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(54) **Title:** CELLS FOR IMMUNOTHERAPY ENGINEERED FOR TARGETING ANTIGEN PRESENT BOTH ON IMMUNE CELLS AND PATHOLOGICAL CELLS

(57) **Abstract:** Methods of developing genetically engineered immune cells for immunotherapy, which can be endowed with Chimeric Antigen Receptors targeting an antigen marker that is common to both the pathological cells and said immune cells (ex: CD38, CS1 or CD70) by the fact that the genes encoding said markers are inactivated in said immune cells by a rare cutting endonuclease such as TALEN, Cas9 or argonaute.



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**CELLS FOR IMMUNOTHERAPY ENGINEERED FOR TARGETING ANTIGEN PRESENT BOTH ON IMMUNE
CELLS AND PATHOLOGICAL CELLS**

5 Field of the invention

The present invention relates to methods of developing genetically engineered, preferably non-alloreactive, immune cells for immunotherapy, which are endowed with Chimeric Antigen Receptors targeting an antigen marker that is common to both the pathological cells and the immune cells (ex: CD38).

10 The method comprises expressing a CAR directed against said antigen marker and inactivating the genes in the immune cells contributing to the presence of said antigen marker on the surface of said immune cells. This inactivation is typically performed by using transgenes encoding RNA-guided endonucleases (ex: Cas9/CRISPR), meganucleases, Zinc-finger nucleases or TAL nucleases. The engineered immune cells, preferably T-cells, direct their immune activity towards
15 malignant, infected cells or defective immune cells, while avoiding their mutual destruction, auto-stimulation or aggregation. The invention opens the way to standard and affordable adoptive immunotherapy strategies using immune cells for treating cancer, infections and auto-immune diseases.

20 Background of the invention

Adoptive immunotherapy, which involves the transfer of autologous antigen-specific immune cells generated *ex vivo*, is a promising strategy to treat viral infections and cancer. The T cells used for adoptive immunotherapy, for instance, can be generated either by expansion of antigen-specific T-cells or redirection of T-cells through genetic engineering (Park, Rosenberg et al. 2011).

25 Novel specificities in T-cells have been successfully generated through the genetic transfer of transgenic T-cell receptors or chimeric antigen receptors (CARs) (Jena, Dotti et al. 2010). CARs are synthetic receptors consisting of a targeting moiety that is associated with one or more signaling domains in a single fusion molecule. In general, the binding moiety of a CAR consists of an antigen-binding domain of a single-chain antibody (scFv), comprising the light and variable fragments of a
30 monoclonal antibody joined by a flexible linker. Binding moieties based on receptor or ligand domains have also been used successfully. The signaling domains for first generation CARs are derived from the cytoplasmic region of the CD3zeta or the Fc receptor gamma chains. First

generation CARs have been shown to successfully redirect T cell cytotoxicity, however, they failed to provide prolonged expansion and anti-tumor activity *in vivo*. Signaling domains from co-stimulatory molecules including CD28, OX-40 (CD134), and 4-1BB (CD137) have been added alone (second generation) or in combination (third generation) to enhance survival and increase proliferation of CAR modified T cells. CARs have successfully allowed T cells to be redirected against antigens expressed at the surface of tumor cells from various malignancies including lymphomas and solid tumors (Jena, Dotti et al. 2010).

The current protocol for treatment of patients using adoptive immunotherapy is based on autologous cell transfer. In this approach, T lymphocytes are recovered from patients, genetically modified or selected *ex vivo*, cultivated *in vitro* in order to amplify the number of cells if necessary and finally infused into the patient. In addition to lymphocyte infusion, the host may be manipulated in other ways that support the engraftment of the T cells or their participation in an immune response, for example pre-conditioning (with radiation or chemotherapy) and administration of lymphocyte growth factors (such as IL-2). Each patient receives an individually fabricated treatment, using the patient's own lymphocytes (i.e. an autologous therapy). Autologous therapies face substantial technical and logistic hurdles to practical application, their generation requires expensive dedicated facilities and expert personnel, they must be generated in a short time following a patient's diagnosis, and in many cases, pretreatment of the patient has resulted in degraded immune function, such that the patient's lymphocytes may be poorly functional and present in very low numbers. Because of these hurdles, each patient's autologous cell preparation is effectively a new product, resulting in substantial variations in efficacy and safety.

Ideally, one would like to use a standardized therapy in which allogeneic therapeutic cells could be pre-manufactured, characterized in detail, and available for immediate administration to patients. By allogeneic it is meant that the cells are obtained from individuals belonging to the same species but are genetically dissimilar. However, the use of allogeneic cells presently has many drawbacks. In immune-competent hosts allogeneic cells are rapidly rejected, a process termed host versus graft rejection (HvG), and this substantially limits the efficacy of the transferred cells. In immune-incompetent hosts, allogeneic cells are able to engraft, but their endogenous T-cell receptors (TCR) specificities may recognize the host tissue as foreign, resulting in graft versus host disease (GvHD), which can lead to serious tissue damage and death.

In order to provide allogeneic T-cells, the inventors previously disclosed a method to genetically engineer T-Cells, in which different effector genes, in particular those encoding T-cell receptors, were inactivated by using specific TAL-nucleases, better known under the trade mark

TALEN™ (Cellestis, 8, rue de la Croix Jarry, 75013 PARIS). This method has proven to be highly efficiency in primary cells using RNA transfection as part of a platform allowing the mass production of allogeneic T-cells (WO 2013/176915).

CD38 (cluster of differentiation 38), also known as cyclic ADP ribose hydrolase is a glycoprotein found on the surface of many immune cells (white blood cells), in particular T-cells, including CD4+, CD8+, B lymphocytes and natural killer cells. CD38 also functions in cell adhesion, signal transduction and calcium signaling. Structural information about this protein can be found in the UniProtKB/Swiss-Prot database under reference P28907. In humans, the CD38 protein is encoded by the CD38 gene which located on chromosome 4. CD38 is a multifunctional ectoenzyme that catalyzes the synthesis and hydrolysis of cyclic ADP-ribose (cADPR) from NAD⁺ to ADP-ribose. These reaction products are deemed essential for the regulation of intracellular Ca²⁺. Also, loss of CD38 function was associated with impaired immune responses and metabolic disturbances (Malavasi F., et al. (2008). "Evolution and function of the ADP ribosyl cyclase/CD38 gene family in physiology and pathology". *Physiol. Rev.* 88(3): 841–86).

On another hand, CD38 protein is a marker of HIV infection, leukemias, myelomas, solid tumors, type II diabetes mellitus and bone metabolism, as well as some other genetically determined conditions. In particular, it has been used as a prognostic marker in leukemia (Ibrahim, S. et al. (2001) CD38 expression as an important prognostic factor in B-cell chronic lymphocytic leukemia. *Blood* 98:181-186).

Although, cells expressing CD38, as well as many other tumor antigen markers referred to in Table 1, such as CD70 and CS1 could be regarded as attractive targets for CARs, the fact that such antigen markers are also expressed at the surface of most T-cells, has hampered significantly the selection of these markers to perform immunotherapy.

The inventors here provide strategies for immunotherapy involving pathological cells expressing specific antigen markers also present at the surface of T-cells, like for instance malignant CD38 positive B-cells causing leukemia, CD70 and CS1.

Summary of the invention

According to a first aspect, the present invention provides a method of preparing T-cells for immunotherapy against pathological cells comprising the step of:

- (a) Genetically inactivating a gene in a T-cell, which encodes an antigen marker, said antigen marker being present both on the surface of said T-cell and the pathological cell, resulting in the absence of said antigen marker on the surface of said T-cell;;
- (b) Expressing into said T-cell a transgene encoding a chimeric antigen receptor directed against said antigen marker present at the surface of said pathological cell.

According to a second aspect, the present invention provides a population of T cells prepared according to the method of the first aspect.

According to a third aspect, the present invention provides use of a population of T cells according to the second aspect in the manufacture of a medicament for the treatment of a cancer, an immune disease or an infection in a patient in need thereof.

According to a fourth aspect, the present invention provides a method for treating a cancer, an immune disease or an infection in a patient in need thereof, comprising administering to said patient a population of T cells according to the second aspect.

According to a fifth aspect, the present invention provides an engineered T-cell wherein a gene encoding an antigen marker, which is present both on the surface of said T-cell and a pathological cell, is genetically inactivated thereby resulting in the absence of said antigen marker on the surface of said T-cell; and wherein said T-cell expresses a chimeric antigen receptor directed against said antigen marker present at the surface of said pathological cell.

According to a sixth aspect, the present invention provides a method for treating a patient comprising:

- (a) Diagnosing said patient for the presence of pathological cells presenting specific antigen markers in common with T-cells;
- (b) preparing a population of engineered T-cells according to the fifth aspect or according to the method of the first aspect; and

- (c) administering said engineered T-cells to said patient diagnosed for said pathological cells.

The present invention discloses methods to engineer T-cells intended to target pathological cells, whereas said pathological cells express one or several antigen markers that are also present on the surface of T-cells. Examples of such antigen markers are found in Table 1. An example of such antigen marker is CD38. Other examples are CD70 and CS1. By antigen marker is meant the whole protein of an immune-reactive fragment thereof.

According to the invention, the T-cells are engineered in order to inactivate the expression of the genes encoding such antigen markers, or involved into the presentation of such antigen marker on the cell surface.

This inactivation is preferably performed by a genome modification, more particularly through the expression in the T-cell of a specific rare-cutting endonuclease able to target a genetic locus directly or indirectly involved in the production or presentation of said antigen marker at the surface of the T-cell. Different types of rare-cutting endonucleases can be used, such as Meganucleases, TAL-nucleases, zing-finger nucleases (ZFN), or NA/DNA guided endonucleases like Cas9/CRISPR or Argonaute.

According to a preferred embodiment, the T-cells are endowed with at least one chimeric antigen receptors (CAR) allowing a specific binding of said cells bearing said targeted antigen marker.

According to another embodiment, the T-cells can be further engineered to make them allogeneic, especially by deleting genes involved into self-recognition, such as those, for instance, encoding components of T-cell receptors (TCR) or HLA complex.

The present invention encompasses the isolated cells or cell lines comprising the genetic modifications set forth in the detailed description, examples and figures, as well as any of the proteins, polypeptides or vectors useful to engineer said T-cells.

As a result of the invention, the engineered T-cells can be used as therapeutic products, ideally as an "off the shelf" product, in methods for treating or preventing cancer, infections or autoimmune disease.

Preferred immune cells according to the present invention are those resulting into the phenotypes:

- [CAR targeting an antigen marker of Table 1]⁺[antigen marker of Table 1]⁻ such as the following ones:
 - [CAR CD38]⁺[CD38]⁻, preferably also [TCR] negative;

- [CAR CD70]⁺[CD70]⁻ , preferably also [TCR] negative;
- [CAR CS1]⁺[CS1]⁻ , preferably also [TCR] negative;

for their use as therapeutic products, preferably allogeneic ones.

5 Brief description of the figures and tables

Figure 1: Schematic representation of an engineered T-cell according to the present invention disrupted for CD38 and endowed with a chimeric antigen receptor (represented as a single-chain CAR) targeting a malignant cell bearing the antigen marker CD38.

Figure 2: Schematic representation of a multi-subunit chimeric antigen receptor.

10 **Figure 3:** Schematic representation of a therapeutic strategy according to the invention combining T-cells endowed with a multi-subunit CAR and circulating bi-specific antibody. In this particular aspect, the receptor present on the extracellular chain of the multi-subunit CAR is composed of an epitope which is recognized by a bi-specific antibody. The bi-specific antibody is intended to bind said epitope on the one hand and the antigen marker on the other hand to
15 facilitate the binding of the T-cell to the pathological cell.

Figure 4: Schematic representation of a therapeutic strategy according to the invention combining T-cells endowed with a multi-subunit CAR and circulating monoclonal antibody. In this particular aspect, the receptor present on the extracellular chain of the multi-subunit CAR is composed, for instance, of a Fc receptor intended to bind a monoclonal antibody that is directed
20 against the antigen marker. The monoclonal antibody increases the chance of T-cells binding the pathological cells.

Figure 5: Schematic representation of a therapeutic strategy according to the invention combining T-cells endowed with a multi-subunit CAR that comprises two extracellular cellular domains and one circulating bi-specific antibody. In this particular aspect, the extracellular cellular
25 domains are located on distinct sub-units. These domains are respectively composed of an epitope that is recognized by a bi-specific antibody and of a receptor targeting an antigen. The receptor is directed against a first antigen marker, whereas the bi-specific antibody is intended to bind the epitope and a second antigen marker. This display aims to selectively target pathological cells bearing at their surface both the first and second antigen markers.

30 **Figure 6:** display is similar to Figure 5, but stimulation and co-stimulation domains (respectively 4-1BB and CD3zeta protein domains) have been exchanged to modulate the intensity of

the activation of the T-cell resulting from the binding of the chimeric antigen receptor with the pathological cell.

Figure 7: display is similar to Figure 5, but stimulation and co-stimulation domains (respectively 4-1BB and CD3zeta protein domains) have been exchanged and one CD3zeta domain has been added to increase the intensity of the activation of the T-cell resulting from the binding of the chimeric antigen receptor with the pathological cell.

Figure 8: Schematic representation of a therapeutic strategy according to the invention combining T-cells endowed with a multi-subunit CAR that comprises two extracellular cellular domains and one circulating monoclonal antibody. In this particular aspect, the extracellular cellular domains are located on distinct sub-units. These domains are respectively composed of an antigen binding domain targeting an antigen marker and a Fc receptor intended to bind a monoclonal antibody that is directed against a second antigen marker. This display aims to selectively target pathological cells bearing at their surface both the first and second antigen markers.

Figure 9: CD38 expression by activated T cells. **A.** CD38 expression by T cells at day 6 after activation with CD3/CD28 coated beads + IL2. **B.** Longitudinal analysis of CD38 expression by T cells during 17 days after activation.

Figure 10 Knock-out (KO) on CD38 gene : **A.** Position on CD38 exon 1 sequence of the 3 different TALEN (T2, T4 and T5) designed to knock out Cd38 in T cell. **B.** Expression of CD38 in T cells after transfection with the TALEN CD38ex1_T2. **C.** CD38 staining to control for the purification of CD38 KO T cells.

Figure 11: CD38 CAR : **A.** Representation of the 3 versions of CARs designed. **B.** CD38 expression level by the target cell lines.

Figure 12: Timing experiment for the engineering of the CAR CS1+ and KO CS1 T-cells and their subsequent testing;

Figure 13: Constructs of T01, T02 and T03 with the TAL repeats used for the KO of CS1 gene;

Figure 14: Target location for the TALs T01, T02 and T03 within the CS1 (SLAMF7) gene. T01 and T02 target the exon 1 (Figure 14A), whereas T03 targets the exon 2 (Figure 14B).

Figure 15A : Measurement of percentage of target cell viability for TALEn or not TALEn transfected combined with CAR+ or not transduced cells: a reduced cell viability of CS1(+) cells shown when they were co-cultured with CAR+ T-cells, while no impact on CS1(-) cell viability was observed.

Figure 15B: Measurement of percentage of specific cell lysis (CS1+) calculated using the flow cytometry data. It is shown that specific cell lysis is 2-times higher when T-cells have been transfected with TALEn targeting the CS1 gene prior to CAR transduction.

Figure 16: Results of FACS analysis from cytotoxic activity experiment, which show that transduction efficiencies are higher in mock transfected cells than in cells that have been transfected with TALEn targeting the CS1 gene (NTD: not transduced).

Figure 17: Results from FACS analysis when the different samples are reactivated with CD3/CD28 beads at D11 after transduction, showing the transduction efficiencies and CD8/CS1 expression levels in each sample. An increase in CS1 levels upon re-activation is observed in mock transfected cells, while a low amount of cells are able to express CS1 in the TALEn transfected populations.

Table 1: Different cytopulse programs used for T-cells electroporation.

Table 2: appropriate target sequences for the guide RNA using Cas9 in T-cells

Table 3: List of genes encoding immune checkpoint proteins

Table 4: Cluster of differentiation (CD) antigen markers found to be expressed on the surface of T-cells, while being characteristic of different types of tumors.

Table 5 to 13: Main surface antigen markers expressed in T-cells, while being over-expressed in solid tumor cells from various types of cancer. The listed antigen markers were identified as explained in Example 1.

Table 5: colon tumor cells;

Table 6: breast tumor cells;

Table 7: digestive track tumor cells;

Table 8: kidney tumor cells;

Table 9: liver tumor cells;

Table 10: lung tumor cells;

Table 11: ovary tumor cells;

Table 12: pancreas tumor cells;

Table 13: prostate tumor cells;

Table 14: Main surface antigen markers expressed in T-cells, while being over-expressed in liquid tumor cells from various types of cancer (ALL, AML, CML, MDS, CLL, CTRL). The listed antigen markers were identified as explained in Example 1.

Table 15: Sequences of the tested CD38 target and TALENs for inactivation of the CD38 antigen;

Table 16: Sequences of two other CD38 targets and the corresponding TALENs for their inactivation;

Table 17: Sequences of VH and VL chains of the scFv anti-CD38 antibodies daratumumab and MOR202 and of specific CDRs for VH and VL chains

Table 18: Polypeptide sequence of the 3 different structures of scFv daratumumab-based anti-CD38 CARs and of the individual components used;

Table 19: Sequences of VH and VL chains of the scFv anti-CS1 antibodies;

Table 20: Polypeptide sequence of anti-CS1 CARs based on the V1, V2 and V3 versions in Figure 11A;

Table 21: Sequences of the CS1 target and TALENs for its inactivation;

Table 22: Sequences of the CD70 target and TALENs for its inactivation;

Table 23: Polynucleotide and nucleic acid sequences of VH and VL chains of the scFv anti-CD70 Ab4, Ab8 and 1F6 antibodies;

Table 24: Polypeptide sequence of anti-CD70 CARs based on the V1, V2 and V3 versions in Figure 11A

Detailed description of the invention

Unless specifically defined herein, all technical and scientific terms used have the same meaning as commonly understood by a skilled artisan in the fields of gene therapy, biochemistry, genetics, and molecular biology.

5 All methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, with suitable methods and materials being described herein. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will prevail. Further, the materials, methods, and examples are illustrative only and are
10 not intended to be limiting, unless otherwise specified.

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, Current Protocols in Molecular Biology (Frederick
15 M. AUSUBEL, 2000, Wiley and son Inc, Library of Congress, USA); Molecular Cloning: A Laboratory Manual, Third Edition, (Sambrook et al, 2001, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press); Oligonucleotide Synthesis (M. J. Gait ed., 1984); Mullis et al. U.S. Pat. No. 4,683,195; Nucleic Acid Hybridization (B. D. Harries & S. J. Higgins eds. 1984); Transcription And Translation (B. D. Hames & S. J. Higgins eds. 1984); Culture Of Animal Cells (R. I. Freshney, Alan R.
20 Liss, Inc., 1987); Immobilized Cells And Enzymes (IRL Press, 1986); B. Perbal, A Practical Guide To Molecular Cloning (1984); the series, Methods In ENZYMOLOGY (J. Abelson and M. Simon, eds.-in-chief, Academic Press, Inc., New York), specifically, Vols.154 and 155 (Wu et al. eds.) and Vol. 185, "Gene Expression Technology" (D. Goeddel, ed.); Gene Transfer Vectors For Mammalian Cells (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); Immunochemical Methods In Cell
25 And Molecular Biology (Mayer and Walker, eds., Academic Press, London, 1987); Handbook Of Experimental Immunology, Volumes I-IV (D. M. Weir and C. C. Blackwell, eds., 1986); and Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986).

