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(71) Applicant: THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA [US/US]; 3160 Chestnut Street, Suite 200, Philadelphia, Pennsylvania 19104 (US).

(72) Inventors: GILL, Saar; 438 Poplar Street, Philadelphia, Pennsylvania 19123 (US). HOGAN, Jonathan; 311 Linden Avenue, Haddonfield, New Jersey 08033 (US). PAYNE, Aimee S.; 536 Hamilton Road, Merion Station, Pennsylvania 19066 (US). WANG, Baomei; c/o The Trustees of the University of Pennsylvania, 3160 Chestnut Street, Suite 200, Philadelphia, Pennsylvania 19104 (US).

(74) Agent: DOYLE, Kathryn et al.; Saul Ewing Arnstein & Lehr LLP, Centre Square West, 1500 Market Street, 38th Floor, Philadelphia, Pennsylvania 19102 (US).

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(54) Title: COMPOSITIONS AND METHODS OF PHOSPHOLIPASE A2 RECEPTOR CHIMERIC AUTOANTIBODY RECEPTOR T CELLS

(57) Abstract: The invention includes compositions comprising at least one chimeric autoantibody receptor (CAAR) specific for an anti-phospholipase A2 receptor (PLA2R) autoantibody-based B cell receptor, polynucleotides encoding the CAAR, vectors comprising a polynucleotide encoding the CAAR, and recombinant T cells comprising the CAAR. The invention also includes methods of making a genetically modified cell, e.g., a genetically modified T cell, expressing a PLA2R-CAAR wherein the expressed CAAR comprises a PLA2R extracellular domain.



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COMPOSITIONS AND METHODS OF PHOSPHOLIPASE A2 RECEPTOR CHIMERIC AUTOANTIBODY RECEPTOR T CELLS

CROSS-REFERENCE TO RELATED APPLICATION

The present application is entitled to priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 62/665,863 filed May 2, 2018, which is hereby incorporated by reference in its entirety herein.

BACKGROUND OF THE INVENTION

Membranous nephropathy (MN) is among the most common primary causes of nephrotic syndrome in adults (up to one-third of cases). About 15-25% of membranous nephropathy cases are secondary membranous nephropathy, caused by drugs, infections, tumors, or immune diseases. The remaining 75-85% of membranous nephropathy cases are idiopathic, also called primary membranous nephropathy. MN is caused by immune complex formation in the glomerulus. The immune complexes are formed by binding of antibodies to antigens on the podocyte. The immune complex serves as an activator that triggers complement-mediated lysis of glomerular epithelial cells and the release of proteases and oxidants damaging capillary walls. Up to 40% of patients with primary membranous nephropathy who do not receive immunosuppressive treatment develop end-stage renal disease requiring dialysis or kidney transplantation.

The M-type phospholipase A2 receptor (PLA2R) has been described as a major autoantigen in primary membranous nephropathy. Autoantibodies to PLA2R are present in 70-80% of cases of primary membranous nephropathy, and can be used for the diagnosis and monitoring of treatment of primary membranous nephropathy both in the native kidneys and after kidney transplant.

Current guidelines suggest treatment with alkylating agents or calcineurin inhibitors as first-line therapy for the treatment of severe, primary membranous nephropathy. Rituximab, an anti-CD20 antibody, has also shown promise and is being evaluated for treating MN. However, since these treatments lack specificity for the autoreactive B cells that produce the serum anti-PLA2R antibody, they can be associated

with risk of life-threatening infections. Moreover, relapse can occur in patients who achieve remission in proteinuria, and disease can recur after kidney transplantation. Importantly, relapse is usually associated with recurrence in detectable anti-PLA2R autoantibody, thus further supporting the role of this antibody in disease pathogenesis.

5 There is an urgent need in the art for achieving a more specific and effective treatment for primary membranous nephropathy. This invention addresses this need.

SUMMARY OF THE INVENTION

10 In one aspect, the invention includes a polynucleotide encoding a chimeric autoantibody receptor (CAAR), wherein the CAAR comprises a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, and optionally, a transmembrane domain, an intracellular domain of a costimulatory molecule, and/or a signaling domain.

 In another aspect, the invention includes a vector comprising any one of the polynucleotides disclosed herein.

15 In yet another aspect, the invention includes a chimeric autoantibody receptor (CAAR) comprising an extracellular domain comprising a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof.

 In still another aspect, the invention includes a chimeric autoantibody receptor (CAAR) comprising an extracellular domain comprising a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, and optionally, a transmembrane domain, an intracellular domain of a costimulatory molecule, and/or a signaling domain.

 Another aspect of the invention includes a genetically modified cell comprising any one of the CAARs disclosed herein.

25 Yet another aspect of the invention includes genetically modified cell comprising:
(a) a chimeric autoantibody receptor (CAAR) comprising an extracellular domain comprising a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, a killer immunoglobulin-like receptor (KIR) transmembrane domain and a KIR cytoplasmic domain; and (b) DAP12.

30 Still another aspect of the invention includes a pharmaceutical composition comprising any one of the polynucleotides disclosed herein, any one of the CAARs

disclosed herein or any one of the cells disclosed herein, and a pharmaceutically acceptable excipient.

In another aspect, the invention includes a method for treating an autoantibody-mediated kidney disease in a subject. The method comprises administering to the subject an effective amount of a genetically modified T cell comprising a polynucleotide encoding a chimeric autoantibody receptor (CAAR), wherein the polynucleotide encodes a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, and optionally, a transmembrane domain, an intracellular domain of a costimulatory molecule, and/or a signaling domain, thereby treating the autoantibody mediated kidney disease in the subject.

In yet another aspect, the invention includes a method for preventing or reducing glomerulus damage in a subject at risk of or suffering from an autoantibody-mediated kidney disease, the method comprising: administering to the subject an effective amount of a genetically modified T cell comprising a polynucleotide encoding a chimeric autoantibody receptor (CAAR), wherein the polynucleotide encodes a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, and optionally a transmembrane domain, an intracellular domain of a costimulatory molecule, and/or a signaling domain, thereby preventing or reducing glomerulus damage in the subject.

In still another aspect, the invention includes a method for treating an autoantibody-mediated kidney disease in a subject. The method comprises administering to the subject an effective amount of a genetically modified T cell comprising: (a) a polynucleotide encoding a chimeric autoantibody receptor (CAAR) comprising an extracellular domain comprising phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, a killer immunoglobulin-like receptor (KIR) transmembrane domain and a KIR cytoplasmic domain; and (b) a polynucleotide encoding DAP12, thereby treating the autoantibody-mediated kidney disease in the subject.

In another aspect, the invention includes a method for preventing or reducing glomerulus damage in a subject at risk of or suffering from an autoantibody-mediated kidney disease. The method comprises administering to the subject an effective amount of a genetically modified T cell comprising: (a) a polynucleotide encoding a chimeric autoantibody receptor (CAAR) comprising an extracellular domain comprising

phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, a killer immunoglobulin-like receptor (KIR) transmembrane domain and a KIR cytoplasmic domain; and (b) a polynucleotide encoding DAP12, thereby preventing or reducing glomerulus damage in the subject.

5 In various embodiments of the above aspects or any other aspect of the invention delineated herein, the PLA2R autoantigen or fragment thereof is selected from the group consisting of: (a) an extracellular domain comprising a CysR or ricin B type lectin domain, a fibronectin type II domain, a C-type lectin domain 1 and a C-type lectin domain 2; and (b) an extracellular domain comprising a CysR or ricin B type lectin
10 domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2 and a C-type lectin domain 3.

In certain embodiments, the PLA2R autoantigen or fragment thereof is selected from the group consisting of: (a) an extracellular domain comprising a cysteine rich domain, (b) an extracellular domain comprising a cysteine rich domain, a fibronectin type
15 II domain, and a C-type lectin domain 1, (c) an extracellular domain comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2, and a C-type lectin domain 3, (d) an extracellular domain comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2, a C-type lectin domain 3, and a C-type lectin domain 7, (e) an
20 extracellular domain comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, and a C-type lectin domain 7, or (f) an extracellular domain comprising a cysteine rich domain, a C-type lectin domain 1, and a C-type lectin domain 7.

In certain embodiments, the PLA2R extracellular domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 8 or SEQ ID NO: 15 or SEQ ID NO: 47 or SEQ
25 ID NO: 60 or SEQ ID NO: 50 or SEQ ID NO: 62 or SEQ ID NO: 52 or SEQ ID NO: 54 or SEQ ID NO: 56 or SEQ ID NO: 58.

In certain embodiments, the transmembrane domain comprises a CD8 alpha chain transmembrane domain. In certain embodiments, the CD8 alpha chain transmembrane
30 domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 20. In certain

embodiments, the CD8 alpha chain transmembrane domain comprises the amino acid sequence of SEQ ID NO: 19.

5 In certain embodiments, the CAAR further comprises a hinge domain. In certain embodiments, the hinge domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 10 or SEQ ID NO: 42 or SEQ ID NO: 64. In certain embodiments, the hinge domain comprises the amino acid sequence of SEQ ID NO: SEQ ID NO: 43 or SEQ ID NO: 44.

10 In certain embodiments, the CAAR further comprises a GS linker. In certain embodiments, the GS linker is encoded by a nucleic acid sequence comprising SEQ ID NO: 68. In certain embodiments, the GS linker comprises SEQ ID NO: 69.

15 In certain embodiments, the intracellular domain of a costimulatory molecule comprises 4-1BB. In certain embodiments, the 4-1BB intracellular domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 22 or SEQ ID NO: 66. In certain embodiments, the 4-1BB intracellular domain comprises the amino acid sequence of SEQ ID NO: 21.

20 In certain embodiments, the signaling domain comprises a CD3 zeta signaling domain. In certain embodiments, the CD3 zeta signaling domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 24 or SEQ ID NO: 72. In certain embodiments, the CD3 zeta signaling domain comprises an amino acid sequence of SEQ ID NO: 23 or SEQ ID NO: 45.

25 In certain embodiments, the CAAR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 11, 17, 25, 27, 29, 31, 33, 35, 37, and 39. In certain embodiments, the CAAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 18, 26, 28, 30, 32, 34, 36, 38, and 40.

30 In certain embodiments, the CAAR comprises a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, a killer immunoglobulin-like receptor (KIR) transmembrane domain and a KIR cytoplasmic domain.

In certain embodiments, the vector is a lentiviral vector. In certain embodiments, the vector is a RNA vector.

35 In certain embodiments, the cell expresses the CAAR and has high affinity to autoantibody-based BCRs on B cells. In certain embodiments, the cell expresses the

CAAR and induces killing of B cells expressing autoantibodies. In certain embodiments, the cell expresses the CAAR and has limited toxicity toward healthy cells.

In certain embodiments, the cell is selected from the group consisting of a helper T cell, a cytotoxic T cell, a memory T cell, regulatory T cell, gamma delta T cell, a
5 natural killer cell, a cytokine induced killer cell, a cell line thereof, a T memory stem cell, a T cell derived from a pluripotent stem and other effector cell.

In certain embodiments, the autoantibody mediated kidney disease is selected from the group consisting of a glomerular disease and a primary membranous nephropathy.

10 In certain embodiments, the subject is a human.

In certain embodiments, the modified T cell targets B cells.

In certain embodiments, the KIR is KIRS2 or KIR2DS2.

In certain embodiments, the vector comprises an inducible promoter operably linked to the polynucleotide encoding the CAAR.

15 In certain embodiments, the cell comprises a polynucleotide encoding the CAAR operably linked to an inducible promoter.

BRIEF DESCRIPTION OF THE DRAWINGS

The following detailed description of preferred embodiments of the invention will
20 be better understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there are shown in the drawings embodiments which are presently preferred. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities of the embodiments shown in the drawings.

25 Figure 1 is an illustration showing a schematic of the native PLA2R molecule. The N terminal cysteine-rich (CysR) domain (Ricin B type lectin domain) is the immunodominant epitope that is recognized by patient serum antibodies. In non-reducing conditions, serum antibody recognition has been reported to be dependent on the first 3 C-type lectin domains (CTLD). In addition to the cysteine-rich domain, serum antibody
30 immunoreactivity to the C-type lectin domains 1 and 7 has also been reported. A

commercial Novus monoclonal antibody (mAb) and polyclonal Sigma antibody bind to the CTLD2 domain.

Figures 2A-2G are a series of schematic diagrams illustrating the various PLA2R CAAR constructs described in this invention. Abbreviations for here and throughout: ECD: extracellular domain; TMD: transmembrane domain; BBZ: cytoplasmic tandem 41BB (CD137) and CD3-zeta signaling domain; CysR = cysteine rich domain; FNII = fibronectin type II domain; CTLD = C-type lectin domain. All constructs use a CD8 transmembrane domain and BBZ cytoplasmic domain and differ in their extracellular composition as follows: Figure 2A depicts construct 4025.C (or construct C), whose extracellular domain consists of the PLA2R CysR domain, followed by a CD8 hinge domain. Figure 2B depicts construct 4026.CF1 (or construct CF1), consisting of the CysR, FNII, and CTLD1 domains followed by a CD8 hinge domain. Figure 2C depicts construct 4027.CF12, consisting of the CysR, FNII, CTLD1, and CTLD2 domains, followed by a CD8 hinge domain. Figure 2D depicts construct 4028.CF123 (or construct CF123), consisting of the CysR, FNII, CTLD1, CTLD2, and CTLD3 domains, followed by either a CD8 hinge (4028.CF123) or GS linker (CF123). Figure 2E depicts construct CF1237, consisting of the CysR, FNII, CTLD1, CTLD2, CTLD3, and CTLD7 domains followed by a GS linker. Figure 2F depicts construct CF17, consisting of the CysR, FNII, CTLD1, and CTLD7 domains, followed by a GS linker. Figure 2G depicts construct C17, consisting of the CysR, CTLD1, and CTLD7 domains, followed by a GS linker.

Figure 3A is an illustration showing a portion of the plasmid map comprising the 4028.CF123 CAAR. Figure 3B is a table distinguishing the compositions of the CAAR constructs described in this invention.

Figure 4 is a series of flow cytometry plots demonstrating surface expression of a subset of PLA2R CAARs (4027.CF12 and 4028.CF123) on Jurkat NFAT-GFP cells. The expression of PLA2R CAAR by Jurkat NFAT-GFP cells transduced with different PLA2R lentiviral constructs was measured (MOI 5:1, 48h) using a commercial Novus monoclonal antibody (mAb) specific for the PLA2R CTLD2 domain. Jurkat T cells expressing construct 4027.CF12 or 4028.CF123, but not those T cells bearing 4025.C, which does not include the CTLD2 domain and hence is not detectable by the mAb used,

or untransduced Jurkat NFAT-GFP cells, exhibited detectable surface expression of the CAAR.

Figure 5 is a series of flow cytometry plots showing the negative and positive controls for PLA2R CAAR T cell activation using an isotype control (top, negative control) or PMA + ionomycin (bottom, positive control).

Figure 6 is a series of flow cytometry plots showing the activation of 4027.CF12 and 4028.CF123 PLA2R CAAR T cells by plate-bound monoclonal or polyclonal antibodies specific for the PLA2R CTLD2 domain, measured as GFP expression by Jurkat NFAT-GFP cells (6h activation). No evidence of T cell activation is seen in construct 4025.C, as expected as this construct does not contain the CTLD2 domain, and untransduced cells upon exposure to the anti-PLA2R monoclonal antibody (mAb) or the polyclonal anti-PLA2R antibody (Ab). Specific T cell activation in response to cross-linking of the PLA2R CAAR by the monoclonal anti-PLA2R mAb but not the polyclonal anti-PLA2R Ab is observed.

Figures 7A-7B are a series of plots illustrating that PLA2R MN patient IgG detects PLA2R CAAR expression on transduced Jurkat NFAT-GFP and primary human T cells. Flow cytometry plots demonstrate robust PLA2R CAAR surface expression on Jurkat NFAT-GFP cells (Figure 7A) and primary human T cells (Figure 7B) for all constructs evaluated (4025.C, 4026.CF1, 4027.CF12, 4028.CF123, C, CF1, CF123, CF1237, CF17, C17). The expression of PLA2R CAAR by Jurkat NFAT-GFP and primary human T cells transduced with different PLA2R lentiviral constructs (72h) was detected by incubation with MN patient IgG followed by APC-conjugated anti-human IgG.

Figure 8 is a series of plots illustrating that plate-bound MN patient IgG activates PLA2R CAAR transduced Jurkat-NFAT-GFP cells. Flow cytometry plots show the activation of PLA2R CAAR T cells by MN patient IgG measured as GFP expression by Jurkat NFAT-GFP cells (6h activation). All evaluated PLA2R CAAR T cells (4025.C, 4026.CF1, 4027.CF12, 4028.CF123, C, CF1, CF123, CF1237, CF17, C17) transduced signal after cross-linking by plate-bound anti-PLA2R IgG.

Figure 9 is a set of graphs illustrating that plate-bound MN patient IgG stimulates IFN- γ secretion from PLA2R CAAR-transduced primary human T cells. 5×10^4 primary

human T cells were cultured for 24h in a 96-well plate coated with 10 µg/ml of either MN patient IgG or control human IgG. Culture supernatants were then harvested for detection of IFN- γ by ELISA. IFNγ production was detectable in all culture supernatants and was elevated relative to untransduced T cells, or PLA2R CAAR T cells stimulated with control (Ctrl) human IgG.

DETAILED DESCRIPTION

The invention includes a chimeric autoantibody receptor (CAAR) specific for anti-phospholipase A2 receptor (PLA2R) B cell receptor (BCR), compositions comprising the CAAR, polynucleotides encoding the CAAR, vectors comprising a polynucleotide encoding the CAAR, and recombinant T cells comprising the CAAR. The invention also includes methods of making a genetically modified cell, *e.g.*, a genetically modified T cell, expressing a PLA2R-CAAR wherein the expressed CAAR comprises a PLA2R extracellular domain.

The present invention also relates generally to the use of cells, *e.g.*, T cells, engineered to express a CAAR to treat an autoantibody-mediated kidney disease associated with targeting of self-antigens (*e.g.* PLA2R). In one embodiment, the cells, *e.g.*, T cells expressing the CAAR of the invention specifically bind to and kill anti-PLA2R BCR-expressing cells, but do not bind to and kill normal BCR-expressing cells.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although any methods and materials similar or equivalent to those described herein can be used in the practice of and/or for the testing of the present invention, the preferred materials and methods are described herein. In describing and claiming the present invention, the following terminology will be used according to how it is defined, where a definition is provided.

It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

The articles “a” and “an” are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

“About,” as used herein, when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of $\pm 20\%$ or $\pm 10\%$, in some instances $\pm 5\%$, in some instances $\pm 1\%$, and in some instance $\pm 0.1\%$ from the specified value, as such variations are appropriate to perform the disclosed methods.

The term “antibody,” as used herein, refers to an immunoglobulin molecule that binds with an antigen. Antibodies can be intact immunoglobulins derived from natural sources or from recombinant sources and can be immunoreactive portions of intact immunoglobulins. Antibodies are typically tetramers of immunoglobulin molecules. The antibody in the present invention may exist in a variety of forms where the antibody is expressed as part of a contiguous polypeptide chain including, for example, a single domain antibody fragment (sdAb), a single chain antibody (scFv) and a humanized antibody (Harlow et al., 1999, In: Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, NY; Harlow et al., 1989, In: Antibodies: A Laboratory Manual, Cold Spring Harbor, New York; Houston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; Bird et al., 1988, Science 242:423-426).

The term “high affinity,” as used herein, refers to high specificity in binding or interacting or attraction of a binding molecule to a target molecule. For example, in some embodiments, the binding molecule may have an affinity for the target molecule stronger than 100nM, 50 nM, 20 nM, 15 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, or 1 nM, *e.g.*, as determined by surface plasmon resonance.

The term “antigen” or “Ag,” as used herein, is defined as a molecule that provokes an immune response. This immune response may involve either antibody production, or the activation of specific immunologically competent cells, or both. The skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. Furthermore, antigens can be derived from recombinant or genomic DNA. A skilled artisan will understand that any DNA, which comprises a nucleotide sequences or a partial nucleotide sequence encoding a protein that elicits an immune response therefore encodes an “antigen” as that term is used herein.

Furthermore, one skilled in the art will understand that an antigen need not be encoded solely by a full length nucleotide sequence of a gene. It is readily apparent that the present invention includes, but is not limited to, the use of partial nucleotide sequences of more than one gene and that these nucleotide sequences are arranged in various combinations to encode polypeptides that elicit the desired immune response. Moreover, a skilled artisan will understand that an antigen need not be encoded by a “gene” at all. It is readily apparent that an antigen can be generated synthesized or can be derived from a biological sample. Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a biological fluid.

By “autoantigen” is meant an endogenous antigen that stimulates production of an autoimmune response, such as production of autoantibodies. Autoantigen also includes a self-antigen or antigen from a normal tissue that is the target of a cell-mediated or an antibody-mediated immune response that may result in the development of an autoimmune disease. Examples of autoantigens include, but are not limited to, PLA2R, and fragments thereof.

The term “limited toxicity,” as used herein, refers to the peptides, polynucleotides, cells and/or antibodies of the invention manifesting a lack of substantially negative biological effects, anti-tumor effects, or substantially negative physiological symptoms toward a healthy cell, non-tumor cell, non-diseased cell, non-target cell or population of such cells either in vitro or in vivo.

“Autoantibody” refers to an antibody that is specific for an autoantigen.

The term “autoimmune disease,” as used herein, is defined as a disorder or condition that results from an antibody-mediated autoimmune response against autoantigens. An autoimmune disease results in the production of autoantibodies that are inappropriately produced and/or excessively produced to a self-antigen or autoantigen.

As used herein, the term “autologous” is meant to refer to any material derived from the same individual to which it is later to be re-introduced into the individual.

“Allogeneic” refers to any material derived from a different animal of the same species.

“Xenogeneic” refers to any material derived from an animal of a different species.

“Chimeric autoantibody receptor” or “CAAR” refers to an engineered receptor that is expressed on cell, *e.g.*, a T cell or any other effector cell type, *e.g.*, an effector cell type capable of cell-mediated cytotoxicity. The CAAR includes an antigen or fragment thereof that is specific for an autoantibody and/or BCR, *e.g.*, a pathogenic autoantibody and/or BCR. The CAAR optionally also includes a transmembrane domain, an
5 intracellular domain and/or a signaling domain.

As used herein, the term “conservative sequence modifications” is intended to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence. Such conservative
10 modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into an antibody of the invention by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having
15 similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.*,
20 threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, for example, one or more amino acid residues within the extracellular regions of the CAAR of the invention can be replaced with other amino acid residues having a similar side chain or charge and the altered CAAR can be tested for the ability to bind autoantibodies using the functional assays described herein.

“Co-stimulatory ligand,” as the term is used herein, includes a molecule on an antigen presenting cell (*e.g.*, an aAPC, dendritic cell, B cell, and the like) that specifically binds a cognate co-stimulatory molecule on a T cell, thereby providing a signal which, in addition to the primary signal provided by, for instance, binding of a TCR/CD3 complex with an MHC molecule loaded with peptide, mediates a T cell response, including, but
25 not limited to, proliferation, activation, differentiation, and the like.

A “co-stimulatory molecule” refers to the cognate binding partner on a T cell that specifically binds with a co-stimulatory ligand, thereby mediating a co-stimulatory response by the T cell, such as, but not limited to, proliferation. Co-stimulatory molecules include, but are not limited to an MHC class I molecule, BTLA and a Toll ligand receptor.

“Encoding” refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (*i.e.*, rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

“Effective amount” or “therapeutically effective amount” are used interchangeably herein, and refer to an amount of a compound, formulation, material, or composition, as described herein effective to achieve a particular biological result. Such results may include, but are not limited to, the inhibition of virus infection as determined by any means suitable in the art.

The term “effector function” refers to a specialized function of a cell.

As used herein, “endogenous” refers to any material from or produced inside an organism, cell, tissue or system.

As used herein, the term “exogenous” refers to any material introduced from or produced outside an organism, cell, tissue or system.

The term “expression,” as used herein, is defined as the transcription and/or translation of a particular nucleotide sequence driven by a promoter.

“Expression vector” refers to a vector comprising a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for

expression; other elements for expression can be supplied by the host cell or in an in vitro expression system. Expression vectors include all those known in the art, such as cosmids, plasmids (*e.g.*, naked or contained in liposomes), retrotransposons (*e.g.* piggyback, sleeping beauty), and viruses (*e.g.*, lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses) that incorporate the recombinant polynucleotide.

“Homologous,” as used herein, refers to the subunit sequence identity between two polymeric molecules, *e.g.*, between two nucleic acid molecules, such as, two DNA molecules or two RNA molecules, or between two polypeptide molecules. When a subunit position in both of the two molecules is occupied by the same monomeric subunit; *e.g.*, if a position in each of two DNA molecules is occupied by adenine, then they are homologous at that position. The homology between two sequences is a direct function of the number of matching or homologous positions; *e.g.*, if half (*e.g.*, five positions in a polymer ten subunits in length) of the positions in two sequences are homologous, the two sequences are 50% homologous; if 90% of the positions (*e.g.*, 9 of 10), are matched or homologous, the two sequences are 90% homologous.

“Identity,” as used herein, refers to the subunit sequence identity between two polymeric molecules particularly between two amino acid molecules, such as, between two polypeptide molecules. When two amino acid sequences have the same residues at the same positions; *e.g.*, if a position in each of two polypeptide molecules is occupied by an Arginine, then they are identical at that position. The identity or extent to which two amino acid sequences have the same residues at the same positions in an alignment is often expressed as a percentage. The identity between two amino acid sequences is a direct function of the number of matching or identical positions; *e.g.*, if half (*e.g.*, five positions in a polymer ten amino acids in length) of the positions in two sequences are identical, the two sequences are 50% identical; if 90% of the positions (*e.g.*, 9 of 10), are matched or identical, the two amino acids sequences are 90% identical.

As used herein, an “instructional material” includes a publication, a recording, a diagram, or any other medium of expression which can be used to communicate the usefulness of the compositions and methods of the invention. The instructional material of the kit of the invention may, for example, be affixed to a container which contains the nucleic acid, peptide, and/or composition of the invention or be shipped together with a

container which contains the nucleic acid, peptide, and/or composition. Alternatively, the instructional material may be shipped separately from the container with the intention that the instructional material and the compound be used cooperatively by the recipient.

5 “Intracellular domain” refers to a portion or region of a molecule that resides inside a cell.

The term “intracellular signaling domain” is meant to include any full-length or truncated portion of the intracellular domain sufficient to transduce the effector function signal.

10 “Isolated” means altered or removed from the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not “isolated,” but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is “isolated.” An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

15 In the context of the present invention, the following abbreviations for the commonly occurring nucleic acid bases are used. “A” refers to adenosine, “C” refers to cytosine, “G” refers to guanosine, “T” refers to thymidine, and “U” refers to uridine.

20 Unless otherwise specified, a “nucleotide sequence encoding an amino acid sequence” includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or an RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s).

25 A “lentivirus,” as used herein, refers to a genus of the Retroviridae family. Lentiviruses are unique among the retroviruses in being able to infect non-dividing cells; they can deliver a significant amount of genetic information into the DNA of the host cell, so they are one of the most efficient methods of a gene delivery vector. HIV, SIV, and FIV are all examples of lentiviruses. Vectors derived from lentiviruses offer the means to achieve significant levels of gene transfer in vivo.

30 The term “operably linked” refers to functional linkage between a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the latter. For example, a first nucleic acid sequence is operably linked with a second nucleic acid

sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Generally, operably linked DNA sequences are contiguous and, where necessary to join two protein coding regions, in the same reading frame.

“Parenteral” administration of an immunogenic composition includes, *e.g.*, subcutaneous (s.c.), intravenous (i.v.), intramuscular (i.m.), or intrasternal injection, or infusion techniques.

As used herein, “plasma cells,” refer to a type of white blood cells which can produce and secrete antibodies. Plasma cells are also referred to as plasmocytes, plasmacytes, or effector B cells. In some embodiments, these cells comprise B cell precursors capable of B-cell differentiation or B cells in the early stages of B cell differentiation, expressing a μ chain on the cell surface as antigen receptor; B cells in which the transcription process has changed and IgM production has changed from membrane-type IgMs to secreted-type IgMs; mature B cells that have completed class-switching and secrete IgGs, IgAs, and IgMs; and B cells in the final stages of differentiation.

As used herein, the terms “phospholipase A2 receptor” or “M-type phospholipase A2 receptor” (PLA2R) are used interchangeably and refer to the major target antigen expressed in the kidney glomeruli in primary membranous nephropathy (MN) (Beck et al. 2009 N Engl J Med; 361: 11-21). The anti-PLA2R autoantibodies are predominantly of the IgG4 subclass but subclasses IgG1, IgG2, and IgG3 are also represented. Genetic variants of PLA2R were also shown to be associated with MN (Stanescu et al. 2011 N Engl J Med; 364(7):616-26).

As used herein, a PLA2R fragment refers to a shortened or truncated PLA2R protein. The polypeptide can have N-terminus or C-terminus truncations and/or also internal deletions. Examples of fragments are fragments comprising the C-type lectin domains (“CTLD”) of PLA2R. In one embodiment, a PLA2R fragment includes the external domain of PLA2R, which is the amino acid residues 21-1397 of the human PLA2R (UniProtKB, Q13018) or any shorter portion of the amino acid residues 21-1397.

The term “polynucleotide,” as used herein, is defined as a chain of nucleotides. Furthermore, nucleic acids are polymers of nucleotides. Thus, nucleic acids and polynucleotides, as used herein, are interchangeable. One skilled in the art has the general knowledge that nucleic acids are polynucleotides, which can be hydrolyzed into the monomeric “nucleotides.” The monomeric nucleotides can be hydrolyzed into nucleosides. As used herein, polynucleotides include, but are not limited to, all nucleic acid sequences which are obtained by any means available in the art, including, without limitation, recombinant means, i.e., the cloning of nucleic acid sequences from a recombinant library or a cell genome, using ordinary cloning technology and PCRTM, and the like, and by synthetic means. In some embodiments, a nucleic acid sequence is considered to have at least 95%, 96%, 97%, 98%, or 99% identity or homology to any nucleic acid sequence disclosed herein.

As used herein, the terms “peptide,” “polypeptide,” and “protein” are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein’s or peptide’s sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. “Polypeptides” include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. The polypeptides include natural peptides, recombinant peptides, synthetic peptides, or a combination thereof. In some embodiments, an amino acid sequence is considered to have at 95%, 96%, 97%, 98%, or 99% identity or homology to any amino acid sequence described herein.

The term “proinflammatory cytokine” refers to a cytokine or factor that promotes inflammation or inflammatory responses. Examples of proinflammatory cytokines include, but are not limited to, chemokines (CCL, CXCL, CX3CL, XCL), interleukins

(such as, IL-1, IL-2, IL-3, IL-5, IL-6, IL-7, IL-9, IL10 and IL-15), interferons (IFN γ), and tumor necrosis factors (TNF α and TNF β).

5 The term “promoter,” as used herein, is defined as a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a polynucleotide sequence.

As used herein, the term “promoter/regulatory sequence” means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence
10 and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue specific manner.

A “constitutive” promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product
15 to be produced in a cell under most or all physiological conditions of the cell.

An “inducible” promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell substantially only when an inducer which corresponds to the promoter is present in the cell.

20 A “tissue-specific” promoter is a nucleotide sequence which, when operably linked with a polynucleotide encodes or specified by a gene, causes the gene product to be produced in a cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

A “signal transduction pathway” refers to the biochemical relationship between a
25 variety of signal transduction molecules that play a role in the transmission of a signal from one portion of a cell to another portion of a cell. The phrase “cell surface receptor” includes molecules and complexes of molecules capable of receiving a signal and transmitting signal across the membrane of a cell.

30 “Signaling domain” refers to the portion or region of a molecule that recruits and interacts with specific proteins in response to an activating signal.

The term “subject” is intended to include living organisms in which an immune response can be elicited (e.g., mammals).

As used herein, a “substantially purified” cell is a cell that is essentially free of other cell types. A substantially purified cell also refers to a cell which has been separated from other cell types with which it is normally associated in its naturally occurring state. In some instances, a population of substantially purified cells refers to a homogenous population of cells. In other instances, this term refers simply to cells that have been separated from the cells with which they are naturally associated in their natural state. In some embodiments, the cells are cultured *in vitro*. In other embodiments, the cells are not cultured *in vitro*.

The term “therapeutic,” as used herein, means a treatment and/or prophylaxis. A therapeutic effect is obtained by suppression, remission, or eradication of a disease state.

The term “transfected” or “transformed” or “transduced,” as used herein, refers to a process by which exogenous nucleic acid is transferred or introduced into the host cell. A “transfected” or “transformed” or “transduced” cell is one which has been transfected, transformed or transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny.

“Transmembrane domain” refers to a portion or a region of a molecule that spans a lipid bilayer membrane.

The phrase “under transcriptional control” or “operatively linked,” as used herein, means that the promoter is in the correct location and orientation in relation to a polynucleotide to control the initiation of transcription by RNA polymerase and expression of the polynucleotide.

A “vector” is a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell.

Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term “vector” includes an autonomously replicating plasmid or a virus. The term should also be construed to include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, polylysine compounds, liposomes, and the like. Examples of viral vectors include, but are

not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like.

By the term “specifically binds,” as used herein, is meant an antibody, or a ligand, which recognizes and binds with a cognate binding partner (*e.g.*, a stimulatory and/or costimulatory molecule present on a T cell) protein present in a sample, but which antibody or ligand does not substantially recognize or bind other molecules in the sample.

By the term “stimulation,” is meant a primary response induced by binding of a stimulatory molecule (*e.g.*, a TCR/CD3 complex) with its cognate ligand thereby mediating a signal transduction event, such as, but not limited to, signal transduction via the TCR/CD3 complex. Stimulation can mediate altered expression of certain molecules, such as downregulation of TGF- β , and/or reorganization of cytoskeletal structures, and the like.

A “stimulatory molecule,” as the term is used herein, means a molecule on a T cell that specifically binds with a cognate stimulatory ligand present on an antigen presenting cell.

A “stimulatory ligand,” as used herein, means a ligand that when present on an antigen presenting cell (*e.g.*, an aAPC, a dendritic cell, a B-cell, and the like) can specifically bind with a cognate binding partner (referred to herein as a “stimulatory molecule”) on a T cell, thereby mediating a primary response by the T cell, including, but not limited to, activation, initiation of an immune response, proliferation, and the like. Stimulatory ligands are well-known in the art and encompass, *inter alia*, an MHC Class I molecule loaded with a peptide, an anti-CD3 antibody, a superagonist anti-CD28 antibody, and a superagonist anti-CD2 antibody.

Ranges: throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual

numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. This applies regardless of the breadth of the range.

Description

5

Chimeric Autoantibody Receptor (CAAR)

The present invention is partly based on the discovery that chimeric autoantibody receptors can be used to target B cells that express autoantibody-based B cell receptors, which after activation and autoantibody secretion, may cause an autoantibody-mediated kidney disease. The invention includes a chimeric autoantibody receptor (CAAR) specific for anti-phospholipase A2 receptor (PLA2R) B cell receptor (BCR), compositions comprising the CAAR, polynucleotides encoding the CAAR, vectors comprising a polynucleotide encoding the CAAR, and recombinant T cells comprising the CAAR. The invention also includes methods of making a genetically modified cell, *e.g.*, a genetically modified T cell, expressing a PLA2R-CAAR wherein the expressed CAAR comprises a phospholipase PLA2R extracellular domain.

The present invention includes a technology for treating an autoantibody-mediated kidney disease. In particular, technologies that target B cells that ultimately produce the autoantibodies and display the autoantibodies on their cell surfaces, mark these B cells as disease-specific targets for therapeutic intervention. The invention therefore includes a method for efficiently targeting and killing the pathogenic B cells in autoantibody-mediated kidney diseases by targeting the disease-causing B cells using an antigen-specific (*e.g.*, PLA2R) chimeric autoantibody receptor (or CAAR). In one embodiment of the present invention, only specific anti-PLA2R BCR-expressing B cells are killed, leaving intact the beneficial B cells and antibodies that protect from infection.

In one aspect, the invention includes a polynucleotide encoding a chimeric autoantibody receptor (CAAR), wherein the polynucleotide encodes a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, and optionally, a transmembrane domain, an intracellular domain of a costimulatory molecule, and/or a signaling domain.

30

Autoantigen Moiety

In one embodiment, the CAAR of the invention comprises an autoantibody binding domain otherwise referred to as an autoantigen or a fragment thereof. The choice of autoantigen for use in the present invention depends upon the type of autoantibody or BCR being targeted (e.g. anti-PLA2R). For example, the autoantigen may be chosen because it recognizes a BCR or autoantibody on a target cell, such as a BCR-expressing B cell, associated with a particular autoantibody mediated kidney disease state, e.g. a glomerular disease and an primary membranous nephropathy.

In some instances, it is beneficial that the autoantibody binding domain is derived from the same species in which the CAAR will ultimately be used. For example, for use in humans, it may be beneficial that the autoantibody binding domain of the CAAR comprises a human autoantigen (or fragment thereof) that binds a human BCR or autoantibody.

In one exemplary embodiment, a genetically engineered chimeric autoantibody receptor includes PLA2R or fragments thereof, which binds an anti-PLA2R BCR, e.g., anti-PLA2R BCR on a B cell in a subject.

In one embodiment, the CAAR comprises an extracellular domain of PLA2R.

In some embodiments, the extracellular domain of PLA2R comprises an N-terminal cysteine rich domain (Ricin B type lectin domain), a Fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2, a C-type lectin domain 3, a C-type lectin domain 7, or a combination of any of the foregoing.

In some embodiments, the extracellular domain of PLA2R comprises the immunodominant epitope, N-terminal cysteine rich (CysR) domain (Ricin B type lectin domain), encoded by SEQ ID NO: 1, a Fibronectin type II domain encoded by SEQ ID NO: 3, a C-type lectin domain 1 encoded by SEQ ID NO: 5, and a C-type lectin domain 2 encoded by SEQ ID NO: 7. This extracellular domain of PLA2R is the extracellular domain of the construct designated as construct 4027.CF12 herein and is encoded by SEQ ID NO: 8, wherein the linker between the immunodominant epitope, N-terminal cysteine rich domain and the Fibronectin type II domain is encoded by SEQ ID NO: 2 and the linker between the Fibronectin type II domain and the C-type lectin domain 1 is

encoded by SEQ ID NO: 4, and the linker between the C-type lectin domain 1 and the C-type lectin domain 2 is encoded by SEQ ID NO: 6.

In another embodiment, the extracellular domain of PLA2R comprises the extracellular domain of construct 4027.CF12 and additionally a C-type lectin domain 3
5 encoded by SEQ ID NO: 14. This latter extracellular domain of PLA2R is the extracellular domain of the construct designated as construct 4028.CF123 herein and is encoded by SEQ ID NO: 15, wherein the linkers between the immunodominant epitope, N-terminal cysteine rich domain, the Fibronectin type II, the C-type lectin domain 1 and the C-type lectin domain 2 are the same as those listed above herein for construct
10 4027.CF12 (SEQ ID NOS: 2, 4 and 6) and further wherein the linker between the C-type lectin domain 2 and the C-type lectin domain 3 is encoded by SEQ ID NO: 13.

In another embodiment, the extracellular domain of PLA2R comprises the extracellular domain of the construct referred to herein as construct C, comprising a cysteine rich domain. In certain embodiments, the cysteine rich domain comprises SEQ
15 ID NO: 49, and may be encoded by SEQ ID NO: 47. In certain embodiments, the cysteine rich domain comprises SEQ ID NO: 1.

In another embodiment, the extracellular domain of PLA2R comprises the extracellular domain of the construct referred to herein as construct CF1, comprising a cysteine rich domain, a fibronectin type II domain, and a C-type lectin domain 1. In certain embodiments, the extracellular domain comprises SEQ ID NO: 51, and may be encoded by SEQ ID NO: 50.

In another embodiment, the extracellular domain of PLA2R comprises the extracellular domain of the construct referred to herein as construct CF123, comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2, and a C-type lectin domain 3. In certain embodiments, the extracellular domain comprises SEQ ID NO: 53, and may be encoded by SEQ ID NO: 52.

In another embodiment, the extracellular domain of PLA2R comprises the extracellular domain of the construct referred to herein as construct CF1237, comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2, a C-type lectin domain 3, and a C-type lectin domain 7. In certain

embodiments, the extracellular domain comprises SEQ ID NO: 55, and may be encoded by SEQ ID NO: 54.

In another embodiment, the extracellular domain of PLA2R comprises the extracellular domain of the construct referred to herein as construct CF17, comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, and a C-type lectin domain 7. In certain embodiments, the extracellular domain comprises SEQ ID NO: 57, and may be encoded by SEQ ID NO: 56.

In another embodiment, the extracellular domain of PLA2R comprises the extracellular domain of the construct referred to herein as construct C17, comprising a cysteine rich domain, a C-type lectin domain 1, and a C-type lectin domain 7. In certain embodiments, the extracellular domain comprises SEQ ID NO: 59, and may be encoded by SEQ ID NO: 58.

In another embodiment, the extracellular domain of PLA2R comprises the extracellular domain of the construct referred to herein as construct 4025.C, comprising a cysteine rich domain. In certain embodiments, the extracellular domain comprises SEQ ID NO: 61, and may be encoded by SEQ ID NO: 60.

In another embodiment, the extracellular domain of PLA2R comprises the extracellular domain of the construct referred to herein as construct 4026.CF1, comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1. In certain embodiments, the extracellular domain comprises SEQ ID NO: 40, and may be encoded by SEQ ID NO: 39.

In another embodiment, the extracellular domain of PLA2R comprises the extracellular domain of the construct referred to herein as construct 4027.CF12, comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, and a C-type lectin domain 2. In certain embodiments, the extracellular domain comprises SEQ ID NO: 70, and may be encoded by SEQ ID NO: 8.

In another embodiment, the extracellular domain of PLA2R comprises the extracellular domain of the construct referred to herein as construct 4028.CF123, comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2, and a C-type lectin domain 3. In certain embodiments, the

extracellular domain comprises SEQ ID NO: 71, and may be encoded by SEQ ID NO: 15.

Tolerable variations of the autoantigen or a fragment thereof will be known to those of skill in the art. For example, in some embodiments the autoantigen or a fragment thereof comprises an amino acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to any of the amino acid sequences set forth in SEQ ID NO: 49, 51, 53, 55, 57, 59, 61, 63, 70 or 71. In some embodiments the autoantigen or a fragment thereof is encoded by a nucleic acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least or 99% sequence identity to the nucleic acid sequence set forth in SEQ ID NO: 8, 15, 47, 50, 52, 54, 56, 58, 60, or 62.

Transmembrane domain

In some embodiments, the PLA2R CAAR comprises a transmembrane domain that is fused to the extracellular domain of the PLA2R CAAR. In one embodiment, the PLA2R CAAR comprises a transmembrane domain that naturally is associated with one of the domains in the PLA2R CAAR. In some instances, the transmembrane domain is selected or modified by amino acid substitution to avoid binding to the transmembrane domains of the same or different surface membrane proteins in order to minimize interactions with other members of the receptor complex.

