17 second generation, version 1) at various effector to target ratio (E:T) ratios. Open squares represent percent lysis of target CHO cells co-cultured with cells expressing SEQ ID NO: 42 (CD276.1 second generation, version 1), closed squares represent percent lysis of target CHO-276 cells co-cultured with cells expressing SEQ ID NO: 42 (CD276.1 second generation, version 1), open circles represent percent lysis of target CHO cells co-cultured with cells expressing SEQ ID NO: 45 (CD276.17 second generation, version 1), and closed circles represent percent lysis of target CHO-276 cells co-cultured with cells expressing SEQ ID NO: 45 (CD276.17 second generation, version 1) at the indicated effector to target ratio (E:T) ratios.

[0009] FIG. **2** is a graph showing percent lysis of target cells CHO K1 (open squares), 5838 (closed circles), CHO 276 (closed squares), or K562 (diamonds) by effector human cells transduced with a nucleotide sequence encoding a CAR comprising SEQ ID NO: 42 (CD276.1 second generation, version 1) at the indicated effector to target ratios.

[0010] FIG. **3** is a graph showing percent lysis of target cells CHO K1 (open squares), 5838 (closed circles), CHO 276 (closed squares), K562 (diamonds), or TC71 (triangles) by effector human cells transduced with a nucleotide sequence encoding a CAR comprising SEQ ID NO: 39 (CD276.6 second generation, version 1) at the indicated effector to target ratios.

[0011] FIG. **4** is a graph showing percent lysis of target cells CHO K1 (open squares), 5838 (closed circles), CHO 276 (closed squares), K562 (diamonds), or TC71 (triangles) by effector human cells transduced with a nucleotide sequence encoding a CAR comprising SEQ ID NO: 45 (CD276.17 second generation, version 1) at the indicated effector to target ratios.

[0012] FIG. **5** is a graph showing the number of spots measured by interferon (IFN)-gamma ELISPOT assay per million effector T cells cultured alone (T cells only) or co-cultured with CHO-K1, TC71, CHO-276, K562, or 5838 cells. The effector T cells were transduced with a nucleotide sequence encoding a CAR comprising SEQ ID NO: 39 (CD276.6 second generation, version 1) (grey bars) or SEQ ID NO: 45 (CD276.17 second generation, version 1) (black bars).

[0013] FIGS. **6** and **7** are graphs showing the optical density (OD) reading at 450 nm as measured in an ELISA binding assay for scFv-Fc fusion proteins comprising heavy and light chain amino acid sequences as follows: (1) Clone CD276.1 (m851) (comprising a heavy chain comprising SEQ ID NO: 17 and a light chain comprising SEQ ID NO: 18) (diamonds), (2) Clone CD276.6 (m856) (comprising a heavy chain comprising SEQ ID NO: 7 and a light chain comprising SEQ ID NO: 8) (squares), or (3) Clone CD276.17 (m8517) (comprising a heavy chain comprising SEQ ID NO: 26 and a light chain comprising SEQ ID NO: 27) (triangles), incubated with human (FIG. **6**) or mouse (FIG. **7**) CD276 at the dilutions indicated.

[0014] FIG. **8** is a graph showing the binding affinity (response, (RU)) of Clone CD276.6 (m856) (comprising a heavy chain comprising SEQ ID NO: 7 and a light chain comprising SEQ ID NO: 8) to human CD276 over time (s) as measured by surface plasmon resonance at $KD=1.3\times10^{-9}$ M. The dotted line corresponds to the raw data and the solid line corresponds to the line generated by the software when the fitting was performed to calculate the KD.

DETAILED DESCRIPTION OF THE INVENTION

[0015] An embodiment of the invention provides polypeptides and proteins comprising an antigen binding domain of an anti-CD276 antibody. The polypeptides and proteins advantageously specifically recognize and bind to CD276 (also known as B7-H3). CD276 is expressed or overex-

pressed on a variety of human tumors, including pediatric solid tumors and adult carcinomas. Examples of cancers that express or overexpress CD276 include, but are not limited to, neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma, and prostate, ovarian, colorectal, and lung cancers. Without being bound to a particular theory or mechanism, it is believed that by specifically recognizing and binding to CD276, the inventive polypeptides and proteins may, advantageously, target CD276-expressing cancer cells. In an embodiment of the invention, the inventive polypeptides and proteins may elicit an antigen-specific response against CD276. Accordingly, without being bound to a particular theory or mechanism, it is believed that by eliciting an antigen-specific response against CD276, the inventive proteins and polypeptides may provide for one or more of the following: targeting and destroying CD276-expressing cancer cells, reducing or eliminating cancer cells, facilitating infiltration of immune cells and/or effector molecules to tumor site(s), and enhancing/extending anti-cancer responses.

[0016] The term. "polypeptide" as used herein includes oligopeptides and refers to a single chain of amino acids connected by one or more peptide bonds. The polypeptide may comprise one or more variable regions (e.g., two variable regions) of an antigen binding domain of an anti-CD276 antibody, each variable region comprising a complementarity determining region (CDR) 1, a CDR2, and a CDR3. Preferably, a first variable region comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1, 11, or 20 (CDR1 of first variable region), a CDR2 comprising the amino acid sequence of SEQ ID NO: 2, 12, or 21 (CDR2 of first variable region), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 3, 13, or 22 (CDR3 of first variable region), and the second variable region comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 4, 14, or 23 (CDR1 of second variable region), a CDR2 comprising the amino acid sequence of SEQ ID NO: 5, 15, or 24 (CDR2 of second variable region), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 6, 16, or 25 (CDR3 of second variable region). In this regard, the inventive polypeptide can comprise SEQ ID NOs: 1-3, 4-6, 11-13, 14-16, 20-22, 23-25, 1-6, 11-16, or 20-25. Accordingly, an embodiment of the invention provides a polypeptide comprising (i) SEQ ID NOs: 1-6, (ii) SEQ ID NOs: 11-16, or (iii) SEQ ID NOs: 20-25. Preferably, the polypeptide comprises the amino acid sequences of SEQ ID NOs: 20-25.

[0017] In an embodiment, the polypeptides each comprise one or more variable regions (e.g., first and second variable regions) of an antigen binding domain of an anti-CD276 antibody, each comprising the CDRs as described above. The first variable region may comprise SEQ ID NO: 8, 18, or 27. The second variable region may comprise SEQ ID NO: 7, 17, or 26. Accordingly, in an embodiment of the invention, the polypeptide comprises SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NOs: 7 and 8, SEQ ID NOs: 17 and 18, or SEQ ID NOs: 26 and 27. Preferably, the polypeptide comprises SEQ ID NOs: 26 and 27.

[0018] In an embodiment of the invention, the variable regions of the polypeptide may be joined by a linker. The linker may comprise any suitable amino acid sequence. In an embodiment of the invention, the linker may comprise SEQ ID NO: 9 or 115.

[0019] In an embodiment of the invention, the polypeptide comprises two variable regions, each comprising the CDRs as described above, with a linker positioned between the two variable regions. In this regard, the polypeptide may comprise SEQ ID NOs: 10, 19, or 28.

[0020] In an embodiment, the polypeptide comprises a leader sequence. The leader sequence may be positioned at the amino terminus of the light chain variable region. The leader sequence may comprise any suitable leader sequence. In an embodiment, the leader sequence is a human granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor sequence. The leader sequence may comprise, for example, SEQ ID NO: 60, 61, or 62. In an embodiment of the invention, while the leader sequence may facilitate expression of the polypeptide on the surface of the cell, the presence of the leader sequence in an expressed polypeptide is not necessary in order for the polypeptide to function. In an embodiment of the invention, upon expression of the polypeptide on the cell surface, the leader sequence may be cleaved off of the polypeptide. Accordingly, in an embodiment of the invention, the polypeptide lacks a leader sequence.

[0021] The invention further provides a protein comprising at least one of the polypeptides described herein. By "protein" is meant a molecule comprising one or more polypeptide chains.

[0022] The protein of the invention can comprise a first polypeptide chain comprising the amino acid sequences of (i) SEQ ID NOs: 1-3, (ii) SEQ ID NOs: 11-13, or (iii) SEQ ID NOs: 20-22 and a second polypeptide chain comprising (i) SEQ ID NOs: 4-6, (ii) SEQ ID NOs: 14-16, or (iii) SEQ ID NOs: 23-25. The protein of the invention can, for example, comprise a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 7, 17, or 26 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 8, 18, or 27. In this regard, the protein may comprise a first polypeptide chain comprising SEQ ID NO: 7, 17, or 26 and a second polypeptide chain comprising SEQ ID NO: 8, 18, or 27.

[0023] The protein may further comprise a leader sequence and/or a linker as described herein with respect to other aspects of the invention. In an embodiment, the protein lacks a leader sequence.

[0024] The protein of the invention can be, for example, a fusion protein. If, for example, the protein comprises a single polypeptide chain comprising (i) SEQ ID NO: 7, 17, or 26 and (ii) SEQ ID NO: 8, 18, or 27, or if the first and/or second polypeptide chain(s) of the protein further comprise (s) other amino acid sequences, e.g., an amino acid sequence encoding an immunoglobulin or a portion thereof, then the inventive protein can be a fusion protein. In this regard, the invention also provides a fusion protein comprising at least one of the inventive polypeptides described herein along with at least one other polypeptide. The other polypeptide can exist as a separate polypeptide of the fusion protein, or can exist as a polypeptide, which is expressed in frame (in tandem) with one of the inventive polypeptides described herein. The other polypeptide can encode any peptidic or proteinaceous molecule, or a portion thereof, including, but not limited to an immunoglobulin, CD3, CD4, CD8, an MHC molecule, a CD1 molecule, e.g., CD1a, CD1b, CD1c, CD1d, etc.

[0025] The fusion protein can comprise one or more copies of the inventive polypeptide and/or one or more

copies of the other polypeptide. For instance, the fusion protein can comprise 1, 2, 3, 4, 5, or more, copies of the inventive polypeptide and/or of the other polypeptide. Suitable methods of making fusion proteins are known in the art, and include, for example, recombinant methods. See, for instance, Choi et al., *Mol. Biotechnol.* 31: 193-202 (2005).

[0026] It is contemplated that the polypeptides and proteins of the invention may be useful as anti-CD276 binding moieties. In this regard, an embodiment of the invention provides an anti-CD276 binding moiety comprising any of the polypeptides or proteins described herein. In an embodiment of the invention, the anti-CD276 binding moiety comprises an antigen binding portion of any of the polypeptides or proteins described herein. The antigen binding portion can be any portion that has at least one antigen binding site. In an embodiment, the anti-CD276 binding moiety is a Fab fragment (Fab), $F(ab')_2$ fragment, diabody, triabody, tetrabody, single-chain variable region fragment (scFv), or disulfide-stabilized variable region fragment (dsFv).

[0027] In an embodiment, the anti-CD276 binding moiety can be an antibody. The antibody may be, for example, a recombinant antibody comprising at least one of the inventive polypeptides described herein. As used herein, "recombinant antibody" refers to a recombinant (e.g., genetically engineered) protein comprising at least one of the polypeptides or proteins of the invention and one or more polypeptide chains of an antibody, or a portion thereof. The polypeptide of an antibody, or portion thereof, can be, for example, a constant region of a heavy or light chain, or an Fe fragment of an antibody, etc. The polypeptide chain of an antibody, or portion thereof, can exist as a separate polypeptide of the recombinant antibody. Alternatively, the polypeptide chain of an antibody, or portion thereof, can exist as a polypeptide, which is expressed in frame (in tandem) with the polypeptide or protein of the invention. The polypeptide of an antibody, or portion thereof, can be a polypeptide of any antibody or any antibody fragment.

[0028] The antibody of the invention can be any type of immunoglobulin that is known in the art. For instance, the anti-CD276 binding moiety can be an antibody of any isotype, e.g., IgA, IgD, IgE, IgG, IgM, etc. The antibody can be monoclonal or polyclonal. The antibody can be a naturally-occurring antibody, e.g., an antibody isolated and/or purified from a mammal, e.g., mouse, rabbit, goat, horse, chicken, hamster, human, etc. Alternatively, the antibody can be a genetically-engineered antibody, e.g., a humanized antibody or a chimeric antibody. The antibody can be in monomeric or polymeric form. Also, the antibody can have any level of affinity or avidity for CD276.

[0029] Methods of testing antibodies for the ability to bind to CD276 are known in the art and include any antibody-antigen binding assay, such as, for example, radioimmunoassay (RIA), ELISA, Western blot, immunoprecipitation, and competitive inhibition assays (see, e.g., Murphy et al., infra, and U.S. Patent Application Publication No. 2002/0197266 A1).

[0030] Suitable methods of making antibodies are known in the art. For instance, standard hybridoma methods are described in, e.g., Köhler and Milstein, *Eur. J. Immunol.,* 5, 511-519 (1976), Harlow and Lane (eds.), *Antibodies: A Laboratory Manual*, CSH Press (1988), and Murphy et al. (eds.), *Murphy's Immunobiology,* 7th Ed., Garland Science, New York, N.Y. (2008)). Alternatively, other methods, such as EBV-hybridoma methods (Haskard and Archer, *J. Immunol. Methods,* 74(2), 361-67 (1984), and Roder et al., *Methods Enzymol.,* 121, 140-67 (1986)), and bacteriophage vector expression systems (see, e.g., Huse et al., *Science,* 246, 1275-81 (1989)) are known in the art. Further, methods of producing antibodies in non-human animals are described in, e.g., U.S. Pat. Nos. 5,545,806, 5,569,825, and 5,714,352, and U.S. Patent Application Publication No. 2002/0197266 A1.

[0031] Phage display furthermore can be used to generate an antibody. In this regard, phage libraries encoding antigen-binding variable (V) domains of antibodies can be generated using standard molecular biology and recombinant DNA techniques. See, for instance, Green et al. (eds.), *Molecular Cloning, A Laboratory Manual,* 4th Edition, Cold Spring Harbor Laboratory Press, New York (2012) and Ausubel et al., *Current Protocols in Molecular Biology*, Greene Publishing Associates and John Wiley & Sons, *NY* (2007). Phage encoding a variable region with the desired specificity are selected for specific binding to the desired antigen, and a complete or partial antibody is reconstituted comprising the selected variable domain. Nucleic acid sequences encoding the reconstituted antibody are introduced into a suitable cell line, such as a myeloma cell used for hybridoma production, such that antibodies having the characteristics of monoclonal antibodies are secreted by the cell (see, e.g., Murphy et al., supra, Huse et al., supra, and U.S. Pat. No. 6,265,150).

[0032] Antibodies can be produced by transgenic mice that are transgenic for specific heavy and light chain immunoglobulin genes. Such methods are known in the art and described in, for example U.S. Pat. Nos. 5,545,806 and 5,569,825, and Murphy et al., supra.

[0033] Methods for generating humanized antibodies are well known in the art and are described in detail in, for example, Murphy et al., supra, U.S. Pat. Nos. 5,225,539, 5,585,089 and 5,693,761, European Patent No. 0239400 B1, and United Kingdom Patent No. 2188638. Humanized antibodies can also be generated using the antibody resurfacing technology described in U.S. Pat. No. 5,639,641 and Pedersen et al., *J. Mol. Biol.,* 235, 959-973 (1994).

[0034] In a preferred embodiment, the anti-CD276 binding moiety is a single-chain variable region fragment (scFv). A single-chain variable region fragment (scFv) antibody fragment, which is a truncated Fab fragment including the variable (V) domain of an antibody heavy chain linked to a V domain of a light antibody chain via a synthetic peptide, can be generated using routine recombinant DNA technology techniques (see, e.g., Murphy et al., supra). Similarly, disulfide-stabilized variable region fragments (dsFv) can be prepared by recombinant DNA technology (see, e.g., Reiter et al., *Protein Engineering,* 7, 697-704 (1994)). The anti-CD276 binding moieties of the invention, however, are not limited to these exemplary types of antibody fragments.

[0035] Also, the anti-CD276 binding moiety can be modified to comprise a detectable label, such as, for instance, a radioisotope, a fluorophore (e.g., fluorescein isothiocyanate (FITC), phycoerythrin (PE)), an enzyme (e.g., alkaline phosphatase, horseradish peroxidase), and element particles (e.g., gold particles).

[0036] Another embodiment of the invention provides chimeric antigen receptors (CARs) comprising: (a) an antigen binding domain comprising any of the polypeptides or

proteins described herein, (b) a transmembrane domain, and (c) an intracellular T cell signaling domain.

[0037] A chimeric antigen receptor (CAR) is an artificially constructed hybrid protein or polypeptide containing the antigen binding domains of an antibody (e.g., single chain variable fragment (scFv)) linked to T-cell signaling domains. Characteristics of CARs include their ability to redirect T-cell specificity and reactivity toward a selected target in a non-MHC-restricted manner, exploiting the antigen-binding properties of monoclonal antibodies. The non-MHC-restricted antigen recognition gives cells expressing CARs the ability to recognize antigen independent of antigen processing, thus bypassing a major mechanism of tumor escape. Moreover, when expressed in T-cells, CARs advantageously do not dimerize with endogenous T cell receptor (TCR) alpha and beta chains.

[0038] The phrases "have antigen specificity" and "elicit antigen-specific response" as used herein means that the CAR can specifically bind to and immunologically recognize an antigen, such that binding of the CAR to the antigen elicits an immune response.

[0039] The CARs of the invention have antigen specificity for CD276 (also known as B7-H3). Without being bound to a particular theory or mechanism, it is believed that by eliciting an antigen-specific response against CD276, the inventive CARs provide for one or more of the following: targeting and destroying CD276-expressing cancer cells, reducing or eliminating cancer cells, facilitating infiltration of immune cells to tumor site(s), and enhancing/extending anti-cancer responses.

[0040] An embodiment of the invention provides a CAR comprising an antigen binding domain of an anti-CD276 antibody. The antigen binding domain of the anti-CD276 antibody specifically binds to CD276. The antigen binding domain of the CARs may comprise any of the polypeptides or proteins described herein. In an embodiment of the invention, the CAR comprises an anti-CD276 single chain variable fragment (scFv). In this regard, a preferred embodiment of the invention provides CARs comprising an antigen-binding domain comprising a single chain variable fragment (scFv) that comprises any of the polypeptides or proteins described herein.

[0041] In a preferred embodiment of the invention, the CAR comprises a heavy chain and a light chain each of which comprises a variable region comprising a complementarity determining region (CDR) 1, a CDR2, and a CDR3. Preferably, the heavy chain comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1, 11, or 20 (CDR1 of heavy chain), a CDR2 comprising the amino acid sequence of SEQ ID NO: 2, 12, or 21 (CDR2 of heavy chain), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 3, 13, or 22 (CDR3 of heavy chain), and the light chain comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 4, 14, or 23 (CDR1 of light chain), a CDR2 comprising the amino acid sequence of SEQ ID NO: 5, 15, or 24 (CDR2 of light chain), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 6, 16, or 25 (CDR3 of light chain). In this regard, the inventive CAR can comprise SEQ ID NOs: 1-3, 4-6, 11-13, 14-16, 20-22, 23-25, 1-6, 11-16, or 20-25. Preferably the CAR comprises the amino acid sequences of SEQ ID NOs: 20-25.

[0042] The antigen binding domains of the CARs each comprise a light chain and a heavy chain. The light chain may comprise SEQ ID NO: 8, 18, or 27. The heavy chain may comprise SEQ ID NO: 7, 17, or 26. Accordingly, in an embodiment of the invention, the antigen binding domain comprises SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NOs: 7 and 8, SEQ ID NOs: 17 and 18, or SEQ ID NOs: 26 and 27. Preferably, the CAR comprises SEQ ID NOs: 26 and 27.

[0043] In an embodiment of the invention, the antigen binding domain of the CAR comprises a light chain and a heavy chain, each comprising the CDRs as described above, with a linker positioned between the light chain and the heavy chain. The linker may be as described herein with respect to other aspects of the invention. In this regard, the CAR may comprise SEQ ID NOs: 10, 19, or 28.

[0044] In an embodiment, the antigen binding domain of the CAR comprises a leader sequence. The leader sequence may be as described herein with respect to other aspects of the invention. In an embodiment of the invention, the CAR lacks a leader sequence.

[0045] In an embodiment, the CAR comprises an immunoglobulin constant domain. Preferably, the immunoglobulin domain is a human immunoglobulin sequence. In an embodiment, the immunoglobulin constant domain comprises an immunoglobulin CH2 and CH3 immunoglobulin G (IgG1) domain sequence (CH2CH3). In this regard, the CAR may comprise an immunoglobulin constant domain comprising SEQ ID NO: 71. In an embodiment of the invention, the CAR may comprise an amino acid sequence encoding an antigen binding domain and an immunoglobulin constant domain comprising any one of SEQ ID NOs: 80, 82, and 84. Without being bound to a particular theory, it is believed that the CH2CH3 domain extends the binding motif of the scFv away from the membrane of the CAR-expressing cells and may more accurately mimic the size and domain structure of a native TCR. In some embodiments, the CAR may lack an immunoglobulin constant domain.

[0046] In an embodiment of the invention, the CAR comprises a transmembrane domain. In an embodiment of the invention, the transmembrane domain comprises i) CD8 and/or ii) CD28. In a preferred embodiment, the CD8 and CD28 are human. The CD8 or CD28 may comprise less than the whole CD8 or CD28, respectively. In this regard, the CAR comprises a transmembrane domain comprising any one or more of a CD8 amino acid sequence comprising SEQ ID NO: 29, a CD28 amino acid sequence comprising SEQ ID NO: 30, and a CD8 amino acid sequence comprising SEQ ID NO: 31.

[0047] In an embodiment of the invention, the CAR comprises an intracellular T cell signaling domain comprising one or more of i) CD28, ii) CD137, and iii) CD3 zeta (ζ). In a preferred embodiment, the one or more of CD28, CD137, and CD3 zeta are human. CD28 is a T cell marker important in T cell co-stimulation. CD137, also known as 4-1BB, transmits a potent costimulatory signal to T cells, promoting differentiation and enhancing long-term survival of T lymphocytes. CD3ζ associates with TCRs to produce a signal and contains immunoreceptor tyrosine-based activation motifs (ITAMs). One or more of CD28, CD137, and CD3 zeta may comprise less than the whole CD28, CD137, or CD3 zeta, respectively. In an embodiment of the invention, intracellular T cell signaling domain comprises a CD28 amino acid sequence comprising SEQ ID NO: 32 and/or SEQ ID NO: 35. In another embodiment of the invention, the intracellular T cell signaling domain comprises a CD137

amino acid sequence comprising SEQ ID NO: 33 and/or SEQ ID NO: 37. In another embodiment of the invention, the intracellular T cell signaling domain comprises a CD3 zeta amino acid sequence comprising any one or more of SEQ ID NOs: 34, 36, and 38.

[0048] In an embodiment of the invention, the CAR comprises a transmembrane domain comprising CD28 and an intracellular T cell signaling domain comprising CD28 and CD3 zeta. In this regard, the CAR may comprise each of SEQ ID NOs: 30, 35, and 36. In an embodiment, a transmembrane domain comprising CD28 and an intracellular T cell signaling domain comprising CD28 and CD3 zeta comprises SEQ ID NO: 73. Preferably, the CAR comprises (a) each of SEQ ID NOs: 1-6, 71, 30, 35, and 36; (b) each of SEQ ID NOs: 7, 8, 71, 30, 35, and 36; (c) each of SEQ ID NOs: 10, 71, 30, 35, and 36; (d) each of SEQ ID NOs: 11-16, 71, 30, 35, and 36; (e) each of SEQ ID NOs: 17, 18, 71, 30, 35, and 36; (f) each of SEQ ID NOs: 19, 71, 30, 35, and 36; (g) each of SEQ ID NOs: 20-25, 71, 30, 35, and 36; (h) each of SEQ ID NOs: 26, 27, 71, 30, 35, and 36; or (i) each of SEQ ID NOs: 28, 71, 30, 35, and 36.

[0049] In an embodiment of the invention, the CAR comprises a transmembrane domain comprising CD8 and an intracellular T cell signaling domain comprising CD28, CD137, and CD3 zeta. In this regard, the CAR may comprise each of SEQ ID NOs: 29 and 32-34. In an embodiment, a transmembrane domain comprising CD8 and an intracellular T cell signaling domain comprising CD28, CD137, and CD3 zeta comprises SEQ ID NO: 75. Preferably, the CAR comprises (a) each of SEQ ID NOs: 1-6, 71, 29, and 32-34; (b) each of SEQ ID NOs: 7, 8, 71, 29, and 32-34; (c) each of SEQ ID NOs: 10, 71, 29, and 32-34; (d) each of SEQ ID NOs: 11-16, 71, 29, and 32-34; (e) each of SEQ ID NOs: 17, 18, 71, 29, and 32-34; (f) each of SEQ ID NOs: 19, 71, 29, and 32-34; (g) each of SEQ ID NOs: 20-25, 71, 29, and 32-34; (h) each of SEQ ID NOs: 26, 27, 71, 29, and 32-34; or (i) each of SEQ ID NOs: 28, 71, 29, and 32-34.

[0050] In an embodiment of the invention, the CAR comprises a transmembrane domain comprising CD8 and an intracellular T cell signaling domain comprising CD137 and CD3 zeta. In this regard, the CAR may comprise each of SEQ ID NOs: 31, 37, and 38. In an embodiment, a transmembrane domain comprising CD8 and an intracellular T cell signaling domain comprising CD137 and CD3 zeta comprises SEQ ID NO: 74. Preferably, the CAR comprises each of (a) each of SEQ ID NOs: 1-6, 71, 31, 37, and 38; (b) each of SEQ ID NOs: 7, 8, 71, 31, 37, and 38; (c) each of SEQ ID NOs: 10, 71, 31, 37, and 38; (d) each of SEQ ID NOs: 11-16, 71, 31, 37, and 38; (e) each of SEQ ID NOs: 17, 18, 71, 31, 37, and 38; (f) each of SEQ ID NOs: 19, 71, 31, 37, and 38; (g) each of SEQ ID NOs: 20-25, 71, 31, 37, and 38; (h) each of SEQ ID NOs: 26, 27, 71, 31, 37, and 38; or (i) each of SEQ ID NOs: 28, 71, 31, 37, and 38.

[0051] Additional embodiments of the invention provide CARs comprising one or more of any of the amino acid sequences set forth in Tables 1A and 1B.