In a general aspect, the present invention relates to methods for new adoptive
30 immunotherapy strategies in treating diseases linked with the development of pathological cells, such as cancer, infections and auto-immune diseases.

As a main objective of the invention is the possibility to target pathological cells that bear specific antigen markers in common with T-cells. By pathological cell is meant any types of cells present in a patient, which are deemed causing health deterioration.

In general, pathological cells are malignant or infected cells that need to be reduced or eliminated to obtain remission of a patient.

In a first embodiment, the method of the invention concerns a method of preparing appropriate immune cells, preferably T-cells for immunotherapy comprising the step of:

(a) Genetically inactivating or mutating a gene in an immune cell, which is involved in the expression or presentation of an antigen marker, said antigen marker being known to be present both on the surface of said T-cell and the pathological cell;

(b) Expressing into said immune cell a transgene encoding a chimeric antigen receptor directed against said antigen marker present at the surface of said pathological cell.

The immune cells according to the invention are endowed with a chimeric antigen receptor directed to an antigen marker that is commonly expressed by the pathological cells and immune cells, or known to be present on the surface of said T Cells. The expression "known to be present" means that the antigen marker is reported to be found on the surface of the immune cells grown in natural conditions *in-vivo*, especially in the blood, but not necessarily when they are cultured *in-vitro*. In any event, the method of the invention results into the absence of the antigen marker on the surface of the immune cell, thereby preventing the chimeric antigen receptor from reacting with the engineered T-cell surface. In this respect, the method may include a further step of purifying the resulting T-cells by excluding the cells presenting said marker antigen on their surface.

As shown in Table 4, this invention relates to an important number of antigen marker candidates reported to be expressed by tumor cells, but also by T-cells. Some of them, like CD38, have been used as specific markers in diagnostic methods for a while, especially with respect to Leukemia pathological cells, but not in therapy. Indeed, although these markers were identified in the art as quite specific markers, they could not be used as targets for immunotherapy because antibodies directed against these markers would have destroyed or interfered with patients' T-cells. The present inventors have established that CS1 and CD70 are also present on the surface of T-cells and that expressing CARs targeting CS1 and CD70 in such T cells leads to their depletion (see example 2).

According to a preferred embodiment of the invention, the gene mutation or inactivation of step a) of the above method is performed using a rare-cutting endonuclease.

By inactivating a gene it is intended that the gene of interest is not expressed in a functional protein form. In particular embodiments, the genetic modification of the method relies on the expression, in provided cells to engineer, of a rare-cutting endonuclease such that same catalyzes cleavage in one targeted gene thereby inactivating said targeted gene. The nucleic acid strand breaks caused by the endonuclease are commonly repaired through the distinct mechanisms of homologous recombination or non-homologous end joining (NHEJ). However, NHEJ is an imperfect repair process that often results in changes to the DNA sequence at the site of the cleavage. Mechanisms involve rejoining of what remains of the two DNA ends through direct re-ligation (Critchlow and Jackson 1998) or via the so-called microhomology-mediated end joining (Betts, Brenchley et al. 2003; Ma, Kim et al. 2003). Repair via non-homologous end joining (NHEJ) often results in small insertions or deletions and can be used for the creation of specific gene knockouts. Said modification may be a substitution, deletion, or addition of at least one nucleotide. Cells in which a cleavage-induced mutagenesis event, i.e. a mutagenesis event consecutive to an NHEJ event, has occurred can be identified and/or selected by well-known method in the art.

The term "rare-cutting endonuclease" refers to a wild type or variant enzyme capable of catalyzing the hydrolysis (cleavage) of bonds between nucleic acids within a DNA or RNA molecule, preferably a DNA molecule. Particularly, said nuclease can be an endonuclease, more preferably a rare-cutting endonuclease which is highly specific, recognizing nucleic acid target sites ranging from 10 to 45 base pairs (bp) in length, usually ranging from 10 to 35 base pairs in length, more usually from 12 to 20 base pairs. The endonuclease according to the present invention recognizes at specific polynucleotide sequences, further referred to as "target sequence" and cleaves nucleic acid inside these target sequences or into sequences adjacent thereto, depending on the molecular structure of said endonuclease. The rare-cutting endonuclease can recognize and generate a single- or double-strand break at specific polynucleotides sequences.

In a particular embodiment, said rare-cutting endonuclease according to the present invention is a RNA-guided endonuclease such as the Cas9/CRISPR complex. RNA guided endonucleases constitute a new generation of genome engineering tool where an endonuclease associates with a RNA molecule. In this system, the RNA molecule nucleotide sequence determines the target specificity and activates the endonuclease (Gasiunas, Barrangou et al. 2012; Jinek, Chylinski et al. 2012; Cong, Ran et al. 2013; Mali, Yang et al. 2013).

Cas 9

Cas9, also named Csn1 (COG3513) is a large protein that participates in both crRNA biogenesis and in the destruction of invading DNA. Cas9 has been described in different bacterial species such as *S. thermophiles*, *Listeria innocua* (Gasiunas, Barrangou et al. 2012; Jinek, Chylinski et al. 2012) and *S. Pyogenes* (Deltcheva, Chylinski et al. 2011). The large Cas9 protein (>1200 amino acids) contains two predicted nuclease domains, namely HNH (McrA-like) nuclease domain that is located in the middle of the protein and a splitted RuvC-like nuclease domain (RNase H fold) (Makarova, Grishin et al. (2006).

By "Cas9" is meant an engineered endonuclease or a homologue of Cas9 which is capable of processing target nucleic acid sequence. In particular embodiment, Cas9 can induce a cleavage in the nucleic acid target sequence which can correspond to either a double-stranded break or a single-stranded break. Cas9 variant can be a Cas9 endonuclease that does not naturally exist in nature and that is obtained by protein engineering or by random mutagenesis. Cas9 variants according to the invention can for example be obtained by mutations i.e. deletions from, or insertions or substitutions of at least one residue in the amino acid sequence of a *S. pyogenes* Cas9 endonuclease (COG3513). In the frame aspects of the present invention, such Cas9 variants remain functional, i.e. they retain the capacity of processing a target nucleic acid sequence. Cas9 variant can also be homologues of *S. pyogenes* Cas9 which can comprise deletions from, or insertions or substitutions of, at least one residue within the amino acid sequence of *S. pyogenes* Cas9. Any combination of deletion, insertion, and substitution may also be made to arrive at the final construct, provided that the final construct possesses the desired activity, in particular the capacity of binding a guide RNA or nucleic acid target sequence.

RuvC/RNaseH motif includes proteins that show wide spectra of nucleolytic functions, acting both on RNA and DNA (RNaseH, RuvC, DNA transposases and retroviral integrases and PIWI domain of Argonaut proteins). In the present invention the RuvC catalytic domain of the Cas9 protein can be characterized by the sequence motif: D-[I/L]-G-X-X-S-X-G-W-A, wherein X represents any one of the natural 20 amino acids and [I/L] represents isoleucine or leucine. In other terms, the present invention relates to Cas9 variant which comprises at least D-[I/L]-G-X-X-S-X-G-W-A sequence, wherein X represents any one of the natural 20 amino acids and [I/L] represents isoleucine or leucine.

HNH motif is characteristic of many nucleases that act on double-stranded DNA including colicins, restriction enzymes and homing endonucleases. The domain HNH (SMART ID: SM00507, SCOP nomenclature:HNH family) is associated with a range of DNA binding proteins, performing a variety of binding and cutting functions. The ones with known function are involved in a range of

cellular processes including bacterial toxicity, homing functions in groups I and II introns and inteins, recombination, developmentally controlled DNA rearrangement, phage packaging, and restriction endonuclease activity (Dalgaard, Klar et al. 1997). These proteins are found in viruses, archaeobacteria, eubacteria, and eukaryotes. Interestingly, as with the LAGLI-DADG and the GIY-YIG motifs, the HNH motif is often associated with endonuclease domains of self-propagating elements like inteins, Group I, and Group II introns (Dalgaard, Klar et al. 1997). The HNH domain can be characterized by the presence of a conserved Asp/His residue flanked by conserved His (amino-terminal) and His/Asp/Glu (carboxy-terminal) residues at some distance. A substantial number of these proteins can also have a CX₂C motif on either side of the central Asp/His residue. Structurally, the HNH motif appears as a central hairpin of twisted β -strands, which are flanked on each side by an α helix (Kleanthous, Kuhlmann et al. 1999). The large HNH domain of Cas9 is represented by SEQ ID NO.5. In the present invention, the HNH motif can be characterized by the sequence motif: Y-X-X-D-H-X-X-P-X-S-X-X-X-D-X-S, wherein X represents any one of the natural 20 amino acids. The present invention relates to a Cas9 variant which comprises at least Y-X-X-D-H-X-X-P-X-S-X-X-X-D-X-S sequence wherein X represents any one of the natural 20 amino acids.

This invention can be of particular interest to easily do targeted multiplex gene modifications and to create an inducible nuclease system by introduction of the guide RNA to the Cas9 cells. For the purpose of the present invention, the inventors have established that Cas9 protein can be divided into two separate split Cas9 RuvC and HNH domains which can process target nucleic acid sequence together or separately with the guide RNA.

Also the RuvC and HNH domains from different RNA guided endonucleases or Cas homologues may be assembled to improve nuclease efficiency or specificity. The domains from different species can be either split into two proteins or fused to each other to form a variant Cas protein. The Cas9 split system is deemed particularly suitable for an inducible method of genome targeting and to avoid the potential toxic effect of the Cas9 overexpression within the cell. Indeed, a first split Cas9 domain can be introduced into the cell, preferably by stably transforming said cell with a transgene encoding said split domain. Then, the complementary split part of Cas9 can be introduced into the cell, such that the two split parts reassemble into the cell to reconstitute a functional Cas9 protein at the desired time.

The reduction of the size of the split Cas9 compared to wild type Cas9 ease the vectorization and the delivery into the cell, for example, by using cell penetrating peptides. Re-arranging domains from different Cas proteins, allows to modulate the specificity and nuclease activity, for instance, by targeting PAM motifs that are slightly different from *S. pyogenes* Cas9

Split Cas9 system

The previous characterization of the RuvC and HNH domains has prompted the inventors to engineer Cas9 protein to create split Cas9 protein. Surprisingly, the inventors showed that these two split Cas9 could process together or separately the nucleic acid target. This observation allows developing a new Cas9 system using split Cas9 protein. Each split Cas9 domains can be prepared and used separately. Thus, this split system displays several advantages for vectorization and delivery of the RNA guided endonuclease in T-cells, allowing delivering a shorter and/or inactive protein, and is particularly suitable to induce genome engineering in T-cells at the desired time and thus limiting the potential toxicity of an integrated Cas9 nuclease.

By "Split Cas9" is meant here a reduced or truncated form of a Cas9 protein or Cas9 variant, which comprises either a RuvC or HNH domain, but not both of these domains. Such "Split Cas9" can be used independently with guide RNA or in a complementary fashion, like for instance, one Split Cas9 providing a RuvC domain and another providing the HNH domain. Different split RNA guided endonucleases may be used together having either RuvC and/or HNH domains.

Each Cas9 split domain can be derived from the same or from different Cas9 homologues. Many homologues of Cas9 have been identified in genome databases.

Said Cas9 split domains (RuvC and HNH domains) can be simultaneously or sequentially introduced into the cell such that said split Cas9 domain(s) process the target nucleic acid sequence in the cell. Said Cas9 split domains and guide RNA can be introduced into the cell by using cell penetrating peptides or other transfection methods as described elsewhere.

In another aspect of the invention, only one split Cas9 domain, referred to as compact Cas9 is introduced into said cell. Indeed, surprisingly the inventors showed that the split Cas9 domain comprising the RuvC motif as described above is capable of cleaving a target nucleic acid sequence independently of split domain comprising the HNH motif. Thus, they could establish that the guideRNA does not need the presence of the HNH domain to bind to the target nucleic acid sequence and is sufficiently stable to be bound by the RuvC split domain. In a preferred embodiment, said split Cas9 domain alone is capable of nicking said target nucleic acid sequence.

Each split domain can be fused to at least one active domain in the N-terminal and/or C-terminal end, said active domain can be selected from the group consisting of: nuclease (e.g. endonuclease or exonuclease), polymerase, kinase, phosphatase, methylase, demethylase, acetylase, desacetylase, topoisomerase, integrase, transposase, ligase, helicase, recombinase, transcriptional activator(e.g. VP64, VP16), transcriptional inhibitor (e. g; KRAB), DNA end processing enzyme (e.g. Trex2, Tdt), reporter molecule (e.g. fluorescent proteins, lacZ, luciferase).

HNH domain is responsible for nicking of one strand of the target double-stranded DNA and the RuvC-like RNaseH fold domain is involved in nicking of the other strand (comprising the PAM motif) of the double-stranded nucleic acid target (Jinek, Chylinski et al. 2012). However, in wild-type Cas9, these two domains result in blunt cleavage of the invasive DNA within the same target sequence (proto-spacer) in the immediate vicinity of the PAM (Jinek, Chylinski et al. 2012). Cas 9 can be a nickase and induces a nick event within different target sequences.

As non-limiting example, Cas9 or split Cas9 can comprise mutation(s) in the catalytic residues of either the HNH or RuvC-like domains, to induce a nick event within different target sequences. As non-limiting example, the catalytic residues of the Cas9 protein are those corresponding to amino acids D10, D31, H840, H868, N882 and N891 or aligned positions using CLUSTALW method on homologues of Cas Family members. Any of these residues can be replaced by any other amino acids, preferably by alanine residue. Mutation in the catalytic residues means either substitution by another amino acids, or deletion or addition of amino acids that induce the inactivation of at least one of the catalytic domain of cas9. (cf.. In a particular embodiment, Cas9 or split Cas9 may comprise one or several of the above mutations. In another particular embodiment, split Cas9 comprises only one of the two RuvC and HNH catalytic domains. In the present invention, Cas9 from different species, Cas9 homologues, Cas9 engineered and functional variant thereof can be used. The invention envisions the use of any RNA guided endonuclease or split RNA guided endonucleases variants to perform nucleic acid cleavage in a genetic sequence of interest.

Preferably, the Cas9 variants according to the invention have an amino acid sequence sharing at least 70 %, preferably at least 80 %, more preferably at least 90%, and even more preferably 95 % identity with Cas9 of *S. Pyogenes* (COG3513).

Meganucleases

Rare-cutting endonuclease can also be a homing endonuclease, also known under the name of meganuclease. Such homing endonucleases are well-known to the art (Stoddard 2005). Homing endonucleases are highly specific, recognizing DNA target sites ranging from 12 to 45 base pairs (bp) in length, usually ranging from 14 to 40 bp in length. The homing endonuclease according to the invention may for example correspond to a LAGLIDADG endonuclease, to a HNH endonuclease, or to a GIY-YIG endonuclease. Preferred homing endonuclease according to the present invention can be an I-CreI variant. A "variant" endonuclease, i.e. an endonuclease that does not naturally exist in nature and that is obtained by genetic engineering or by random mutagenesis can bind DNA sequences different from that recognized by wild-type endonucleases (see international application WO2006/097854).

Said rare-cutting endonuclease can be a modular DNA binding nuclease. By modular DNA binding nuclease is meant any fusion proteins comprising at least one catalytic domain of an endonuclease and at least one DNA binding domain or protein specifying a nucleic acid target sequence. The DNA binding domain is generally a RNA or DNA-binding domain formed by an independently folded polypeptide or protein domain that contains at least one motif that recognizes double- or single-stranded polynucleotides. Many such polypeptides have been described in the art having the ability to bind specific nucleic acid sequences. Such binding domains often comprise, as non-limiting examples, helix-turn helix domains, leucine zipper domains, winged helix domains, helix-loop-helix domains, HMG-box domains, Immunoglobulin domains, B3 domain or engineered zinc finger domain.

Zinc-Finger Nucleases

Initially developed to cleave DNA in vitro, "Zinc Finger Nucleases" (ZFNs) are a fusion between the cleavage domain of the type IIS restriction enzyme, FokI, and a DNA recognition domain containing 3 or more C2H2 zinc finger motifs. The heterodimerization at a particular position in the DNA of two individual ZFNs in precise orientation and spacing leads to a double-strand break (DSB) in the DNA. The use of such chimeric endonucleases have been extensively reported in the art as reviewed by Urnov et al. (Genome editing with engineered zinc finger nucleases (2010) *Nature reviews Genetics* 11:636-646).

Standard ZFNs fuse the cleavage domain to the C-terminus of each zinc finger domain. In order to allow the two cleavage domains to dimerize and cleave DNA, the two individual ZFNs bind opposite strands of DNA with their C-termini a certain distance apart. The most commonly used linker sequences between the zinc finger domain and the cleavage domain requires the 5' edge of each binding site to be separated by 5 to 7 bp.

The most straightforward method to generate new zinc-finger arrays is to combine smaller zinc-finger "modules" of known specificity. The most common modular assembly process involves combining three separate zinc fingers that can each recognize a 3 base pair DNA sequence to generate a 3-finger array that can recognize a 9 base pair target site. Numerous selection methods have been used to generate zinc-finger arrays capable of targeting desired sequences. Initial selection efforts utilized phage display to select proteins that bound a given DNA target from a large pool of partially randomized zinc-finger arrays. More recent efforts have utilized yeast one-hybrid systems, bacterial one-hybrid and two-hybrid systems, and mammalian cells.

TAL-nucleases

“TALE-nuclease” or “MBBBD-nuclease” refers to engineered proteins resulting from the fusion of a DNA binding domain typically derived from Transcription Activator Like Effector proteins (TALE) or Modular Base-per-Base Binding domain (MBBBD), with a catalytic domain having endonuclease activity. Such catalytic domain usually comes from enzymes, such as for instance I-TevI, ColE7, NucA and Fok-I. TALE-nuclease can be formed under monomeric or dimeric forms depending of the selected catalytic domain (WO2012138927). Such engineered TALE-nucleases are commercially available under the trade name TALENTM (Cellestis, 8 rue de la Croix Jarry, 75013 Paris, France).

According to a preferred embodiment of the invention, the DNA binding domain is derived from a Transcription Activator like Effector (TALE), wherein sequence specificity is driven by a series of 33-35 amino acids repeats originating from *Xanthomonas* or *Ralstonia* bacterial proteins AvrBs3, PthXo1, AvrHah1, PthA, Tal1c as non-limiting examples.