The transmembrane domain may be derived either from a natural or from a synthetic source. When the source is natural, the domain may be derived from any membrane-bound or transmembrane protein. In one embodiment, the transmembrane domain may be synthetic, in which case it will comprise predominantly hydrophobic residues such as leucine and valine. In one aspect a triplet of phenylalanine, tryptophan and valine will be found at each end of a synthetic transmembrane domain. Optionally, a

short oligo- or polypeptide linker, between 2 and 10 amino acids in length may form the linkage between the transmembrane domain and the cytoplasmic signaling domain of the PLA2R CAAR. A glycine-serine doublet provides a particularly suitable linker.

In some instances, a variety of spacer domains before the transmembrane domain can be employed as well including a hinge (e.g. a CD8 or human Ig (immunoglobulin) hinge), or a glycine-serine (GS) linker.

Examples of the hinge and/or transmembrane domain include, but are not limited to, a hinge and/or transmembrane domain of an alpha, beta or zeta chain of a T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, killer immunoglobulin-like receptor (KIR), OX40, CD2, CD27, LFA-1 (CD11a, CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD40, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), CD160, CD19, IL2R beta, IL2R gamma, IL7R α , ITGA1, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, PAG/Cbp, NKp44, NKp30, NKp46, NKG2D, and/or NKG2C.

In some embodiments, the PLA2R CAAR comprises a transmembrane domain, such as, but not limited to, a CD8 alpha transmembrane domain. In some embodiments, the CD8 alpha transmembrane domain comprises the amino acid sequence IYIWAPLAGTCGVLLLSLVITLYC (SEQ ID NO: 19). In some embodiments, the CD8 alpha transmembrane domain is encoded by the nucleotide sequence ATCTACATCTGGGCGCCCTTGCCGGGACTTGTGGGGTCCTTCTCCTGTCCTGGTTATCACCCCTTTACTGC (SEQ ID NO: 20).

In some embodiments the transmembrane domain comprises an amino acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence

identity to SEQ ID NO: 19, or is encoded by a nucleic acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 20.

In some embodiments, the PLA2R CAAR comprises a hinge domain such as, but not limited to, a CD8 alpha hinge domain. In some embodiments, the hinge domain comprises the amino acid sequence

TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD (SEQ ID NO:

43). In some embodiments, the hinge domain comprises the amino acid sequence

FVPVFLPAKPTTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD

(SEQ ID NO: 44). In some embodiments, the hinge domain is encoded by the nucleotide sequence of SEQ ID NO: 10. In some embodiments, the hinge domain is encoded by the

nucleotide sequence

ACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACCATCGCGTCGC
AGCCCCTGTCCCTGCGCCCAGAGGCGTGCCGGCCAGCGGCGGGGGGCGCAGT
GCACACGAGGGGGCTGGACTTCGCCTGTGAT (SEQ ID NO: 42). In some

embodiments, the hinge domain is encoded by the nucleotide sequence

TTCGTGCCGGTCTTCCTGCCAGCGAAGCCAACCACGACGCCAGCACCGCGAC
CACCAACACCTGCGCCCACCATCGCGTCGCAGCCCCTGTCCCTGCGCCCAGA
GGCGTGACAGACCAGCAGCGGGGGGCGCAGTGCACACGAGGGGGCTGGACTT
CGCCTGTGAT (SEQ ID NO: 64). In some embodiments, the PLA2R CAAR comprises

a transmembrane domain and a hinge domain.

In some embodiments the hinge domain comprises an amino acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to

SEQ ID NO:43 or SEQ ID NO: 44, or is encoded by a nucleic acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least

82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 42 or SEQ ID NO: 64.

5 In some embodiments, the PLA2R CAAR comprises a glycine serine (GS) linker. In some embodiments, the PLA2R CAAR comprises a GS linker and a transmembrane domain. In some embodiments, the GS linker is encoded by the nucleotide sequence: GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC (SEQ ID NO: 68). In some
10 embodiments, the GS linker comprises the amino acid sequence: GGGGSGGGGS (SEQ ID NO: 69). Those of skill in the art would be able to select the appropriate linker sequence, when appropriate for use in a CAAR construct.

Intracellular domain of a costimulatory molecule

15 In some embodiments, the PLA2R CAAR comprises an intracellular domain of a costimulatory molecule. The intracellular domain of a costimulatory molecule of the PLA2R CAAR of the invention is a cytoplasmic domain responsible for the activation of at least one of the normal effector functions of the immune cell in which the PLA2R CAAR has been placed in.

20 Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines. Thus the term “intracellular domain of a costimulatory molecule” refers to the portion of a protein which transduces the effector function signal and directs the cell to perform a specialized function. While the entire intracellular domain of a costimulatory molecule can be employed, in many cases it is not necessary to use the entire domain. To the extent that a truncated portion of the
25 intracellular domain of a costimulatory molecule is used, such truncated portion may be used in place of the intact domain as long as it transduces the effector function signal.

30 The intracellular domain of a costimulatory molecule refers to a portion of the CAAR comprising the intracellular domain of a costimulatory molecule. A costimulatory molecule is a cell surface molecule other than an antigen receptor or its ligands that is required for an efficient response of lymphocytes to an antigen. Examples of such molecules include CD27, CD28, 4-1BB (CD137), OX40, CD30, CD40, PD-1, ICOS,

lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, and a ligand that specifically binds with CD83, CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), CD127, CD160, CD19, CD4, CD8 alpha, CD8 beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, NKp44, NKp30, NKp46, NKG2D, other co-stimulatory molecules described herein, any derivative, variant, or fragment thereof, any synthetic sequence of a co-stimulatory molecule that has the same functional capability, and any combination thereof. Thus, while the invention is exemplified primarily with 4-1BB (CD137) as the co-stimulatory signaling domains, other costimulatory domains are within the scope of the invention.

In one embodiment, the nucleic acid sequence of the intracellular domain of a costimulatory molecule encodes an amino acid sequence comprising costimulatory molecule 4-1BB (also known and referred to as CD137) intracellular domain:

KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCEL (SEQ ID NO: 21).

In still another embodiment, the nucleic acid sequence encoding the 4-1BB intracellular domain comprises:

AAACGGGGCAGAAAGAACTCCTGTATATATTCAAACAACCATTTATGAGAC
CAGTACAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGA
AGAAGAAGGAGGATGTGAACTG (SEQ ID NO: 22). In still another embodiment,

the nucleic acid sequence encoding the 4-1BB intracellular domain comprises: SEQ ID NO: 66. The human intracellular 4-1BB domain provides co-stimulatory intracellular signaling upon binding to the extracellular autoantigen, such as PLA2R, or a fragment thereof, without the need of its original ligand.

In some embodiments the intracellular domain of a costimulatory molecule comprises an amino acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least

85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 21, or is encoded by a nucleic acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%,
5 at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 22 or SEQ ID NO: 66.

It is well recognized that signals generated through the TCR alone are insufficient
10 for full activation of the T cell and that a secondary or co-stimulatory signal is also required. Thus, T cell activation can be said to be mediated by two distinct classes of cytoplasmic signaling sequence: those that initiate antigen-dependent primary activation through the TCR (primary cytoplasmic signaling sequences) and those that act in an antigen-independent manner to provide a secondary or co-stimulatory signal (secondary
15 cytoplasmic signaling sequences).

Signaling domain

In some embodiments, the PLA2R CAAR comprises a signaling domain. Primary cytoplasmic signaling sequences regulate primary activation of the TCR complex either
20 in a stimulatory manner or in an inhibitory manner. Primary cytoplasmic signaling sequences that act in a stimulatory manner may contain signaling motifs which are known as immunoreceptor tyrosine-based activation motifs or ITAMs.

Examples of ITAM containing primary signaling sequences that are of particular use in the invention include those derived from TCR zeta, FcR gamma, FcR beta, CD3
25 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d. It is particularly preferred that signaling molecule in the CAAR of the invention comprises a signaling domain derived from CD3-zeta.

In one embodiment, the signaling domain of the CAAR can be designed to comprise the CD3-zeta signaling domain by itself or combined with any other desired
30 cytoplasmic domain(s) useful in the context of the CAAR of the invention. For example,

the signaling domain of the CAAR can comprise a CD3 zeta chain portion and a costimulatory signaling domain.

In some embodiments, the PLA2R CAAR comprises a CD3-zeta signaling domain by itself or in combination with any other desired cytoplasmic domain(s) useful in the context of the PLA2R CAAR of the invention. For example, the PLA2R CAAR can comprise a CD3 zeta chain portion and an intracellular domain of a costimulatory molecule. In some embodiments, the CD3 zeta chain portion is a human T-cell surface glycoprotein CD3 zeta chain isoform 3 intracellular domain (human CD247). The human intracellular CD3 zeta domain provides stimulatory intracellular signaling upon binding to the extracellular autoantigen, such as PLA2R or a fragment thereof, without HLA restriction.

In one embodiment, the nucleic acid sequence of the signaling domain comprises a nucleic acid sequence encoding a CD3 zeta signaling domain. In another embodiment, the nucleic acid sequence of the CD3 zeta signaling domain encodes an amino acid sequence comprising

RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK
NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL
HMQALPPR (SEQ ID NO: 23). In another embodiment, the nucleic acid sequence of the CD3 zeta signaling domain encodes an amino acid sequence comprising

RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK
NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL
HMQALPPR (SEQ ID NO: 45). In another embodiment, the nucleic acid sequence encoding the CD3 zeta signaling domain comprises:

AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCGCGTACCAGCAGGGCCAG
AACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTT
TGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGGGAAGCCGAGAAGGA
AGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGATGGCGG
AGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGC
ACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTACGACGC
CCTTCACATGCAGGCCCTGCCCCCTCGC (SEQ ID NO: 24). In another

embodiment, the nucleic acid sequence encoding the CD3 zeta signaling domain comprises SEQ ID NO: 74.

In some embodiments, the signaling domain comprises an amino acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%,
 5 at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 23 or SEQ ID NO: 45, or is encoded by a nucleic acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least
 10 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 24 or SEQ ID NO: 74.

15 Other Domains

In some embodiments, the PLA2R CAAR and the polynucleotide encoding the PLA2R CAAR comprise a human T cell surface glycoprotein CD8 alpha chain signal peptide. The human CD8 alpha signal peptide is responsible for the translocation of the receptor to the T cell surface.

20 In one embodiment, the polynucleotide encoding the PLA2R CAAR comprises a nucleic acid sequence of a peptide linker. In another embodiment, the PLA2R CAAR comprises a peptide linker. In yet another embodiment, the cytoplasmic signaling sequences within the intracellular signaling domain of the PLA2R CAAR can be linked to each other in a random or specified order. Optionally, a short oligo- or polypeptide
 25 linker, for example, between 2 and 10 amino acids in length may form the linkage. A glycine-serine doublet is a particularly suitable linker.

In some embodiments, the CAAR comprises a transmembrane domain and/or a cytoplasmic (intracellular) domain from a killer immunoglobulin-like receptor (KIR) family protein. The KIR gene family has at least 15 gene loci (KIR2DL1, KIR2DL2/L3,
 30 KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1/S1, KIR3DL2, KIR3DL3) and two pseudogenes (KIR2DP1 and

KIR3DP1) encoded within a 100-200 Kb region of the Leukocyte Receptor Complex (LRC) located on chromosome 19 (19q13.4). The LRC constitutes a large, 1 Mb, and dense cluster of rapidly evolving immune genes which contains genes encoding other cell surface molecules with distinctive Ig-like extra-cellular domains. In addition, the extended LRC contains genes encoding the transmembrane adaptor molecules DAP10 and DAP12. Thus, a cell comprising the CAAR of the invention comprising a KIR transmembrane domain and/or cytoplasmic domain may also comprise a polynucleotide encoding DAP10 or DAP12. In certain embodiments, the KIR is KIRS2 or KIR2DS2

In certain embodiments, the CAAR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 11, 17, 25, 27, 29, 31, 33, 35, 37, and 39. In certain embodiments, the CAAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 18, 26, 28, 30, 32, 34, 36, 38, 40, and 42.

Tolerable variations of the CAAR sequences will be known to those of skill in the art. For example, in some embodiments the CAAR comprises an amino acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to any of the amino acid sequences set forth in SEQ ID NOs: 12, and 18, 26, 28, 30, 32, 34, 36, 38, or 40. In some embodiments the CAAR is encoded by a nucleic acid sequence that has at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the nucleic acid sequence set forth in SEQ ID NO: 11, 17, 25, 27, 29, 31, 33, 35, 37, or 39.

Vector Comprising the PLA2R CAAR

In some embodiments, a 3rd generation self-inactivating lentiviral vector plasmid can be used in which the expression of the CAR is regulated by the human elongation factor 1 alpha promoter. This results in stable (permanent) expression of the CAR in the

host T cell. As an alternative approach, the encoding mRNA can be electroporated into the host cell, which would achieve the same therapeutic effect as the virally transduced T cells, but would not be permanent because the mRNA would dilute out with cell division.

In one aspect, the invention includes a vector comprising a polynucleotide
5 encoding a chimeric autoantibody receptor (CAAR), wherein the polynucleotide comprises an extracellular domain comprising a human PLA2R autoantigen or fragment thereof, and optionally, a transmembrane domain, and/or an intracellular signaling domain. In one embodiment, the vector comprises any of the nucleic acid sequences encoding the CAAR as described herein. In another embodiment, the vector comprises a
10 plasmid vector, viral vector, retrotransposon (*e.g.* piggyback, sleeping beauty), site directed insertion vector (*e.g.* CRISPR, Zinc finger nucleases, TALEN), or suicide expression vector, or other known vector in the art.

All constructs disclosed herein can be used with 3rd generation lentiviral vector plasmids, other viral vectors, or RNA approved for use in human cells. In one
15 embodiment, the vector is a viral vector, such as a lentiviral vector. In another embodiment, the vector is a RNA vector.

The expression of the PLA2R CAAR can be verified by sequencing. Expression of the full length CAAR protein may be verified using immunoblot, immunohistochemistry, flow cytometry or other technology well known and available in
20 the art.

The present invention also provides a vector in which DNA encoding the CAAR of the present invention is inserted. Vectors, including those derived from retroviruses such as lentivirus, are suitable tools to achieve long-term gene transfer since they allow long-term, stable integration of a transgene and its propagation in daughter cells.
25 Lentiviral vectors have the added advantage over vectors derived from onco-retroviruses, such as murine leukemia viruses, in that they can transduce non-proliferating cells, such as hepatocytes. They also have the added advantage of resulting in low immunogenicity in the subject into which they are introduced.

In brief summary, the expression of natural or synthetic polynucleotides encoding
30 CAARs is typically achieved by operably linking a nucleic acid encoding the CAAR polypeptide or portions thereof to a promoter (*e.g.* EF1alpha promoter), and incorporating

the construct into an expression vector. The vector is one generally capable of replication in a mammalian cell, and/or also capable of integration into the cellular genome of the mammal. Typical vectors contain transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the desired nucleic acid sequence.

The nucleic acid can be cloned into any number of different types of vectors. For example, the nucleic acid can be cloned into a vector including, but not limited to a plasmid, a phagemid, a phage derivative, an animal virus, and a cosmid. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors, and sequencing vectors.

The expression vector may be provided to a cell in the form of a viral vector. Viral vector technology is well known in the art and is described, for example, in Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1 -4, Cold Spring Harbor Press, NY), and in other virology and molecular biology manuals. Viruses, which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno- associated viruses, herpes viruses, and lentiviruses. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient restriction endonuclease sites, and one or more selectable markers, (e.g., WO 01/96584; WO 01/29058; and U.S. Pat. No. 6,326,193).

Additional promoter elements, e.g., enhancers, regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 bp upstream of the start site, although a number of promoters have recently been shown to contain functional elements downstream of the start site as well. The spacing between promoter elements frequently is flexible, so that promoter function is preserved when elements are inverted or moved relative to one another. In the thymidine kinase (tk) promoter, the spacing between promoter elements can be increased to 50 bp apart before activity begins to decline. Depending on the promoter, it appears that individual elements can function either cooperatively or independently to activate transcription.

An example of a promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence

capable of driving high levels of expression of any polynucleotide sequence operatively linked thereto. However, other constitutive promoter sequences may also be used, including, but not limited to the simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, the elongation factor-1 α promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the hemoglobin promoter, when appropriate for use in a CAAR construct.

Further, the invention should not be limited to the use of constitutive promoters. Inducible promoters are also contemplated as part of the invention. The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence, which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metallothionine promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter. In some embodiments, an inducible promoter is activated in response to an extracellular ligand. For example, in some embodiments, the inducible promoter is activated (and the expression of the CAAR is regulated) by an extracellular ligand binding to a synthetic receptor. For example, in some embodiments, a synthetic receptor, *e.g.*, a synthetic Notch receptor (*i.e.*, "synNotch") may be employed as a binding-triggered transcriptional switch that, when bound to its ligand, activates a promoter to which a nucleic acid sequence encoding the CAAR is operably linked. Accordingly, as a non-limiting example, such systems may require the presence of a ligand (*e.g.*, to which the synNotch binds) for the immune cell to be responsive to a BCR or autoantibody (*e.g.*, to which the CAAR binds). The requirement of particular combinations to generate certain signaling outputs in molecular circuits results in a logic gate. See, for example, Roybal *et al.*, 2016 *Cell* 164(4):770-9.

Examples of other systems for expressing or regulating expression of a chimeric receptor include those described in Wu *et al.* (2015) *Science* 350: aab4077; Fedorov *et al.* (2014) *Cancer Journal* 20:160-165; Kloss *et al.* (2013) *Nature Biotechnology* 31: 71-75; Sakemura *et al.* (2016) *Cancer Immunol. Res.* 4:658-668; Hill *et al.* (2018) *Nature*

Chemical Biology 14:112-117; Di Stasi *et al.* (2011) N. Engl. J. Med. 365:1673-1683; Budde *et al.* (2013) PLoS One 8: e82742; Wei *et al.* (2012) Nature 488: 384-388; Ma *et al.* (2016) Proc. Natl. Acad. Sci. USA 113: E450-458; Rodgers *et al.* (2016) Proc. Natl. Acad. Sci. USA 113: E459-468; Kudo *et al.* (2014) Cancer Res. 74: 93-103, and Chen *et al.* (2010) Proc. Natl. Acad. Sci. USA 107, 8531-8536.

In order to assess the expression of a CAAR polypeptide or portions thereof, the expression vector to be introduced into a cell can also contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of expressing cells from the population of cells sought to be transfected or infected through viral vectors. In other aspects, the selectable marker may be carried on a separate piece of DNA and used in a co- transfection procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers include, for example, antibiotic-resistance genes, such as neo and the like.

Reporter genes are used for identifying potentially transfected cells and for evaluating the functionality of regulatory sequences. In general, a reporter gene is a gene that is not present in or expressed by the recipient organism or tissue and that encodes a polypeptide whose expression is manifested by some easily detectable property, e.g., enzymatic activity. Expression of the reporter gene is assessed at a suitable time after the DNA has been introduced into the recipient cells. Suitable reporter genes may include genes encoding luciferase, beta-galactosidase, chloramphenicol acetyl transferase, secreted alkaline phosphatase, or the green fluorescent protein gene (e.g., Ui-Tei et al., 2000 FEBS Letters 479: 79-82). Suitable expression systems are well known and may be prepared using known techniques or obtained commercially. In general, the construct with the minimal 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter. Such promoter regions may be linked to a reporter gene and used to evaluate agents for the ability to modulate promoter- driven transcription.

Methods of introducing and expressing genes into a cell are known in the art. In the context of an expression vector, the vector can be readily introduced into a host cell, e.g., mammalian, bacterial, yeast, or insect cell by any method in the art. For example,

the expression vector can be transferred into a host cell by physical, chemical, or biological means.

Physical methods for introducing a polynucleotide into a host cell include calcium phosphate precipitation, lipofection, particle bombardment, microinjection, electroporation, and the like. Methods for producing cells comprising vectors and/or exogenous nucleic acids are well-known in the art. See, for example, Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1 -4, Cold Spring Harbor Press, NY).

Biological methods for introducing a polynucleotide of interest into a host cell include the use of DNA and RNA vectors. RNA vectors include vectors having a RNA promoter and/ other relevant domains for production of a RNA transcript. Viral vectors, and especially retroviral vectors, have become the most widely used method for inserting genes into mammalian, e.g., human cells. Other viral vectors may be derived from lentivirus, poxviruses, herpes simplex virus, adenoviruses and adeno-associated viruses, and the like. See, for example, U.S. Pat. Nos. 5,350,674 and 5,585,362.

Chemical means for introducing a polynucleotide into a host cell include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. An exemplary colloidal system for use as a delivery vehicle in vitro and in vivo is a liposome (e.g., an artificial membrane vesicle).

In the case where a non-viral delivery system is utilized, an exemplary delivery vehicle is a liposome. The use of lipid formulations is contemplated for the introduction of the nucleic acids into a host cell (in vitro, ex vivo or in vivo). In another aspect, the nucleic acid may be associated with a lipid. The nucleic acid associated with a lipid may be encapsulated in the aqueous interior of a liposome, interspersed within the lipid bilayer of a liposome, attached to a liposome via a linking molecule that is associated with both the liposome and the oligonucleotide, entrapped in a liposome, complexed with a liposome, dispersed in a solution containing a lipid, mixed with a lipid, combined with a lipid, contained as a suspension in a lipid, contained or complexed with a micelle, or otherwise associated with a lipid. Lipid, lipid/DNA or lipid/expression vector associated compositions are not limited to any particular structure in solution. For example, they

may be present in a bilayer structure, as micelles, or with a “collapsed” structure. They may also simply be interspersed in a solution, possibly forming aggregates that are not uniform in size or shape. Lipids are fatty substances, which may be naturally occurring or synthetic lipids. For example, lipids include the fatty droplets that naturally occur in the cytoplasm as well as the class of compounds which contain long-chain aliphatic hydrocarbons and their derivatives, such as fatty acids, alcohols, amines, amino alcohols, and aldehydes.

Lipids suitable for use can be obtained from commercial sources. For example, dimyristyl phosphatidylcholine (“DMPC”) can be obtained from Sigma, St. Louis, MO; dicetyl phosphate (“DCP”) can be obtained from K & K Laboratories (Plainview, NY); cholesterol (“Choi”) can be obtained from Calbiochem-Behring; dimyristyl phosphatidylglycerol (“DMPG”) and other lipids may be obtained from Avanti Polar Lipids, Inc. (Birmingham, AL.). Stock solutions of lipids in chloroform or chloroform/methanol can be stored at about -20°C. Chloroform is used as the only solvent since it is more readily evaporated than methanol. “Liposome” is a generic term encompassing a variety of single and multilamellar lipid vehicles formed by the generation of enclosed lipid bilayers or aggregates. Liposomes can be characterized as having vesicular structures with a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh et al., 1991 Glycobiology 5: 505-10). However, compositions that have different structures in solution than the normal vesicular structure are also encompassed. For example, the lipids may assume a micellar structure or merely exist as nonuniform aggregates of lipid molecules. Also contemplated are lipofectamine-nucleic acid complexes.

Any domains and/or fragments of the CAAR, vector, and the promoter may be synthesized gene fragments amplified by PCR or any other means known in the art.

Cells Comprising the CAAR

In another aspect, the invention includes a genetically modified cell comprising the PLA2R chimeric autoantibody receptor (CAAR) disclosed herein.

In another embodiment, the genetically modified cell expresses the PLA2R CAAR. In this embodiment, the cell has high affinity for PLA2R autoantibody-based B cell receptors (BCRs) on B cells or rarely, on B cells that have differentiated into plasma cells that have not yet downregulated their BCR. As a result, the genetically modified cell can induce direct killing of anti-PLA2R B cells or indirect killing of plasma cells expressing PLA2R autoantibodies. In yet another embodiment, the genetically modified cell has low affinity for antibodies bound to an Fc receptor.

In one embodiment, the genetically modified cell is a T cell, such as a helper T cell, a cytotoxic T cell, a memory T cell, regulatory T cell, gamma delta T cell, a natural killer cell, cytokine induced killer cell, a cell line thereof, a T memory stem cell, or other T effector cell. It is also useful for the T cell to have limited toxicity toward healthy cells and specificity to cells expressing autoantibodies. Such specificity prevents or reduces off-target toxicity that is prevalent in current therapies that are not specific for autoantibodies. In one embodiment, the T cell has limited toxicity toward healthy cells. In one embodiment the T cell is an autologous cell. In another embodiment, the T cell is an allogeneic cell.

In some embodiments, the invention includes genetically modified immune cells derived from pluripotent stem cells that were differentiated in vitro. In other embodiments, the invention includes T cells, such as primary cells, expanded T cells derived from primary T cells, T cells derived from stem cells differentiated in vitro, T cell lines such as Jurkat cells, other sources of T cells, combinations thereof, and other effector cells. For example, a transduced Jurkat cell line with a NFAT response element followed by GFP can be used to detect and isolate PLA2R specific B cells and to clone the PLA2R specific antibody repertoire in a comprehensive and unbiased fashion. The interacting B and Jurkat cells can be detected as GFP positive doublets or multimers and sorted by flow cytometry. Expression cloning of the B cell receptor encoding genes will provide further information on how autoimmunity and autoantibodies in autoantibody-mediated kidney diseases, such as glomerular disease and primary membranous nephropathy develop.

The functional ability of CAARs to specifically bind to autoantibodies and sera, for example, primary membranous nephropathy sera, can be assessed in a Jurkat reporter cell line, which depends on activation of the CAAR by binding to plate-bound autoantibody (in response to which the activated cells fluoresce green due to an NFAT-GFP reporter construct contained therein). Such methods are useful and reliable qualitative measures for functional binding ability. The proper processing of the autoantigen on the cell surface is also important and can be measured using monoclonal antibodies. Furthermore, truncations of PLA2R based on major disease epitopes are also useful and included herein. Versions using a different length hinge region or GS linker are also useful. With regard to safety, preventing or reducing possible homophilic and heterophilic interactions and activation (e.g. PLA2R - PLA2R) between the transduced cells or toward podocytes is preferred.

Further assessment of efficacy and safety of the CAAR can be performed, for example, as follows:

Constructs can be transiently transfected into human cells, such as 293T/17. The surface expression can be detected with monoclonal antibodies (either IgG or ScFv) or serum antibodies from PLA2R MN patients specific for the abovementioned extracellular domains, the linker between the domains, or other structure included in the CAAR. Binding can be verified with specific secondary antibodies and quantified by flow cytometry.

Production of membrane expressed constructs of human anti- PLA2R antibodies of any isotype can serve as target cells for testing the different PLA2R-CAARs. Additional target cell lines can be produced as needed by expression of human monoclonal antibodies on the surface of cell lines (e.g. Nalm6 or K562 cells).

Autoimmune Diseases

The present invention also provides methods for preventing, treating and/or managing a disorder or autoimmune disease associated with autoantibody-expressing cells in the context of an autoantibody-mediated kidney disease. The methods comprise administering to a subject in need thereof a genetically modified T cell comprising the CAAR of the invention that binds to the autoantibody-expressing cell. In one aspect, the

subject is a human. Non-limiting examples of an autoantibody-mediated kidney disease include to glomerular disease and primary membranous nephropathy.

In the methods of treatment, T cells isolated from a subject can be modified to express the appropriate CAAR, expanded ex vivo and then reinfused into the same
5 subject (e.g., the T cells are autologous T cells). In some embodiments, the T cells are reinfused into a different subject than the original T cells' donor (e.g., the T cells are allogeneic T cells). The modified T cells recognize target cells, such as anti-PLA2R B cells or PLA2R autoantibody producing B cells or plasma cells, and become activated, resulting in killing of the autoimmune target cells.

10 Relapse may also occur in patients with an autoimmune disease, for example in primary membranous nephropathy patients. In patients treated with rituximab, the relapse may be mediated by persistence of the same autoantibody B cell clones, whereas remission is associated with disappearance of these clones. By infusing PLA2R CAAR T cells, the autoimmune cells are depleted to induce long-term remission, possibly due to
15 the longevity of the PLA2R CAAR T cells and/or autoantigen-reactive clones do not re-appear.

To monitor PLA2R CAAR-expressing cells in vitro, in situ, or in vivo, PLA2R CAAR cells can further express a detectable marker. When the PLA2R CAAR binds the target, the detectable marker is activated and expressed, which can be detected by assays
20 known in the art, such as flow cytometry. In one embodiment, the PLA2R CAAR includes a NFAT response element and a detectable marker, such as a green fluorescent protein (GFP), to detect and quantify PLA2R CAAR expressing cells.

Sources of T cells

25 Prior to expansion and genetic modification, T cells (e.g., autologous or allogeneic T cells) are obtained from a subject. Examples of subjects include humans, dogs, cats, mice, rats, and transgenic species thereof. T cells can be obtained from a number of sources, including skin, peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites,
30 pleural effusion, spleen tissue, and tumors. In certain embodiments of the present invention, any number of T cell lines available in the art, may be used. In certain

embodiments of the present invention, T cells can be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, such as Ficoll™ separation. In one preferred embodiment, cells from the circulating blood of an individual are obtained by apheresis. The apheresis product typically contains lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and platelets. In one embodiment, the cells collected by apheresis may be washed to remove the plasma fraction and to place the cells in an appropriate buffer or media for subsequent processing steps. In one embodiment of the invention, the cells are washed with phosphate buffered saline (PBS). In an alternative embodiment, the wash solution lacks calcium and may lack magnesium or may lack many if not all divalent cations. Again, surprisingly, initial activation steps in the absence of calcium lead to magnified activation. As those of ordinary skill in the art would readily appreciate a washing step may be accomplished by methods known to those in the art, such as by using a semi-automated “flow-through” centrifuge (for example, the Cobe 2991 cell processor, the Baxter CytoMate, or the Haemonetics Cell Saver 5) according to the manufacturer’s instructions. After washing, the cells may be resuspended in a variety of biocompatible buffers, such as, for example, Ca-free, Mg-free PBS, PlasmaLyte A, or other saline solution with or without buffer. Alternatively, the undesirable components of the apheresis sample may be removed and the cells directly resuspended in culture media.

In another embodiment, T cells are isolated from peripheral blood lymphocytes by lysing the red blood cells and depleting the monocytes, for example, by centrifugation through a PERCOLL™ gradient or by counterflow centrifugal elutriation. A specific subpopulation of T cells, such as CD3⁺, CD28⁺, CD4⁺, CD8⁺, CD45RA⁺, and CD45RO⁺T cells, can be further isolated by positive or negative selection techniques. For example, in one embodiment, T cells are isolated by incubation with anti-CD3/anti-CD28 (*i.e.*, 3x28)-conjugated beads, such as DYNABEADS® M-450 CD3/CD28 T, for a time period sufficient for positive selection of the desired T cells. In one embodiment, the time period is about 30 minutes. In a further embodiment, the time period ranges from 30 minutes to 36 hours or longer and all integer values there between. In a further embodiment, the time period is at least 1, 2, 3, 4, 5, or 6 hours. In yet another preferred embodiment, the time period is 10 to 24 hours. In one preferred embodiment, the

incubation time period is 24 hours. For isolation of T cells from patients with leukemia, use of longer incubation times, such as 24 hours, can increase cell yield. Longer incubation times may be used to isolate T cells in any situation where there are few T cells as compared to other cell types, such in isolating tumor infiltrating lymphocytes (TIL) from tumor tissue or from immunocompromised individuals. Further, use of longer incubation times can increase the efficiency of capture of CD8⁺ T cells. Thus, by simply shortening or lengthening the time T cells are allowed to bind to the CD3/CD28 beads and/or by increasing or decreasing the ratio of beads to T cells (as described further herein), subpopulations of T cells can be preferentially selected for or against at culture initiation or at other time points during the process. Additionally, by increasing or decreasing the ratio of anti-CD3 and/or anti-CD28 antibodies on the beads or other surface, subpopulations of T cells can be preferentially selected for or against at culture initiation or at other desired time points. The skilled artisan would recognize that multiple rounds of selection can also be used in the context of this invention. In certain embodiments, it may be desirable to perform the selection procedure and use the “unselected” cells in the activation and expansion process. “Unselected” cells can also be subjected to further rounds of selection.

Enrichment of a T cell population by negative selection can be accomplished with a combination of antibodies directed to surface markers unique to the negatively selected cells. One method is cell sorting and/or selection via negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for CD4⁺ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8. In certain embodiments, it may be desirable to enrich for or positively select for regulatory T cells which typically express CD4⁺, CD25⁺, CD62L⁺, GITR⁺, and FoxP3⁺. Alternatively, in certain embodiments, T regulatory cells are depleted by anti-CD25 conjugated beads or other similar method of selection. In other embodiments, subpopulation of T cells, such as, but not limited to, cells positive or expressing high levels of one or more surface markers e.g. CD28⁺, CD8⁺, CCR7⁺, CD27⁺, CD127⁺, CD45RA⁺, and/or CD45RO⁺ T cells, can be isolated by positive or negative selection techniques.

For isolation of a desired population of cells by positive or negative selection, the concentration of cells and surface (*e.g.*, particles such as beads) can be varied. In certain embodiments, it may be desirable to significantly decrease the volume in which beads and cells are mixed together (*i.e.*, increase the concentration of cells), to ensure maximum contact of cells and beads. For example, in one embodiment, a concentration of 2 billion cells/ml is used. In one embodiment, a concentration of 1 billion cells/ml is used. In a further embodiment, greater than 100 million cells/ml is used. In a further embodiment, a concentration of cells of 10, 15, 20, 25, 30, 35, 40, 45, or 50 million cells/ml is used. In yet another embodiment, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In further embodiments, concentrations of 125 or 150 million cells/ml can be used. Using high concentrations can result in increased cell yield, cell activation, and cell expansion. Further, use of high cell concentrations allows more efficient capture of cells that may weakly express target antigens of interest, such as CD28-negative T cells, or from samples where there are many tumor cells present (*i.e.*, leukemic blood, tumor tissue, *etc.*). Such populations of cells may have therapeutic value and would be desirable to obtain. For example, using high concentration of cells allows more efficient selection of CD8⁺ T cells that normally have weaker CD28 expression.

In a related embodiment, it may be desirable to use lower concentrations of cells. By significantly diluting the mixture of T cells and surface (*e.g.*, particles such as beads), interactions between the particles and cells is minimized. This selects for cells that express high amounts of desired antigens to be bound to the particles. For example, CD4⁺ T cells express higher levels of CD28 and are more efficiently captured than CD8⁺ T cells in dilute concentrations. In one embodiment, the concentration of cells used is 5 X 10⁶/ml. In other embodiments, the concentration used can be from about 1 X 10⁵/ml to 1 X 10⁶/ml, and any integer value in between.

In other embodiments, the cells may be incubated on a rotator for varying lengths of time at varying speeds at either 2-10°C or at room temperature.

T cells for stimulation can also be frozen after a washing step. Wishing not to be bound by theory, the freeze and subsequent thaw step provides a more uniform product by removing granulocytes and to some extent monocytes in the cell population. After the washing step that removes plasma and platelets, the cells may be suspended in a freezing

solution. While many freezing solutions and parameters are known in the art and will be useful in this context, one method involves using PBS containing 20% DMSO and 8% human serum albumin, or culture media containing 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin and 7.5% DMSO, or 31.25% Plasmalyte-A, 31.25% Dextrose 5%, 0.45% NaCl, 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin, and 7.5% DMSO or other suitable cell freezing media containing for example, Hespan and PlasmaLyte A, the cells then are frozen to -80°C at a rate of 1° per minute and stored in the vapor phase of a liquid nitrogen storage tank. Other methods of controlled freezing may be used as well as uncontrolled freezing immediately at -20° C or in liquid nitrogen.

In certain embodiments, cryopreserved cells are thawed and washed as described herein and allowed to rest for one hour at room temperature prior to activation using the methods of the present invention.

Also contemplated in the context of the invention is the collection of blood samples or apheresis product from a subject at a time period prior to when the expanded cells as described herein might be needed. As such, the source of the cells to be expanded can be collected at any time point necessary, and desired cells, such as T cells, isolated and frozen for later use in T cell therapy for any number of diseases or conditions that would benefit from T cell therapy, such as those described herein. In one embodiment, a blood sample or an apheresis is taken from a generally healthy subject. In certain embodiments, a blood sample or an apheresis is taken from a generally healthy subject who is at risk of developing a disease, but who has not yet developed a disease, and the cells of interest are isolated and frozen for later use. In certain embodiments, the T cells may be expanded, frozen, and used at a later time. In certain embodiments, samples are collected from a patient shortly after diagnosis of a particular disease as described herein but prior to any treatments. In a further embodiment, the cells are isolated from a blood sample or an apheresis from a subject prior to any number of relevant treatment modalities, including but not limited to treatment with agents such as natalizumab, efalizumab, antiviral agents, chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies, cytoxan,

fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, and irradiation. These drugs may, for example, inhibit either the calcium dependent phosphatase calcineurin (cyclosporine and FK506) or inhibit the p70S6 kinase that is important for growth factor induced signaling (rapamycin). (Liu et al., Cell 66:807-815, 1991; Henderson et al., Immun. 73:316-321, 1991; Bierer et al., Curr. Opin. Immun. 5:763-773, 1993). In another embodiment, the cells are isolated prior to and can be frozen for later use for treatment following B-cell ablative therapy, *e.g.*, Rituxan.

In a further embodiment of the present invention, T cells are obtained from a patient directly following treatment. In this regard, it has been observed that following certain treatments, in particular treatments with drugs that damage the immune system, shortly after treatment during the period when patients would normally be recovering from the treatment, the quality of T cells obtained may be optimal or improved for their ability to expand *ex vivo*. Likewise, following *ex vivo* manipulation using the methods described herein, these cells may be in a preferred state for enhanced engraftment and *in vivo* expansion. Thus, it is contemplated within the context of the present invention to collect blood cells, including T cells, dendritic cells, or other cells of the hematopoietic lineage, during this recovery phase. Further, in certain embodiments, mobilization (for example, mobilization with GM-CSF) and conditioning regimens can be used to create a condition in a subject wherein repopulation, recirculation, regeneration, and/or expansion of particular cell types is favored, especially during a defined window of time following therapy. Illustrative cell types include T cells, B cells, dendritic cells, and other cells of the immune system.

Activation and Expansion of T Cells

T cells are activated and expanded generally using methods as described, for example, in U.S. Patents 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005.

Generally, the T cells of the invention are expanded by contact with a surface having attached thereto an agent that stimulates a CD3/TCR complex associated signal

and a ligand that stimulates a co-stimulatory molecule on the surface of the T cells. In particular, T cell populations may be stimulated as described herein, such as by contact with an anti-CD3 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody immobilized on a surface, or by contact with a protein kinase C activator (*e.g.*, bryostatin) in conjunction with a calcium ionophore. For co-stimulation of an accessory molecule on the surface of the T cells, a ligand that binds the accessory molecule is used. For example, a population of T cells can be contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. To stimulate proliferation of either CD4⁺ T cells or CD8⁺ T cells, an anti-CD3 antibody and an anti-CD28 antibody. Examples of an anti-CD28 antibody include 9.3, B-T3, XR-CD28 (Diaclone, Besançon, France) can be used as can other methods commonly known in the art (Berg *et al.*, *Transplant Proc.* 30(8):3975-3977, 1998; Haanen *et al.*, *J. Exp. Med.* 190(9):1319-1328, 1999; Garland *et al.*, *J. Immunol Meth.* 227(1-2):53-63, 1999).

In certain embodiments, the primary stimulatory signal and the co-stimulatory signal for the T cell may be provided by different protocols. For example, the agents providing each signal may be in solution or coupled to a surface. When coupled to a surface, the agents may be coupled to the same surface (*i.e.*, in “cis” formation) or to separate surfaces (*i.e.*, in “trans” formation). Alternatively, one agent may be coupled to a surface and the other agent in solution. In one embodiment, the agent providing the co-stimulatory signal is bound to a cell surface and the agent providing the primary activation signal is in solution or coupled to a surface. In certain embodiments, both agents can be in solution. In another embodiment, the agents may be in soluble form, and then cross-linked to a surface, such as a cell expressing Fc receptors or an antibody or other binding agent which will bind to the agents. In this regard, see for example, U.S. Patent Application Publication Nos. 20040101519 and 20060034810 for artificial antigen presenting cells (aAPCs) that are contemplated for use in activating and expanding T cells in the present invention.

In one embodiment, the two agents are immobilized on beads, either on the same bead, *i.e.*, “cis,” or to separate beads, *i.e.*, “trans.” By way of example, the agent providing the primary activation signal is an anti-CD3 antibody or an antigen-binding fragment thereof and the agent providing the co-stimulatory signal is an anti-CD28

antibody or antigen-binding fragment thereof; and both agents are co-immobilized to the same bead in equivalent molecular amounts. In one embodiment, a 1:1 ratio of each antibody bound to the beads for CD4⁺ T cell expansion and T cell growth is used. In certain aspects of the present invention, a ratio of anti CD3:CD28 antibodies bound to the beads is used such that an increase in T cell expansion is observed as compared to the expansion observed using a ratio of 1:1. In one particular embodiment an increase of from about 1 to about 3 fold is observed as compared to the expansion observed using a ratio of 1:1. In one embodiment, the ratio of CD3:CD28 antibody bound to the beads ranges from 100:1 to 1:100 and all integer values there between. In one aspect of the present invention, more anti-CD28 antibody is bound to the particles than anti-CD3 antibody, *i.e.*, the ratio of CD3:CD28 is less than one. In certain embodiments of the invention, the ratio of anti CD28 antibody to anti CD3 antibody bound to the beads is greater than 2:1. In one particular embodiment, a 1:100 CD3:CD28 ratio of antibody bound to beads is used. In another embodiment, a 1:75 CD3:CD28 ratio of antibody bound to beads is used. In a further embodiment, a 1:50 CD3:CD28 ratio of antibody bound to beads is used. In another embodiment, a 1:30 CD3:CD28 ratio of antibody bound to beads is used. In one preferred embodiment, a 1:10 CD3:CD28 ratio of antibody bound to beads is used. In another embodiment, a 1:3 CD3:CD28 ratio of antibody bound to the beads is used. In yet another embodiment, a 3:1 CD3:CD28 ratio of antibody bound to the beads is used.

Ratios of particles to cells from 1:500 to 500:1 and any integer values in between may be used to stimulate T cells or other target cells. As those of ordinary skill in the art can readily appreciate, the ratio of particles to cells may depend on particle size relative to the target cell. For example, small sized beads could only bind a few cells, while larger beads could bind many. In certain embodiments the ratio of cells to particles ranges from 1:100 to 100:1 and any integer values in-between and in further embodiments the ratio comprises 1:9 to 9:1 and any integer values in between, can also be used to stimulate T cells. The ratio of anti-CD3- and anti-CD28-coupled particles to T cells that result in T cell stimulation can vary as noted above, however certain preferred values include 1:100, 1:50, 1:40, 1:30, 1:20, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, and 15:1 with one preferred ratio being at least 1:1 particles per T

cell. In one embodiment, a ratio of particles to cells of 1:1 or less is used. In one particular embodiment, a preferred particle: cell ratio is 1:5. In further embodiments, the ratio of particles to cells can be varied depending on the day of stimulation. For example, in one embodiment, the ratio of particles to cells is from 1:1 to 10:1 on the first day and additional particles are added to the cells every day or every other day thereafter for up to 10 days, at final ratios of from 1:1 to 1:10 (based on cell counts on the day of addition). In one particular embodiment, the ratio of particles to cells is 1:1 on the first day of stimulation and adjusted to 1:5 on the third and fifth days of stimulation. In another embodiment, particles are added on a daily or every other day basis to a final ratio of 1:1 on the first day, and 1:5 on the third and fifth days of stimulation. In another embodiment, the ratio of particles to cells is 2:1 on the first day of stimulation and adjusted to 1:10 on the third and fifth days of stimulation. In another embodiment, particles are added on a daily or every other day basis to a final ratio of 1:1 on the first day, and 1:10 on the third and fifth days of stimulation. One of skill in the art will appreciate that a variety of other ratios may be suitable for use in the present invention. In particular, ratios will vary depending on particle size and on cell size and type.