TABLE 1A

SEQ ID NO:	Antigen Binding Domain	Further Components
SEQ ID NO: 39 (CD276.6 CAR-second generation, version 1)	CD276.6 scFv (SEQ ID NO: 10)	CH2CH3 CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 40 (CD276.6 CAR-second generation, version 2)	CD276.6 scFv (SEQ ID NO: 10)	CH2CH3 CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 41 (CD276.6 CAR-third generation)	CD276.6 scFv (SEQ ID NO: 10)	CH2CH3 CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 42 (CD276.1 CAR-second generation, version 1)	CD276.1 scFv (SEQ ID NO: 19)	CH2CH3 CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 43 (CD276.1 CAR-second generation, version 2)	CD276.1 scFv (SEQ ID NO: 19)	CH2CH3 CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 44 (CD276.1 CAR-third generation)	CD276.1 scFv (SEQ ID NO: 19)	CH2CH3 CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 45 (CD276.17 CAR-second generation, version 1)	CD276.17 scFv (SEQ ID NO: 28)	CH2CH3 CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 46 (CD276.17 CAR-second generation, version 2)	CD276.17 scFv (SEQ ID NO: 28)	CH2CH3 CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 47 (CD276.17 CAR-third generation)	CD276.17 scFv (SEQ ID NO: 28)	CH2CH3 CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains

TABLE IB

SEQ ID NO:	Antigen Binding Domain	Further Components
SEQ ID NO: 122 (CD276.6 CAR-second generation, version 1)	CD276.6 scFv (SEQ ID NO: 10)	CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 123 (CD276.6 CAR-second generation, version 2)	CD276.6 scFv (SEQ ID NO: 10)	CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 124 (CD276.6 CAR-third generation)	CD276.6 scFv (SEQ ID NO: 10)	CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 125 (CD276.1 CAR-second generation, version 1)	CD276.1 scFv (SEQ ID NO: 19)	CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 126 (CD276.1 CAR-second generation, version 2)	CD276.1 scFv (SEQ ID NO: 19)	CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 127 (CD276.1 CAR-third generation)	CD276.1 scFv (SEQ ID NO: 19)	CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains

TABLE IB-continued

SEQ ID NO:	Antigen Binding Domain	Further Components
SEQ ID NO: 128 (CD276.17 CAR-second generation, version 1)	CD276.17 scFv (SEQ ID NO: 28)	CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 129 (CD276.17 CAR-second generation, version 2)	CD276.17 scFv (SEQ ID NO: 28)	CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 130 (CD276.17 CAR-third generation)	CD276.17 scFv (SEQ ID NO: 28)	CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains

[0052] Included in the scope of the invention are functional portions of the inventive polypeptides, proteins, and CARs described herein. The term "functional portion" when used in reference to a polypeptide, protein, or CAR refers to any part or fragment of the polypeptide, protein, or CAR of the invention, which part or fragment retains the biological activity of the polypeptide, protein, or CAR of which it is a part (the parent polypeptide, protein, or CAR). Functional portions encompass, for example, those parts of a polypeptide, protein, or CAR that retain the ability to recognize target cells, or detect, treat, or prevent a disease, to a similar extent, the same extent, or to a higher extent, as the parent polypeptide, protein, or CAR. In reference to the parent polypeptide, protein, or CAR, the functional portion can comprise, for instance, about 10%, 25%, 30%, 50%, 68%, 80%, 90%, 95%, or more, of the parent polypeptide, protein, or CAR.

[0053] The functional portion can comprise additional amino acids at the amino or carboxy terminus of the portion, or at both termini, which additional amino acids are not found in the amino acid sequence of the parent polypeptide, protein, or CAR. Desirably, the additional amino acids do not interfere with the biological function of the functional portion, e.g., recognize target cells, detect cancer, treat or prevent cancer, etc. More desirably, the additional amino acids enhance the biological activity, as compared to the biological activity of the parent polypeptide, protein, or CAR.

[0054] Included in the scope of the invention are functional variants of the inventive polypeptides, proteins, or CARs described herein. The term "functional variant" as used herein refers to a polypeptide, protein, or CAR having substantial or significant sequence identity or similarity to a parent polypeptide, protein, or CAR, which functional variant retains the biological activity of the polypeptide, protein, or CAR of which it is a variant. Functional variants encompass, for example, those variants of the polypeptide, protein, or CAR described herein (the parent polypeptide, protein, or CAR) that retain the ability to recognize target cells to a similar extent, the same extent, or to a higher extent, as the parent polypeptide, protein, or CAR. In reference to the parent polypeptide, protein, or CAR, the functional variant can, for instance, be at least about 30%, about 50%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or more identical in amino acid sequence to the parent polypeptide, protein, or CAR.

[0055] A functional variant can, for example, comprise the amino acid sequence of the parent polypeptide, protein, or CAR with at least one conservative amino acid substitution. Alternatively or additionally, the functional variants can comprise the amino acid sequence of the parent polypeptide, protein, or CAR with at least one non-conservative amino acid substitution. In this case, it is preferable for the non-conservative amino acid substitution to not interfere with or inhibit the biological activity of the functional variant. The non-conservative amino acid substitution may enhance the biological activity of the functional variant, such that the biological activity of the functional variant is increased as compared to the parent polypeptide, protein, or CAR.

[0056] Amino acid substitutions of the inventive polypeptides, proteins, or CARs are preferably conservative amino acid substitutions. Conservative amino acid substitutions are known in the art, and include amino acid substitutions in which one amino acid having certain physical and/or chemical properties is exchanged for another amino acid that has the same or similar chemical or physical properties. For instance, the conservative amino acid substitution can be an acidic/negatively charged polar amino acid substituted for another acidic/negatively charged polar amino acid (e.g., Asp or Glu), an amino acid with a nonpolar side chain substituted for another amino acid with a nonpolar side chain (e.g., Ala, Gly, Val, Ile, Leu, Met, Phe, Pro, Trp, Cys, Val, etc.), a basic/positively charged polar amino acid substituted for another basic/positively charged polar amino acid (e.g. Lys, His, Arg, etc.), an uncharged amino acid with a polar side chain substituted for another uncharged amino acid with a polar side chain (e.g., Asn, Gln, Ser, Thr, Tyr, etc.), an amino acid with a beta-branched side-chain substituted for another amino acid with a beta-branched side-chain (e.g., Ile, Thr, and Val), an amino acid with an aromatic side-chain substituted for another amino acid with an aromatic side chain (e.g., His, Phe, Trp, and Tyr), etc.

[0057] The polypeptide, protein, or CAR can consist essentially of the specified amino acid sequence or sequences described herein, such that other components, e.g., other amino acids, do not materially change the biological activity of the polypeptide, protein, CAR, functional portion, or functional variant.

[0058] The polypeptides, proteins, or CARs of embodiments of the invention (including functional portions and functional variants) can be of any length, i.e., can comprise any number of amino acids, provided that the polypeptides, proteins, or CARs (or functional portions or functional variants thereof) retain their biological activity, e.g., the ability to specifically bind to antigen, detect diseased cells in a mammal, or treat or prevent disease in a mammal, etc. For example, the polypeptide, protein, or CAR can be about 50 to about 5000 amino acids long, such as 50, 70, 75, 100, 125, 150, 175, 200, 300, 400, 500, 600, 700, 800, 900, 1000 or more amino acids in length.

[0059] The polypeptides, proteins, or CARs of embodiments of the invention (including functional portions and functional variants of the invention) can comprise synthetic amino acids in place of one or more naturally-occurring amino acids. Such synthetic amino acids are known in the art, and include, for example, aminocyclohexane carboxylic acid, norleucine, α-amino n-decanoic acid, homoserine, S-acetylaminomethyl-cysteine, trans and trans-4-hydroxy-proline, 4-aminophenylalanine, 4-nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine, β-phenyl-

serine β-hydroxyphenylalanine, phenylglycine, α-naphthylalanine, cyclohexylalanine, cyclohexylglycine, indoline carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aminomalonic acid, aminomalonic acid monoamide, N'-benzyl-N'-methyl-lysine, N',N'-dibenzyl-lysine, 6-hydroxylysine, ornithine, α-aminocyclopentane carboxylic acid, α-aminocyclohexane carboxylic acid, α-aminocycloheptane carboxylic acid, α-(2-amino-2-norbornane)-carboxylic acid, α,γ-diaminobutyric acid, α,β-diaminopropionic acid, homophenylalanine, and α-tert-butylglycine.

[0060] The polypeptides, proteins, or CARs of embodiments of the invention (including functional portions and functional variants) can be glycosylated, amidated, carboxylated, phosphorylated, esterified, N-acylated, cyclized via, e.g., a disulfide bridge, or converted into an acid addition salt and/or optionally dimerized or polymerized.

[0061] The polypeptides, proteins, or CARs of embodiments of the invention (including functional portions and functional variants thereof) can be obtained by methods known in the art. The polypeptides, proteins, or CARs may be made by any suitable method of making polypeptides or proteins. Suitable methods of de novo synthesizing polypeptides and proteins are described in references, such as Chan et al., *Fmoc Solid Phase Peptide Synthesis*, Oxford University Press, Oxford, United Kingdom, 2000; *Peptide and Protein Drug Analysis*, ed. Reid, R., Marcel Dekker, Inc., 2000; *Epitope Mapping*, ed. Westwood et al., Oxford University Press, Oxford, United Kingdom, 2001; and U.S. Pat. No. 5,449,752. Also, polypeptides and proteins can be recombinantly produced using the nucleic acids described herein using standard recombinant methods. See, e.g., Green et al., supra, and Ausubel et al., supra. Further, some of the polypeptides, proteins, or CARs of the invention (including functional portions and functional variants thereof) can be isolated and/or purified from a source, such as a plant, a bacterium, an insect, a mammal, e.g., a rat, a human, etc. Methods of isolation and purification are well-known in the art. Alternatively, the polypeptides, proteins, or CARs described herein (including functional portions and functional variants thereof) can be commercially synthesized by companies, such as Synpep (Dublin, Calif.), Peptide Technologies Corp. (Gaithersburg, Md.), and Multiple Peptide Systems (San Diego, Calif.). In this respect, the inventive polypeptides, proteins, or CARs can be synthetic, recombinant, isolated, and/or purified.

[0062] Included in the scope of the invention are conjugates, e.g., bioconjugates, comprising any of the inventive polypeptides, proteins, CARs, anti-CD276 binding moieties, conjugates, or functional portions or functional variants thereof. Conjugates, as well as methods of synthesizing conjugates in general, are known in the art (See, for instance, Hudecz, F., *Methods Mol. Biol.* 298: 209-223 (2005) and Kirin et al., *Inorg Chem.* 44(15): 5405-5415 (2005)). In this regard, an embodiment of the invention provides a conjugate comprising (a) any of the polypeptides, proteins, CARs, anti-CD276 binding moieties described herein conjugated to (b) an effector molecule. The effector molecule may be any therapeutic molecule or a molecule that facilitates the detection of the conjugate. The effector molecule is not limited and may be any suitable effector molecule. For example, the effector molecule may be any one or more of a drug, toxin, label (e.g., any of the detectable labels described herein), small molecule, or another antibody. For example, the toxin may be *Pseudomonas* exotoxin A ("PE") or variants thereof such as, e.g., any of PE4E, PE40, PE38, PE25, PE38QQR, PE38KDEL, PE-LR, and PE35, as described in, e.g., U.S. Pat. Nos. 4,892,827; 5,512,658; 5,602,095; 5,608,039; 5,821,238; 5,854,044; U.S. Patent Application Publication No. US 2010/0215656; and WO 2012/041234, each of which is incorporated herein by reference.

[0063] Further provided by an embodiment of the invention is a nucleic acid comprising a nucleotide sequence encoding any of the polypeptides, proteins, CARs, anti-CD276 binding moieties, conjugates, or functional portions or functional variants thereof. The nucleic acids of the invention may comprise a nucleotide sequence encoding any of the leader sequences, linkers, antigen binding domains, immunoglobulin domains, transmembrane domains, and/or intracellular T cell signaling domains described herein. For example, the nucleic acids may comprise a nucleotide sequence encoding a leader, the nucleotide sequence comprising SEQ ID NO: 63 or 64. Alternatively or additionally, the nucleic acids may comprise a nucleotide sequence encoding an immunoglobulin constant domain, the nucleotide sequence comprising SEQ ID NO: 72. Alternatively or additionally, the nucleic acids may comprise a nucleotide sequence encoding a transmembrane domain comprising CD28 and an intracellular T cell signaling domain comprising CD28 and CD3 zeta, the nucleotide sequence comprising SEQ ID NO: 76. Alternatively or additionally, the nucleic acids may comprise a nucleotide sequence encoding a transmembrane domain comprising CD8 and an intracellular T cell signaling domain comprising CD28, CD137, and CD3 zeta, the nucleotide sequence comprising SEQ ID NO: 78. Alternatively or additionally, the nucleic acids may comprise a nucleotide sequence encoding a transmembrane domain comprising CD8 and an intracellular T cell signaling domain comprising CD137 and CD3 zeta, the nucleotide sequence comprising SEQ ID NO: 77. Alternatively or additionally, the nucleic acids may comprise a nucleotide sequence encoding a leader, an antigen binding domain, and an immunoglobulin domain, the nucleotides sequence comprising SEQ ID NO: 79, 81, or 83.

[0064] An embodiment of the invention provides a nucleic acid comprising a nucleotide sequence encoding any of the polypeptides, proteins, or antigen binding domains described herein. In this regard, the nucleic acid encoding a polypeptide or protein may comprise a nucleotide sequence comprising SEQ ID NO: 57 (CD276.1 antigen binding domain), SEQ ID NO: 58 (CD276.6 antigen binding domain), or SEQ ID NO: 59 (CD276.17 antigen binding domain). In another embodiment of the invention, the nucleic acid encoding the variable regions of a polypeptide or protein may comprise a nucleotide sequence comprising (i) SEQ ID NOs: 116 and 117, (ii) SEQ ID NOs: 118 and 119, or (iii) SEQ ID NOs: 120 and 121. Another embodiment of the invention provides a nucleic acid comprising a nucleotide sequence encoding any of the CARs described herein. In this regard, the nucleic acid may comprise one or more of any of the nucleotide sequences set forth in Tables 2A and 2B. Any of the nucleic acids described herein may further comprise, on the 5' end, a nucleotide sequence encoding a leader sequence comprising, for example, SEQ ID NO: 140.

TABLE 2A

SEQ ID NO:	Antigen Binding Domain	Further Components
SEQ ID NO: 48 (CD276.6 CAR-second generation, version 1)	CD276.6 scFv (SEQ ID NO: 58)	CH2CH3 CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 49 (CD276.6 CAR-second generation, version 2)	CD276.6 scFv (SEQ ID NO: 58)	CH2CH3 CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 50 (CD276.6 CAR-third generation)	CD276.6 scFv (SEQ ID NO: 58)	CH2CH3 CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 51 (CD276.1 CAR-second generation, version 1)	CD276.1 scFv (SEQ ID NO: 57)	CH2CH3 CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 52 (CD276.1 CAR-second generation, version 2)	CD276.1 scFv (SEQ ID NO: 57)	CH2CH3 CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 53 (CD276.1 CAR-third generation)	CD276.1 scFv (SEQ ID NO: 57)	CH2CH3 CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 54 (CD276.17 CAR-second generation, version 1)	CD276.17 scFv (SEQ ID NO: 59)	CH2CH3 CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 55 (CD276.17 CAR-second generation, version 2)	CD276.17 scFv (SEQ ID NO: 59)	CH2CH3 CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 56 (CD276.17 CAR-third generation)	CD276.17 scFv (SEQ ID NO: 59)	CH2CH3 CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains

TABLE 2B

SEQ ID NO:	Antigen Binding Domain	Further Components
SEQ ID NO: 131 (CD276.6 CAR-second generation, version 1)	CD276.6 scFv (SEQ ID NO: 58)	CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 132 (CD276.6 CAR-second generation, version 2)	CD276.6 scFv (SEQ ID NO: 58)	CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 133 (CD276.6 CAR-third generation)	CD276.6 scFv (SEQ ID NO: 58)	CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 134 (CD276.1 CAR-second generation, version 1)	CD276.1 scFv (SEQ ID NO: 57)	CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 135 (CD276.1 CAR-second generation, version 2)	CD276.1 scFv (SEQ ID NO: 57)	CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 136 (CD276.1 CAR-third generation)	CD276.1 scFv (SEQ ID NO: 57)	CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains

TABLE 2B-continued

SEQ ID NO:	Antigen Binding Domain	Further Components
SEQ ID NO: 137 (CD276.17 CAR-second generation, version 1)	CD276.17 scFv (SEQ ID NO: 59)	CD28 transmembrane domain CD28 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 138 (CD276.17 CAR-second generation, version 2)	CD276.17 scFv (SEQ ID NO: 59)	CD8 transmembrane domain CD137 and CD3ζ intracellular T cell signaling domains
SEQ ID NO: 139 (CD276.17 CAR-third generation)	CD276.17 scFv (SEQ ID NO: 59)	CD8 transmembrane domain CD28, CD137, and CD3ζ intracellular T cell signaling domains

[0065] "Nucleic acid" as used herein includes "polynucleotide," "oligonucleotide," and "nucleic acid molecule," and generally means a polymer of DNA or RNA, which can be single-stranded or double-stranded, synthesized or obtained (e.g., isolated and/or purified) from natural sources, which can contain natural, non-natural or altered nucleotides, and which can contain a natural, non-natural or altered internucleotide linkage, such as a phosphoroamidate linkage or a phosphorothioate linkage, instead of the phosphodiester found between the nucleotides of an unmodified oligonucleotide. In some embodiments, the nucleic acid does not comprise any insertions, deletions, inversions, and/or substitutions. However, it may be suitable in some instances, as discussed herein, for the nucleic acid to comprise one or more insertions, deletions, inversions, and/or substitutions. In some embodiments, the nucleic acid may encode additional amino acid sequences that do not affect the function of the polypeptide, protein, or CAR and which may or may not be translated upon expression of the nucleic acid by a host cell (e.g., AAA). In an embodiment of the invention, the nucleic acid is complementary DNA (cDNA).

[0066] The nucleic acids of an embodiment of the invention may be recombinant. As used herein, the term "recombinant" refers to (i) molecules that are constructed outside living cells by joining natural or synthetic nucleic acid segments to nucleic acid molecules that can replicate in a living cell, or (ii) molecules that result from the replication of those described in (i) above. For purposes herein, the replication can be in vitro replication or in vivo replication.

[0067] The nucleic acids can consist essentially of the specified nucleotide sequence or sequences described herein, such that other components, e.g., other nucleotides, do not materially change the biological activity of the encoded CAR, polypeptide, protein, functional portion, or functional variant.

[0068] A recombinant nucleic acid may be one that has a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques, such as those described in Green et al., supra. The nucleic acids can be constructed based on chemical synthesis and/or enzymatic ligation reactions using procedures known in the art. See, for example, Green et al., supra, and Ausubel et al., supra. For example, a nucleic acid can be chemically synthesized using naturally occurring nucleotides or variously

modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed upon hybridization (e.g., phosphorothioate derivatives and acridine substituted nucleotides). Examples of modified nucleotides that can be used to generate the nucleic acids include, but are not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N^6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N^6-substituted adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N^6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, 3-(3-amino-3-N-2-carboxypropyl) uracil, and 2,6-diaminopurine. Alternatively, one or more of the nucleic acids of the invention can be purchased from companies, such as Macromolecular Resources (Fort Collins, Colo.) and Synthegen (Houston, Tex.).

[0069] The nucleic acid can comprise any isolated or purified nucleotide sequence which encodes any of the polypeptides, proteins, CARs, anti-CD276 binding moieties, conjugates, or functional portions or functional variants thereof. Alternatively, the nucleotide sequence can comprise a nucleotide sequence which is degenerate to any of the sequences or a combination of degenerate sequences.

[0070] An embodiment of the invention also provides an isolated or purified nucleic acid comprising a nucleotide sequence which is complementary to the nucleotide sequence of any of the nucleic acids described herein or a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of any of the nucleic acids described herein.

[0071] The nucleotide sequence which hybridizes under stringent conditions may hybridize under high stringency conditions. By "high stringency conditions" is meant that the nucleotide sequence specifically hybridizes to a target sequence (the nucleotide sequence of any of the nucleic acids described herein) in an amount that is detectably stronger than non-specific hybridization. High stringency conditions include conditions which would distinguish a polynucleotide with an exact complementary sequence, or one containing only a few scattered mismatches from a random sequence that happened to have a few small regions (e.g., 3-10 bases) that matched the nucleotide sequence. Such small regions of complementarity are more easily melted than a full-length complement of 14-17 or more bases, and high stringency hybridization makes them easily distinguishable. Relatively high stringency conditions would include, for example, low salt and/or high temperature conditions, such as provided by about 0.02-0.1 M NaCl or the equivalent, at temperatures of about 50-70° C. Such high stringency conditions tolerate little, if any, mismatch between the nucleotide sequence and the template or target strand, and are particularly suitable for detecting expression of any of the inventive polypeptides, proteins, CARs, anti-CD276 binding moieties, conjugates, or functional portions or functional variants thereof. It is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide.

[0072] The invention also provides a nucleic acid comprising a nucleotide sequence that is at least about 70% or more, e.g., about 80%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to any of the nucleic acids described herein.

[0073] In an embodiment, the nucleic acids of the invention can be incorporated into a recombinant expression vector. In this regard, an embodiment of the invention provides recombinant expression vectors comprising any of the nucleic acids of the invention. For purposes herein, the term "recombinant expression vector" means a genetically-modified oligonucleotide or polynucleotide construct that permits the expression of an mRNA, protein, polypeptide, or peptide by a host cell, when the construct comprises a nucleotide sequence encoding the mRNA, protein, polypeptide, or peptide, and the vector is contacted with the cell under conditions sufficient to have the mRNA, protein, polypeptide, or peptide expressed within the cell. The vectors of the invention are not naturally-occurring as a whole. However, parts of the vectors can be naturally-occurring. The inventive recombinant expression vectors can comprise any type of nucleotides, including, but not limited to DNA and RNA, which can be single-stranded or double-stranded, synthesized or obtained in part from natural sources, and which can contain natural, non-natural or altered nucleotides. The recombinant expression vectors can comprise naturally-occurring or non-naturally-occurring internucleotide linkages, or both types of linkages. Preferably, the non-naturally occurring or altered nucleotides or internucleotide linkages do not hinder the transcription or replication of the vector.

[0074] In an embodiment, the recombinant expression vector of the invention can be any suitable recombinant expression vector, and can be used to transform or transfect any suitable host cell. Suitable vectors include those designed for propagation and expansion or for expression or both, such as plasmids and viruses. The vector can be selected from the group consisting of the pUC series (Fermentas Life Sciences, Glen Burnie, Md.), the pBluescript series (Stratagene, LaJolla, Calif.), the pET series (Novagen, Madison, Wis.), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clontech, Palo Alto, Calif.). Bacteriophage vectors, such as λGT10, λGT11, λZapII (Stratagene), λEMBL4, and λNM1149, also can be used. Examples of plant expression vectors include pBI01, pBI101.2, pB1101.3, pBI121 and pBIN19 (Clontech). Examples of animal expression vectors include pEUK-Cl, pMAM, and pMAMneo (Clontech). The recombinant expression vector may be a viral vector, e.g., a retroviral vector.

[0075] A number of transfection techniques are generally known in the art (see, e.g., Graham et al., *Virology,* 52: 456-467 (1973); Green et al., supra; Davis et al., *Basic Methods in Molecular Biology, Elsevier* (1986); and Chu et al., *Gene,* 13: 97 (1981). Transfection methods include calcium phosphate co-precipitation (see, e.g., Graham et al., supra), direct micro injection into cultured cells (see, e.g., Capecchi, *Cell,* 22: 479-488 (1980)), electroporation (see, e.g., Shigekawa et al., *BioTechniques,* 6: 742-751 (1988)), liposome mediated gene transfer (see, e.g., Mannino et al.,

BioTechniques, 6: 682-690 (1988)), lipid mediated transduction (see, e.g., Felgner et al., *Proc. Natl. Acad. Sci. USA,* 84: 7413-7417 (1987)), and nucleic acid delivery using high velocity microprojectiles (see, e.g., Klein et al., *Nature,* 327: 70-73 (1987)).

[0076] In an embodiment, the recombinant expression vectors of the invention can be prepared using standard recombinant DNA techniques described in, for example, Green et al., supra, and Ausubel et al., supra. Constructs of expression vectors, which are circular or linear, can be prepared to contain a replication system functional in a prokaryotic or eukaryotic host cell. Replication systems can be derived, e.g., from ColE1, 2μ plasmid, λ, SV40, bovine papilloma virus, and the like.

[0077] The recombinant expression vector may comprise regulatory sequences, such as transcription and translation initiation and termination codons, which are specific to the type of host cell (e.g., bacterium, fungus, plant, or animal) into which the vector is to be introduced, as appropriate, and taking into consideration whether the vector is DNA- or RNA-based. The recombinant expression vector may comprise restriction sites to facilitate cloning. Examples of sequences including restriction sites include SEQ ID NOs: 65-70.

[0078] The recombinant expression vector can include one or more marker genes, which allow for selection of transformed or transfected host cells. Marker genes include biocide resistance, e.g., resistance to antibiotics, heavy metals, etc., complementation in an auxotrophic host to provide prototrophy, and the like. Suitable marker genes for the inventive expression vectors include, for instance, neomycin/G418 resistance genes, hygromycin resistance genes, histidinol resistance genes, tetracycline resistance genes, and ampicillin resistance genes.

[0079] The recombinant expression vector can comprise a native or nonnative promoter operably linked to the nucleotide sequence encoding the polypeptides, proteins, CARs, anti-CD276 binding moieties, conjugates, or functional portions or functional variants thereof, or to the nucleotide sequence which is complementary to or which hybridizes to the nucleotide sequence encoding the inventive polypeptides, proteins, CARs, anti-CD276 binding moieties, conjugates, or functional portions or functional variants thereof. The selection of promoters, e.g., strong, weak, inducible, tissue-specific and developmental-specific, is within the ordinary skill of the artisan. Similarly, the combining of a nucleotide sequence with a promoter is also within the ordinary skill of the artisan. The promoter can be a non-viral promoter or a viral promoter, e.g., a cytomegalovirus (CMV) promoter, an SV40 promoter, an RSV promoter, or a promoter found in the long-terminal repeat of the murine stem cell virus.

[0080] The inventive recombinant expression vectors can be designed for either transient expression, for stable expression, or for both. Also, the recombinant expression vectors can be made for constitutive expression or for inducible expression.

[0081] Further, the recombinant expression vectors can be made to include a suicide gene. As used herein, the term "suicide gene" refers to a gene that causes the cell expressing the suicide gene to die. The suicide gene can be a gene that confers sensitivity to an agent, e.g., a drug, upon the cell in which the gene is expressed, and causes the cell to die when the cell is contacted with or exposed to the agent. Suicide genes are known in the art (see, for example, *Suicide Gene Therapy: Methods and Reviews*, Springer, Caroline J. (Cancer Research UK Centre for Cancer Therapeutics at the Institute of Cancer Research, Sutton, Surrey, UK), Humana Press, 2004) and include, for example, the Herpes Simplex Virus (HSV) thymidine kinase (TK) gene, cytosine daminase, purine nucleoside phosphorylase, and nitroreductase.

[0082] An embodiment of the invention further provides a host cell comprising any of the recombinant expression vectors described herein. As used herein, the term "host cell" refers to any type of cell that can contain the inventive recombinant expression vector. The host cell can be a eukaryotic cell, e.g., plant, animal, fungi, or algae, or can be a prokaryotic cell, e.g., bacteria or protozoa. The host cell can be a cultured cell or a primary cell, i.e., isolated directly from an organism, e.g., a human. The host cell can be an adherent cell or a suspended cell, i.e., a cell that grows in suspension. Suitable host cells are known in the art and include, for instance, DH5α *E. coli* cells, Chinese hamster ovarian cells, monkey VERO cells, COS cells, HEK293 cells, and the like. For purposes of amplifying or replicating the recombinant expression vector, the host cell may be a prokaryotic cell, e.g., a DH5α cell. For purposes of producing a recombinant polypeptide, protein, CAR, anti-CD276 binding moiety, conjugate, or functional portion or functional variant thereof, the host cell may be a mammalian cell. The host cell may be a human cell. While the host cell can be of any cell type, can originate from any type of tissue, and can be of any developmental stage, the host cell may be a peripheral blood lymphocyte (PBL) or a peripheral blood mononuclear cell (PBMC). The host cell may be a B cell or a T cell.