These repeats differ essentially by two amino acids positions that specify an interaction with a base pair (Boch, Scholze et al. 2009; Moscou and Bogdanove 2009). Each base pair in the DNA target is contacted by a single repeat, with the specificity resulting from the two variant amino acids of the repeat (the so-called repeat variable dipeptide, RVD). TALE binding domains may further comprise an N-terminal translocation domain responsible for the requirement of a first thymine base (T0) of the targeted sequence and a C-terminal domain that containing a nuclear localization signals (NLS). A TALE nucleic acid binding domain generally corresponds to an engineered core TALE scaffold comprising a plurality of TALE repeat sequences, each repeat comprising a RVD specific to each nucleotides base of a TALE recognition site. In the present invention, each TALE repeat sequence of said core scaffold is made of 30 to 42 amino acids, more preferably 33 or 34 wherein two critical amino acids (the so-called repeat variable dipeptide, RVD) located at positions 12 and 13 mediates the recognition of one nucleotide of said TALE binding site sequence; equivalent two critical amino acids can be located at positions other than 12 and 13 specially in TALE repeat sequence taller than 33 or 34 amino acids long. Preferably, RVDs associated with recognition of the different nucleotides are HD for recognizing C, NG for recognizing T, NI for recognizing A, NN for recognizing G or A. In another embodiment, critical amino acids 12 and 13 can be mutated towards other amino acid residues in order to modulate their specificity towards nucleotides A, T, C and G and in particular to enhance this specificity. A TALE nucleic acid binding domain usually comprises between 8 and 30 TALE repeat sequences. More preferably, said core scaffold of the present invention comprises between 8 and 20 TALE repeat sequences; again more preferably 15 TALE repeat sequences. It can also comprise an additional single truncated TALE repeat sequence made of 20 amino acids located

at the C-terminus of said set of TALE repeat sequences, i.e. an additional C-terminal half- TALE repeat sequence.

Other engineered DNA binding domains can be used as alternative sequences to form so-called modular base-per-base specific nucleic acid binding domains (MBBBD) as described in WO 2014/018601. Said MBBBD can be engineered, for instance, from newly identified proteins, namely EAV36_BURRH, E5AW43_BURRH, E5AW45_BURRH and E5AW46_BURRH proteins from the recently sequenced genome of the endosymbiont fungi *Burkholderia Rhizoxinica* (Lackner, Moebius et al. 2011). These nucleic acid binding polypeptides comprise modules of about 31 to 33 amino acids that are base specific. These modules display less than 40 % sequence identity with *Xanthomonas* TALE common repeats and present more polypeptides sequence variability. The different domains from the above proteins (modules, N and C-terminals) from *Burkholderia* and *Xanthomonas* are useful to engineer new proteins or scaffolds having binding properties to specific nucleic acid sequences and may be combined to form chimeric TALE-MBBBD proteins.

As examples, the present invention encompasses a method for engineered T-cells in order to inactivate the expression of the genes encoding antigen markers such as CD38, CS1 and CD70 by using specific TALE-nucleases.

Particularly suitable for the realization of the invention, TALE-nucleases such as the ones in SEQ ID NO: 2-3;5-6;8-9, SEQ ID NO: 64-65;67-68;70-71 and SEQ ID NO: 73-74;76-77;79-80 for respectively CD38, CS1 and CD70 genes. These specific TALE-nucleases, their sequence target and the protocol used are presented more thoroughly in the following Examples 1-3.

Delivery methods

The inventors have considered any means known in the art to allow delivery inside cells or subcellular compartments of said cells the polynucleotides expressing the endonucleases, their possible co-effectors (e.g. guide RNA or DNA associated with Cas9 or Argonaute nucleases) as well as the chimeric antigen receptors. These means include viral transduction, electroporation and also liposomal delivery means, polymeric carriers, chemical carriers, lipoplexes, polyplexes, dendrimers, nanoparticles, emulsion, natural endocytosis or phagocytose pathway as non-limiting examples.

As a preferred embodiment of the invention, polynucleotides encoding the endonucleases of the present invention are transfected under mRNA form in order to obtain transient expression and avoid chromosomal integration of foreign DNA, for example by electroporation. The inventors have determined different optimal conditions for mRNA electroporation in T-cell displayed in Table 1. The inventor used the cytoPulse technology which allows, by the use of pulsed electric fields, to

transiently permeabilize living cells for delivery of material into the cells (U.S. patent 6,010,613 and WO 2004/083379). Pulse duration, intensity as well as the interval between pulses can be modified in order to reach the best conditions for high transfection efficiency with minimal mortality. Basically, the first high electric field pulses allow pore formation, while subsequent lower electric field pulses allow to moving the polynucleotide into the cell. In one aspect of the present invention, the inventor describe the steps that led to achievement of >95% transfection efficiency of mRNA in T cells, and the use of the electroporation protocol to transiently express different kind of proteins in T cells. In particular the invention relates to a method of transforming T cell comprising contacting said T cell with RNA and applying to T cell an agile pulse sequence consisting of:

- (a) one electrical pulse with a voltage range from 2250 to 3000 V per centimeter, a pulse width of 0.1 ms and a pulse interval of 0.2 to 10 ms between the electrical pulses of step (a) and (b);
- (b) one electrical pulse with a voltage range from 2250 to 3000 V with a pulse width of 100 ms and a pulse interval of 100 ms between the electrical pulse of step (b) and the first electrical pulse of step (c) ; and
- (c) 4 electrical pulses with a voltage of 325 V with a pulse width of 0.2 ms and a pulse interval of 2 ms between each of 4 electrical pulses.

In particular embodiment, the method of transforming T cell comprising contacting said T cell with RNA and applying to T cell an agile pulse sequence consisting of:

- (a) one electrical pulse with a voltage of 2250, 2300, 2350, 2400, 2450, 2500, 2550, 2400, 2450, 2500, 2600, 2700, 2800, 2900 or 3000V per centimeter, a pulse width of 0.1 ms and a pulse interval of 0.2, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 ms between the electrical pulses of step (a) and (b);
- (b) one electrical pulse with a voltage range from 2250, of 2250, 2300, 2350, 2400, 2450, 2500, 2550, 2400, 2450, 2500, 2600, 2700, 2800, 2900 or 3000V with a pulse width of 100 ms and a pulse interval of 100 ms between the electrical pulse of step (b) and the first electrical pulse of step (c); and
- (c) 4 electrical pulses with a voltage of 325 V with a pulse width of 0.2 ms and a pulse interval of 2 ms between each of 4 electrical pulses.

Any values included in the value range described above are disclosed in the present application. Electroporation medium can be any suitable medium known in the art. Preferably, the electroporation medium has conductivity in a range spanning 0.01 to 1.0 milliSiemens.

Table 1 : Different cytopulse programs used to determine the minimal voltage required for electroporation in PBMC derived T-cells.

<u>Cyto-pulse program</u>	Group 1				Group 2				Group 3			
	Pul-ses	V	duration (ms)	Interval (ms)	Pul-ses	V	duration (ms)	Interval (ms)	Pul-ses	V	duration (ms)	Interval (ms)
1	1	600	0.1	0.2	1	600	0.1	100	4	130	0.2	2
2	1	900	0.1	0.2	1	900	0.1	100	4	130	0.2	2
3	1	1200	0.1	0.2	1	1200	0.1	100	4	130	0.2	2
4	1	1200	0.1	10	1	900	0.1	100	4	130	0.2	2
5	1	900	0.1	20	1	600	0.1	100	4	130	0.2	2

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Viral transduction

According to the present invention, the use of retroviral vectors and more preferably of lentiviral vectors is particularly suited for expressing the chimeric antigen receptors into the T-cells. Methods for viral transduction are well known in the art (Walther et al. (2000) Viral Vectors for Gene Transfer. *Drugs*. 60(2):249-271). Integrative viral vectors allow the stable integration of the polynucleotides in the T-cells genome and to expressing the chimeric antigen receptors over a longer period of time.

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Non alloreactive T cells

Although the method of the invention could be carried out *in-vivo* as part of a gene therapy, for instance, by using viral vectors targeting T-cells in blood circulation, which would include genetic sequences expressing a specific rare-cutting endonuclease along with other genetic sequences expressing a CAR, the method of the invention is more generally intended to be practiced *ex-vivo* on cultured T-cells obtainable from patients or donors. The engineered T-cells engineered *ex-vivo* can be either re-implanted into a patient from where they originate, as part of an autologous treatment, or to be used as part of an allogeneic treatment. In this later case, it is preferable to further engineer the cells to make them non-alloreactive to ensure their proper engraftment. Accordingly, the method of the invention may include additional steps of procuring the T-cells from a donor and to inactivate genes thereof involved in MHC recognition and or being targets of immunosuppressive drugs such as described for instance in WO 2013/176915.

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T cell receptors (TCR) are cell surface receptors that participate in the activation of T cells in response to the presentation of antigen. The TCR is generally made from two chains, alpha and beta, which assemble to form a heterodimer and associates with the CD3-transducing subunits to form the T-cell receptor complex present on the cell surface. Each alpha and beta chain of the TCR consists of an immunoglobulin-like N-terminal variable (V) and constant (C) region, a hydrophobic transmembrane domain, and a short cytoplasmic region. As for immunoglobulin molecules, the variable region of the alpha and beta chains are generated by V(D)J recombination, creating a large diversity of antigen specificities within the population of T cells. However, in contrast to immunoglobulins that recognize intact antigen, T cells are activated by processed peptide fragments in association with an MHC molecule, introducing an extra dimension to antigen recognition by T cells, known as MHC restriction. Recognition of MHC disparities between the donor and recipient through the T cell receptor leads to T cell proliferation and the potential development of GVHD. It has been shown that normal surface expression of the TCR depends on the coordinated synthesis and assembly of all seven components of the complex (Ashwell and Klusner 1990). The inactivation of TCRalpha or TCRbeta can result in the elimination of the TCR from the surface of T cells preventing recognition of alloantigen and thus GVHD.

Thus, still according to the invention, engraftment of the T-cells may be improved by inactivating at least one gene encoding a TCR component. TCR is rendered not functional in the cells by inactivating TCR alpha gene and/or TCR beta gene(s).

With respect to the use of Cas9/CRISPR system, the inventors have determined appropriate target sequences within the 3 exons encoding TCR, allowing a significant reduction of toxicity in living cells, while retaining cleavage efficiency. The preferred target sequences are noted in Table 2 (+ for lower ratio of TCR negative cells, ++ for intermediate ratio, +++ for higher ratio).

Table 2: appropriate target sequences for the guide RNA using Cas9 in T-cells

Exon TCR	Position	Strand	Target genomic sequence	SEQ ID	efficiency
Ex1	78	-1	GAGAATCAAAATCGGTGAATAGG	102	+++
Ex3	26	1	TTCAAAACCTGTCAGTGATTGGG	103	+++
Ex1	153	1	TGTGCTAGACATGAGGTCTATGG	104	+++
Ex3	74	-1	CGTCATGAGCAGATTAAACCCGG	105	+++
Ex1	4	-1	TCAGGGTTCTGGATATCTGTGGG	106	+++
Ex1	5	-1	GTCAGGGTTCTGGATATCTGTGG	107	+++
Ex3	33	-1	TCGGAACCCAATCACTGACAGG	108	+++
Ex3	60	-1	TAAACCCGGCCACTTTCAGGAGG	109	+++
Ex1	200	-1	AAAGTCAGATTTGTTGCTCCAGG	110	++
Ex1	102	1	AACAAATGTGTCACAAAGTAAGG	111	++
Ex1	39	-1	TGGATTTAGAGTCTCTCAGCTGG	112	++
Ex1	59	-1	TAGGCAGACAGACTTGTCACTGG	113	++
Ex1	22	-1	AGCTGGTACACGGCAGGGTCAGG	114	++
Ex1	21	-1	GCTGGTACACGGCAGGGTCAGGG	115	++
Ex1	28	-1	TCTCTCAGCTGGTACACGGCAGG	116	++
Ex3	25	1	TTTCAAAACCTGTCAGTGATTGG	117	++
Ex3	63	-1	GATTAAACCCGGCCACTTTCAGG	118	++
Ex2	17	-1	CTCGACCAGCTTGACATCACAGG	119	++
Ex1	32	-1	AGAGTCTCTCAGCTGGTACACGG	120	++
Ex1	27	-1	CTCTCAGCTGGTACACGGCAGGG	121	++
Ex2	12	1	AAGTTCCTGTGATGTCAAGCTGG	122	++
Ex3	55	1	ATCCTCCTCCTGAAAGTGGCCGG	123	++
Ex3	86	1	TGCTCATGACGCTGCGGCTGTGG	124	++
Ex1	146	1	ACAAAACCTGTGCTAGACATGAGG	125	+
Ex1	86	-1	ATTTGTTTGAGAATCAAAATCGG	126	+
Ex2	3	-1	CATCACAGGAACCTTCTAAAAGG	127	+
Ex2	34	1	GTCGAGAAAAGCTTTGAAACAGG	128	+
Ex3	51	-1	CCACTTTCAGGAGGAGGATTCGG	129	+
Ex3	18	-1	CTGACAGGTTTTGAAAGTTTAGG	130	+
Ex2	43	1	AGCTTTGAAACAGGTAAGACAGG	131	+
Ex1	236	-1	TGGAATAATGCTGTTGTTGAAGG	132	+
Ex1	182	1	AGAGCAACAGTGCTGTGGCCTGG	133	+
Ex3	103	1	CTGTGGTCCAGCTGAGGTGAGGG	134	+
Ex3	97	1	CTGCGGCTGTGGTCCAGCTGAGG	135	+
Ex3	104	1	TGTGGTCCAGCTGAGGTGAGGGG	136	+
Ex1	267	1	CTTCTTCCCAGCCCAGGTAAGG	137	+
Ex1	15	-1	ACACGGCAGGGTCAGGGTTCTGG	138	+
Ex1	177	1	CTTCAAGAGCAACAGTGCTGTGG	139	+
Ex1	256	-1	CTGGGGAAGAAGGTGTCTTCTGG	140	+
Ex3	56	1	TCCTCCTCCTGAAAGTGGCCGGG	141	+
Ex3	80	1	TTAATCTGCTCATGACGCTGCGG	142	+
Ex3	57	-1	ACCCGGCCACTTTCAGGAGGAGG	143	+
Ex1	268	1	TTCTTCCCCAGCCCAGGTAAGGG	144	+
Ex1	266	-1	CTTACCTGGGCTGGGGAAGAAGG	145	+
Ex1	262	1	GACACCTTCTTCCCCAGCCCAGG	146	+
Ex3	102	1	GCTGTGGTCCAGCTGAGGTGAGG	147	+
Ex3	51	1	CCGAATCCTCCTCCTGAAAGTGG	148	+

MHC antigens are also proteins that played a major role in transplantation reactions. Rejection is mediated by T cells reacting to the histocompatibility antigens on the surface of implanted tissues, and the largest group of these antigens is the major histocompatibility antigens (MHC). These proteins are expressed on the surface of all higher vertebrates and are called HLA antigens (for human leukocyte antigens) in human cells. Like TCR, the MHC proteins serve a vital role in T cell stimulation. Antigen presenting cells (often dendritic cells) display peptides that are the degradation products of foreign proteins on the cell surface on the MHC. In the presence of a co-stimulatory signal, the T cell becomes activated, and will act on a target cell that also displays that same peptide/MHC complex. For example, a stimulated T helper cell will target a macrophage displaying an antigen in conjunction with its MHC, or a cytotoxic T cell (CTL) will act on a virally infected cell displaying foreign viral peptides.

Thus, in order to provide less alloreactive T-cells, the method of the invention can further comprise the step of inactivating or mutating one HLA gene.

The class I HLA gene cluster in humans comprises three major loci, B, C and A, as well as several minor loci. The class II HLA cluster also comprises three major loci, DP, DQ and DR, and both the class I and class II gene clusters are polymorphic, in that there are several different alleles of both the class I and II genes within the population. There are also several accessory proteins that play a role in HLA functioning as well. The Tap1 and Tap2 subunits are parts of the TAP transporter complex that is essential in loading peptide antigens on to the class I HLA complexes, and the LMP2 and LMP7 proteasome subunits play roles in the proteolytic degradation of antigens into peptides for display on the HLA. Reduction in LMP7 has been shown to reduce the amount of MHC class I at the cell surface, perhaps through a lack of stabilization (Fehling et al. (1999) *Science* 265:1234-1237). In addition to TAP and LMP, there is the tapasin gene, whose product forms a bridge between the TAP complex and the HLA class I chains and enhances peptide loading. Reduction in tapasin results in cells with impaired MHC class I assembly, reduced cell surface expression of the MHC class I and impaired immune responses (Grande et al. (2000) *Immunity* 13:213-222 and Garbi et al. (2000) *Nat. Immunol.* 1:234-238). Any of the above genes may be inactivated as part of the present invention as disclosed, for instance in WO 2012/012667.

Method of engineering drug-resistant T-cells:

To improve cancer therapy and selective engraftment of allogeneic T-cells, drug resistance can be conferred to the engineered T-cells to protect them from the toxic side effects of chemotherapy or immunosuppressive agents. Indeed, the inventors have observed that most patients were treated with chemotherapy and immune depleting agents as a standard of care, prior

to receiving T-cell immunotherapy. Also they found that they could take advantage of these treatments to help the selection of the engineered T-cells, either by adding chemotherapy drugs in culture media for expansion of the cells *ex-vivo* prior to treatment, or by obtaining a selective expansion of the engineered T-cells *in-vivo* in patients under chemotherapy or immunosuppressive treatments.

Also the drug resistance of T-cells also permits their enrichment *in* or *ex vivo*, as T-cells which express the drug resistance gene, will survive and multiply relative to drug sensitive cells. In particular, the present invention relates to a method of engineering allogeneic and drug resistance T-cells resistant for immunotherapy comprising:

- (a) Providing a T-cell;
- (b) Selecting at least one drug;
- (c) Modifying T-cell to confer drug resistance to said T-cell;
- (d) Expanding said engineered T-cell in the presence of said drug, and optionally

the preceding steps may be combined with the steps of the methods as previously described.

Drug resistance can be conferred to a T-cell by inactivating one or more gene(s) responsible for the cell's sensitivity to the drug (drug sensitizing gene(s)), such as the hypoxanthine-guanine phosphoribosyl transferase (HPRT) gene (Genbank: M26434.1). In particular HPRT can be inactivated in engineered T-cells to confer resistance to a cytostatic metabolite, the 6-thioguanine (6TG) which is converted by HPRT to cytotoxic thioguanine nucleotide and which is currently used to treat patients with cancer, in particular leukemias (Hacke, Treger et al. 2013). Another example if the inactivation of the CD3 normally expressed at the surface of the T-cell can confer resistance to anti-CD3 antibodies such as teplizumab.

Drug resistance can also be conferred to a T-cell by expressing a drug resistance gene. Said drug resistance gene refers to a nucleic acid sequence that encodes "resistance" to an agent, such as a chemotherapeutic agent (e.g. methotrexate). In other words, the expression of the drug resistance gene in a cell permits proliferation of the cells in the presence of the agent to a greater extent than the proliferation of a corresponding cell without the drug resistance gene. A drug resistance gene of the invention can encode resistance to anti-metabolite, methotrexate, vinblastine, cisplatin, alkylating agents, anthracyclines, cytotoxic antibiotics, anti-immunophilins, their analogs or derivatives, and the like.

Variant alleles of several genes such as dihydrofolate reductase (DHFR), inosine monophosphate dehydrogenase 2 (IMPDH2), calcineurin or methylguanine transferase (MGMT) have been identified to confer drug resistance to a cell. Said drug resistance gene can be expressed in the cell either by introducing a transgene encoding said gene into the cell or by integrating said drug

resistance gene into the genome of the cell by homologous recombination. Several other drug resistance genes have been identified that can potentially be used to confer drug resistance to targeted cells (Takebe, Zhao et al. 2001; Sugimoto, Tsukahara et al. 2003; Zielske, Reese et al. 2003; Nivens, Felder et al. 2004; Bardenheuer, Lehmborg et al. 2005; Kushman, Kabler et al. 2007).