In further embodiments of the present invention, the cells, such as T cells, are combined with agent-coated beads, the beads and the cells are subsequently separated, and then the cells are cultured. In an alternative embodiment, prior to culture, the agent-coated beads and cells are not separated but are cultured together. In a further embodiment, the beads and cells are first concentrated by application of a force, such as a magnetic force, resulting in increased ligation of cell surface markers, thereby inducing cell stimulation.

By way of example, cell surface proteins may be ligated by allowing paramagnetic beads to which anti-CD3 and anti-CD28 are attached (3x28 beads) to contact the T cells. In one embodiment, the cells (for example, 10^4 to 10^9 T cells) and beads (for example, DYNABEADS® M-450 CD3/CD28 T paramagnetic beads at a ratio of 1:1) are combined in a buffer, for example PBS (without divalent cations such as, calcium and magnesium). Again, those of ordinary skill in the art can readily appreciate any cell concentration may be used. For example, the target cell may be very rare in the sample and comprise only 0.01% of the sample or the entire sample (*i.e.*, 100%) may

comprise the target cell of interest. Accordingly, any cell number is within the context of the present invention. In certain embodiments, it may be desirable to significantly decrease the volume in which particles and cells are mixed together (*i.e.*, increase the concentration of cells), to ensure maximum contact of cells and particles. For example, in one embodiment, a concentration of about 2 billion cells/ml is used. In another embodiment, greater than 100 million cells/ml is used. In a further embodiment, a concentration of cells of 10, 15, 20, 25, 30, 35, 40, 45, or 50 million cells/ml is used. In yet another embodiment, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In further embodiments, concentrations of 125 or 150 million cells/ml can be used. Using high concentrations can result in increased cell yield, cell activation, and cell expansion. Further, use of high cell concentrations allows more efficient capture of cells that may weakly express target antigens of interest, such as CD28-negative T cells. Such populations of cells may have therapeutic value and would be desirable to obtain in certain embodiments. For example, using high concentration of cells allows more efficient selection of CD8⁺ T cells that normally have weaker CD28 expression.

In one embodiment of the present invention, the mixture may be cultured for several hours (about 3 hours) to about 14 days or any hourly integer value in between. In another embodiment, the mixture may be cultured for 21 days. In one embodiment of the invention the beads and the T cells are cultured together for about eight days. In another embodiment, the beads and T cells are cultured together for 2-3 days. Several cycles of stimulation may also be desired such that culture time of T cells can be 60 days or more. Conditions appropriate for T cell culture include an appropriate media (*e.g.*, Minimal Essential Media or RPMI Media 1640 or, X-vivo 15, (Lonza)) that may contain factors necessary for proliferation and viability, including serum (*e.g.*, fetal bovine or human serum), interleukin-2 (IL-2), insulin, IFN- γ , IL-4, IL-7, GM-CSF, IL-10, IL-12, IL-15, TGF β , and TNF- α or any other additives for the growth of cells known to the skilled artisan. Other additives for the growth of cells include, but are not limited to, surfactant, plasmanate, and reducing agents such as N-acetyl-cysteine and 2-mercaptoethanol. Media can include RPMI 1640, AIM-V, DMEM, MEM, α -MEM, F-12, X-Vivo 15, and X-Vivo 20, Optimizer, with added amino acids, sodium pyruvate, and vitamins, either serum-free or supplemented with an appropriate amount of serum (or plasma) or a defined set of

hormones, and/or an amount of cytokine(s) sufficient for the growth and expansion of T cells. Antibiotics, *e.g.*, penicillin and streptomycin, are included only in experimental cultures, not in cultures of cells that are to be infused into a subject. The target cells are maintained under conditions necessary to support growth, for example, an appropriate
5 temperature (*e.g.*, 37° C) and atmosphere (*e.g.*, air plus 5% CO₂).

T cells that have been exposed to varied stimulation times may exhibit different characteristics. For example, typical blood or apheresed peripheral blood mononuclear cell products have a helper T cell population (T_H, CD4⁺) that is greater than the cytotoxic or suppressor T cell population (T_C, CD8⁺). *Ex vivo* expansion of T cells by stimulating
10 CD3 and CD28 receptors produces a population of T cells that prior to about days 8-9 consists predominately of T_H cells, while after about days 8-9, the population of T cells comprises an increasingly greater population of T_C cells. Accordingly, depending on the purpose of treatment, infusing a subject with a T cell population comprising
predominately of T_C cells or T_H cells may be advantageous. Similarly, if an antigen-
15 specific subset of T_C cells has been isolated it may be beneficial to expand this subset to a greater degree.

Further, in addition to CD4 and CD8 markers, other phenotypic markers vary significantly, but in large part, reproducibly during the course of the cell expansion process. Thus, such reproducibility enables the ability to tailor an activated T cell product
20 for specific purposes.

Therapeutic Application

In one aspect, the invention includes a method for treating an autoantibody-mediated kidney disease in a subject. The method comprises: administering to the
25 subject an effective amount of a genetically modified T cell comprising a polynucleotide encoding a chimeric autoantibody receptor (CAAR), wherein the polynucleotide encodes a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, and optionally, a transmembrane domain, an intracellular domain of a costimulatory molecule, and/or a signaling domain, thereby treating the autoantibody-mediated kidney disease in the
30 subject.

In another aspect, the invention includes a method for preventing or reducing glomerulus damage in a subject at risk or suffering from an autoantibody-mediated kidney disease. The method comprises: administering to the subject an effective amount of a genetically modified T cell comprising a polynucleotide encoding a CAAR, wherein
5 the polynucleotide encodes a PLA2R autoantigen or fragment thereof, and optionally, a transmembrane domain, an intracellular domain of a costimulatory molecule, and/or a signaling domain, thereby preventing or reducing glomerulus damage in the subject.

In one embodiment, the autoantibody-mediated kidney disease is selected from the group consisting of a glomerular disease and a primary membranous nephropathy,
10 e.g., a primary membranous nephropathy mediated by or otherwise associated with a known anti-PLA2R autoantibody and/or BCR. In another embodiment, the subject is a human.

Without wishing to be bound by any particular theory, the anti-autoantibody immune response elicited by the CAAR-modified T cells may be an active or a passive
15 immune response. In yet another embodiment, the modified T cell targets a B cell. For example, autoantibody expressing B cells may be susceptible to indirect destruction by CAAR-redirection T cells that have previously reacted against adjacent autoantibody-expressing cells.

In one embodiment, the genetically modified T cells of the invention are modified
20 by a fully-human CAAR. In one embodiment, the fully-human CAAR-genetically modified T cells may be a type of vaccine for *ex vivo* immunization and/or *in vivo* therapy in a mammal. In one embodiment, the mammal is a human.

With respect to *ex vivo* immunization, at least one of the following occurs *in vitro* prior to administering the cell into a mammal: i) expansion of the cells, ii) introducing to
25 the cells a polynucleotide encoding a CAAR iii) cryopreservation of the cells.

Ex vivo procedures are well known in the art and are discussed more fully below. Briefly, cells are isolated from a mammal (e.g., a human) and genetically modified (i.e., transduced or transfected *in vitro*) with a vector expressing a CAAR disclosed herein. The CAAR-modified cell can be administered to a mammalian recipient to provide a
30 therapeutic benefit. The mammalian recipient may be a human and the CAAR-modified

cell can be autologous with respect to the recipient. Alternatively, the cells can be allogeneic, syngeneic or xenogeneic with respect to the recipient.

The procedure for ex vivo expansion of hematopoietic stem and progenitor cells is described in U.S. Pat. No. 5,199,942, incorporated herein by reference, can be applied to the cells of the present invention. Other suitable methods are known in the art, therefore the present invention is not limited to any particular method of ex vivo expansion of the cells. Briefly, ex vivo culture and expansion of T cells comprises: (1) collecting CD34+ hematopoietic stem and progenitor cells from a mammal from peripheral blood harvest or bone marrow explants; and (2) expanding such cells ex vivo. In addition to the cellular growth factors described in U.S. Pat. No. 5,199,942, other factors such as flt3-L, IL-1, IL-3 and c-kit ligand, can be used for culturing and expansion of the cells.

In addition to using a cell-based vaccine in terms of ex vivo immunization, the present invention also includes compositions and methods for in vivo immunization to elicit an immune response directed against an antigen in a patient.

Generally, the cells activated and expanded as described herein may be utilized in the treatment and prevention of diseases that arise in individuals who are immunocompromised. In particular, the PLA2R CAAR-modified T cells of the invention are used in the treatment of diseases, disorders and conditions associated with expression of autoantibodies. In certain embodiments, the cells of the invention are used in the treatment of patients at risk for developing autoimmune kidney diseases, disorders and conditions associated with expression of autoantibodies. Thus, the present invention provides methods for the treatment or prevention of autoimmune kidney diseases, disorders and conditions associated with expression of autoantibodies (PLA2R) comprising administering to a subject in need thereof, a therapeutically effective amount of the CAAR-modified T cells of the invention.

The CAAR-modified T cells of the present invention may be administered either alone, or as a pharmaceutical composition in combination with diluents and/or with other components such as IL-2 or other cytokines or cell populations. Briefly, pharmaceutical compositions of the present invention may comprise a target cell population as described herein, in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers such as neutral

buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (*e.g.*, aluminum hydroxide); and preservatives. Compositions of the present invention are in one aspect formulated for intravenous administration.

Pharmaceutical compositions of the present invention may be administered in a manner appropriate to the disease to be treated (or prevented). The quantity and frequency of administration will be determined by such factors as the condition of the patient, and the type and severity of the patient's disease, although appropriate dosages may be determined by clinical trials.

When "an immunologically effective amount," "an anti-BCR effective amount," "an autoimmune disease-inhibiting effective amount," or "therapeutic amount" is indicated, the precise amount of the compositions of the present invention to be administered can be determined by a physician with consideration of individual differences in age, weight, tumor size, extent of infection or metastasis, and condition of the patient (subject). It can generally be stated that a pharmaceutical composition comprising the T cells described herein may be administered at a dosage of 10^4 to 10^9 cells/kg body weight, in some instances 10^5 to 10^6 cells/kg body weight, including all integer values within those ranges. T cell compositions may also be administered multiple times at these dosages. The cells can be administered by using infusion techniques that are commonly known in immunotherapy (see, *e.g.*, Rosenberg et al., New Eng. J. of Med. 319:1676, 1988). The optimal dosage and treatment regime for a particular patient can readily be determined by one skilled in the art of medicine by monitoring the patient for signs of disease and adjusting the treatment accordingly.

In certain embodiments, activated T cells are administered to a subject. Subsequent to administration, blood is redrawn or apheresis is performed, and T cells are activated and expanded therefrom using the methods described here, and are then reinfused back into the patient. This process can be carried out multiple times every few weeks. In certain embodiments, T cells can be activated from blood draws of from 10cc to 400cc. In certain embodiments, T cells are activated from blood draws of 20cc, 30cc, 40cc, 50cc, 60cc, 70cc, 80cc, 90cc, or 100cc. Not to be bound by theory, using this

multiple blood draw/multiple reinfusion protocol, may select out certain populations of T cells.

The cells of the invention to be administered may be autologous, allogeneic or xenogeneic with respect to the subject undergoing therapy.

5 Administration of the cells of the invention may be carried out using any convenient means, including by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. The compositions described herein may be administered to a patient transarterially, subcutaneously, intradermally, intranodally, intramedullary, intramuscularly, by intravenous (*i.v.*) injection, or intraperitoneally. In one embodiment,
10 the T cell compositions of the present invention are administered to a patient by intradermal or subcutaneous injection. In another embodiment, the T cell compositions of the present invention are administered by *i.v.* injection. The compositions of T cells may be injected directly into a lymph node, or other site of pathophysiologic activity.

In certain embodiments of the present invention, cells activated and expanded
15 using the methods described herein, or other methods known in the art where T cells are expanded to therapeutic levels, are administered to a patient in conjunction with (*e.g.*, before, simultaneously or following) any number of relevant treatment modalities, including but not limited to treatment with agents such as immunosuppressive agents, such as azathioprine, methotrexate, mycophenolate, antibodies, or other immunoablative
20 agents such as CAMPATH, anti-CD3 antibodies or other antibody therapies, Cytosan, fludarabine, mycophenolic acid, steroids, FR901228, cytokines, and irradiation. These drugs may, for example, inhibit either the calcium dependent phosphatase calcineurin (cyclosporine and FK506) or inhibit the p70S6 kinase that is important for growth factor induced signaling (rapamycin). (Liu et al., Cell 66:807-815, 1991; Henderson et al.,
25 Immun. 73:316-321, 1991; Bierer et al., Curr. Opin. Immun. 5:763-773, 1993). In a further embodiment, the cell compositions of the present invention are administered to a patient in conjunction with (*e.g.*, before, simultaneously or following) T cell ablative therapy using either chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, or antibodies such as OKT3 or CAMPATH. In
30 another embodiment, the cell compositions of the present invention are administered following B-cell ablative therapy such as agents that react with CD20, *e.g.*, Rituxan. In

further embodiments, the T cells of the invention may be used in combination with complement inhibitors to reduce risk of complement-mediated cytotoxicity or an antibody anti-FcRn, IVIg, or plasmapheresis in order to reduce the anti-PLA2R antibody concentration before therapy. In yet other embodiments, a mild lymphodepletion regimen (e.g. Low-dose fludarabine or Cytosan) might precede treatment with the T cells of the invention.

The dosage of the above treatments to be administered to a patient will vary with the precise nature of the condition being treated and the recipient of the treatment. The scaling of dosages for human administration can be performed according to art-accepted practices. The dose for CAMPATH, for example, will generally be in the range 1 to about 100 mg for an adult patient, usually administered daily for a period between 1 and 30 days. The preferred daily dose is 1 to 10 mg per day although in some instances larger doses of up to 40 mg per day may be used (described in U.S. Patent No. 6,120,766).

EXPERIMENTAL EXAMPLES

The invention is further described in detail by reference to the following experimental examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless otherwise specified. Thus, the invention should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. The following working examples therefore, specifically point out the preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

The Materials and Methods used in the performance of the experiments disclosed herein are now described.

-CAAR constructs

A) Domains comprised in PLA2R-CAAR Construct 4027.CF12

Cysteine-rich (CysR) domain (Ricin B type lectin domain) (SEQ ID NO: 1)

AAGGGCATCTTCGTGATCCAGAGCGAGAGCCTGAAGAAGTGCATCCAGGCCG
 GCAAGAGCGTGCTGACCCTGGAAAATTGCAAGCAGGCCAACAAGCACATGC
 TGTGGAAATGGGTGTCCAACACGGCCTGTTCAACATCGGCGGCTCTGGATG
 5 TCTGGGCCTGAATTTCTCTGCCCCTGAGCAGCCTCTGAGCCTGTACGAGTGTG
 ATAGCACCCCTGGTGTCCCTGAGATGGCGGTGCAACCGGAAGATGATCACAGG
 CCCTCTGCAGTACTCTGTGCAGGTCGCCACGACAATACCGTGGTGGCCAGC
 AGAAAGTACATCCACAAGTGGATCAGCTACGGCAGCGGCGGAGGCGACATC
 10 TGTGAATAC

Linker between ricin B type lectin domain and fibronectin type II domain (SEQ ID NO: 2)

CTGCACAAGGATCTGCACACCATCAAGGGCAAC

Fibronectin type-2 domain (SEQ ID NO: 3)

ACCCACGGAATGCCCTGCATGTTCCCGTTTCAGTACAACCACCAGTGGCACC
 ACGAGTGCACCAGAGAAGGCAGAGAGGACGACCTGCTTTGGTGCGCCACAA
 CCAGCAGATACGAGCGGGATGAGAAGTGGGGCTTCTGCCCTGAT

Linker between fibronectin type II domain and C-type lectin domain 1 (SEQ ID NO: 4)

CCTACCTCTGCCGAAGTGGGCTGCGATACCATCTGGGAGAAAGACCTG

C-type lectin domain 1 (SEQ ID NO: 5)

AACAGCCACATCTGCTACCAGTTCAACCTGCTGTCCAGCCTGTCTTGGAGCGA
 25 GGCCACAGCAGCTGTCAAATGCAAGGCGGCACACTGCTGAGCATCACCGAC
 GAGACAGAGGAAACTTCATCCGCGAGCACATGAGCAGCAAGACCGTGGAA
 GTGTGGATGGGACTGAACCAGCTGGATGAGCATGCCGGATGGCAGTGGAGTG
 ATGGCACCCCTCTGAACTACCTGAACTGGTCCCCTGAAGTGAAGTTCGAGCC
 30 CTTCGTGGAAGATCACTGCGGCACCTTCAGCAGCTTCATGCCAGCGCTTGG
 AGAAGCAGAGACTGCGAGAGCACCCCTGCCTTACATCTGCAAG

Linker between C-type lectin domain 1 and C-type lectin domain 2 (SEQ ID NO: 6)

AAGTACCTGAACCACATCGACCACGAGATCGTGGAAGGACGCCTGGAAG
 35 TACTACGCCACACACTGCGAGCCTGGCTGGAACCC

C-type lectin domain 2 (SEQ ID NO: 7)

TACAACCGGAACTGCTACAAGCTGCAGAAAGAGGAAAAGACCTGGCACGAG
 GCCCTGAGAAGCTGCCAGGCCGATAATAGCGCCCTGATCGACATCACAAGCC
 TGGCCGAGGTGGAATTTCTGGTCACTCTGCTGGGCGACGAGAACGCCTCTGA
 GACATGGATCGGCCTGTCCAGCAACAAGATCCCCGTGTCCTTCGAGTGGTCC
 5 AACGACAGCAGCGTGATCTTCACCAACTGGCACACCCTGGAACCTCACATCT
 TCCCCAACAGATCCCAGCTGTGTGTGTCCGCCGAGCAGTCTGAAGGCCACTG
 GAAAGTGAAGAACTGCGAGGAACGGCTGTTCTACATCTGTAAA

Extracellular domains of PLA2R CAAR Construct 4027.CF12 (SEQ ID NO: 8; See Figure 2D)

AAGGGCATCTTCGTGATCCAGAGCGAGAGCCTGAAGAAGTGCATCCAGGCCG
 GCAAGAGCGTGCTGACCCTGGAAAATTGCAAGCAGGCCAACAAGCACATGC
 TGTGGAAATGGGTGTCCAACACGGCCTGTTCAACATCGGCGGCTCTGGATG
 TCTGGGCCTGAATTTCTCTGCCCTGAGCAGCCTCTGAGCCTGTACGAGTGTG
 15 ATAGCACCTGGTGTCCCTGAGATGGCGGTGCAACCGGAAGATGATCACAGG
 CCCTCTGCAGTACTCTGTGCAGGTCGCCCACGACAATAACCGTGGTGGCCAGC
 AGAAAGTACATCCACAAGTGGATCAGCTACGGCAGCGGCGGAGGCGACATC
 TGTGAATACCTGCACAAGGATCTGCACACCATCAAGGGCAACACCCACGGAA
 TGCCCTGCATGTTCCCGTTTCAGTACAACCACCAAGTGGCACCACGAGTGCACC
 20 AGAGAAGGCAGAGAGGACGACCTGCTTTGGTGCGCCACAACCAGCAGATAC
 GAGCGGGATGAGAAGTGGGGCTTCTGCCCTGATCCTACCTCTGCCGAAGTGG
 GCTGCGATAACCATCTGGGAGAAAGACCTGAACAGCCACATCTGCTACCAGTT
 CAACCTGCTGTCCAGCCTGTCTTGGAGCGAGGCCACAGCAGCTGTCAAATG
 CAAGGCGGCACACTGCTGAGCATCACCGACGAGACAGAGGAAAACCTTCATC
 25 CGCGAGCACATGAGCAGCAAGACCGTGGAAGTGTGGATGGGACTGAACCAG
 CTGGATGAGCATGCCGGATGGCAGTGGAGTGATGGCACCCCTCTGAACTACC
 TGAAGTGGTCCCTGAAGTGAACCTTCGAGCCCTTCGTGGAAGATCACTGCGG
 CACCTTCAGCAGCTTCATGCCCAGCGCTTGGAGAAGCAGAGACTGCGAGAGC
 ACCCTGCCTTACATCTGCAAGAAGTACCTGAACCACATCGACCACGAGATCG
 30 TGGAAAAGGACGCCTGGAAGTACTACGCCACACACTGCGAGCCTGGCTGGA
 ACCCTTACAACCGGAACTGCTACAAGCTGCAGAAAGAGGAAAAGACCTGGC
 ACGAGGCCCTGAGAAGCTGCCAGGCCGATAATAGCGCCCTGATCGACATCAC
 AAGCCTGGCCGAGGTGGAATTTCTGGTCACTCTGCTGGGCGACGAGAACGCC
 TCTGAGACATGGATCGGCCTGTCCAGCAACAAGATCCCCGTGTCCTTCGAGT
 35 GGTCCAACGACAGCAGCGTGATCTTCACCAACTGGCACACCCTGGAACCTCA
 CATCTTCCCCAACAGATCCCAGCTGTGTGTGTCCGCCGAGCAGTCTGAAGGC
 CACTGGAAAGTGAAGAACTGCGAGGAACGGCTGTTCTACATCTGTAAA

Extracellular domains of Construct 4027.CF12 (SEQ ID NO: 70)

40 KGIFVIQSESLKKCIQAGKSVLTLENCKQANKHMLWKWVSNHGLFNIGGSGCLG
 LNFSAPEQPLSLYECDSTLVSLRWRCNRKMITGPLQYSVQVAHDNTVVASRKYI
 HKWISYSGGGDICEYLHKDLHTIKGNTHGMPCMFQYNHQWHHECTREGRE
 DLLWCATTSTRYERDEKWGFCDPTSAEVGCDTIWEKDLNSHICYQFNLLSSLS
 WSEAHSSCQMGGTLLSITDETEENFIREHMSSKTVEVWMGLNQLDEHAGWQW

SDGTPLNYLNWSPEVNFEPFVEDHCGTFSSFMPSAWRSRDCESTLPYICKKYLNH
IDHEIVEKDAWKYYATHCEPGWNPYNRNCYKLQKEEKTWHEALRSCQADNSAL
IDITSLAEVEFLVTLLGDENASETWIGLSSNKIPVSFEWSNDSSVIFTNWHLEPHIF
PNRSQLCVSAEQSEGHWKVKNCERLFYICKKAGHVLSDAESGCQ

5

Link between C-type lectin domain 2 and CD8 hinge (SEQ ID NO: 9)

AAGGCCGGCCACGTGCTGTCCGATGCCGAGAGTGGATGTCAATCCGGA

CD8 hinge (SEQ ID NO: 10)

10 ACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACCATCGCGTCGC
AGCCCCTGTCCCTGCGCCCAGAGGCGTGCCGGCCAGCGGCGGGGGGCGCAGT
GCACACGAGGGGGCTGGACTTCGCCTGT

Nucleic acid sequence of PLA2R-CAAR Construct 4027.CF12 (SEQ ID NO: 11)

15 ATGCTGCTGAGCCCTAGCCTGCTGCTGCTCCTGCTTCTTGGAGCCCCTAGAGG
ATGTGCCGGATCTGAAGGTGTTGCCGCCGCTCTGACACCCGAGAGACTGCTG
GAATGGCAGGACAAGGGCATCTTCGTGATCCAGAGCGAGAGCCTGAAGAAG
TGCATCCAGGCCGGCAAGAGCGTGCTGACCCTGGAAAATTGCAAGCAGGCCA
ACAAGCACATGCTGTGGAAATGGGTGTCCAACCACGGCCTGTTCAACATCGG
20 CGGCTCTGGATGTCTGGGCCTGAATTTCTCTGCCCTGAGCAGCCTCTGAGCC
TGTACGAGTGTGATAGCACCCTGGTGTCCCTGAGATGGCGGTGCAACCGGAA
GATGATCACAGGCCCTCTGCAGTACTCTGTGCAGGTCGCCCACGACAATACC
GTGGTGGCCAGCAGAAAGTACATCCACAAGTGGATCAGCTACGGCAGCGGC
GGAGGCGACATCTGTGAATACCTGCACAAGGATCTGCACACCATCAAGGGCA
25 ACACCCACGGAATGCCCTGCATGTTCCCGTTTCAGTACAACCACAGTGGCA
CCACGAGTGCACCAGAGAAGGCAGAGAGGACGACCTGCTTTGGTGCGCCAC
AACCAGCAGATACGAGCGGGATGAGAAGTGGGGCTTCTGCCCTGATCCTACC
TCTGCCGAAGTGGGCTGCGATACCATCTGGGAGAAAGACCTGAACAGCCACA
TCTGCTACCAGTTCAACCTGCTGTCCAGCCTGTCTTGGAGCGAGGCCACAGC
30 AGCTGTCAAATGCAAGGCGGCACACTGCTGAGCATCACCGACGAGACAGAG
GAAAACCTTCATCCGCGAGCACATGAGCAGCAAGACCGTGGAAGTGTGGATG
GGACTGAACCAGCTGGATGAGCATGCCGGATGGCAGTGGAGTGATGGCACCC
CTCTGAACTACCTGAACTGGTCCCCTGAAGTGAACCTCGAGCCCTTCGTGGAA
GATCACTGCGGCACCTTCAGCAGCTTCATGCCCAGCGCTTGGAGAAGCAGAG
35 ACTGCGAGAGCACCCCTGCCTTACATCTGCAAGAAGTACCTGAACCACATCGA
CCACGAGATCGTGGAAGAGGACGCCTGGAAGTACTACGCCACACACTGCGA
GCCTGGCTGGAACCCCTACAACCGGAAGTCTACAAGCTGCAGAAAGAGGA
AAAGACCTGGCACGAGGCCCTGAGAAGCTGCCAGGCCGATAATAGCGCCCT
GATCGACATCACAAGCCTGGCCGAGGTGGAATTTCTGGTCACTCTGCTGGGC
40 GACGAGAACGCCTCTGAGACATGGATCGGCCTGTCCAGCAACAAGATCCCCG
TGTCCTTCGAGTGGTCCAACGACAGCAGCGTGATCTTCACCAACTGGCACAC
CCTGGAACCTCACATCTTCCCCAACAGATCCCAGCTGTGTGTGTCCGCCGAGC

AGTCTGAAGGCCACTGGAAAGTGAAGAACTGCGAGGAACGGCTGTTCTACAT
 CTGTAAAAAGGCCGGCCACGTGCTGTCCGATGCCGAGAGTGGATGTCAATCC
 GGAACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACCATCGCGT
 CGCAGCCCCCTGTCCCTGCGCCCAGAGGCGTGCCGGCCAGCGGGCGGGGGGCGC
 5 AGTGCACACGAGGGGGCTGGACTTCGCCTGTGATATCTACATCTGGGCGCCC
 TTGGCCGGGACTTGTGGGGTCCTTCTCCTGTCACTGGTTATCACCCTTTACTGC
 AAACGGGGCAGAAAGAACTCCTGTATATATTCAAACAACCATTTATGAGAC
 CAGTACAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGA
 AGAAGAAGGAGGATGTGAACTGAGAGTGAAGTTCAGCAGGAGCGCAGACGC
 10 CCCC GCGTACAAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGA
 CGAAGAGAGGAGTACGATGTTTTGGACAAGAGACGTGGCCGGGACCCTGAG
 ATGGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAA
 CTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGC
 GAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACA
 15 GCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCT
 AA

Amino acid sequence of PLA2R-CAAR (Construct 4027.CF12; SEQ ID NO: 12)

MLLSPSLLLLLLLGAPRGCAGSEGVAALTPERLLEWQDKGIFVIQSESLKKCIQA
 20 GKSVLTLENCKQANKHMLWKWVSNHGLFNIGSGCLGLNFSAPEQPLSLYECD
 STLVSLRWRCNRKMITGPLQYSVQVAHDNTVVASRKYIHKWISYSGGGDICEY
 LHKDLHTIKGNTHGMPCMFPFQYNHQWHHECTREGREDDLLWCATTSTRYERDE
 KWGFCPDPTSAEVGCDTIWEKDLNSHICYQFNLLSSLWSSEAHSSCQMGGTLL
 25 SITDETEENFIREHMSSKTVEVWMGLNQLDEHAGWQWSDGTPLNYLNWSPEVN
 FEPFVEDHCGTFSSFMPSAWRSRDCESTLPYICKKYLNHIDHEIVEKDAWKYYAT
 HCEPGWNPNRNCYKLQKEEKTWHEALRSCQADNSALIDITSLAEVEFLVTLLG
 DENASETWIGLSSNKIPVSFEWSNDSSVIFTNWHITLPHIFPNRSQLCVSAEQSEG
 HWKVKNCEERLFYICKKAGHVLSDAESGCQSGTTTPAPRPPTPAPTIASQPLSLRP
 30 EACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYI
 FKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYN
 ELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG
 MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

B) Domains comprised in PLA2R-CAAR Construct 4028.CF123

35 Cysteine-rich (CysR) domain (Ricin B type lectin domain) (SEQ ID NO: 1)
 Linker between ricin B type lectin domain and fibronectin type II domain
 (SEQ ID NO: 2)
 Fibronectin type II domain (SEQ ID NO: 3)
 Linker between fibronectin type II domain and C-type lectin domain 1 (SEQ
 40 ID NO: 4)
 C-type lectin 1 domain (SEQ ID NO: 5)

Linker between C-type lectin domain 1 and C-type lectin domain 2 (SEQ ID NO: 6)

C-type lectin domain 2 (SEQ ID NO: 7)

Linker between C-type lectin domain 2 and C-type lectin domain 3 (SEQ ID NO: 13)

AAGGCCGGCCACGTGCTGTCCGATGCCGAGAGTGGATGTCAAGAAGGCTGGG
AGAGA

C-type lectin domain 3 (SEQ ID NO: 14)

CACGGCGGCTTTTGCTACAAGATCGACACCGTGCTGCGGAGCTTCGATCAGG
CCAGCAGCGGCTACTATTGCCCTCCTGCTCTGGTCACCATCACCAACAGATTC
GAGCAGGCCTTCATCACCAGCCTGATCAGCAGCGTCGTGAAGATGAAGGACA
GCTACTTCTGGATCGCCCTGCAGGACCAGAACGACACCGGCCGAGTACACATG
GAAGCCCGTGCGGACAGAAACCCGAGCCTGTGCAGTACACCCACTGGAACAC
ACACCAGCCTAGATACTCCGGCGGCTGCGTGGCAATGAGAGGCAGACATCCT
CTCGGCAGATGGGAAGTGAAGCACTGTCGGCACTTCAAGGCCATGTCTCTGT
GC

Extracellular domains of PLA2R (SEQ ID NO: 15; See Figure 2D, Construct 4028.CF123)

AAGGGCATCTTCGTGATCCAGAGCGAGAGCCTGAAGAAGTGCATCCAGGCCG
GCAAGAGCGTGCTGACCCTGGAAAATTGCAAGCAGGCCAACAAGCACATGC
TGTGGAAATGGGTGTCCAACCACGGCCTGTTCAACATCGGCGGCTCTGGATG
TCTGGGCCTGAATTTCTCTGCCCTGAGCAGCCTCTGAGCCTGTACGAGTGTG
ATAGCACCCCTGGTGTCCCTGAGATGGCGGTGCAACCGGAAGATGATCACAGG
CCCTCTGCAGTACTCTGTGCAGGTCGCCCACGACAATAACCGTGGTGGCCAGC
AGAAAGTACATCCACAAGTGGATCAGCTACGGCAGCGGCGGAGGCGACATC
TGTGAATACCTGCACAAGGATCTGCACACCATCAAGGGCAACACCCACGGAA
TGCCCTGCATGTTCCCGTTTCAGTACAACCACCAAGTGGCACCAACGAGTGCACC
AGAGAAGGCAGAGAGGACGACCTGCTTTGGTGCGCCACAACCAGCAGATAC
GAGCGGGATGAGAAGTGGGGCTTCTGCCCTGATCCTACCTCTGCCGAAGTGG
GCTGCGATACCATCTGGGAGAAAGACCTGAACAGCCACATCTGCTACCAGTT
CAACCTGCTGTCCAGCCTGTCTTGGAGCGAGGCCACAGCAGCTGTCAAATG
CAAGGCGGCACACTGCTGAGCATCACCGACGAGACAGAGGAAAACCTTCATC
CGCGAGCACATGAGCAGCAAGACCGTGGAAGTGTGGATGGGACTGAACCAG
CTGGATGAGCATGCCGGATGGCAGTGGAGTGTGGCACCCTCTGAACTACC
TGAACCTGGTCCCTGAAGTGAACCTTCGAGCCCTTCGTGGAAGATCACTGCGG
CACCTTCAGCAGCTTCATGCCAGCGCTTGGAGAAGCAGAGACTGCGAGAGC
ACCCTGCCTTACATCTGCAAGAAGTACCTGAACCACATCGACCACGAGATCG
TGGAAGGACGCCTGGAAGTACTACGCCACACACTGCGAGCCTGGCTGGA
ACCCCTACAACCGGAAGTGTCTACAAGCTGCAGAAAGAGGAAAAGACCTGGC

ACGAGGCCCTGAGAAGCTGCCAGGCCGATAATAGCGCCCTGATCGACATCAC
 AAGCCTGGCCGAGGTGGAATTTCTGGTCACTCTGCTGGGCGACGAGAACGCC
 TCTGAGACATGGATCGGCCTGTCCAGCAACAAGATCCCCGTGTCCTTCGAGT
 5 GGTCCAACGACAGCAGCGTGATCTTCACCAACTGGCACACCCTGGAACCTCA
 CATCTTCCCCAACAGATCCCAGCTGTGTGTGTCCGCCGAGCAGTCTGAAGGC
 CACTGGAAAGTGAAGAACTGCGAGGAACGGCTGTTCTACATCTGTAAAAAGG
 CCGGCCACGTGCTGTCCGATGCCGAGAGTGGATGTCAAGAAGGCTGGGAGAG
 ACACGGCGGCTTTTGCTACAAGATCGACACCGTGCTGCGGAGCTTCGATCAG
 10 GCCAGCAGCGGCTACTATTGCCCTCCTGCTCTGGTCACCATCACCAACAGATT
 CGAGCAGGCCTTCATCACCAGCCTGATCAGCAGCGTCGTGAAGATGAAGGAC
 AGCTACTTCTGGATCGCCCTGCAGGACCAGAACGACACCGGCGAGTACACAT
 GGAAGCCCGTGGGACAGAAACCCGAGCCTGTGCAGTACACCCACTGGAACA
 CACACCAGCCTAGATACTCCGGCGGCTGCGTGGCAATGAGAGGCAGACATCC
 15 TCTCGGCAGATGGGAAGTGAAGCACTGTCGGCACTTCAAGGCCATGTCTCTG
 TGC

Extracellular domains of Construct 4028.CF123 (SEQ ID NO: 71)

KGIFVIQSESLKKCIQAGKSVLTLENCKQANKHMLWKWVSNHGLFNIGGSGCLG
 LNFSAPEQPLSLYECDSLVSRLWRNCNRKMITGPLQYSVQVAHDNTVVASRKYI
 20 HKWISYSGGGDICEYLHKDLHTIKGNTHGMPMFPFQYNHQWHHECTREGRE
 DDLLWCATTSRYERDEKWGFCDPTSAEVGCDTIWEKDLNSHICYQFNLLSSL
 WSEAHSSCQMGGTLLSITDETEENFIREHMSSKTVEVWMGLNQLDEHAGWQW
 SDGTPLNYLNWSPEVNFEPFVEDHCGTFSSFMPSAWRSRDCESTLPYICKKYLNH
 IDHEIVEKDAWKYYATHCEPGWNPYNRNCYKLQKEEKTWHEALRSCQADNSAL
 25 IDITSLAEVEFLVTLLGDENASETWIGLSSNKIPVSFEWSNDSSVIFTNWHTLEPHIF
 PNRSQLCVSAEQSEGHWKVKNCEERLFYICKKAGHVLSDAESGCQEGWERHGG
 FCYKIDTVLRSFDQASSGYCPPALVTITNRFEQAFITSLISSVVKMKDSYFWIAL
 QDQNDTGEYTWKPVGQKPEPVQYTHWNTHQPRYSGGCVAMRGRHPLGRWEV
 KCHRHFKAAMSLCKQPVENQEKA EYEERWPFHPCYL
 30

Linker between C-type lectin domain 3 and CD8 hinge (SEQ ID NO: 16)

AAGCAGCCCGTGGAATAATCAAGAGAAGGCCGAGTACGAGGAACGCTGGCCT
 TTTCACCCTTGCTACCTGTCCGGA

35 **CD8 hinge (SEQ ID NO: 10)**

Nucleic acid sequence of PLA2R-CAAR (Construct 4028.CF123; SEQ ID NO: 17)

ATGCTGCTGAGCCCTAGCCTGCTGCTGCTCCTGCTTCTTGAGCCCTAGAGG
 ATGTGCCCGATCTGAAGGTGTTGCCGCCGCTCTGACACCCGAGAGACTGCTG
 40 GAATGGCAGGACAAGGGCATCTTCGTGATCCAGAGCGAGAGCCTGAAGAAG
 TGCATCCAGGCCGGCAAGAGCGTGCTGACCCTGGAAAATTGCAAGCAGGCCA

ACAAGCACATGCTGTGGAAATGGGTGTCCAACCACGGCCTGTTCAACATCGG
CGGCTCTGGATGTCTGGGCCTGAATTTCTCTGCCCCTGAGCAGCCTCTGAGCC
TGTACGAGTGTGATAGCACCTGGTGTCCCTGAGATGGCGGTGCAACCGGAA
GATGATCACAGGCCCTCTGCAGTACTCTGTGCAGGTCGCCCACGACAATACC
5 GTGGTGGCCAGCAGAAAGTACATCCACAAGTGGATCAGCTACGGCAGCGGC
GGAGGCGACATCTGTGAATACCTGCACAAGGATCTGCACACCATCAAGGGCA
ACACCCACGGAATGCCCTGCATGTTCCCGTTTCAGTACAACCACCAAGTGGCA
CCACGAGTGCACCAGAGAAGGCAGAGAGGACGACCTGCTTTGGTGCGCCAC
AACCAGCAGATACGAGCGGGATGAGAAGTGGGGCTTCTGCCCTGATCCTACC
10 TCTGCCGAAGTGGGCTGCGATACCATCTGGGAGAAAGACCTGAACAGCCACA
TCTGCTACCAGTTCAACCTGCTGTCCAGCCTGTCTTGGAGCGAGGCCACAGC
AGCTGTCAAATGCAAGGCGGCACACTGCTGAGCATCACCGACGAGACAGAG
GAAAACCTTCATCCGCGAGCACATGAGCAGCAAGACCGTGGAAGTGTGGATG
GGACTGAACCAGCTGGATGAGCATGCCGGATGGCAGTGGAGTGATGGCACCC
15 CTCTGAACTACCTGAACTGGTCCCCCTGAAGTGAACCTTCGAGCCCTTCGTGGAA
GATCACTGCGGCACCTTCAGCAGCTTCATGCCCAGCGCTTGGAGAAGCAGAG
ACTGCGAGAGCACCCCTGCCTTACATCTGCAAGAAGTACCTGAACCACATCGA
CCACGAGATCGTGGAAGAGGACGCCTGGAAGTACTACGCCACACACTGCGA
GCCTGGCTGGAACCCCTACAACCGGAAGTGTACAAGCTGCAGAAAGAGGA
20 AAAGACCTGGCACGAGGCCCTGAGAAGCTGCCAGGCCGATAATAGCGCCCT
GATCGACATCACAAGCCTGGCCGAGGTGGAATTTCTGGTCACTCTGCTGGGC
GACGAGAACGCCTCTGAGACATGGATCGGCCTGTCCAGCAACAAGATCCCCG
TGTCCTTCGAGTGGTCCAACGACAGCAGCGTGATCTTCACCAACTGGCACAC
CCTGGAACCTCACATCTTCCCCAACAGATCCCAGCTGTGTGTGTCCGCCGAGC
25 AGTCTGAAGGCCACTGGAAAGTGAAGAACTGCGAGGAACGGCTGTTCTACAT
CTGTAAAAAGGCCGGCCACGTGCTGTCCGATGCCGAGAGTGGATGTCAAGAA
GGCTGGGAGAGACACGGCGGCTTTTGCTACAAGATCGACACCGTGCTGCGGA
GCTTCGATCAGGCCAGCAGCGGCTACTATTGCCCTCCTGCTCTGGTCACCATC
ACCAACAGATTTCGAGCAGGCCTTCATCACCAGCCTGATCAGCAGCGTCGTGA
30 AGATGAAGGACAGCTACTTCTGGATCGCCCTGCAGGACCAGAACGACACCGG
CGAGTACACATGGAAGCCCGTGGGACAGAAACCCGAGCCTGTGCAGTACAC
CCACTGGAACACACACCAGCCTAGATACTCCGGCGGCTGCGTGGAATGAGA
GGCAGACATCCTCTCGGCAGATGGGAAGTGAAGCACTGTGCGGCACTTCAAGG
CCATGTCTCTGTGCAAGCAGCCCGTGGAAAATCAAGAGAAGGCCGAGTACGA
35 GGAACGCTGGCCTTTTCACCCTTGCTACCTGTCCGGAACACGACGCCAGCG
CCGCGACCACCAACACCGGCGCCACCATCGCGTCGCAGCCCTGTCCCTGC
GCCAGAGGCGTGCCGGCCAGCGGCGGGGGGCGCAGTGACACGAGGGGGC
TGGACTTCGCCTGTGATATCTACATCTGGGCGCCCTTGGCCGGGACTTGTGGG
GTCCTTCTCCTGTCACTGGTTATCACCTTTACTGCAAACGGGGCAGAAAGAA
40 ACTCCTGTATATATTCAAACAACCATTTATGAGACCAGTACAACTACTCAAG
AGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAAGAGGAGGATGTG
AACTGAGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACAAGCAGG
GCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACG
ATGTTTTGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGGGAAAGCCGA
45 GAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGA
TGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCA

AGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTA
CGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTAA

Amino acid sequence of PLA2R-CAAR (Construct 4028.CF123; SEQ ID NO: 18)