[0083] For purposes herein, the T cell can be any T cell, such as a cultured T cell, e.g., a primary T cell, or a T cell from a cultured T cell line, e.g., Jurkat, SupT1, etc., or a T cell obtained from a mammal. If obtained from a mammal, the T cell can be obtained from numerous sources, including but not limited to blood, bone marrow, lymph node, the thymus, or other tissues or fluids. T cells can also be enriched for or purified. The T cell may be a human T cell. The T cell may be a T cell isolated from a human. The T cell can be any type of T cell and can be of any developmental stage, including but not limited to, $CD4^+/CD8^+$ double positive T cells, $CD4^+$ helper T cells, e.g., Th_1 and Th_2 cells, $CD8^+$ T cells (e.g., cytotoxic T cells), tumor infiltrating cells, memory T cells, naïve T cells, and the like. The T cell may be a $CD8^+$ T cell or a $CD4^+$ T cell.

[0084] Also provided by an embodiment of the invention is a population of cells comprising at least one host cell described herein. The population of cells can be a heterogeneous population comprising the host cell comprising any of the recombinant expression vectors described, in addition to at least one other cell, e.g., a host cell (e.g., a T cell), which does not comprise any of the recombinant expression vectors, or a cell other than a T cell, e.g., a B cell, a macrophage, a neutrophil, an erythrocyte, a hepatocyte, an endothelial cell, an epithelial cell, a muscle cell, a brain cell, etc. Alternatively, the population of cells can be a substantially homogeneous population, in which the population comprises mainly host cells (e.g., consisting essentially of) comprising the recombinant expression vector. The population also can be a clonal population of cells, in which all cells of the population are clones of a single host cell comprising a recombinant expression vector, such that all

cells of the population comprise the recombinant expression vector. In one embodiment of the invention, the population of cells is a clonal population comprising host cells comprising a recombinant expression vector as described herein.

[0085] The polypeptides, proteins, CARs (including functional portions and variants thereof), nucleic acids, recombinant expression vectors, host cells (including populations thereof), anti-CD276 binding moieties, and conjugates, all of which are collectively referred to as "inventive anti-CD276 materials" hereinafter, can be isolated and/or purified. The term "isolated" as used herein means having been removed from its natural environment. The term "purified" or "isolated" does not require absolute purity or isolation; rather, it is intended as a relative term. Thus, for example, a purified (or isolated) host cell preparation is one in which the host cell is more pure than cells in their natural environment within the body. Such host cells may be produced, for example, by standard purification techniques. In some embodiments, a preparation of a host cell is purified such that the host cell represents at least about 50%, for example, at least about 70%, of the total cell content of the preparation. For example, the purity can be at least about 50%, can be greater than about 60%, about 70% or about 80%, or can be about 100%.

[0086] The inventive anti-CD276 materials can be formulated into a composition, such as a pharmaceutical composition. In this regard, an embodiment of the invention provides a pharmaceutical composition comprising any of the inventive anti-CD276 materials described herein and a pharmaceutically acceptable carrier. The inventive pharmaceutical compositions containing any of the inventive anti-CD276 materials can comprise more than one inventive anti-CD276 material, e.g., a CAR and a nucleic acid, or two or more different CARs. Alternatively, the pharmaceutical composition can comprise an inventive CAR material in combination with other pharmaceutically active agents or drugs, such as chemotherapeutic agents, e.g., asparaginase, busulfan, carboplatin, cisplatin, daunorubicin, doxorubicin, fluorouracil, gemcitabine, hydroxyurea, methotrexate, paclitaxel, rituximab, vinblastine, vincristine, etc. In a preferred embodiment, the pharmaceutical composition comprises the inventive host cell or populations thereof.

[0087] The inventive anti-CD276 materials can be provided in the form of a salt, e.g., a pharmaceutically acceptable salt. Suitable pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, and sulphuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, and arylsulphonic acids, for example, p-toluenesulphonic acid.

[0088] With respect to pharmaceutical compositions, the pharmaceutically acceptable carrier can be any of those conventionally used and is limited only by chemico-physical considerations, such as solubility and lack of reactivity with the active agent(s), and by the route of administration. The pharmaceutically acceptable carriers described herein, for example, vehicles, adjuvants, excipients, and diluents, are well-known to those skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one which is chemically inert to the active agent(s) and one which has no detrimental side effects or toxicity under the conditions of use.

[0089] The choice of carrier will be determined in part by the particular inventive CAR material, as well as by the particular method used to administer the inventive CAR material. Accordingly, there are a variety of suitable formulations of the pharmaceutical composition of the invention. Preservatives may be used. Suitable preservatives may include, for example, methylparaben, propylparaben, sodium benzoate, and benzalkonium chloride. A mixture of two or more preservatives optionally may be used. The preservative or mixtures thereof are typically present in an amount of about 0.0001% to about 2% by weight of the total composition.

[0090] Suitable buffering agents may include, for example, citric acid, sodium citrate, phosphoric acid, potassium phosphate, and various other acids and salts. A mixture of two or more buffering agents optionally may be used. The buffering agent or mixtures thereof are typically present in an amount of about 0.001% to about 4% by weight of the total composition.

[0091] The concentration of inventive anti-CD276 material in the pharmaceutical formulations can vary, e.g., from less than about 1%, usually at or at least about 10%, to as much as, for example, about 20% to about 50% or more by weight, and can be selected primarily by fluid volumes, and viscosities, in accordance with the particular mode of administration selected.

[0092] Methods for preparing administrable (e.g., parenterally administrable) compositions are known or apparent to those skilled in the art and are described in more detail in, for example, *Remington: The Science and Practice of Pharmacy*, Lippincott Williams & Wilkins; 21st ed. (May 1, 2005).

[0093] The following formulations for oral, aerosol, parenteral (e.g., subcutaneous, intravenous, intraarterial, intramuscular, intradermal, interperitoneal, and intrathecal), and topical administration are merely exemplary and are in no way limiting. More than one route can be used to administer the inventive anti-CD276 materials, and in certain instances, a particular route can provide a more immediate and more effective response than another route.

[0094] Formulations suitable for oral administration can comprise or consist of (a) liquid solutions, such as an effective amount of the inventive anti-CD276 material dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant. Capsule foul's can be of the ordinary hard or softshelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and other pharmacologically compatible excipients. Lozenge forms can comprise the inventive anti-CD276 material

in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the inventive anti-CD276 material in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to, such excipients as are known in the art.

[0095] Formulations suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and nonaqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The inventive anti-CD276 material can be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol or hexadecyl alcohol, a glycol, such as propylene glycol or polyethylene glycol, dimethylsulfoxide, glycerol, ketals such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, poly(ethyleneglycol) 400, oils, fatty acids, fatty acid esters or glycerides, or acetylated fatty acid glycerides with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

[0096] Oils, which can be used in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

[0097] Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-β-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

[0098] The parenteral formulations will typically contain, for example, from about 0.5% to about 25% by weight of the inventive anti-CD276 material in solution. Preservatives and buffers may be used. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having, for example, a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations will typically range, for example, from about 5% to about 15% by weight. Suitable surfactants include polyethylene glycol sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0099] Injectable formulations are in accordance with an embodiment of the invention. The requirements for effective pharmaceutical carriers for injectable compositions are well-known to those of ordinary skill in the art (see, e.g., *Pharmaceutics and Pharmacy Practice*, J.B. Lippincott Company, Philadelphia, Pa., Banker and Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., pages 622-630 (1986)).

[0100] Topical formulations, including those that are useful for transdermal drug release, are well known to those of skill in the art and are suitable in the context of embodiments of the invention for application to skin. The inventive anti-CD276 material, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer. Such spray formulations also may be used to spray mucosa.

[0101] An "effective amount" or "an amount effective to treat" refers to a dose that is adequate to prevent or treat cancer in an individual. Amounts effective for a therapeutic or prophylactic use will depend on, for example, the stage and severity of the disease or disorder being treated, the age, weight, and general state of health of the patient, and the judgment of the prescribing physician. The size of the dose will also be determined by the active selected, method of administration, timing and frequency of administration, the existence, nature, and extent of any adverse side-effects that might accompany the administration of a particular active, and the desired physiological effect. It will be appreciated by one of skill in the art that various diseases or disorders could require prolonged treatment involving multiple administrations, perhaps using the inventive anti-CD276 materials in each or various rounds of administration. By way of example and not intending to limit the invention, the dose of the inventive anti-CD276 material can be about 0.001 to about 1000 mg/kg body weight of the subject being treated/day, from about 0.01 to about 10 mg/kg body weight/day, about 0.01 mg to about 1 mg/kg body weight/day. When the inventive anti-CD276 material is a host cell, an exemplary dose of host cells may be a minimum of one million cells (1 mg cells/dose). When the inventive anti-CD276 material is a nucleic acid packaged in a virus, an exemplary dose of virus may be 1 ng/dose.

[0102] For purposes of the invention, the amount or dose of the inventive anti-CD276 material administered should be sufficient to effect a therapeutic or prophylactic response in the subject or animal over a reasonable time frame. For example, the dose of the inventive anti-CD276 material should be sufficient to bind to antigen, or detect, treat or prevent disease in a period of from about 2 hours or longer, e.g., about 12 to about 24 or more hours, from the time of administration. In certain embodiments, the time period could be even longer. The dose will be determined by the efficacy of the particular inventive anti-CD276 material and

the condition of the animal (e.g., human), as well as the body weight of the animal (e.g., human) to be treated.

[0103] For purposes of the invention, an assay, which comprises, for example, comparing the extent to which target cells are lysed and/or IFN-γ is secreted by T cells expressing the inventive anti-CD276 material upon administration of a given dose of such T cells to a mammal, among a set of mammals of which is each given a different dose of the T cells, could be used to determine a starting dose to be administered to a mammal. The extent to which target cells are lysed and/or IFN-γ is secreted upon administration of a certain dose can be assayed by methods known in the art.

[0104] In addition to the aforedescribed pharmaceutical compositions, the inventive anti-CD276 materials can be formulated as inclusion complexes, such as cyclodextrin inclusion complexes, or liposomes. Liposomes can serve to target the inventive anti-CD276 materials to a particular tissue. Liposomes also can be used to increase the half-life of the inventive anti-CD276 materials. Many methods are available for preparing liposomes, as described in, for example, Szoka et al., *Ann. Rev. Biophys. Bioeng.*, 9, 467 (1980) and U.S. Pat. Nos. 4,235,871, 4,501,728, 4,837,028, and 5,019,369.

[0105] The delivery systems useful in the context of embodiments of the invention may include time-released, delayed release, and sustained release delivery systems such that the delivery of the inventive composition occurs prior to, and with sufficient time to cause, sensitization of the site to be treated. The inventive composition can be used in conjunction with other therapeutic agents or therapies. Such systems can avoid repeated administrations of the inventive composition, thereby increasing convenience to the subject and the physician, and may be particularly suitable for certain composition embodiments of the invention.

[0106] Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones, polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Pat. No. 5,075,109. Delivery systems also include non-polymer systems that are lipids including sterols such as cholesterol, cholesterol esters, and fatty acids or neutral fats such as mono-di- and tri-glycerides; hydrogel release systems; sylastic systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which the active composition is contained in a form within a matrix such as those described in U.S. Pat. Nos. 4,452,775, 4,667,014, 4,748,034, and 5,239,660 and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Pat. Nos. 3,832,253 and 3,854,480. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

[0107] One of ordinary skill in the art will readily appreciate that the inventive anti-CD276 materials of the invention can be modified in any number of ways, such that the therapeutic or prophylactic efficacy of the inventive anti-CD276 materials is increased through the modification. For instance, the inventive anti-CD276 materials can be conjugated either directly or indirectly through a bridge to a targeting moiety. The practice of conjugating compounds, e.g., inventive anti-CD276 materials, to targeting moieties is known in the art. See, for instance, Wadwa et al., *J. Drug Targeting* 3: 111 (1995) and U.S. Pat. No. 5,087,616.

[0108] Alternatively, the inventive anti-CD276 materials can be modified into a depot form, such that the manner in which the inventive anti-CD276 materials is released into the body to which it is administered is controlled with respect to time and location within the body (see, for example, U.S. Pat. No. 4,450,150). Depot forms of inventive anti-CD276 materials can be, for example, an implantable composition comprising the inventive anti-CD276 materials and a porous or non-porous material, such as a polymer, wherein the inventive anti-CD276 materials are encapsulated by or diffused throughout the material and/or degradation of the non-porous material. The depot is then implanted into the desired location within the body and the inventive anti-CD276 materials are released from the implant at a predetermined rate.

[0109] When the inventive anti-CD276 materials are administered with one or more additional therapeutic agents, one or more additional therapeutic agents can be coadministered to the mammal. By "coadministering" is meant administering one or more additional therapeutic agents and the inventive CAR materials sufficiently close in time such that the inventive anti-CD276 materials can enhance the effect of one or more additional therapeutic agents, or vice versa. In this regard, the inventive anti-CD276 materials can be administered first and the one or more additional therapeutic agents can be administered second, or vice versa. Alternatively, the inventive anti-CD276 materials and the one or more additional therapeutic agents can be administered simultaneously. An exemplary therapeutic agent that can be co-administered with the anti-CD276 materials is IL-2. It is believed that IL-2 enhances the therapeutic effect of the inventive anti-CD276 materials. For purposes of the inventive methods, wherein host cells or populations of cells are administered to the mammal, the cells can be cells that are allogeneic or autologous to the mammal.

[0110] It is contemplated that the inventive anti-CD276 materials and pharmaceutical compositions can be used in methods of treating or preventing a disease in a mammal. Without being bound to a particular theory or mechanism, the inventive anti-CD276 materials have biological activity, e.g., ability to recognize antigen, e.g., CD276, such that the anti-CD276 material, when expressed by a cell, is able to mediate an immune response against the cell expressing the antigen, e.g., CD276, for which the anti-CD276 material is specific. In this regard, an embodiment of the invention provides a method of treating or preventing cancer in a mammal, comprising administering to the mammal any of the polypeptides, proteins, CARs, functional portions, functional variants, nucleic acids, recombinant expression vectors, host cells, population of cells, anti-CD276 binding moieties, conjugates, and/or the pharmaceutical compositions of the invention in an amount effective to treat or prevent cancer in the mammal.

[0111] An embodiment of the invention further comprises lymphodepleting the mammal prior to administering the inventive anti-CD276 materials. Examples of lymphodepletion include, but may not be limited to, nonmyeloablative lymphodepleting chemotherapy, myeloablative lymphodepleting chemotherapy, total body irradiation, etc.

[0112] For purposes of the inventive methods, wherein host cells or populations of cells are administered, the cells can be cells that are allogeneic or autologous to the mammal. Preferably, the cells are autologous to the mammal.

[0113] The mammal referred to herein can be any mammal. As used herein, the term "mammal" refers to any mammal, including, but not limited to, mammals of the order Rodentia, such as mice and hamsters, and mammals of the order Logomorpha, such as rabbits. The mammals may be from the order Carnivora, including Felines (cats) and Canines (dogs). The mammals may be from the order Artiodactyla, including Bovines (cows) and Swines (pigs) or of the order Perssodactyla, including Equines (horses). The mammals may be of the order Primates, Ceboids, or Simoids (monkeys) or of the order Anthropoids (humans and apes). Preferably, the mammal is a human.

[0114] With respect to the inventive methods, the cancer can be any cancer, including any of acute lymphocytic cancer, acute myeloid leukemia, rhabdomyosarcoma, bladder cancer (e.g., bladder carcinoma), bone cancer, brain cancer (e.g., medulloblastoma), breast cancer, cancer of the anus, anal canal, or anorectum, cancer of the eye, cancer of the intrahepatic bile duct, cancer of the joints, cancer of the neck, gallbladder, or pleura, cancer of the nose, nasal cavity, or middle ear, cancer of the oral cavity, cancer of the vulva, chronic lymphocytic leukemia, chronic myeloid cancer, colon cancer, Ewing's sarcoma, esophageal cancer, cervical cancer, fibrosarcoma, gastrointestinal carcinoid tumor, head and neck cancer (e.g., head and neck squamous cell carcinoma), Hodgkin lymphoma, hypopharynx cancer, kidney cancer, larynx cancer, leukemia, liquid tumors, liver cancer, lung cancer (e.g., non-small cell lung carcinoma), lymphoma, malignant mesothelioma, mastocytoma, melanoma, multiple myeloma, nasopharynx cancer, neuroblastoma, non-Hodgkin lymphoma, B-chronic lymphocytic leukemia, hairy cell leukemia, acute lymphocytic leukemia (ALL), and Burkitt's lymphoma, ovarian cancer, pancreatic cancer, peritoneum, omentum, and mesentery cancer, pharynx cancer, prostate cancer, rectal cancer, renal cancer, skin cancer, small intestine cancer, soft tissue cancer, solid tumors, stomach cancer, testicular cancer, thyroid cancer, and ureter cancer. Preferably, the cancer is a pediatric solid tumor, adult carcinoma, neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma, and prostate, ovarian, colorectal, or lung cancer. Preferably, the cancer is characterized by the expression or overexpression of CD276.

[0115] The terms "treat," and "prevent" as well as words stemming therefrom, as used herein, do not necessarily imply 100% or complete treatment or prevention. Rather, there are varying degrees of treatment or prevention of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the inventive methods can provide any amount of any level of treatment or prevention of cancer in a mammal. Furthermore, the treatment or prevention provided by the inventive method can include treatment or prevention of one or more conditions or symptoms of the disease, e.g., cancer, being treated or prevented. Also, for purposes herein, "prevention" can encompass delaying the onset of the disease, or a symptom or condition thereof.

[0116] Another embodiment of the invention provides a use of any of the polypeptides, proteins, CARs, functional portions, functional variants, nucleic acids, recombinant expression vectors, host cells, population of cells, anti-CD276 binding moieties, conjugates, or pharmaceutical compositions of the invention for the treatment or prevention of cancer in a mammal.

[0117] Another embodiment of the invention provides a method of detecting the presence of cancer in a mammal, comprising: (a) contacting a sample comprising one or more cells from the mammal with any of the polypeptides, proteins, CARs, functional portions, functional variants, nucleic acids, recombinant expression vectors, host cells, population of cells, anti-CD276 binding moieties, or conjugates of the invention, thereby forming a complex, (b) and detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the mammal.

[0118] The sample may be obtained by any suitable method, e.g., biopsy or necropsy. A biopsy is the removal of tissue and/or cells from an individual. Such removal may be to collect tissue and/or cells from the individual in order to perform experimentation on the removed tissue and/or cells. This experimentation may include experiments to determine if the individual has and/or is suffering from a certain condition or disease-state. The condition or disease may be, e.g., cancer.

[0119] With respect to an embodiment of the inventive method of detecting the presence of cancer in a mammal, the sample comprising cells of the mammal can be a sample comprising whole cells, lysates thereof, or a fraction of the whole cell lysates, e.g., a nuclear or cytoplasmic fraction, a whole protein fraction, or a nucleic acid fraction. If the sample comprises whole cells, the cells can be any cells of the mammal, e.g., the cells of any organ or tissue, including blood cells or endothelial cells.

[0120] For purposes of the inventive detecting method, the contacting can take place in vitro or in vivo with respect to the mammal. Preferably, the contacting is in vitro.

[0121] Also, detection of the complex can occur through any number of ways known in the art. For instance, the inventive CARs, polypeptides, proteins, functional portions, functional variants, nucleic acids, recombinant expression vectors, host cells, populations of cells, anti-CD276 binding moieties, or conjugates, described herein, can be labeled with a detectable label such as, for instance, a radioisotope, a fluorophore (e.g., fluorescein isothiocyanate (FITC), phycoerythrin (PE)), an enzyme (e.g., alkaline phosphatase, horseradish peroxidase), and element particles (e.g., gold particles).

[0122] Methods of testing an anti-CD276 material for the ability to recognize target cells and for antigen specificity are known in the art. For instance, Clay et al., *J. Immunol.,* 163: 507-513 (1999), teaches methods of measuring the release of cytokines (e.g., interferon-γ, granulocyte/monocyte colony stimulating factor (GM-CSF), tumor necrosis factor α (TNF-α.) or interleukin 2 (IL-2)). In addition, anti-CD276 material function can be evaluated by measurement of cellular cytoxicity, as described in Zhao et al., *J. Immunol.,* 174: 4415-4423 (2005).

[0123] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

Example 1

[0124] This example demonstrates the identification, purification, and characterization of anti-CD276 binding domains.

Yeast Display Naïve Human Antibody Library, Antibodies, Biotinylation Kit, Cells

[0125] A large yeast display naïve single chain variable fragment (scFv) human antibody library was constructed using a collection of human antibody gene repertoires, including the genes used for the construction of a phage display Fab library (Zhu et al., *Methods Mol. Biol.,* 525: 129-142, xv (2009)).

[0126] Mouse monoclonal anti-c-Myc antibody was purchased from Roche (Pleasanton, Calif.). PE-conjugated streptavidin and Alexa-488 conjugated goat anti-mouse antibody were purchased from Invitrogen (Carlsbad, Calif.). Protein G columns were purchased from GE healthcare (Waukesha, Wis.). Avi-tag specific biotinylation kits were purchased from Avidity (Aurora, Colo.). Yeast plasmid extraction kits were purchased from Zymo Research (Irvine, Calif.). 293 free style protein expression kits were purchased from Invitrogen. An AutoMACS System was purchased from Miltenyi Biotec (Cologne, Germany).

MACS Sorting Downsize of the Initial Yeast Display Human Antibody Library

[0127] Biotinylated human and mouse CD276 extracellular domain was used as the target for three rounds of sorting to downsize the initial yeast display naïve human antibody library. Approximately 1010 cells from the initial naïve antibody library and 10 μg of biotinylated CD276 ecto-domain were incubated in 50 ml PBSA (phosphate-buffered saline containing 0.1% bovine serum albumin) at room temperature (RT) for 2 hr with rotation. The mixture of biotinylated CD276 ecto-domain bound to displayed antibody on cells from the library was washed three times with PBSA and incubated with 100 μl of streptavidin conjugated microbeads at RT from Miltenyi Biotec. The resultant mixture was washed once with PBSA and loaded onto the AutoMACS system for the first round of sorting. The sorted cells were amplified in SDCAA media (20 g dextrose, 6.7 g DIFCO yeast nitrogen base without (w/o) amino acids, 5 g BACTO casamino acids, 5.4 g Na_2HPO_4 and 8.56 g $NaH_2PO_4.H_2O$ in 1 liter water) at 30° C. and 250 revolutions per minute (rpm) for 24 hours (hr). The culture was then induced in SGCAA media (20 g galactose, 20 g raffinose, 1 g dextrose, 6.7 g DIFCO yeast nitrogen base w/o amino acids, 5 g BACTO casamino acids, 5.4 g Na_2HPO_4 and 8.56 g $NaH_2PO_4.H_2O$ in 1 liter water) at 20° C. and 250 rpm for 16-18 hr.

[0128] The same amounts of antigen and incubation volume were used for the next two rounds of sorting. The cell numbers used for these two rounds of sorting were set at 100 times the size of the sorted pool from the previous round of sorting to keep the diversity of each sorted pool.

Expression and Purification of scFv-Fc Proteins

[0129] Plasmids were extracted from the identified yeast clones using yeast plasmid extraction kits (Zymo Research, Irvine, Calif.), following the manufacturer's instructions. Extracted plasmids were transformed into 10G chemical competent *E. coli* (Lucigen, Middleton, Wis.) for further amplification. Plasmids extracted from the bacteria were used for DNA sequencing to obtain the nucleic acid sequences encoding the positive binder antibodies.

[0130] Three anti-CD276 antibodies were identified, each comprising heavy and light chain amino acid sequences as follows: (1) Clone CD276.1 (m851) (comprising a heavy chain comprising SEQ ID NO: 17 and a light chain comprising SEQ ID NO: 18), (2) Clone CD276.6 (m856) (comprising a heavy chain comprising SEQ ID NO: 7 and a light chain comprising SEQ ID NO: 8), and (3) Clone CD276.17 (m8517) (comprising a heavy chain comprising SEQ ID NO: 26 and a light chain comprising SEQ ID NO: 27).

[0131] The scFv-encoding inserts of the unique clones were digested with SfiI and ligated into modified pSecTag bearing the same set of SfiI sites and Fc-Avi tag for soluble expression. These constructs were transfected into 293T cells for expression following the manufacturer's protocol. After 72 hr of growth, the scFv-Fc fusion proteins in the culture medium were used for the ELISA binding assay.

ELISA Binding Assay

[0132] 50 μl of the diluted mouse or human CD276-AP fusion protein in PBS at 2 μg/ml was coated in a 96-well plate at 4° C. overnight. Transiently expressed scFv-Fc fusion protein in the culture medium was serially diluted and added into the target protein coated wells. After washing, a 1:3000 diluted horseradish peroxidase (HRP) conjugated goat anti-human IgG antibody was added for 1 hr at RT. After washing, 3, 3, 5, 5'-Tetramethylbenzidine (TMB) substrate was added, and the optical density (O.D.) was read at 450 nm. The results are shown in FIGS. **6** and **7**. As shown in FIG. **6**, scFv-Fc fusion proteins comprising heavy and light chain amino acid sequences as follows: (1) Clone CD276.1 (m851) (comprising a heavy chain comprising SEQ ID NO: 17 and a light chain comprising SEQ ID NO: 18), (2) Clone CD276.6 (m856) (comprising a heavy chain comprising SEQ ID NO: 7 and a light chain comprising SEQ ID NO: 8), and (3) Clone CD276.17 (m8517) (comprising a heavy chain comprising SEQ ID NO: 26 and a light chain comprising SEQ ID NO: 27) bound to human CD276. As shown in FIG. **7**, all the clones except for m851 (CD276.1) showed cross reactivity to both human and mouse CD276, while m851 (CD276.1) is human CD276-specific.

Affinity Determination by Surface Plasmon Resonance

[0133] Binding affinities of human anti-CD276 scFv CD276.6 to human CD276 Ecto-domain were analyzed by surface plasmon resonance technology using a Biacore X100 instrument (GE healthcare). The human CD276 soluble extracellular domain was covalently immobilized onto a sensor chip (CM5) using carbodiimide coupling chemistry. A control reference surface was prepared for nonspecific binding and refractive index changes. For analysis of the kinetics of interactions, varying concentrations of antigens were injected at a flow rate of 30 μl/min using running buffer containing 10 mM HEPES, 150 mM NaCl, 3 mM EDTA, and 0.05% Surfactant β-20 (pH 7.4). The association and dissociation phase data were fitted simultaneously to a 1:1 Langumir global model, using the nonlinear data analysis program BIAevaluation 3.2. All of the experiments were done at 25° C. The affinity of the antibody CD276.6 (m856) (comprising a heavy chain comprising SEQ ID NO: 7 and a light chain comprising SEQ ID NO: 8) is shown in FIG. **8**.

Example 2

[0134] This example demonstrates the activity of chimeric antigen receptors (CARs) comprising anti-CD276 binding domains identified in Example 1.

[0135] Chimeric antigen receptors (CARs) (second generation-version 1) were produced including single chain variable fragments comprising the anti-CD276 binding domains identified in Example 1. In addition to the anti-CD276 binding domains, the CARs also included an immunoglobulin domain comprising an immunoglobulin CH2 and CH3 immunoglobulin G (IgG1) domain sequence (CH2CH3), a CD28 transmembrane domain, a CD28 intracellular T cell signaling domain, and a CD3ζ (intracellular T cell signaling domain. The full length sequences of these CARs comprised SEQ ID NO: 39 (CD276.6 second generation, version 1), SEQ ID NO: 42 (CD276.1 second generation, version 1), or SEQ ID NO: 45 (CD276.17 second generation, version 1).