5 DHFR is an enzyme involved in regulating the amount of tetrahydrofolate in the cell and is essential to DNA synthesis. Folate analogs such as methotrexate (MTX) inhibit DHFR and are thus used as anti-neoplastic agents in clinic. Different mutant forms of DHFR which have increased resistance to inhibition by anti-folates used in therapy have been described. In a particular embodiment, the drug resistance gene according to the present invention can be a nucleic acid
10 sequence encoding a mutant form of human wild type DHFR (GenBank: AAH71996.1) which comprises at least one mutation conferring resistance to an anti-folate treatment, such as methotrexate. In particular embodiment, mutant form of DHFR comprises at least one mutated amino acid at position G15, L22, F31 or F34, preferably at positions L22 or F31 ((Schweitzer, Dicker et al. 1990); International application WO 94/24277; US patent US 6,642,043).

15 As used herein, "antifolate agent" or "folate analogs" refers to a molecule directed to interfere with the folate metabolic pathway at some level. Examples of antifolate agents include, e.g., methotrexate (MTX); aminopterin; trimetrexate (Neutrexin™); edatrexate; N10-propargyl-5,8-dideazafolic acid (CB3717); ZD1694 (Tumodex), 5,8-dideazaisofolic acid (IAHQ); 5,10-dideazatetrahydrofolic acid (DDATHF); 5-deazafolic acid; PT523 (N alpha-(4-amino-4- deoxypteroyl)-N
20 delta-hemiphthaloyl-L-ornithine); 10-ethyl-10-deazaaminopterin (DDATHF, lomatrexol); piritrexim; 10-EDAM; ZD1694; GW1843; Pemetrexate and PDX (10-propargyl-10- deazaaminopterin).

Another example of drug resistance gene can also be a mutant or modified form of ionisine-5'- monophosphate dehydrogenase II (IMPDH2), a rate-limiting enzyme in the *de novo* synthesis of guanosine nucleotides. The mutant or modified form of IMPDH2 is a IMPDH inhibitor resistance
25 gene. IMPDH inhibitors can be mycophenolic acid (MPA) or its prodrug mycophenolate mofetil (MMF). The mutant IMPDH2 can comprises at least one, preferably two mutations in the MAP binding site of the wild type human IMPDH2 (NP_000875.2) that lead to a significantly increased resistance to IMPDH inhibitor. The mutations are preferably at positions T333 and/or S351 (Yam, Jensen et al. 2006; Sangiolo, Lesnikova et al. 2007; Jonnalagadda, Brown et al. 2013). In a particular
30 embodiment, the threonine residue at position 333 is replaced with an isoleucine residue and the serine residue at position 351 is replaced with a tyrosine residue.

Another drug resistance gene is the mutant form of calcineurin. Calcineurin (PP2B) is an ubiquitously expressed serine/threonine protein phosphatase that is involved in many biological processes and which is central to T-cell activation. Calcineurin is a heterodimer composed of a

catalytic subunit (CnA; three isoforms) and a regulatory subunit (CnB; two isoforms). After engagement of the T-cell receptor, calcineurin dephosphorylates the transcription factor NFAT, allowing it to translocate to the nucleus and active key target gene such as IL2. FK506 in complex with FKBP12, or cyclosporine A (CsA) in complex with CyPA block NFAT access to calcineurin's active site, preventing its dephosphorylation and thereby inhibiting T-cell activation (Brewin, Mancao et al. 2009). The drug resistance gene of the present invention can be a nucleic acid sequence encoding a mutant form of calcineurin resistant to calcineurin inhibitor such as FK506 and/or CsA. In a particular embodiment, said mutant form can comprise at least one mutated amino acid of the wild type calcineurin heterodimer a at positions: V314, Y341, M347, T351, W352, L354, K360, preferably double mutations at positions T351 and L354 or V314 and Y341. Correspondence of amino acid positions described herein is frequently expressed in terms of the positions of the amino acids of the form of wild-type human calcineurin heterodimer (GenBank: ACX34092.1).

In another particular embodiment, said mutant form can comprise at least one mutated amino acid of the wild type calcineurin heterodimer b at positions: V120, N123, L124 or K125, preferably double mutations at positions L124 and K125. Correspondence of amino acid positions described herein is frequently expressed in terms of the positions of the amino acids of the form of wild-type human calcineurin heterodimer b polypeptide (GenBank: ACX34095.1).

Another drug resistance gene is O(6)-methylguanine methyltransferase (MGMT) encoding human alkyl guanine transferase (hAGT). AGT is a DNA repair protein that confers resistance to the cytotoxic effects of alkylating agents, such as nitrosoureas and temozolomide (TMZ). 6-benzylguanine (6-BG) is an inhibitor of AGT that potentiates nitrosourea toxicity and is co-administered with TMZ to potentiate the cytotoxic effects of this agent. Several mutant forms of MGMT that encode variants of AGT are highly resistant to inactivation by 6-BG, but retain their ability to repair DNA damage (Maze, Kurpad et al. 1999). In a particular embodiment, AGT mutant form can comprise a mutated amino acid of the wild type AGT position P140 (UniProtKB: P16455).

Another drug resistance gene can be multidrug resistance protein 1 (MDR1) gene. This gene encodes a membrane glycoprotein, known as P-glycoprotein (P-GP) involved in the transport of metabolic byproducts across the cell membrane. The P-Gp protein displays broad specificity towards several structurally unrelated chemotherapy agents. Thus, drug resistance can be conferred to cells by the expression of nucleic acid sequence that encodes MDR-1 (NP_000918).

Drug resistance gene can also be cytotoxic antibiotics, such as *ble* gene or *mcrA* gene. Ectopic expression of *ble* gene or *mcrA* in an immune cell gives a selective advantage when exposed to the chemotherapeutic agent, respectively the bleomycine or the mitomycin C.

The T-cells can also be made resistant to immunosuppressive agents. An immunosuppressive agent is an agent that suppresses immune function by one of several mechanisms of action. In other words, an immunosuppressive agent is a role played by a compound which is exhibited by a capability to diminish the extent and/or voracity of an immune response. As non-limiting example, an immunosuppressive agent can be a calcineurin inhibitor, a target of rapamycin, an interleukin-2 α -chain blocker, an inhibitor of inosine monophosphate dehydrogenase, an inhibitor of dihydrofolic acid reductase, a corticosteroid or an immunosuppressive antimetabolite. Classical cytotoxic immunosuppressants act by inhibiting DNA synthesis. Others may act through activation of T-cells or by inhibiting the activation of helper cells. The method according to the invention allows conferring immunosuppressive resistance to T cells for immunotherapy by inactivating the target of the immunosuppressive agent in T cells. As non-limiting examples, targets for immunosuppressive agent can be a receptor for an immunosuppressive agent such as: CD52, glucocorticoid receptor (GR), a FKBP family gene member and a cyclophilin family gene member.

In immunocompetent hosts, allogeneic cells are normally rapidly rejected by the host immune system. It has been demonstrated that, allogeneic leukocytes present in non-irradiated blood products will persist for no more than 5 to 6 days. Thus, to prevent rejection of allogeneic cells, the host's immune system must be effectively suppressed. Glucocorticosteroids are widely used therapeutically for immunosuppression. This class of steroid hormones binds to the glucocorticoid receptor (GR) present in the cytosol of T cells resulting in the translocation into the nucleus and the binding of specific DNA motifs that regulate the expression of a number of genes involved in the immunologic process. Treatment of T cells with glucocorticoid steroids results in reduced levels of cytokine production leading to T cell anergy and interfering in T cell activation. Alemtuzumab, also known as CAMPATH1-H, is a humanized monoclonal antibody targeting CD52, a 12 amino acid glycosylphosphatidyl-inositol- (GPI) linked glycoprotein (Waldmann and Hale, 2005). CD52 is expressed at high levels on T and B lymphocytes and lower levels on monocytes while being absent on granulocytes and bone marrow precursors. Treatment with Alemtuzumab, a humanized monoclonal antibody directed against CD52, has been shown to induce a rapid depletion of circulating lymphocytes and monocytes. It is frequently used in the treatment of T cell lymphomas and in certain cases as part of a conditioning regimen for transplantation. However, in the case of adoptive immunotherapy the use of immunosuppressive drugs will also have a detrimental effect on the introduced therapeutic T cells. Therefore, to effectively use an adoptive immunotherapy approach in these conditions, the introduced cells would need to be resistant to the immunosuppressive treatment.

As a preferred embodiment of the above steps, said gene of step (b), specific for an immunosuppressive treatment, is CD52, and the immunosuppressive treatment of step (d) comprises a humanized antibody targeting CD52 antigen. As another embodiment, said gene of step (b), specific for an immunosuppressive treatment, is a glucocorticoid receptor (GR) and the immunosuppressive treatment of step d) comprises a corticosteroid such as dexamethasone. As another embodiment, said target gene of step (b), specific for an immunosuppressive treatment, is a FKBP family gene member or a variant thereof and the immunosuppressive treatment of step (d) comprises FK506 also known as Tacrolimus or fujimycin. As another embodiment, said FKBP family gene member is FKBP12 or a variant thereof. As another embodiment, said gene of step (b), specific for an immunosuppressive treatment, is a cyclophilin family gene member or a variant thereof and the immunosuppressive treatment of step (d) comprises cyclosporine.

In a particular embodiment of the invention, the genetic modification step of the method relies on the inactivation of two genes selected from the group consisting of CD52 and GR, CD52 and TCR alpha, CDR52 and TCR beta, GR and TCR alpha, GR and TCR beta, TCR alpha and TCR beta. In another embodiment, the genetic modification step of the method relies on the inactivation of more than two genes. The genetic modification is preferably operated ex-vivo using at least two RNA guides targeting the different genes.

By inactivating a gene it is intended that the gene of interest is not expressed in a functional protein form.

Engineering highly active T cells for immunotherapy

According to the present invention, the T-cells can be selected from the group consisting of inflammatory T-lymphocytes, cytotoxic T-lymphocytes, regulatory T-lymphocytes or helper T-lymphocytes. In another embodiment, said cell can be derived from the group consisting of CD4+ T-lymphocytes and CD8+ T-lymphocytes. They can be extracted from blood or derived from stem cells. The stem cells can be adult stem cells, embryonic stem cells, more particularly non-human stem cells, cord blood stem cells, progenitor cells, bone marrow stem cells, induced pluripotent stem cells, totipotent stem cells or hematopoietic stem cells. Representative human cells are CD34+ cells. Prior to expansion and genetic modification of the cells of the invention, a source of cells can be obtained from a subject through a variety of non-limiting methods. T-cells can be obtained from a number of non-limiting sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments of the present invention, any number of T cell lines available and known to those skilled in the art, may be used. In another embodiment, said cell can be derived from

a healthy donor, from a patient diagnosed with cancer or from a patient diagnosed with an infection. In another embodiment, said cell is part of a mixed population of cells which present different phenotypic characteristics. In the scope of the present invention is also encompassed a cell line obtained from a transformed T- cell according to the method previously described.

5 As a further aspect of the invention, the T-cells according to the invention may be further engineered, preferably genetically engineered, to enhance their activity and/or activation, especially by modulating the expression of proteins involved in overall T-cell regulation, referred to as "immune-checkpoints".

Immune check points

10 It will be understood by those of ordinary skill in the art, that the term "immune checkpoints" means a group of molecules expressed by T cells. These molecules effectively serve as "brakes" to down-modulate or inhibit an immune response. Immune checkpoint molecules include, but are not limited to Programmed Death 1 (PD-1, also known as PDCD1 or CD279, accession number: NM_005018), Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4, also known as CD152, GenBank accession
15 number AF414120.1), LAG3 (also known as CD223, accession number: NM_002286.5), Tim3 (also known as HAVCR2, GenBank accession number: JX049979.1), BTLA (also known as CD272, accession number: NM_181780.3), BY55 (also known as CD160, GenBank accession number: CR541888.1), TIGIT (also known as IVSTM3, accession number: NM_173799), LAIR1 (also known as CD305, GenBank accession number: CR542051.1, {Meyaard, 1997 #122}), SIGLEC10 (GeneBank accession
20 number: AY358337.1), 2B4 (also known as CD244, accession number: NM_001166664.1), PPP2CA, PPP2CB, PTPN6, PTPN22, CD96, CRTAM, SIGLEC7 {Nicoll, 1999 #123}, SIGLEC9 {Zhang, 2000 #124; Ikehara, 2004 #125}, TNFRSF10B, TNFRSF10A, CASP8, CASP10, CASP3, CASP6, CASP7, FADD, FAS, TGFBR2, TGFBR1, SMAD2, SMAD3, SMAD4, SMAD10, SKI, SKIL, TGIF1, IL10RA, IL10RB, HMOX2, IL6R, IL6ST, EIF2AK4, CSK, PAG1, SIT1, FOXP3, PRDM1, BATF {Quigley, 2010 #121}, GUCY1A2,
25 GUCY1A3, GUCY1B2, GUCY1B3 which directly inhibit immune cells. For example, CTLA-4 is a cell-surface protein expressed on certain CD4 and CD8 T cells; when engaged by its ligands (B7-1 and B7-2) on antigen presenting cells, T-cell activation and effector function are inhibited. Thus the present invention relates to a method of engineering T-cells, especially for immunotherapy, comprising genetically modifying T-cells by inactivating at least one protein involved in the immune check-point,
30 in particular PD1 and/or CTLA-4 or any immune-checkpoint proteins referred to in Table 3.

Table 3: List of genes encoding immune checkpoint proteins.

Pathway		Genes that can be inactivated In the pathway
Co-inhibitory receptors	CTLA4 (CD152)	CTLA4, PPP2CA, PPP2CB, PTPN6, PTPN22
	PDCD1 (PD-1, CD279)	PDCD1
	CD223 (lag3)	LAG3
	HAVCR2 (tim3)	HAVCR2
	BTLA(cd272)	BTLA
	CD160(by55)	CD160
	IgSF family	TIGIT
		CD96
		CRTAM
	LAIR1(cd305)	LAIR1
	SIGLECs	SIGLEC7
		SIGLEC9
	CD244(2b4)	CD244
Death receptors	TRAIL	TNFRSF10B, TNFRSF10A, CASP8, CASP10, CASP3, CASP6, CASP7
	FAS	FADD, FAS
Cytokine signalling	TGF-beta signaling	TGFBRII, TGFBRI, SMAD2, SMAD3, SMAD4, SMAD10, SKI, SKIL, TGIF1
	IL10 signalling	IL10RA, IL10RB, HMOX2
	IL6 signalling	IL6R, IL6ST
Arginine/tryptophan starvation		EIF2AK4
Prevention of TCR signalling		CSK, PAG1
		SIT1
Induced Treg	induced Treg	FOXP3
Transcription factors controlling exhaustion	transcription factors controlling exhaustion	PRDM1 (=blimp1, heterozygotes mice control chronic viral infection better than wt or conditional KO)
		BATF
Hypoxia mediated tolerance	iNOS induced guanylated cyclase	GUCY1A2, GUCY1A3, GUCY1B2, GUCY1B3

Engineered T-cells expressing chimeric antigen receptors against pathological cells

The chimeric antigen receptors introduced into the T-cells according to the invention can adopt different design such as single-chain or multi-chain CARs. These different designs allow various strategies for improving specificity and binding efficiency towards the targeted pathological cells. Some of these strategies are illustrated in the figures of the present application. Single-chain CARs are the most classical version in the art. Multi-chain CAR architectures were developed by the applicant as allowing modulation of the activity of T-cells in terms of specificity and intensity. The multiple subunits can shelter additional co-stimulation domains or keep such domains at a distance, as well as other types of receptors, whereas classical single chain architecture can sometimes be regarded as too much sensitive and less permissive to multispecific interactions.

Single-Chain CAR

Adoptive immunotherapy, which involves the transfer of autologous antigen-specific T cells generated *ex vivo*, is a promising strategy to treat viral infections and cancer. The T cells used for adoptive immunotherapy can be generated either by expansion of antigen-specific T cells or redirection of T cells through genetic engineering (Park, Rosenberg et al. 2011). Transfer of viral antigen specific T cells is a well-established procedure used for the treatment of transplant associated viral infections and rare viral-related malignancies. Similarly, isolation and transfer of tumor specific T cells has been shown to be successful in treating melanoma.

Novel specificities in T cells have been successfully generated through the genetic transfer of transgenic T cell receptors or chimeric antigen receptors (CARs) (Jena, Dotti et al. 2010). CARs are synthetic receptors consisting of a targeting moiety that is associated with one or more signaling domains in a single fusion molecule. In general, the binding moiety of a CAR consists of an antigen-binding domain of a single-chain antibody (scFv), comprising the light and variable fragments of a monoclonal antibody joined by a flexible linker. Binding moieties based on receptor or ligand domains have also been used successfully. The signaling domains for first generation CARs are derived from the cytoplasmic region of the CD3zeta or the Fc receptor gamma chains. First generation CARs have been shown to successfully redirect T cell cytotoxicity. However, they failed to provide prolonged expansion and anti-tumor activity *in vivo*. Signaling domains from co-stimulatory molecules including CD28, OX-40 (CD134), and 4-1BB (CD137) have been added alone (second generation) or in combination (third generation) to enhance survival and increase proliferation of CAR modified T cells. CARs have successfully allowed T cells to be redirected against antigens

expressed at the surface of tumor cells from various malignancies including lymphomas and solid tumors (Jena, Dotti et al. 2010).

In addition to the CAR targeting the antigen marker, which is common to the pathological cells and the T-cells, such as CD38, it is envisioned to express further CARs directed towards other
5 antigen markers not necessarily expressed by the T-cells, so as to enhancing T-cells specificity.

Examples of chimeric antigen receptor that can be further expressed by the T-cells to create multi-specific cells, are antigen receptors directed against multiple myeloma or lymphoblastic leukemia antigen markers, such as TNFRSF17 (UNIPROT Q02223), SLAMF7 (UNIPROT Q9NQ25), GPRC5D (UNIPROT Q9NZD1), FKBP11 (UNIPROT Q9NYL4), KAMP3, ITGA8 (UNIPROT P53708), and
10 FCRL5 (UNIPROT Q68SN8).

As further examples, the antigen of the target can be from any cluster of differentiation molecules (e.g. CD16, CD64, CD78, CD96, CLL1, CD116, CD117, CD71, CD45, CD71, CD123 and CD138), a tumor-associated surface antigen, such as ErbB2 (HER2/neu), carcinoembryonic antigen (CEA), epithelial cell adhesion molecule (EpCAM), epidermal growth factor receptor (EGFR), EGFR variant III
15 (EGFRvIII), CD19, CD20, CD30, CD40, disialoganglioside GD2, ductal-epithelial mucine, gp36, TAG-72, glycosphingolipids, glioma-associated antigen, β -human chorionic gonadotropin, alphafetoprotein (AFP), lectin-reactive AFP, thyroglobulin, RAGE-1, MN-CA IX, human telomerase reverse transcriptase, RU1, RU2 (AS), intestinal carboxyl esterase, mut hsp70-2, M-CSF, prostase, prostase specific antigen (PSA), PAP, NY-ESO-1, LAGA-1a, p53, prostein, PSMA, surviving and telomerase,
20 prostate-carcinoma tumor antigen-1 (PCTA-1), MAGE, ELF2M, neutrophil elastase, ephrin B2, CD22, insulin growth factor (IGF1)-I, IGF-II, IGFI receptor, mesothelin, a major histocompatibility complex (MHC) molecule presenting a tumor-specific peptide epitope, 5T4, ROR1, Nkp30, NKG2D, tumor stromal antigens, the extra domain A (EDA) and extra domain B (EDB) of fibronectin and the A1 domain of tenascin-C (TnC A1) and fibroblast associated protein (fap); a lineage-specific or tissue specific antigen such as CD3, CD4, CD8, CD24, CD25, CD33, CD34, CD133, CD138, CTLA-4, B7-1
25 (CD80), B7-2 (CD86), GM-CSF, cytokine receptors, endoglin, a major histocompatibility complex (MHC) molecule, BCMA (CD269, TNFRSF 17), or a virus-specific surface antigen such as an HIV-specific antigen (such as HIV gp120); an EBV-specific antigen, a CMV-specific antigen, a HPV-specific antigen, a Lasse Virus-specific antigen, an Influenza Virus-specific antigen as well as any derivate or
30 variant of these surface markers. Antigens are not necessarily surface marker antigens but can be also endogenous small antigens presented by HLA class I at the surface of the cells.