5 MLLSPSLLLLLLLLGAPRGCAGSEGVAAALTPERLLEWQDKGIFVIQSESLKKCIQA
GKSVLTLENCKQANKHMLWKWVSNHGLFNIGGSGCLGLNFSAPEQPLSLYECD
STLVSLRWRCNRKMITGPLQYSVQVAHDNTVVASRKYIHKWISYSGGGDICEY
LHKDLHTIKGNTHGMPCMFPFQYNHQWHHECTREGREDDLLWCATTSTRYERDE
10 KWGFCPDPTSAEVGCDTIWEKDLNSHICYQFNLLSSLWSSEAHSSCQMGGTLL
SITDETEENFIREHMSSKTVEVWMGLNQLDEHAGWQWSDGTPLNYLNWSPEVN
FEPFVEDHCGTFSSFMPSAWRSRDCESTLPYICKKYLNHIDHEIVEKDAWKYYAT
HCEPGWNPYNRNCYKLQKEEKTWHEALRSCQADNSALIDITSLAEVEFLVTLLG
DENASETWIGLSSNKIPVSFEWSNDSSVIFTNWHTLEPHIFPNRSQLCVSAEQSEG
HWKVKNCEERLFYICKKAGHVLSDAESGCQEGWERHGGFCYKIDTVLRSFDQA
15 SSGYYCPPALVTITNRFEQAFITSLISSVVKMKDSYFWIALQDQNDTGEYTWKPV
GQKPEPVQYTHWNTHQPRYSGGCVAMRGRHPLGRWEVKHCRHFKAMSLCKQP
VENQEKA EYEERWPFHPCYLSGTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA
VHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ
TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY
20 DVLDKRRGRDPGEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGK
GHDGLYQGLSTATKDTYDALHMQALPPR

Nucleotide sequence of pTRPE.CysR.CD8H.BBz CAAR (Construct C) (SEQ ID NO: 25)

25	<i>IgG Signal peptide</i>	1-57 (SEQ ID NO: 46)
	<u>CysR</u>	64-459 (SEQ ID NO: 47)
	<i>CD8 Hinge region</i>	466-630 (SEQ ID NO: 64)
	CD8 TMD	631-702 (SEQ ID NO: 20)
	<u>4-1BB intracellular domain</u>	703-828 (SEQ ID NO: 66)
30	<u>CD3zeta intracellular domain</u>	829-1164 (SEQ ID NO: 24)
	Stop codon	1165-1167

35 ATGGAGTTTGGGCTGAGCTGGCTTTTTCTTGTGGCTATTTTAAAAGGTGTCCAG
TGCggaatccAAAGGAATATTTGTCATTTCAGTCAGAGTCTTTGAAAAAGTGCATAC
AGGCTGGAAAAAGCGTGCTTACCCTGGAGAACTGCAAGCAAGCTAATAAGC
ATATGCTTTGGAAATGGGTAGCAACCACGGACTCTTTAATATCGGAGGCTCC
GGCTGTCTGGGCCTGAACCTTCAGTGCACCGGAGCAACCGCTTTCTCTGTACGA
ATGTGATAGCACACTTGTTAGTCTTCGGTGGCGGTGTAACCGAAAAATGATT
40 ACAGGCCCTCTGCAATATAGTGTTCAAGTGGCCACGACAATACAGTTGTGG
CGTCTAGAAAAATATATTCACAAAGTGGATTTCCTACGGGAGCGGCGGAGGGGA
TATATGTGAATATCTTCACAAAGACTTGCATACAATCgtagcTTCGTGCCGGTCT
TCCTGCCAGCGAAGCCAACACGACGCCAGCACCACGACCAACACCTGCGC
CCACCATCGCGTCGACGCCCTGTCCCTGCGCCAGAGGCGTGCAGACCAGCAG
45 CGGGGGGCGCAGTGCACACGAGGGGGGCTGGACTTCGCCTGTGATATCTACATC

TGGGCGCCCTTGGCCGGGACTTGTGGGGTCCTTCTCCTGTCACCTGGTTA
 TCACCCTTTACTGCAAGCGCGGTGCGCAAGAACTGCTCTATATTTTAAACA
 GCCATTCATGAGACCTGTCCAGACCACTCAAGAGGAGGACGGATGTTCTGT
 AGATTTCCTGAAGAGGAAGAGGGGGGGTGCAGCTGAGAGTGAAGTTCAGC
 5 AGGAGCGCAGACGCCCCCGGTACCAGCAGGGCCAGAACCAGCTCTATAAC
 GAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGACGT
 GGCCGGGACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAA
 GGCCTGTACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAG
 ATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTAC
 10 CAGGGTCTCAGTACAGCCACCAAGGACACCTACGACGCCCTTCACATGCAGG
 CCCTGCCCCCTCGCTAA

Amino acid sequence of pTRPE.CysR.CD8H.BBz CAAR (Construct C) (SEQ ID NO:26)

15 *IgG Signal peptide* 1-19 (SEQ ID NO: 48)
CysR 22-153 (SEQ ID NO: 49)
CD8 Hinge region 156-210 (SEQ ID NO: 44)
CD8 TMD 211-234 (SEQ ID NO: 19)
 20 4-1BB intracellular domain 235-276 (SEQ ID NO: 21)
CD3zeta intracellular domain 277-388 (SEQ ID NO: 45)

25 MEFGLSWLFLVAILKGVQCGSKGIFVIOSESLKKCIQAGKSVLTLENCKQANKH
MLWKWVSNHGLFNIGSGCLGLNFSAPQLSLYECSTLVSLRWRCNRKMITG
PLQYSVQVAHDNTVVASRKYIHKWISYSGSGGGDICEYLHKDLHTIASFVPVFLPA
KPTTTPAPRPPTAPTASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT
CGVLLLSLVITLYCKRGRKLLYIEKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE
LRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPGEMGGKPRRK
 30 NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL
HMQUALPPR

Nucleotide sequence of pTRPE.CysR-FNII-CTLD1.CD8H.BBz CAAR (construct CF1) (SEQ ID NO: 27)

35 *IgG Signal peptide* 1-57 (SEQ ID NO: 46)
CysR-FNII-CTLD1 64-1053 (SEQ ID NO: 50)
CD8 Hinge region 1060-1224 (SEQ ID NO: 64)
CD8 TMD 1225-1296 (SEQ ID NO: 20)
4-1BB intracellular domain 1297-1422 (SEQ ID NO: 66)
CD3zeta intracellular domain 1423-1758 (SEQ ID NO: 24)
 40 Stop codon 1759-1761

45 ATGGAGTTTGGGCTGAGCTGGCTTTTTCTTGTGGCTATTTTAAAAGGTGTCCAG
TGCggatccAAAGGGATCTTTGTTATACAAAGTGAGAGCTTGAAAAAATGTATA
CAGGCTGGCAAAAGTGTACTGACTCTTGAAAATTGCAAACAAGCCAACAAAC
ACATGCTGTGGAAATGGGTGTCTAATCACGGTCTCTTCAATATTGGGGGAAG
TGGATGCCTCGGCCTGAATTTCTCCGCTCCCGAACAGCCCCTCTCACTTTATG

AGTGTGATTCAACTCTGGTGTCTTGAGGTGGCGATGTAACCGCAAGATGAT
 AACCGGCCCTCCAGTATTCCGTCCAAGTAGCACACGACAATACCGTGGTG
 GCATCTAGGAAATACATTCATAAGTGGATATCTTATGGCAGTGGTGGCGGTG
 ACATATGCGAGTACCTGCACAAGGACCTCCACACAATAAAGGGGAACACGC
 5 ACGGGATGCCGTGTATGTTCCCGTTCCAATATAATCATCAATGGCACCATGAG
 TGTACGAGAGAGGGGCGAGAAGACGACCTCCTGTGGTGTGCGACCACCTCAA
 GATATGAACGGGATGAGAAGTGGGGCTTTTGCCCCGACCCAACCTCCGCCGA
 GGTTGGTTGCGACACTATTTGGGAAAAAGATTTGAACAGTCATATATGCTATC
 AATTTAATTTGTTGAGTTCCTCTCCTGGAGCGAAGCGCACAGCTCTTGTCAG
 10 ATGCAAGGTGGTACATTGCTTAGCATTACTGATGAAACTGAGGAGAATTTCA
 TTAGGGAGCATATGTCCTCAAAGACAGTAGAGGTGTGGATGGGTCTGAACCA
 GCTCGACGAACACGCCGGTTGGCAGTGGTCAGATGGAACGCCCTCTGAATTAT
 CTCAACTGGTCCCCTGAGGTCAACTTTGAACCGTTTGTGGAAGATCATTGTGG
 TACTTTTTCCAGTTTTATGCCAAGCGCCTGGCGAAGCCGAGACTGCGAGTCTA
 15 CGTTGCCCTATATCTGCAAGAAGTATTTGAATCACATAGATCATGAAATTGTT
 GA_{Agctagc}TTTCGTGCCGGTCTTCCTGCCAGCGAAGCCAACACGACGCCAGCACC
 GCGACCACCAACACCTGCGCCCACCATCGCGTTCGCAGCCCCCTGTCCCTGCGCCC
 AGAGGCGTGCAGACCAGCAGCGGGGGGCGCAGTGCACACGAGGGGGGCTGGACT
 TCGCCTGTGATATCTACATCTGGGCGCCCTTGGCCGGGACTTGTGGGGTCTC
 20 CTTCCTCTGTCACTGGTTATCACCCCTTACTGCAAGCGCGGTTCGCAAGAA
 ACTGCTCTATATTTTTAAACAGCCATTTCATGAGACCTGTCCAGACCACTCAAG
 AGGAGGACGGATGTTCTGTAGATTTCTGAAGAGGAAGAGGGGGGGTTCGCG
 AGCTGAGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAGG
 GCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACG
 25 ATGTTTTGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGGGAAAGCCGA
 GAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGA
 TGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCA
 AGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTA
 CGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTAA

Amino acid sequence of pTRPE.CysR-FNII-CTLD1.CD8H.BBz CAAR (construct CF1) (SEQ ID NO: 28)

35 *IgG Signal peptide* 1-19 (SEQ ID NO: 48)
CysR-FNII-CTLD1 22-351 (SEQ ID NO: 51)
CD8 Hinge region 354-408 (SEQ ID NO: 43)
CD8 TMD 409-432 (SEQ ID NO: 19)
4-1BB intracellular domain 433-474 (SEQ ID NO: 21)
CD3zeta intracellular domain 475-586 (SEQ ID NO: 45)

40 MEFGLSWLFLVAILKGVQCGSKGIFVIOSESLKKCIQAGKSVLTLENCKQANKHML
WKWVSNHGLFNIGGSGCLGLNFSAPEQPLSLYECDSTLVSLRWRCNRKMITGPL
QYSVQVAHDNTVVASRKYIHKWISYSGGGDICEYLHKDLHTIKGNTHGMPCMF
 45 PFQYNHQWHHECTREGREDDLLWCATTSRYERDEKWFPCPDPTSAEVGCDTI
WEKDLNSHICYQFNLLSSLWSSEAHSSCOMQGGTLLSITDETEENFIREHMSSKT
VEVWMGLNQLDEHAGWQWSDGTPLNYLNWSPEVNFEPFVEDHCGTFSSFMPS

5 AWRSRDCESTLPYICKKYLNHIDHEIVEASFVPVFLPAKPTTTPAPRPPTPAPTIASQ
PLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGR
KKLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRSADAPAYOQGO
NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAE
AYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMOALPPR

**Nucleotide sequence of pTRPE.CysR-FNII-CTLD1-3.GS linker.BBz CAAR
 (construct CF123) (SEQ ID NO: 29)**

	<i>IgG Signal peptide</i>	1-57 (SEQ ID NO: 46)
10	<u>CysR-FNII-CTLD1-3</u>	64-1911 (SEQ ID NO: 52)
	<i>GS linker</i>	1918-1947 (SEQ ID NO: 68)
	CD8 TMD	1954-2025 (SEQ ID NO: 20)
	<u>4-1BB intracellular domain</u>	2026-2151 (SEQ ID NO: 66)
	CD3zeta intracellular domain	2152-2487 (SEQ ID NO: 24)
15	Stop codon	2488-2490

ATGGAGTTTGGGCTGAGCTGGCTTTTTCTTGTGGCTATTTTAAAAGGTGTCCAG
TGCg gatccAAAGGGATTTTCGTGATACAGTCCGAGAGTCTCAAAAAGTGTATC
CAGGCAGGCAAAAGTGTCTCACTCTGGAAACTGCAAACAAGCGAACAAG
 20 CACATGTTGTGGAAGTGGGTAGTAACCATGGACTGTTCAACATCGGAGGTA
GTGGATGCCTTGGTCTCAATTTCTCTGCTCCGGAACAGCCTTTGTCAGTGTAC
GAATGCGACTCCACTCTCGTTAGTCTTAGATGGCGATGCAATCGCAAAATGA
TTACGGGACCACTTCAATATTCAGTTCAAGTGGCACATGATAACACCGTAGT
GGCCTCACGGAAATACATCCATAAATGGATTTCTTATGGTAGCGGGGGCGGC
 25 GATATATGTGAATACCTCCATAAGGATCTCCACACCATTAAAGGGTAATACTC
ACGGTATGCCGTGTATGTTTCCTTTTCAGTACAATCATCAGTGGCATCATGAA
TGCACGAGGGAAGGACGCGAGGACGATTTGCTCTGGTGC GCAACCACCTCAC
GCTACGAGAGAGACGAAAAATGGGGCTTTTGCCCGGACCCCACTAGTGCTGA
GGTAGGATGTGATACGATTTGGGAAAAGGATTTGAATTCTCATATTTGCTACC
 30 AGTTTAATCTTCTTTTCATCCCTGTCCTGGTCTGAGGCTCATTCTAGTTGCCAGA
TGCAAGGTGGGACTTTGCTTTCAATTACTGACGAGACTGAGGAAAATTTTATC
CGAGAGCATATGTCTTCTAAAACCGTAGAGGTATGGATGGGCCTGAACCAAT
TGGACGAACACGCGGGCTGGCAGTGGAGCGACGGGACACCTCTCAACTACCT
TAATTGGAGCCCTGAGGTAACTTTGAACCGTTTGTGCGAGGATCACTGCGGA
 35 ACTTTCAGCAGCTTCATGCCTAGTGCATGGCGGTCCCGAGACTGTGAGAGCA
CCCTTCCATACATATGTAAAAAATACCTCAATCACATAGACCACGAGATCGT
AGAGAAGGATGCATGGAAATATTATGCTACGCACTGTGAGCCGGGATGGAAT
CCTTATAACCGCAACTGTTACAAGCTGCAAAAAGAAGAGAAGACATGGCATG
AGGCGCTGCGCTCATGTCAAGCGGACAATTCTGCACTTATAGATATAACTAG
 40 TTTGGCGGAGGTAGAATTTTTGGTTACGCTTCTCGGCGATGAGAATGCGTCCG
AGACGTGGATAGGGTTGTCAAGCAATAAAATTCCTGTAAGTTTTGAATGGTC
AAATGACTCTTCTGTCATCTTCACCAATTGGCACACACTCGAACCCCATATCT
TCCCAAACCGAAGCCAGTTGTGTGTCAGCGCTGAGCAATCAGAAGGACATTG
GAAAGTTAAAACTGTGAAGAAAGACTGTTCTACATCTGTAAGAAGGCAGGA
 45 CATGTGCTTTCAGATGCGGAAAGCGGCTGTCAAGAAGGTTGGGAGCGCCATG
GAGGTTTCTGTTATAAAATCGACACAGTTTTGCGATCTTTCGATCAGGCTTCA

AGCGGGTACTATTGTCCTCCTGCACTGGTTACAATCACGAACCGGTTTGAACA
 GGCTTTTATAACTTCTTTGATTTCCAGCGTGGTTAAAATGAAGGACTCTTATTT
 CTGGATAGCCCTGCAAGACCAAAATGATACCGGTGAGTACACATGGAAACCG
 GTAGGTCAAAAGCCAGAGCCAGTCCAGTACACTCATTGGAATACCCACCAGC
 5 CTAGGTACTCCGGCGGGTGTGTGGCGATGCGGGGTCGCCACCCTCTCGGACG
 CTGGGAGGTGAAGCATTGCCGCCACTTCAAGGCGATGAGCTTGTGTAAACAG
 CCCGTCGAAAATCAGGAAAAGGCAgctagcGGTGGCGGAGGTTCTGGAGGTGGA
 GGTTCCtccggaATCTACATCTGGGCGCCCTTGGCCGGGACTTGTGGGGTCC
 TTCTCCTGTCACTGGTTATCACCTTTACTGCAAGCGCGGTGCGAAGAAAC
 10 TGCTCTATATTTTAAACAGCCATTCATGAGACCTGTCCAGACCACTCAAGAG
 GAGGACGGATGTTCTGTAGATTTCTGAAGAGGAAGAGGGGGGGTTCGAG
 CTGAGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAGGGC
 CAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGAT
 GTTTTGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGGGAAAGCCGAGA
 15 AGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGATG
 GCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAG
 GGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTACG
 ACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTAA

20 **Amino acid sequence of pTRPE.CysR-FNII-CTLD1-3.GS linker.BBz CAAR**
 (construct CF123) (SEQ ID NO: 30)

<i>IgG Signal peptide</i>	1-19 (SEQ ID NO: 48)
<u>CysR-FNII-CTLD1-3</u>	22-637 (SEQ ID NO: 53)
<i>GS linker</i>	640-649 (SEQ ID NO: 69)
CD8 TMD	652-675 (SEQ ID NO: 19)
<u>4-1BB intracellular domain</u>	676-717 (SEQ ID NO: 21)
<u>CD3zeta intracellular domain</u>	718-829 (SEQ ID NO: 45)

30 MEFGLSWLFLVAILKGVQCGSKGIFVIOSESLKKCIQAGKSVLTLENCKQANKH
MLWKWVSNHGLFNIGSGCLGLNFSAPEQPLSLYECDSLVSRLWRNCRKMITG
PLQYSVQVAHDNTVVASRKYIHKWISYSGGGDICEYLHKDLHTIKGNTHGMP
MFPFQYNHQWHHECTREGREDDLLWCATTSRYERDEKWGFCPDPTSAEVGCDT
IWEKDLNSHICYQFNLLSSLWSSEAHSSCQMGGTLLSITDETEENFIREHMSST
 35 VEVWMGLNQLDEHAGWQWSDGTPLNYLNWSPEVNFEPFVEDHCGTFSSFMPS
AWRSRDCESTLPYICKKYLNHIDHEIVEKDAWKYYATHCEPGWNPYNRNCYKL
QKEEKTWHEALRSCQADNSALIDITSLAEVEFLVTLLGDENASETWIGLSSNKIPV
SFEWSNDSSVIFTNWHITLPHIFPNRSQLCVSAEQSEGHWKVKNCERLFYICKK
AGHVLSDAESGCQEGWERHGGFCYKIDTVLRSFDQASSGYPCPPALVTITNRF
 40 QAFITSLISSVVKMKDSYFWIALODQNDTGEYTWKPVGQKPEPVQYTHWNTHOP
RYSGGCVAMRGRHPLGRWEVKHCRHFKAMSLCKQPVENQEKAASGGGGSGGG
GSSGIYIWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED
GCSCRFPEEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDR
RGRDPENMGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDLGY
 45 QGLSTATKDTYDALHMQALPPR

**Nucleotide sequence of pTRPE.CysR-FNII-CTLD1-3 7.GS linker.BBz CAAR
(construct CF1237) (SEQ ID NO: 31)**

<i>IgG Signal peptide</i>	1-57 (SEQ ID NO: 46)
<u>CysR-FNII-CTLD1-3 7</u>	64-2331 (SEQ ID NO: 54)
<i>GS linker</i>	2338-2367 (SEQ ID NO: 68)
CD8 TMD	2374-2445 (SEQ ID NO: 20)
<u>4-1BB intracellular domain</u>	2446-2571 (SEQ ID NO: 66)
<u>CD3zeta intracellular domain</u>	2572-2907 (SEQ ID NO: 24)
Stop codon	2908-2910

10 ATGGAGTTTGGGCTGAGCTGGCTTTTTCTTGTGGCTATTTTAAAAGGTGTCCAG
TGCg gatccAAAGGGATTTTCGTGATACAGTCCGAGAGTCTCAAAAAGTGTATC
CAGGCAGGCAAAAGTGTTCTCACTCTGGAAAACTGCAAACAAGCGAACAAG
CACATGTTGTGGAAGTGGGTAGTAACCATGGACTGTTCAACATCGGAGGTA
15 GTGGATGCCTTGGTCTCAATTTCTCTGCTCCGGAACAGCCTTTGTCACTGTAC
GAATGCGACTCCACTCTCGTTAGTCTTAGATGGCGATGCAATCGCAAAATGA
TTACGGGACCACTTCAATATTCAGTTCAAGTGGCACATGATAACACCGTAGT
GGCCTCACGGAAATACATCCATAAATGGATTTCTTATGGTAGCGGGGGCGGC
GATATATGTGAATACCTCCATAAGGATCTCCACACCATTAAGGGTAATACTC
20 ACGGTATGCCGTGTATGTTTCCTTTTCAGTACAATCATCAGTGGCATCATGAA
TGCACGAGGGAAGGACGCGAGGACGATTTGCTCTGGTGCGCAACCACCTCAC
GCTACGAGAGAGACGAAAAATGGGGCTTTTGCCCGGACCCCACTAGTGCTGA
GGTAGGATGTGATACGATTTGGGAAAAGGATTTGAATTCTCATATTTGCTACC
AGTTTAATCTTCTTTTCATCCCTGTCCTGGTCTGAGGCTCATTCTAGTTGCCAGA
25 TGCAAGGTGGGACTTTGCTTTCAATTACTGACGAGACTGAGGAAAATTTTATC
CGAGAGCATATGTCTTCTAAAACCGTAGAGGTATGGATGGGCCTGAACCAAT
TGGACGAACACGCGGGCTGGCAGTGGAGCGACGGGACACCTCTCAACTACCT
TAATTGGAGCCCTGAGGTAAACTTTGAACCGTTTGTCGAGGATCACTGCGGA
ACTTTTCAGCAGCTTCATGCCTAGTGCATGGCGGTCCCGAGACTGTGAGAGCA
30 CCCTTCCATACATATGTAAAAAATACCTCAATCACATAGACCACGAGATCGT
AGAGAAGGATGCATGGAAATATTATGCTACGCACTGTGAGCCGGGATGGAAT
CCTTATAACCGCAACTGTTACAAGCTGCAAAAAGAAGAGAAGACATGGCATG
AGGCGCTGCGCTCATGTCAAGCGGACAATTCTGCACTTATAGATATAACTAG
TTTGGCGGAGGTAGAATTTTGGTTACGCTTCTCGGCGATGAGAATGCGTCCG
35 AGACGTGGATAGGGTTGTCAAGCAATAAAATTCCTGTAAGTTTTGAATGGTC
AAATGACTCTTCTGTCATCTTCACCAATTGGCACACACTCGAACCCCATATCT
TCCCAAACCGAAGCCAGTTGTGTGTGTCAGCGCTGAGCAATCAGAAGGACATTG
GAAAGTTAAAAACTGTGAAGAAAGACTGTTCTACATCTGTAAGAAGGCAGGA
CATGTGCTTTCAGATGCGGAAAGCGGCTGTCAAGAAGGTTGGGAGCGCCATG
40 GAGGTTTCTGTTATAAAATCGACACAGTTTTGCGATCTTTCGATCAGGCTTCA
AGCGGGTACTATTGTCCTCCTGCACTGGTTACAATCACGAACCGGTTTGAACA
GGCTTTTATAACTTCTTTGATTTCCAGCGTGGTTAAAATGAAGGACTCTTATTT
CTGGATAGCCCTGCAAGACCAAAAATGATACCGGTGAGTACACATGGAAACCG
GTAGGTCAAAAGCCAGAGCCAGTCCAGTACACTCATTGGAATACCCACCAGC
45 CTAGGTACTCCGGCGGGTGTGTGGCGATGCGGGGTCGCCACCCTCTCGGACG
CTGGGAGGTGAAGCATTGCCGCCACTTCAAGGCGATGAGCTTGTGTAAACAG

CCGGTCGAAAATCAGGAAAAGGCAGTTAACACATCTGATATGTACCCTATGC
 CTAACACACTCGAATATGGGAATAGGACGTACAAGATTATAAACGCGAACAT
 GACGTGGTATGCTGCAATCAAGACGTGCCTCATGCACAAAGCTCAGCTTGTG
 TCTATTACTGACCAATACCACCAATCATTTTTGACAGTCGTGTTGAATCGATT
 5 GGGGTACGCCCATTGGATCGGTCTCTTCACGACGGACAATGGGCTCAATTTTG
 ACTGGAGTGACGGTACTAAATCATCCTTTACTTTTTGGAAGGATGAAGAAAG
 TTCTCTGTTGGGCGATTGCGTGTTTGCTGACTCAAATGGCCGATGGCATTCCA
 CAGCCTGTGAAAGTTTTCTGCAGGGAGCTATTTGCCACGTGCCTCCCGAAACG
 CGGCAGTCCGAACACCCGGAATTGgctagcGGTGGCGGAGGTTCTGGAGGTGGAG
 10 GTTCCtccggaATCTACATCTGGGCGCCCTTGGCCGGGACTTGTGGGGTCTCT
 TCTCCTGTCACTGGTTATCACCTTTACTGCAAGCGCGGTTCGCAAGAAACT
 GCTCTATATTTTTTAAACAGCCATTTCATGAGACCTGTCCAGACCACTCAAGAGG
 AGGACGGATGTTCTCTGTAGATTTCTCTGAAGAGGAAGAGGGGGGGGTGCGAGCT
 GAGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCTACCAGCAGGGCCA
 15 GAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTT
 TTGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGGGAAAGCCGAGAAGG
 AAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGATGGCG
 GAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGGCAAGGGG
 CACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTACGACG
 20 CCCTTCACATGCAGGCCCTGCCCCCTCGCTAA

**Amino acid sequence of pTRPE.CysR-FNII-CTLD1-3 7.GS linker.BBz CAAR
(construct CF1237) (SEQ ID NO: 32)**

25	<i>IgG Signal peptide</i>	1-19 (SEQ ID NO: 48)
	<u>CysR-FNII-CTLD1-3 7</u>	22-777 (SEQ ID NO: 55)
	<i>GS linker</i>	780-789 (SEQ ID NO: 69)
	CD8 TMD	792-815 (SEQ ID NO: 19)
	<u>4-1BB intracellular domain</u>	816-857 (SEQ ID NO: 21)
30	<u>CD3zeta intracellular domain</u>	858-969 (SEQ ID NO: 45)

MEFGLSWLFLVAILKGVQCGSKGIFVIQSESLKKCIQAGKSVLTLENCKQANKH
 MLWKWVSNHGLFNIGGSGCLGLNFSAPEQPLSLYECDSLTVSLRWRCNRKMITG
 35 PLQYSVQVAHDNTVVASRKYIHKWISYSGGGGDICEYLHKDLHTIKGNTHGMPC
 MFPFQYNHQWHHECTREGREDDLLWCATTSTRYERDEKWGFCDPDTSAEVGCDT
 IWEKDLNSHICYQFNLLSSLWSSEAHSSCQMGGTLLSITDETEENFIREHMSSKT
 VEVWMGLNQLDEHAGWQWSDGTPLNYLNWSPEVNFEPFVEDHCGTFSSFMPS
 AWRSRDCESTLPYICKKYLNHIDHEIVEKDAWKYYATHCEPGWNPYNRNCYKL
 QKEEKTWHEALRSCQADNSALIDITSLAEVEFLVTLLGDENASETWIGLSSNKIPV
 40 SFEWSNDSSVIFTNWHTLEPHIFPNRSQLCVSAEQSEGHWKVKNCERLFYICKK
 AGHVLSDAESGCQEGWERHGGFCYKIDTVLRSFDQASSGYCPCPALVTITNRFE
 QAFITSLISSVVKMKDSYFWIALQDQNDTGEYTWKPVGQKPEPVQYTHWNTHQP
 RYSGGCVAMRGRHPLGRWEVKHCRHFKAMSLCKQPVENQEKAVNTSDMYPMP
 PNTLEYGNRTYKIINANMTWYAAIKTCLMHKAQLVSITDQYHQSFLLTVVLNRLG
 45 YAHWIGLFTTDNGLNFDWSDGTKSSFTFWKDEESSLLGDCVFADSNRWHSTA
 CESFLQGAICHVPPETRQSEHPELASGGGGSGGGGSSGIYIWAPLAGTCGVLLLS
 LVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSR

SADAPAYQOGONOLYNELNLGRREEYDVLDKRRGRDPENMGKPRRKNPQEGLYNELOKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP
PR

5 **Nucleotide sequence of pTRPE.CysR-FNII-CTLD1 7.GS linker.BBz CAAR**
(construct CF17) (SEQ ID NO: 33)

<i>IgG Signal peptide</i>	1-57 (SEQ ID NO: 46)
<u>CysR-FNII-CTLD1 7</u>	64-1473 (SEQ ID NO: 56)
<i>GS linker</i>	1480-1509 (SEQ ID NO: 68)
10 CD8 TMD	1516-1587 (SEQ ID NO: 20)
<u>4-1BB intracellular domain</u>	1588-1713 (SEQ ID NO: 66)
<u>CD3zeta intracellular domain</u>	1714-2049 (SEQ ID NO: 24)
Stop codon	2050-2052

15 ATGGAGTTTGGGCTGAGCTGGCTTTTTCTTGTGGCTATTTTAAAAGGTGTCCAG
TGCg gatccAAAGGCATCTTCGTAATCCAGTCAGAAAGTTTGAAAAATGTATC
CAAGCTGGCAAATCAGTACTTACCCTTGAGAACTGCAAGCAAGCCAATAAAC
ATATGCTGTGGAAATGGGTCTCAAACCACGGCCTCTTCAATATTGGTGGGTCA
GGTTGCTTGGGGTTGAATTTCTCCGCCCCAGAGCAACCACTCAGCCTTTACGA
20 GTGTGATTCCACACTTGTCTCTTTGCGATGGCGCTGCAATAGGAAAATGATCA
CAGGCCCTTCAGTACTCTGTGCAAGTTGCTCATGATAACACAGTCGTGGCG
AGTCGGAAATATATTCACAAATGGATTTCTTATGGGAGTGGTGGAGGAGATA
TATGCGAGTATTTGCATAAGGACTTGCACACCATCAAGGGAAACACTCACGG
TATGCCATGTATGTTTCCGTTCCAATATAATCATCAATGGCACCACGAATGTA
25 CCCGAGAGGGACGCGAGGACGATCTTCTTTGGTGCGCCACAACCTCTCGATA
TGAACGAGATGAGAAGTGGGGGTTTGTCTGACCCCAACCAGTGCAGAAAGTA
GGGTGCGATACCATCTGGGAGAAAGACTTGAACCTCACACATATGCTATCAGT
TTAATTTGTTGTCTTCTTTGTCTATGGAGCGAAGCTCATTATCATGCCAGATG
CAGGGCGGGACACTGCTTTCTATCACCGACGAGACTGAGGAAAATTTTATCC
30 GCGAGCACATGTCAAGCAAGACAGTTGAGGTTTGGATGGGGCTCAATCAACT
GGACGAACACGCAGGGTGGCAGTGGTCCGATGGCACTCCGCTCAACTACCTT
AACTGGAGCCCAGAGGTGAACCTTTGAGCCGTTTGTCTGAAGATCACTGTGGTA
CTTTTAGCTCCTTCATGCCGTCCGCATGGAGAAGTCGCGACTGCGAGTCAACC
CTCCCTTACATCTGTAAGAAATACCTCAACCACATAGATCACGAAATCGTAG
35 AGGTCAATACGTCCGACATGTACCCAATGCCAAATACGTTGGAATATGGGAA
TAGGACATACAAGATAATTAACGCAAATATGACGTGGTATGCCGCAATCAAA
ACGTGCCTCATGCACAAGGCACAGCTCGTGTCAATTACGGACCAGTACCACC
AATCATTTCTCACAGTCGTTCTTAATCGATTGGGTATGCACACTGGATAGGC
TTGTTACGACGGACAATGGTTTGAACCTTTGACTGGTCCGATGGAACATAAAA
40 GTTCTTTCACTTTTTTGGAAAGGATGAGGAGTCCTCCTTGCTCGGGGACTGCGTC
TTGCGAGATTCAAACGGGCGCTGGCACTCAACGGCATGTGAGTCCTTCCTGC
AGGGAGCTATATGCCATGTGCCACCAGAAACACGCCAGTCTGAGCACCCCTGA
GTTGgctagcGGTGGCGGAGGTTCTGGAGGTGGAGGTTCCtccggaATCTACATCTG
GGCGCCCTTGGCCGGGACTTGTGGGGTTCCTTCTCCTGTCACTGGTTATC
45 ACCCTTTACTGCAAGCGCGGTTCGCAAGAACTGCTCTATATTTTAAACAGC
CATTCATGAGACCTGTCCAGACCACTCAAGAGGAGGACGGATGTTCTCTGTAG

ATTTCCTGAAGAGGAAGAGGGGGGGTGCAGCTGAGAGTGAAGTTCAGCAG
GAGCGCAGACGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTATAACGA
GCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGACGTGGC
CGGGACCCTGAGATGGGGGGAAGCCGAGAAGGAAGAACCCTCAGGAAGGC
CTGTACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTG
GGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGG
GTCTCAGTACAGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCT
GCCCCCTCGCTAA

10 **Amino acid sequence of pTRPE.CysR-FNII-CTLD1 7.GS linker.BBz CAAR**
(construct CF17) (SEQ ID NO: 34)

15 *IgG Signal peptide* 1-19 (SEQ ID NO: 48)
CysR-FNII-CTLD1 7 22-491 (SEQ ID NO: 57)
GS linker 494-503 (SEQ ID NO: 69)
CD8 TMD 506-529 (SEQ ID NO: 19)
4-1BB intracellular domain 530-571 (SEQ ID NO: 21)
CD3zeta intracellular domain 572-683 (SEQ ID NO: 45)

20 MEFGLSWLFLVAILKGVQCGSKGIFVIQSESLKKCIQAGKSVLTLENCKQANKH
MLWKWVSNHGLFNIGGSGCLGLNFSAPEQPLSLYECDSLVSRLWRNRCNRMITG
PLQYSVQVAHDNTVVASRKYIHKWISYSGGGGDICEYLHKDLHTIKGNTHGMPC
MPFQYNHQWHHECTREGREDDLLWCATTSRYERDEKWGFCDPTSAEVGCDT
IWEKDLNSHICYQFNLLSSLSWSEAHSSCQMGGTLLSITDETEENFIREHMSSKT
 25 VEVWMGLNQLDEHAGWQWSDGTPLNYLNWSPEVNFEPFVEDHCGTFSSFMPS
AWRSRDCESTLPYICKKYLNHIDHEIVEVNTSDMYPMPNTLEYGNRTYKIINANM
TWYAAIKTCLMHKAQLVSITDQYHQSFSLTVVLNRLGYAHWIGLFTTDNGLNFD
WSDGTKSSFTFWKDEESSLLGDCVFADSNRWHSTACESFLOGAICHVPPETRO
SEHPELASGGGGSGGGGSSGIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLLYI
 30 FKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYN
ELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG
MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

35 **Nucleotide sequence of pTRPE.CysR-CTLD1 7.GS linker.BBz CAAR (construct**
C17) (SEQ ID NO: 35)

40 *IgG Signal peptide* 1-57 (SEQ ID NO: 46)
CysR-CTLD1 7 64-1314 (SEQ ID NO: 58)
GS linker 1321-1350 (SEQ ID NO: 68)
CD8 TMD 1357-1428 (SEQ ID NO: 20)
 4-1BB intracellular domain 1429-1554 (SEQ ID NO: 66)
 CD3zeta intracellular domain 1555-1890 (SEQ ID NO: 24)
 Stop codon 1891-1893

45 ATGGAGTTTGGGCTGAGCTGGCTTTTTCTTGTGGCTATTTTAAAAGGTGTCCAG
TGCGgatccAAAGGAATCTTCGTAATTCAATCTGAGAGTCTGAAAAAATGTATTC

AGGCCGGTAAGAGCGTACTCACGCTTGAAAATTGCAAACAGGCCAACAAAC
 ACATGCTTTGGAAATGGGTTTCAAATCACGGGTGTTTAAACATAGGGGGATC
 AGGATGTCTGGGCCTTAACCTTTCCGCACCTGAACAACCTCTTAGTCTGTATG
 AGTGTGACTCAACGCTGGTCTCCTTGCCTGGAGATGCAATCGGAAGATGAT
 5 AACC GGGCCCTCCAGTATTCCGTT CAGGTCGCCACGATAATACTGTTGTTG
 CATCCCGAAAATATATTCATAAGTGGATCTCCTACGGGAGTGGAGGGGGCGA
 TATTTGTGAATACCTCCACAAGGATCTGCACACTATCACTTCTGCGGAAGTAG
 GCTGTGACACAATCTGGGAGAAAGATCTGAATTCACACATTTGCTATCAGTTC
 AATCTTCTGAGTTCTTTGAGCTGGTCCGAAGCACATTCATCCTGTCAGATGCA
 10 AGGTGGAACACTCTTGTCAATAACAGATGAAACGGAAGAGAAGCTTTATTAGA
 GAACATATGTCCTCAAAGACTGTGGAGGTGTGGATGGGACTTAACCAGCTCG
 ATGAACATGCAGGATGGCAGTGGAGTGACGGAACGCCACTGAACTACCTGA
 ATTGGAGCCCAGAGGTGAATTTTCGAGCCTTTCTAGAGGACCATTGCGGTAC
 TTTTTCATCTTTTATGCCAGCGCATGGAGATCCCGAGATTGTGAAAGCACGC
 15 TGCCCTATATTTGTAAAAAGTACCTGAACCACATAGATCATGAGATAGTTGA
 GGTAATAACAAGTGATATGTACCCCATGCCGAACACACTCGAGTACGGAAAT
 AGAACCTACAAGATAATCAACGCTAACATGACCTGGTACGCGGCCATTAAAGA
 CCTGCCTCATGCACAAGGCTCAACTCGTCAGTATTACTGACCAATATCACCAG
 TCATTTCTCACCGTCGTGTTGAATCGCCTCGGTTACGCCCACTGGATCGGTTT
 20 GTTTACAACGGACAATGGACTCAATTTTCGATTGGTCAGACGGAACCAATCT
 AGTTTTACCTTCTGGAAAGACGAGGAATCAAGCCTGCTTGGGGACTGCGTAT
 TTGCGGACTCTAATGGCCGATGGCATAGTACAGCGTGTGAGAGCTTTTGTCA
 GGGGGCGATTTGTTCATGTTCCGCCGGAACCCGCCAAAGCGAGCATCCAGAA
 TTGgctagcGGTGGCGGAGGTTCTGGAGGTGGAGGTTCCtccggaATCTACATCTGG
 25 GCGCCCTTGGCCGGGACTTGTGGGGTCCCTTCTCCTGTCCTGTTATCA
 CCCTTTACTGCAAGCGCGGTGCGCAAGAACTGCTCTATATTTTAAACAGCC
 ATTCATGAGACCTGTCCAGACCACTCAAGAGGAGGACGGATGTTTCTGTAGA
 TTTCTGAAGAGGAAGAGGGGGGGTGGAGCTGAGAGTGAAAGTTCAGCAGG
 AGCGCAGACGCCCCCGCGTACCAGCAGGGCCAGAACCCAGCTCTATAACGAG
 30 CTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGACGTGGCC
 GGGACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCC
 TGTACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTG
 GGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGG
 GTCTCAGTACAGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCT
 35 GCCCCTCGCTAA

Amino acid sequence of pTRPE.CysR-CTLD1 7.GS linker.BBz CAAR (construct C17) (SEQ ID NO: 36)

40	<i>IgG Signal peptide</i>	1-19 (SEQ ID NO: 48)
	<u>CysR-CTLD1 7</u>	22-438 (SEQ ID NO: 59)
	<i>GS linker</i>	441-450 (SEQ ID NO: 69)
	CD8 TMD	453-476 (SEQ ID NO: 19)
	<u>4-1BB intracellular domain</u>	477-518 (SEQ ID NO: 21)
45	<u>CD3zeta intracellular domain</u>	519-630 (SEQ ID NO: 45)

MEFGLSWLFLVAILKGVQCGSKGIFVIQSESLKKCIQAGKSVLTLENCKQANKH
MLWKWVSNHGLFNIGGSGCLGLNFSAPEQPLSLYECDSLVSRLWRNCRKMITG
PLQYSVQVAHDNTVVASRKYIHKWISYGSGGGDICEYLHKDLHTITSAEVGCDTI
WEKDLNSHICYQFNLLSSLWSSEAHSSCOMQGGTLLSITDETEENFIREHMSSKT
 5 VEVWMGLNQLDEHAGWQWSDGTPLNYLNWSPEVNFEPFVEDHCGTFSSFMPS
AWRSRDCESTLPYICKKYLNHIDHEIVEVNTSDMYPMPNTLEYGNRTYKIINANM
TWYAAIKTCLMHKAQLVSITDQYHQSFLLTVVLNRLGYAHWIGLFTTDNGLNFD
WSDGTKSSFTFWKDEESSLLGDCVFADSNRWHSTACESFLQGAICHVPPETRO
SEHPELASGGGGSGGGGSSGIYIWAPLAGTCGVLLLSLVITLYCKRGRKLLLYI
 10 FKOPFMRPVOTTOEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYOOGONOLYN
ELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG
MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

15 **Nucleotide sequence of 4025 pTRPE.CysR.CD8H.BBz CAAR (construct 4025.C)**
(SEQ ID NO: 37)

	<i>PLA2R Signal peptide</i>	1-60 (SEQ ID NO: 65)
	<i>PLA2R pro-peptide</i>	61-117 (SEQ ID NO: 67)
20	<i>CysR</i>	118-504 (SEQ ID NO: 60)
	<i>CD8 Hinge region</i>	511-645 (SEQ ID NO: 42)
	CD8 TMD	646-717 (SEQ ID NO: 20)
	<i>4-1BB intracellular domain</i>	718-843 (SEQ ID NO: 22)
	<i>CD3zeta intracellular domain</i>	844-1179 (SEQ ID NO: 72)
25	Stop codon	1180-1182

ATGCTGCTGAGCCCTAGCCTGCTGCTGCTCCTGCTTCTTGGAGCCCCTAGAGG
ATGTGCCGGATCTGAAGGTGTTGCCGCCGCTCTGACACCCGAGAGACTG
CTGGAATGGCAGGACAAGGGCATCTTCGTGATCCAGAGCGAGAGCCTGAAG
 30 AAGTGCATCCAGGCCCGCAAGAGCGTGCTGACCCTGGAAAATTGCAAGCAG
GCCAACAAGCACATGCTGTGGAAATGGGTGTCCAACCACGGCCTGTTCAACA
TCCGCGGCTCTGGATGTCTGGGCCTGAATTTCTCTGCCCCTGAGCAGCCTCTG
AGCCTGTACGAGTGTGATAGCACCCCTGGTGTCCCTGAGATGGCGGTGCAACC
GGAAGATGATCACAGGCCCTCTGCAGTACTCTGTGCAGGTCGCCACGACAA
 35 TACCGTGGTGGCCAGCAGAAAGTACATCCACAAGTGGATCAGCTACGGCAGC
GGCGGAGGCGACATCTGTGAATACCTGCACAAGGATCTGtccggaACCACGACG
CCAGCGCCGCGACCACCAACACCGGCGCCCAACCATCGCGTCGCAGCCCCTGTCC
CTGCGCCCAGAGGCGTGCCGGCCAGCGGCGGGGGGCGCAGTGCACACGAGGG
GGCTGGACTTCGCCTGTGATATCTACATCTGGGCGCCCTTGGCCGGGACTT
 40 GTGGGGTCCTTCTCCTGTCACTGGTTATCACCTTTACTGCAAACGGGGC
AGAAAGAACTCCTGTATATATTCAAACAACCATTATGAGACCAGTACAAA
CTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCAGAGAAGAAGAAG
GAGGATGTGAAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGT
ACAAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAG
 45 AGGAGTACGATGTTTTGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGG
GAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGA

AAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCC
GGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCA
AGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTAA

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Amino acid sequence of 4025 pTRPE.CysR.CD8H.BBz CAAR (construct 4025.C)
(SEQ ID NO: 38)

PLA2R Signal peptide 1-20
CysR 40-168 (SEQ ID NO: 61)
CD8 Hinge region 171-215 (SEQ ID NO: 43)
CD8 TMD 216-239 (SEQ ID NO: 19)
4-1BB intracellular domain 240-281 (SEQ ID NO: 21)
CD3zeta intracellular domain 282-393 (SEQ ID NO: 23)

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15

MLLSPSLLLLLLLGAPRGCAGSEGVAALTPERLLEWQDKGIFVIOSESLKKCIO
AGKSVLTLENCKQANKHMLWKWVSNHGLFNIGGSGCLGLNFSAP EQPLSLYEC
DSTLVSLRWRCNRKMITGPLOYSVQVAHDNTVVASRKYIHKWISYSGGGDICE
YLHKDLSGTTTPAPRPPTAPTASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWA
PLAGTCGVLLLSLVITLYCKRGRKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE
EEGGCEL RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG
GKPRRK NPOEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATK
DTYDALHMQALPPR

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Nucleotide sequence of 4026 pTRPE. CysR-FNII-CTLD1.CD8H.BBz CAAR
(construct 4026.CF1) (SEQ ID NO: 39)

PLA2R Signal peptide 1-60 (SEQ ID NO: 65)
PLA2R pro-peptide 61-117
CysR-FNII-CTLD1 118-1143 (SEQ ID NO: 62)
CD8 Hinge region 1149-1284 (SEQ ID NO: 42)
CD8 TMD 1285-1356 (SEQ ID NO: 20)
4-1BB intracellular domain 1357-1482 (SEQ ID NO: 22)
CD3zeta intracellular domain 1483-1818 (SEQ ID NO: 72)
Stop codon 1819-1821

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ATGCTGCTGAGCCCTAGCCTGCTGCTGCTCCTGCTTCTTGAGCCCCTAGAGG
ATGTGCCGGATCTGAAGGTGTTGCCGCCGCTCTGACACCCGAGAGACTG
CTGGAATGGCAGGACAAGGGCATCTTCGTGATCCAGAGCGAGAGCCTGAAG
AAGTGCATCCAGGCCGGCAAGAGCGTGCTGACCCTGGAAAATTGCAAGCAG
GCCAACAAGCACATGCTGTGGAAATGGGTGTCCAACCACGGCCTGTTCAACA
TCGGCGGCTCTGGATGTCTGGGCCTGAATTTCTCTGCCCCTGAGCAGCCTCTG
AGCCTGTACGAGTGTGATAGCACCTGGTGTCCCTGAGATGGCGGTGCAACC
GGAAGATGATCACAGGCCCTCTGCAGTACTCTGTGCAGGTCGCCACGACAA
TACCGTGGTGGCCAGCAGAAAGTACATCCACAAGTGGATCAGCTACGGCAGC
GGCGGAGGCGACATCTGTGAATACCTGCACAAGGATCTGCACACCATCAAGG

40

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5 GCAACACCCACGGAATGCCCTGCATGTTCCCGTTTCAGTACAACCACCAGTG
GCACCACGAGTGCACCAGAGAAGGCAGAGAGGACGACCTGCTTTGGTGCGC
CACAACCAGCAGATACGAGCGGGATGAGAAGTGGGGCTTCTGCCCTGATCCT
ACCTCTGCCGAAGTGGGCTGCGATACCATCTGGGAGAAAGACCTGAACAGCC
 10 ACATCTGCTACCAGTTCAACCTGCTGTCCAGCCTGTCTTGGAGCGAGGCCAC
AGCAGCTGTCAAATGCAAGGCGGCACACTGCTGAGCATCACCGACGAGACA
GAGGAAAACCTTCATCCGCGAGCACATGAGCAGCAAGACCGTGGAAGTGTGG
ATGGGACTGAACCAGCTGGATGAGCATGCCGGATGGCAGTGGAGTGATGGC
ACCCCTCTGAACTACCTGAACTGGTCCCCTGAAGTGAAGTTCGAGCCCTTCGT
GGAAGATCACTGCGGCACCTTCAGCAGCTTCATGCCCAGCGCTTGGAGAAGC
AGAGACTGCGAGAGCACCTGCCTTACATCTGCAAGAAGTACCTGAACCACA
TCGACCACGAGATCGTGGAAGGACGCCTGGAAGTACTACGCCACACACTG
CGAGtccggaACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCACCATCG
CGTCGACGCCCTGTCCCTGCGCCAGAGGCGTGCCGGCCAGCGGCGGGGGGC
 15 GCAGTGCACACGAGGGGGCTGGACTTCGCTGTGATATCTACATCTGGGCGCC
CTTGGCCGGGACTTGTGGGGTCCTTCTCCTGTCACTGGTTATCACCCTTT
ACTGCAAAACGGGGCAGAAAGAACTCCTGTATATATTCAAACAACCATTAT
GAGACCAGTACAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTC
GAAGAAGAAGAAGGAGGATGTGAACTGAGAGTGAAGTTCAGCAGGAGCGCA
 20 GACGCCCCCGCGTACAAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATC
TAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGACGTGGCCGGGACC
CTGAGATGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACA
ATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGA
AAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCA
 25 GTACAGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCC
TCGCTAA

30 **Amino acid sequence of 4026 pTRPE. CysR-FNII-CTLD1.CD8H.BBz CAAR**
(construct 4026.CF1) (SEQ ID NO: 40)

35 ***PLA2R Signal peptide*** 1-20
CysR-FNII-CTLD1 40-381 (SEQ ID NO: 63)
CD8 Hinge region 384-428 (SEQ ID NO: 43)
CD8 TMD 429-452 (SEQ ID NO: 19)
4-1BB intracellular domain 453-494 (SEQ ID NO: 21)
CD3zeta intracellular domain 495-606 (SEQ ID NO: 23)

40 MLLSPSLLLLLLLGAPRGCAGSEGVAALTPERLLEWQDKGIFVIQSESLKKCIQA
GKSVLTLENCKQANKHMLWKWVSNHGLFNIGSGCLGLNFSAPQPLSLYECD
STLVSLRWRCNRKMITGPLQYSVQVAHDNTVVASRKYIHKWISYSGGGDICEY
LHKDLHTIKGNTHGMPMPFQYNHQQWHHECTREGREDDLLWCATTSTRYERDE
KWGFCPDPTSAEVGCDTIWEKDLNSHICYQFNLLSSLWSSEAHSSCQMGGTLL
 45 SITDETEENFIREHMSSKTVEVWMGLNQLDEHAGWQWSDGTPLNYLNWSPEVN
FEPFVEDHCGTFSSFMPSAWRSRDCESTLPYICKKYLNHIDHEIVEKDAWKYYAT
HCESGTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLA

GTCGVLLLLSLVITLYCKRGRKLLYIFKOPFMRPVOTTOEEDGCSCRFPEEEEEG
GCELRVKFSRSADAPAYKOGONQLYNELNLGRREEYDVLDRRRGRDPEMGGKP
RRKNPQEGLYNELOKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTY
DALHMQALPPR

5

>BC144631.1 Homo sapiens phospholipase A2 receptor 1, 180kDa, mRNA (cDNA clone MGC:178179 IMAGE:9053162), complete cds (SEQ ID NO: 41)

CCGGAGAGCCCAGTGGTTAGCGATGCTGCTGTGCGCCGTGCTGCTGCTGCTGCTGCTGGGGGCGCCG
 CGGGGCTGCGCCGAGGGTGTGGCGGCGGCGCTTACCCCCGAGCGGCTCCTGGAGTGGCAGGATAAAGGAA
 10 TATTTGTTATCCAAAGTGAGAGTCTCAAGAAATGCATTCAAGCAGGTAAATCGGTTCTGACCCTGGAGAA
 CTGCAAGCAAGCAAACAAGCACATGCTGTGGAAATGGGTTTCAAACCATGGCCTCTTTAACATAGGAGGC
 AGCGGTTGCCTGGGCTGAATTTCTCCGCCCCAGAGCAGCCATTAAGCTTATATGAATGTGACTCCACCC
 TCGTTTCCTTACGGTGGCGCTGTAACAGGAAGATGATCACAGGCCCGCTGCAGTACTCTGTCCAGGTGGC
 15 GCATGACAACACAGTGGTGGCCTCACGGAAGTATATTCTAAGTGGATTTCTTATGGGTGAGGTGGTGGGA
 GACATTTGTGAATATCTACACAAAGATTTGCATACAATCAAAGGGAACACCCACGGGATGCCGTGTATGT
 TTCCCTTCCAGTATAACCATCAGTGGCATCATGAATGTACCCGTGAAGGTCGGGAAGATGACTTACTGTG
 GTGTGCCACGACAAGCCGTATGAAAGAGATGAAAAGTGGGGATTTTGCCCTGATCCCACCTCTGCAGAA
 GTAGGTTGTGATACTATTTGGGAGAAGGACCTCAATTACACATTTGCTACCAGTTCAACCTGCTTTCAT
 20 CTCTCTCTTGGAGTGAGGCACATTCTTCATGCCAGATGCAAGGAGGTACGCTGTTAAGTATTACAGATGA
 AACTGAAGAAAATTTCTAAGGGAGCACATGAGCAGTAAACAGTGGAGGTGTGGATGGGCCTCAATCAG
 CTGGATGAACACGCTGGCTGGCAGTGGTCTGATGGAACGCCGCTCAACTATCTGAATTGGAGCCAGAGG
 TAAATTTTGAGCCATTTGTTGAAGATCACTGTGGAACATTTAGTTCATTTATGCCAAGTGCCTGGAGGAG
 TCGGGATTGTGAGTCCACCTTGCCATATATATGTAAAAAATATCTAAACCACATTGATCATGAAATAGTT
 25 GAAAAAGATGCGTGGAATATTATGCTACCCACTGTGAGCCTGGCTGGAATCCCTACAATCGTAATTGCT
 ACAAACCTTCAGAAAGAAGAAAAGACCTGGCATGAGGCTCTGCGTTCTTGTGAGGCTGATAACAGTGCATT
 AATAGACATAACCTCATTAGCAGAGGTGGAGTTTCTTGTAAACCTCCTTGGAGATGAAAATGCATCAGAA
 ACATGGATTGGTTTGAGCAGCAATAAAATTCAGTTTCTTTGAATGGTCTAATGACTCTTCAGTCATCT
 TTACTAATTGGCACACACTTGAGCCCCACATTTTTTCAAATAGAAGCCAGCTGTGTGTCTCAGCAGAGCA
 30 GTCTGAGGGACACTGGAAAGTCAAAAATTGTGAAGAAAGACTTTTTTACATTTGTAAAAAAGCAGGCCAT
 GTCCTCTCTGATGCTGAATCAGGATGTCAAGAGGGATGGGAGAGACATGGTGGATTCTGTTACAAAATTG
 ACACAGTCCCTCGAAGCTTTGACCAAGCTTCAGCGGTTATTACTGTCTCCTGCACTTGTAACCATTAC
 AAACAGGTTTGAACAGGCTTTTATTACCAGTTTGATCAGTAGTGTGGTAAAAATGAAGGACAGTTATTTT
 TGGATAGCTCTTCAGGACCAAAAATGATACGGGAGAATACACTTGGAAGCCAGTAGGGCAGAAACCCGAGC
 35 CGGTGCAGTACACACACTGGAACACACACCAGCCGCGCTACAGTGGTGGCTGTGTTGCCATGCGAGGAAG
 GCATCCACTTGGTCGCTGGGAAGTGAAGCACTGTGCGCACTTTAAGGCAATGTCCTTGTGCAAGCAGCCA
 GTTGAAGATCAGGAAAAAGCAGAGTATGAAGAGAGATGGCCCTTTCACCCCTGCTATTTGGACTGGGAGT
 CAGAGCCTGGTCTGGCCAGTTGCTTCAAGGTATTTCTAAGTGAAGAAAGTTCTGATGAAAAGAACATGGAG
 AGAAGCTGAAGCATTTTTCGAAGAATTTGGAGCTCATCTTGCAAGCTTTGCCCATATTGAGGAAGAGAAT
 40 TTTGTGAATGAGCTCTTACATTCAAAATTTAATTGGACAGAAGAAAGGCAGTTCTGGATTGGATTAAATA
 AAAGAAACCCACTGAATGCCGGCTCATGGGAGTGGTCTGATAGAACTCCTGTTGTCTCTTCGTTTTTGA
 CAACACTTATTTTGGAGAAGATGCAAGAACTGTGCTGTTTATAAGGCAAACAAAACATTGCTGCCCTTA
 CACTGTGGTTCCAAACGTGAATGGATATGCAAAATCCCAAGAGATGTGAAACCCAAGATTCCGTTCTGGT
 ACCAGTACGATGTACCCTGGCTCTTTTATCAGGATGCAGAATACCTTTTTTCATACCTTTGCCCTCAGAA
 45 GTTGAACCTTGAGTTGTCTGTAGCTGGCTGCACAGTGATCTTCTCACAATTCATTCTGCACATGAGCAA
 GAATTCATCCACAGCAAAAATAAAGCGCTATCAAAGTATGGTGCAAGTTGGTGGATTGGACTTCAAGAAG
 AAAGAGCCAATGATGAATTTTCGCTGGAGAGATGGAACACCAGTGATATACCAGAACTGGGACACAGGAAG
 AGAAAGAACTGTGAATAATCAGAGCCAGAGATGTGGCTTTATTTCTTCTATAACAGGACTCTGGGGTAGT
 GAAGAGTGTTCAGTTTCTATGCCTAGTATCTGTAAGCGAAAAAAGGTTTGGCTCATAGAGAAAAAGAAAG
 ATACACCAAAAACATGGAACGTGTCCCAAAGGATGGCTATATTTTAACTATAAGTGCCTTCTGCTGAA

TATCCCCAAAGACCCAAGCAGTTGGAAGAACTGGACGCATGCTCAACATTTCTGTGCTGAAGAAGGGGGG
 ACCCTGGTCGCCATTGAAAGTGAGGTGGAGCAAGCTTTCATTACTATGAATCTTTTTGGCCAGACCACCA
 GTGTGTGGATAGGTTTACAAAATGATGATTATGAAACATGGCTAAATGGAAAGCCTGTGGTATATCTAA
 CTGGTCTCCATTTGATATAATAAATATTCCAAGTCACAATACCACTGAAGTTCAGAAACACATTCTCTC
 5 TGTGCCTTACTCTCAAGTAATCCTAATTTTCATTTCACTGGAAAATGGTATTTTGAAGACTGTGGAAGG
 AAGGCTATGGGTTTGTGTGAAAAAATGCAAGATACTTCTGGACACGGTGTAATACATCTGATATGTA
 TCCAATGCCCAATACCTTAGAATATGGAAACAGAACTTACAAAATAATTAATGCAATATGACTTGGTAT
 GCAGCAATAAAAACTGCCTGATGCACAAAGCACAACCTGGTCAGCATCACAGACCAGTATCACCAGTCCT
 10 TCCTCACTGTTGTCTCAACCGGCTAGGATATGCCCACTGGATTGGACTGTTCAACACAGATAATGGTCT
 TAATTTTGAAGTGGTCTGATGGCACCAAATCTTCTTTCATTTTGGAAAGATGAGGAGTCTCTCCCTCCTT
 GGTGACTGCGTTTTTGGCGACAGCAACGGACGCTGGCATAGCACAGCCTGCGAGTCATTTCTGCAAGGTG
 CCATTTGTGATGTGCCACCTGAAACAAGACAATCTGAACACCCAGAGTTGTGCTCAGAAACATCTATTCC
 CTGGATAAAATTTAAAAAGTAATTGCTACAGTTTTTCTACAGTCTTAGACAGTATGAGTTTTGAGGCTGCT
 CATGAATTTTGCAAAAAGGAAGGTTCTAATCTTTTAACAATCAAGGATGAGGCTGAAAATGCATTTCTCC
 15 TAGAAGAGCTGTTTGGTTCTTCTGTCCAGATGGTTTGGTTGAATGCTCAATTTGATGATGAAAC
 CATAAAGTGGTTTGTGGAACCTCCACAGACCAGTCAAACCTGGGGCATTGCGAAGCCAGACACAGACTAC
 TTCAAGCCCCATCATTGTGTTGCCTTGAGGATCCCTGAAGGATTATGGCAGCTATCCCCGTGTCAAGAAA
 AAAAGGCTTTATATGTAAAATGGAGGCAGATATTCACACTGCAGAGGCGCTGCCAGAAAAAGGACCAAG
 20 TCACAGCATCATTCTCTTGCCTTGTACTGACACTGATAGTCATTGTGGCCATTTGCACACTTCTCTC
 TGCATATACAAGCATAACGGTGGCTTCTTCAGGAGACTTGCAGGGTTTCGGAATCCTTACTATCCTGCAA
 CCAACTTTAGTACAGTATATTTAGAAGAAAATATTCTCATTTCTGATCTTGAGAAGAGTGACCAATAATA
 ATGAGGTCAGAGAATGCCACAGACACCAGG

- Production of HIV-1 based self-inactivating lentivirus

25 293T cells were transfected at a confluence of 90% with a mixture of the pTRPE-
 gene-of-interest, the packaging plasmid pGAG-Pol and pRSV-Rev and the envelope
 plasmid pCI VSVg in a complex with Lipofectamine 2000. Lentivirus containing
 supernatant was harvested after 24 and 48 hours, filtered through a 0.45 micron
 polyethersulfone (PES) membrane, concentrated at 12,000×g for 24 hours at 4°C, and
 30 stored at -80°C.

- Stimulation, transduction, and expansion of primary human T cells.

Primary human T cells were cultured in CTS OpTmizer T cell expansion SFM
 with 5% HSAB, 2.6% supplement, 1% penicillin/streptomycin and 1% glutamax. Bulk T
 35 cells (CD4⁺ and CD8⁺) were stimulated with anti-CD3 and anti-CD28 beads at a
 bead:cell ratio of 3:1. The culture medium was supplemented with 100 IU/ml interleukin
 2. 24 hours after stimulation, 10⁶ T cells were transduced with CAAR or mock
 transduced. Expansion of the T cells were monitored for 8-12 days. Cell surface
 expression of the CAAR constructs was validated by flow cytometry with IgG purified

from the plasma of a patient with primary membranous nephropathy and isotype control antibody.

- Reporter assay with NFAT-GFP Jurkat T cells

Jurkat cells were cultured at 37°C with 5% CO₂ in a completely humidified environment using RPMI1640, HEPES 10mM, and FBS at 10%. To test signal transduction by CAAR-target interaction, the CAAR constructs were expressed in a Jurkat reporter cell line that has been selected (G418) for stable expression of GFP controlled under an NFAT response element, facilitating GFP expression after CAAR engagement and PLCgamma and IP₃ mediated intracellular calcium release. Jurkat cells were transduced with CAAR lentivirus at a multiplicity of infection of 3 and expression of the CAAR construct was validated after >72 hours with an anti-PLA2R monoclonal antibody (Novus Biologicals[®]) and IgG purified from the plasma of a patient with primary membranous nephropathy by flow cytometry. For characterization of CAAR-target interaction, the CAAR Jurkat cells were incubated at 37°C for 6 hours with plate-bound anti-PLA2R monoclonal as below. GFP expression was validated by flow cytometry.

- Stimulation

1 million Jurkat-NFAT-GFP cells were transduced with each lentivirus encoding for PLA2R CAAR construct C, CF1, CF123, CF1237, CD17, C17, 4025.C, 4026.CF1, 4027.CF12, 4028.CF123 and untransduced Jurkat cells were used as negative control. Transduced and untransduced cells were plated in a 96-well plate at 2x10⁵ cells/well in 100 µl cell culture medium.

The stimulation conditions were as follows:

- Novus monoclonal antibody (mAb) anti-PLA2R either 0.5 µg/well or 1 µg/well; Clone 12-6-5
- Sigma polyclonal antibody anti-PLA2R 0.5 µg/well;
- Isotype antibody for Novus mAb anti-PLA2R (0.5 µg/stain)
- medium only (no stimulation)
- PMA/Ionomycin (maximum activation)

Or, transduced and untransduced cells were plated in a 96-well plate at 5×10^4 cells/well in 100 μ l cell culture medium.

Cells and antibodies were incubated at 37°C for 6 hours. At the end of the 6 h, cells were examined by flow cytometry for expression of NFAT-GFP as an indicator of T cell activation.

- In vitro IFN γ cytokine assay

PLA2R CAAR or mock transduced primary human T cells were cultured for 24h at 5×10^4 /well in a 96-well plate coated with 10 μ g/ml either IgG purified from plasma of patient with primary membranous nephropathy or control human IgG. Culture supernatants were then harvested for detection of IFN- γ by ELISA.

- In vivo efficacy testing of CAAR T cells

To test the *in vivo* efficacy, anti-PLA2R BCR-expressing cells, for example hybridoma cells or human cell lines, targeting human PLA2R are generated. PLA2R BCR-expressing cells are transduced with lentiviral vectors expressing click-beetle green or click-beetle red luciferase and GFP. To test the efficacy of CAAR-T cells against the PLA2R-specific target cells, approximately 2×10^5 anti-PLA2R cells are injected intravenously into NSG mice (age 6-8 weeks), after pre-treatment of mice daily for 2 days with 600 mg/kg intravenous immunoglobulin to minimize Fc γ R-mediated toxicity against BCR-expressing cells. After 4-5 days, PLA2R CAAR T cells (approximately 10^7 cells per mouse) are injected intravenously. Bioluminescence and/or serum autoantibodies are quantified every 2-3 days after injection to monitor CAAR T cell efficacy.

The results of the experiments are now described.

Example 1:

Four PLA2R constructs representing different domains of the PLA2R were cloned into a CAAR expression system (4025.C, 4026.CF1, Construct 4027.CF12 and 4028.CF123). The general schematics of the extracellular domains of PLA2R of particular interest in the invention are illustrated in Figure 1. The N terminal domain is an

immunodominant epitope that is recognized by patient serum antibodies. The CysR and CTLD3 domain interact to form a ring-like structure that may better present immunodominant epitopes; hence constructs including the CysR through CTLD3 domains were generated. In addition to the cysteine-rich domain, serum antibody immunoreactivity to the C-type lectin domains 1 and 7 has also been reported.

The PLA2R CAAR constructs illustrated in Figures 2A-2G. All constructs use the CD8 transmembrane domain and BBZ intracellular domain and differ in their extracellular composition.

Construct 4025.C was comprised of a cysteine rich extracellular domain, a CD8 hinge region, a CD8 transmembrane domain, a 4-1BB intracellular domain and CD3 zeta signaling domain (Figure 2A, SEQ ID NOs: 37 & 38).

Construct 4026.CF1 was comprised of an extracellular domain comprising a cysteine rich domain, a fibronectin II domain, and a C-type lectin 1 domain. Construct 4026.CF1 also included a CD8 hinge region, a CD8 transmembrane domain, a 4-1BB intracellular domain and CD3 zeta signaling domain (Figure 2B, SEQ ID NOs: 39 & 40).

Construct 4027.CF12 was comprised of an extracellular domain comprising a cysteine rich domain, a fibronectin II domain, a C-type lectin 1 domain, and a C-type lectin 2 domain. Construct 4027.CF12 also included a CD8 hinge region, a CD8 transmembrane domain, a 4-1BB intracellular domain and CD3 zeta signaling domain (Figure 2C, SEQ ID NOs: 11 & 12).

Construct 4028.CF123 was comprised of an extracellular domain comprising a cysteine rich domain, a fibronectin II domain, a C-type lectin 1 domain, a C-type lectin 2 domain, and a C-type lectin 3 domain. Construct 4028.CF123 also included a CD8 hinge region, a CD8 transmembrane domain, a 4-1BB intracellular domain and CD3 zeta signaling domain (Figure 2D, SEQ ID NOs: 17 & 18). A detailed map of PLA2R CAAR Construct 4028.CF123 is shown in Figure 3A.

To test whether the CAAR molecules were functional, the following experiments were conducted:

1 million Jurkat-NFAT-GFP cells were transduced with each lentivirus encoding for 4025.C, 4027.CF12, 4028.CF123 and untransduced Jurkat cells were used as negative control. Transduced and untransduced cells were plated in a 96-well plate at 2×10^5

cells/well in 100 ul cell culture medium. Figure 4 shows the PLA2R CAAR expression. The expression of PLA2R CAAR by Jurkat NFAT-GFP cells transduced with different PLA2R lentiviral constructs was measured by staining with soluble anti-PLA2R monoclonal antibody conjugated to PE. Jurkat T cells bearing construct 4027.CF12 or 4028.CF123, but not those T cells bearing construct 4025.C, which does not include the CTLD2 domain and hence is not detectable by the mAb used, exhibited detectable surface expression of the CAAR.

Figures 5 and 6 show T cell activation by GFP expression of Jurkat cells transduced with the indicated constructs. Negative and positive controls are shown in Figure 5. Test samples are shown in Figure 6.

Cells and antibodies were incubated at 37°C for 6 hours. At the end of the 6 h, cells were examined for expression of NFAT-GFP as an indicator of T cell activation.

Figure 5 depicts the negative and positive controls for PLA2R CAAR T cell activation using an isotype control (top, negative control) or PMA+ionomycin (bottom, positive control).

Figure 6 illustrates the activation of PLA2R CAAR T cells by specific antibodies measured as GFP expression by Jurkat NFAT-GFP cells (6h activation). No evidence of T cell activation is seen in construct 4025.C and untransduced cells upon exposure to the monoclonal anti-PLA2R Mab or the polyclonal anti-PLA2R Ab. Specific T cell activation in response to cross-linking by the monoclonal anti-PLA2R Ab but not the polyclonal anti-PLA2R Ab is seen using constructs 4027.CF12 and 4028.CF123.

Example 2:

Six additional PLA2R CAAR constructs were designed and generated herein. Construct C was comprised of a cysteine rich domain, a CD8 hinge region, a CD8 transmembrane domain, a 4-1BB intracellular domain and CD3 zeta signaling domain (Figure 2A, SEQ ID NOs: 25 & 26).

Construct CF1 was comprised of an extracellular domain comprising a cysteine rich domain, a fibronectin II domain, and a C-type lectin 1 domain. Construct CF1 also included a CD8 hinge region, a CD8 transmembrane domain, a 4-1BB intracellular domain and CD3 zeta signaling domain (Figure 2B, SEQ ID NOs: 27 & 28).

Construct CF123 was comprised of an extracellular domain comprising a cysteine rich domain, a fibronectin II domain, a C-type lectin 1 domain, a C-type lectin 2 domain, and a C-type lectin 3 domain. Also included in construct CF123 was a GS linker, a CD8 transmembrane domain, a 4-1BB intracellular domain and CD3 zeta signaling domain (Figure 2C, SEQ ID NOs: 29 & 30).

Construct CF1237 was comprised of an extracellular domain comprising a cysteine rich domain, a fibronectin II domain, a C-type lectin 1 domain, a C-type lectin 2 domain, a C-type lectin 3 domain and a C-type lectin 7 domain. Additionally included in construct CF1237 was a GS linker, a CD8 transmembrane domain, a 4-1BB intracellular domain and CD3 zeta signaling domain (Figure 2D, SEQ ID NOs: 31 & 32).

Construct CF17 was comprised of an extracellular domain comprising a cysteine rich domain, a fibronectin II domain, a C-type lectin 1 domain, and a C-type lectin 7 domain. Construct CF17 also included a GS linker, a CD8 transmembrane domain, a 4-1BB intracellular domain and CD3 zeta signaling domain (Figure 7E, SEQ ID NOs: 33 & 34).

Construct C17 was comprised of an extracellular domain comprising a cysteine rich domain, a C-type lectin 1 domain, and a C-type lectin 7 domain. Construct C17 also included a GS linker, a CD8 transmembrane domain, a 4-1BB intracellular domain and CD3 zeta signaling domain (Figure 7F, SEQ ID NOs: 35 & 36).

The various PLA2R CAAR constructs were transduced into Jurkat cells and primary human T cells. Surface expression of the PLA2R CAARs was assessed by flow cytometry using MN patient IgG, followed by APC-labeled anti-human IgG secondary antibody. All of the transduced Jurkat (Figure 7A) and primary human T cells (Figure 7B), but not the untransduced control cells, exhibited detectable surface expression of the CAAR constructs.

To evaluate whether plate-bound anti-PLA2R IgG, which mimics the surface of an anti-PLA2R B cell, can lead to CAAR T cell activation, 5×10^4 Jurkat NFAT-GFP reporter cells were cultured for 6h in 96-well plate coated with 10 μ g/ml either MN patient IgG or control human IgG. Cells were then harvested for flow cytometry analysis. MN patient IgG, but not control human IgG activated Jurkat cells transduced with each of the 10 constructs (Figure 8). No evidence of T cell activation was seen in untransduced

Jurkat cells upon exposure to either MN patient IgG or control human IgG (Figure 8). These studies indicate that CAAR signaling is activated upon target encounter.

To evaluate whether primary human PLA2R CAAR T cells can be activated by plate-bound anti-PLA2R IgG, PLA2R CAAR T cells were exposed to either plate-bound MN patient IgG or control human IgG for 24h. IFN- γ secretion was measured by ELISA of culture supernatants. MN patient IgG stimulated markedly higher IFN- γ production compared to the control human IgG, reflecting primary human CAAR T cell activation after target engagement (Figure 9).

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

CLAIMS

What is claimed:

1. A polynucleotide encoding a chimeric autoantibody receptor (CAAR), wherein the CAAR comprises a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, and optionally, a transmembrane domain, an intracellular domain of a costimulatory molecule, and/or a signaling domain.
2. The polynucleotide of claim 1, wherein the PLA2R autoantigen or fragment thereof is selected from the group consisting of:
 - (a) an extracellular domain comprising a CysR or ricin B type lectin domain, a fibronectin type II domain, a C-type lectin domain 1 and a C-type lectin domain 2; and,
 - (b) an extracellular domain comprising a CysR or ricin B type lectin domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2 and a C-type lectin domain 3.
3. The polynucleotide of claim 2, wherein
 - the PLA2R extracellular domain (a) is encoded by a nucleic acid sequence comprising SEQ ID NO: 8, or
 - the PLA2R extracellular domain (b) is encoded by a nucleic acid sequence comprising SEQ ID NO: 15.
4. The polynucleotide of claim 1, wherein the PLA2R autoantigen or fragment thereof is selected from the group consisting of:
 - (a) an extracellular domain comprising a cysteine rich domain,
 - (b) an extracellular domain comprising a cysteine rich domain, a fibronectin type II domain, and a C-type lectin domain 1,
 - (c) an extracellular domain comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2, and a C-type lectin domain 3,

- (d) an extracellular domain comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2, a C-type lectin domain 3, and a C-type lectin domain 7,
 - (e) an extracellular domain comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, and a C-type lectin domain 7, and
 - (f) an extracellular domain comprising a cysteine rich domain, a C-type lectin domain 1, and a C-type lectin domain 7.
- 5. The polynucleotide of claim 4, wherein
 - the PLA2R extracellular domain (a) is encoded by a nucleic acid sequence comprising SEQ ID NO: 47 or SEQ ID NO: 60,
 - the PLA2R extracellular domain (b) is encoded by a nucleic acid sequence comprising SEQ ID NO: 50 or SEQ ID NO: 62,
 - the PLA2R extracellular domain (c) is encoded by a nucleic acid sequence comprising SEQ ID NO: 52,
 - the PLA2R extracellular domain (d) is encoded by a nucleic acid sequence comprising SEQ ID NO: 54,
 - the PLA2R extracellular domain (e) is encoded by a nucleic acid sequence comprising SEQ ID NO: 56, or
 - the PLA2R extracellular domain (f) is encoded by a nucleic acid sequence comprising SEQ ID NO: 58.
- 6. The polynucleotide of any one of claims 1-5, wherein the transmembrane domain comprises a CD8 alpha chain transmembrane domain.
- 7. The polynucleotide of claim 6, wherein the CD8 alpha chain transmembrane domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 20.
- 8. The polynucleotide of claim 6, wherein the CD8 alpha chain transmembrane domain comprises the amino acid sequence of SEQ ID NO: 19.

9. The polynucleotide of any one of claims 1-8, wherein the CAAR further comprises a hinge domain.
10. The polynucleotide of claim 9, wherein the hinge domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 10 or SEQ ID NO: 42 or SEQ ID NO: 64.
11. The polynucleotide of claim 9, wherein the hinge domain comprises the amino acid sequence of SEQ ID NO: 43 or SEQ ID NO: 44.
12. The polynucleotide of any one of claims 1-8, wherein the CAAR further comprises a GS linker.
13. The polynucleotide of claim 11, wherein the GS linker is encoded by a nucleic acid sequence comprising SEQ ID NO: 68.
14. The polynucleotide of claim 11, wherein the GS linker comprises SEQ ID NO: 69.
15. The polynucleotide of any one of claims 1-14, wherein the intracellular domain of a costimulatory molecule comprises 4-1BB.
16. The polynucleotide of claim 15, wherein the 4-1BB intracellular domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 22 or SEQ ID NO: 66.
17. The polynucleotide of claim 15, wherein the 4-1BB intracellular domain comprises the amino acid sequence of SEQ ID NO: 21.
18. The polynucleotide of any one of claims 1-17, wherein the signaling domain comprises a CD3 zeta signaling domain.
19. The polynucleotide of claim 18, wherein the CD3 zeta signaling domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 24 or SEQ ID NO: 72.

20. The polynucleotide of claim 18, wherein the CD3 zeta signaling domain comprises an amino acid sequence of SEQ ID NO: 23 or SEQ ID NO: 45.
21. The polynucleotide of any one of claims 1-20, wherein the CAAR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 11, 17, 25, 27, 29, 31, 33, 35, 37, and 39.
22. The polynucleotide of any one of claims 1-20, wherein the CAAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 18, 26, 28, 30, 32, 34, 36, 38, and 40.
23. The polynucleotide of any one of claims 1-5, wherein the CAAR comprises a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, a killer immunoglobulin-like receptor (KIR) transmembrane domain and a KIR cytoplasmic domain.
24. A vector comprising the polynucleotide of any one of claims 1-23.
25. The vector of claim 24, wherein the vector is a lentiviral vector.
26. The vector of claim 24, wherein the vector is a RNA vector.
27. A chimeric autoantibody receptor (CAAR) comprising an extracellular domain comprising a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof.
28. A chimeric autoantibody receptor (CAAR) comprising an extracellular domain comprising a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, and optionally, a transmembrane domain, an intracellular domain of a costimulatory molecule, and/or a signaling domain.
29. The CAAR of claim 27 or 28, wherein the PLA2R autoantigen or fragment thereof is selected from the group consisting of:

- (a) an extracellular domain comprising a ricin B type lectin domain, a fibronectin type II domain, a C-type lectin domain 1 and a C-type lectin domain 2; and,
 - (b) an extracellular domain comprising a ricin B type lectin domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2 and a C-type lectin domain 3.
- 30. The CAAR of claim 29, wherein
 - the PLA2R extracellular domain (a) is encoded by a nucleic acid sequence comprising SEQ ID NO: 8, or
 - the PLA2R extracellular domain (b) is encoded by a nucleic acid sequence comprising SEQ ID NO: 15.
- 31. The CAAR of claim 27 or 28, wherein the PLA2R autoantigen or fragment thereof is selected from the group consisting of:
 - (a) an extracellular domain comprising a cysteine rich domain,
 - (b) an extracellular domain comprising a cysteine rich domain, a fibronectin type II domain, and a C-type lectin domain 1,
 - (c) an extracellular domain comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2, a C-type lectin domain 3, and a C-type lectin domain 7,
 - (d) an extracellular domain comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, a C-type lectin domain 2, a C-type lectin domain 3, and a C-type lectin domain 7,
 - (e) an extracellular domain comprising a cysteine rich domain, a fibronectin type II domain, a C-type lectin domain 1, and a C-type lectin domain 7, and
 - (f) an extracellular domain comprising a cysteine rich domain, a C-type lectin domain 1, and a C-type lectin domain 7.
- 32. The CAAR of claim 31, wherein

the PLA2R extracellular domain (a) comprises SEQ ID NO: 49 or SEQ ID NO: 61,

the PLA2R extracellular domain (b) comprises the amino acid sequence of SEQ ID NO: 51 or SEQ ID NO: 63,

the PLA2R extracellular domain (c) comprises the amino acid sequence of SEQ ID NO: 53,

the PLA2R extracellular domain (d) comprises the amino acid sequence of SEQ ID NO: 55, or

the PLA2R extracellular domain (e) comprises the amino acid sequence of SEQ ID NO: 57, or

the PLA2R extracellular domain (f) comprises the amino acid sequence of SEQ ID NO: 59.

33. The CAAR of any one of claims 28-32, wherein the transmembrane domain comprises a CD8 alpha chain transmembrane domain.
34. The CAAR of claim 33, wherein the CD8 alpha chain transmembrane domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 20.
35. The CAAR of claim 33, wherein the CD8 alpha chain transmembrane domain comprises the amino acid sequence of SEQ ID NO: 19.
36. The CAAR of any one of claims 27-35, wherein the CAAR further comprises a hinge domain.
37. The CAAR of claim 36, wherein the hinge domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 10 or SEQ ID NO: 42 or SEQ ID NO: 64.
38. The CAAR of claim 36, wherein the hinge domain comprises the amino acid sequence of SEQ ID NO: SEQ ID NO: 43 or SEQ ID NO: 44.
39. The CAAR of any one of claims 27-35, wherein the CAAR further comprises a GS linker.

40. The CAAR of claim 39, wherein the GS linker is encoded by a nucleic acid sequence comprising SEQ ID NO: 68.
41. The CAAR of claim 39, wherein the GS linker comprises SEQ ID NO: 69.
42. The CAAR of any one of claims 28-41, wherein the intracellular domain of a costimulatory molecule comprises 4-1BB.
43. The CAAR of claim 42, wherein the 4-1BB intracellular domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 22 or SEQ ID NO: 66.
44. The CAAR of claim 42, wherein the 4-1BB intracellular domain comprises the amino acid sequence of SEQ ID NO: 21.
45. The CAAR of any one of claims 28-44, wherein the signaling domain comprises a CD3 zeta signaling domain.
46. The CAAR of claim 45, wherein the CD3 zeta signaling domain is encoded by a nucleic acid sequence comprising SEQ ID NO: 24 or SEQ ID NO: 72.
47. The CAAR of claim 45, wherein the CD3 zeta signaling domain comprises the amino acid sequence of SEQ ID NO: 23 or SEQ ID NO: 45.
48. The CAAR of any one of claims 28-47, wherein the CAAR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 11, 17, 25, 27, 29, 31, 33, 35, 37, and 39.
49. The CAAR of any one of claims 28-47, wherein the CAAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 18, 26, 28, 30, 32, 34, 36, 38, and 40.
50. The CAAR of any one of claims 27-32, wherein the CAAR comprises an extracellular domain comprising phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, a killer immunoglobulin-like receptor (KIR) transmembrane domain and a KIR cytoplasmic domain.

51. A genetically modified cell comprising the CAAR of any one of claims 27-50.
52. The cell of claim 51, wherein the cell expresses the CAAR and has high affinity to autoantibody-based BCRs on B cells.
53. The cell of claim 51 or 52, wherein the cell expresses the CAAR and induces killing of B cells expressing autoantibodies.
54. The cell of any one of claims 51-53, wherein the cell expresses the CAAR and has limited toxicity toward healthy cells.
55. The cell of any one of claims 51-54, wherein the cell is selected from the group consisting of a helper T cell, a cytotoxic T cell, a memory T cell, regulatory T cell, gamma delta T cell, a natural killer cell, a cytokine induced killer cell, a cell line thereof, a T memory stem cell, a T cell derived from a pluripotent stem and other effector cell.
56. A genetically modified cell comprising: (a) a chimeric autoantibody receptor (CAAR) comprising an extracellular domain comprising a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, a killer immunoglobulin-like receptor (KIR) transmembrane domain and a KIR cytoplasmic domain; and (b) DAP12.
57. A pharmaceutical composition comprising the polynucleotide of any one of claims 1-23, the CAAR of any one of claims 27-50 or the cell of any one of claims 51-57, and a pharmaceutically acceptable excipient.
58. A method for treating an autoantibody-mediated kidney disease in a subject, the method comprising: administering to the subject an effective amount of a genetically modified T cell comprising a polynucleotide encoding a chimeric autoantibody receptor (CAAR), wherein the polynucleotide encodes a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, and optionally, a transmembrane domain, an intracellular domain of a costimulatory

molecule, and/or a signaling domain, thereby treating the autoantibody mediated kidney disease in the subject.

59. A method for preventing or reducing glomerulus damage in a subject at risk of or suffering from an autoantibody-mediated kidney disease, the method comprising: administering to the subject an effective amount of a genetically modified T cell comprising a polynucleotide encoding a chimeric autoantibody receptor (CAAR), wherein the polynucleotide encodes a phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, and optionally a transmembrane domain, an intracellular domain of a costimulatory molecule, and/or a signaling domain, thereby preventing or reducing glomerulus damage in the subject.
60. The method of any one of claims 58-59, wherein the autoantibody mediated kidney disease is selected from the group consisting of a glomerular disease and a primary membranous nephropathy.
61. The method of any one of claims 58-60, wherein the subject is a human.
62. The method of any one of claims 58-61, wherein the modified T cell targets B cells.
63. A method for treating an autoantibody-mediated kidney disease in a subject, the method comprising: administering to the subject an effective amount of a genetically modified T cell comprising: (a) a polynucleotide encoding a chimeric autoantibody receptor (CAAR) comprising an extracellular domain comprising phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, a killer immunoglobulin-like receptor (KIR) transmembrane domain and a KIR cytoplasmic domain; and (b) a polynucleotide encoding DAP12, thereby treating the autoantibody-mediated kidney disease in the subject.
64. A method for preventing or reducing glomerulus damage in a subject at risk of or suffering from an autoantibody-mediated kidney disease, the method comprising: administering to the subject an effective amount of a genetically modified T cell comprising: (a) a polynucleotide encoding a chimeric autoantibody receptor

(CAAR) comprising an extracellular domain comprising phospholipase A2 receptor (PLA2R) autoantigen or fragment thereof, a killer immunoglobulin-like receptor (KIR) transmembrane domain and a KIR cytoplasmic domain; and (b) a polynucleotide encoding DAP12, thereby preventing or reducing glomerulus damage in the subject.