[0136] These CARs were tested against tumor cell lines expressing CD276 as well as a laboratory cell line, CHO, that was transfected to permanently express either CD276 or a control vector, serving as a positive control (CHO-276) and a negative control (CHO), respectively, in assays of immunological function of CAR-transduced T cells. To test CAR activity, human T cells were activated with anti-CD3/CD28 beads in the presence of interleukin (IL)-2. These T cells were then transduced with retroviral CAR expression vectors and tested for activity against tumor cell lines in a chromium release assay. The transduced T cells (effectors) were cultured with chromium-labeled target cells CHO or CHO-276 at the effector to target ratios (number of effector T cells per target cell in the assay well) shown in FIG. **1**. The percentage of target cells that were lysed was measured. The results are shown in FIG. **1**. The activities of cells expressing SEQ ID NO: 42 (CD276.1 second generation, version 1) or SEQ ID NO: 45 (CD276.17 second generation, version 1) are shown in FIG. **1**.

[0137] As shown in FIG. **1**, while both the CAR comprising SEQ ID NO: 42 (CD276.1 second generation, version 1) and the CAR comprising SEQ ID NO: 45 (CD276.17 second generation, version 1) were active against CHO-276 (the CD276-expressing, positive control cell line), the CAR comprising SEQ ID NO: 45 (CD276.17 second generation, version 1) showed very low activity against the control cell line, indicating a high degree of specific lytic activity.

[0138] Human cells transduced with nucleotide sequences encoding SEQ ID NO: 39 (CD276.6 second generation, version 1), SEQ ID NO: 42 (CD276.1 second generation, version 1), or SEQ ID NO: 45 (CD276.17 second generation, version 1) CARs (effectors) were co-cultured with chromium-labeled target CHO K1 cells (negative control), positive control CHO-276 cells, or one of the $CD276^+$ tumor cell lines K562 (leukemia cell line), 5838 (patient-derived sarcoma cell line), and TC71 (patient-derived sarcoma cell line) at the effector to target ratios shown in FIGS. **2-4**. The percentage of target cells that were lysed was measured. The results are shown in FIGS. **2-4**.

[0139] As shown in FIGS. **2-4**, all CARs were active against CHO-276 (the positive control) and the 5838 Ewing sarcoma cell line. However, CARs differed in their reactivity to the control cell line, with SEQ ID NO: 42 (CD276.1 second generation, version 1) and SEQ ID NO: 39 (CD276.6 second generation, version 1) showing moderate reactivity to CHO-K1, and SEQ ID NO: 45 (CD276.17 second generation, version 1) showing very low activity. Thus, the CD276.17 second generation, version 1 CAR has the highest degree of specific lytic activity.

[0140] The production of interferon (IFN)-gamma was tested in an enzyme-linked immunosorbent spot (ELISPOT) assay. In the ELISPOT assay, CAR-transduced T cells were co-incubated with tumor cells for 24 hours and the number of IFN-gamma producing cells was enumerated by the capture of IFN-gamma on the micro-well filter upon which the assay was performed. Thus, the ELISPOT assay both verifies the production of IFN-gamma by CAR-expressing T cells and quantifies the number of T cells in the culture that are able to express IFN-gamma. The results obtained for cells transduced with nucleotide sequences encoding SEQ ID NO: 45 (CD276.17 second generation, version 1) or SEQ ID NO: 39 (CD276.6 second generation, version 1) are shown in FIG. **5**. As shown in FIG. **5**, the CD276.17 second generation, version 1 CAR showed a high degree of specific activity in that the greatest number of spots was seen when CAR-transduced T cells were incubated with the CD276-positive cells lines K562 and 5838 and the positive control cell line, CHO-CD276. Low numbers of spots were seen with the negative control cell line or when T cells were incubated alone. Lower levels of activity were seen against the TC71 tumor cell line. As in the tumor lysis assay, the CD276.6 second generation, version 1 CAR T cells had high levels of lysis against CD276-expressing targets, but also a higher level of activity against the negative control cell line.

[0141] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0142] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0143] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

SEQUENCE LISTING

Sequence total quantity: 140

SEQ ID NO: 1 moltype = AA length = 8
FEATURE Location/Qualifiers
REGION 1..8
note = Synthetic
source 1..8
mol_type = protein
organism = synthetic construct
SEQUENCE: 1
GGTFSSYA 8

SEQ ID NO: 2 moltype = AA length = 8
FEATURE Location/Qualifiers
REGION 1..8
note = Synthetic
source 1..8
mol_type = protein
organism = synthetic construct
SEQUENCE: 2
IIPILGIA 8

SEQ ID NO: 3 moltype = AA length = 12
FEATURE Location/Qualifiers
REGION 1..12
note = Synthetic
source 1..12
mol_type = protein
organism = synthetic construct
SEQUENCE: 3
ATGGSGRYAL DI 12

SEQ ID NO: 4 moltype = AA length = 6
FEATURE Location/Qualifiers
REGION 1..6
note = Synthetic
source 1..6
mol_type = protein
organism = synthetic construct
SEQUENCE: 4
QSVSSY 6

SEQ ID NO: 5 moltype = length =
SEQUENCE: 5
000

SEQ ID NO: 6 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Synthetic
source 1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 6
QQRSNWPPSY T 11

SEQ ID NO: 7 moltype = AA length = 119
FEATURE Location/Qualifiers
REGION 1..119
note = Synthetic
source 1..119
mol_type = protein
organism = synthetic construct
SEQUENCE: 7
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCATGG SGRYALDIWG QGTMVTVSS 119

SEQ ID NO: 8 moltype = AA length = 109
FEATURE Location/Qualifiers
REGION 1..109
note = Synthetic
source 1..109
mol_type = protein
organism = synthetic construct
SEQUENCE: 8
EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA 60

-continued

RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPSYTF GQGTKLEIK 109

SEQ ID NO: 9 moltype = AA length = 17
FEATURE Location/Qualifiers
REGION 1..17
note = Synthetic
source 1..17
mol_type = protein
organism = synthetic construct
SEQUENCE: 9
SSGGGGSGGG GSGGGGS 17

SEQ ID NO: 10 moltype = AA length = 244
FEATURE Location/Qualifiers
REGION 1..244
note = Synthetic
source 1..244
mol_type = protein
organism = synthetic construct
SEQUENCE: 10
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCATGG SGRYALDIWG QGTMVTVSSG 120
GGGSGGGGSG GGGSEIVLTQ SPATLSLSPG ERATLSCRAS QSVSSYLAWY QQKPGQAPRL 180
LIYDASNRAT GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQRSNWPP SYTFGQGTKL 240
EIKR 244

SEQ ID NO: 11 moltype = AA length = 8
FEATURE Location/Qualifiers
REGION 1..8
note = Synthetic
source 1..8
mol_type = protein
organism = synthetic construct
SEQUENCE: 11
GGTFSSYA 8

SEQ ID NO: 12 moltype = AA length = 8
FEATURE Location/Qualifiers
REGION 1..8
note = Synthetic
source 1..8
mol_type = protein
organism = synthetic construct
SEQUENCE: 12
IIPILGIA 8

SEQ ID NO: 13 moltype = AA length = 15
FEATURE Location/Qualifiers
REGION 1..15
note = Synthetic
source 1..15
mol_type = protein
organism = synthetic construct
SEQUENCE: 13
ARGGAGGSGS YYPLI 15

SEQ ID NO: 14 moltype = AA length = 7
FEATURE Location/Qualifiers
REGION 1..7
note = Synthetic
source 1..7
mol_type = protein
organism = synthetic construct
SEQUENCE: 14
QSVSSSY 7

SEQ ID NO: 15 moltype = length =
SEQUENCE: 15
000

SEQ ID NO: 16 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Synthetic
source 1..11
mol_type = protein

-continued

```
                    organism = synthetic construct
SEQUENCE: 16
QQRSSWPPTW T                                                    11

SEQ ID NO: 17       moltype = AA  length = 122
FEATURE             Location/Qualifiers
REGION              1..122
                    note = Synthetic
source              1..122
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 17
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARGG AGGSGSYYPL IWGQGTTVTV  120
SS                                                              122

SEQ ID NO: 18       moltype = AA  length = 110
FEATURE             Location/Qualifiers
REGION              1..110
                    note = Synthetic
source              1..110
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 18
EIVLTQSPAT LSLSPGERAT LSCGASQSVS SSYLAWYQQK PGQAPRLLIY DASSRATGIP  60
ARFSGSGSGT DFTLTISSLE PEDFAVYYCQ QRSSWPPTWT FGQGTKLEIK             110

SEQ ID NO: 19       moltype = AA  length = 248
FEATURE             Location/Qualifiers
REGION              1..248
                    note = Synthetic
source              1..248
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 19
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARGG AGGSGSYYPL IWGQGTTVTV  120
SSGGGGSGGG GSGGGGSEIV LTQSPATLSL SPGERATLSC GASQSVSSSY LAWYQQKPGQ  180
APRLLIYDAS SRATGIPARF SGSGSGTDFT LTISSLEPED FAVYYCQQRS SWPPTWTFGQ  240
GTKLEIKR                                                        248

SEQ ID NO: 20       moltype = AA  length = 8
FEATURE             Location/Qualifiers
REGION              1..8
                    note = Synthetic
source              1..8
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 20
GGTFSSYA                                                        8

SEQ ID NO: 21       moltype = AA  length = 8
FEATURE             Location/Qualifiers
REGION              1..8
                    note = Synthetic
source              1..8
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 21
IIPILGTA                                                        8

SEQ ID NO: 22       moltype = AA  length = 10
FEATURE             Location/Qualifiers
REGION              1..10
                    note = Synthetic
source              1..10
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 22
ARWGGGAFDI                                                      10

SEQ ID NO: 23       moltype = AA  length = 6
FEATURE             Location/Qualifiers
REGION              1..6
                    note = Synthetic
source              1..6
```

-continued

```
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 23
QSVGGY                                                          6

SEQ ID NO: 24       moltype =   length =
SEQUENCE: 24
000

SEQ ID NO: 25       moltype = AA  length = 11
FEATURE             Location/Qualifiers
REGION              1..11
                    note = Synthetic
source              1..11
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 25
QQRNNWPPMY T                                                    11

SEQ ID NO: 26       moltype = AA  length = 117
FEATURE             Location/Qualifiers
REGION              1..117
                    note = Synthetic
source              1..117
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 26
QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGTANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARWG GGAFDIWGQG TMVTVSS     117

SEQ ID NO: 27       moltype = AA  length = 109
FEATURE             Location/Qualifiers
REGION              1..109
                    note = Synthetic
source              1..109
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 27
EIVLTQSPGT LSLSPGERAT LSCRASQSVG GYLAWYQQKP GQAPRLLIYD ASNRATGIPA  60
RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RNNWPPMYTF GQGTKLEIK              109

SEQ ID NO: 28       moltype = AA  length = 242
FEATURE             Location/Qualifiers
REGION              1..242
                    note = Synthetic
source              1..242
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 28
QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGTANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARWG GGAFDIWGQG TMVTVSSGGG  120
GSGGGGSGGG GSEIVLTQSP GTLSLSPGER ATLSCRASQS VGGYLAWYQQ KPGQAPRLLI  180
YDASNRATGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC QQRNNWPPMY TFGQGTKLEI  240
KR                                                              242

SEQ ID NO: 29       moltype = AA  length = 84
FEATURE             Location/Qualifiers
REGION              1..84
                    note = Synthetic
source              1..84
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 29
FVPVFLPAKP TTTPAPRPPT PAPTIASQPL SLRPEACRPA AGGAVHTRGL DFACDIYIWA  60
PLAGTCGVLL LSLVITLYCN HRNR                                      84

SEQ ID NO: 30       moltype = AA  length = 67
FEATURE             Location/Qualifiers
REGION              1..67
                    note = Synthetic
source              1..67
                    mol_type = protein
                    organism = synthetic construct
SEQUENCE: 30
IEVMYPPPYL DNEKSNGTII HVKGKHLCPS PLFPGPSKPF WVLVVVGGVL ACYSLLVTVA  60
FIIFWVR                                                         67
```

-continued

SEQ ID NO: 31 moltype = AA length = 69
FEATURE Location/Qualifiers
REGION 1..69
note = Synthetic
source 1..69
mol_type = protein
organism = synthetic construct
SEQUENCE: 31
TTTPAPRPPT PAPTIASQPL SLRPEACRPA AGGAVHTRGL DFACDIYIWA PLAGTCGVLL 60
LSLVITLYC 69

SEQ ID NO: 32 moltype = AA length = 40
FEATURE Location/Qualifiers
REGION 1..40
note = Synthetic
source 1..40
mol_type = protein
organism = synthetic construct
SEQUENCE: 32
SKRSRLLHSD YMNMTPRRPG PTRKHYQPYA PPRDFAAYRS 40

SEQ ID NO: 33 moltype = AA length = 47
FEATURE Location/Qualifiers
REGION 1..47
note = Synthetic
source 1..47
mol_type = protein
organism = synthetic construct
SEQUENCE: 33
RFSVVKRGRK KLLYIFKQPF MRPVQTTQEE DGCSCRFPEE EEGGCEL 47

SEQ ID NO: 34 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = Synthetic
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 34
RVKFSRSADA PAYQQGQNQL YNELNLGRRE EYDVLDKRRG RDPEMGGKPR RKNPQEGLYN 60
ELQKDKMAEA YSEIGMKGER RRGKGHDGLY QGLSTATKDT YDALHMQALP PR 112

SEQ ID NO: 35 moltype = AA length = 40
FEATURE Location/Qualifiers
REGION 1..40
note = Synthetic
source 1..40
mol_type = protein
organism = synthetic construct
SEQUENCE: 35
SKRSRLLHSD YMNMTPRRPG PTRKHYQPYA PPRDFAAYRS 40

SEQ ID NO: 36 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = Synthetic
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 36
RVKFSRSADA PAYQQGQNQL YNELNLGRRE EYDVLDKRRG RDPEMGGKPR RKNPQEGLYN 60
ELQKDKMAEA YSEIGMKGER RRGKGHDGLY QGLSTATKDT YDALHMQALP PR 112

SEQ ID NO: 37 moltype = AA length = 42
FEATURE Location/Qualifiers
REGION 1..42
note = Synthetic
source 1..42
mol_type = protein
organism = synthetic construct
SEQUENCE: 37
KRGRKKLLYI FKQPFMRPVQ TTQEEDGCSC RFPEEEEGGC EL 42

SEQ ID NO: 38 moltype = AA length = 112
FEATURE Location/Qualifiers

-continued

REGION 1..112
note = Synthetic
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 38
RVKFSRSADA PAYKQGQNQL YNELNLGRRE EYDVLDKRRG RDPEMGGKPR RKNPQEGLYN 60
ELQKDKMAEA YSEIGMKGER RRGKGHDGLY QGLSTATKDT YDALHMQALP PR 112

SEQ ID NO: 39 moltype = AA length = 703
FEATURE Location/Qualifiers
REGION 1..703
note = Synthetic
source 1..703
mol_type = protein
organism = synthetic construct
SEQUENCE: 39
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCATGG SGRYALDIWG QGTMVTVSSG 120
GGGSGGGGSG GGGSEIVLTQ SPATLSLSPG ERATLSCRAS QSVSSYLAWY QQKPGQAPRL 180
LIYDASNRAT GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQRSNWPP SYTFGQGTKL 240
EIKRAEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED 300
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 360
PIEKTISKAK GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 420
YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGKKDP 480
KAAAIEVMYP PPYLDNEKSN GTIIHVKGKH LCPSPLFPGP SKPFWVLVVV GGVLACYSLL 540
VTVAFIIFWV RSKRSRLLHS DYMNMTPRRP GPTRKHYQPY APPRDFAAYR SRVKFSRSAD 600
APAYQQGQNQ LYNELNLGRR EEYDVLDKRR GRDPEMGGKP RRKNPQEGLY NELQKDKMAE 660
AYSEIGMKGE RRRGKGHDGL YQGLSTATKD TYDALHMQAL PPR 703

SEQ ID NO: 40 moltype = AA length = 707
FEATURE Location/Qualifiers
REGION 1..707
note = Synthetic
source 1..707
mol_type = protein
organism = synthetic construct
SEQUENCE: 40
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCATGG SGRYALDIWG QGTMVTVSSG 120
GGGSGGGGSG GGGSEIVLTQ SPATLSLSPG ERATLSCRAS QSVSSYLAWY QQKPGQAPRL 180
LIYDASNRAT GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQRSNWPP SYTFGQGTKL 240
EIKRAEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED 300
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 360
PIEKTISKAK GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 420
YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGKKDP 480
KAAATTTPAP RPPTPAPTIA SQPLSLRPEA CRPAAGGAVH TRGLDFACDI YIWAPLAGTC 540
GVLLLSLVIT LYCKRGRKKL LYIFKQPFMR PVQTTQEEDG CSCRFPEEEE GGCELRVKFS 600
RSADAPAYKQ GQNQLYNELN LGRREEYDVL DKRRGRDPEM GGKPRRKNPQ EGLYNELQKD 660
KMAEAYSEIG MKGERRRGKG HDGLYQGLST ATKDTYDALH MQALPPR 707

SEQ ID NO: 41 moltype = AA length = 767
FEATURE Location/Qualifiers
REGION 1..767
note = Synthetic
source 1..767
mol_type = protein
organism = synthetic construct
SEQUENCE: 41
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCATGG SGRYALDIWG QGTMVTVSSG 120
GGGSGGGGSG GGGSEIVLTQ SPATLSLSPG ERATLSCRAS QSVSSYLAWY QQKPGQAPRL 180
LIYDASNRAT GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQRSNWPP SYTFGQGTKL 240
EIKRAEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED 300
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 360
PIEKTISKAK GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 420
YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGKKDP 480
KAAAFVPVFL PAKPTTTPAP RPPTPAPTIA SQPLSLRPEA CRPAAGGAVH TRGLDFACDI 540
YIWAPLAGTC GVLLLSLVIT LYCNHRNRSK RSRLLHSDYM NMTPRRPGPT RKHYQPYAPP 600
RDFAAYRSRF SVVKRGRKKL LYIFKQPFMR PVQTTQEEDG CSCRFPEEEE GGCELRVKFS 660
RSADAPAYQQ GQNQLYNELN LGRREEYDVL DKRRGRDPEM GGKPRRKNPQ EGLYNELQKD 720
KMAEAYSEIG MKGERRRGKG HDGLYQGLST ATKDTYDALH MQALPPR 767

SEQ ID NO: 42 moltype = AA length = 714
FEATURE Location/Qualifiers
REGION 1..714

-continued

```
                     note = Synthetic
source               1..714
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 42
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARGG AGGSGSYYPL IWGQGTTVTV  120
SSGGGGSGGG GSGGGGSEIV LTQSPATLSL SPGERATLSC GASQSVSSSY LAWYQQKPGQ  180
APRLLIYDAS SRATGIPARF SGSGSGTDFT LTISSLEPED FAVYYCQQRS SWPPTWTFGQ  240
GTKLEIKRAE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV  300
SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK  360
ALPAPIEKTI SKAKGQPREP QVYTLPPSRD ELTKNQVSLT CLVKGFYPSD IAVEWESNGQ  420
PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG  480
KKDPKAAAIE GAAAAIEVMY PPPYLDNEKS NGTIIHVKGK HLCPSPLFPG PSKPFWVLVV  540
VGGVLACYSL LVTVAFIIFW VRSKRSRLLH SDYMNMTPRR PGPTRKHYQP YAPPRDFAAY  600
RSRVKFSRSA DAPAYQQGQN QLYNELNLGR REEYDVLDKR RGRDPEMGGK PRRKNPQEGL  660
YNELQKDKMA EAYSEIGMKG ERRRGKGHDG LYQGLSTATK DTYDALHMQA LPPR        714

SEQ ID NO: 43        moltype = AA  length = 711
FEATURE              Location/Qualifiers
REGION               1..711
                     note = Synthetic
source               1..711
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 43
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARGG AGGSGSYYPL IWGQGTTVTV  120
SSGGGGSGGG GSGGGGSEIV LTQSPATLSL SPGERATLSC GASQSVSSSY LAWYQQKPGQ  180
APRLLIYDAS SRATGIPARF SGSGSGTDFT LTISSLEPED FAVYYCQQRS SWPPTWTFGQ  240
GTKLEIKRAE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV  300
SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK  360
ALPAPIEKTI SKAKGQPREP QVYTLPPSRD ELTKNQVSLT CLVKGFYPSD IAVEWESNGQ  420
PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG  480
KKDPKAAATT TPAPRPPTPA PTIASQPLSL RPEACRPAAG GAVHTRGLDF ACDIYIWAPL  540
AGTCGVLLLS LVITLYCKRG RKKLLYIFKQ PFMRPVQTTQ EEDGCSCRFP EEEEGGCELR  600
VKFSRSADAP AYKQGQNQLY NELNLGRREE YDVLDKRRGR DPEMGGKPRR KNPQEGLYNE  660
LQKDKMAEAY SEIGMKGERR RGKGHDGLYQ GLSTATKDTY DALHMQALPP R           711

SEQ ID NO: 44        moltype = AA  length = 771
FEATURE              Location/Qualifiers
REGION               1..771
                     note = Synthetic
source               1..771
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 44
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARGG AGGSGSYYPL IWGQGTTVTV  120
SSGGGGSGGG GSGGGGSEIV LTQSPATLSL SPGERATLSC GASQSVSSSY LAWYQQKPGQ  180
APRLLIYDAS SRATGIPARF SGSGSGTDFT LTISSLEPED FAVYYCQQRS SWPPTWTFGQ  240
GTKLEIKRAE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV  300
SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK  360
ALPAPIEKTI SKAKGQPREP QVYTLPPSRD ELTKNQVSLT CLVKGFYPSD IAVEWESNGQ  420
PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG  480
KKDPKAAAFV PVFLPAKPTT TPAPRPPTPA PTIASQPLSL RPEACRPAAG GAVHTRGLDF  540
ACDIYIWAPL AGTCGVLLLS LVITLYCNHR NRSKRSRLLH SDYMNMTPRR PGPTRKHYQP  600
YAPPRDFAAY RSRFSVVKRG RKKLLYIFKQ PFMRPVQTTQ EEDGCSCRFP EEEEGGCELR  660
VKFSRSADAP AYQQGQNQLY NELNLGRREE YDVLDKRRGR DPEMGGKPRR KNPQEGLYNE  720
LQKDKMAEAY SEIGMKGERR RGKGHDGLYQ GLSTATKDTY DALHMQALPP R           771

SEQ ID NO: 45        moltype = AA  length = 701
FEATURE              Location/Qualifiers
REGION               1..701
                     note = Synthetic
source               1..701
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 45
QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGTANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARWG GGAFDIWGQG TMVTVSSGGG  120
GSGGGGSGGG GSEIVLTQSP GTLSLSPGER ATLSCRASQS VGGYLAWYQQ KPGQAPRLLI  180
YDASNRATGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC QQRNNWPPMY TFGQGTKLEI  240
KRAEPKSCDK THTCPPCPAP ELLGGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE  300
VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI  360
EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK  420
```

-continued

TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGKKDPKA 480
AAIEVMYPPP YLDNEKSNGT IIHVKGKHLC PSPLFPGPSK PFWVLVVVGG VLACYSLLVT 540
VAFIIFWVRS KRSRLLHSDY MNMTPRRPGP TRKHYQPYAP PRDFAAYRSR VKFSRSADAP 600
AYQQGQNQLY NELNLGRREE YDVLDKRRGR DPEMGGKPRR KNPQEGLYNE LQKDKMAEAY 660
SEIGMKGERR RGKGHDGLYQ GLSTATKDTY DALHMQALPP R 701

SEQ ID NO: 46 moltype = AA length = 705
FEATURE Location/Qualifiers
REGION 1..705
note = Synthetic
source 1..705
mol_type = protein
organism = synthetic construct
SEQUENCE: 46
QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGTANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARWG GGAFDIWGQG TMVTVSSGGG 120
GSGGGGSGGG GSEIVLTQSP GTLSLSPGER ATLSCRASQS VGGYLAWYQQ KPGQAPRLLI 180
YDASNRATGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC QQRNNWPPMY TFGQGTKLEI 240
KRAEPKSCDK THTCPPCPAP ELLGGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE 300
VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI 360
EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK 420
TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGKKDPKA 480
AATTTPAPRP PTPAPTIASQ PLSLRPEACR PAAGGAVHTR GLDFACDIYI WAPLAGTCGV 540
LLLSLVITLY CKRGRKKLLY IFKQPFMRPV QTTQEEDGCS CRFPEEEEGG CELRVKFSRS 600
ADAPAYKQGQ NQLYNELNLG RREEYDVLDK RRGRDPEMGG KPRRKNPQEG LYNELQKDKM 660
AEAYSEIGMK GERRRGKGHD GLYQGLSTAT KDTYDALHMQ ALPPR 705

SEQ ID NO: 47 moltype = AA length = 765
FEATURE Location/Qualifiers
REGION 1..765
note = Synthetic
source 1..765
mol_type = protein
organism = synthetic construct
SEQUENCE: 47
QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGTANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARWG GGAFDIWGQG TMVTVSSGGG 120
GSGGGGSGGG GSEIVLTQSP GTLSLSPGER ATLSCRASQS VGGYLAWYQQ KPGQAPRLLI 180
YDASNRATGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC QQRNNWPPMY TFGQGTKLEI 240
KRAEPKSCDK THTCPPCPAP ELLGGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE 300
VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI 360
EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK 420
TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGKKDPKA 480
AAFVPVFLPA KPTTTPAPRP PTPAPTIASQ PLSLRPEACR PAAGGAVHTR GLDFACDIYI 540
WAPLAGTCGV LLLSLVITLY CNHRNRSKRS RLLHSDYMNM TPRRPGPTRK HYQPYAPPRD 600
FAAYRSRFSV VKRGRKKLLY IFKQPFMRPV QTTQEEDGCS CRFPEEEEGG CELRVKFSRS 660
ADAPAYQQGQ NQLYNELNLG RREEYDVLDK RRGRDPEMGG KPRRKNPQEG LYNELQKDKM 720
AEAYSEIGMK GERRRGKGHD GLYQGLSTAT KDTYDALHMQ ALPPR 765