As examples, the present invention encompasses single-chain CARs which target specifically cell surface marker, such as CD38, CS1 and/or CD70 as described in the examples, together with an

inactivation of the genes encoding respectively CD38, CS1 and/or CD70 in the cells expressing said CARs.

As a specific example, the VH and VL chains of the scFv anti-CD38 share at least 80%, preferably 90% and more preferably 95% of identity with respectively SEQ ID NO:10 and 12 and SEQ ID NO: 11 and 13.

As a specific example, the antibody or epitope-binding on CD38 antigen, characterized in that said antibody or epitope-binding fragment thereof comprises at least one heavy chain and at least one light chain, wherein said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 14-17, and wherein said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 21-23.

As a another specific example, the antibody or epitope-binding on CD38 antigen, characterized in that said antibody or epitope-binding fragment thereof comprises at least one heavy chain and at least one light chain, wherein said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 18-20, and wherein said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 24-26.

As another specific example, the VH and VL chains of the scFv anti-CS1 share at least 80%, preferably 90% and more preferably 95% of identity with respectively SEQ ID NO:38-40-42-44-46 and SEQ ID NO: 39-41-42-45-46.

As still another specific example, the VH and VL chains of the scFv anti-CD70 share at least 80%, preferably 90% and more preferably 95% of identity at the polynucleotide or nucleic acid level with respectively SEQ ID NO:81-82; 85-86; 89-91 and SEQ ID NO: 83-84; 87-88; 91-92.

In an embodiment, the invention encompasses a polynucleotide encoding a single CAR anti-CD38 which shares at least 80%, preferably 90% and more preferably 95% of identity with SEQ ID NO: 35-37. In another embodiment, the invention encompassed a polynucleotide encoding a single CAR anti-CS1 which shares at least 80%, preferably 90% and more preferably 95% of identity with SEQ ID NO: 48-62.

In still another embodiment, the invention encompasses a polynucleotide encoding a single CAR anti-CD70 which shares at least 80%, preferably 90% and more preferably 95% of identity with SEQ ID NO: 93-101.

The present invention is more particularly drawn to immune cells that are endowed with a CAR presenting some identity with those described in the present application and that would bear rare-cutting endonuclease induced mutations in a gene encoding the cell marker targeted by said CAR (i.e. the CAR displays affinity with the product of said inactivated gene). By identity is meant at least 70%, preferably 80%, more preferably 90% and even more preferably 95% polynucleotide or polypeptide identity as determined by the software such as FASTA, or BLAST which are available as a part of the GCG sequence analysis package (University of Wisconsin, Madison, Wis.). BLASTP "Identities" shows the number and fraction of total residues in the high scoring sequence pairs which are identical. Amino acid sequences having these degrees of identity or similarity or any intermediate degree of identity of similarity to the amino acid sequences disclosed herein are contemplated and encompassed by this disclosure. The same applies with respect to polynucleotide sequences using BLASTN.

Multi-subunit CAR

Chimeric antigen receptors from the prior art introduced in T-cells have been formed of single chain polypeptides that necessitate serial appending of signaling domains. However, by moving signaling domains from their natural juxtamembrane position may interfere with their function. To overcome this drawback, the applicant recently designed a multi-chain CAR derived from FcεRI to allow normal juxtamembrane position of all relevant signaling domains. In this new architecture, the high affinity IgE binding domain of FcεRI alpha chain is replaced by an extracellular ligand-binding domain such as scFv to redirect T-cell specificity against cell targets and the N and/or C-termini tails of FcεRI beta chain are used to place costimulatory signals in normal juxtamembrane positions.

Accordingly, the CAR expressed by the engineered T-cell according to the invention can be a multi-chain chimeric antigen receptor (CAR) particularly adapted to the production and expansion of engineered T-cells of the present invention. Such multi-chain CARs comprise at least two of the following components:

- a) one polypeptide comprising the transmembrane domain of FcεRI alpha chain and an extracellular ligand-binding domain,
- b) one polypeptide comprising a part of N- and C- terminal cytoplasmic tail and the transmembrane domain of FcεRI beta chain and/or

- c) at least two polypeptides comprising each a part of intracytoplasmic tail and the transmembrane domain of FcεRI gamma chain, whereby different polypeptides multimerize together spontaneously to form dimeric, trimeric or tetrameric CAR.

According to such architectures, ligands binding domains and signaling domains are born on separate polypeptides. The different polypeptides are anchored into the membrane in a close proximity allowing interactions with each other. In such architectures, the signaling and co-stimulatory domains can be in juxtamembrane positions (i.e. adjacent to the cell membrane on the internal side of it), which is deemed to allow improved function of co-stimulatory domains. The multi-subunit architecture also offers more flexibility and possibilities of designing CARs with more control on T-cell activation. For instance, it is possible to include several extracellular antigen recognition domains having different specificity to obtain a multi-specific CAR architecture. It is also possible to control the relative ratio between the different subunits into the multi-chain CAR. This type of architecture has been recently described by the applicant in PCT/US2013/058005 (WO2014/039523).

The assembly of the different chains as part of a single multi-chain CAR is made possible, for instance, by using the different alpha, beta and gamma chains of the high affinity receptor for IgE (FcεRI) (Metzger, Alcaraz et al. 1986) to which are fused the signaling and co-stimulatory domains. The gamma chain comprises a transmembrane region and cytoplasmic tail containing one immunoreceptor tyrosine-based activation motif (ITAM) (Cambier 1995).

The multi-chain CAR can comprise several extracellular ligand-binding domains, to simultaneously bind different elements in target thereby augmenting immune cell activation and function. In one embodiment, the extracellular ligand-binding domains can be placed in tandem on the same transmembrane polypeptide, and optionally can be separated by a linker. In another embodiment, said different extracellular ligand-binding domains can be placed on different transmembrane polypeptides composing the multi-chain CAR. In another embodiment, the present invention relates to a population of multi-chain CARs comprising each one different extracellular ligand binding domains. In a particular, the present invention relates to a method of engineering immune cells comprising providing an immune cell and expressing at the surface of said cell a population of multi-chain CAR each one comprising different extracellular ligand binding domains. In another particular embodiment, the present invention relates to a method of engineering an immune cell comprising providing an immune cell and introducing into said cell polynucleotides encoding polypeptides composing a population of multi-chain CAR each one comprising different extracellular ligand binding domains. In a particular embodiment the method of engineering an immune cell comprises expressing at the surface of the cell at least a part of FcεRI beta and/or

gamma chain fused to a signal-transducing domain and several part of FcεRI alpha chains fused to different extracellular ligand binding domains. In a more particular embodiment, said method comprises introducing into said cell at least one polynucleotide which encodes a part of FcεRI beta and/or gamma chain fused to a signal-transducing domain and several FcεRI alpha chains fused to different extracellular ligand biniding domains. By population of multi-chain CARs, it is meant at least two, three, four, five, six or more multi-chain CARs each one comprising different extracellular ligand binding domains. The different extracellular ligand binding domains according to the present invention can preferably simultaneously bind different elements in target thereby augmenting immune cell activation and function.

The present invention also relates to an isolated immune cell which comprises a population of multi-chain CARs each one comprising different extracellular ligand binding domains.

The signal transducing domain or intracellular signaling domain of the multi-chain CAR of the invention is responsible for intracellular signaling following the binding of extracellular ligand binding domain to the target resulting in the activation of the immune cell and immune response. In other words, the signal transducing domain is responsible for the activation of at least one of the normal effector functions of the immune cell in which the multi-chain CAR is expressed. For example, the effector function of a T cell can be a cytolytic activity or helper activity including the secretion of cytokines.

In the present application, the term "signal transducing domain" refers to the portion of a protein which transduces the effector signal function signal and directs the cell to perform a specialized function.

Preferred examples of signal transducing domain for use in single or multi-chain CAR can be the cytoplasmic sequences of the Fc receptor or T cell receptor and co-receptors that act in concert to initiate signal transduction following antigen receptor engagement, as well as any derivate or variant of these sequences and any synthetic sequence that as the same functional capability. Signal transduction domain comprises two distinct classes of cytoplasmic signaling sequence, those that initiate antigen-dependent primary activation, and those that act in an antigen-independent manner to provide a secondary or co-stimulatory signal. Primary cytoplasmic signaling sequence can comprise signaling motifs which are known as immunoreceptor tyrosine-based activation motifs of ITAMs. ITAMs are well defined signaling motifs found in the intracytoplasmic tail of a variety of receptors that serve as binding sites for syk/zap70 class tyrosine kinases. Examples of ITAM used in the invention can include as non-limiting examples those derived from TCRzeta, FcRgamma, FcRbeta, FcRepsilon, CD3gamma, CD3delta, CD3epsilon, CD5, CD22, CD79a, CD79b and CD66d. In a preferred

embodiment, the signaling transducing domain of the multi-chain CAR can comprise the CD3zeta signaling domain, or the intracytoplasmic domain of the FcεRI beta or gamma chains.

In particular embodiment the signal transduction domain of the multi-chain CAR of the present invention comprises a co-stimulatory signal molecule. A co-stimulatory molecule is a cell surface molecule other than an antigen receptor or their ligands that is required for an efficient immune response.

Ligand binding-domains can be any antigen receptor previously used, and referred to, with respect to single-chain CAR referred to in the literature, in particular scFv from monoclonal antibodies. Bispecific or multi-specific CARs as described in WO 2014/4011988 are incorporated by reference.

Similarly as described before with respect to single-chain CARs, the present invention encompasses immune cells endowed with multi-chain CARs which target specifically a cell surface marker such as CD38, CS1 or CD70. According to a preferred embodiment of the invention the CARs described above are expressed in immune cells, whereas inactivation of the endogenous genes encoding said surface marker(s) is induced by expression of a rare-cutting endonuclease.

Activation and expansion of T cells

The method according to the invention generally includes a further step of activating and/or expanding the T-cells. This can be done prior to or after genetic modification of the T cells, using the 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. According to these methods, the T cells of the invention can be 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 *in vitro* 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. For example, the agents providing each signal may be in solution or coupled to a surface. 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. 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. 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, 4 to 10 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, preferably 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. 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. Conditions appropriate for T cell culture include an appropriate media (e.g., Minimal Essential Media or RPMI Media 1640 or, X-vivo 5, (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-g, 1L-4, 1L-7, GM-CSF, -10, -2, 1L-15, TGFp, and TNF- 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, A1M-V, DMEM, MEM, a-MEM, F-12, X-Vivo 1, 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 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.

In another particular embodiment, said cells can be expanded by co-culturing with tissue or cells. Said cells can also be expanded *in vivo*, for example in the subject's blood after administering said cell into the subject.

Therapeutic applications

The T-cells obtainable by the different methods described above are intended to be used as a medicament for treating, among others, cancer, infections or immune diseases in a patient in need thereof.

Said treatment can be ameliorating, curative or prophylactic. It may be either part of an autologous immunotherapy or part of an allogenic immunotherapy treatment. By autologous, it is meant that cells, cell line or population of cells used for treating patients are originating from said patient or from a Human Leucocyte Antigen (HLA) compatible donor. By allogeneic is meant that the
5 cells or population of cells used for treating patients are not originating from said patient but from a donor.

The T-cells engineered according to one of the previous methods may be pooled, frozen, and administrated to one or several patients. When they are made non-alloreactive, they are available as an "off the shelf" therapeutic product, which means that they can be universally infused to patients
10 in need thereof.

Said treatments are primarily intended to patients diagnosed with cancer, viral infection, autoimmune disorders or Graft versus Host Disease (GvHD). Cancers are preferably leukemias and lymphomas, which have liquid tumors, but may also concern solid tumors. Types of cancers to be treated with the CARs of the invention include, but are not limited to, carcinoma, blastoma, and
15 sarcoma, and certain leukemia or lymphoid malignancies, benign and malignant tumors, and malignancies e.g., sarcomas, carcinomas, and melanomas. Adult tumors/cancers and pediatric tumors/cancers are also included.

The present invention provides in Tables 4 to 14 with examples of antigen markers, which can be targeted with the engineered-cells of the invention for treating different types of cancer.

Preferred antigen markers used for the immunotherapy of the present invention are more particularly CD38, CD319 (CS1) and CD70.
20

The present T-cells, when armed with specific CARs directed against patient's own immune cells, especially T-cells, allow the inhibition or regulation of said cells, which is a key step for treating auto-immune disease, such as rheumatoid polyarthritis, systemic lupus erythematosus, Sjogren's syndrome, scleroderma, fibromyalgia, myositis, ankylosing spondylitis, insulin dependent diabetes of
25 type I, Hashimoto's thyroiditis, Addison's disease, Crohn's disease, Celiac's disease, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). Accordingly the present invention encompass a method for treating an immune disease by directing engineered T-cells as previously described against patient's own T-cells.

The above treatments can take place in combination with one or more therapies selected from the group of antibodies therapy, chemotherapy, cytokines therapy, dendritic cell therapy, gene therapy, hormone therapy, laser light therapy and radiation therapy.
30

The engineered T-cells as previously described, when they are made resistant to chemotherapy drugs and immunosuppressive drugs that are used as standards of care, especially

methotrexate and the combination of fludarabine and Cyclophosphamide, are particularly suited for treating various forms of cancer. Indeed, the present invention preferably relies on cells or population of cells, In this aspect, it is expected that the chemotherapy and/or immunosuppressive treatment should help the selection and expansion of the engineered T-cells in-vivo.

5 In certain embodiments of the present invention, cells 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 antiviral therapy, cidofovir and interleukin-2, Cytarabine (also known as ARA-C) or natalizimab treatment for MS patients or efalizumab treatment for psoriasis patients or other treatments for PML patients. In further
10 embodiments, the T cells of the invention may be used in combination with chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies or other antibody therapies, cytoxin, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, cytokines, and irradiation. These drugs inhibit either the calcium dependent phosphatase
15 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., Crit. 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) bone marrow transplantation, T cell ablative therapy using either
20 chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, or antibodies such as OKT3 or CAMPATH, In 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. For example, in one embodiment, subjects may undergo standard treatment with high dose chemotherapy followed by peripheral blood stem
25 cell transplantation. In certain embodiments, following the transplant, subjects receive an infusion of the expanded immune cells of the present invention. In an additional embodiment, expanded cells are administered before or following surgery. Said modified cells obtained by any one of the methods described here can be used in a particular aspect of the invention for treating patients in need thereof against Host versus Graft (HvG) rejection and Graft versus Host Disease (GvHD); therefore in
30 the scope of the present invention is a method of treating patients in need thereof against Host versus Graft (HvG) rejection and Graft versus Host Disease (GvHD) comprising treating said patient by administering to said patient an effective amount of modified cells comprising inactivated TCR alpha and/or TCR beta genes.

According to one embodiment, said T cells of the invention can undergo robust *in vivo* T cell expansion upon administration to a patient, and can persist in the body fluids for an extended amount of time, preferably for a week, more preferably for 2 weeks, even more preferably for at least one month. Although the T-cells according to the invention are expected to persist during these periods, their life span into the patient's body are intended not to exceed a year, preferably 6 months, more preferably 2 months, and even more preferably one month.

The administration of the cells or population of cells according to the present invention may be carried out in any convenient manner, including by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. The compositions described herein may be administered to a patient subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, by intravenous or intralymphatic injection, or intraperitoneally. In one embodiment, the cell compositions of the present invention are preferably administered by intravenous injection.

The administration of the cells or population of cells can consist of the administration of 10^4 - 10^9 cells per kg body weight, preferably 10^5 to 10^6 cells/kg body weight including all integer values of cell numbers within those ranges. The cells or population of cells can be administered in one or more doses. In another embodiment, said effective amount of cells are administered as a single dose. In another embodiment, said effective amount of cells are administered as more than one dose over a period time. Timing of administration is within the judgment of managing physician and depends on the clinical condition of the patient. The cells or population of cells may be obtained from any source, such as a blood bank or a donor. While individual needs vary, determination of optimal ranges of effective amounts of a given cell type for a particular disease or conditions within the skill of the art. An effective amount means an amount which provides a therapeutic or prophylactic benefit. The dosage administered will be dependent upon the age, health and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired.

In another embodiment, said effective amount of cells or composition comprising those cells are administered parenterally. Said administration can be an intravenous administration. Said administration can be directly done by injection within a tumor.

Identification of surface antigen marker expressed on the surface of T-cells, while being overexpressed in solid tumors involved into different types of cancer (Tables 5 to 13)

We used BioGPS microarray data from a panel of normal tissues (Human U133A/GNF1H Gene Atlas) cancer microarray data that also can be downloaded from BioGPS (Human Primary Tumors (U95)) uniprot data that contains the subcellular localization.

We drew the distribution of values coming from normal tissues and determined a threshold value of 5 for the relative expression.

We browsed all the genes assayed with microarrays (44.000 probes representing about 13 000 genes) and checked their localization in the membrane (protein not referred to as being a membrane protein were discarded). Expression in CD8+ T-cells was checked from the BioGPS database. The genes were listed according to the type of cancer where the corresponding expression was the highest (Tables 5 to 13).

Identification of surface antigen marker expressed on the surface of T-cells, while being overexpressed in different liquid blood tumors (Table 14)

For that study, no RNA-seq data were available and thus we used microarray data that were obtained from a large study from the MILE consortium (Microarray Innovations in Leukemia), involving 11 laboratories (http://www.ngri.org.uk/wessex/downloads/tm08/TM08-S4-1_KenMills.pdf - Haferlach et al. 2010, <http://www.ncbi.nlm.nih.gov/pubmed/20406941>). This raw data include results for ALL (acute lymphoblastic leukemia), AML (acute myelogenous leukemia), CLL (chronic lymphoblastic leukemia) and CML (chronic myelogenous leukemia) and MDS (myelodysplastic syndrome). We also used uniprot data for subcellular localization as usual.

We first drew the overall distribution of values from all genes on all studied tissues. Then, to have an idea of the level necessary for expression, we took a list of genes which are expressed in some liquid tumors and for which therapeutic antibodies are available (CD52, CD 20, CD33, CD19, CD25, CD44, CD47, CD96, CD116, CD117, CD135, TIM-3). For each gene, we looked at the value obtained in the tumor in which it is expressed. Then, we computed the average for each tumor and gene pair for which the gene seems to give a cell membrane protein (cell membrane localization + description of at least one transmembrane domain in the protein). We discarded genes for which the expression in all the tissues was below this threshold of 0.15. We listed and ranked in Table 14, those genes which relative expression in T-cells was above 0.2. Thus, Table 4 provides putative antigen marker candidates for targeting liquid tumor cells as per the invention, in particular for treating ALL, AML, CLL, CML and MDS.