65. The method of any one of claims 58-64, wherein the polynucleotide is the polynucleotide of any one of claims 1-23.
66. The method of any one of claims 58-65, wherein the genetically modified cell is the cell of any one of claims 52-56.
67. The polynucleotide of claim 23, the CAAR of claim 50, the genetically modified cell of claim 56, or the method of claim 63 or 64, wherein the KIR is KIRS2 or KIR2DS2.
68. The vector of any one of claims 24-26, wherein the vector comprises an inducible promoter operably linked to the polynucleotide encoding the CAAR.
69. The cell of any one of claims 51-56, wherein the cell comprises a polynucleotide encoding the CAAR operably linked to an inducible promoter.

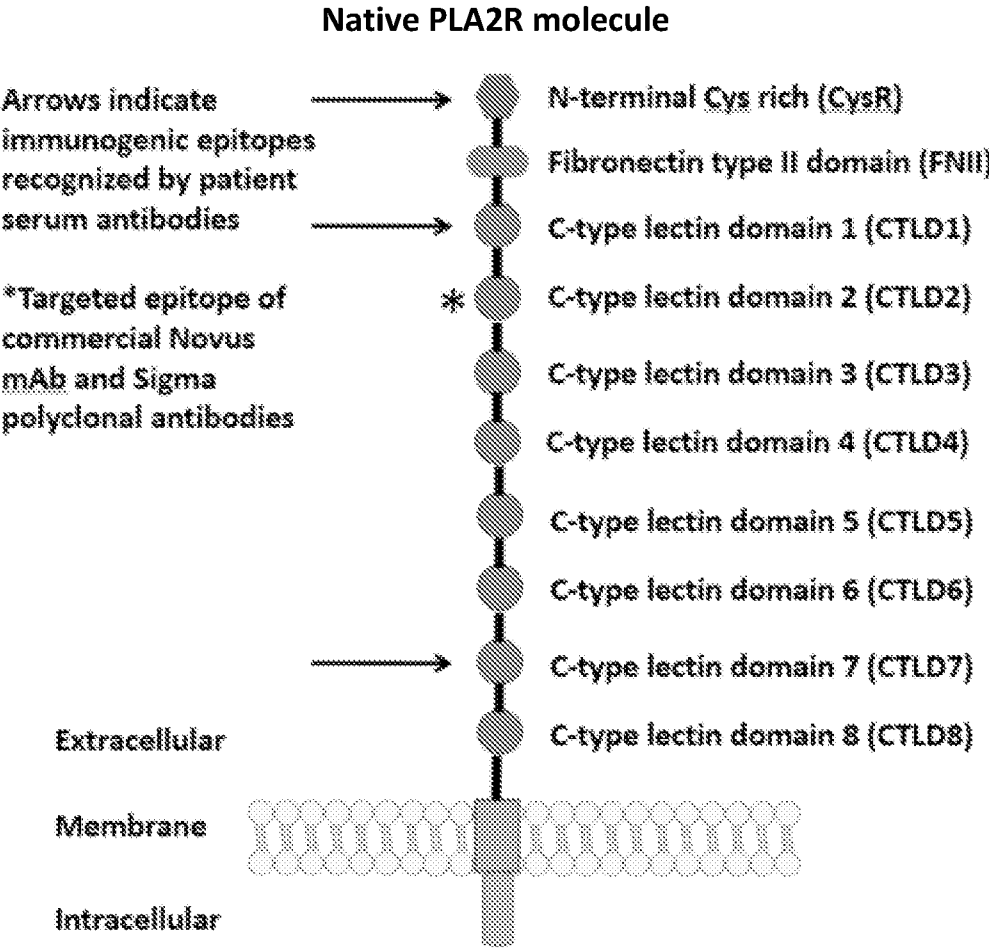


FIG. 1

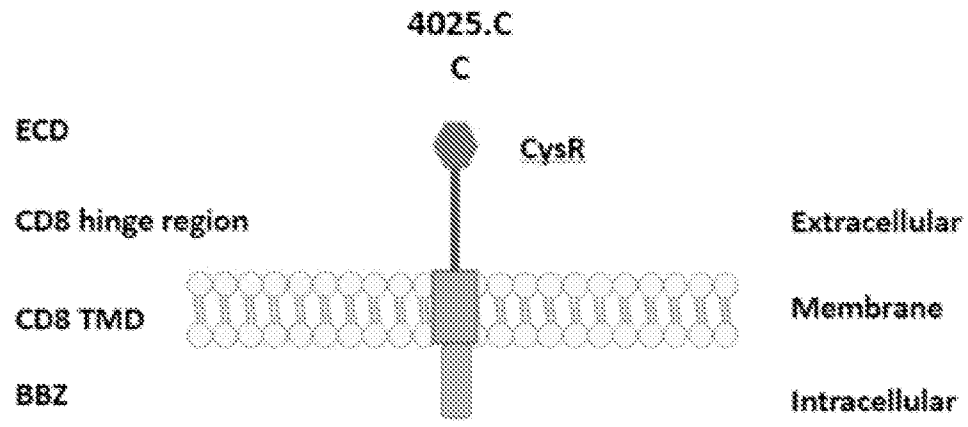


FIG. 2A

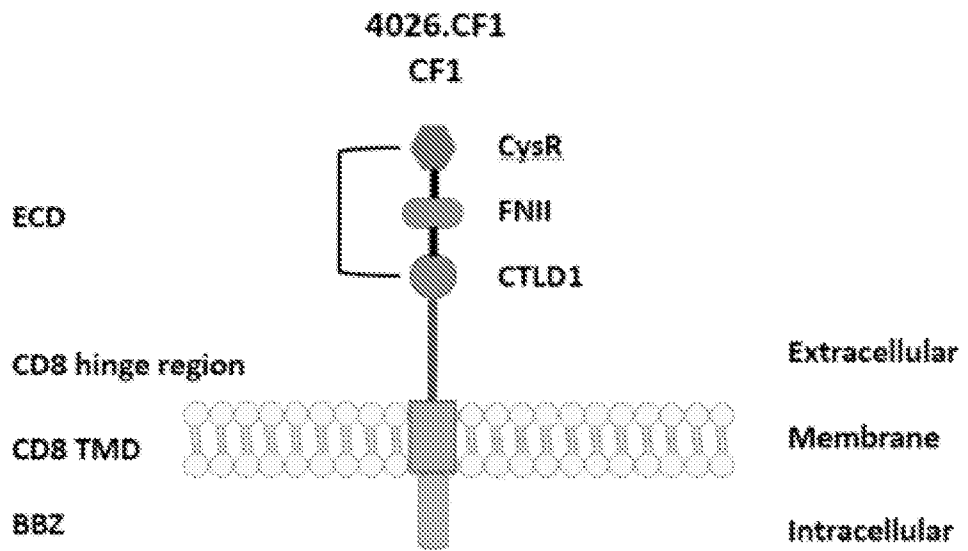


FIG. 2B

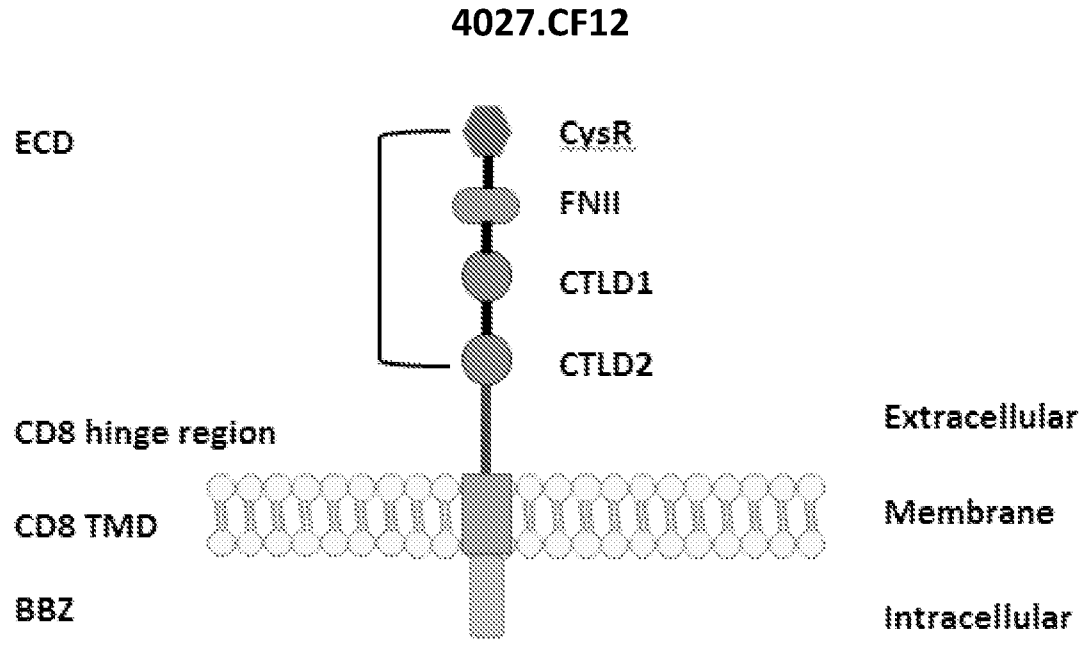


FIG. 2C

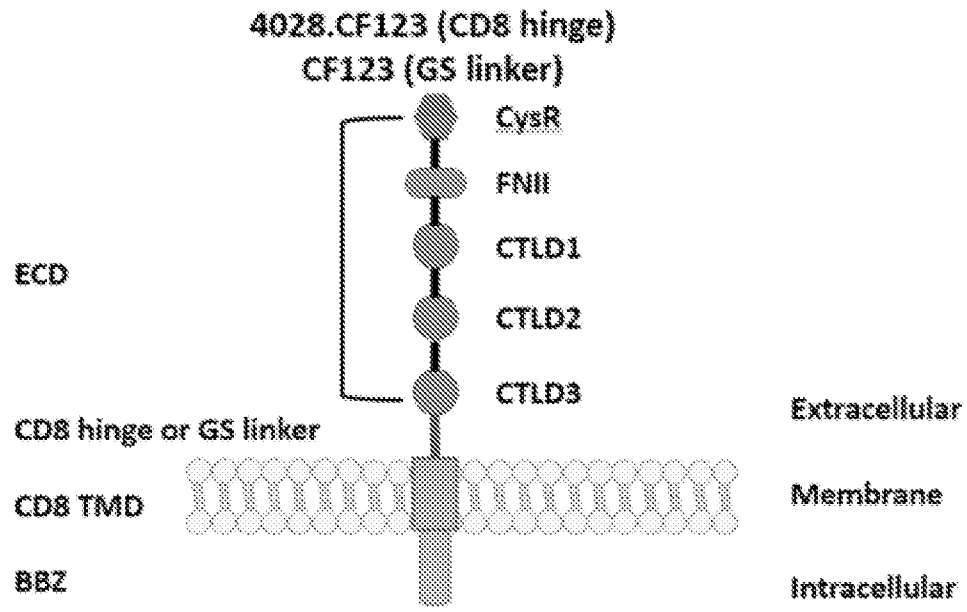


FIG. 2D

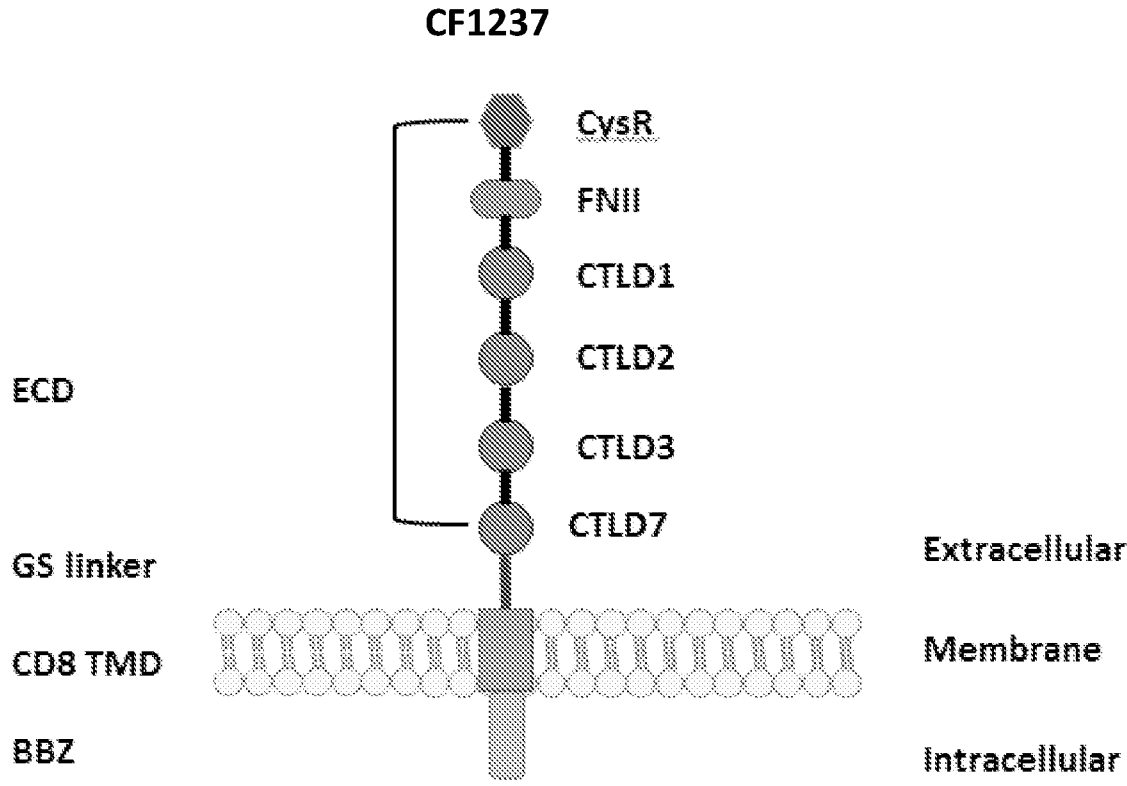


FIG. 2E

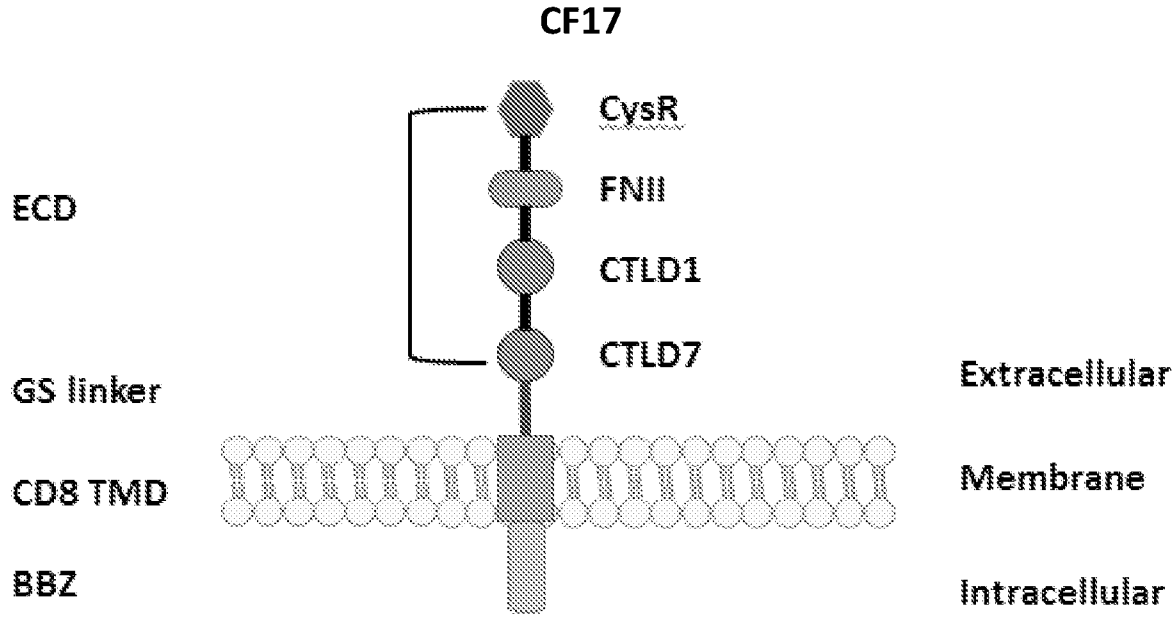


FIG. 2F

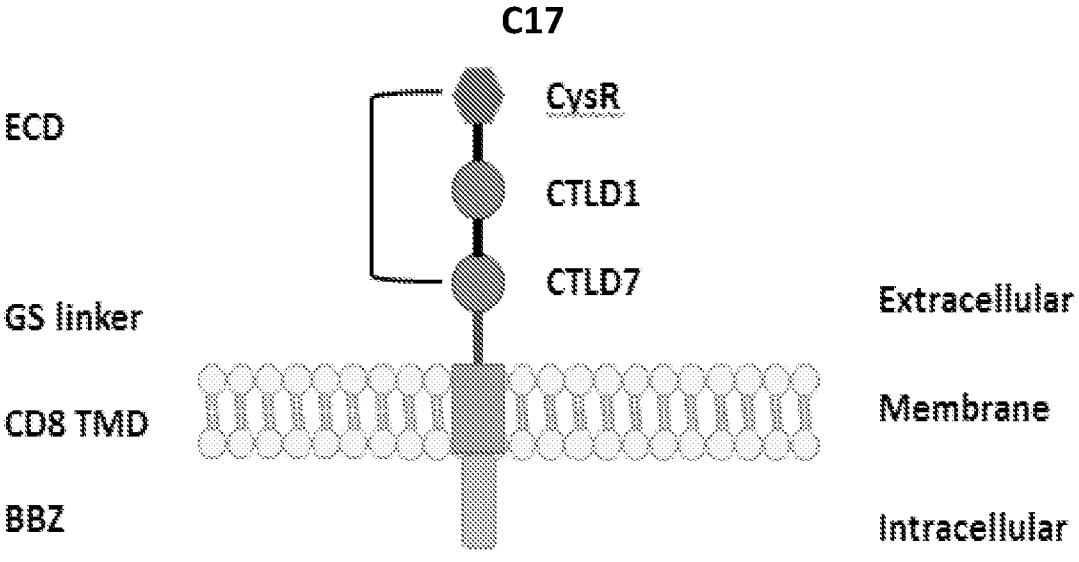


FIG. 2G

4028 pTRPE.CysR-FNII-CTLD1-3.CD8H.BBz CAAR
(4028.CF123)

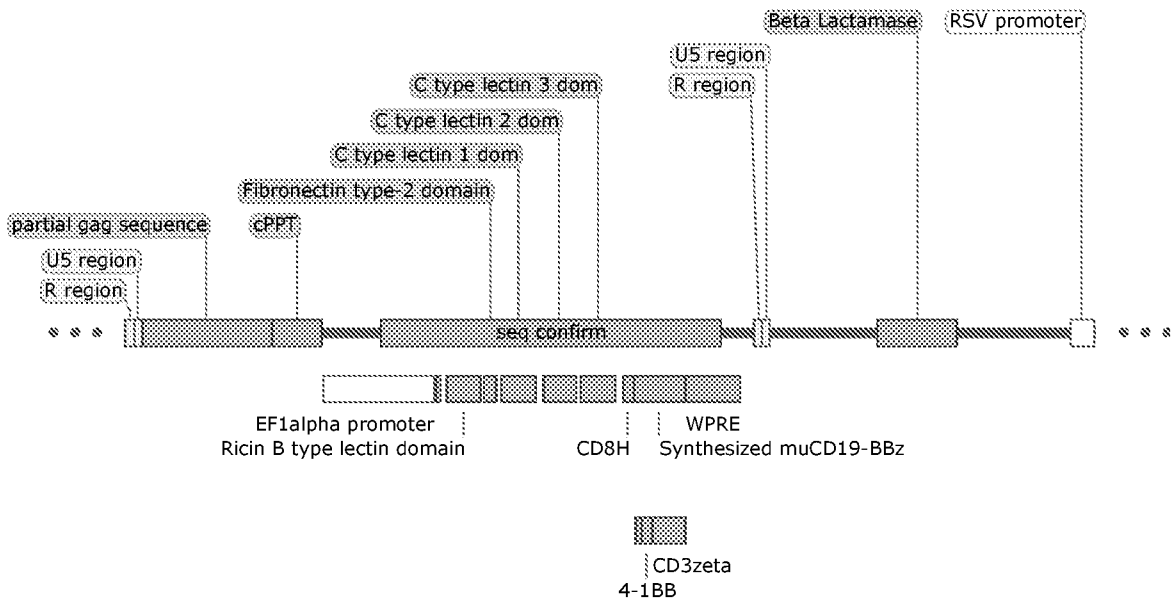


FIG. 3A

Construct name	Vector used	Signal sequence	Propeptide	Spacer	nt sequence (complete CAAR)	aa sequence (PLA2R domains only)
4025.C	pTRPE	native PLA2R	native PLA2R	CD8 hinge, aa 45	Codon optimized, length 1182	CysR aa 38-166
C	pTRPE	Ig	none	CD8 hinge, aa 55	Codon optimized, length 1167	CysR aa 38-169
4026.CF1	pTRPE	native PLA2R	native PLA2R	CD8 hinge, aa 45	Codon optimized, length 1821	CF1 aa 38-379
CF1	pTRPE	Ig	none	CD8 hinge, aa 55	Codon optimized, length 1761	CF1 aa 38-367
4027.CF12	pTRPE	native PLA2R	native PLA2R	CD8 hinge, aa 45	Codon optimized, length 2232	CF12 aa 38-516
4028.CF123	pTRPE	native PLA2R	native PLA2R	CD8 hinge, aa 45	Codon optimized, length 2682	CF123 aa 38-666
CF123	pTRPE	Ig	none	GS linker	Codon optimized, length 2490	CF123 aa 38-653
CF1237	pTRPE	Ig	none	GS linker	Codon optimized, length 2910	CF1237 aa 38-653, aa 1107-1246
CF17	pTRPE	Ig	none	GS linker	Codon optimized, length 2052	CF17 aa 38-367, aa 1107-1246
C17	pTRPE	Ig	none	GS linker	Codon optimized, length 1893	C17 aa 38-169, aa 223-367, aa 1107-1246

FIG. 3B

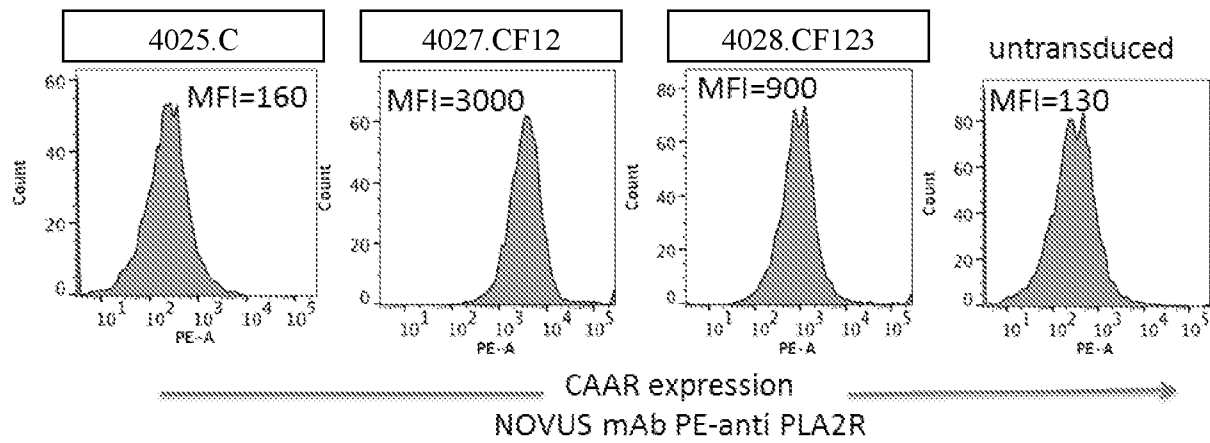
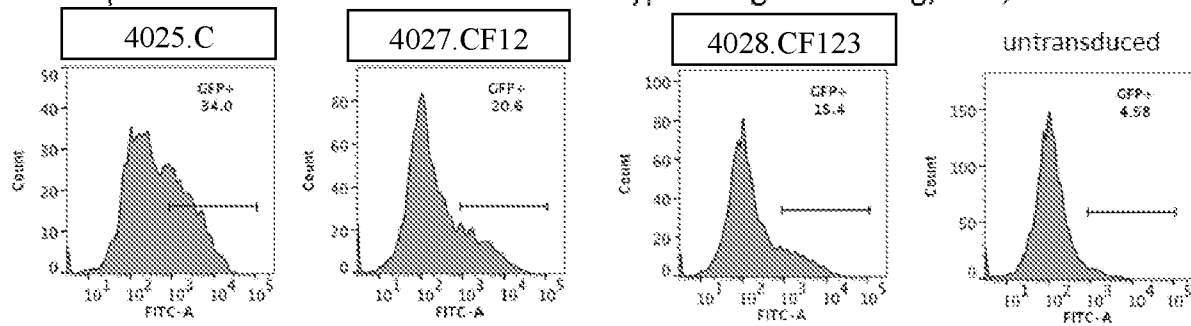


FIG. 4

Non-specific activation of CAAR with isotype Ab IgG2a 0.5 ug/well; 6h



Maximum activation of CAAR induced by PMA/Ionomycin treatment 6h

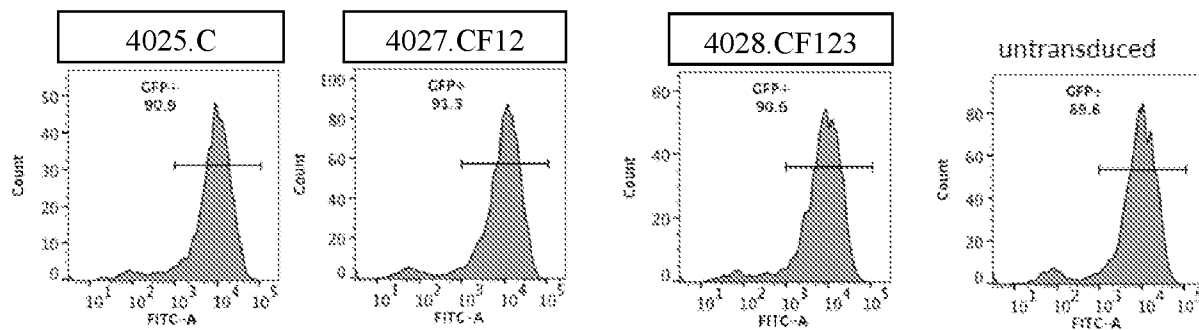


FIG. 5

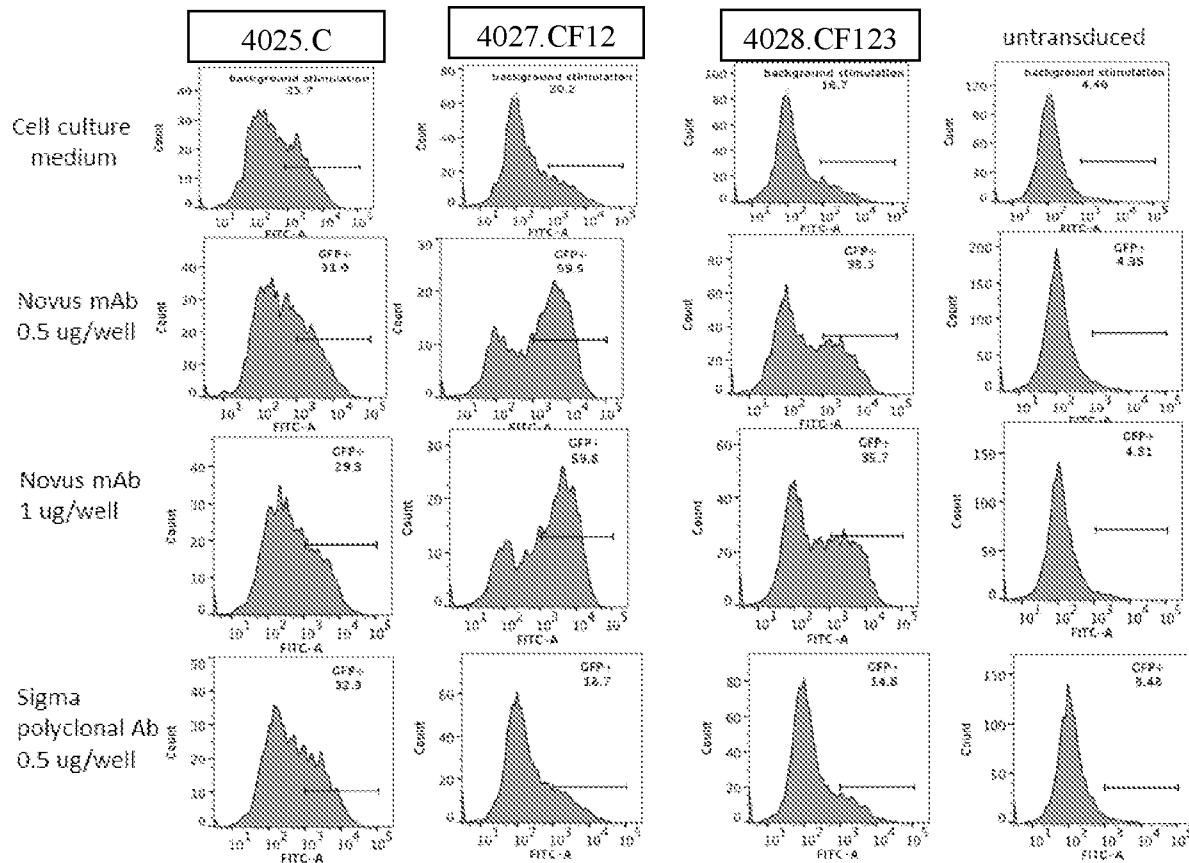


FIG. 6

Jurkat cell

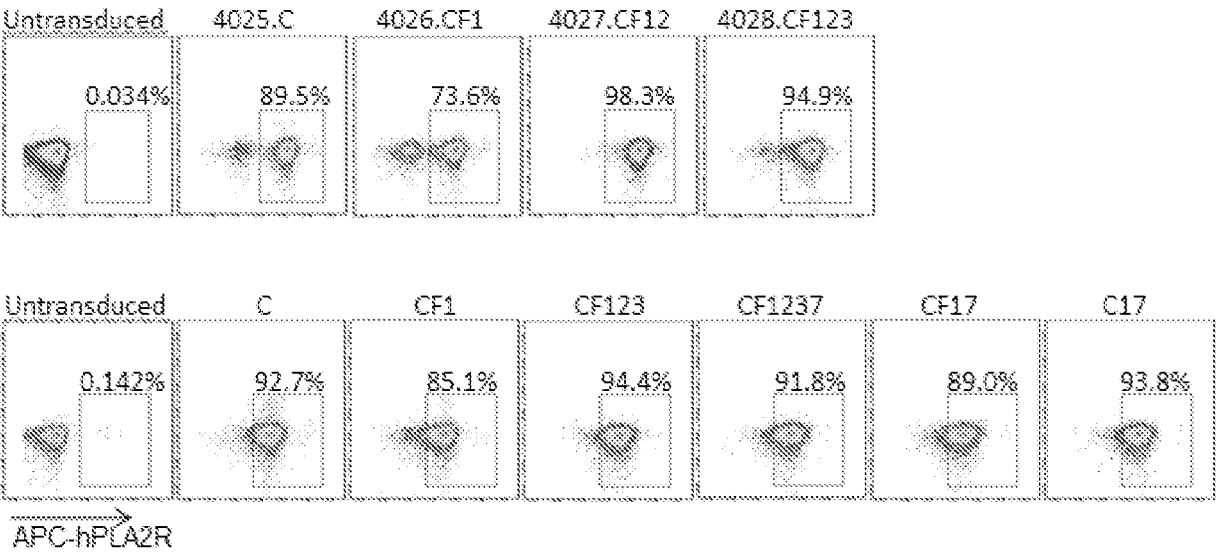


FIG. 7A

Human Primary T cell

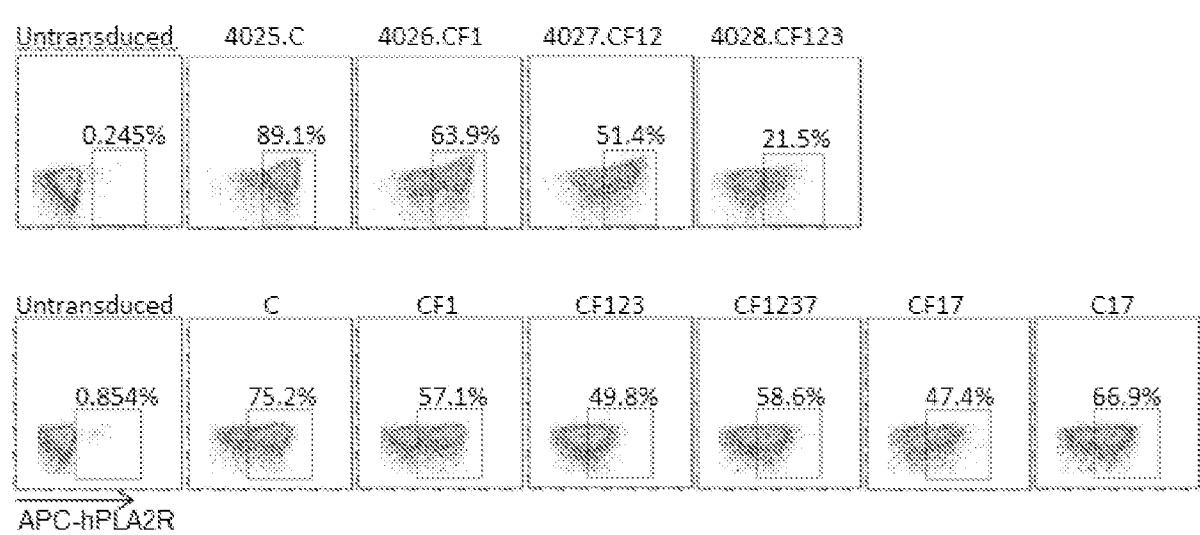


FIG. 7B

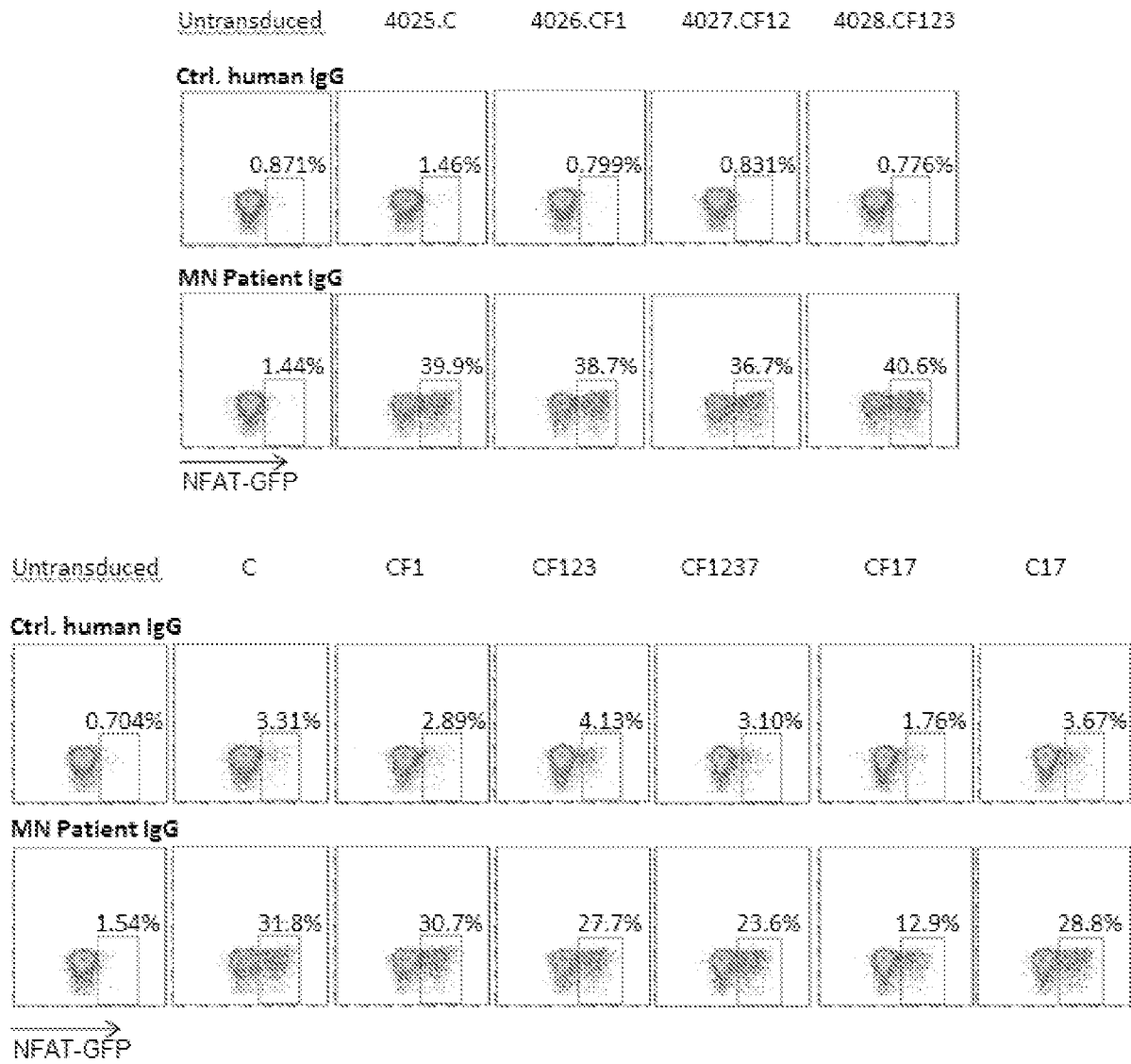


FIG. 8

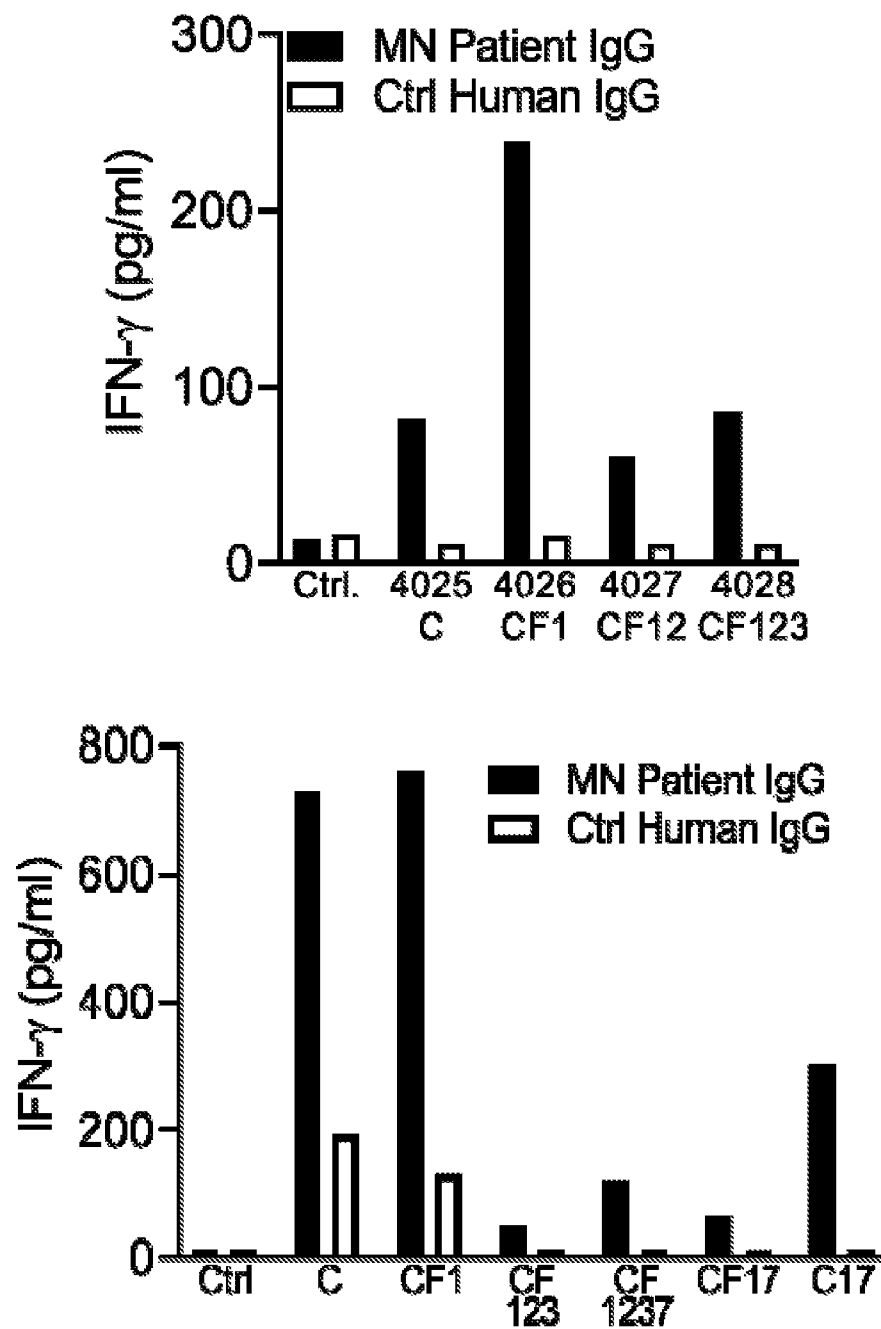


FIG. 9

046483-7207W01_Seq_List.txt
SEQUENCE LISTING

<110> The Trustees of the University of Pennsylvania
Gill, Saar
Payne, Aimee
Hogan, Jonathan
Wang, Baomei

<120> COMPOSITIONS AND METHODS OF PHOSPHOLIPASE A2 RECEPTOR CHIMERIC
AUTOANTIBODY RECEPTOR T CELLS

<130> 046483-7207W01(02014)

<150> 62/665,863
<151> 2018-05-02

<160> 72

<170> PatentIn version 3.5

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 35 40 45

Ser Leu Lys Lys Cys Ile Gln Ala Gly Lys Ser Val Leu Thr Leu Glu
 50 55 60

Asn Cys Lys Gln Ala Asn Lys His Met Leu Trp Lys Trp Val Ser Asn
 65 70 75 80

His Gly Leu Phe Asn Ile Gly Gly Ser Gly Cys Leu Gly Leu Asn Phe
 85 90 95

Ser Ala Pro Glu Gln Pro Leu Ser Leu Tyr Glu Cys Asp Ser Thr Leu
 100 105 110

Val Ser Leu Arg Trp Arg Cys Asn Arg Lys Met Ile Thr Gly Pro Leu
 115 120 125

Gln Tyr Ser Val Gln Val Ala His Asp Asn Thr Val Val Ala Ser Arg
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Lys Tyr Ile His Lys Trp Ile Ser Tyr Gly Ser Gly Gly Gly Asp Ile
 145 150 155 160

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Glu Cys Thr Arg Glu Gly Arg Glu Asp Asp Leu Leu Trp Cys Ala Thr
195 200 205