SEQ ID NO: 48 moltype = DNA length = 2112
FEATURE Location/Qualifiers
misc_feature 1..2112
note = Synthetic
source 1..2112
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 48
caagtccaac ttcagcagtc aggggcggag gtgaagaagc cgggctcctc cgtaaaggtg 60
tcgtgcaaag catcgggcgg tacattctcc tcctatgcga tctcatgggt gcgacaggca 120
cccgggcagg ggttggaatg gatgggtggt atcattccca ttctcgggat cgcgaactac 180
gcgcagaagt ttcaaggcag agtaacaatt actgcagacg agtccacctc aaccgcctat 240
atggaactgt cgtcacttcg gtccgaagat acagccgtgt actattgtgc aacgggaggc 300
agcgggaggt atgcccttga catttgggga caggggacaa tggtcacagt aagctccgga 360
ggtgggggat caggaggcgg tggatcgggt gggggaggat cggaaattgt actcactcag 420
tcaccggcga ctctctccct cagcccggga gagcgggcca ccttgtcatg cagagccagc 480
cagagcgtat catcctatct tgcgtggtat cagcaaaaac ccggtcaggc cccaaggttg 540
ctgatctacg atgcgtcgaa tcgcgcgaca ggaatccctg ctaggttctc cgggtcgggc 600
tcggggaccg actttacgct tacgatcagc tcgctggaac cggaggactt cgccgtctac 660
tactgccagc agcggtcgaa ttggccgcct tcctacacat ttggacaagg aacaaagctg 720
gaaatcaaga gagcggaacc gaaatcatgc gacaaaacgc acacctgtcc cccttgtccc 780
gctcccgagt tgctgggagg accgtcggtg ttcctctttc cgccaaaacc caaagatacg 840
ttgatgatct cgcgcacgcc cgaggtgaca tgtgtggtag tcgatgtctc gcacgaggac 900
cccgaagtca agttcaattg gtacgtggac ggggtggaag tccataatgc caagacgaaa 960
cctcgggagg agcagtacaa ctccacatat cgcgtagtct cggtgctcac cgtactgcat 1020
caggactggc ttaacggaaa ggaatacaag tgcaaagtgt caaacaaggc gttgccggca 1080
ccgattgaga aaacgatctc caaagccaag gggcaacccc gcgagcccca ggtctatact 1140

-continued

```
ctcccgccgt cgcgagatga gctcacgaag aaccaagtct cgcttacgtg cctcgtgaag  1200
ggtttctacc caagcgatat tgcggtggag tgggagagca atggacagcc ggagaacaac  1260
tataagacta ccccacccgt gcttgactcg gatggcagct tctttctgta ctcgaaactg  1320
accgtggaca aatcgagatg gcaacagggg aatgtctttt catgttccgt gatgcacgag  1380
gcgctccaca accactacac gcagaagagc ttgtcattga gcccagggaa gaaagaccca  1440
aaggcggccg caattgaagt tatgtatcct cctccttacc tagacaatga gaagagcaat  1500
ggaaccatta tccatgtgaa agggaaacac ctttgtccaa gtcccctatt tcccggacct  1560
tctaagccct tttgggtgct ggtggtggtt gggggagtcc tggcttgcta tagcttgcta  1620
gtaacagtgg cctttattat tttctgggtg aggagtaaga ggagcaggct cctgcacagt  1680
gactacatga acatgactcc ccgccgcccc gggcccaccc gcaagcatta ccagccctat  1740
gccccaccac gcgacttcgc agcctatcgc tccagagtga agttcagcag gagcgcagac  1800
gccccccgcgt accagcaggg ccagaaccag ctctataacg agctcaatct aggacgaaga  1860
gaggagtacg atgttttgga caagagacgt ggccgggacc ctgagatggg gggaaagccg  1920
agaaggaaga accctcagga aggcctgtac aatgaactgc agaaagataa gatggcggag  1980
gcctacagtg agattgggat gaaaggcgag cgccggaggg gcaaggggca cgatggcctt  2040
taccagggtc tcagtacagc caccaaggac acctacgacg cccttcacat gcaggccctg  2100
ccccctcgct aa                                                      2112
```

```
SEQ ID NO: 49          moltype = DNA  length = 2124
FEATURE                Location/Qualifiers
misc_feature           1..2124
                       note = Synthetic
source                 1..2124
                       mol_type = other DNA
                       organism = synthetic construct
SEQUENCE: 49
caagtccaac ttcagcagtc aggggcggag gtgaagaagc cgggctcctc cgtaaaggtg  60
tcgtgcaaag catcgggcgg tacattctcc tcctatgcga tctcatgggt gcgacaggca  120
cccgggcagg ggttggaatg gatgggtggt atcattccca ttctcgggat cgcgaactac  180
gcgcagaagt ttcaaggcag agtaacaatt actgcagacg agtccacctc aaccgcctat  240
atggaactgt cgtcacttcg gtccgaagat acagccgtgt actattgtgc aacgggaggc  300
agcgggaggt atgcccttga catttgggga caggggacaa tggtcacagt aagctccgga  360
ggtgggggat caggaggcgg tggatcgggt gggggaggat cggaaattgt actcactcag  420
tcaccggcga ctctctccct cagcccggga gagcgggcca ccttgtcatg cagagccagc  480
cagagcgtat catcctatct tgcgtggtat cagcaaaaac ccggtcaggc cccaaggttg  540
ctgatctacg atgcgtcgaa tcgcgcgaca ggaatccctg ctaggttctc cgggtcgggc  600
tcggggaccg actttacgct tacgatcagc tcgctggaac cggaggactt cgccgtctac  660
tactgccagc agcggtcgaa ttggccgcct tcctacacat ttggacaagg aacaaagctg  720
gaaatcaaga gagcggaacc gaaatcatgc gacaaaacgc acacctgtcc cccttgtccc  780
gctcccgagt tgctgggagg accgtcggtg ttcctctttc cgccaaaacc caaagatacg  840
ttgatgatct cgcgcacgcc cgaggtgaca tgtgtggtag tcgatgtctc gcacgaggac  900
cccgaagtca agttcaattg gtacgtggac ggggtggaag tccataatgc caagacgaaa  960
cctcgggagg agcagtacaa ctccacatat cgcgtagtct cggtgctcac cgtactgcat  1020
caggactggc ttaacggaaa ggaatacaag tgcaaagtgt caaacaaggc gttgccggca  1080
ccgattgaga aaacgatctc caaagccaag gggcaacccc gcgagcccca ggtctatact  1140
ctcccgccgt cgcgagatga gctcacgaag aaccaagtct cgcttacgtg cctcgtgaag  1200
ggtttctacc caagcgatat tgcggtggag tgggagagca atggacagcc ggagaacaac  1260
tataagacta ccccacccgt gcttgactcg gatggcagct tctttctgta ctcgaaactg  1320
accgtggaca aatcgagatg gcaacagggg aatgtctttt catgttccgt gatgcacgag  1380
gcgctccaca accactacac gcagaagagc ttgtcattga gcccagggaa gaaagaccca  1440
aaggcggccg caaccacgac gccagcgccg cgaccaccaa caccggcgcc caccatcgcg  1500
tcgcagcccc tgtccctgcg cccagaggcg tgccggccag cggcgggggg cgcagtgcac  1560
acgaggggcc tggacttcgc ctgtgatatc tacatctggg cgcccttggc cgggacttgt  1620
ggggtccttc tcctgtcact ggttatcacc ctttactgca aacggggcag aaagaaactc  1680
ctgtatatat tcaaacaacc atttatgaga ccagtacaaa ctactcaaga ggaagatggc  1740
tgtagctgcc gatttccaga agaagaagaa ggaggatgtg aactgagagt gaagttcagc  1800
aggagcgcag acgcccccgc gtacaagcag ggccagaacc agctctataa cgagctcaat  1860
ctaggacgaa gagaggagta cgatgttttg gacaagagac gtggccggga ccctgagatg  1920
gggggaaagc cgagaaggaa gaaccctcag gaaggcctgt acaatgaact gcagaaagat  1980
aagatggcgg aggcctacag tgagattggg atgaaaggcg agcgccggag gggcaagggg  2040
cacgatggcc tttaccaggg tctcagtaca gccaccaagg acacctacga cgcccttcac  2100
atgcaggccc tgccccctcg ctaa                                         2124
```

```
SEQ ID NO: 50          moltype = DNA  length = 2304
FEATURE                Location/Qualifiers
misc_feature           1..2304
                       note = Synthetic
source                 1..2304
                       mol_type = other DNA
                       organism = synthetic construct
SEQUENCE: 50
caagtccaac ttcagcagtc aggggcggag gtgaagaagc cgggctcctc cgtaaaggtg  60
tcgtgcaaag catcgggcgg tacattctcc tcctatgcga tctcatgggt gcgacaggca  120
cccgggcagg ggttggaatg gatgggtggt atcattccca ttctcgggat cgcgaactac  180
gcgcagaagt ttcaaggcag agtaacaatt actgcagacg agtccacctc aaccgcctat  240
atggaactgt cgtcacttcg gtccgaagat acagccgtgt actattgtgc aacgggaggc  300
```

-continued

```
agcgggaggt atgcccttga catttgggga caggggacaa tggtcacagt aagctccgga  360
ggtgggggat caggaggcgg tggatcgggt gggggaggat cggaaattgt actcactcag  420
tcaccggcga ctctctccct cagcccggga gagcgggcca ccttgtcatg cagagccagc  480
cagagcgtat catcctatct tgcgtggtat cagcaaaaac ccggtcaggc cccaaggttg  540
ctgatctacg atgcgtcgaa tcgcgcgaca ggaatccctg ctaggttctc cgggtcgggc  600
tcggggaccg actttacgct tacgatcagc tcgctggaac cggaggactt cgccgtctac  660
tactgccagc agcggtcgaa ttggccgcct tcctacacat ttggacaagg aacaaagctg  720
gaaatcaaga gagcggaacc gaaatcatgc gacaaaacgc acacctgtcc cccttgtccc  780
gctcccgagt tgctgggagg accgtcggtg ttcctctttc cgccaaaacc caaagatacg  840
ttgatgatct cgcgcacgcc cgaggtgaca tgtgtggtag tcgatgtctc gcacgaggac  900
cccgaagtca agttcaattg gtacgtggac ggggtggaag tccataatgc caagacgaaa  960
cctcgggagg agcagtacaa ctccacatat cgcgtagtct cggtgctcac cgtactgcat  1020
caggactggc ttaacggaaa ggaatacaag tgcaaagtgt caaacaaggc gttgccggca  1080
ccgattgaga aaacgatctc caaagccaag gggcaacccc gcgagcccca ggtctatact  1140
ctcccgccgt cgcgagatga gctcacgaag aaccaagtct cgcttacgtg cctcgtgaag  1200
ggtttctacc caagcgatat tgcggtggag tgggagagca atggacagcc ggagaacaac  1260
tataagacta ccccacccgt gcttgactcg gatggcagct tctttctgta ctcgaaactg  1320
accgtggaca aatcgagatg gcaacagggg aatgtctttt catgttccgt gatgcacgag  1380
gcgctccaca accactacac gcagaagagc ttgtcattga gcccagggaa gaaagaccca  1440
aaggcggccg cattcgtgcc ggtcttcctg ccagcgaagc ccaccacgac gccagcgccg  1500
cgaccaccaa caccggcgcc caccatcgcg tcgcagcccc tgtccctgcg cccagaggcg  1560
tgccggccag cggcgggggg cgcagtgcac acgaggggcc tggacttcgc ctgtgatatc  1620
tacatctggg cgcccttggc cgggacttgt ggggtccttc tcctgtcact ggttatcacc  1680
ctttactgca accacaggaa caggagtaag aggagcaggc tcctgcacag tgactacatg  1740
aacatgactc cccgccgccc cgggcccacc cgcaagcatt accagcccta tgccccacca  1800
cgcgacttcg cagcctatcg ctcccgtttc tctgttgtta aacggggcag aaagaagctc  1860
ctgtatatat tcaaacaacc atttatgaga ccagtacaaa ctactcaaga ggaagatggc  1920
tgtagctgcc gatttccaga agaagaagaa ggaggatgtg aactgagagt gaagttcagc  1980
aggagcgcag acgccccccgc gtaccagcag ggccagaacc agctctataa cgagctcaat  2040
ctaggacgaa gagaggagta cgatgttttg gacaagagac gtggccggga ccctgagatg  2100
gggggaaagc cgagaaggaa gaaccctcag gaaggcctgt acaatgaact gcagaaagat  2160
aagatggcgg aggcctacag tgagattggg atgaaaggcg agcgccggag gggcaagggg  2220
cacgatggcc tttaccaggg tctcagtaca gccaccaagg acacctacga cgcccttcac  2280
atgcaggccc tgcccccctcg ctaa                                        2304

SEQ ID NO: 51          moltype = DNA  length = 2112
FEATURE                Location/Qualifiers
misc_feature           1..2112
                       note = Synthetic
source                 1..2112
                       mol_type = other DNA
                       organism = synthetic construct
SEQUENCE: 51
caagtccaac ttcagcagtc aggggcggag gtgaagaagc cgggctcctc cgtaaaggtg  60
tcgtgcaaag catcgggcgg tacattctcc tcctatgcga tctcatgggt gcgacaggca  120
cccgggcagg ggttggaatg gatgggtggt atcattccca ttctcgggat cgcgaactac  180
gcgcagaagt ttcaaggcag agtaacaatt actgcagacg agtccacctc aaccgcctat  240
atggaactgt cgtcacttcg gtccgaagat acagccgtgt actattgtgc aacgggaggc  300
agcgggaggt atgcccttga catttgggga caggggacaa tggtcacagt aagctccgga  360
ggtgggggat caggaggcgg tggatcgggt gggggaggat cggaaattgt actcactcag  420
tcaccggcga ctctctccct cagcccggga gagcgggcca ccttgtcatg cagagccagc  480
cagagcgtat catcctatct tgcgtggtat cagcaaaaac ccggtcaggc cccaaggttg  540
ctgatctacg atgcgtcgaa tcgcgcgaca ggaatccctg ctaggttctc cgggtcgggc  600
tcggggaccg actttacgct tacgatcagc tcgctggaac cggaggactt cgccgtctac  660
tactgccagc agcggtcgaa ttggccgcct tcctacacat ttggacaagg aacaaagctg  720
gaaatcaaga gagcggaacc gaaatcatgc gacaaaacgc acacctgtcc cccttgtccc  780
gctcccgagt tgctgggagg accgtcggtg ttcctctttc cgccaaaacc caaagatacg  840
ttgatgatct cgcgcacgcc cgaggtgaca tgtgtggtag tcgatgtctc gcacgaggac  900
cccgaagtca agttcaattg gtacgtggac ggggtggaag tccataatgc caagacgaaa  960
cctcgggagg agcagtacaa ctccacatat cgcgtagtct cggtgctcac cgtactgcat  1020
caggactggc ttaacggaaa ggaatacaag tgcaaagtgt caaacaaggc gttgccggca  1080
ccgattgaga aaacgatctc caaagccaag gggcaacccc gcgagcccca ggtctatact  1140
ctcccgccgt cgcgagatga gctcacgaag aaccaagtct cgcttacgtg cctcgtgaag  1200
ggtttctacc caagcgatat tgcggtggag tgggagagca atggacagcc ggagaacaac  1260
tataagacta ccccacccgt gcttgactcg gatggcagct tctttctgta ctcgaaactg  1320
accgtggaca aatcgagatg gcaacagggg aatgtctttt catgttccgt gatgcacgag  1380
gcgctccaca accactacac gcagaagagc ttgtcattga gcccagggaa gaaagaccca  1440
aaggcggccg caattgaagt tatgtatcct cctccttacc tagacaatga gaagagcaat  1500
ggaaccatta tccatgtgaa agggaaacac ctttgtccaa gtcccctatt tcccggacct  1560
tctaagccct tttgggtgct ggtggtggtt gggggagtcc tggcttgcta tagcttgcta  1620
gtaacagtgg cctttattat tttctgggtg aggagtaaga ggagcaggct cctgcacagt  1680
gactacatga acatgactcc ccgccgcccc gggcccaccc gcaagcatta ccagccctat  1740
gccccaccac gcgacttcgc agcctatcgc tccagagtga agttcagcag gagcgcagac  1800
gccccccgcgt accagcaggg ccagaaccag ctctataacg agctcaatct aggacgaaga  1860
gaggagtacg atgttttgga caagagacgt ggccgggacc ctgagatggg gggaaagccg  1920
agaaggaaga accctcagga aggcctgtac aatgaactgc agaaagataa gatggcggag  1980
```

-continued

gcctacagtg agattgggat gaaaggcgag cgccggaggg gcaaggggca cgatggcctt 2040
taccagggtc tcagtacagc caccaaggac acctacgacg cccttcacat gcaggccctg 2100
ccccctcgct aa 2112

SEQ ID NO: 52 moltype = DNA length = 2136
FEATURE Location/Qualifiers
misc_feature 1..2136
note = Synthetic
source 1..2136
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 52
caagtccagc tgcagcagtc aggagctgag gtgaagaagc ctggtagctc tgtcaaagtg 60
tcttgcaaag cctctggtgg tactttcagc tcttacgcca tttcttgggt gagacaggca 120
cccggacagg gtcttgaatg gatgggtgga atcatcccga ttcttgggat tgctaattac 180
gcacaaaagt tccagggaag ggtgaccatc accgcagacg aatctacctc cactgcttac 240
atggaactct cttccctgcg gtccgaggac accgccgtct actattgtgc caggggcggt 300
gccggaggaa gcggttctta ctatccgctg atttggggac aaggaaccac tgtgaccgtg 360
agctctggtg gaggcggatc cggtggtgga gggtccggag gcggaggatc tgagatcgtg 420
ctcactcaga gcccagccac ccttagcctg agccctggtg agcgcgccac cctctcatgc 480
ggtgcctcac agagcgtgag ctcaagctat ctggcatggt accagcaaaa gccagggcag 540
gccccgaggc tcctgatcta cgacgcatca tcacgggcta ccggtatccc ggcacgcttc 600
tctggaagcg gatcaggcac cgacttcacc ctgaccattt cttcacttga gccagaggac 660
tttgccgtgt actactgcca gcagcgctca agctggccgc ctacttggac tttcggacag 720
gggaccaagc tggagatcaa gcgcgctgaa cccaagtcat gcgataagac ccacacttgt 780
ccaccctgtc cagcccctga actgctcgga ggtccgtcag tgtttctttt cccgccaaag 840
cctaaggaca ctctgatgat ctctcggacc cctgaagtga cttgcgtcgt cgtggacgtg 900
tcacacgagg atcccgaggt gaagttcaac tggtatgtgg acggggtgga agtgcataat 960
gctaagacca agcccaggga ggaacaatac aactcaacct accgcgtggt gtccgtgctc 1020
accgtccttc atcaagactg gctgaacgga aaagagtata agtgcaaagt ctccaataag 1080
gctctgccag cccctatcga aaagaccatt tcaaaggcca aggggcagcc tagagagccc 1140
caagtgtaca cccttcctcc ctcaagagat gagctcacta agaatcaggt cagcctgact 1200
tgtcttgtga aaggcttcta tcccagcgat attgccgtcg aatgggaaag caatggacaa 1260
ccagagaaca actacaagac caccccgcct gtgctggact ccgacggctc tttcttcctt 1320
tactcaaagc tgaccgtcga taagagccgg tggcaacagg ggaatgtgtt cagctgctcc 1380
gtcatgcacg aggctctcca taaccactac acccagaaaa gcctgtctct ttctccgggc 1440
aaaaaggacc caaaggcggc cgcaaccacg acgccagcgc cgcgaccacc aacaccggcg 1500
cccaccatcg cgtcgcagcc cctgtccctg cgcccagagg cgtgccggcc agcggcgggg 1560
ggcgcagtgc acacgagggg gctggacttc gcctgtgata tctacatctg ggcgcccttg 1620
gccgggactt gtggggtcct tctcctgtca ctggttatca ccctttactg caaacggggc 1680
agaaagaaac tcctgtatat attcaaacaa ccatttatga gaccagtaca aactactcaa 1740
gaggaagatg gctgtagctg ccgatttcca gaagaagaag aaggaggatg tgaactgaga 1800
gtgaagttca gcaggagcgc agacgccccc gcgtacaagc agggccagaa ccagctctat 1860
aacgagctca atctaggacg aagagaggag tacgatgttt tggacaagag acgtggccgg 1920
gaccctgaga tgggggggaaa gccgagaagg aagaaccctc aggaaggcct gtacaatgaa 1980
ctgcagaaag ataagatggc ggaggcctac agtgagattg ggatgaaagg cgagcgccgg 2040
aggggcaagg ggcacgatgg cctttaccag ggtctcagta cagccaccaa ggacacctac 2100
gacgcccttc acatgcaggc cctgcccccc cgctaa 2136

SEQ ID NO: 53 moltype = DNA length = 2316
FEATURE Location/Qualifiers
misc_feature 1..2316
note = Synthetic
source 1..2316
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 53
caagtccagc tgcagcagtc aggagctgag gtgaagaagc ctggtagctc tgtcaaagtg 60
tcttgcaaag cctctggtgg tactttcagc tcttacgcca tttcttgggt gagacaggca 120
cccggacagg gtcttgaatg gatgggtgga atcatcccga ttcttgggat tgctaattac 180
gcacaaaagt tccagggaag ggtgaccatc accgcagacg aatctacctc cactgcttac 240
atggaactct cttccctgcg gtccgaggac accgccgtct actattgtgc caggggcggt 300
gccggaggaa gcggttctta ctatccgctg atttggggac aaggaaccac tgtgaccgtg 360
agctctggtg gaggcggatc cggtggtgga gggtccggag gcggaggatc tgagatcgtg 420
ctcactcaga gcccagccac ccttagcctg agccctggtg agcgcgccac cctctcatgc 480
ggtgcctcac agagcgtgag ctcaagctat ctggcatggt accagcaaaa gccagggcag 540
gccccgaggc tcctgatcta cgacgcatca tcacgggcta ccggtatccc ggcacgcttc 600
tctggaagcg gatcaggcac cgacttcacc ctgaccattt cttcacttga gccagaggac 660
tttgccgtgt actactgcca gcagcgctca agctggccgc ctacttggac tttcggacag 720
gggaccaagc tggagatcaa gcgcgctgaa cccaagtcat gcgataagac ccacacttgt 780
ccaccctgtc cagcccctga actgctcgga ggtccgtcag tgtttctttt cccgccaaag 840
cctaaggaca ctctgatgat ctctcggacc cctgaagtga cttgcgtcgt cgtggacgtg 900
tcacacgagg atcccgaggt gaagttcaac tggtatgtgg acggggtgga agtgcataat 960
gctaagacca agcccaggga ggaacaatac aactcaacct accgcgtggt gtccgtgctc 1020
accgtccttc atcaagactg gctgaacgga aaagagtata agtgcaaagt ctccaataag 1080
gctctgccag cccctatcga aaagaccatt tcaaaggcca aggggcagcc tagagagccc 1140

-continued

caagtgtaca cccttcctcc ctcaagagat gagctcacta agaatcaggt cagcctgact 1200
tgtcttgtga aaggcttcta tcccagcgat attgccgtcg aatgggaaag caatggacaa 1260
ccagagaaca actacaagac caccccgcct gtgctggact ccgacggctc tttcttcctt 1320
tactcaaagc tgaccgtcga taagagccgg tggcaacagg ggaatgtgtt cagctgctcc 1380
gtcatgcacg aggctctcca taaccactac acccagaaaa gcctgtctct ttctccgggc 1440
aaaaaggacc caaaggcggc cgcattcgtg ccggtcttcc tgccagcgaa gcccaccacg 1500
acgccagcgc cgcgaccacc aacaccggcg cccaccatcg cgtcgcagcc cctgtccctg 1560
cgcccagagg cgtgccggcc agcggcgggg ggcgcagtgc acacgagggg gctggacttc 1620
gcctgtgata tctacatctg ggcgcccttg gccgggactt gtggggtcct tctcctgtca 1680
ctggttatca ccctttactg caaccacagg aacaggagta agaggagcag gctcctgcac 1740
agtgactaca tgaacatgac tccccgccgc cccgggccca cccgcaagca ttaccagccc 1800
tatgccccac cacgcgactt cgcagcctat cgctcccgtt tctctgttgt taaacggggc 1860
agaaagaagc tcctgtatat attcaaacaa ccatttatga gaccagtaca aactactcaa 1920
gaggaagatg gctgtagctg ccgatttcca gaagaagaag aaggaggatg tgaactgaga 1980
gtgaagttca gcaggagcgc agacgccccc gcgtaccagc agggccagaa ccagctctat 2040
aacgagctca atctaggacg aagagaggag tacgatgttt tggacaagag acgtggccgg 2100
gaccctgaga tgggggaaa gccgagaagg aagaaccctc aggaaggcct gtacaatgaa 2160
ctgcagaaag ataagatggc ggaggcctac agtgagattg ggatgaaagg cgagcgccgg 2220
aggggcaagg ggcacgatgg cctttaccag ggtctcagta cagccaccaa ggacacctac 2280
gacgcccttc acatgcaggc cctgcccct cgctaa 2316

SEQ ID NO: 54 moltype = DNA length = 2106
FEATURE Location/Qualifiers
misc_feature 1..2106
note = Synthetic
source 1..2106
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 54
caagtccagc tggtgcaaag cggagcagaa gtgaagaagc ctggatcctc tgtgaaggtc 60
agctgcaagg cctctggagg taccttcagc tcttacgcaa tttcttgggt gcgccaggct 120
cccgggcagg gactggagtg gatgggagga atcatcccga tccttggtac cgctaattac 180
gcccagaaat ttcagggtcg ggtgaccatc accgcagacg agtcaacctc aaccgcttac 240
atggaacttt ctagcctccg cagcgaggac accgccgtct actattgcgc aagatggggt 300
ggtggtgcct tcgacatttg gggacagggc actatggtca ccgtgagctc cggtggagga 360
ggatctggcg gaggagggtc aggcggaggt gggtcagaga ttgtgctgac ccagtcaccc 420
gggactctgt ccctttctcc tggtgagcgc gctactctgt cttgtagggc ctcacaatca 480
gtgggcggct atctcgcctg gtatcagcag aaaccagggc aggcccctag gcttctcatc 540
tacgacgcct ccaaccgggc aactggcatt ccagcccgct tcagcggaag cggatccgga 600
accgacttta ctctgactat ctcctcactg gaaccggagg acttcgcagt gtactactgc 660
cagcagcgga ataactggcc accgatgtac actttcggac aggggaccaa gctggagatc 720
aagcgcgctg aacccaagtc atgcgataag acccacactt gtccaccctg tccagccccc 780
gaactgctcg gaggtccgtc agtgtttctt ttcccgccaa agcctaagga cactctgatg 840
atctctcgga cccctgaagt gacttgcgtc gtcgtggacg tgtcacacga ggatcccgag 900
gtgaagttca actggtatgt ggacggggtg gaagtgcata atgctaagac caagcccagg 960
gaggaacaat acaactcaac ctaccgcgtg gtgtccgtgc tcaccgtcct tcatcaagac 1020
tggctgaacg gaaaagagta taagtgcaaa gtctccaata aggctctgcc agcccctatc 1080
gaaaagacca tttcaaaggc caaggggcag cctagagagc cccaagtgta caccttcct 1140
ccctcaagag atgagctcac taagaatcag gtcagcctga cttgtcttgt gaaaggcttc 1200
tatcccagcg atattgccgt cgaatgggaa agcaatggac aaccagagaa caactacaag 1260
accaccccgc ctgtgctgga ctccgacggc tctttcttcc tttactcaaa gctgaccgtc 1320
gataagagcc ggtggcaaca ggggaatgtg ttcagctgct ccgtcatgca cgaggctctc 1380
cataaccact acacccagaa aagcctgtct ctttctccgg gcaaaaagga cccaaaggcg 1440
gccgcaattg aagttatgta tcctcctcct tacctagaca atgagaagag caatggaacc 1500
attatccatg tgaaagggaa acacctttgt ccaagtcccc tatttcccgg accttctaag 1560
ccctttgggg tgctggtggt ggttgggggga gtcctggctt gctatagctt gctagtaaca 1620
gtggccttta ttatttctg ggtgaggagt aagaggagca ggctcctgca cagtgactac 1680
atgaacatga ctccccgccg ccccgggccc acccgcaagc attaccagcc ctatgcccca 1740
ccacgcgact tcgcagccta tcgctccaga gtgaagttca gcaggagcgc agacgccccc 1800
gcgtaccagc agggccagaa ccagctctat aacgagctca atctaggacg aagagaggag 1860
tacgatgttt tggacaagag acgtggccgg gaccctgaga tgggggaaa gccgagaagg 1920
aagaaccctc aggaaggcct gtacaatgaa ctgcagaaag ataagatggc ggaggcctac 1980
agtgagattg ggatgaaagg cgagcgccgg aggggcaagg ggcacgatgg cctttaccag 2040
ggtctcagta cagccaccaa ggacacctac gacgcccttc acatgcaggc cctgcccct 2100
cgctaa 2106