Example of steps to engineer T-cells according to the invention for immunotherapy

For a better understanding of the invention, it is provided below an example of the steps to follow to produce T-cells directed against leukemia CD38 positive cells:

- 5 1. Providing T-cells from a cell culture or from a blood sample from one individual patient or from blood bank and activating said T cells using anti-CD3/C28 activator beads (Dynabeads®). The beads provide both the primary and co-stimulatory signals that are required for activation and expansion of T cells.
- 10 2. Transducing said cells with a retroviral vector comprising a transgene encoding a Chimeric antigen receptor consisting of the fusion of CD3zeta activation domain, 4-1BB co-stimulation domain, a transmembrane domain and a hinge from CD28 fused to a sequence encoding the variable chain of an anti-CD38 antibody. For security improvement of the transformed T-cell, a suicide gene sensitive to rituximab may further be introduced as described in WO 2013/153391 into the lentiviral vector separated by T2A splitting sequences.
- 15 3. (Optionally) Engineering non alloreactive and/or resistant T cells:
 - a) It is possible to Inactivate TCR alpha in said cells to eliminate the TCR from the surface of the cell and prevent recognition of host tissue as foreign by TCR of allogenic and thus to avoid GvHD by following the protocols set forth in WO 2013/176915.
 - 20 b) It is also possible to inactive one gene encoding target for an immunosuppressive agent or a chemotherapy drug to render said cells resistant to immunosuppressive or chemotherapy treatment to prevent graft rejection without affecting transplanted T cells. In this example, target of immunosuppressive agents is CD52 and immunosuppressive agent is a humanized monoclonal anti-CD52 antibody (ex: Alemtuzumab) as described in WO 2013/176915.
- 25 4. Gene Inactivation is performed by electroporating T-cells with mRNA encoding specific TAL-endonuclease (TALENTM – Collectis, 8 rue de la Croix Jarry, France). Inactivated T cells are sorted using magnetic beads. For example, T cells still expressing the targeted gene (e.g. CD38, CD70 and CD70) can be removed by fixation on a solid surface, and inactivated cells are not exposed of the stress of being passed through a column. This gentle method increases the
30 concentration of properly engineered T-cells.
5. Expansion *in vitro* of engineered T-cells prior to administration to a patient or *in vivo* following administration to a patient through stimulation of CD3 complex. Before administration step,

patients can be subjected to an immunosuppressive treatment such as CAMPATH1-H, a humanized monoclonal anti-CD52 antibody.

6. Optionally exposed said cells with bispecific antibodies *ex vivo* prior to administration to a patient or *in vivo* following administration to a patient to bring the engineered cells into proximity to a target antigen.

Functional analysis of the engineered T-cells electroporated with a monocistronic mRNA encoding for an anti-CD38 single chain chimeric antigen receptor (CAR CD38):

To verify that genome engineering did not affect the ability of the engineered T-cells to present anti-tumor activity, especially when provided with a chimeric antigen receptor (CAR CD38), The engineered T-cells were incubated for 4 hours with Daudi cells expressing CD38 on their surface. The cell surface upregulation of CD107a, a marker of cytotoxic granule release by T lymphocytes (called degranulation) was measured by flow cytometry analysis (Betts, Brenchley et al. 2003).

24 hours post electroporation, cells were stained with a fixable viability dye eFluor-780 and a PE-conjugated goat anti mouse IgG F(ab')₂ fragment specific to assess the cell surface expression of the CAR on the live cells. The vast majority of the live T-cells genetically disrupted for CD38, express the CAR on their surface. T cells were co-cultured with Daudi (CD38⁺) cells for 6 hours and analyzed by flow cytometry to detect the expression of the degranulation marker CD107a at their surface (Betts, Brenchley et al. 2003).

The results showed that CD38 disrupted T-cells kept the same ability to degranulate in response to PMA /ionomycin (positive control) or CD38⁺ Daudi cells. CD107 upregulation is dependent on the presence of a CD38⁺. These data suggest that the genome engineering of the present T-cells had no negative impact on the ability of T cells to mount a controlled anti-tumor response.

Table 4: Cluster of differentiation (CD) antigen markers of various cancers found to be expressed on the surface of T-cells

Antigen	Other Names	Structure	main Distribution	Function
CD1a	T6	IgSF, MHC-like	cortical thymocytes, Langerhans cells, DC	antigen presentation, with beta2m
CD1b	T6	IgSF, MHC-like	cortical thymocytes, Langerhans cells, DC	antigen presentation, with beta2m
CD1c	T6	IgSF, MHC-like	cortical thymocytes, Langerhans cells, DC, B subset	antigen presentation, with beta2m
CD1d		IgSF, MHC-like	intestinal epith, B subset, monolow, DC	antigen presentation, with beta2m
CD3 gamma, CD3 delta	T3	IgSF	T, thymocyte subset	with TCR, TCR surface expression / signal transduction
CD3 epsilon	T3	IgSF	T, thymocyte subset	with TCR, TCR surface expression / signal transduction
CD4	T4	IgSF	thymocyte subset, T subset, mono, mac	MHC class II coreceptor, HIV receptor, T cell differentiation / activation
CD5	T1, Tp67	Scavenger R SF	thymocytes, T, B subset, B-CLL	CD72 receptor, TCR or BCR signaling, T-B interaction
CD7		IgSF	hematopoietic progenitors, thymocytes, T, NK	T costimulation
CD8a	T8, Leu-2	IgSF	thymocyte subset, T subset, NK	MHC class I coreceptor, receptor for some mutated HIV-1, T cell differentiation / activation
CD8b		IgSF	thymocyte subset, T subset	
CD9	p24, MRP-1	TM4SF	pre-B, eosinophils, basophils, platelets, Tact	cellular adhesion and migration
CD10	CALLA, NEP, gp100	type II TM	B precursors, neutrophils	zinc-binding metalloproteinase, B cell development
CD11a	LFA-1, integrin alphaL	Integrin family	lymph, gran, mono, mac	CD11a / CD18 receptor for ICAM-1, -2, -3, intercellular adhesion, T costimulation
CD11b	Mac-1, integrin alphaM	Integrin family	myeloid cells, NK	binds CD54, ECM, iC3b
CD11c	p150, 95, CR4, integrin alphaX	Integrin family	DC, myeloid cells, NK, B, T subset	binds CD54, fibrinogen and iC3b
CD13	Aminopeptidase N, APN	type II TM	myeloid cells	zinc-binding metalloproteinase, antigen processing, receptor for corona virus strains
CD14	LPS-R	GPI-linked	mono, mac, Langerhans cells, granlow	receptor for LPS/LBP, LPS recognition

CD15		Lewis-x, Lex	CHO	neutrophils, eosinophils, mono	adhesion
CD16a		FcgammaRIIIA	IgSF	neutrophils, mac, NK	component of low affinity Fc receptor, phagocytosis and ADCC
CD16b		FcgammaRIIIB	IgSF	neutrophils	component of low affinity Fc receptor, phagocytosis and ADCC
CD20		B1, Bp35	TM4SF	B, T subset	B cell activation
CD21		C3DR, CR2, EBV-R	CCRSF	B, FDC, T subset	complement C3d and EBV receptor, complex with CD19 and CD81, BCR coreceptor
CD22		BL-CAM, Siglec-2	IgSF, sialoadhesins	B	adhesion, B-mono, B-T interactions
CD23		FcepsilonRII	C-type lectin	B, activated mac, eosinophils, FDC, platelets	CD19-CD21-CD81 receptor, IgE low affinity receptor, signal transduction
CD24		BA-1	GPI-linked	thymocytes, erythrocytes, peripheral lymph, myeloid	binds P-selectin
CD25		Tac, p55	type I TM	Tact, Bact, lymph progenitors	IL-2Ralpha, with IL-2Rbeta and gamma to form high affinity complex
CD31		PECAM-1	IgSF	mono, platelets, gran, endoth, lymph subset	CD38 receptor, adhesion
CD33		p67, Siglec-3	IgSF, sialoadhesins	myeloid progenitors, mono, gran, DC, mast cells, Tact	adhesion
CD37			TM4SF	B, Tlow, granlow	signal transduction
CD38		T10		variable levels on majority of hematopoietic cells, high expression on plasma cells, B and Tact	ecto-ADP-ribosyl cyclase, cell activation
CD40			TNFRSF	B, mono, mac, FDC, endoth, T subset	CD154 receptor, B differentiation / costimulation, isotype-switching, rescues B cells from apoptosis
CD43		Leukosialin, sialophorin	Sialomucin, type I TM	leukocytes, except resting B, plateletslow	inhibition of T cell interaction, CD54R, adhesion
CD44		H-CAM, Pgp-1	hyaladherin family	hematopoietic and non-hematopoietic cells, except platelets, hepatocytes, testis	binds hyaluronic acid, adhesion
CD45		LCA, T200, B220		hematopoietic cells, multiple isoforms from alternative splicing	tyrosine phosphatase, enhanced TCR & BCR signals
CD45RA				B, T subset(naive), mono	exon A isoforms of CD45
CD45RB				T subset, B, mono, mac, gran	exon B isoforms of CD45

CD45RO					Tact, memory T, B subset, mono, mac, gran nucleated cells	isoform of CD45 lacking A, B, C exons
CD46	MCP	CCRSF				membrane cofactor protein, binds C3b & C4b allowing degradation by Factor I, measles virus receptor
CD47	IAP	IgSF			hematopoietic cells, epith, endoth, fibroblasts, other tissues	leukocyte adhesion, migration, activation
CD48	Blast-1	IgSF			broad, all leukocytes	cell adhesion
CD52	CAMPATH-1				thymocytes, T, B (not plasma cells), mono, mac	
CD53		TM4SF			leukocytes, DC, osteoblasts, osteoclasts	signal transduction
CD55	DAF	GPI-linked			hematopoietic, endoth	binds C3b, complement regulation
CD56	NCAM	IgSF			NK, T subset, neurons, some large granular lymphocyte leukemias, myeloid leukemias	adhesion
CD57	HNK-1, Leu-7				NK subset, T subset	
CD58	LFA-3	IgSF			hematopoietic, non-hematopoietic cells	CD2 receptor, adhesion
CD59	Protectin, MAC-inhibitor	GPI-linked			hematopoietic, non-hematopoietic cells	binds complement C8 and C9, blocks assembly of membrane attack complex
CD60a	GD3	CHO			T subset, platelets, thymic epith, astrocytes	costimulation
CD63	LIMP, LAMP-3	TM4SF			activated platelets, mono, mac	lysosomal membrane protein, moves to cell surface after activation
CD68	Macrosialin, gp110	Sialomucin			intracellularly in mono, mac, neutrophils, basophils, progenitors, liver	
CD69	AIM	C-type lectin			Tact, B, NK and gran, thymocytes, platelets, Langerhans cells	signal transduction
CD70	Ki-24	TNFSF			Bact and Tact	CD27 ligand, T and B cell costimulation
CD74	Ii, invariant chain	B, mac, mono, Langerhans cells, DC, Tact				MHC class II traffic and function
CD79a	Iga	IgSF		B		component of BCR, BCR surface expression and signal transduction
CD79b	Igb	IgSF		B		component of BCR, BCR surface expression and signal transduction
CD81	TAPA-1	TM4SF			T, B, NK, thymocytes, DC, endoth, fibroblast, neuroblastomas, melanomas	complex with CD19 & CD21, signaling, T costimulation
CD82	R2	TM4SF			leukocytes	signal transduction

CD83	HB15	IgSF	Bact and Tact, DC, Langerhans cells	
CDw84			mono, platelets, B, T subset, mac subset	
CD86	B70, B7-2	IgSF	mono, DC, Bact and Tact	binds to CD28, CD152, T costimulation
CD87	UPA-R	GPI-linked	gran, mono, NK, Tact, endoth, fibroblasts	urokinase plasminogen activator receptor, inflammatory cell invasion, metastasis
CD90	Thy-1	IgSF, GPI-linked	CD34+ hematopoietic subset, neurons	hematopoietic stem cell and neuron differentiation
CD94	KP43	C-type lectin	NK, T subset	complex with NKG2, inhibits NK function
CD95	Apo-1, Fas	TNFRSF	lymph (high upon activation), mono, neutrophils	FasL (CD178) receptor, apoptosis
CD96	TACTILE	IgSF	NK, Tact	adhesion of activated T and NK
CD97		TM7SF	Bact and Tact, mono, gran	
CD98	4F2		T, B, NK, gran, all human cell lines	cellular activation
CD99	MIC2, E2		leukocytes	T cell activation, adhesion
CD100			hematopoietic cells except immature bone marrow cells, RBC and platelets	cell adhesion, cellular activation
CD103	HML-1, alpha6, integrin alphaE	Integrin family	intraepithelial lymph, lymph subset, activated lymph	with integrin beta7, binds E-cadherin, lymph homing/retention
CD107a	LAMP-1		activated platelets, T, endoth, metastatic tumors	a lysosomal membrane protein
CD107b	LAMP-2		activated platelets, T, endoth, metastatic tumors	a lysosomal membrane protein
CD109			Tact and platelets, CD34+ subset, endoth	
CD123	IL-3R	CRSF	lymph subset, basophils, hematopoietic progenitors, mac, DC, megakaryocytes	IL-3Ralpha, with CDw131
CD146	MUC18, S-endo	IgSF	endoth, melanomas, FDC, Tact	adhesion
CD154	CD40L, gp39, TRAP	TNFSF	Tact	CD40 ligand, B and DC costimulation
CD158a	p58.1	IgSF, KIR family	NK subset, T subset	inhibition of NK cell cytolytic activity, MHC class-I specific NK receptor
CD158b	p58.2	IgSF, KIR family	NK subset, T subset	inhibition of NK cell cytolytic activity, MHC class-I specific NK receptor
CD163	130kD	Scavenger receptor SF	mono, mac	
CD164	MGC-24	epith, mono,	hematopoietic progenitor cell-stromal cell interaction	

CD168	RHAMM	lymphlow, bone marrow stromal cells, CD34+ erythroid progenitors			
CD171	L1	IgSF		mono, T subset, thymocyte subset, intracellularly in breast cancer cells	adhesion, tumor migration, metastasis
CD177	NB1			CNS, PNS, glial cells, mono, T subset, B, DC, several human tumor cells	kidney morphogenesis, lymph node architecture, T costimulation, neurohistogenesis, homotypic interaction, binds CD9, CD24, CD56, CD142, CD166, integrins
CD178	FasL, CD95L	TNFSF		neutrophil subset	
CD180	RP-105	LRRF, TLR family		Tact, testis	CD95 ligand, apoptosis, immune privilege, soluble form in serum
CD182	CXCR2, IL-8RB	GPCR1 family		B subset, mono, DC	B cell activation, LPS signaling, with MD-1
CD185	CXCR5, BLR1	GPCR1 family		neutrophils, basophils, NK, T subset, mono	binding of IL-8 induces chemotaxis of neutrophils
CD191	CCR1, MIP-1alphaR, RANTES-R	GPCR1 family		mature B and Burkitt Lymphoma cells	with chemokine BLC, possible regulatory function in Burkitt Lymphomagenesis and/or B differentiation, activation of mature B
CD193	CCR3, CKR3	GPCR1 family		T, mono, stem cell subset	binds C-C type chemokines and transduces signal by increasing intracellular calcium ion levels
CD196	CCR6, LARC receptor, DRY6	GPCR1 family		eosinophils, lower expression in neutrophils and mono, T subset	binds eotaxin, eotaxin-3, MCP-3, MCP-4, RANTES & MIP-1delta, alternative coreceptor with CD4 for HIV-1 infection
CD197	CCR7	GPCR1 family		T subset, B, DC subset	binds MIP-3alpha/LARC
CD200	OX-2			T subset, DC Subset	6CKine and MIP-2beta receptor
CD209	DC-SIGN			thymocytes, endoth, B, Tact	inhibition of immune response
CD227	MUC1, EMA	Mucin family, type I TM		DC subset	ICAM-3 receptor, HIV-1 binding protein
CD231	TALLA-1, A15	TM4SF		epith, stem cell subset, FDC, mono, B subset, some myelomas	adhesion, signaling, binds CD169, CD54, & selectins
				T leukemias, neuroblastomas, brain neurons	marker for T cell acute lymphoblastic leukemia

CD246	ALK, Ki-1			anaplastic T cell leukemias, small intestine, testis, brain, not on normal lymph	brain development, implicated in ALK lymphomas
CD254	TRANCE, RANKL, OPGL	TNFSF		lymph node & BM stroma Tact	binds OPG and RANK, osteoclast differentiation, enhances DC to stimulate naïve-T proliferation
CD263	TRAIL-R3, DcR1, LIT			peripheral blood lymphocytes	receptor for TRAIL but lacks death domain
CD272	BTLA	IgSF		Tact, B , remains on Th1	HVEM receptor, inhibitory response
CD273	B7DC, PD-L2, PDCD1L2	IgSF		DC subset, mono, mac	PD-1 receptor, costimulation or suppression of T proliferation
CD276	B7-H3	B7 Family, ASV		in vitro cultured DC and mono, Tact, mammary tissue	costimulation, T activation
CD277	BT3.1, butyrophilin SF3 A1, BTF5	B7/BT family, ASV		T, B, NK, mono, DC, endoth, CD34+ cells, tumor cell lines	T activation
CD279	PD1, SLEB2			Tact and Bact	B7-H1 & B7-DC receptor, autoimmune disease and peripheral tolerance
CD298	Na+/K+-ATPase beta3 subunit			broad	transport sodium & potassium ions across membrane
CD300a	CMRF35H, IRC1, IRp60	IgSF, ASV		NK, mono, neutrophils, T and B subset and lymphocytic cell lines, AML	unknown
CD300c	CMRF35A, LIR	IgSF		mono, neutrophils, monocytic cell lines, B & T subsets	unknown
CD304	BDC4, neuropilin 1	semaphorin family		neurons, CD4+/CD25+ Treg, DC, endothelial and tumor cells	interacts with VEGF165 & semaphorins, co-receptor with plexin, axonal guidance, angiogenesis, cell survival, migration
CD305	LAIR1	IgSF, ASV		NK, B, T, mono	inhibitory receptor on NK and T cells
CD314	NKG2D, KLR	Type II lectin-like receptor		NK, CD8+ activated, NK1.1+ T, some myeloid cells	binds MHC class I, MICA, MICB, Rae1 & ULBP4, activates cytotoxicity and cytokine production, costimulation
CD317	BST2, HM1.24	Type II		B, T, NK, mono, DC, fibroblast cell line, myeloma	pre-B cell growth, overexpressed in multiple myeloma
CD319	CS1, CRACC, SLAMF7	SLAM receptor family		B Cells, Dendritic Cells, NK, NKT	multiple myeloma

Table 5: antigen markers expressed on the surface of both colon tumor cells and T-cells