Thr Ser Arg Tyr Glu Arg Asp Glu Lys Trp Gly Phe Cys Pro Asp Pro
210 215 220

Thr Ser Ala Glu Val Gly Cys Asp Thr Ile Trp Glu Lys Asp Leu Asn
225 230 235 240

Ser His Ile Cys Tyr Gln Phe Asn Leu Leu Ser Ser Leu Ser Trp Ser
245 250 255

Glu Ala His Ser Ser Cys Gln Met Gln Gly Gly Thr Leu Leu Ser Ile
260 265 270

Thr Asp Glu Thr Glu Glu Asn Phe Ile Arg Glu His Met Ser Ser Lys
275 280 285

Thr Val Glu Val Trp Met Gly Leu Asn Gln Leu Asp Glu His Ala Gly
290 295 300

Trp Gln Trp Ser Asp Gly Thr Pro Leu Asn Tyr Leu Asn Trp Ser Pro
305 310 315 320

Glu Val Asn Phe Glu Pro Phe Val Glu Asp His Cys Gly Thr Phe Ser
325 330 335

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Asp Ile Thr Ser Leu Ala Glu Val Glu Phe Leu Val Thr Leu Leu Gly
420 425 430

Asp Glu Asn Ala Ser Glu Thr Trp Ile Gly Leu Ser Ser Asn Lys Ile
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Val Ser Ala Glu Gln Ser Glu Gly His Trp Lys Val Lys Asn Cys Glu
485 490 495

Glu Arg Leu Phe Tyr Ile Cys Lys Lys Ala Gly His Val Leu Ser Asp
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Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
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Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
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Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
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agctgtcaaa tgcaaggcgg cacactgctg agcatcaccg acgagacaga ggaaaacttc 840

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046483-7207W01_Seq_List.txt

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ctctataacg agctcaatct aggacgaaga gaggagtacg atgttttgga caagagacgt	2460
ggccgggacc ctgagatggg gggaaagccg agaaggaaga accctcagga aggcctgtac	2520
aatgaactgc agaaagataa gatggcggag gcctacagtg agattgggat gaaaggcgag	2580

cgccggaggg gcaaggggca cgatggcctt taccagggtc tcagtacagc caccaaggac 2640

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<210> 18

<211> 893

<212> PRT

<213> Artificial Sequence

<220>

<223> PLA2R-CAAR Construct 4028.CF123

<400> 18

Met Leu Leu Ser Pro Ser Leu Leu Leu Leu Leu Leu Leu Gly Ala Pro
1 5 10 15

Arg Gly Cys Ala Gly Ser Glu Gly Val Ala Ala Ala Leu Thr Pro Glu
20 25 30

Arg Leu Leu Glu Trp Gln Asp Lys Gly Ile Phe Val Ile Gln Ser Glu
35 40 45

Ser Leu Lys Lys Cys Ile Gln Ala Gly Lys Ser Val Leu Thr Leu Glu
50 55 60

Asn Cys Lys Gln Ala Asn Lys His Met Leu Trp Lys Trp Val Ser Asn
65 70 75 80

His Gly Leu Phe Asn Ile Gly Gly Ser Gly Cys Leu Gly Leu Asn Phe
85 90 95

Ser Ala Pro Glu Gln Pro Leu Ser Leu Tyr Glu Cys Asp Ser Thr Leu
100 105 110

Val Ser Leu Arg Trp Arg Cys Asn Arg Lys Met Ile Thr Gly Pro Leu
115 120 125

Gln Tyr Ser Val Gln Val Ala His Asp Asn Thr Val Val Ala Ser Arg
130 135 140

046483-7207W01_Seq_List.txt

Lys Tyr Ile His Lys Trp Ile Ser Tyr Gly Ser Gly Gly Gly Asp Ile
145 150 155 160

Cys Glu Tyr Leu His Lys Asp Leu His Thr Ile Lys Gly Asn Thr His
165 170 175

Gly Met Pro Cys Met Phe Pro Phe Gln Tyr Asn His Gln Trp His His
180 185 190

Glu Cys Thr Arg Glu Gly Arg Glu Asp Asp Leu Leu Trp Cys Ala Thr
195 200 205

Thr Ser Arg Tyr Glu Arg Asp Glu Lys Trp Gly Phe Cys Pro Asp Pro
210 215 220

Thr Ser Ala Glu Val Gly Cys Asp Thr Ile Trp Glu Lys Asp Leu Asn
225 230 235 240

Ser His Ile Cys Tyr Gln Phe Asn Leu Leu Ser Ser Leu Ser Trp Ser
245 250 255

Glu Ala His Ser Ser Cys Gln Met Gln Gly Gly Thr Leu Leu Ser Ile
260 265 270

Thr Asp Glu Thr Glu Glu Asn Phe Ile Arg Glu His Met Ser Ser Lys
275 280 285

Thr Val Glu Val Trp Met Gly Leu Asn Gln Leu Asp Glu His Ala Gly
290 295 300

Trp Gln Trp Ser Asp Gly Thr Pro Leu Asn Tyr Leu Asn Trp Ser Pro
305 310 315 320

Glu Val Asn Phe Glu Pro Phe Val Glu Asp His Cys Gly Thr Phe Ser
325 330 335

Ser Phe Met Pro Ser Ala Trp Arg Ser Arg Asp Cys Glu Ser Thr Leu
340 345 350

046483-7207W01_Seq_List.txt

Pro Tyr Ile Cys Lys Lys Tyr Leu Asn His Ile Asp His Glu Ile Val
355 360 365

Glu Lys Asp Ala Trp Lys Tyr Tyr Ala Thr His Cys Glu Pro Gly Trp
370 375 380

Asn Pro Tyr Asn Arg Asn Cys Tyr Lys Leu Gln Lys Glu Glu Lys Thr
385 390 395 400

Trp His Glu Ala Leu Arg Ser Cys Gln Ala Asp Asn Ser Ala Leu Ile
405 410 415

Asp Ile Thr Ser Leu Ala Glu Val Glu Phe Leu Val Thr Leu Leu Gly
420 425 430

Asp Glu Asn Ala Ser Glu Thr Trp Ile Gly Leu Ser Ser Asn Lys Ile
435 440 445

Pro Val Ser Phe Glu Trp Ser Asn Asp Ser Ser Val Ile Phe Thr Asn
450 455 460

Trp His Thr Leu Glu Pro His Ile Phe Pro Asn Arg Ser Gln Leu Cys
465 470 475 480

Val Ser Ala Glu Gln Ser Glu Gly His Trp Lys Val Lys Asn Cys Glu
485 490 495

Glu Arg Leu Phe Tyr Ile Cys Lys Lys Ala Gly His Val Leu Ser Asp
500 505 510

Ala Glu Ser Gly Cys Gln Glu Gly Trp Glu Arg His Gly Gly Phe Cys
515 520 525

Tyr Lys Ile Asp Thr Val Leu Arg Ser Phe Asp Gln Ala Ser Ser Gly
530 535 540

Tyr Tyr Cys Pro Pro Ala Leu Val Thr Ile Thr Asn Arg Phe Glu Gln
545 550 555 560

046483-7207W01_Seq_List.txt

Ala Phe Ile Thr Ser Leu Ile Ser Ser Val Val Lys Met Lys Asp Ser
565 570 575

Tyr Phe Trp Ile Ala Leu Gln Asp Gln Asn Asp Thr Gly Glu Tyr Thr
580 585 590

Trp Lys Pro Val Gly Gln Lys Pro Glu Pro Val Gln Tyr Thr His Trp
595 600 605

Asn Thr His Gln Pro Arg Tyr Ser Gly Gly Cys Val Ala Met Arg Gly
610 615 620

Arg His Pro Leu Gly Arg Trp Glu Val Lys His Cys Arg His Phe Lys
625 630 635 640

Ala Met Ser Leu Cys Lys Gln Pro Val Glu Asn Gln Glu Lys Ala Glu
645 650 655

Tyr Glu Glu Arg Trp Pro Phe His Pro Cys Tyr Leu Ser Gly Thr Thr
660 665 670

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
675 680 685

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
690 695 700

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
705 710 715 720

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
725 730 735

Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
740 745 750

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
755 760 765

046483-7207W01_Seq_List.txt

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
770 775 780

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln
785 790 795 800

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
805 810 815

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
820 825 830

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
835 840 845

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
850 855 860

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
865 870 875 880

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
885 890

<210> 19
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> CD8 alpha transmembrane domain

<400> 19

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr Leu Tyr Cys
20

<210> 20
<211> 72

<212> DNA

<213> Artificial Sequence

<220>

<223> CD8 alpha transmembrane domain

<400> 20

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accctttact gc 72

<210> 21

<211> 42

<212> PRT

<213> Artificial Sequence

<220>

<223> 4-1BB

<400> 21

Lys	Arg	Gly	Arg	Lys	Lys	Leu	Leu	Tyr	Ile	Phe	Lys	Gln	Pro	Phe	Met
1				5					10					15	

Arg	Pro	Val	Gln	Thr	Thr	Gln	Glu	Glu	Asp	Gly	Cys	Ser	Cys	Arg	Phe
			20					25					30		

Pro	Glu	Glu	Glu	Glu	Gly	Gly	Cys	Glu	Leu
		35					40		

<210> 22

<211> 126

<212> DNA

<213> Artificial Sequence

<220>

<223> 4-1BB

<400> 22

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actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120

gaactg 126

<210> 23

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> CD3 zeta signaling domain

<400> 23

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
 1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
 20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
 35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
 50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
 65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
 85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
 100 105 110

<210> 24

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> CD3 zeta signaling domain

<400> 24

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 cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180
 gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240

cggagggggca aggggacacga tggccttttac cagggtctca gtacagccac caaggacacc 300
 tacgacgccc ttacatgca ggccctgccc cctcgc 336

<210> 25
 <211> 1167
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PLA2R-CAAR Construct C

<400> 25
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 agcgtgctta ccctggagaa ctgcaagcaa gctaataagc atatgctttg gaaatgggtt 180
 agcaaccacg gactctttaa tatcggaggc tccggctgtc tgggcctgaa cttcagtgc 240
 ccggagcaac cgctttctct gtacgaatgt gatagcacac ttgttagtct tcggtggcgg 300
 tgtaaccgaa aaatgattac aggcctctg caatatagtg ttcaagtggc ccacgacaat 360
 acagttgttg cgtctagaaa atatattcac aagtggattt cctacgggag cggcggaggg 420
 gatatatgtg aatatcttca caaagacttg catacaatcg ctagcttcgt gccggtcttc 480
 ctgccagcga agccaaccac gacgccagca ccgcgaccac caacacctgc gcccaccatc 540
 gcgtcgcagc ccctgtccct gcgcccagag gcgtgcagac cagcagcggg gggcgcagtg 600
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 tgtgggggtc ttctcctgtc actggttatc accctttact gcaagcgcgg tcgcaagaaa 720
 ctgctctata tttttaaaca gccattcatg agacctgtcc agaccactca agaggaggac 780
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 gggcacgatg gcctttacca gggctctcagt acagccacca aggacaccta cgacgccctt 1140

cacatgcagg ccctgcccc tcgctaa

1167

<210> 26

<211> 388

<212> PRT

<213> Artificial Sequence

<220>

<223> PLA2R-CAAR Construct C

<400> 26

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
 1 5 10 15

Val Gln Cys Gly Ser Lys Gly Ile Phe Val Ile Gln Ser Glu Ser Leu
 20 25 30

Lys Lys Cys Ile Gln Ala Gly Lys Ser Val Leu Thr Leu Glu Asn Cys
 35 40 45

Lys Gln Ala Asn Lys His Met Leu Trp Lys Trp Val Ser Asn His Gly
 50 55 60

Leu Phe Asn Ile Gly Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala
 65 70 75 80

Pro Glu Gln Pro Leu Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser
 85 90 95

Leu Arg Trp Arg Cys Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr
 100 105 110

Ser Val Gln Val Ala His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr
 115 120 125

Ile His Lys Trp Ile Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu
 130 135 140

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

Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
 165 170 175

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
 180 185 190

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
 195 200 205

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
 210 215 220

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
 225 230 235 240

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
 245 250 255

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
 260 265 270

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
 275 280 285

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
 290 295 300

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
 305 310 315 320

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
 325 330 335

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
 340 345 350

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
 355 360 365

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
 370 375 380

Leu Pro Pro Arg
 385

<210> 27
 <211> 1761
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PLA2R-CAAR construct CF1

<400> 27
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 agtgtactga ctcttgaaaa ttgcaaacia gccaaacaa acatgctgtg gaaatgggtg 180
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 accgtgggtg catctaggaa atacattcat aagtggatat cttatggcag tgggtggcgg 420
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 ccgtgtatgt tcccgttcca atataatcat caatggcacc atgagtgtac gagagagggg 540
 cgagaagacg acctcctgtg gtgtgcgacc acctcaagat atgaacggga tgagaagtgg 600
 ggcttttggc cggacccaac ctccgccgag gttggttgcg acactatttg ggaaaaagat 660
 ttgaacagtc atatatgcta tcaatttaat ttgttgagtt cactctcctg gagcgaagcg 720
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 aatttcatta gggagcatat gtcctcaaag acagtagagg tgtggatggg tctgaaccag 840
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 tcccctgagg tcaactttga accgtttgtg gaagatcatt gtggtacttt ttccagtttt 960
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agggggctgg acttcgcctg tgatatctac atctgggcgc ctttgccgg gacttgtggg	1260
gtccttctcc tgtcactggt taccacctt tactgcaagc gcggtcgcaa gaaactgctc	1320
tatatattta aacagccatt catgagacct gtccagacca ctcaagagga ggacggatgt	1380
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agcgcagacg ccccgcgta ccagcagggc cagaaccagc tctataacga gctcaatcta	1500
ggacgaagag aggagtacga tgttttggac aagagacgtg gccgggaccc tgagatgggg	1560
ggaaagccga gaaggaagaa ccctcaggaa ggcctgtaca atgaactgca gaaagataag	1620
atggcggagg cctacagtga gattgggatg aaaggcgagc gccggagggg caaggggcac	1680
gatggccttt accagggtct cagtacagcc accaaggaca cctacgacgc cttcacatg	1740
caggccctgc cccctcgcta a	1761

<210> 28

<211> 586

<212> PRT

<213> Artificial Sequence

<220>

<223> PLA2R-CAAR construct CF1

<400> 28

Met	Glu	Phe	Gly	Leu	Ser	Trp	Leu	Phe	Leu	Val	Ala	Ile	Leu	Lys	Gly
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Val	Gln	Cys	Gly	Ser	Lys	Gly	Ile	Phe	Val	Ile	Gln	Ser	Glu	Ser	Leu
			20					25					30		

Lys	Lys	Cys	Ile	Gln	Ala	Gly	Lys	Ser	Val	Leu	Thr	Leu	Glu	Asn	Cys
		35					40					45			

Lys	Gln	Ala	Asn	Lys	His	Met	Leu	Trp	Lys	Trp	Val	Ser	Asn	His	Gly
	50					55					60				

Leu Phe Asn Ile Gly Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala
65 70 75 80

Pro Glu Gln Pro Leu Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser
85 90 95

Leu Arg Trp Arg Cys Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr
100 105 110

Ser Val Gln Val Ala His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr
115 120 125

Ile His Lys Trp Ile Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu
130 135 140

Tyr Leu His Lys Asp Leu His Thr Ile Lys Gly Asn Thr His Gly Met
145 150 155 160

Pro Cys Met Phe Pro Phe Gln Tyr Asn His Gln Trp His His Glu Cys
165 170 175

Thr Arg Glu Gly Arg Glu Asp Asp Leu Leu Trp Cys Ala Thr Thr Ser
180 185 190

Arg Tyr Glu Arg Asp Glu Lys Trp Gly Phe Cys Pro Asp Pro Thr Ser
195 200 205

Ala Glu Val Gly Cys Asp Thr Ile Trp Glu Lys Asp Leu Asn Ser His
210 215 220

Ile Cys Tyr Gln Phe Asn Leu Leu Ser Ser Leu Ser Trp Ser Glu Ala
225 230 235 240

His Ser Ser Cys Gln Met Gln Gly Gly Thr Leu Leu Ser Ile Thr Asp
245 250 255

Glu Thr Glu Glu Asn Phe Ile Arg Glu His Met Ser Ser Lys Thr Val
260 265 270

046483-7207W01_Seq_List.txt

Glu Val Trp Met Gly Leu Asn Gln Leu Asp Glu His Ala Gly Trp Gln
275 280 285

Trp Ser Asp Gly Thr Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val
290 295 300

Asn Phe Glu Pro Phe Val Glu Asp His Cys Gly Thr Phe Ser Ser Phe
305 310 315 320

Met Pro Ser Ala Trp Arg Ser Arg Asp Cys Glu Ser Thr Leu Pro Tyr
325 330 335

Ile Cys Lys Lys Tyr Leu Asn His Ile Asp His Glu Ile Val Glu Ala
340 345 350

Ser Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala
355 360 365

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
370 375 380

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
385 390 395 400

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
405 410 415

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
420 425 430

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
435 440 445

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
450 455 460

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
465 470 475 480

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
 485 490 495

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
 500 505 510

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
 515 520 525

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
 530 535 540

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
 545 550 555 560

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
 565 570 575

Ala Leu His Met Gln Ala Leu Pro Pro Arg
 580 585

<210> 29
 <211> 2490
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PLA2R-CAAR Construct CF123

<400> 29
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 tccaaaggga ttttcgtgat acagtccgag agtctcaaaa agtgtatcca ggcaggcaaa 120
 agtgttctca ctctggaaaa ctgcaaaca gcaacaagc acatgttgtg gaagtgggtt 180
 agtaaccatg gactgttcaa catcggaggt agtggatgcc ttggtctcaa tttctctgct 240
 ccggaacagc ctttgtcact gtacgaatgc gactccactc tcgttagtct tagatggcga 300
 tgcaatcgca aaatgattac gggaccactt caatattcag ttcaagtggc acatgataac 360
 accgtagtgg cctcacggaa atacatccat aaatggattt cttatggtag cgggggcggc 420

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gatatatgtg aatacctcca taaggatctc cacaccatta agggtaatac tcacggtatg	480
ccgtgtatgt ttccttttca gtacaatcat cagtggcatc atgaatgcac gagggaagga	540
cgcgaggacg atttgctctg gtgcgcaacc acctcacgct acgagagaga cgaaaaatgg	600
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gaaggttggg agcgccatgg aggtttctgt tataaaatcg acacagtttt gcgatctttc	1560
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tggatagccc tgcaagacca aaatgatacc ggtgagtaca catggaaacc ggtaggtcaa	1740
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046483-7207W01_Seq_List.txt

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acttgtgggg tccttctcct gtcactgggt atcacccttt actgcaagcg cggtcgcaag    2040
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gacggatggt cctgtagatt tcctgaagag gaagaggggg ggtgcgagct gagagtgaag    2160
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<210> 30
 <211> 829
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> PLA2R-CAAR Construct CF123

<400> 30

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Val Gln Cys Gly Ser Lys Gly Ile Phe Val Ile Gln Ser Glu Ser Leu
 20 25 30

Lys Lys Cys Ile Gln Ala Gly Lys Ser Val Leu Thr Leu Glu Asn Cys
 35 40 45

Lys Gln Ala Asn Lys His Met Leu Trp Lys Trp Val Ser Asn His Gly
 50 55 60

Leu Phe Asn Ile Gly Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala
 65 70 75 80

Pro Glu Gln Pro Leu Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser
 85 90 95

046483-7207W01_Seq_List.txt

Leu Arg Trp Arg Cys Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr
100 105 110

Ser Val Gln Val Ala His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr
115 120 125

Ile His Lys Trp Ile Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu
130 135 140

Tyr Leu His Lys Asp Leu His Thr Ile Lys Gly Asn Thr His Gly Met
145 150 155 160

Pro Cys Met Phe Pro Phe Gln Tyr Asn His Gln Trp His His Glu Cys
165 170 175

Thr Arg Glu Gly Arg Glu Asp Asp Leu Leu Trp Cys Ala Thr Thr Ser
180 185 190

Arg Tyr Glu Arg Asp Glu Lys Trp Gly Phe Cys Pro Asp Pro Thr Ser
195 200 205

Ala Glu Val Gly Cys Asp Thr Ile Trp Glu Lys Asp Leu Asn Ser His
210 215 220

Ile Cys Tyr Gln Phe Asn Leu Leu Ser Ser Leu Ser Trp Ser Glu Ala
225 230 235 240

His Ser Ser Cys Gln Met Gln Gly Gly Thr Leu Leu Ser Ile Thr Asp
245 250 255

Glu Thr Glu Glu Asn Phe Ile Arg Glu His Met Ser Ser Lys Thr Val
260 265 270

Glu Val Trp Met Gly Leu Asn Gln Leu Asp Glu His Ala Gly Trp Gln
275 280 285

Trp Ser Asp Gly Thr Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val
290 295 300

046483-7207W01_Seq_List.txt

Asn Phe Glu Pro Phe Val Glu Asp His Cys Gly Thr Phe Ser Ser Phe
305 310 315 320

Met Pro Ser Ala Trp Arg Ser Arg Asp Cys Glu Ser Thr Leu Pro Tyr
325 330 335

Ile Cys Lys Lys Tyr Leu Asn His Ile Asp His Glu Ile Val Glu Lys
340 345 350

Asp Ala Trp Lys Tyr Tyr Ala Thr His Cys Glu Pro Gly Trp Asn Pro
355 360 365

Tyr Asn Arg Asn Cys Tyr Lys Leu Gln Lys Glu Glu Lys Thr Trp His
370 375 380

Glu Ala Leu Arg Ser Cys Gln Ala Asp Asn Ser Ala Leu Ile Asp Ile
385 390 395 400

Thr Ser Leu Ala Glu Val Glu Phe Leu Val Thr Leu Leu Gly Asp Glu
405 410 415

Asn Ala Ser Glu Thr Trp Ile Gly Leu Ser Ser Asn Lys Ile Pro Val
420 425 430

Ser Phe Glu Trp Ser Asn Asp Ser Ser Val Ile Phe Thr Asn Trp His
435 440 445

Thr Leu Glu Pro His Ile Phe Pro Asn Arg Ser Gln Leu Cys Val Ser
450 455 460

Ala Glu Gln Ser Glu Gly His Trp Lys Val Lys Asn Cys Glu Glu Arg
465 470 475 480

Leu Phe Tyr Ile Cys Lys Lys Ala Gly His Val Leu Ser Asp Ala Glu
485 490 495

Ser Gly Cys Gln Glu Gly Trp Glu Arg His Gly Gly Phe Cys Tyr Lys
500 505 510

046483-7207W01_Seq_List.txt

Ile Asp Thr Val Leu Arg Ser Phe Asp Gln Ala Ser Ser Gly Tyr Tyr
515 520 525

Cys Pro Pro Ala Leu Val Thr Ile Thr Asn Arg Phe Glu Gln Ala Phe
530 535 540

Ile Thr Ser Leu Ile Ser Ser Val Val Lys Met Lys Asp Ser Tyr Phe
545 550 555 560

Trp Ile Ala Leu Gln Asp Gln Asn Asp Thr Gly Glu Tyr Thr Trp Lys
565 570 575

Pro Val Gly Gln Lys Pro Glu Pro Val Gln Tyr Thr His Trp Asn Thr
580 585 590

His Gln Pro Arg Tyr Ser Gly Gly Cys Val Ala Met Arg Gly Arg His
595 600 605

Pro Leu Gly Arg Trp Glu Val Lys His Cys Arg His Phe Lys Ala Met
610 615 620

Ser Leu Cys Lys Gln Pro Val Glu Asn Gln Glu Lys Ala Ala Ser Gly
625 630 635 640

Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Gly Ile Tyr Ile Trp Ala
645 650 655

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
660 665 670

Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
675 680 685

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
690 695 700

Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
705 710 715 720

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
 725 730 735

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
 740 745 750

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
 755 760 765

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
 770 775 780

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
 785 790 795 800

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
 805 810 815

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
 820 825

<210> 31
 <211> 2910
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PLA2R-CAAR Construct CF1237

<400> 31
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 agtaaccatg gactgttcaa catcggaggt agtggatgcc ttggtctcaa tttctctgct 240
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046483-7207W01_Seq_List.txt

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ttcaaggcga tgagcttgtg taaacagccc gtcgaaaatc aggaaaaggc agttaacaca	1920
tctgatatgt accctatgcc taacacactc gaatatggga ataggacgta caagattata	1980

046483-7207W01_Seq_List.txt

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tacgcccatt ggatcgggtct cttcacgacg gacaatgggc tcaattttga ctggagtgac      2160
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gctatttgcc acgtgcctcc cgaaacgcgg cagtccgaac acccggaatt ggctagcggg      2340
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acttgtaggg tccttctcct gtcactggtt atcacccttt actgcaagcg cggtcgcaag      2460
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cttcacatgc aggccttgcc ccctcgctaa      2910

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<210> 32
 <211> 969
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> PLA2R-CAAR Construct CF1237

<400> 32

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Val Gln Cys Gly Ser Lys Gly Ile Phe Val Ile Gln Ser Glu Ser Leu
          20          25          30

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046483-7207W01_Seq_List.txt

Lys Lys Cys Ile Gln Ala Gly Lys Ser Val Leu Thr Leu Glu Asn Cys
35 40 45

Lys Gln Ala Asn Lys His Met Leu Trp Lys Trp Val Ser Asn His Gly
50 55 60

Leu Phe Asn Ile Gly Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala
65 70 75 80

Pro Glu Gln Pro Leu Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser
85 90 95

Leu Arg Trp Arg Cys Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr
100 105 110

Ser Val Gln Val Ala His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr
115 120 125

Ile His Lys Trp Ile Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu
130 135 140

Tyr Leu His Lys Asp Leu His Thr Ile Lys Gly Asn Thr His Gly Met
145 150 155 160

Pro Cys Met Phe Pro Phe Gln Tyr Asn His Gln Trp His His Glu Cys
165 170 175

Thr Arg Glu Gly Arg Glu Asp Asp Leu Leu Trp Cys Ala Thr Thr Ser
180 185 190

Arg Tyr Glu Arg Asp Glu Lys Trp Gly Phe Cys Pro Asp Pro Thr Ser
195 200 205

Ala Glu Val Gly Cys Asp Thr Ile Trp Glu Lys Asp Leu Asn Ser His
210 215 220

Ile Cys Tyr Gln Phe Asn Leu Leu Ser Ser Leu Ser Trp Ser Glu Ala
225 230 235 240

046483-7207W01_Seq_List.txt

His Ser Ser Cys Gln Met Gln Gly Gly Thr Leu Leu Ser Ile Thr Asp
245 250 255

Glu Thr Glu Glu Asn Phe Ile Arg Glu His Met Ser Ser Lys Thr Val
260 265 270

Glu Val Trp Met Gly Leu Asn Gln Leu Asp Glu His Ala Gly Trp Gln
275 280 285

Trp Ser Asp Gly Thr Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val
290 295 300

Asn Phe Glu Pro Phe Val Glu Asp His Cys Gly Thr Phe Ser Ser Phe
305 310 315 320

Met Pro Ser Ala Trp Arg Ser Arg Asp Cys Glu Ser Thr Leu Pro Tyr
325 330 335

Ile Cys Lys Lys Tyr Leu Asn His Ile Asp His Glu Ile Val Glu Lys
340 345 350

Asp Ala Trp Lys Tyr Tyr Ala Thr His Cys Glu Pro Gly Trp Asn Pro
355 360 365

Tyr Asn Arg Asn Cys Tyr Lys Leu Gln Lys Glu Glu Lys Thr Trp His
370 375 380

Glu Ala Leu Arg Ser Cys Gln Ala Asp Asn Ser Ala Leu Ile Asp Ile
385 390 395 400

Thr Ser Leu Ala Glu Val Glu Phe Leu Val Thr Leu Leu Gly Asp Glu
405 410 415

Asn Ala Ser Glu Thr Trp Ile Gly Leu Ser Ser Asn Lys Ile Pro Val
420 425 430

Ser Phe Glu Trp Ser Asn Asp Ser Ser Val Ile Phe Thr Asn Trp His
435 440 445

046483-7207W01_Seq_List.txt

Thr Leu Glu Pro His Ile Phe Pro Asn Arg Ser Gln Leu Cys Val Ser
450 455 460

Ala Glu Gln Ser Glu Gly His Trp Lys Val Lys Asn Cys Glu Glu Arg
465 470 475 480

Leu Phe Tyr Ile Cys Lys Lys Ala Gly His Val Leu Ser Asp Ala Glu
485 490 495

Ser Gly Cys Gln Glu Gly Trp Glu Arg His Gly Gly Phe Cys Tyr Lys
500 505 510

Ile Asp Thr Val Leu Arg Ser Phe Asp Gln Ala Ser Ser Gly Tyr Tyr
515 520 525

Cys Pro Pro Ala Leu Val Thr Ile Thr Asn Arg Phe Glu Gln Ala Phe
530 535 540

Ile Thr Ser Leu Ile Ser Ser Val Val Lys Met Lys Asp Ser Tyr Phe
545 550 555 560

Trp Ile Ala Leu Gln Asp Gln Asn Asp Thr Gly Glu Tyr Thr Trp Lys
565 570 575

Pro Val Gly Gln Lys Pro Glu Pro Val Gln Tyr Thr His Trp Asn Thr
580 585 590

His Gln Pro Arg Tyr Ser Gly Gly Cys Val Ala Met Arg Gly Arg His
595 600 605

Pro Leu Gly Arg Trp Glu Val Lys His Cys Arg His Phe Lys Ala Met
610 615 620

Ser Leu Cys Lys Gln Pro Val Glu Asn Gln Glu Lys Ala Val Asn Thr
625 630 635 640

Ser Asp Met Tyr Pro Met Pro Asn Thr Leu Glu Tyr Gly Asn Arg Thr
645 650 655

046483-7207W01_Seq_List.txt

Tyr Lys Ile Ile Asn Ala Asn Met Thr Trp Tyr Ala Ala Ile Lys Thr
660 665 670

Cys Leu Met His Lys Ala Gln Leu Val Ser Ile Thr Asp Gln Tyr His
675 680 685

Gln Ser Phe Leu Thr Val Val Leu Asn Arg Leu Gly Tyr Ala His Trp
690 695 700

Ile Gly Leu Phe Thr Thr Asp Asn Gly Leu Asn Phe Asp Trp Ser Asp
705 710 715 720

Gly Thr Lys Ser Ser Phe Thr Phe Trp Lys Asp Glu Glu Ser Ser Leu
725 730 735

Leu Gly Asp Cys Val Phe Ala Asp Ser Asn Gly Arg Trp His Ser Thr
740 745 750

Ala Cys Glu Ser Phe Leu Gln Gly Ala Ile Cys His Val Pro Pro Glu
755 760 765

Thr Arg Gln Ser Glu His Pro Glu Leu Ala Ser Gly Gly Gly Gly Ser
770 775 780

Gly Gly Gly Gly Ser Ser Gly Ile Tyr Ile Trp Ala Pro Leu Ala Gly
785 790 795 800

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
805 810 815

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
820 825 830

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
835 840 845

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
850 855 860

046483-7207W01_Seq_List.txt

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
865 870 875 880

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
885 890 895

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
900 905 910

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
915 920 925

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
930 935 940

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
945 950 955 960

Leu His Met Gln Ala Leu Pro Pro Arg
965

<210> 33
<211> 2052
<212> DNA
<213> Artificial Sequence

<220>
<223> PLA2R-CAAR Construct CF17

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tcaaaccacg gcctcttcaa tattggtggg tcaggttgct tggggttgaa tttctccgcc 240
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gatatatgag agtatttgca taaggacttg cacaccatca agggaaacac tcacggtatg 480

046483-7207W01_Seq_List.txt

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tacctcaacc acatagatca cgaaatcgta gaggtcaata cgtccgacat gtaccaatg	1080
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agaaggaaga accctcagga aggcctgtac aatgaactgc agaaagataa gatggcggag	1920
gcctacagtg agattgggat gaaaggcgag cgccggaggg gcaaggggca cgatggcctt	1980
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ccccctcgct aa

2052

<210> 34

<211> 683

<212> PRT

<213> Artificial Sequence

<220>

<223> PLA2R-CAAR Construct CF17

<400> 34

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 20 25 30

Lys Lys Cys Ile Gln Ala Gly Lys Ser Val Leu Thr Leu Glu Asn Cys
 35 40 45

Lys Gln Ala Asn Lys His Met Leu Trp Lys Trp Val Ser Asn His Gly
 50 55 60

Leu Phe Asn Ile Gly Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala
 65 70 75 80

Pro Glu Gln Pro Leu Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser
 85 90 95

Leu Arg Trp Arg Cys Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr
 100 105 110

Ser Val Gln Val Ala His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr
 115 120 125

Ile His Lys Trp Ile Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu
 130 135 140

Tyr Leu His Lys Asp Leu His Thr Ile Lys Gly Asn Thr His Gly Met
 145 150 155 160

046483-7207W01_Seq_List.txt

Pro Cys Met Phe Pro Phe Gln Tyr Asn His Gln Trp His His Glu Cys
165 170 175

Thr Arg Glu Gly Arg Glu Asp Asp Leu Leu Trp Cys Ala Thr Thr Ser
180 185 190

Arg Tyr Glu Arg Asp Glu Lys Trp Gly Phe Cys Pro Asp Pro Thr Ser
195 200 205

Ala Glu Val Gly Cys Asp Thr Ile Trp Glu Lys Asp Leu Asn Ser His
210 215 220

Ile Cys Tyr Gln Phe Asn Leu Leu Ser Ser Leu Ser Trp Ser Glu Ala
225 230 235 240

His Ser Ser Cys Gln Met Gln Gly Gly Thr Leu Leu Ser Ile Thr Asp
245 250 255

Glu Thr Glu Glu Asn Phe Ile Arg Glu His Met Ser Ser Lys Thr Val
260 265 270

Glu Val Trp Met Gly Leu Asn Gln Leu Asp Glu His Ala Gly Trp Gln
275 280 285

Trp Ser Asp Gly Thr Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val
290 295 300

Asn Phe Glu Pro Phe Val Glu Asp His Cys Gly Thr Phe Ser Ser Phe
305 310 315 320

Met Pro Ser Ala Trp Arg Ser Arg Asp Cys Glu Ser Thr Leu Pro Tyr
325 330 335

Ile Cys Lys Lys Tyr Leu Asn His Ile Asp His Glu Ile Val Glu Val
340 345 350

Asn Thr Ser Asp Met Tyr Pro Met Pro Asn Thr Leu Glu Tyr Gly Asn
355 360 365

046483-7207W01_Seq_List.txt

Arg Thr Tyr Lys Ile Ile Asn Ala Asn Met Thr Trp Tyr Ala Ala Ile
370 375 380

Lys Thr Cys Leu Met His Lys Ala Gln Leu Val Ser Ile Thr Asp Gln
385 390 395 400

Tyr His Gln Ser Phe Leu Thr Val Val Leu Asn Arg Leu Gly Tyr Ala
405 410 415

His Trp Ile Gly Leu Phe Thr Thr Asp Asn Gly Leu Asn Phe Asp Trp
420 425 430

Ser Asp Gly Thr Lys Ser Ser Phe Thr Phe Trp Lys Asp Glu Glu Ser
435 440 445

Ser Leu Leu Gly Asp Cys Val Phe Ala Asp Ser Asn Gly Arg Trp His
450 455 460

Ser Thr Ala Cys Glu Ser Phe Leu Gln Gly Ala Ile Cys His Val Pro
465 470 475 480

Pro Glu Thr Arg Gln Ser Glu His Pro Glu Leu Ala Ser Gly Gly Gly
485 490 495

Gly Ser Gly Gly Gly Gly Ser Ser Gly Ile Tyr Ile Trp Ala Pro Leu
500 505 510

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
515 520 525

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
530 535 540

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
545 550 555 560

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
565 570 575

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
580 585 590

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
595 600 605

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
610 615 620

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
625 630 635 640

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
645 650 655

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
660 665 670

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
675 680

<210> 35
<211> 1893
<212> DNA
<213> Artificial Sequence

<220>
<223> PLA2R-CAAR Construct C17

<400> 35
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tccaaaggaa tcttcgtaat tcaatctgag agtctgaaaa aatgtattca ggccggtaag 120
agcgtactca cgcttgaaaa ttgcaaacag gccacaacac acatgctttg gaaatgggtt 180
tcaaatacag ggttggtttta cataggggga tcaggatgtc tgggccttaa cttttccgca 240
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tgcaatcgga agatgataac cgggcccttc cagtattccg ttcaggtcgc ccacgataat 360
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046483-7207W01_Seq_List.txt

gatatttgtg aatacctcca caaggatctg cacactatca cttctgcgga agtaggctgt	480
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ataacagatg aaacggaaga gaactttatt agagaacata tgtcctcaaa gactgtggag	660
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acaagtgata tgtaccccat gccgaacaca ctcgagtacg gaaatagaac ctacaagata	960
atcaacgcta acatgacctg gtacgcggcc attagacct gcctcatgca caaggctcaa	1020
ctcgtcagta ttactgacca atatcaccag tcatttctca ccgtcgtgtt gaatcgctc	1080
ggttacgcc actggatcgg tttgtttaca acggacaatg gactcaattt cgattgggtca	1140
gacggaacca aatctagttt taccttctgg aaagacgagg aatcaagcct gcttggggac	1200
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gaggacggat gttcctgtag atttcctgaa gaggaagagg ggggggtgcga gctgagagt	1560
aagttcagca ggagcgcaga cgccccgcg taccagcagg gccagaacca gctctataac	1620
gagctcaatc taggacgaag agaggagtac gatgttttgg acaagagacg tggccgggac	1680
cctgagatgg ggggaaagcc gagaaggaag aaccctcagg aaggcctgta caatgaactg	1740
cagaaagata agatggcgga ggcctacagt gagattggga tgaaaggcga gcgccggagg	1800
ggcaaggggc acgatggcct ttaccagggt ctgagtacag ccaccaagga cacctacgac	1860
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<210> 36

<211> 630

<212> PRT

<213> Artificial Sequence

<220>

<223> PLA2R-CAAR Construct C17

<400> 36

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
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Val Gln Cys Gly Ser Lys Gly Ile Phe Val Ile Gln Ser Glu Ser Leu
 20 25 30

Lys Lys Cys Ile Gln Ala Gly Lys Ser Val Leu Thr Leu Glu Asn Cys
 35 40 45

Lys Gln Ala Asn Lys His Met Leu Trp Lys Trp Val Ser Asn His Gly
 50 55 60

Leu Phe Asn Ile Gly Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala
 65 70 75 80

Pro Glu Gln Pro Leu Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser
 85 90 95

Leu Arg Trp Arg Cys Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr
 100 105 110

Ser Val Gln Val Ala His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr
 115 120 125

Ile His Lys Trp Ile Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu
 130 135 140

Tyr Leu His Lys Asp Leu His Thr Ile Thr Ser Ala Glu Val Gly Cys
 145 150 155 160

Asp Thr Ile Trp Glu Lys Asp Leu Asn Ser His Ile Cys Tyr Gln Phe
 165 170 175

046483-7207W01_Seq_List.txt

Asn Leu Leu Ser Ser Leu Ser Trp Ser Glu Ala His Ser Ser Cys Gln
180 185 190

Met Gln Gly Gly Thr Leu Leu Ser Ile Thr Asp Glu Thr Glu Glu Asn
195 200 205

Phe Ile Arg Glu His Met Ser Ser Lys Thr Val Glu Val Trp Met Gly
210 215 220

Leu Asn Gln Leu Asp Glu His Ala Gly Trp Gln Trp Ser Asp Gly Thr
225 230 235 240

Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val Asn Phe Glu Pro Phe
245 250 255

Val Glu Asp His Cys Gly Thr Phe Ser Ser Phe Met Pro Ser Ala Trp
260 265 270

Arg Ser Arg Asp Cys Glu Ser Thr Leu Pro Tyr Ile Cys Lys Lys Tyr
275 280 285

Leu Asn His Ile Asp His Glu Ile Val Glu Val Asn Thr Ser Asp Met
290 295 300

Tyr Pro Met Pro Asn Thr Leu Glu Tyr Gly Asn Arg Thr Tyr Lys Ile
305 310 315 320

Ile Asn Ala Asn Met Thr Trp Tyr Ala Ala Ile Lys Thr Cys Leu Met
325 330 335

His Lys Ala Gln Leu Val Ser Ile Thr Asp Gln Tyr His Gln Ser Phe
340 345 350

Leu Thr Val Val Leu Asn Arg Leu Gly Tyr Ala His Trp Ile Gly Leu
355 360 365

Phe Thr Thr Asp Asn Gly Leu Asn Phe Asp Trp Ser Asp Gly Thr Lys
370 375 380

046483-7207W01_Seq_List.txt

Ser Ser Phe Thr Phe Trp Lys Asp Glu Glu Ser Ser Leu Leu Gly Asp
385 390 395 400

Cys Val Phe Ala Asp Ser Asn Gly Arg Trp His Ser Thr Ala Cys Glu
405 410 415

Ser Phe Leu Gln Gly Ala Ile Cys His Val Pro Pro Glu Thr Arg Gln
420 425 430

Ser Glu His Pro Glu Leu Ala Ser Gly Gly Gly Gly Ser Gly Gly Gly
435 440 445

Gly Ser Ser Gly Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
450 455 460

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
465 470 475 480

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
485 490 495

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
500 505 510

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
515 520 525

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
530 535 540

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
545 550 555 560

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
565 570 575

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
580 585 590

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
 595 600 605

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
 610 615 620

Gln Ala Leu Pro Pro Arg
 625 630

<210> 37
 <211> 1182
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PLA2R-CAAR Construct 4025.C

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 ggcatcttcg tgatccagag cgagagcctg aagaagtgc tccaggccgg caagagcgtg 180
 ctgaccctgg aaaattgcaa gcaggccaac aagcacatgc tgtggaaatg ggtgtccaac 240
 cacggcctgt tcaacatcgg cggctctgga tgtctgggcc tgaatttctc tgcccctgag 300
 cagcctctga gcctgtacga gtgtgatagc accctgggtgt ccctgagatg gcggtgcaac 360
 cggaagatga tcacaggccc tctgcagtac tctgtgcagg tcgcccacga caataccgtg 420
 gtggccagca gaaagtacat ccacaagtgg atcagctacg gcagcggcgg aggcgacatc 480
 tgtgaatacc tgcacaagga tctgtccgga accacgacgc cagcgccgcg accaccaaca 540
 ccggcgccca ccatcgcgtc gcagcccctg tccctgcgcc cagaggcgtg ccggccagcg 600
 gcggggggcg cagtgcacac gagggggctg gacttcgcct gtgatattcta catctgggcg 660
 cccttgggcg ggacttgtgg ggtccttctc ctgtcactgg ttatcaccct ttactgcaaa 720
 cggggcagaa agaaactcct gtatatattc aaacaaccat ttatgagacc agtacaaact 780
 actcaagagg aagatggctg tagctgccga tttccagaag aagaagaagg aggatgtgaa 840
 ctgagagtga agttcagcag gagcgcagac gccccgcgt acaagcaggg ccagaaccag 900

046483-7207W01_Seq_List.txt

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ggccgggacc ctgagatggg gggaaagccg agaaggaaga accctcagga aggcctgtac 1020
aatgaactgc agaaagataa gatggcggag gcctacagtg agattgggat gaaaggcgag 1080
cgccggaggg gcaaggggca cgatggcctt taccagggtc tcagtacagc caccaaggac 1140
acctacgacg cccttcacat gcaggccctg cccctcgct aa 1182