SEQ ID NO: 55 moltype = DNA length = 2118
FEATURE Location/Qualifiers
misc_feature 1..2118
note = Synthetic
source 1..2118
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 55
caagtccagc tggtgcaaag cggagcagaa gtgaagaagc ctggatcctc tgtgaaggtc 60
agctgcaagg cctctggagg taccttcagc tcttacgcaa tttcttgggt gcgccaggct 120

-continued

```
cccgggcagg gactggagtg gatgggagga atcatcccga tccttggtac cgctaattac  180
gcccagaaat ttcagggtcg ggtgaccatc accgcagacg agtcaacctc aaccgcttac  240
atggaacttt ctagcctccg cagcgaggac accgccgtct actattgcgc aagatggggt  300
ggtggtgcct tcgacatttg gggacagggc actatggtca ccgtgagctc cggtggagga  360
ggatctggcg gaggagggtc aggcggaggt gggtcagaga ttgtgctgac ccagtcaccc  420
gggactctgt ccctttctcc tggtgagcgc gctactctgt cttgtagggc ctcacaatca  480
gtgggcggct atctcgcctg gtatcagcag aaaccagggc aggcccctag gcttctcatc  540
tacgacgcct ccaaccgggc aactggcatt ccagcccgct tcagcggaag cggatccgga  600
accgacttta ctctgactat ctcctcactg gaaccggagg acttcgcagt gtactactgc  660
cagcagcgga ataactggcc accgatgtac actttcggac aggggaccaa gctggagatc  720
aagcgcgctg aacccaagtc atgcgataag acccacactt gtccaccctg tccagccccc  780
gaactgctcg gaggtccgtc agtgtttctt ttcccgccaa agcctaagga cactctgatg  840
atctctcgga cccctgaagt gacttgcgtc gtcgtggacg tgtcacacga ggatcccgag  900
gtgaagttca actggtatgt ggacggggtg gaagtgcata atgctaagac caagcccagg  960
gaggaacaat acaactcaac ctaccgcgtg gtgtccgtgc tcaccgtcct tcatcaagac  1020
tggctgaacg gaaaagagta taagtgcaaa gtctccaata aggctctgcc agcccctatc  1080
gaaaagacca tttcaaaggc caaggggcag cctagagagc cccaagtgta caccttcct  1140
ccctcaagag atgagctcac taagaatcag gtcagcctga cttgtcttgt gaaaggcttc  1200
tatcccagcg atattgccgt cgaatgggaa agcaatggac aaccagagaa caactacaag  1260
accaccccgc ctgtgctgga ctccgacggc tctttcttcc tttactcaaa gctgaccgtc  1320
gataagagcc ggtggcaaca ggggaatgtg ttcagctgct ccgtcatgca cgaggctctc  1380
cataaccact acacccagaa aagcctgtct ctttctccgg gcaaaaagga cccaaaggcg  1440
gccgcaacca cgacgccagc gccgcgacca ccaacaccgg cgcccaccat cgcgtcgcag  1500
cccctgtccc tgcgcccaga ggcgtgccgg ccagcggcgg ggggcgcagt gcacacgagg  1560
gggctggact tcgcctgtga tatctacatc tgggcgccct tggccgggac ttgtggggtc  1620
cttctcctgt cactggttat cacccttac tgcaaacggg gcagaaagaa actcctgtat  1680
atattcaaac aaccatttat gagaccagta caaactactc aagaggaaga tggctgtagc  1740
tgccgatttc cagaagaaga agaaggagga tgtgaactga gagtgaagtt cagcaggagc  1800
gcagacgccc ccgcgtacaa gcagggccag aaccagctct ataacgagct caatctagga  1860
cgaagagagg agtacgatgt tttggacaag agacgtggcc gggaccctga gatgggggga  1920
aagccgagaa ggaagaaccc tcaggaaggc ctgtacaatg aactgcagaa agataagatg  1980
gcggaggcct acagtgagat tgggatgaaa ggcgagcgcc ggaggggcaa ggggcacgat  2040
ggcctttacc agggtctcag tacagccacc aaggacacct acgacgccct tcacatgcag  2100
gccctgcccc ctcgctaa                                               2118
```

```
SEQ ID NO: 56          moltype = DNA  length = 2298
FEATURE                Location/Qualifiers
misc_feature           1..2298
                       note = Synthetic
source                 1..2298
                       mol_type = other DNA
                       organism = synthetic construct
SEQUENCE: 56
caagtccagc tggtgcaaag cggagcagaa gtgaagaagc ctggatcctc tgtgaaggtc  60
agctgcaagg cctctggagg taccttcagc tcttacgcaa tttcttgggt gcgccaggct  120
cccgggcagg gactggagtg gatgggagga atcatcccga tccttggtac cgctaattac  180
gcccagaaat ttcagggtcg ggtgaccatc accgcagacg agtcaacctc aaccgcttac  240
atggaacttt ctagcctccg cagcgaggac accgccgtct actattgcgc aagatggggt  300
ggtggtgcct tcgacatttg gggacagggc actatggtca ccgtgagctc cggtggagga  360
ggatctggcg gaggagggtc aggcggaggt gggtcagaga ttgtgctgac ccagtcaccc  420
gggactctgt ccctttctcc tggtgagcgc gctactctgt cttgtagggc ctcacaatca  480
gtgggcggct atctcgcctg gtatcagcag aaaccagggc aggcccctag gcttctcatc  540
tacgacgcct ccaaccgggc aactggcatt ccagcccgct tcagcggaag cggatccgga  600
accgacttta ctctgactat ctcctcactg gaaccggagg acttcgcagt gtactactgc  660
cagcagcgga ataactggcc accgatgtac actttcggac aggggaccaa gctggagatc  720
aagcgcgctg aacccaagtc atgcgataag acccacactt gtccaccctg tccagccccc  780
gaactgctcg gaggtccgtc agtgtttctt ttcccgccaa agcctaagga cactctgatg  840
atctctcgga cccctgaagt gacttgcgtc gtcgtggacg tgtcacacga ggatcccgag  900
gtgaagttca actggtatgt ggacggggtg gaagtgcata atgctaagac caagcccagg  960
gaggaacaat acaactcaac ctaccgcgtg gtgtccgtgc tcaccgtcct tcatcaagac  1020
tggctgaacg gaaaagagta taagtgcaaa gtctccaata aggctctgcc agcccctatc  1080
gaaaagacca tttcaaaggc caaggggcag cctagagagc cccaagtgta caccttcct  1140
ccctcaagag atgagctcac taagaatcag gtcagcctga cttgtcttgt gaaaggcttc  1200
tatcccagcg atattgccgt cgaatgggaa agcaatggac aaccagagaa caactacaag  1260
accaccccgc ctgtgctgga ctccgacggc tctttcttcc tttactcaaa gctgaccgtc  1320
gataagagcc ggtggcaaca ggggaatgtg ttcagctgct ccgtcatgca cgaggctctc  1380
cataaccact acacccagaa aagcctgtct ctttctccgg gcaaaaagga cccaaaggcg  1440
gccgcattcg tgccggtctt cctgccagcg aagcccacca cgacgccagc gccgcgacca  1500
ccaacaccgg cgcccaccat cgcgtcgcag cccctgtccc tgcgcccaga ggcgtgccgg  1560
ccagcggcgg ggggcgcagt gcacacgagg gggctggact tcgcctgtga tatctacatc  1620
tgggcgccct tggccgggac ttgtggggtc cttctcctgt cactggttat cacccttac  1680
tgcaaccaca ggaacaggag taagaggagc aggctcctgc acagtgacta catgaacatg  1740
actccccgcc gccccgggcc cacccgcaag cattaccagc cctatgcccc accacgcgac  1800
ttcgcagcct atcgctcccg tttctctgtt gttaaacggg gcagaaagaa gctcctgtat  1860
atattcaaac aaccatttat gagaccagta caaactactc aagaggaaga tggctgtagc  1920
tgccgatttc cagaagaaga agaaggagga tgtgaactga gagtgaagtt cagcaggagc  1980
```

-continued

gcagacgccc ccgcgtacca gcagggccag aaccagctct ataacgagct caatctagga 2040
cgaagagagg agtacgatgt tttggacaag agacgtggcc gggaccctga gatgggggga 2100
aagccgagaa ggaagaaccc tcaggaaggc ctgtacaatg aactgcagaa agataagatg 2160
gcggaggcct acagtgagat tgggatgaaa ggcgagcgcc ggaggggcaa ggggcacgat 2220
ggcctttacc agggtctcag tacagccacc aaggacacct acgacgccct tcacatgcag 2280
gccctgcccc ctcgctaa 2298

SEQ ID NO: 57 moltype = DNA length = 744
FEATURE Location/Qualifiers
misc_feature 1..744
note = Synthetic
source 1..744
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 57
caggtacagc tgcagcagtc aggggctgag gtgaagaagc ctggatcctc agtgaaggtc 60
tcctgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcatcccta tccttggtat agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaggaggg 300
gcgggcggtt cggggagtta ttatcccctc atctggggcc aagggaccac ggtcaccgtc 360
tcctcaggag gtggcgggtc tggtggaggc ggtagcggtg gtggcggatc cgaaattgtg 420
ttgacgcagt ctccagccac cctgtctttg tctccagggg aaagagccac cctctcctgc 480
ggggccagtc agagtgttag cagcagctac ttagcctggt accagcagaa acctggccag 540
gctcccaggc tcctcatcta tgatgcatcc agcagggcca ctggcatccc ggccaggttc 600
agtggcagtg ggtctgggac agacttcact ctcaccatca gcagcctaga gcctgaagat 660
tttgcagttt attactgtca gcagcgtagt agctggcctc ccacgtggac gttcggccaa 720
gggaccaagc tggaaatcaa acgt 744

SEQ ID NO: 58 moltype = DNA length = 732
FEATURE Location/Qualifiers
misc_feature 1..732
note = Synthetic
source 1..732
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 58
caggtacagc tgcagcagtc aggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcttgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggctcgagtg gatgggaggg atcatcccta tccttggtat agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc aacaggtggt 300
tcggggagat atgctttgga tatctggggc caagggacaa tggtcaccgt ctcttcagga 360
ggtggcgggt ctggtggagg cggtagcggt ggtggcggat ccgaaattgt gttgacgcag 420
tctccagcca ccctgtcctt gtctccaggg gaaagagcca ccctctcctg cagggccagt 480
cagagtgtta gcagctactt agcctggtac caacagaaac ctggccaggc tcccaggctc 540
ctcatctatg atgcatccaa cagggccact ggcatcccag ccaggttcag tggcagtggg 600
tctgggacag acttcactct caccatcagc agcctagagc ctgaagattt tgcagtttat 660
tactgtcagc agcgtagcaa ctggcctccg tcgtacactt ttggccaggg gaccaagctg 720
gagatcaaac gt 732

SEQ ID NO: 59 moltype = DNA length = 726
FEATURE Location/Qualifiers
misc_feature 1..726
note = Synthetic
source 1..726
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 59
caggtgcagc tggtgcaatc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcatcccta tccttggtac agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagatggggt 300
gggggagctt ttgatatctg gggccaaggg acaatggtca ccgtctcttc aggaggtggc 360
gggtctggtg gaggcggtag cggtggtggc ggatccgaaa ttgtgttgac gcagtctcca 420
ggcaccctgt ctttgtctcc aggggaaaga gccaccctct cctgcagggc cagtcagagt 480
gttgggggct acttagcctg gtaccaacag aaacctggcc aggctcccag gctcctcatc 540
tatgatgcat ccaacagggc caccggcatc ccagccaggt tcagtggcag tgggtctggg 600
acagacttca ctctcaccat cagcagccta gagcctgaag attttgcagt ttattactgt 660
cagcagcgta acaactggcc tccgatgtac acttttggcc aggggaccaa gctggaaatc 720
aaacgt 726

SEQ ID NO: 60 moltype = AA length = 21
FEATURE Location/Qualifiers
REGION 1..21

-continued

```
                     note = Synthetic
source               1..21
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 60
LLLVTSLLLC ELPHPAFLLI P                                          21

SEQ ID NO: 61        moltype = AA  length = 22
FEATURE              Location/Qualifiers
REGION               1..22
                     note = Synthetic
source               1..22
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 61
LLVTSLLLCE LPHPAFLLIP DT                                         22

SEQ ID NO: 62        moltype = AA  length = 24
FEATURE              Location/Qualifiers
REGION               1..24
                     note = Synthetic
source               1..24
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 62
MVLLVTSLLL CELPHPAFLL IPDT                                       24

SEQ ID NO: 63        moltype = DNA  length = 72
FEATURE              Location/Qualifiers
misc_feature         1..72
                     note = Synthetic
source               1..72
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 63
atggttttgc tggtgacatc gcttctgttg tgcgaattgc cccatcccgc attcctcctt  60
atccccgata cg                                                      72

SEQ ID NO: 64        moltype = DNA  length = 72
FEATURE              Location/Qualifiers
misc_feature         1..72
                     note = Synthetic
source               1..72
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 64
atggttctgc tggtgacttc actcctgctc tgtgaacttc cccatcccgc ttttctcctg  60
atccccgaca cc                                                      72

SEQ ID NO: 65        moltype = DNA  length = 16
FEATURE              Location/Qualifiers
misc_feature         1..16
                     note = Synthetic
source               1..16
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 65
ccctcgagcc gccacc                                                16

SEQ ID NO: 66        moltype =   length =
SEQUENCE: 66
000

SEQ ID NO: 67        moltype =   length =
SEQUENCE: 67
000

SEQ ID NO: 68        moltype =   length =
SEQUENCE: 68
000

SEQ ID NO: 69        moltype = DNA  length = 22
FEATURE              Location/Qualifiers
misc_feature         1..22
                     note = Synthetic
source               1..22
```

-continued

```
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 69
ccctcgagcc gccaccatgg tt                                          22

SEQ ID NO: 70        moltype = DNA  length = 21
FEATURE              Location/Qualifiers
misc_feature         1..21
                     note = Synthetic
source               1..21
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 70
gcggccgcaa ttgaaggcgc g                                           21

SEQ ID NO: 71        moltype = AA  length = 237
FEATURE              Location/Qualifiers
REGION               1..237
                     note = Synthetic
source               1..237
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 71
AEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK  60
FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK  120
TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT  180
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGKKDPK     237

SEQ ID NO: 72        moltype = DNA  length = 711
FEATURE              Location/Qualifiers
misc_feature         1..711
                     note = Synthetic
source               1..711
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 72
gctgaaccca agtcatgcga taagacccac acttgtccac cctgtccagc ccctgaactg  60
ctcggaggtc cgtcagtgtt tcttttcccg ccaaagccta aggacactct gatgatctct  120
cggacccctg aagtgacttg cgtcgtcgtg gacgtgtcac acgaggatcc cgaggtgaag  180
ttcaactggt atgtggacgg ggtggaagtg cataatgcta agaccaagcc cagggaggaa  240
caatacaact caacctaccg cgtggtgtcc gtgctcaccg tccttcatca agactggctg  300
aacggaaaag agtataagtg caaagtctcc aataaggctc tgccagcccc tatcgaaaag  360
accatttcaa aggccaaggg gcagcctaga gagccccaag tgtacaccct tcctccctca  420
agagatgagc tcactaagaa tcaggtcagc ctgacttgtc ttgtgaaagg cttctatccc  480
agcgatattg ccgtcgaatg ggaaagcaat ggacaaccag agaacaacta caagaccacc  540
ccgcctgtgc tggactccga cggctctttc ttcctttact caaagctgac cgtcgataag  600
agccggtggc aacaggggaa tgtgttcagc tgctccgtca tgcacgaggc tctccataac  660
cactacaccc agaaaagcct gtctctttct ccgggcaaaa aggacccaaa g           711

SEQ ID NO: 73        moltype = AA  length = 219
FEATURE              Location/Qualifiers
REGION               1..219
                     note = Synthetic
source               1..219
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 73
IEVMYPPPYL DNEKSNGTII HVKGKHLCPS PLFPGPSKPF WVLVVVGGVL ACYSLLVTVA  60
FIIFWVRSKR SRLLHSDYMN MTPRRPGPTR KHYQPYAPPR DFAAYRSRVK FSRSADAPAY  120
QQGQNQLYNE LNLGRREEYD VLDKRRGRDP EMGGKPRRKN PQEGLYNELQ KDKMAEAYSE  180
IGMKGERRRG KGHDGLYQGL STATKDTYDA LHMQALPPR                         219

SEQ ID NO: 74        moltype = AA  length = 223
FEATURE              Location/Qualifiers
REGION               1..223
                     note = Synthetic
source               1..223
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 74
TTTPAPRPPT PAPTIASQPL SLRPEACRPA AGGAVHTRGL DFACDIYIWA PLAGTCGVLL  60
LSLVITLYCK RGRKKLLYIF KQPFMRPVQT TQEEDGCSCR FPEEEEGGCE LRVKFSRSAD  120
APAYKQGQNQ LYNELNLGRR EEYDVLDKRR GRDPEMGGKP RRKNPQEGLY NELQKDKMAE  180
AYSEIGMKGE RRRGKGHDGL YQGLSTATKD TYDALHMQAL PPR                    223

SEQ ID NO: 75        moltype = AA  length = 283
```

-continued

FEATURE Location/Qualifiers
REGION 1..283
note = Synthetic
source 1..283
mol_type = protein
organism = synthetic construct
SEQUENCE: 75
FVPVFLPAKP TTTPAPRPPT PAPTIASQPL SLRPEACRPA AGGAVHTRGL DFACDIYIWA 60
PLAGTCGVLL LSLVITLYCN HRNRSKRSRL LHSDYMNMTP RRPGPTRKHY QPYAPPRDFA 120
AYRSRFSVVK RGRKKLLYIF KQPFMRPVQT TQEEDGCSCR FPEEEEGGCE LRVKFSRSAD 180
APAYQQGQNQ LYNELNLGRR EEYDVLDKRR GRDPEMGGKP RRKNPQEGLY NELQKDKMAE 240
AYSEIGMKGE RRRGKGHDGL YQGLSTATKD TYDALHMQAL PPR 283

SEQ ID NO: 76 moltype = DNA length = 657
FEATURE Location/Qualifiers
misc_feature 1..657
note = Synthetic
source 1..657
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 76
attgaagtta tgtatcctcc tccttaccta gacaatgaga agagcaatgg aaccattatc 60
catgtgaaag ggaaacacct ttgtccaagt cccctatttc ccggaccttc taagcccttt 120
tgggtgctgg tggtggttgg gggagtcctg gcttgctata gcttgctagt aacagtggcc 180
tttattattt tctgggtgag gagtaagagg agcaggctcc tgcacagtga ctacatgaac 240
atgactcccc gccgccccgg gcccacccgc aagcattacc agccctatgc cccaccacgc 300
gacttcgcag cctatcgctc cagagtgaag ttcagcagga gcgcagacgc ccccgcgtac 360
cagcagggcc agaaccagct ctataacgag ctcaatctag gacgaagaga ggagtacgat 420
gttttggaca agagacgtgg ccgggaccct gagatggggg gaaagccgag aaggaagaac 480
cctcaggaag gcctgtacaa tgaactgcag aaagataaga tggcggaggc ctacagtgag 540
attgggatga aaggcgagcg ccggaggggc aaggggcacg atggccttta ccagggtctc 600
agtacagcca ccaaggacac ctacgacgcc cttcacatgc aggccctgcc ccctcgc 657

SEQ ID NO: 77 moltype = DNA length = 669
FEATURE Location/Qualifiers
misc_feature 1..669
note = Synthetic
source 1..669
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 77
accacgacgc cagcgccgcg accaccaaca ccggcgccca ccatcgcgtc gcagcccctg 60
tccctgcgcc cagaggcgtg ccggccagcg gcgggggggcg cagtgcacac gaggggggctg 120
gacttcgcct gtgatatcta catctgggcg cccttggccg ggacttgtgg ggtccttctc 180
ctgtcactgg ttatcaccct ttactgcaaa cggggcagaa agaaactcct gtatatattc 240
aaacaaccat ttatgagacc agtacaaact actcaagagg aagatggctg tagctgccga 300
tttccagaag aagaagaagg aggatgtgaa ctgagagtga agttcagcag gagcgcagac 360
gcccccgcgt acaagcaggg ccagaaccag ctctataacg agctcaatct aggacgaaga 420
gaggagtacg atgttttgga caagagacgt ggccgggacc ctgagatggg gggaaagccg 480
agaaggaaga accctcagga aggcctgtac aatgaactgc agaaagataa gatggcggag 540
gcctacagtg agattgggat gaaaggcgag cgccggaggg gcaaggggca cgatggcctt 600
taccagggtc tcagtacagc caccaaggac acctacgacg cccttcacat gcaggccctg 660
ccccctcgc 669

SEQ ID NO: 78 moltype = DNA length = 849
FEATURE Location/Qualifiers
misc_feature 1..849
note = Synthetic
source 1..849
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 78
ttcgtgccgg tcttcctgcc agcgaagccc accacgacgc cagcgccgcg accaccaaca 60
ccggcgccca ccatcgcgtc gcagcccctg tccctgcgcc cagaggcgtg ccggccagcg 120
gcgggggggcg cagtgcacac gaggggggctg gacttcgcct gtgatatcta catctgggcg 180
cccttggccg ggacttgtgg ggtccttctc ctgtcactgg ttatcaccct ttactgcaac 240
cacaggaaca ggagtaagag gagcaggctc ctgcacagtg actacatgaa catgactccc 300
cgccgccccg ggcccacccg caagcattac cagccctatg ccccaccacg cgacttcgca 360
gcctatcgct cccgtttctc tgttgttaaa cggggcagaa agaagctcct gtatatattc 420
aaacaaccat ttatgagacc agtacaaact actcaagagg aagatggctg tagctgccga 480
tttccagaag aagaagaagg aggatgtgaa ctgagagtga agttcagcag gagcgcagac 540
gcccccgcgt accagcaggg ccagaaccag ctctataacg agctcaatct aggacgaaga 600
gaggagtacg atgttttgga caagagacgt ggccgggacc ctgagatggg gggaaagccg 660
agaaggaaga accctcagga aggcctgtac aatgaactgc agaaagataa gatggcggag 720
gcctacagtg agattgggat gaaaggcgag cgccggaggg gcaaggggca cgatggcctt 780
taccagggtc tcagtacagc caccaaggac acctacgacg cccttcacat gcaggccctg 840

-continued

cccccctcgc 849

SEQ ID NO: 79 moltype = DNA length = 1521
FEATURE Location/Qualifiers
misc_feature 1..1521
note = Synthetic
source 1..1521
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 79
ctgctggtga cttcactcct gctctgtgaa cttccccatc ccgcttttct cctgatcccc 60
gacacccaag tccagctgca gcagtcagga gctgaggtga agaagcctgg tagctctgtc 120
aaagtgtctt gcaaagcctc tggtggtact ttcagctctt acgccatttc ttgggtgaga 180
caggcacccg gacagggtct tgaatggatg ggtggaatca tcccgattct tgggattgct 240
aattacgcac aaaagttcca gggaagggtg accatcaccg cagacgaatc tacctccact 300
gcttacatgg aactctcttc cctgcggtcc gaggacaccg ccgtctacta ttgtgccagg 360
ggcggtgccg gaggaagcgg ttcttactat ccgctgattt ggggacaagg aaccactgtg 420
accgtgagct ctggtggagg cggatccggt ggtggagggt ccggaggcgg aggatctgag 480
atcgtgctca ctcagagccc agccaccctt agcctgagcc ctggtgagcg cgccaccctc 540
tcatgcggtg cctcacagag cgtgagctca agctatctgg catggtacca gcaaaagcca 600
gggcaggccc cgaggctcct gatctacgac gcatcatcac gggctaccgg tatcccggca 660
cgcttctctg gaagcggatc aggcaccgac ttcaccctga ccatttcttc acttgagcca 720
gaggactttg ccgtgtacta ctgccagcag cgctcaagct ggccgcctac ttggactttc 780
ggacagggga ccaagctgga gatcaagcgc gctgaaccca agtcatgcga taagacccac 840
acttgtccac cctgtccagc ccctgaactg ctcggaggtc cgtcagtgtt tcttttcccg 900
ccaaagccta aggacactct gatgatctct cggacccctg aagtgacttg cgtcgtcgtg 960
gacgtgtcac acgaggatcc cgaggtgaag ttcaactggt atgtggacgg ggtggaagtg 1020
cataatgcta agaccaagcc cagggaggaa caatacaact caacctaccg cgtggtgtcc 1080
gtgctcaccg tccttcatca agactggctg aacggaaaag agtataagtg caaagtctcc 1140
aataaggctc tgccagcccc tatcgaaaag accatttcaa aggccaaggg gcagcctaga 1200
gagccccaag tgtacaccct tcctccctca agagatgagc tcactaagaa tcaggtcagc 1260
ctgacttgtc ttgtgaaagg cttctatccc agcgatattg ccgtcgaatg ggaaagcaat 1320
ggacaaccag agaacaacta caagaccacc ccgcctgtgc tggactccga cggctctttc 1380
ttcctttact caaagctgac cgtcgataag agccggtggc aacaggggaa tgtgttcagc 1440
tgctccgtca tgcacgaggc tctccataac cactacaccc agaaaagcct gtctctttct 1500
ccgggcaaaa aggacccaaa g 1521

SEQ ID NO: 80 moltype = AA length = 485
FEATURE Location/Qualifiers
REGION 1..485
note = Synthetic
source 1..485
mol_type = protein
organism = synthetic construct
SEQUENCE: 80
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARGG AGGSGSYYPL IWGQGTTVTV 120
SSGGGGSGGG GSGGGGSEIV LTQSPATLSL SPGERATLSC GASQSVSSSY LAWYQQKPGQ 180
APRLLIYDAS SRATGIPARF SGSGSGTDFT LTISSLEPED FAVYYCQQRS SWPPTWTFGQ 240
GTKLEIKRAE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV 300
SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK 360
ALPAPIEKTI SKAKGQPREP QVYTLPPSRD ELTKNQVSLT CLVKGFYPSD IAVEWESNGQ 420
PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG 480
KKDPK 485