Antigen	Protein Name	Relative expression in T-Cell	Relative Expression in colon cancer cells
EPCAM	Epithelial cell adhesion molecule	2,97	13,99
IFITM1	Interferon-induced transmembrane protein 1	10,55	13,06
CLDN4	Claudin-4	2,87	11,62
CDH17	Cadherin-17	1,85	11,52
CEACAM1	Carcinoembryonic antigen-related cell adhesion molecule 1	3,33	10,84
SLC26A3	Chloride anion exchanger	2,57	10,59
ATP1A1	Sodium/potassium-transporting ATPase subunit alpha-1	9,28	10,51
SI	Isomaltase	2,86	10,46
ABCB1	Multidrug resistance protein 1	6,09	10,24
KCNQ1	Potassium voltage-gated channel subfamily KQT member 1	3,36	9,99
FCGRT	IgG receptor FcRn large subunit p51	4,8	9,98
EPHB3	Ephrin type-B receptor 3	5,23	9,74
DSG2	Desmoglein-2	3,04	8,5
EPHB4	Ephrin type-B receptor 4	6,5	8,44
GUCY2C	Heat-stable enterotoxin receptor	2,23	8,05
EPHA2	Ephrin type-A receptor 2	2,8	7,95
LY6G6D	Lymphocyte antigen 6 complex locus protein G6f	2,02	7,91
CD97	CD97 antigen subunit beta	7,7	7,87
SIGMAR1	Sigma non-opioid intracellular receptor 1	4,58	7,85
EREG	Epiregulin	2,93	6,9
FAIM2	Protein lifeguard 2	2,94	6,82
PIGR	Secretory component	4,2	6,8
SLC7A6	Y+L amino acid transporter 2	8,06	6,55
SCNN1D	Amiloride-sensitive sodium channel subunit delta	1,77	5,74
GPR35	G-protein coupled receptor 35	1,98	5,5
ABCG2	ATP-binding cassette sub-family G member 2	1,79	5,35
LPAR4	Lysophosphatidic acid receptor 4	2,93	5,05
GPR161	G-protein coupled receptor 161	2,71	4,96
CD1C	T-cell surface glycoprotein CD1c	2,73	4,89
SGCA	Alpha-sarcoglycan	2,32	4,84
CD22	B-cell receptor CD22	4,12	4,75
CD22	B-cell receptor CD22	3,58	4,75
CD22	B-cell receptor CD22	2,73	4,75
CD22	B-cell receptor CD22	2,14	4,75
SLC22A18	Solute carrier family 22 member 18	2,32	4,62
HTR7	5-hydroxytryptamine receptor 7	3,02	4,46
LCT	Phlorizin hydrolase	2,32	4,24
CD33	Myeloid cell surface antigen CD33	3,42	4,14
PVR	Poliovirus receptor	5,07	4,07
PLXDC1	Plexin domain-containing protein 1	5,85	3,99
P2RY2	P2Y purinoceptor 2	2,15	3,97
CHRNA2	Neuronal acetylcholine receptor subunit beta-2	6,31	3,88
PTGDR	Prostaglandin D2 receptor	4,08	3,65
NCR1	Natural cytotoxicity triggering receptor 1	2,63	3,33

GYPA	Glycophorin-A	3,18	3,31
TNFRSF8	Tumor necrosis factor receptor superfamily member 8	2	2,75
KEL	Kell blood group glycoprotein	1,93	2,48
EDA	Ectodysplasin-A, secreted form	2,7	2,42
ACE	Angiotensin-converting enzyme, soluble form	2,39	2,19
DRD2	D(2) dopamine receptor	2,49	1,97
CXCR3	C-X-C chemokine receptor type 3	4,19	1,66
MC2R	Adrenocorticotrophic hormone receptor	1,94	1,43

Table 6: antigen markers expressed on the surface of both breast tumor cells and T-cells

Antigen	Protein Name	Relative expression in T-Cell	Relative Expression in colon cancer cells
ABCA8	ATP-binding cassette sub-family A member 8	3,15	7,73
ABCC10	Multidrug resistance-associated protein 7	6,48	5,29
ABCC6	Multidrug resistance-associated protein 6	2,67	2,17
ACCN2	Acid-sensing ion channel 1	3,62	2,49
ADAM12	Disintegrin and metalloproteinase domain-containing protein 12	4,96	7,72
ADCYAP1R1	Pituitary adenylate cyclase-activating polypeptide type I receptor	2,17	2,88
ADRA1A	Alpha-1A adrenergic receptor	3,31	4,85
ADRA1B	Alpha-1B adrenergic receptor	1,49	1,6
ADRA1D	Alpha-1D adrenergic receptor	2,39	3,38
ADRA2A	Alpha-2A adrenergic receptor	2,64	1,79
ADRB3	Beta-3 adrenergic receptor	2,36	2,16
AGER	Advanced glycosylation end product-specific receptor	2,85	2,38
AGTR2	Type-2 angiotensin II receptor	3,08	3,7
ALK	ALK tyrosine kinase receptor	4,97	4,27
ANO3	Anoctamin-3	2,39	3,69
ANPEP	Aminopeptidase N	3,26	10,78
APLNR	Apelin receptor	2,47	2,06
AQP2	Aquaporin-2	2,12	1,43
ATP10A	Probable phospholipid-transporting ATPase VA	3,96	6,02
ATP2B2	Plasma membrane calcium-transporting ATPase 4	2,75	4,81
ATP2B3	Plasma membrane calcium-transporting ATPase 3	3,7	4,14
ATP4A	Potassium-transporting ATPase alpha chain 1	1,56	11,49
ATP4B	Potassium-transporting ATPase subunit beta	2,49	13,56
ATP6V0A2	V-type proton ATPase 116 kDa subunit a isoform 2	2,51	2,57
ATRN	Attractin	4,09	9,44
AVPR1A	Vasopressin V1a receptor	2,52	4,03
AVPR1B	Vasopressin V1b receptor	2,97	3,32
AVPR2	Vasopressin V2 receptor	2,68	2,93
BAI1	Brain-specific angiogenesis inhibitor 1	2,73	0,33
BAI2	Brain-specific angiogenesis inhibitor 2	2,34	4,14
BAI3	Brain-specific angiogenesis inhibitor 3	2,73	4,76

BDKRB1	B1 bradykinin receptor	2,07	3,28
BRS3	Bombesin receptor subtype-3	2,74	4,12
BTF3	Butyrophilin subfamily 3 member A2	11,29	13,02
C18orf1	Low-density lipoprotein receptor class A domain-containing protein 4	3,18	8,45
C3AR1	C3a anaphylatoxin chemotactic receptor	3,04	5,15
C6orf105	Androgen-dependent TFPI-regulating protein	2,34	3,84
CASR	Extracellular calcium-sensing receptor	2,52	5
CCBP2	Atypical chemokine receptor 2	1,72	3,29
CCKAR	Cholecystokinin receptor type A	2,46	3
CCKBR	Gastrin/cholecystokinin type B receptor	2,25	5,66
CCR2	C-C chemokine receptor type 2	5,94	3,56
CCR3	C-C chemokine receptor type 3	1,89	4,17
CCR6	C-C chemokine receptor-like 2	3,33	5,23
CCR8	C-C chemokine receptor type 8	2,28	3,93
CCR9	C-C chemokine receptor type 9	1,68	1,98
CD1A	T-cell surface glycoprotein CD1a	1,98	4,88
CD1B	T-cell surface glycoprotein CD1b	2,35	4,94
CD1D	Antigen-presenting glycoprotein CD1d	2,82	4,96
CD300C	CMRF35-like molecule 6	2,04	5,04
CD4	T-cell surface glycoprotein CD4	2,84	6,17
CD40LG	CD40 ligand, soluble form	2,1	3,49
CD5	T-cell surface glycoprotein CD5	3,14	1,01
CD63	CD63 antigen	8,6	13,18
CD84	SLAM family member 5	4,7	3,17
CDH15	Cadherin-15	2,07	3,55
CDH19	Protocadherin-16	2,82	8,4
CDH22	Cadherin-22	3	4,9
CDH8	Cadherin-8	3,63	5,87
CDON	Cell adhesion molecule-related/down-regulated by oncogenes	2,35	3,61
CHRNA4	Neuronal acetylcholine receptor subunit alpha-4	2,14	3,33
CHRNA5	Neuronal acetylcholine receptor subunit alpha-5	2,2	4,88
CHRNA6	Neuronal acetylcholine receptor subunit alpha-6	2,26	4,93
CHRNA3	Neuronal acetylcholine receptor subunit beta-3	1,85	3,91
CHRNE	Acetylcholine receptor subunit epsilon	2,56	2,83
CLDN3	Claudin-3	2,91	13,56
CLDN7	Claudin-7	1,89	12,87
CLDN8	Claudin-8	2,46	10,67
CLDN9	Claudin-9	1,74	1,69
CLEC4M	C-type lectin domain family 4 member M	2,7	3,32
CMKLR1	Chemokine-like receptor 1	2,62	5
CNNM2	Metal transporter CNNM2	2,47	5,32
CNR2	Cannabinoid receptor 2	2,38	3,66
CRHR1	Corticotropin-releasing factor receptor 1	2,15	10,71
CRHR2	Corticotropin-releasing factor receptor 2	2,32	6,44
CSF1	Processed macrophage colony-stimulating factor 1	5,63	7,61
CSF1R	Macrophage colony-stimulating factor 1 receptor	2,2	4,02
CSF3R	Granulocyte colony-stimulating factor receptor	1,85	2,8
CX3CL1	Processed fractalkine	2,35	9,31
CXCR5	C-X-C chemokine receptor type 5	2,07	6,06
DAGLA	Sn1-specific diacylglycerol lipase alpha	2,6	2,11

DRD1	D(1A) dopamine receptor	2,67	5,71
DRD3	D(3) dopamine receptor	2,72	4,99
DRD4	D(4) dopamine receptor	1,49	0,89
DRD5	D(1B) dopamine receptor	2,26	4,91
DSC2	Desmocollin-2	2,26	11,12
DSCAM	Down syndrome cell adhesion molecule	2,54	3,76
DSG1	Desmoglein-1	2,62	7,71
EMR2	EGF-like module-containing mucin-like hormone receptor-like 2	2,25	3,38
EPHA5	Ephrin type-A receptor 5	2,42	7,48
EPHA7	Ephrin type-A receptor 7	2,61	4,87
ERBB3	Receptor tyrosine-protein kinase erbB-3	2,39	12,76
F2RL2	Proteinase-activated receptor 3	3,2	5,16
FAM168B	Myelin-associated neurite-outgrowth inhibitor	8,34	11,16
FAP	Seprase	1,87	10,15
FAS	Tumor necrosis factor receptor superfamily member 6	5,68	7,24
FASLG	FasL intracellular domain	2,23	2,66
FCAR	Immunoglobulin alpha Fc receptor	2,8	3,85
FCER1A	High affinity immunoglobulin epsilon receptor subunit alpha	2,54	4,59
FCGR2A	Low affinity immunoglobulin gamma Fc region receptor II-a	2,77	8,81
FCGR2B	Low affinity immunoglobulin gamma Fc region receptor II-b	2,46	5,35
FGFR2	Fibroblast growth factor receptor 2	4,01	9,83
FGFR4	Fibroblast growth factor receptor 4	2,56	7,42
FLT3LG	Fms-related tyrosine kinase 3 ligand	7,86	4,37
FPR1	fMet-Leu-Phe receptor	3,38	5,92
FPR3	N-formyl peptide receptor 3	1,91	2,61
FSHR	Follicle-stimulating hormone receptor	1,89	3,78
FZD5	Frizzled-5	2,82	5,2
FZD5	Frizzled-5	1,81	5,2
FZD9	Frizzled-9	2,66	3,16
GABRA1	Gamma-aminobutyric acid receptor subunit alpha-1	2,2	6,26
GABRA5	Gamma-aminobutyric acid receptor subunit alpha-5	2,49	3,24
GABRA6	Gamma-aminobutyric acid receptor subunit alpha-6	2,54	2,98
GABRB1	Gamma-aminobutyric acid receptor subunit beta-1	1,89	2,37
GABRB2	Gamma-aminobutyric acid receptor subunit beta-2	2,26	3,89
GABRG3	Gamma-aminobutyric acid receptor subunit gamma-3	2,23	2,85
GABRP	Gamma-aminobutyric acid receptor subunit pi	2,93	12,34
GABRR1	Gamma-aminobutyric acid receptor subunit rho-1	2,35	3,47
GABRR2	Gamma-aminobutyric acid receptor subunit rho-2	4,16	5,43
GALR2	Galanin receptor type 2	1,85	0,46
GALR3	Galanin receptor type 3	0,68	0,48
GCGR	Glucagon receptor	1,38	3,4
GHRHR	Growth hormone-releasing hormone receptor	1,61	3,49
GJA5	Gap junction alpha-5 protein	1,72	2,05
GJA8	Gap junction alpha-8 protein	2,39	6,51
GJC1	Gap junction delta-3 protein	1,94	3,89
GLP1R	Glucagon-like peptide 1 receptor	5,72	3,41
GLRA1	Glycine receptor subunit alpha-1	2,15	3,87
GLRA3	Glycine receptor subunit alpha-3	3,19	3,1
GNRHR	Gonadotropin-releasing hormone receptor	2,72	4,1
GPMB	Transmembrane glycoprotein NMB	2,14	13,94
GPR1	G-protein coupled receptor 1	3,83	4,1

GPR135	Probable G-protein coupled receptor 135	4,15	1,91
GPR143	G-protein coupled receptor 143	1,93	3,65
GPR15	G-protein coupled receptor 15	1,81	4,41
GPR17	Uracil nucleotide/cysteinyl leukotriene receptor	1,93	1,74
GPR171	Probable G-protein coupled receptor 171	7,73	6,32
GPR18	N-arachidonyl glycine receptor	7,05	3,52
GPR182	G-protein coupled receptor 182	1,66	1,29
GPR19	Probable G-protein coupled receptor 19	1,89	5,26
GPR20	G-protein coupled receptor 20	2,02	2,53
GPR3	G-protein coupled receptor 3	3,01	5,36
GPR31	12-(S)-hydroxy-5,8,10,14-eicosatetraenoic acid receptor	1,63	1,64
GPR37L1	Prosaposin receptor GPR37L1	2,23	4
GPR39	G-protein coupled receptor 39	1,81	1,36
GPR44	Prostaglandin D2 receptor 2	2	2,32
GPR45	Probable G-protein coupled receptor 45	2,78	5,31
GPR6	G-protein coupled receptor 6	2,56	3,38
GPR65	Psychosine receptor	6,59	4,5
GPR68	Ovarian cancer G-protein coupled receptor 1	2,12	1,09
GPR98	G-protein coupled receptor 98	1,89	4,7
GRIA1	Glutamate receptor 1	4,17	4,77
GRIA3	Glutamate receptor 3	2,51	6,83
GRIK2	Glutamate receptor ionotropic, kainate 5	2,56	4,94
GRIK3	Glutamate receptor ionotropic, kainate 3	2,05	3,58
GRIN1	Glutamate receptor ionotropic, NMDA 1	4,52	1,49
GRIN2B	Glutamate receptor ionotropic, NMDA 2B	2,22	3,56
GRIN2C	Glutamate receptor ionotropic, NMDA 2C	2,56	3,37
GRM1	Metabotropic glutamate receptor 1	3,21	3,69
GRM2	Metabotropic glutamate receptor 2	2,04	0,44
GRM3	Metabotropic glutamate receptor 3	2,39	3,41
GRM4	Metabotropic glutamate receptor 4	5,2	3,78
GRM5	Metabotropic glutamate receptor 5	2,26	5,28
GRM7	Metabotropic glutamate receptor 7	2,86	3,07
GYPB	Glycophorin-B	2,43	4,02
HBP1	Glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1	7,32	9,27
HCRT2	Orexin receptor type 2	2,32	2,42
HTR1B	5-hydroxytryptamine receptor 1B	2,82	3,51
HTR1D	5-hydroxytryptamine receptor 1D	2,29	2,33
HTR1E	5-hydroxytryptamine receptor 1E	1,72	2,4
HTR2A	5-hydroxytryptamine receptor 2A	2,1	3,67
HTR2C	5-hydroxytryptamine receptor 2C	2,49	5,18
HTR4	5-hydroxytryptamine receptor 4	3,86	4,25
ICAM4	Intercellular adhesion molecule 4	2,51	2,16
ICOS	Inducible T-cell costimulator	3,91	3,86
IL6R	Interleukin-6 receptor subunit alpha	4,24	3,08
IL6R	Interleukin-6 receptor subunit alpha	2,64	3,08
IL6ST	Interleukin-6 receptor subunit beta	9,43	12,67
IL9R	Interleukin-9 receptor	2,71	2,86
ITGB3	Integrin beta-3	4,16	3,69
KCNA3	Potassium voltage-gated channel subfamily A member 3	2,09	4,9
KCND2	Potassium voltage-gated channel subfamily D member 2	2,67	4,25
KCNH1	Potassium voltage-gated channel subfamily H member 1	2,31	4,48

KCNJ4	Inward rectifier potassium channel 4	2,43	3,49
KCNMA1	Calcium-activated potassium channel subunit alpha-1	2,35	7,17
KCNS1	Potassium voltage-gated channel subfamily S member 1	5,66	6,49
KCNV2	Potassium voltage-gated channel subfamily V member 2	2,38	4,06
KIR2DL4	Killer cell immunoglobulin-like receptor 2DL4	1,68	3,31
KIR3DL1	Killer cell immunoglobulin-like receptor 3DL1	2,56	2,73
KIR3DL3	Killer cell immunoglobulin-like receptor 3DL3	1,7	3,06
KLRG1	Killer cell lectin-like receptor subfamily G member 1	8,3	5,76
LAMP1	Lysosome-associated membrane glycoprotein 1	10,9	13,6
LHCGR	Lutropin-choriogonadotropic hormone receptor	2,23	4,92
LNPEP	Leucyl-cystinyl aminopeptidase, pregnancy serum form	2,68	5,05
LPAR2	Lysophosphatidic acid receptor 2	5,5	4,23
LRIG2	Leucine-rich repeats and immunoglobulin-like domains protein 2	3,35	5,48
LRRTM2	Leucine-rich repeat transmembrane neuronal protein 2	2,42	4,24
LTB4R	Leukotriene B4 receptor 1	4,96	2,26
MAS1	Proto-oncogene Mas	1,91	3,11
MC1R	Melanocyte-stimulating hormone receptor	2,94	0,96
MC5R	Melanocortin receptor 5	2,28	1,63
MEP1B	Meprin A subunit beta	2,61	3,87
MFSD5	Molybdate-anion transporter	1,98	4,72
MOG	Myelin-oligodendrocyte glycoprotein	3,08	4,74
MTNR1B	Melatonin receptor type 1B	1,61	1,67
MUC1	Mucin-1 subunit beta	2,73	13,68
MUSK	Muscle, skeletal receptor tyrosine-protein kinase	2,39	4,75
NCAM2	Neural cell adhesion molecule 2	2,12	4,49
NCR2	Natural cytotoxicity triggering receptor 2	4,79	7,09
NCR3	Natural cytotoxicity triggering receptor 3	4,55	2,74
NIPA2	Magnesium transporter NIPA2	6,77	3,9
NLGN1	Neuroligin-1	2,62	7,71
NLGN4Y	Neuroligin-4, Y-linked	2,52	5,26
NMBR	Neuromedin-B receptor	1,68	2,47
NPHS1	Nephrin	2,74	4,33
NPY2R	Neuropeptide Y receptor type 2	2,68	4,43
NPY5R	Neuropeptide Y receptor type 5	2,38	5,05
NTSR2	Neurotensin receptor type 2	1,72	3
OPRD1	Delta-type opioid receptor	2,26	2,14
OPRL1	Nociceptin receptor	2,31	1,51
OPRM1	Mu-type opioid receptor	3,18	4,01
OR10H3	Olfactory receptor 10H3	1,63	4,02
OR1E1	Olfactory receptor 1E1	3,04	4,77
OR2F1	Olfactory receptor 2F1	2,64	5,73
OR2F2	Olfactory receptor 2F2	2,19	2,3
OR2H1	Olfactory receptor 2H1	3,39	3,82
OR2H2	Olfactory receptor 2H2	3,79	6,37
OR2J2	Olfactory receptor 2J2	2,41	2,16
OR2J2	Olfactory receptor 2J2	1,93	2,16
OR5I1	Olfactory receptor 5I1	1,85	2,8
OR7E24	Olfactory receptor 7E24	2,5	3,47
P2RX7	P2X purinoceptor 7	2,36	2,15
PANX1	Pannexin-1	2,14	4,38
PCDHA9	Protocadherin alpha-9	2,82	3,56