<210> 38
<211> 393
<212> PRT
<213> Artificial Sequence

<220>
<223> PLA2R-CAAR Construct 4025.C

<400> 38

Met Leu Leu Ser Pro Ser Leu Leu Leu Leu Leu Leu Gly Ala Pro
1 5 10 15

Arg Gly Cys Ala Gly Ser Glu Gly Val Ala Ala Ala Leu Thr Pro Glu
20 25 30

Arg Leu Leu Glu Trp Gln Asp Lys Gly Ile Phe Val Ile Gln Ser Glu
35 40 45

Ser Leu Lys Lys Cys Ile Gln Ala Gly Lys Ser Val Leu Thr Leu Glu
50 55 60

Asn Cys Lys Gln Ala Asn Lys His Met Leu Trp Lys Trp Val Ser Asn
65 70 75 80

His Gly Leu Phe Asn Ile Gly Gly Ser Gly Cys Leu Gly Leu Asn Phe
85 90 95

Ser Ala Pro Glu Gln Pro Leu Ser Leu Tyr Glu Cys Asp Ser Thr Leu
100 105 110

Val Ser Leu Arg Trp Arg Cys Asn Arg Lys Met Ile Thr Gly Pro Leu
115 120 125

046483-7207W01_Seq_List.txt

Gln Tyr Ser Val Gln Val Ala His Asp Asn Thr Val Val Ala Ser Arg
130 135 140

Lys Tyr Ile His Lys Trp Ile Ser Tyr Gly Ser Gly Gly Gly Asp Ile
145 150 155 160

Cys Glu Tyr Leu His Lys Asp Leu Ser Gly Thr Thr Thr Pro Ala Pro
165 170 175

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
180 185 190

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
195 200 205

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
210 215 220

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
225 230 235 240

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
245 250 255

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
260 265 270

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
275 280 285

Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu
290 295 300

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
305 310 315 320

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
325 330 335

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
 340 345 350

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
 355 360 365

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
 370 375 380

Leu His Met Gln Ala Leu Pro Pro Arg
 385 390

<210> 39
 <211> 1821
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PLA2R-CAAR Construct 4026.CF1

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 ggcatcttcg tgatccagag cgagagcctg aagaagtgc tccaggccgg caagagcgtg 180
 ctgaccctgg aaaattgcaa gcaggccaac aagcacatgc tgtggaaatg ggtgtccaac 240
 cacggcctgt tcaacatcgg cggctctgga tgtctgggcc tgaatttctc tgcccctgag 300
 cagcctctga gcctgtacga gtgtgatagc accctgggtg ccctgagatg gcggtgcaac 360
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 gtggccagca gaaagtacat ccacaagtgg atcagctacg gcagcggcgg aggcgacatc 480
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 atgttcccgt ttcagtacaa ccaccagtgg caccacgagt gcaccagaga aggcagagag 600
 gacgacctgc tttggtgcgc cacaaccagc agatacgagc gggatgagaa gtggggcctc 660
 tgccctgatc ctacctctgc cgaagtgggc tgcgatacca tctgggagaa agacctgaac 720
 agccacatct gctaccagtt caacctgctg tccagcctgt cttggagcga ggcccacagc 780

046483-7207W01_Seq_List.txt

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gagcatgccg gatggcagtg gagtgatggc acccctctga actacctgaa ctggtcccct      960
gaagtgaact tcgagccctt cgtggaagat cactgcggca ctttcagcag cttcatgccc     1020
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aaccacatcg accacgagat cgtggaaaag gacgcctgga agtactacgc cacacactgc     1140
gagtccggaa ccacgacgcc agcgccgcga ccaccaacac cggcgcccac catcgcgtcg     1200
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caggccctgc cccctcgcta a                                           1821

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<210> 40

<211> 606

<212> PRT

<213> Artificial Sequence

<220>

<223> PLA2R-CAAR Construct 4026.CF1

<400> 40

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1           5           10           15

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046483-7207W01_Seq_List.txt

Arg Gly Cys Ala Gly Ser Glu Gly Val Ala Ala Ala Leu Thr Pro Glu
20 25 30

Arg Leu Leu Glu Trp Gln Asp Lys Gly Ile Phe Val Ile Gln Ser Glu
35 40 45

Ser Leu Lys Lys Cys Ile Gln Ala Gly Lys Ser Val Leu Thr Leu Glu
50 55 60

Asn Cys Lys Gln Ala Asn Lys His Met Leu Trp Lys Trp Val Ser Asn
65 70 75 80

His Gly Leu Phe Asn Ile Gly Gly Ser Gly Cys Leu Gly Leu Asn Phe
85 90 95

Ser Ala Pro Glu Gln Pro Leu Ser Leu Tyr Glu Cys Asp Ser Thr Leu
100 105 110

Val Ser Leu Arg Trp Arg Cys Asn Arg Lys Met Ile Thr Gly Pro Leu
115 120 125

Gln Tyr Ser Val Gln Val Ala His Asp Asn Thr Val Val Ala Ser Arg
130 135 140

Lys Tyr Ile His Lys Trp Ile Ser Tyr Gly Ser Gly Gly Gly Asp Ile
145 150 155 160

Cys Glu Tyr Leu His Lys Asp Leu His Thr Ile Lys Gly Asn Thr His
165 170 175

Gly Met Pro Cys Met Phe Pro Phe Gln Tyr Asn His Gln Trp His His
180 185 190

Glu Cys Thr Arg Glu Gly Arg Glu Asp Asp Leu Leu Trp Cys Ala Thr
195 200 205

Thr Ser Arg Tyr Glu Arg Asp Glu Lys Trp Gly Phe Cys Pro Asp Pro
210 215 220

046483-7207W01_Seq_List.txt

Thr Ser Ala Glu Val Gly Cys Asp Thr Ile Trp Glu Lys Asp Leu Asn
225 230 235 240

Ser His Ile Cys Tyr Gln Phe Asn Leu Leu Ser Ser Leu Ser Trp Ser
245 250 255

Glu Ala His Ser Ser Cys Gln Met Gln Gly Gly Thr Leu Leu Ser Ile
260 265 270

Thr Asp Glu Thr Glu Glu Asn Phe Ile Arg Glu His Met Ser Ser Lys
275 280 285

Thr Val Glu Val Trp Met Gly Leu Asn Gln Leu Asp Glu His Ala Gly
290 295 300

Trp Gln Trp Ser Asp Gly Thr Pro Leu Asn Tyr Leu Asn Trp Ser Pro
305 310 315 320

Glu Val Asn Phe Glu Pro Phe Val Glu Asp His Cys Gly Thr Phe Ser
325 330 335

Ser Phe Met Pro Ser Ala Trp Arg Ser Arg Asp Cys Glu Ser Thr Leu
340 345 350

Pro Tyr Ile Cys Lys Lys Tyr Leu Asn His Ile Asp His Glu Ile Val
355 360 365

Glu Lys Asp Ala Trp Lys Tyr Tyr Ala Thr His Cys Glu Ser Gly Thr
370 375 380

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
385 390 395 400

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
405 410 415

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
420 425 430

046483-7207W01_Seq_List.txt

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
435 440 445

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
450 455 460

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
465 470 475 480

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

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn
500 505 510

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
515 520 525

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
530 535 540

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
545 550 555 560

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
565 570 575

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
580 585 590

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
595 600 605

<210> 41

<211> 4441

<212> DNA

<213> Homo sapiens

<400> 41

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60

046483-7207W01_Seq_List.txt

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tttctccgcc ccagagcagc cattaagctt atatgaatgt gactccaccc tcgtttcctt	360
acggtggcgc tgtaacagga agatgatcac agggccgctg cagtactctg tccaggtggc	420
gcatgacaac acagtgggtg cctcacggaa gtatattcat aagtggattt cttatgggtc	480
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ccacgggatg ccgtgtatgt ttcccttcca gtataaccat cagtggcatc atgaatgtac	600
ccgtgaaggt cgggaagatg acttactgtg gtgtgccacg acaagccgtt atgaaagaga	660
tgaaaagtgg ggattttgcc ctgatccac ctctgcagaa gtaggttctg atactatttg	720
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cctcaatcag ctggatgaac acgctggctg gcagtggctt gatggaacgc cgctcaacta	960
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35 40 45

<210> 44
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Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
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35 40 45

Gly Leu Asp Phe Ala Cys Asp
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<210> 45
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<223> CD3 zeta signaling domain

<400> 45

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20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
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 <223> CysR

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<400> 48

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Val Gln Cys

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<400> 49

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 20 25 30

His Met Leu Trp Lys Trp Val Ser Asn His Gly Leu Phe Asn Ile Gly
 35 40 45

Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala Pro Glu Gln Pro Leu
 50 55 60

Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser Leu Arg Trp Arg Cys
 65 70 75 80

Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr Ser Val Gln Val Ala
 85 90 95

His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr Ile His Lys Trp Ile
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Leu His Thr Ile
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<212> DNA

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<223> CysR-FNII-CTLD1

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 <211> 330
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 51

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			20					25					30		

His	Met	Leu	Trp	Lys	Trp	Val	Ser	Asn	His	Gly	Leu	Phe	Asn	Ile	Gly
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Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser Leu Arg Trp Arg Cys
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Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr Ser Val Gln Val Ala
85 90 95

His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr Ile His Lys Trp Ile
100 105 110

Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu Tyr Leu His Lys Asp
115 120 125

Leu His Thr Ile Lys Gly Asn Thr His Gly Met Pro Cys Met Phe Pro
130 135 140

Phe Gln Tyr Asn His Gln Trp His His Glu Cys Thr Arg Glu Gly Arg
145 150 155 160

Glu Asp Asp Leu Leu Trp Cys Ala Thr Thr Ser Arg Tyr Glu Arg Asp
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Glu Lys Trp Gly Phe Cys Pro Asp Pro Thr Ser Ala Glu Val Gly Cys
180 185 190

Asp Thr Ile Trp Glu Lys Asp Leu Asn Ser His Ile Cys Tyr Gln Phe
195 200 205

Asn Leu Leu Ser Ser Leu Ser Trp Ser Glu Ala His Ser Ser Cys Gln
210 215 220

Met Gln Gly Gly Thr Leu Leu Ser Ile Thr Asp Glu Thr Glu Glu Asn
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Phe Ile Arg Glu His Met Ser Ser Lys Thr Val Glu Val Trp Met Gly
245 250 255

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260 265 270

Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val Asn Phe Glu Pro Phe
275 280 285

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

210

215

220

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

420

425

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Gly Trp Glu Arg His Gly Gly Phe Cys Tyr Lys Ile Asp Thr Val Leu
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Arg Ser Phe Asp Gln Ala Ser Ser Gly Tyr Tyr Cys Pro Pro Ala Leu
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Val Thr Ile Thr Asn Arg Phe Glu Gln Ala Phe Ile Thr Ser Leu Ile
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Ser Ser Val Val Lys Met Lys Asp Ser Tyr Phe Trp Ile Ala Leu Gln
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Pro Glu Pro Val Gln Tyr Thr His Trp Asn Thr His Gln Pro Arg Tyr
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Ser Gly Gly Cys Val Ala Met Arg Gly Arg His Pro Leu Gly Arg Trp
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<223> CysR-FNII-CTLD1-3 7

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gtggcgatgc ggggtcgcca cctctcggga cgctgggagg tgaagcattg ccgccacttc	1800
aaggcgatga gcttgtgtaa acagcccgtc gaaaatcagg aaaaggcagt taacacatct	1860
gatatgtacc ctatgcctaa cacactcgaa tatgggaata ggacgtacaa gattataaac	1920
gcgaacatga cgtggtatgc tgcaatcaag acgtgcctca tgcacaaagc tcagcttgtg	1980
tctattactg accaatacca ccaatcattt ttgacagtcg tgttgaatcg attggggtag	2040
gcccattgga tcggtctctt cacgacggac aatgggctca attttgactg gagtgacggt	2100
actaaatcat cttttacttt ttggaaggat gaagaaagt ctctgttggg cgattgcgtg	2160
tttgctgact caaatggccg atggcattcc acagcctgtg aaagttttct gcaggagct	2220
atttgccacg tgcctccga aacgcggcag tccgaacacc cggaattg	2268

<210> 55
 <211> 756
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CysR-FNII-CTLD1-3 7

<400> 55

Lys	Gly	Ile	Phe	Val	Ile	Gln	Ser	Glu	Ser	Leu	Lys	Lys	Cys	Ile	Gln
1				5					10					15	

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

His	Met	Leu	Trp	Lys	Trp	Val	Ser	Asn	His	Gly	Leu	Phe	Asn	Ile	Gly
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

35

40

45

Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala Pro Glu Gln Pro Leu
 50 55 60

Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser Leu Arg Trp Arg Cys
 65 70 75 80

Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr Ser Val Gln Val Ala
 85 90 95

His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr Ile His Lys Trp Ile
 100 105 110

Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu Tyr Leu His Lys Asp
 115 120 125

Leu His Thr Ile Lys Gly Asn Thr His Gly Met Pro Cys Met Phe Pro
 130 135 140

Phe Gln Tyr Asn His Gln Trp His His Glu Cys Thr Arg Glu Gly Arg
 145 150 155 160

Glu Asp Asp Leu Leu Trp Cys Ala Thr Thr Ser Arg Tyr Glu Arg Asp
 165 170 175

Glu Lys Trp Gly Phe Cys Pro Asp Pro Thr Ser Ala Glu Val Gly Cys
 180 185 190

Asp Thr Ile Trp Glu Lys Asp Leu Asn Ser His Ile Cys Tyr Gln Phe
 195 200 205

Asn Leu Leu Ser Ser Leu Ser Trp Ser Glu Ala His Ser Ser Cys Gln
 210 215 220

Met Gln Gly Gly Thr Leu Leu Ser Ile Thr Asp Glu Thr Glu Glu Asn
 225 230 235 240

Phe Ile Arg Glu His Met Ser Ser Lys Thr Val Glu Val Trp Met Gly

245

250

255

Leu Asn Gln Leu Asp Glu His Ala Gly Trp Gln Trp Ser Asp Gly Thr
 260 265 270

Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val Asn Phe Glu Pro Phe
 275 280 285

Val Glu Asp His Cys Gly Thr Phe Ser Ser Phe Met Pro Ser Ala Trp
 290 295 300

Arg Ser Arg Asp Cys Glu Ser Thr Leu Pro Tyr Ile Cys Lys Lys Tyr
 305 310 315 320

Leu Asn His Ile Asp His Glu Ile Val Glu Lys Asp Ala Trp Lys Tyr
 325 330 335

Tyr Ala Thr His Cys Glu Pro Gly Trp Asn Pro Tyr Asn Arg Asn Cys
 340 345 350

Tyr Lys Leu Gln Lys Glu Glu Lys Thr Trp His Glu Ala Leu Arg Ser
 355 360 365

Cys Gln Ala Asp Asn Ser Ala Leu Ile Asp Ile Thr Ser Leu Ala Glu
 370 375 380

Val Glu Phe Leu Val Thr Leu Leu Gly Asp Glu Asn Ala Ser Glu Thr
 385 390 395 400

Trp Ile Gly Leu Ser Ser Asn Lys Ile Pro Val Ser Phe Glu Trp Ser
 405 410 415

Asn Asp Ser Ser Val Ile Phe Thr Asn Trp His Thr Leu Glu Pro His
 420 425 430

Ile Phe Pro Asn Arg Ser Gln Leu Cys Val Ser Ala Glu Gln Ser Glu
 435 440 445

Gly His Trp Lys Val Lys Asn Cys Glu Glu Arg Leu Phe Tyr Ile Cys

450

455

460

Lys Lys Ala Gly His Val Leu Ser Asp Ala Glu Ser Gly Cys Gln Glu
 465 470 475 480

Gly Trp Glu Arg His Gly Gly Phe Cys Tyr Lys Ile Asp Thr Val Leu
 485 490 495

Arg Ser Phe Asp Gln Ala Ser Ser Gly Tyr Tyr Cys Pro Pro Ala Leu
 500 505 510

Val Thr Ile Thr Asn Arg Phe Glu Gln Ala Phe Ile Thr Ser Leu Ile
 515 520 525

Ser Ser Val Val Lys Met Lys Asp Ser Tyr Phe Trp Ile Ala Leu Gln
 530 535 540

Asp Gln Asn Asp Thr Gly Glu Tyr Thr Trp Lys Pro Val Gly Gln Lys
 545 550 555 560

Pro Glu Pro Val Gln Tyr Thr His Trp Asn Thr His Gln Pro Arg Tyr
 565 570 575

Ser Gly Gly Cys Val Ala Met Arg Gly Arg His Pro Leu Gly Arg Trp
 580 585 590

Glu Val Lys His Cys Arg His Phe Lys Ala Met Ser Leu Cys Lys Gln
 595 600 605

Pro Val Glu Asn Gln Glu Lys Ala Val Asn Thr Ser Asp Met Tyr Pro
 610 615 620

Met Pro Asn Thr Leu Glu Tyr Gly Asn Arg Thr Tyr Lys Ile Ile Asn
 625 630 635 640

Ala Asn Met Thr Trp Tyr Ala Ala Ile Lys Thr Cys Leu Met His Lys
 645 650 655

Ala Gln Leu Val Ser Ile Thr Asp Gln Tyr His Gln Ser Phe Leu Thr

660

665

670

Val Val Leu Asn Arg Leu Gly Tyr Ala His Trp Ile Gly Leu Phe Thr
 675 680 685

Thr Asp Asn Gly Leu Asn Phe Asp Trp Ser Asp Gly Thr Lys Ser Ser
 690 695 700

Phe Thr Phe Trp Lys Asp Glu Glu Ser Ser Leu Leu Gly Asp Cys Val
 705 710 715 720

Phe Ala Asp Ser Asn Gly Arg Trp His Ser Thr Ala Cys Glu Ser Phe
 725 730 735

Leu Gln Gly Ala Ile Cys His Val Pro Pro Glu Thr Arg Gln Ser Glu
 740 745 750

His Pro Glu Leu
 755

<210> 56
 <211> 1410
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> CysR-FNII-CTLD1 7

<400> 56
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 aaccacggcc tcttcaatat tgggtgggtca gggttgcttg ggttgaattt ctccgccccca 180
 gagcaaccac tcagccttta cgagtgtgat tccacacttg tctctttgcg atggcgctgc 240
 aataggaaaa tgatcacagg ccccttcag tactctgtgc aagttgctca tgataacaca 300
 gtcgtggcga gtcggaaata tattcacaaa tggatttctt atgggagtgg tggaggagat 360
 atatgcgagt atttgcataa ggacttgac accatcaagg gaaacactca cggtatgcca 420
 tgtatgtttc cgttccaata taatcatcaa tggcaccacg aatgtaccg agagggacgc 480

046483-7207W01_Seq_List.txt

gaggacgatac	ttcttttggtg	cgccacaacc	tctcgatatg	aacgagatga	gaagtggggg	540
ttttgtcctg	acccaaccag	tgcagaagta	gggtgcgata	ccatctggga	gaaagacttg	600
aactcacaca	tatgctatca	gtttaatttg	ttgtcttctt	tgtcatggag	cgaagctcat	660
tcatcatgcc	agatgcaggg	cgggacactg	ctttctatca	ccgacgagac	tgaggaaaat	720
tttatccgcg	agcacatgtc	aagcaagaca	gttgagggtt	ggatggggct	caatcaactg	780
gacgaacacg	cagggtggca	gtggtccgat	ggcactccgc	tcaactacct	taactggagc	840
ccagagggtga	actttgagcc	gtttgtcgaa	gatcactgtg	gtacttttag	ctccttcatg	900
ccgtccgcat	ggagaagtcg	cgactgcgag	tcaaccctcc	cttacatctg	taagaaatac	960
ctcaaccaca	tagatcacga	aatcgtagag	gtcaatacgt	ccgacatgta	cccaatgcca	1020
aatacgttgg	aatatgggaa	taggacatac	aagataatta	acgcaaatat	gacgtggtat	1080
gccgcaatca	aaacgtgcct	catgcacaag	gcacagctcg	tgtcaattac	ggaccagtac	1140
caccaatcat	ttctcacagt	cgttcttaat	cgattgggtt	atgcacactg	gataggcttg	1200
ttcacgacgg	acaatggttt	gaactttgac	tggtccgatg	gaactaaaag	ttctttcact	1260
ttttggaagg	atgaggagtc	ctccttgctc	ggggactgcg	tcttcgcaga	ttcaaacggg	1320
cgctggcact	caacggcatg	tgagtccttc	ctgcagggag	ctatatgcca	tgtgccacca	1380
gaaacacgcc	agtctgagca	ccctgagttg				1410

<210> 57
 <211> 470
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CysR-FNII-CTLD1 7

<400> 57

Lys	Gly	Ile	Phe	Val	Ile	Gln	Ser	Glu	Ser	Leu	Lys	Lys	Cys	Ile	Gln
1				5						10				15	

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

His	Met	Leu	Trp	Lys	Trp	Val	Ser	Asn	His	Gly	Leu	Phe	Asn	Ile	Gly
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

35

40

45

Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala Pro Glu Gln Pro Leu
 50 55 60

Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser Leu Arg Trp Arg Cys
 65 70 75 80

Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr Ser Val Gln Val Ala
 85 90 95

His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr Ile His Lys Trp Ile
 100 105 110

Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu Tyr Leu His Lys Asp
 115 120 125

Leu His Thr Ile Lys Gly Asn Thr His Gly Met Pro Cys Met Phe Pro
 130 135 140

Phe Gln Tyr Asn His Gln Trp His His Glu Cys Thr Arg Glu Gly Arg
 145 150 155 160

Glu Asp Asp Leu Leu Trp Cys Ala Thr Thr Ser Arg Tyr Glu Arg Asp
 165 170 175

Glu Lys Trp Gly Phe Cys Pro Asp Pro Thr Ser Ala Glu Val Gly Cys
 180 185 190

Asp Thr Ile Trp Glu Lys Asp Leu Asn Ser His Ile Cys Tyr Gln Phe
 195 200 205

Asn Leu Leu Ser Ser Leu Ser Trp Ser Glu Ala His Ser Ser Cys Gln
 210 215 220

Met Gln Gly Gly Thr Leu Leu Ser Ile Thr Asp Glu Thr Glu Glu Asn
 225 230 235 240

Phe Ile Arg Glu His Met Ser Ser Lys Thr Val Glu Val Trp Met Gly

245

250

255

Leu Asn Gln Leu Asp Glu His Ala Gly Trp Gln Trp Ser Asp Gly Thr
 260 265 270

Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val Asn Phe Glu Pro Phe
 275 280 285

Val Glu Asp His Cys Gly Thr Phe Ser Ser Phe Met Pro Ser Ala Trp
 290 295 300

Arg Ser Arg Asp Cys Glu Ser Thr Leu Pro Tyr Ile Cys Lys Lys Tyr
 305 310 315 320

Leu Asn His Ile Asp His Glu Ile Val Glu Val Asn Thr Ser Asp Met
 325 330 335

Tyr Pro Met Pro Asn Thr Leu Glu Tyr Gly Asn Arg Thr Tyr Lys Ile
 340 345 350

Ile Asn Ala Asn Met Thr Trp Tyr Ala Ala Ile Lys Thr Cys Leu Met
 355 360 365

His Lys Ala Gln Leu Val Ser Ile Thr Asp Gln Tyr His Gln Ser Phe
 370 375 380

Leu Thr Val Val Leu Asn Arg Leu Gly Tyr Ala His Trp Ile Gly Leu
 385 390 395 400

Phe Thr Thr Asp Asn Gly Leu Asn Phe Asp Trp Ser Asp Gly Thr Lys
 405 410 415

Ser Ser Phe Thr Phe Trp Lys Asp Glu Glu Ser Ser Leu Leu Gly Asp
 420 425 430

Cys Val Phe Ala Asp Ser Asn Gly Arg Trp His Ser Thr Ala Cys Glu
 435 440 445

Ser Phe Leu Gln Gly Ala Ile Cys His Val Pro Pro Glu Thr Arg Gln

450

455

460

Ser Glu His Pro Glu Leu
465 470

<210> 58
<211> 1251
<212> DNA
<213> Artificial Sequence

<220>
<223> CysR-CTLD1 7

<400> 58
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gtactcacgc ttgaaaattg caaacaggcc aacaaacaca tgcttttgaa atggggtttca 120
aatcacgggt tgtttaacat aggggggatca ggatgtctgg gccttaactt ttccgcacct 180
gaacaacctc ttagtctgta tgagtgtgac tcaacgctgg tctccttgcg ctggagatgc 240
aatcggaaga tgataaccgg gcccctccag tattccgttc aggtcgccca cgataatact 300
gttggtgcat cccgaaaata tattcataag tggatctcct acgggagtgg agggggcgat 360
atgtgtgaat acctccacaa ggatctgcac actatcactt ctgcggaagt aggctgtgac 420
acaatctggg agaaagatct gaattcacac atttgctatc agttcaatct tctgagttct 480
ttgagctggg ccgaagcaca ttcacacctg cagatgcaag gtggaacact cttgtcaata 540
acagatgaaa cggaagagaa ctttattaga gaacatatgt cctcaaagac tgtggaggtg 600
tggatgggac ttaaccagct cgatgaacat gcaggatggc agtggagtga cggaacgcca 660
ctgaactacc tgaattggag cccagaggtg aatttcgagc ctttcgtaga ggaccattgc 720
ggtaactttt catcttttat gccagcgca tggagatccc gagattgtga aagcacgctg 780
ccctatattt gtaaaaagta cctgaaccac atagatcatg agatagttga ggtaaataca 840
agtgatatgt accccatgcc gaacacactc gagtacggaa atagaacctt caagataatc 900
aacgctaaca tgacctggta cgcggccatt aagacctgcc tcatgcacaa ggctcaactc 960
gtcagtatta ctgaccaata tcaccagtca tttctcaccg tcgtgttgaa tcgcctcggg 1020
tacgccact ggatcggttt gtttacaacg gacaatggac tcaatttcga ttggtcagac 1080

ggaaccaaat ctagttttac cttctggaaa gacgaggaat caagcctgct tggggactgc 1140

gtatttgcgg actctaattgg ccgatggcat agtacagcgt gtgagagctt tttgcagggg 1200

gcgatttgtc atgttccgcc ggaaacccgc caaagcgagc atccagaatt g 1251

<210> 59

<211> 417

<212> PRT

<213> Artificial Sequence

<220>

<223> CysR-CTLD1 7

<400> 59

Lys Gly Ile Phe Val Ile Gln Ser Glu Ser Leu Lys Lys Cys Ile Gln
1 5 10 15

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

His Met Leu Trp Lys Trp Val Ser Asn His Gly Leu Phe Asn Ile Gly
35 40 45

Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala Pro Glu Gln Pro Leu
50 55 60

Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser Leu Arg Trp Arg Cys
65 70 75 80

Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr Ser Val Gln Val Ala
85 90 95

His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr Ile His Lys Trp Ile
100 105 110

Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu Tyr Leu His Lys Asp
115 120 125

Leu His Thr Ile Thr Ser Ala Glu Val Gly Cys Asp Thr Ile Trp Glu
130 135 140

046483-7207W01_Seq_List.txt

Lys Asp Leu Asn Ser His Ile Cys Tyr Gln Phe Asn Leu Leu Ser Ser
145 150 155 160

Leu Ser Trp Ser Glu Ala His Ser Ser Cys Gln Met Gln Gly Gly Thr
165 170 175

Leu Leu Ser Ile Thr Asp Glu Thr Glu Glu Asn Phe Ile Arg Glu His
180 185 190

Met Ser Ser Lys Thr Val Glu Val Trp Met Gly Leu Asn Gln Leu Asp
195 200 205

Glu His Ala Gly Trp Gln Trp Ser Asp Gly Thr Pro Leu Asn Tyr Leu
210 215 220

Asn Trp Ser Pro Glu Val Asn Phe Glu Pro Phe Val Glu Asp His Cys
225 230 235 240

Gly Thr Phe Ser Ser Phe Met Pro Ser Ala Trp Arg Ser Arg Asp Cys
245 250 255

Glu Ser Thr Leu Pro Tyr Ile Cys Lys Lys Tyr Leu Asn His Ile Asp
260 265 270

His Glu Ile Val Glu Val Asn Thr Ser Asp Met Tyr Pro Met Pro Asn
275 280 285

Thr Leu Glu Tyr Gly Asn Arg Thr Tyr Lys Ile Ile Asn Ala Asn Met
290 295 300

Thr Trp Tyr Ala Ala Ile Lys Thr Cys Leu Met His Lys Ala Gln Leu
305 310 315 320

Val Ser Ile Thr Asp Gln Tyr His Gln Ser Phe Leu Thr Val Val Leu
325 330 335

Asn Arg Leu Gly Tyr Ala His Trp Ile Gly Leu Phe Thr Thr Asp Asn
340 345 350

046483-7207W01_Seq_List.txt

Gly Leu Asn Phe Asp Trp Ser Asp Gly Thr Lys Ser Ser Phe Thr Phe
355 360 365

Trp Lys Asp Glu Glu Ser Ser Leu Leu Gly Asp Cys Val Phe Ala Asp
370 375 380

Ser Asn Gly Arg Trp His Ser Thr Ala Cys Glu Ser Phe Leu Gln Gly
385 390 395 400

Ala Ile Cys His Val Pro Pro Glu Thr Arg Gln Ser Glu His Pro Glu
405 410 415

Leu

<210> 60
<211> 387
<212> DNA
<213> Artificial Sequence

<220>
<223> CysR

<400> 60
aagggcatct tcgtgatcca gagcgagagc ctgaagaagt gcatccaggc cggcaagagc 60
gtgctgaccc tggaaaattg caagcaggcc aacaagcaca tgctgtggaa atgggtgtcc 120
aaccacggcc tgttcaacat cggcggctct ggatgtcttg gcctgaattt ctctgcccct 180
gagcagcctc tgagcctgta cgagtgtgat agcaccctgg tgtccctgag atggcgggtgc 240
aaccggaaga tgatcacagg ccctctgcag tactctgtgc aggtcgccca cgacaatacc 300
gtggtggcca gcagaaagta catccacaag tggatcagct acggcagcgg cggaggcgac 360
atctgtgaat acctgcacaa ggatctg 387

<210> 61
<211> 129
<212> PRT
<213> Artificial Sequence

<220>
<223> CysR

<400> 61

Lys Gly Ile Phe Val Ile Gln Ser Glu Ser Leu Lys Lys Cys Ile Gln
 1 5 10 15

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

His Met Leu Trp Lys Trp Val Ser Asn His Gly Leu Phe Asn Ile Gly
 35 40 45

Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala Pro Glu Gln Pro Leu
 50 55 60

Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser Leu Arg Trp Arg Cys
 65 70 75 80

Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr Ser Val Gln Val Ala
 85 90 95

His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr Ile His Lys Trp Ile
 100 105 110

Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu Tyr Leu His Lys Asp
 115 120 125

Leu

<210> 62

<211> 1026

<212> DNA

<213> Artificial Sequence

<220>

<223> CysR-FNII-CTLD1

<400> 62

aagggcatct tcgtgatcca gagcgagagc ctgaagaagt gcatccaggc cggcaagagc 60

gtgctgaccc tggaaaattg caagcaggcc aacaagcaca tgctgtggaa atgggtgtcc 120

046483-7207W01_Seq_List.txt

aaccacggcc tgttcaacat cggcggctct ggatgtctgg gcctgaattt ctctgcccct	180
gagcagcctc tgagcctgta cgagtgtgat agcaccctgg tgtccctgag atggcgggtgc	240
aaccggaaga tgatcacagg ccctctgcag tactctgtgc aggtcgccca cgacaatacc	300
gtggtggcca gcagaaagta catccacaag tggatcagct acggcagcgg cggaggcgac	360
atctgtgaat acctgcacaa ggatctgcac accatcaagg gcaacaccca cggaatgccc	420
tgcatgttcc cgtttcagta caaccaccag tggcaccacg agtgcaccag agaaggcaga	480
gaggacgacc tgctttggtg cgccacaacc agcagatacg agcgggatga gaagtggggc	540
ttctgcccctg atcctacctc tgccgaagtg ggctgcgata ccatctggga gaaagacctg	600
aacagccaca tctgctacca gttcaacctg ctgtccagcc tgtcttggag cgaggcccac	660
agcagctgtc aaatgcaagg cggcacactg ctgagcatca ccgacgagac agaggaaaac	720
ttcatccgcg agcacatgag cagcaagacc gtggaagtgt ggatgggact gaaccagctg	780
gatgagcatg ccggatggca gtggagtgat ggcaccctc tgaactacct gaactggtcc	840
cctgaagtga acttcgagcc cttcgtggaa gatcactgcg gcaccttcag cagcttcatg	900
cccagcgctt ggagaagcag agactgcgag agcaccctgc cttacatctg caagaagtac	960
ctgaaccaca tcgaccacga gatcgtggaa aaggacgcct ggaagtacta cgccacacac	1020
tgcgag	1026

<210> 63
 <211> 342
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CysR-FNII-CTLD1

<400> 63

Lys	Gly	Ile	Phe	Val	Ile	Gln	Ser	Glu	Ser	Leu	Lys	Lys	Cys	Ile	Gln
1				5					10					15	

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

His	Met	Leu	Trp	Lys	Trp	Val	Ser	Asn	His	Gly	Leu	Phe	Asn	Ile	Gly
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

35

40

45

Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala Pro Glu Gln Pro Leu
 50 55 60

Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser Leu Arg Trp Arg Cys
 65 70 75 80

Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr Ser Val Gln Val Ala
 85 90 95

His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr Ile His Lys Trp Ile
 100 105 110

Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu Tyr Leu His Lys Asp
 115 120 125

Leu His Thr Ile Lys Gly Asn Thr His Gly Met Pro Cys Met Phe Pro
 130 135 140

Phe Gln Tyr Asn His Gln Trp His His Glu Cys Thr Arg Glu Gly Arg
 145 150 155 160

Glu Asp Asp Leu Leu Trp Cys Ala Thr Thr Ser Arg Tyr Glu Arg Asp
 165 170 175

Glu Lys Trp Gly Phe Cys Pro Asp Pro Thr Ser Ala Glu Val Gly Cys
 180 185 190

Asp Thr Ile Trp Glu Lys Asp Leu Asn Ser His Ile Cys Tyr Gln Phe
 195 200 205

Asn Leu Leu Ser Ser Leu Ser Trp Ser Glu Ala His Ser Ser Cys Gln
 210 215 220

Met Gln Gly Gly Thr Leu Leu Ser Ile Thr Asp Glu Thr Glu Glu Asn
 225 230 235 240

Phe Ile Arg Glu His Met Ser Ser Lys Thr Val Glu Val Trp Met Gly

245

250

255

Leu Asn Gln Leu Asp Glu His Ala Gly Trp Gln Trp Ser Asp Gly Thr
 260 265 270

Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val Asn Phe Glu Pro Phe
 275 280 285

Val Glu Asp His Cys Gly Thr Phe Ser Ser Phe Met Pro Ser Ala Trp
 290 295 300

Arg Ser Arg Asp Cys Glu Ser Thr Leu Pro Tyr Ile Cys Lys Lys Tyr
 305 310 315 320

Leu Asn His Ile Asp His Glu Ile Val Glu Lys Asp Ala Trp Lys Tyr
 325 330 335

Tyr Ala Thr His Cys Glu
 340

<210> 64

<211> 165

<212> DNA

<213> Artificial Sequence

<220>

<223> CD8 alpha hinge domain

<400> 64

ttcgtgccgg tcttcctgcc agcgaagcca accacgacgc cagcaccgcg accaccaaca 60

cctgcgcca ccatcgcgtc gcagcccctg tccctgcgcc cagaggcgtg cagaccagca 120

gcggggggcg cagtgcacac gagggggctg gacttcgcct gtgat 165

<210> 65

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> PLA2R Signal peptide

<400> 65

atgctgctga gccctagcct gctgctgctc ctgcttcttg gagcccctag aggatgtgcc 60

<210> 66
 <211> 126
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> 4-1BB intracellular domain

<400> 66
 aagcgcggtc gcaagaaact gctctatatt tttaaacagc cattcatgag acctgtccag 60
 accactcaag aggaggacgg atgttcctgt agatttcctg aagaggaaga ggggggggtgc 120
 gagctg 126

<210> 67
 <211> 57
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PLA2R pro-peptide

<400> 67
 ggatctgaag gtgttgccgc cgctctgaca cccgagagac tgctggaatg gcaggac 57

<210> 68
 <211> 30
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> GS linker

<400> 68
 ggtggcggag gttctggagg tggaggttcc 30

<210> 69
 <211> 10
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> GS linker

<400> 69

ggggs

<210> 70
 <211> 479
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Extracellular domains of Construct 4027.CF12

<400> 70

Lys Gly Ile Phe Val Ile Gln Ser Glu Ser Leu Lys Lys Cys Ile Gln
 1 5 10 15

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

His Met Leu Trp Lys Trp Val Ser Asn His Gly Leu Phe Asn Ile Gly
 35 40 45

Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala Pro Glu Gln Pro Leu
 50 55 60

Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser Leu Arg Trp Arg Cys
 65 70 75 80

Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr Ser Val Gln Val Ala
 85 90 95

His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr Ile His Lys Trp Ile
 100 105 110

Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu Tyr Leu His Lys Asp
 115 120 125

Leu His Thr Ile Lys Gly Asn Thr His Gly Met Pro Cys Met Phe Pro
 130 135 140

Phe Gln Tyr Asn His Gln Trp His His Glu Cys Thr Arg Glu Gly Arg
 145 150 155 160

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Glu Asp Asp Leu Leu Trp Cys Ala Thr Thr Ser Arg Tyr Glu Arg Asp
165 170 175

Glu Lys Trp Gly Phe Cys Pro Asp Pro Thr Ser Ala Glu Val Gly Cys
180 185 190

Asp Thr Ile Trp Glu Lys Asp Leu Asn Ser His Ile Cys Tyr Gln Phe
195 200 205

Asn Leu Leu Ser Ser Leu Ser Trp Ser Glu Ala His Ser Ser Cys Gln
210 215 220

Met Gln Gly Gly Thr Leu Leu Ser Ile Thr Asp Glu Thr Glu Glu Asn
225 230 235 240

Phe Ile Arg Glu His Met Ser Ser Lys Thr Val Glu Val Trp Met Gly
245 250 255

Leu Asn Gln Leu Asp Glu His Ala Gly Trp Gln Trp Ser Asp Gly Thr
260 265 270

Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val Asn Phe Glu Pro Phe
275 280 285

Val Glu Asp His Cys Gly Thr Phe Ser Ser Phe Met Pro Ser Ala Trp
290 295 300

Arg Ser Arg Asp Cys Glu Ser Thr Leu Pro Tyr Ile Cys Lys Lys Tyr
305 310 315 320

Leu Asn His Ile Asp His Glu Ile Val Glu Lys Asp Ala Trp Lys Tyr
325 330 335

Tyr Ala Thr His Cys Glu Pro Gly Trp Asn Pro Tyr Asn Arg Asn Cys
340 345 350

Tyr Lys Leu Gln Lys Glu Glu Lys Thr Trp His Glu Ala Leu Arg Ser
355 360 365

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Cys Gln Ala Asp Asn Ser Ala Leu Ile Asp Ile Thr Ser Leu Ala Glu
370 375 380

Val Glu Phe Leu Val Thr Leu Leu Gly Asp Glu Asn Ala Ser Glu Thr
385 390 395 400

Trp Ile Gly Leu Ser Ser Asn Lys Ile Pro Val Ser Phe Glu Trp Ser
405 410 415

Asn Asp Ser Ser Val Ile Phe Thr Asn Trp His Thr Leu Glu Pro His
420 425 430

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

Gly Ser Gly Cys Leu Gly Leu Asn Phe Ser Ala Pro Glu Gln Pro Leu

50

55

60

Ser Leu Tyr Glu Cys Asp Ser Thr Leu Val Ser Leu Arg Trp Arg Cys
65 70 75 80

Asn Arg Lys Met Ile Thr Gly Pro Leu Gln Tyr Ser Val Gln Val Ala
85 90 95

His Asp Asn Thr Val Val Ala Ser Arg Lys Tyr Ile His Lys Trp Ile
100 105 110

Ser Tyr Gly Ser Gly Gly Gly Asp Ile Cys Glu Tyr Leu His Lys Asp
115 120 125

Leu His Thr Ile Lys Gly Asn Thr His Gly Met Pro Cys Met Phe Pro
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Phe Gln Tyr Asn His Gln Trp His His Glu Cys Thr Arg Glu Gly Arg
145 150 155 160

Glu Asp Asp Leu Leu Trp Cys Ala Thr Thr Ser Arg Tyr Glu Arg Asp
165 170 175

Glu Lys Trp Gly Phe Cys Pro Asp Pro Thr Ser Ala Glu Val Gly Cys
180 185 190

Asp Thr Ile Trp Glu Lys Asp Leu Asn Ser His Ile Cys Tyr Gln Phe
195 200 205

Asn Leu Leu Ser Ser Leu Ser Trp Ser Glu Ala His Ser Ser Cys Gln
210 215 220

Met Gln Gly Gly Thr Leu Leu Ser Ile Thr Asp Glu Thr Glu Glu Asn
225 230 235 240

Phe Ile Arg Glu His Met Ser Ser Lys Thr Val Glu Val Trp Met Gly
245 250 255

Leu Asn Gln Leu Asp Glu His Ala Gly Trp Gln Trp Ser Asp Gly Thr

260

265

270

Pro Leu Asn Tyr Leu Asn Trp Ser Pro Glu Val Asn Phe Glu Pro Phe
 275 280 285

Val Glu Asp His Cys Gly Thr Phe Ser Ser Phe Met Pro Ser Ala Trp
 290 295 300

Arg Ser Arg Asp Cys Glu Ser Thr Leu Pro Tyr Ile Cys Lys Lys Tyr
 305 310 315 320

Leu Asn His Ile Asp His Glu Ile Val Glu Lys Asp Ala Trp Lys Tyr
 325 330 335

Tyr Ala Thr His Cys Glu Pro Gly Trp Asn Pro Tyr Asn Arg Asn Cys
 340 345 350

Tyr Lys Leu Gln Lys Glu Glu Lys Thr Trp His Glu Ala Leu Arg Ser
 355 360 365

Cys Gln Ala Asp Asn Ser Ala Leu Ile Asp Ile Thr Ser Leu Ala Glu
 370 375 380

Val Glu Phe Leu Val Thr Leu Leu Gly Asp Glu Asn Ala Ser Glu Thr
 385 390 395 400

Trp Ile Gly Leu Ser Ser Asn Lys Ile Pro Val Ser Phe Glu Trp Ser
 405 410 415

Asn Asp Ser Ser Val Ile Phe Thr Asn Trp His Thr Leu Glu Pro His
 420 425 430

Ile Phe Pro Asn Arg Ser Gln Leu Cys Val Ser Ala Glu Gln Ser Glu
 435 440 445

Gly His Trp Lys Val Lys Asn Cys Glu Glu Arg Leu Phe Tyr Ile Cys
 450 455 460

Lys Lys Ala Gly His Val Leu Ser Asp Ala Glu Ser Gly Cys Gln Glu

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cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat	180
gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc	240
cggaggggca aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc	300
tacgacgccc ttcacatgca ggccctgccc cctcgc	336