SEQ ID NO: 81 moltype = DNA length = 1509
FEATURE Location/Qualifiers
misc_feature 1..1509
note = Synthetic
source 1..1509
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 81
ttgctggtga catcgcttct gttgtgcgaa ttgccccatc ccgcattcct ccttatcccc 60
gatacgcaag tccaacttca gcagtcaggg gcggaggtga agaagccggg ctcctccgta 120
aaggtgtcgt gcaaagcatc gggcggtaca ttctcctcct atgcgatctc atgggtgcga 180
caggcacccg ggcaggggtt ggaatggatg ggtggtatca ttcccattct cgggatcgcg 240
aactacgcgc agaagtttca aggcagagta acaattactg cagacgagtc cacctcaacc 300
gcctatatgg aactgtcgtc acttcggtcc gaagatacag ccgtgtacta ttgtgcaacg 360
ggaggcagcg ggaggtatgc ccttgacatt tggggacagg ggacaatggt cacagtaagc 420
tccggaggtg ggggatcagg aggcggtgga tcgggtgggg gaggatcgga aattgtactc 480
actcagtcac cggcgactct ctccctcagc ccgggagagc gggccacctt gtcatgcaga 540
gccagccaga gcgtatcatc ctatcttgcg tggtatcagc aaaaacccgg tcaggcccca 600
aggttgctga tctacgatgc gtcgaatcgc gcgacaggaa tccctgctag gttctccggg 660
tcgggctcgg ggaccgactt tacgcttacg atcagctcgc tggaaccgga ggacttcgcc 720
gtctactact gccagcagcg gtcgaattgg ccgccttcct acacatttgg acaaggaaca 780

-continued

aagctggaaa tcaagagagc ggaaccgaaa tcatgcgaca aaacgcacac ctgtcccct 840
tgtcccgctc ccgagttgct gggaggaccg tcggtgttcc tctttccgcc aaaacccaaa 900
gatacgttga tgatctcgcg cacgcccgag gtgacatgtg tggtagtcga tgtctcgcac 960
gaggaccccg aagtcaagtt caattggtac gtggacgggg tggaagtcca taatgccaag 1020
acgaaacctc gggaggagca gtacaactcc acatatcgcg tagtctcggt gctcaccgta 1080
ctgcatcagg actggcttaa cggaaaggaa tacaagtgca aagtgtcaaa caaggcgttg 1140
ccggcaccga ttgagaaaac gatctccaaa gccaaggggc aaccccgcga gccccaggtc 1200
tatactctcc cgccgtcgcg agatgagctc acgaagaacc aagtctcgct tacgtgcctc 1260
gtgaagggtt tctacccaag cgatattgcg gtggagtggg agagcaatgg acagccggag 1320
aacaactata agactacccc acccgtgctt gactcggatg gcagcttctt tctgtactcg 1380
aaactgaccg tggacaaatc gagatggcaa caggggaatg tcttttcatg ttccgtgatg 1440
cacgaggcgc tccacaacca ctacacgcag aagagcttgt cattgagccc agggaagaaa 1500
gacccaaag 1509

SEQ ID NO: 82 moltype = AA length = 481
FEATURE Location/Qualifiers
REGION 1..481
note = Synthetic
source 1..481
mol_type = protein
organism = synthetic construct
SEQUENCE: 82
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCATGG SGRYALDIWG QGTMVTVSSG 120
GGGSGGGGSG GGGSEIVLTQ SPATLSLSPG ERATLSCRAS QSVSSYLAWY QQKPGQAPRL 180
LIYDASNRAT GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQRSNWPP SYTFGQGTKL 240
EIKRAEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED 300
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 360
PIEKTISKAK GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 420
YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGKKDP 480
K 481

SEQ ID NO: 83 moltype = DNA length = 1503
FEATURE Location/Qualifiers
misc_feature 1..1503
note = Synthetic
source 1..1503
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 83
ctgctggtga cttcactcct gctctgtgaa cttccccatc ccgcttttct cctgatcccc 60
gacacccaag tccagctggt gcaaagcgga gcagaagtga agaagcctgg atcctctgtg 120
aaggtcagct gcaaggcctc tggaggtacc ttcagctctt acgcaatttc ttgggtgcgc 180
caggctcccg ggcagggact ggagtggatg ggaggaatca tcccgatcct tggtaccgct 240
aattacgccc agaaatttca gggtcgggtg accatcaccg cagacgagtc aacctcaacc 300
gcttacatgg aactttctag cctccgcagc gaggacaccg ccgtctacta ttgcgcaaga 360
tggggtggtg gtgccttcga catttgggga cagggcacta tggtcaccgt gagctccggt 420
ggaggaggat ctggcggagg agggtcaggc ggaggtgggt cagagattgt gctgacccag 480
tcacccggga ctctgtccct ttctcctggt gagcgcgcta ctctgtcttg tagggcctca 540
caatcagtgg gcggctatct cgcctggtat cagcagaaac cagggcaggc ccctaggctt 600
ctcatctacg acgcctccaa ccgggcaact ggcattccag cccgcttcag cggaagcgga 660
tccggaaccg actttactct gactatctcc tcactggaac cggaggactt cgcagtgtac 720
tactgccagc agcggaataa ctggccaccg atgtacactt tcggacaggg gaccaagctg 780
gagatcaagc gcgctgaacc caagtcatgc gataagaccc acacttgtcc accctgtcca 840
gcccctgaac tgctcggagg tccgtcagtg tttcttttcc cgccaaagcc taaggacact 900
ctgatgatct ctcggacccc tgaagtgact tgcgtcgtcg tggacgtgtc acacgaggat 960
cccgaggtga agttcaactg gtatgtggac ggggtggaag tgcataatgc taagaccaag 1020
cccagggagg aacaatacaa ctcaacctac cgcgtggtgt ccgtgctcac cgtccttcat 1080
caagactggc tgaacggaaa agagtataag tgcaaagtct ccaataaggc tctgccagcc 1140
cctatcgaaa agaccatttc aaaggccaag gggcagccta gagagcccca agtgtacacc 1200
cttcctccct caagagatga gctcactaag aatcaggtca gcctgacttg tcttgtgaaa 1260
ggcttctatc ccagcgatat tgccgtcgaa tgggaaagca atggacaacc agagaacaac 1320
tacaagacca ccccgcctgt gctggactcc gacggctctt tcttccttta ctcaaagctg 1380
accgtcgata agagccggtg gcaacagggg aatgtgttca gctgctccgt catgcacgag 1440
gctctccata accactacac ccagaaaagc ctgtctcttt ctccgggcaa aaaggaccca 1500
aag 1503

SEQ ID NO: 84 moltype = AA length = 479
FEATURE Location/Qualifiers
REGION 1..479
note = Synthetic
source 1..479
mol_type = protein
organism = synthetic construct
SEQUENCE: 84
QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGTANY 60

-continued

AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARWG GGAFDIWGQG TMVTVSSGGG 120
GSGGGGSGGG GSEIVLTQSP GTLSLSPGER ATLSCRASQS VGGYLAWYQQ KPGQAPRLLI 180
YDASNRATGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC QQRNNWPPMY TFGQGTKLEI 240
KRAEPKSCDK THTCPPCPAP ELLGGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE 300
VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI 360
EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK 420
TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGKKDPK 479

SEQ ID NO: 85 moltype = length =
SEQUENCE: 85
000

SEQ ID NO: 86 moltype = length =
SEQUENCE: 86
000

SEQ ID NO: 87 moltype = length =
SEQUENCE: 87
000

SEQ ID NO: 88 moltype = length =
SEQUENCE: 88
000

SEQ ID NO: 89 moltype = length =
SEQUENCE: 89
000

SEQ ID NO: 90 moltype = length =
SEQUENCE: 90
000

SEQ ID NO: 91 moltype = AA length = 4
FEATURE Location/Qualifiers
REGION 1..4
note = Synthetic
source 1..4
mol_type = protein
organism = synthetic construct
SEQUENCE: 91
AAAA 4

SEQ ID NO: 92 moltype = AA length = 4
FEATURE Location/Qualifiers
REGION 1..4
note = Synthetic
source 1..4
mol_type = protein
organism = synthetic construct
SEQUENCE: 92
AAAA 4

SEQ ID NO: 93 moltype = AA length = 4
FEATURE Location/Qualifiers
REGION 1..4
note = Synthetic
source 1..4
mol_type = protein
organism = synthetic construct
SEQUENCE: 93
AAAA 4

SEQ ID NO: 94 moltype = AA length = 4
FEATURE Location/Qualifiers
REGION 1..4
note = Synthetic
source 1..4
mol_type = protein
organism = synthetic construct
SEQUENCE: 94
AAAA 4

SEQ ID NO: 95 moltype = AA length = 4
FEATURE Location/Qualifiers
REGION 1..4
note = Synthetic

-continued

source	1..4 mol_type = protein organism = synthetic construct
SEQUENCE: 95	
AAAA	4
SEQ ID NO: 96	moltype = AA length = 4
FEATURE	Location/Qualifiers
REGION	1..4 note = Synthetic
source	1..4 mol_type = protein organism = synthetic construct
SEQUENCE: 96	
AAAA	4
SEQ ID NO: 97	moltype = AA length = 4
FEATURE	Location/Qualifiers
REGION	1..4 note = Synthetic
source	1..4 mol_type = protein organism = synthetic construct
SEQUENCE: 97	
AAAA	4
SEQ ID NO: 98	moltype = AA length = 4
FEATURE	Location/Qualifiers
REGION	1..4 note = Synthetic
source	1..4 mol_type = protein organism = synthetic construct
SEQUENCE: 98	
AAAA	4
SEQ ID NO: 99	moltype = AA length = 4
FEATURE	Location/Qualifiers
REGION	1..4 note = Synthetic
source	1..4 mol_type = protein organism = synthetic construct
SEQUENCE: 99	
AAAA	4
SEQ ID NO: 100	moltype = AA length = 4
FEATURE	Location/Qualifiers
REGION	1..4 note = Synthetic
source	1..4 mol_type = protein organism = synthetic construct
SEQUENCE: 100	
AAAA	4
SEQ ID NO: 101	moltype = AA length = 4
FEATURE	Location/Qualifiers
REGION	1..4 note = Synthetic
source	1..4 mol_type = protein organism = synthetic construct
SEQUENCE: 101	
AAAA	4
SEQ ID NO: 102	moltype = AA length = 4
FEATURE	Location/Qualifiers
REGION	1..4 note = Synthetic
source	1..4 mol_type = protein organism = synthetic construct
SEQUENCE: 102	
AAAA	4

-continued

SEQ ID NO: 103	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 103		
AAAA		4
SEQ ID NO: 104	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 104		
AAAA		4
SEQ ID NO: 105	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 105		
AAAA		4
SEQ ID NO: 106	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 106		
AAAA		4
SEQ ID NO: 107	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 107		
AAAA		4
SEQ ID NO: 108	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 108		
AAAA		4
SEQ ID NO: 109	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 109		
AAAA		4
SEQ ID NO: 110	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	

-continued

	organism = synthetic construct	
SEQUENCE: 110		
AAAA		4
SEQ ID NO: 111	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 111		
AAAA		4
SEQ ID NO: 112	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 112		
AAAA		4
SEQ ID NO: 113	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 113		
AAAA		4
SEQ ID NO: 114	moltype = AA length = 4	
FEATURE	Location/Qualifiers	
REGION	1..4	
	note = Synthetic	
source	1..4	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 114		
AAAA		4
SEQ ID NO: 115	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
REGION	1..15	
	note = Synthetic	
source	1..15	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 115		
GGGGSGGGGS GGGGS		15
SEQ ID NO: 116	moltype = DNA length = 366	
FEATURE	Location/Qualifiers	
misc_feature	1..366	
	note = Synthetic	
source	1..366	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 116		
caggtacagc tgcagcagtc aggggctgag gtgaagaagc ctggatcctc agtgaaggtc		60
tcctgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc		120
cctggacaag ggcttgagtg gatgggaggg atcatcccta tccttggtat agcaaactac		180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac		240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaggaggg		300
gcgggcggtt cggggagtta ttatcccctc atctggggcc aagggaccac ggtcaccgtc		360
tcctca		366
SEQ ID NO: 117	moltype = DNA length = 333	
FEATURE	Location/Qualifiers	
misc_feature	1..333	
	note = Synthetic	
source	1..333	
	mol_type = other DNA	

-continued

organism = synthetic construct

SEQUENCE: 117

gaaattgtgt tgacgcagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgcg gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat gatgcatcca gcagggccac tggcatcccg 180
gccaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagcctagag 240
cctgaagatt ttgcagttta ttactgtcag cagcgtagta gctggcctcc cacgtggacg 300
ttcggccaag ggaccaagct ggaaatcaaa cgt 333

SEQ ID NO: 118 moltype = DNA length = 357
FEATURE Location/Qualifiers
misc_feature 1..357
note = Synthetic
source 1..357
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 118

caggtacagc tgcagcagtc aggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcttgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggctcgagtg gatgggaggg atcatcccta tccttggtat agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc aacaggtggt 300
tcggggagat atgctttgga tatctggggc caagggacaa tggtcaccgt ctcttca 357

SEQ ID NO: 119 moltype = DNA length = 330
FEATURE Location/Qualifiers
misc_feature 1..330
note = Synthetic
source 1..330
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 119

gaaattgtgt tgacgcagtc tccagccacc ctgtccttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agctacttag cctggtacca acagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cagtttatta ctgtcagcag cgtagcaact ggcctccgtc gtacactttt 300
ggccagggga ccaagctgga gatcaaacgt 330

SEQ ID NO: 120 moltype = DNA length = 351
FEATURE Location/Qualifiers
misc_feature 1..351
note = Synthetic
source 1..351
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 120

caggtgcagc tggtgcaatc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcatcccta tccttggtac agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagatggggt 300
gggggagctt ttgatatctg gggccaaggg acaatggtca ccgtctcttc a 351

SEQ ID NO: 121 moltype = DNA length = 330
FEATURE Location/Qualifiers
misc_feature 1..330
note = Synthetic
source 1..330
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 121

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttggg ggctacttag cctggtacca acagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccaccgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cagtttatta ctgtcagcag cgtaacaact ggcctccgat gtacactttt 300
ggccagggga ccaagctgga aatcaaacgt 330

SEQ ID NO: 122 moltype = AA length = 466
FEATURE Location/Qualifiers
REGION 1..466
note = Synthetic
source 1..466
mol_type = protein
organism = synthetic construct

-continued

SEQUENCE: 122
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCATGG SGRYALDIWG QGTMVTVSSG 120
GGGSGGGGSG GGGSEIVLTQ SPATLSLSPG ERATLSCRAS QSVSSYLAWY QQKPGQAPRL 180
LIYDASNRAT GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQRSNWPP SYTFGQGTKL 240
EIKRAAAIEV MYPPPYLDNE KSNGTIIHVK GKHLCPSPLF PGPSKPFWVL VVVGGVLACY 300
SLLVTVAFII FWVRSKRSRL LHSDYMNMTP RRPGPTRKHY QPYAPPRDFA AYRSRVKFSR 360
SADAPAYQQG QNQLYNELNL GRREEYDVLD KRRGRDPEMG GKPRRKNPQE GLYNELQKDK 420
MAEAYSEIGM KGERRRGKGH DGLYQGLSTA TKDTYDALHM QALPPR 466

SEQ ID NO: 123 moltype = AA length = 470
FEATURE Location/Qualifiers
REGION 1..470
note = Synthetic
source 1..470
mol_type = protein
organism = synthetic construct
SEQUENCE: 123
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCATGG SGRYALDIWG QGTMVTVSSG 120
GGGSGGGGSG GGGSEIVLTQ SPATLSLSPG ERATLSCRAS QSVSSYLAWY QQKPGQAPRL 180
LIYDASNRAT GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQRSNWPP SYTFGQGTKL 240
EIKRAAATTT PAPRPPTPAP TIASQPLSLR PEACRPAAGG AVHTRGLDFA CDIYIWAPLA 300
GTCGVLLLSL VITLYCKRGR KKLLYIFKQP FMRPVQTTQE EDGCSCRFPE EEEGGCELRV 360
KFSRSADAPA YKQGQNQLYN ELNLGRREEY DVLDKRRGRD PEMGGKPRRK NPQEGLYNEL 420
QKDKMAEAYS EIGMKGERRR GKGHDGLYQG LSTATKDTYD ALHMQALPPR 470

SEQ ID NO: 124 moltype = AA length = 530
FEATURE Location/Qualifiers
REGION 1..530
note = Synthetic
source 1..530
mol_type = protein
organism = synthetic construct
SEQUENCE: 124
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCATGG SGRYALDIWG QGTMVTVSSG 120
GGGSGGGGSG GGGSEIVLTQ SPATLSLSPG ERATLSCRAS QSVSSYLAWY QQKPGQAPRL 180
LIYDASNRAT GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQRSNWPP SYTFGQGTKL 240
EIKRAAAFVP VFLPAKPTTT PAPRPPTPAP TIASQPLSLR PEACRPAAGG AVHTRGLDFA 300
CDIYIWAPLA GTCGVLLLSL VITLYCNHRN RSKRSRLLHS DYMNMTPRRP GPTRKHYQPY 360
APPRDFAAYR SRFSVVKRGR KKLLYIFKQP FMRPVQTTQE EDGCSCRFPE EEEGGCELRV 420
KFSRSADAPA YQQGQNQLYN ELNLGRREEY DVLDKRRGRD PEMGGKPRRK NPQEGLYNEL 480
QKDKMAEAYS EIGMKGERRR GKGHDGLYQG LSTATKDTYD ALHMQALPPR 530

SEQ ID NO: 125 moltype = AA length = 470
FEATURE Location/Qualifiers
REGION 1..470
note = Synthetic
source 1..470
mol_type = protein
organism = synthetic construct
SEQUENCE: 125
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARGG AGGSGSYYPL IWGQGTTVTV 120
SSGGGGSGGG GSGGGGSEIV LTQSPATLSL SPGERATLSC GASQSVSSSY LAWYQQKPGQ 180
APRLLIYDAS SRATGIPARF SGSGSGTDFT LTISSLEPED FAVYYCQQRS SWPPTWTFGQ 240
GTKLEIKRAA AIEVMYPPPY LDNEKSNGTI IHVKGKHLCP SPLFPGPSKP FWVLVVVGGV 300
LACYSLLVTV AFIIFWVRSK RSRLLHSDYM NMTPRRPGPT RKHYQPYAPP RDFAAYRSRV 360
KFSRSADAPA YQQGQNQLYN ELNLGRREEY DVLDKRRGRD PEMGGKPRRK NPQEGLYNEL 420
QKDKMAEAYS EIGMKGERRR GKGHDGLYQG LSTATKDTYD ALHMQALPPR 470

SEQ ID NO: 126 moltype = AA length = 474
FEATURE Location/Qualifiers
REGION 1..474
note = Synthetic
source 1..474
mol_type = protein
organism = synthetic construct
SEQUENCE: 126
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY 60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARGG AGGSGSYYPL IWGQGTTVTV 120
SSGGGGSGGG GSGGGGSEIV LTQSPATLSL SPGERATLSC GASQSVSSSY LAWYQQKPGQ 180
APRLLIYDAS SRATGIPARF SGSGSGTDFT LTISSLEPED FAVYYCQQRS SWPPTWTFGQ 240
GTKLEIKRAA ATTTPAPRPP TPAPTIASQP LSLRPEACRP AAGGAVHTRG LDFACDIYIW 300
APLAGTCGVL LLSLVITLYC KRGRKKLLYI FKQPFMRPVQ TTQEEDGCSC RFPEEEEGGC 360

-continued

```
ELRVKFSRSA DAPAYKQGQN QLYNELNLGR REEYDVLDKR RGRDPEMGGK PRRKNPQEGL  420
YNELQKDKMA EAYSEIGMKG ERRRGKGHDG LYQGLSTATK DTYDALHMQA LPPR       474

SEQ ID NO: 127          moltype = AA  length = 534
FEATURE                 Location/Qualifiers
REGION                  1..534
                        note = Synthetic
source                  1..534
                        mol_type = protein
                        organism = synthetic construct
SEQUENCE: 127
QVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGIANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARGG AGGSGSYYPL IWGQGTTVTV  120
SSGGGGSGGG GSGGGGSEIV LTQSPATLSL SPGERATLSC GASQSVSSSY LAWYQQKPGQ  180
APRLLIYDAS SRATGIPARF SGSGSGTDFT LTISSLEPED FAVYYCQQRS SWPPTWTFGQ  240
GTKLEIKRAA AFVPVFLPAK PTTTPAPRPP TPAPTIASQP LSLRPEACRP AAGGAVHTRG  300
LDFACDIYIW APLAGTCGVL LLSLVITLYC NHRNRSKRSR LLHSDYMNMT PRRPGPTRKH  360
YQPYAPPRDF AAYRSRFSVV KRGRKKLLYI FKQPFMRPVQ TTQEEDGCSC RFPEEEEGGC  420
ELRVKFSRSA DAPAYQQGQN QLYNELNLGR REEYDVLDKR RGRDPEMGGK PRRKNPQEGL  480
YNELQKDKMA EAYSEIGMKG ERRRGKGHDG LYQGLSTATK DTYDALHMQA LPPR       534

SEQ ID NO: 128          moltype = AA  length = 464
FEATURE                 Location/Qualifiers
REGION                  1..464
                        note = Synthetic
source                  1..464
                        mol_type = protein
                        organism = synthetic construct
SEQUENCE: 128
QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGTANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARWG GGAFDIWGQG TMVTVSSGGG  120
GSGGGGSGGG GSEIVLTQSP GTLSLSPGER ATLSCRASQS VGGYLAWYQQ KPGQAPRLLI  180
YDASNRATGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC QQRNNWPPMY TFGQGTKLEI  240
KRAAAIEVMY PPPYLDNEKS NGTIIHVKGK HLCPSPLFPG PSKPFWVLVV VGGVLACYSL  300
LVTVAFIIFW VRSKRSRLLH SDYMNMTPRR PGPTRKHYQP YAPPRDFAAY RSRVKFSRSA  360
DAPAYQQGQN QLYNELNLGR REEYDVLDKR RGRDPEMGGK PRRKNPQEGL YNELQKDKMA  420
EAYSEIGMKG ERRRGKGHDG LYQGLSTATK DTYDALHMQA LPPR                   464

SEQ ID NO: 129          moltype = AA  length = 468
FEATURE                 Location/Qualifiers
REGION                  1..468
                        note = Synthetic
source                  1..468
                        mol_type = protein
                        organism = synthetic construct
SEQUENCE: 129
QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGTANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARWG GGAFDIWGQG TMVTVSSGGG  120
GSGGGGSGGG GSEIVLTQSP GTLSLSPGER ATLSCRASQS VGGYLAWYQQ KPGQAPRLLI  180
YDASNRATGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC QQRNNWPPMY TFGQGTKLEI  240
KRAAATTTPA PRPPTPAPTI ASQPLSLRPE ACRPAAGGAV HTRGLDFACD IYIWAPLAGT  300
CGVLLLSLVI TLYCKRGRKK LLYIFKQPFM RPVQTTQEED GCSCRFPEEE EGGCELRVKF  360
SRSADAPAYK QGQNQLYNEL NLGRREEYDV LDKRRGRDPE MGGKPRRKNP QEGLYNELQK  420
DKMAEAYSEI GMKGERRRGK GHDGLYQGLS TATKDTYDAL HMQALPPR               468

SEQ ID NO: 130          moltype = AA  length = 528
FEATURE                 Location/Qualifiers
REGION                  1..528
                        note = Synthetic
source                  1..528
                        mol_type = protein
                        organism = synthetic construct
SEQUENCE: 130
QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPILGTANY  60
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARWG GGAFDIWGQG TMVTVSSGGG  120
GSGGGGSGGG GSEIVLTQSP GTLSLSPGER ATLSCRASQS VGGYLAWYQQ KPGQAPRLLI  180
YDASNRATGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC QQRNNWPPMY TFGQGTKLEI  240
KRAAAFVPVF LPAKPTTTPA PRPPTPAPTI ASQPLSLRPE ACRPAAGGAV HTRGLDFACD  300
IYIWAPLAGT CGVLLLSLVI TLYCNHRNRS KRSRLLHSDY MNMTPRRPGP TRKHYQPYAP  360
PRDFAAYRSR FSVVKRGRKK LLYIFKQPFM RPVQTTQEED GCSCRFPEEE EGGCELRVKF  420
SRSADAPAYQ QGQNQLYNEL NLGRREEYDV LDKRRGRDPE MGGKPRRKNP QEGLYNELQK  480
DKMAEAYSEI GMKGERRRGK GHDGLYQGLS TATKDTYDAL HMQALPPR               528

SEQ ID NO: 131          moltype = DNA  length = 1401
FEATURE                 Location/Qualifiers
misc_feature            1..1401
```

-continued

	note = Synthetic
source	1..1401
	mol_type = other DNA
	organism = synthetic construct

SEQUENCE: 131

caagtccaac ttcagcagtc aggggcggag gtgaagaagc cgggctcctc cgtaaaggtg 60
tcgtgcaaag catcgggcgg tacattctcc tcctatgcga tctcatgggt gcgacaggca 120
cccgggcagg ggttggaatg gatgggtggt atcattccca ttctcgggat cgcgaactac 180
gcgcagaagt ttcaaggcag agtaacaatt actgcagacg agtccacctc aaccgcctat 240
atggaactgt cgtcacttcg gtccgaagat acagccgtgt actattgtgc aacgggaggc 300
agcgggaggt atgcccttga catttgggga caggggacaa tggtcacagt aagctccgga 360
ggtgggggat caggaggcgg tggatcgggt gggggaggat cggaaattgt actcactcag 420
tcaccggcga ctctctccct cagcccggga gagcgggcca ccttgtcatg cagagccagc 480
cagagcgtat catcctatct tgcgtggtat cagcaaaaac ccggtcaggc cccaaggttg 540
ctgatctacg atgcgtcgaa tcgcgcgaca ggaatccctg ctaggttctc cgggtcgggc 600
tcggggaccg actttacgct tacgatcagc tcgctggaac cggaggactt cgccgtctac 660
tactgccagc agcggtcgaa ttggccgcct tcctacacat ttggacaagg aacaaagctg 720
gaaatcaaga gagcggccgc aattgaagtt atgtatcctc ctccttacct agacaatgag 780
aagagcaatg gaaccattat ccatgtgaaa gggaaacacc tttgtccaag tcccctattt 840
cccggacctt ctaagccctt ttgggtgctg gtggtggttg ggggagtcct ggcttgctat 900
agcttgctag taacagtggc ctttattatt ttctgggtga ggagtaagag gagcaggctc 960
ctgcacagtg actacatgaa catgactccc cgccgccccg ggcccacccg caagcattac 1020
cagccctatg ccccaccacg cgacttcgca gcctatcgct ccagagtgaa gttcagcagg 1080
agcgcagacg cccccgcgta ccagcagggc cagaaccagc tctataacga gctcaatcta 1140
ggacgaagag aggagtacga tgttttggac aagagacgtg gccgggaccc tgagatgggg 1200
ggaaagccga gaaggaagaa ccctcaggaa ggcctgtaca atgaactgca gaaagataag 1260
atggcggagg cctacagtga gattgggatg aaaggcgagc gccggagggg caaggggcac 1320
gatggccttt accagggtct cagtacagcc accaaggaca cctacgacgc ccttcacatg 1380
caggccctgc cccctcgcta a 1401

SEQ ID NO: 132	moltype = DNA length = 1413
FEATURE	Location/Qualifiers
misc_feature	1..1413
	note = Synthetic
source	1..1413
	mol_type = other DNA
	organism = synthetic construct

SEQUENCE: 132

caagtccaac ttcagcagtc aggggcggag gtgaagaagc cgggctcctc cgtaaaggtg 60
tcgtgcaaag catcgggcgg tacattctcc tcctatgcga tctcatgggt gcgacaggca 120
cccgggcagg ggttggaatg gatgggtggt atcattccca ttctcgggat cgcgaactac 180
gcgcagaagt ttcaaggcag agtaacaatt actgcagacg agtccacctc aaccgcctat 240
atggaactgt cgtcacttcg gtccgaagat acagccgtgt actattgtgc aacgggaggc 300
agcgggaggt atgcccttga catttgggga caggggacaa tggtcacagt aagctccgga 360
ggtgggggat caggaggcgg tggatcgggt gggggaggat cggaaattgt actcactcag 420
tcaccggcga ctctctccct cagcccggga gagcgggcca ccttgtcatg cagagccagc 480
cagagcgtat catcctatct tgcgtggtat cagcaaaaac ccggtcaggc cccaaggttg 540
ctgatctacg atgcgtcgaa tcgcgcgaca ggaatccctg ctaggttctc cgggtcgggc 600
tcggggaccg actttacgct tacgatcagc tcgctggaac cggaggactt cgccgtctac 660
tactgccagc agcggtcgaa ttggccgcct tcctacacat ttggacaagg aacaaagctg 720
gaaatcaaga gagcggccgc aaccacgacg ccagcgccgc gaccaccaac accggcgccc 780
accatcgcgt cgcagccccc gtccctgcgc ccagaggcgt gccggccagc ggcgggggggc 840
gcagtgcaca cgagggggct ggacttcgcc tgtgatatct acatctgggc gcccttggcc 900
gggacttgtg gggtccttct cctgtcactg gttatcaccc tttactgcaa acggggcaga 960
aagaaactcc tgtatatatt caaacaacca tttatgagac cagtacaaac tactcaagag 1020
gaagatggct gtagctgccg atttccagaa gaagaagaag gaggatgtga actgagagtg 1080
aagttcagca ggagcgcaga cgccccgcg tacaagcagg gccagaacca gctctataac 1140
gagctcaatc taggacgaag agaggagtac gatgttttgg acaagagacg tggccgggac 1200
cctgagatgg ggggaaagcc gagaaggaag aaccctcagg aaggcctgta caatgaactg 1260
cagaaagata agatggcgga ggcctacagt gagattggga tgaaaggcga gcgccggagg 1320
ggcaaggggc acgatggcct ttaccagggt ctcagtacag ccaccaagga cacctacgac 1380
gcccttcaca tgcaggccct gccccctcgc taa 1413

SEQ ID NO: 133	moltype = DNA length = 1593
FEATURE	Location/Qualifiers
misc_feature	1..1593
	note = Synthetic
source	1..1593
	mol_type = other DNA
	organism = synthetic construct

SEQUENCE: 133

caagtccaac ttcagcagtc aggggcggag gtgaagaagc cgggctcctc cgtaaaggtg 60
tcgtgcaaag catcgggcgg tacattctcc tcctatgcga tctcatgggt gcgacaggca 120
cccgggcagg ggttggaatg gatgggtggt atcattccca ttctcgggat cgcgaactac 180
gcgcagaagt ttcaaggcag agtaacaatt actgcagacg agtccacctc aaccgcctat 240
atggaactgt cgtcacttcg gtccgaagat acagccgtgt actattgtgc aacgggaggc 300

-continued

agcgggaggt atgcccttga catttgggga caggggacaa tggtcacagt aagctccgga 360
ggtgggggat caggaggcgg tggatcgggt gggggaggat cggaaattgt actcactcag 420
tcaccggcga ctctctccct cagcccggga gagcgggcca ccttgtcatg cagagccagc 480
cagagcgtat catcctatct tgcgtggtat cagcaaaaac ccggtcaggc cccaaggttg 540
ctgatctacg atgcgtcgaa tcgcgcgaca ggaatccctg ctaggttctc cgggtcgggc 600
tcggggaccg actttacgct tacgatcagc tcgctggaac cggaggactt cgccgtctac 660
tactgccagc agcggtcgaa ttggccgcct tcctacacat ttggacaagg aacaaagctg 720
gaaatcaaga gagcggccgc attcgtgccg gtcttcctgc cagcgaagcc caccacgacg 780
ccagcgccgc gaccaccaac accggcgccc accatcgcgt cgcagcccct gtccctgcgc 840
ccagaggcgt gccggccagc ggcgggggggc gcagtgcaca cgagggggct ggacttcgcc 900
tgtgatatct acatctgggc gcccttggcc gggacttgtg gggtccttct cctgtcactg 960
gttatcaccc tttactgcaa ccacaggaac aggagtaaga ggagcaggct cctgcacagt 1020
gactacatga acatgactcc ccgccgcccc gggcccaccc gcaagcatta ccagccctat 1080
gccccaccac gcgacttcgc agcctatcgc tcccgtttct ctgttgttaa acggggcaga 1140
aagaagctcc tgtatatatt caaacaacca tttatgagac cagtacaaac tactcaagag 1200
gaagatggct gtagctgccg atttccagaa gaagaagaag gaggatgtga actgagagtg 1260
aagttcagca ggagcgcaga cgcccccgcg taccagcagg gccagaacca gctctataac 1320
gagctcaatc taggacgaag agaggagtac gatgttttgg acaagagacg tggccgggac 1380
cctgagatgg ggggaaagcc gagaaggaag aaccctcagg aaggcctgta caatgaactg 1440
cagaaagata agatggcgga ggcctacagt gagattggga tgaaaggcga gcgccggagg 1500
ggcaaggggc acgatggcct ttaccagggt ctcagtacag ccaccaagga cacctacgac 1560
gcccttcaca tgcaggccct gccccctcgc taa 1593

SEQ ID NO: 134 moltype = DNA length = 1413
FEATURE Location/Qualifiers
misc_feature 1..1413
note = Synthetic
source 1..1413
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 134
caagtccagc tgcagcagtc aggagctgag gtgaagaagc ctggtagctc tgtcaaagtg 60
tcttgcaaag cctctggtgg tactttcagc tcttacgcca tttcttgggt gagacaggca 120
cccggacagg gtcttgaatg gatgggtgga atcatcccga ttcttgggat tgctaattac 180
gcacaaaagt tccagggaag ggtgaccatc accgcagacg aatctacctc cactgcttac 240
atggaactct cttccctgcg gtccgaggac accgccgtct actattgtgc caggggcggt 300
gccggaggaa gcggttctta ctatccgctg atttggggac aaggaaccac tgtgaccgtg 360
agctctggtg gaggcggatc cggtggtgga gggtccggag gcggaggatc tgagatcgtg 420
ctcactcaga gcccagccac ccttagcctg agccctggtg agcgcgccac cctctcatgc 480
ggtgcctcac agagcgtgag ctcaagctat ctggcatggt accagcaaaa gccagggcag 540
gccccgaggc tcctgatcta cgacgcatca tcacgggcta ccggtatccc ggcacgcttc 600
tctggaagcg gatcaggcac cgacttcacc ctgaccattt cttcacttga gccagaggac 660
tttgccgtgt actactgcca gcagcgctca agctggccgc ctacttggac tttcggacag 720
gggaccaagc tggagatcaa gcgcgcggcc gcaattgaag ttatgtatcc tcctccttac 780
ctagacaatg agaagagcaa tggaaccatt atccatgtga aagggaaaca cctttgtcca 840
agtcccctat ttcccggacc ttctaagccc ttttgggtgc tggtggtggt tgggggagtc 900
ctggcttgct atagcttgct agtaacagtg gcctttatta ttttctgggt gaggagtaag 960
aggagcaggc tcctgcacag tgactacatg aacatgactc cccgccgccc cgggcccacc 1020
cgcaagcatt accagcccta tgccccacca cgcgacttcg cagcctatcg ctccagagtg 1080
aagttcagca ggagcgcaga cgcccccgcg taccagcagg gccagaacca gctctataac 1140
gagctcaatc taggacgaag agaggagtac gatgttttgg acaagagacg tggccgggac 1200
cctgagatgg ggggaaagcc gagaaggaag aaccctcagg aaggcctgta caatgaactg 1260
cagaaagata agatggcgga ggcctacagt gagattggga tgaaaggcga gcgccggagg 1320
ggcaaggggc acgatggcct ttaccagggt ctcagtacag ccaccaagga cacctacgac 1380
gcccttcaca tgcaggccct gccccctcgc taa 1413

SEQ ID NO: 135 moltype = DNA length = 1425
FEATURE Location/Qualifiers
misc_feature 1..1425
note = Synthetic
source 1..1425
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 135
caagtccagc tgcagcagtc aggagctgag gtgaagaagc ctggtagctc tgtcaaagtg 60
tcttgcaaag cctctggtgg tactttcagc tcttacgcca tttcttgggt gagacaggca 120
cccggacagg gtcttgaatg gatgggtgga atcatcccga ttcttgggat tgctaattac 180
gcacaaaagt tccagggaag ggtgaccatc accgcagacg aatctacctc cactgcttac 240
atggaactct cttccctgcg gtccgaggac accgccgtct actattgtgc caggggcggt 300
gccggaggaa gcggttctta ctatccgctg atttggggac aaggaaccac tgtgaccgtg 360
agctctggtg gaggcggatc cggtggtgga gggtccggag gcggaggatc tgagatcgtg 420
ctcactcaga gcccagccac ccttagcctg agccctggtg agcgcgccac cctctcatgc 480
ggtgcctcac agagcgtgag ctcaagctat ctggcatggt accagcaaaa gccagggcag 540
gccccgaggc tcctgatcta cgacgcatca tcacgggcta ccggtatccc ggcacgcttc 600
tctggaagcg gatcaggcac cgacttcacc ctgaccattt cttcacttga gccagaggac 660
tttgccgtgt actactgcca gcagcgctca agctggccgc ctacttggac tttcggacag 720

-continued

gggaccaagc tggagatcaa gcgcgcggcc gcaaccacga cgccagcgcc gcgaccacca 780
acaccggcgc ccaccatcgc gtcgcagccc ctgtccctgc gcccagaggc gtgccggcca 840
gcggcggggg gcgcagtgca cacgaggggg ctggacttcg cctgtgatat ctacatctgg 900
gcgcccttgg ccgggacttg tggggtcctt ctcctgtcac tggttatcac cctttactgc 960
aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 1020
actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 1080
gaactgagag tgaagttcag caggagcgca gacgcccccg cgtacaagca gggccagaac 1140
cagctctata acgagctcaa tctaggacga agagaggagt acgatgtttt ggacaagaga 1200
cgtggccggg accctgagat ggggggaaag ccgagaagga agaaccctca ggaaggcctg 1260
tacaatgaac tgcagaaaga taagatggcg gaggcctaca gtgagattgg gatgaaaggc 1320
gagcgccgga ggggcaaggg gcacgatggc ctttaccagg gtctcagtac agccaccaag 1380
gacacctacg acgcccttca catgcaggcc ctgccccctc gctaa 1425

SEQ ID NO: 136 moltype = DNA length = 1605
FEATURE Location/Qualifiers
misc_feature 1..1605
note = Synthetic
source 1..1605
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 136
caagtccagc tgcagcagtc aggagctgag gtgaagaagc ctggtagctc tgtcaaagtg 60
tcttgcaaag cctctggtgg tactttcagc tcttacgcca tttcttgggt gagacaggca 120
cccggacagg gtcttgaatg gatgggtgga atcatcccga ttcttgggat tgctaattac 180
gcacaaaagt tccagggaag ggtgaccatc accgcagacg aatctacctc cactgcttac 240
atggaactct cttccctgcg gtccgaggac accgccgtct actattgtgc caggggcggt 300
gccggaggaa gcggttctta ctatccgctg atttggggac aaggaaccac tgtgaccgtg 360
agctctggtg gaggcggatc cggtggtgga gggtccggag gcggaggatc tgagatcgtg 420
ctcactcaga gcccagccac ccttagcctg agccctggtg agcgcgccac cctctcatgc 480
ggtgcctcac agagcgtgag ctcaagctat ctggcatggt accagcaaaa gccagggcag 540
gccccgaggc tcctgatcta cgacgcatca tcacgggcta ccggtatccc ggcacgcttc 600
tctggaagcg gatcaggcac cgacttcacc ctgaccattt cttcacttga gccagaggac 660
tttgccgtgt actactgcca gcagcgctca agctggccgc ctacttggac tttcggacag 720
gggaccaagc tggagatcaa gcgcgcggcc gcattcgtgc cggtcttcct gccagcgaag 780
cccaccacga cgccagcgcc gcgaccacca acaccggcgc ccaccatcgc gtcgcagccc 840
ctgtccctgc gcccagaggc gtgccggcca gcggcggggg gcgcagtgca cacgaggggg 900
ctggacttcg cctgtgatat ctacatctgg gcgcccttgg ccgggacttg tggggtcctt 960
ctcctgtcac tggttatcac cctttactgc aaccacagga acaggagtaa gaggagcagg 1020
ctcctgcaca gtgactacat gaacatgact ccccgccgcc ccgggcccac ccgcaagcat 1080
taccagccct atgccccacc acgcgacttc gcagcctatc gctcccgttt ctctgttgtt 1140
aaacggggca gaaagaagct cctgtatata ttcaaacaac catttatgag accagtacaa 1200
actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 1260
gaactgagag tgaagttcag caggagcgca gacgccccg cgtaccagca gggccagaac 1320
cagctctata acgagctcaa tctaggacga agagaggagt acgatgtttt ggacaagaga 1380
cgtggccggg accctgagat ggggggaaag ccgagaagga agaaccctca ggaaggcctg 1440
tacaatgaac tgcagaaaga taagatggcg gaggcctaca gtgagattgg gatgaaaggc 1500
gagcgccgga ggggcaaggg gcacgatggc ctttaccagg gtctcagtac agccaccaag 1560
gacacctacg acgcccttca catgcaggcc ctgccccctc gctaa 1605

SEQ ID NO: 137 moltype = DNA length = 1395
FEATURE Location/Qualifiers
misc_feature 1..1395
note = Synthetic
source 1..1395
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 137
caagtccagc tggtgcaaag cggagcagaa gtgaagaagc ctggatcctc tgtgaaggtc 60
agctgcaagg cctctggagg taccttcagc tcttacgcaa tttcttgggt gcgccaggct 120
cccgggcagg gactggagtg gatgggagga atcatcccga tccttggtac cgctaattac 180
gcccagaaat ttcagggtcg ggtgaccatc accgcagacg agtcaacctc aaccgcttac 240
atggaacttt ctagcctccg cagcgaggac accgccgtct actattgcgc aagatggggt 300
ggtggtgcct tcgacatttg gggacagggc actatggtca ccgtgagctc cggtggagga 360
ggatctggcg gaggagggtc aggcggaggt gggtcagaga ttgtgctgac ccagtcaccc 420
gggactctgt ccctttctcc tggtgagcgc gctactctgt cttgtagggc ctcacaatca 480
gtgggcggct atctcgcctg gtatcagcag aaaccagggc aggcccctag gcttctcatc 540
tacgacgcct ccaaccgggc aactggcatt ccagcccgct tcagcggaag cggatccgga 600
accgacttta ctctgactat ctcctcactg gaaccggagg acttcgcagt gtactactgc 660
cagcagcgga ataactggcc accgatgtac actttcggac aggggaccaa gctggagatc 720
aagcgcgcgg ccgcaattga agttatgtat cctcctcctt acctagacaa tgagaagagc 780
aatggaacca ttatccatgt gaaagggaaa caccttttgtc caagtcccct atttcccgga 840
ccttctaagc ccttttgggt gctggtggtg gttgggggag tcctggcttg ctatagcttg 900
ctagtaacag tggcctttat tattttctgg gtgaggagta agaggagcag gctcctgcac 960
agtgactaca tgaacatgac tccccgccgc cccgggccca cccgcaagca ttaccagccc 1020
tatgccccac cacgcgactt cgcagcctat cgctccagag tgaagttcag caggagcgca 1080
gacgcccccg cgtaccagca gggccagaac cagctctata acgagctcaa tctaggacga 1140

-continued

agagaggagt acgatgtttt ggacaagaga cgtggccggg accctgagat gggggggaaag 1200
ccgagaagga agaaccctca ggaaggcctg tacaatgaac tgcagaaaga taagatggcg 1260
gaggcctaca gtgagattgg gatgaaaggc gagcgccgga ggggcaaggg gcacgatggc 1320
ctttaccagg gtctcagtac agccaccaag gacacctacg acgcccttca catgcaggcc 1380
ctgccccctc gctaa 1395

SEQ ID NO: 138 moltype = DNA length = 1407
FEATURE Location/Qualifiers
misc_feature 1..1407
note = Synthetic
source 1..1407
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 138
caagtccagc tggtgcaaag cggagcagaa gtgaagaagc ctggatcctc tgtgaaggtc 60
agctgcaagg cctctggagg taccttcagc tcttacgcaa tttcttgggt gcgccaggct 120
cccgggcagg gactggagtg gatgggagga atcatcccga tccttggtac cgctaattac 180
gcccagaaat ttcagggtcg ggtgaccatc accgcagacg agtcaacctc aaccgcttac 240
atggaacttt ctagcctccg cagcgaggac accgccgtct actattgcgc aagatggggt 300
ggtggtgcct tcgacatttg gggacagggc actatggtca ccgtgagctc cggtggagga 360
ggatctggcg gaggagggtc aggcggaggt gggtcagaga ttgtgctgac ccagtcaccc 420
gggactctgt ccctttctcc tggtgagcgc gctactctgt cttgtagggc ctcacaatca 480
gtgggcggct atctcgcctg gtatcagcag aaaccagggc aggcccctag gcttctcatc 540
tacgacgcct ccaaccgggc aactggcatt ccagcccgct tcagcggaag cggatccgga 600
accgacttta ctctgactat ctcctcactg gaaccggagg acttcgcagt gtactactgc 660
cagcagcgga ataactggcc accgatgtac actttcggac aggggaccaa gctggagatc 720
aagcgcgcgg ccgcaaccac gacgccagcg ccgcgaccac caacaccggc gcccaccatc 780
gcgtcgcagc ccctgtccct gcgcccagag gcgtgccggc cagcggcggg gggcgcagtg 840
cacacgaggg ggctggactt cgcctgtgat atctacatct gggcgccctt ggccgggact 900
tgtggggtcc ttctcctgtc actggttatc acccttact gcaaacgggg cagaaagaaa 960
ctcctgtata tattcaaaca accatttatg agaccagtac aaactactca agaggaagat 1020
ggctgtagct gccgatttcc agaagaagaa gaaggaggat gtgaactgag agtgaagttc 1080
agcaggagcg cagacgcccc cgcgtacaag cagggccaga accagctcta taacgagctc 1140
aatctaggac gaagagagga gtacgatgtt ttggacaaga gacgtggccg ggaccctgag 1200
atgggggaa agccgagaag gaagaaccct caggaaggcc tgtacaatga actgcagaaa 1260
gataagatgg cggaggccta cagtgagatt gggatgaaag gcgagcgccg gaggggcaag 1320
gggcacgatg gcctttacca gggtctcagt acagccacca aggacaccta cgacgccctt 1380
cacatgcagg ccctgccccc tcgctaa 1407

SEQ ID NO: 139 moltype = DNA length = 1587
FEATURE Location/Qualifiers
misc_feature 1..1587
note = Synthetic
source 1..1587
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 139
caagtccagc tggtgcaaag cggagcagaa gtgaagaagc ctggatcctc tgtgaaggtc 60
agctgcaagg cctctggagg taccttcagc tcttacgcaa tttcttgggt gcgccaggct 120
cccgggcagg gactggagtg gatgggagga atcatcccga tccttggtac cgctaattac 180
gcccagaaat ttcagggtcg ggtgaccatc accgcagacg agtcaacctc aaccgcttac 240
atggaacttt ctagcctccg cagcgaggac accgccgtct actattgcgc aagatggggt 300
ggtggtgcct tcgacatttg gggacagggc actatggtca ccgtgagctc cggtggagga 360
ggatctggcg gaggagggtc aggcggaggt gggtcagaga ttgtgctgac ccagtcaccc 420
gggactctgt ccctttctcc tggtgagcgc gctactctgt cttgtagggc ctcacaatca 480
gtgggcggct atctcgcctg gtatcagcag aaaccagggc aggcccctag gcttctcatc 540
tacgacgcct ccaaccgggc aactggcatt ccagcccgct tcagcggaag cggatccgga 600
accgacttta ctctgactat ctcctcactg gaaccggagg acttcgcagt gtactactgc 660
cagcagcgga ataactggcc accgatgtac actttcggac aggggaccaa gctggagatc 720
aagcgcgcgg ccgcattcgt gccggtcttc ctgccagcga agcccaccac gacgccagcg 780
ccgcgaccac caacaccggc gcccaccatc gcgtcgcagc ccctgtccct gcgcccagag 840
gcgtgccggc cagcggcggg gggcgcagtg cacacgaggg ggctggactt cgcctgtgat 900
atctacatct gggcgccctt ggccgggact tgtggggtcc ttctcctgtc actggttatc 960
acccttact gcaaccacag gaacaggagt aagaggagca ggctcctgca cagtgactac 1020
atgaacatga ctccccgccg ccccgggccc acccgcaagc attaccagcc ctatgcccca 1080
ccacgcgact tcgcagccta tcgctcccgt ttctctgttg ttaaacgggg cagaaagaag 1140
ctcctgtata tattcaaaca accatttatg agaccagtac aaactactca agaggaagat 1200
ggctgtagct gccgatttcc agaagaagaa gaaggaggat gtgaactgag agtgaagttc 1260
agcaggagcg cagacgcccc cgcgtaccag cagggccaga accagctcta taacgagctc 1320
aatctaggac gaagagagga gtacgatgtt ttggacaaga gacgtggccg ggaccctgag 1380
atgggggaa agccgagaag gaagaaccct caggaaggcc tgtacaatga actgcagaaa 1440
gataagatgg cggaggccta cagtgagatt gggatgaaag gcgagcgccg gaggggcaag 1500
gggcacgatg gcctttacca gggtctcagt acagccacca aggacaccta cgacgccctt 1560
cacatgcagg ccctgccccc tcgctaa 1587

SEQ ID NO: 140 moltype = DNA length = 72

-continued

FEATURE	Location/Qualifiers
misc_feature	1..72
	note = Synthetic
source	1..72
	mol_type = other DNA
	organism = synthetic construct

SEQUENCE: 140

atggttctgc tggtgacttc actcctgctc tgtgaacttc cccatcccgc ttttctcctg 60
atccccgaca cc 72

1-29. (canceled)

30. A polypeptide comprising

(a) a heavy and light chain comprising (i) SEQ ID NOs: 1-6;

a heavy and light chain comprising (ii) SEQ ID NOs: 11-16; or

a heavy and light chain comprising (iii) SEQ ID NOs: 20-25;

wherein the heavy and light chains of (i), (ii), or (iii) bind to CD276 and are linked to one or more of the immunoglobulin constant domains CH2 and/or CH3, and

(b) a leader amino acid sequence.

31. The polypeptide according to claim **30**, wherein the leader amino acid sequence comprises SEQ ID NO: 60, SEQ ID NO: 61 or SEQ ID NO: 62.

32. The polypeptide according to claim **30**, wherein the one or more immunoglobulin constant domains comprise SEQ ID NO: 71.

33. The polypeptide according to claim **30**, wherein the heavy and light chains of (i), (ii), or (iii) and the one or more immunoglobulin constant domains comprise SEQ ID NO: 80, SEQ ID NO: 82, or SEQ ID NO: 84.

34. A protein comprising:

(a) a first polypeptide chain comprising (i) a heavy chain comprising SEQ ID NOs: 1-3,

(ii) a heavy chain comprising SEQ ID NOs: 11-13, or

(iii) a heavy chain comprising SEQ ID NOs: 20-22; and

(b) a second polypeptide chain comprising

(iv) a light chain comprising SEQ ID NOs: 4-6,

(v) a light chain comprising SEQ ID NOs: 14-16, or

(vi) a light chain comprising SEQ ID NOs: 23-25,

wherein the first polypeptide of (i), (ii), or (iii) and the second polypeptide of (iv), (v), or (vi) bind to CD276, and are linked to one or more of the immunoglobulin constant domains CH2 and/or CH3, and

(c) a leader amino acid sequence.

35. The protein according to claim **34**, wherein the leader amino acid sequence comprises SEQ ID NO: 60, SEQ ID NO: 61 or SEQ ID NO: 62.

36. The protein according to claim **34**, wherein the one or more immunoglobulin constant domains comprise SEQ ID NO: 71.

37. The protein according to claim **34**, wherein the first polypeptide chain, second polypeptide chain, and one or more immunoglobulin constant domains comprise SEQ ID NO: 80, SEQ ID NO: 82, or SEQ ID NO: 84.

38. The polypeptide according to claim **30**, further comprising a linker amino acid sequence.

39. The polypeptide according to claim **38**, wherein the linker comprises SEQ ID NO: 9 or SEQ ID NO: 115.

40. The polypeptide according to claim **30**, comprising SEQ ID NO: 10, SEQ ID NO: 19, or SEQ ID NO: 28.

41. A chimeric antigen receptor (CAR) comprising

(a) an antigen binding domain formed by a heavy and light chain comprising (i) SEQ ID NOs: 1-6, a heavy and light chain comprising (ii) SEQ ID NOs: 11-16, or a heavy and light chain comprising (iii) SEQ ID NOs: 20-25, wherein the heavy and light chains of (i), (ii), or (iii) bind to CD276;

(b) an immunoglobulin constant domain;

(c) a leader amino acid sequence;

(d) a transmembrane domain, and

(e) an intracellular T cell signaling domain.

42. The CAR according to claim **41**, wherein the leader amino acid sequence comprises SEQ ID NO: 60, SEQ ID NO: 61 or SEQ ID NO: 62.

43. The CAR according to claim **41**, wherein the immunoglobulin constant domain comprises one or more of CH2 and/or CH3 and is effective to extend the antigen binding domain away from a membrane of a CAR expressing cell.

44. The CAR according to claim **41**, wherein the immunoglobulin constant domain comprises SEQ ID NO: 71.

45. The CAR according to claim **41**, wherein the transmembrane domain comprises CD8 and CD28.

46. The CAR according to claim **41**, wherein the transmembrane domain comprises any one or more of a CD8 amino acid sequence comprising SEQ ID NO: 29, a CD28 amino acid sequence comprising SEQ ID NO: 30, and a CD8 amino acid sequence comprising SEQ ID NO: 31.

47. The CAR according to claim **41**, wherein the intracellular T cell signaling domain comprises one or more of i) CD28, ii) CD137, and iii) CD3 zeta.

48. The CAR according to claim **41**, wherein the intracellular T cell signaling domain comprises a CD28 amino acid sequence comprising SEQ ID NO: 32 and/or SEQ ID NO: 35.

49. The CAR according to claim **41**, wherein the intracellular T cell signaling domain comprises a CD137 amino acid sequence comprising SEQ ID NO: 33 and/or SEQ ID NO: 37.

50. A conjugate comprising (a) the polypeptide of claim **30** conjugated to (b) an effector molecule.

51. The conjugate according to claim **50**, wherein the effector molecule is PE4E, PE40, PE38, PE25, PE38QQR, PE38KDEL, PE-LR, or PE35.

52. A nucleic acid comprising a nucleotide sequence encoding the polypeptide of claim **30**.

53. The nucleic acid according to claim **52** comprising a nucleotide sequence comprising SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 72, SEQ ID NOs: 76-79, SEQ ID NO: 81, SEQ ID NO: 83 or SEQ ID NO: 140.

54. A recombinant expression vector comprising the nucleic acid of claim **52** or claim **53**.

55. An isolated host cell comprising the recombinant expression vector of claim **54**.

56. A population of cells comprising at least one isolated host cell of claim **55**.

57. The polypeptide of claim **30** expressed in one or more host cells for use in treating cancer in a mammal.

* * * * *