PCDHB11	Protocadherin beta-11	1,91	5,23
PCDHGA8	Protocadherin gamma-A8	3,13	4,48
PLA2R1	Soluble secretory phospholipase A2 receptor	2,91	5,16
PLXNA3	Plexin-A3	2,42	3,25
POP1	Blood vessel epicardial substance	1,74	2,59
PPYR1	Neuropeptide Y receptor type 4	2,2	2,75
PTGER1	Prostaglandin E2 receptor EP1 subtype	1,96	0,94
PTGFR	Prostaglandin F2-alpha receptor	2,75	4,89
PTGIR	Prostacyclin receptor	2,78	2,12
PTPRJ	Receptor-type tyrosine-protein phosphatase eta	2,63	4,6
PTPRR	Receptor-type tyrosine-protein phosphatase R	2,47	9,99
PVRL1	Poliovirus receptor-related protein 1	2,52	4,51
PVRL2	Poliovirus receptor-related protein 2	3,84	10,05
ROS1	Proto-oncogene tyrosine-protein kinase ROS	2,93	3,38
S1PR2	Sphingosine 1-phosphate receptor 2	1,74	1,17
S1PR4	Sphingosine 1-phosphate receptor 4	4	0,21
SCNN1B	Amiloride-sensitive sodium channel subunit beta	1,89	3,16
SCNN1G	Amiloride-sensitive sodium channel subunit gamma	2,23	2,61
SEMA4D	Semaphorin-4D	10,66	1,56
SEMA6A	Semaphorin-6A	4,55	7,81
SEMA6C	Semaphorin-6C	5,02	3,73
SGCB	Beta-sarcoglycan	2,69	3,45
SGCB	Beta-sarcoglycan	2,04	3,45
SLC12A3	Solute carrier family 12 member 3	2,26	3,36
SLC14A1	Urea transporter 1	2,97	6,21
SLC14A2	Urea transporter 2	2,85	4,4
SLC16A1	Monocarboxylate transporter 1	3,46	8,84
SLC16A2	Monocarboxylate transporter 8	1,77	5,17
SLC16A6	Monocarboxylate transporter 7	2,41	11,66
SLC22A1	Solute carrier family 22 member 1	2,95	11,61
SLC22A6	Solute carrier family 22 member 6	2,26	2,53
SLC5A12	Sodium-coupled monocarboxylate transporter 2	2,98	4,45
SLC6A1	Sodium- and chloride-dependent GABA transporter 1	2,45	4,3
SLC6A4	Sodium-dependent serotonin transporter	2,17	2,66
SLC6A6	Sodium- and chloride-dependent taurine transporter	2,54	4,13
SLC7A7	Y+L amino acid transporter 1	2,22	9,78
SLC8A1	Sodium/calcium exchanger 1	2,07	2,36
SLC9A1	Sodium/hydrogen exchanger 1	3,15	5,54
SLC9A3	Sodium/hydrogen exchanger 3	2,12	3,15
SLCO1A2	Solute carrier organic anion transporter family member 1A2	3,87	4,98
SLCO2B1	Solute carrier organic anion transporter family member 2B1	4,43	8,92
SORT1	Sortilin	2,93	4,6
SSTR2	Somatostatin receptor type 2	3,08	4,47
SSTR3	Somatostatin receptor type 3	2,23	1,5
SSTR4	Somatostatin receptor type 4	1,83	1,53
SSTR5	Somatostatin receptor type 5	2,57	1,47
TACR1	Substance-P receptor	2,66	3,2
TACR3	Neuromedin-K receptor	2,32	5,7
TLR6	Toll-like receptor 6	2,2	4,58
TMPRSS6	Transmembrane protease serine 6	4,02	3,69
TNFSF11	Tumor necrosis factor ligand superfamily member 11,	2,57	5,18
TNFSF14	Tumor necrosis factor ligand superfamily member 14,	3,34	2,83

	soluble form		
TPO	Thyroid peroxidase	1,96	1,89
TRAT1	T-cell receptor-associated transmembrane adapter 1	7,51	5,29
TRHR	Thyrotropin-releasing hormone receptor	2	4,18
TRPM1	Transient receptor potential cation channel subfamily M member 1	2,43	5,22
TSHR	Thyrotropin receptor	2,9	4,87
TSHR	Thyrotropin receptor	2,12	4,87
UNC93A	Protein unc-93 homolog A	2,64	4,94
VIPR2	Vasoactive intestinal polypeptide receptor 2	2,58	3,37
ZP2	Processed zona pellucida sperm-binding protein 2	1,94	3,55

Table 7: antigen markers expressed on the surface of both digestive tumor cells and T-cells

Antigen	Protein Name	Relative expression in T-Cell	Relative Expression in colon cancer cells
ACVR1B	Activin receptor type-1B	5,16	10,48
AMIGO2	Amphoterin-induced protein 2	6,73	8,2
ATP1B1	Sodium/potassium-transporting ATPase subunit beta-1	2,64	12,31
ATP8B1	Probable phospholipid-transporting ATPase IC	8,22	2,17
CCR7	C-C chemokine receptor type 7	10,25	11,52
CD164	Sialomucin core protein 24	10,27	12,12
CD180	CD180 antigen	2,5	6,47
CD40	Tumor necrosis factor receptor superfamily member 5	5,02	6
CD53	Leukocyte surface antigen CD53	10,79	11,3
CD79A	B-cell antigen receptor complex-associated protein alpha chain	3,74	9,17
CD79B	B-cell antigen receptor complex-associated protein beta chain	3,6	6,66
CD8B	T-cell surface glycoprotein CD8 beta chain	8,43	2,62
CELSR1	Cadherin EGF LAG seven-pass G-type receptor 1	2,72	8,68
CLCN5	H(+)/Cl(-) exchange transporter 5	2,71	4,97
CLDN18	Claudin-18	3,05	14,51
CLIC1	Chloride intracellular channel protein 1	9,94	13,83
COL13A1	Collagen alpha-1(XIII) chain	2,96	6,24
DIO3	Type III iodothyronine deiodinase	2,04	2,9
EDNRA	Endothelin-1 receptor	2,9	8,96
EMR1	EGF-like module-containing mucin-like hormone receptor-like 1	1,83	7,29
ENPP1	Nucleotide pyrophosphatase	2,57	9,66
EPHB1	Ephrin type-B receptor 1	2,02	6,33
EPHB1	Ephrin type-B receptor 1	1,81	6,33
F2R	Proteinase-activated receptor 1	3,04	9,78
F2RL1	Proteinase-activated receptor 2, alternate cleaved 2	3,31	9,47
FCER2	Low affinity immunoglobulin epsilon Fc receptor soluble form	2,49	8,77

GABBR1	Gamma-aminobutyric acid type B receptor subunit 1	5,1	8,52
GABRA3	Gamma-aminobutyric acid receptor subunit alpha-3	2,12	3,84
GPR183	G-protein coupled receptor 183	4,79	10,22
GPR37	Prosaposin receptor GPR37	3,1	8,23
GPRC5A	Retinoic acid-induced protein 3	1,87	13,69
GRPR	Gastrin-releasing peptide receptor	2,04	3,35
GYPC	Glycophorin-C	9,22	7,58
IL1R2	Interleukin-1 receptor type 2, soluble form	2,82	12,83
KIAA0319	Dyslexia-associated protein KIAA0319	2,43	5,61
LAMP2	Lysosome-associated membrane glycoprotein 2	4,05	11,29
LRP8	Low-density lipoprotein receptor-related protein 8	4,24	8,84
LSR	Lipolysis-stimulated lipoprotein receptor	4,99	11,48
MICB	MHC class I polypeptide-related sequence B	5,27	9,89
MMP16	Matrix metalloproteinase-16	3,19	6,18
MS4A1	B-lymphocyte antigen CD20	2,15	8,02
MYOF	Myoferlin	2,41	11,56
NAT1	Sodium-coupled neutral amino acid transporter 3	3,49	12,09
NFASC	Neurofascin	3,78	8,28
NPY1R	Neuropeptide Y receptor type 1	2,32	6,93
OR2B6	Olfactory receptor 2B6	2,78	4,24
P2RY10	Putative P2Y purinoceptor 10	3,39	6,62
PCDH1	Protocadherin-1	4,45	10,07
PROM1	Prominin-1	2,52	11,77
PSEN1	Presenilin-1 CTF12	2,94	8,83
PTGER2	Prostaglandin E2 receptor EP2 subtype	6,33	6,74
PTGER4	Prostaglandin E2 receptor EP4 subtype	8,62	5,12
PTPRK	Receptor-type tyrosine-protein phosphatase kappa	2,14	10,9
RET	Extracellular cell-membrane anchored RET cadherin 120 kDa fragment	2,38	12,3
SERINC3	Serine incorporator 3	7,93	12,01
SIT1	Sodium- and chloride-dependent transporter XTRP3	5,92	4,82
SLAMF1	Signaling lymphocytic activation molecule	4,4	9,03
SLC29A1	Equilibrative nucleoside transporter 1	2,07	6,12
SLC39A6	Zinc transporter ZIP6	6,69	15,23
SLC7A5	Large neutral amino acids transporter small subunit 1	3,79	10,98
STX4	Syntaxin-4	5,68	7,67
TGFBR3	Transforming growth factor beta receptor type 3	7,55	7,29
TGOLN2	Trans-Golgi network integral membrane protein 2	9,59	11,3
TLR1	Toll-like receptor 1	2,34	4,57
TMED10	Transmembrane emp24 domain-containing protein 10	9,34	12,24
TMEM97	Transmembrane protein 97	2,75	9,02
TNF	Tumor necrosis factor, soluble form	1,63	3,18
TNFRSF17	Tumor necrosis factor receptor superfamily member 17	1,89	10,47
TNFRSF1B	Tumor necrosis factor-binding protein 2	5,51	9,4
VDAC1	Voltage-dependent anion-selective channel protein 1	6,52	11,5

Table 8: antigen markers expressed on the surface of both kidney tumor cells and T-cells

Antigen	Protein Name	Relative expression in T-Cell	Relative Expression in colon cancer cells
ADORA3	Adenosine receptor A3	1,89	4,56
ATP11A	Probable phospholipid-transporting ATPase 1H	3,62	8,8
BSG	Basigin	4,77	11,34
BTN3A2	Butyrophilin subfamily 3 member A2	10,86	8,19
C10orf72	V-set and transmembrane domain-containing protein 4	2,04	6,85
CADM3	Cell adhesion molecule 3	3,57	6,39
CD8A	T-cell surface glycoprotein CD8 alpha chain	10,35	6,6
CDH16	Cadherin-16	2,17	7,09
CDH4	Cadherin-4	2,15	3,6
CDH5	Cadherin-5	2,5	9,55
CHL1	Processed neural cell adhesion molecule L1-like protein	2,69	10,43
CHRNA1	Acetylcholine receptor subunit beta	2,12	3,6
CLIC4	Chloride intracellular channel protein 4	3,34	13,12
CNR1	Cannabinoid receptor 1	2,26	5,64
CRIM1	Processed cysteine-rich motor neuron 1 protein	3,57	12,39
CSPG4	Chondroitin sulfate proteoglycan 4	3,33	6,59
CYBB	Cytochrome b-245 heavy chain	2,86	8,07
EDNRB	Endothelin B receptor	3,04	8,97
FLT1	Vascular endothelial growth factor receptor 1	2,75	8,5
FZD1	Frizzled-1	2,72	7,59
GJC2	Gap junction gamma-2 protein	2,09	2,94
GLRB	Glycine receptor subunit beta	2,51	7,15
GPER	G-protein coupled estrogen receptor 1	2,34	8,64
GPM6A	Neuronal membrane glycoprotein M6-a	2,95	6,88
GPR162	Probable G-protein coupled receptor 162	2,75	2,81
GPR4	G-protein coupled receptor 4	2,93	8,09
GRM8	Metabotropic glutamate receptor 8	3,43	8,25
HLA-DPB1	HLA class II histocompatibility antigen, DP beta 1 chain	9,93	13,99
HTR6	5-hydroxytryptamine receptor 6	4,83	10,07
INSR	Insulin receptor subunit beta	3,44	8,95
ITM2B	Bri23 peptide	11,16	12,19
KCNJ1	ATP-sensitive inward rectifier potassium channel 1	2,5	4,17
KDR	Vascular endothelial growth factor receptor 2	2,99	9,95
KL	Klotho peptide	2,83	7,59
LAIR1	Leukocyte-associated immunoglobulin-like receptor 1	5,64	4,25
MFAP3	Microfibril-associated glycoprotein 3	3,7	7,3
MFAP3L	Microfibrillar-associated protein 3-like	3,44	8,7
MICA	MHC class I polypeptide-related sequence A	4,07	2,01
NCAM1	Neural cell adhesion molecule 1	2,45	7,31
NOTCH3	Notch 3 intracellular domain	3,21	12,41
NOTCH4	Notch 4 intracellular domain	5,89	8,84
OLR1	Oxidized low-density lipoprotein receptor 1, soluble form	2,84	8,41
P2RY14	P2Y purinoceptor 14	2,63	4,63
PCDH17	Protocadherin-17	1,7	7,36
PDGFRB	Platelet-derived growth factor receptor beta	2,68	10,48
PECAM1	Platelet endothelial cell adhesion molecule	7,7	10,85

PLXND1	Plexin-D1	5,02	11,68
PPAP2B	Lipid phosphate phosphohydrolase 3	4,17	12,46
PTAFR	Platelet-activating factor receptor	3,01	4,81
PTGER3	Prostaglandin E2 receptor EP3 subtype	4,76	10,26
PTH1R	Parathyroid hormone/parathyroid hormone-related peptide receptor	2,35	7,31
RAMP3	Receptor activity-modifying protein 3	1,79	8,84
ROR2	Tyrosine-protein kinase transmembrane receptor ROR2	3,2	5,98
S1PR1	Sphingosine 1-phosphate receptor 1	5,17	6,51
SCARB1	Scavenger receptor class B member 1	3,01	10,4
SLC13A3	Solute carrier family 13 member 3	3,32	7,89
SLC16A4	Monocarboxylate transporter 5	2,88	12,54
SLC17A3	Sodium-dependent phosphate transport protein 4	1,58	11,55
SLC28A1	Sodium/nucleoside cotransporter 1	4,76	6,3
SLC2A5	Solute carrier family 2, facilitated glucose transporter member 5	2,74	8,5
SLC39A14	Zinc transporter ZIP14	2,66	11,63
SLC6A13	Sodium- and chloride-dependent GABA transporter 2	2,75	7,44
SLC7A8	Large neutral amino acids transporter small subunit 2	5,03	10,46
SLCO2A1	Solute carrier organic anion transporter family member 2A1	3,46	8,06
TBXA2R	Thromboxane A2 receptor	4,01	3,64
TGFBR2	TGF-beta receptor type-2	10,41	10,94
THSD7A	Thrombospondin type-1 domain-containing protein 7A	3,05	8
TIE1	Tyrosine-protein kinase receptor Tie-1	2,04	4,41
TNFRSF1A	Tumor necrosis factor-binding protein 1	6,84	10,52
TNFSF12	Tumor necrosis factor ligand superfamily member 12, secreted form	4,35	4,1
VAMP5	Vesicle-associated membrane protein 5	3,49	6,18

Table 9: antigen markers expressed on the surface of both liver tumor cells and T-cells

Antigen	Protein Name	Relative expression in T-Cell	Relative Expression in colon cancer cells
ABCB4	Multidrug resistance protein 3	2,02	3,7
ADAM10	Disintegrin and metalloproteinase domain-containing protein 10	9,42	9,41
ATR	Anthrax toxin receptor 1	6,98	9,9
BST2	Bone marrow stromal antigen 2	7,38	12,45
BTN3A3	Butyrophilin subfamily 3 member A3	9,72	7,48
C9	Complement component C9b	2,41	10,52
CHRND	Acetylcholine receptor subunit delta	2,43	4,05
CLDN14	Claudin-14	2,79	2,4
EPOR	Erythropoietin receptor	4,67	10,55
ERBB2	Receptor tyrosine-protein kinase erbB-2	2,36	14,12
F2RL3	Proteinase-activated receptor 4	2,17	2,61
GJB1	Gap junction beta-1 protein	2,96	9,4
GPR126	G-protein coupled receptor 126	2,23	11,32
IL1R1	Interleukin-1 receptor type 1, soluble form	2,88	12,57
ITGB1	Integrin beta-1	8,76	13,48
NAALADL1	N-acetylated-alpha-linked acidic dipeptidase-like protein	3,03	1,46
OR7A5	Olfactory receptor 7A5	1,51	3,83
SGCD	Delta-sarcoglycan	3,99	7,21
SIGLEC6	Sialic acid-binding Ig-like lectin 6	3,57	3,49
SLC38A3	Sodium-coupled neutral amino acid transporter 3	1,89	8,91
TFR2	Transferrin receptor protein 2	2,74	10,47

Table 10: antigen markers expressed on the surface of both lung tumor cells and T-cells

Antigen	Protein Name	Relative expression in T-Cell	Relative Expression in colon cancer cells
ABCB6	ATP-binding cassette sub-family B member 6, mitochondrial	2,88	9,82
ABCC1	Multidrug resistance-associated protein 1	7,05	8,16
ACCN1	Acid-sensing ion channel 2	2,25	0,8
ADAM23	Disintegrin and metalloproteinase domain-containing protein 23	2,51	4,73
ADORA1	Adenosine receptor A1	4,49	8,22
ADORA2B	Adenosine receptor A2b	1,66	7,5
AJAP1	Adherens junction-associated protein 1	1,85	6,24
APLP1	C30	2,22	6,02
AQP3	Aquaporin-3	8,38	13,88
ATP10D	Probable phospholipid-transporting ATPase VD	2,43	7,4
ATP1A3	Sodium/potassium-transporting ATPase subunit alpha-3	3,01	3,13
ATP1B2	Sodium/potassium-transporting ATPase subunit beta-2	3,21	3,8
ATP1B3	Sodium/potassium-transporting ATPase subunit beta-3	8,6	14,26
AXL	Tyrosine-protein kinase receptor UFO	2,51	9,58
BEST1	Bestrophin-1	2,49	4,44
BTC	Betacellulin	2,86	4,59
BTN3A1	Butyrophilin subfamily 3 member A1	10,66	11,63
CALCR	Calcitonin receptor	2,95	8,62
CALCRL	Calcitonin gene-related peptide type 1 receptor	2,12	7,67
CCR1	C-C chemokine receptor type 1	2,63	9,77
CD163	Soluble CD163	2,66	8,76
CD300A	CMRF35-like molecule 8	7,96	4,23
CD300A	CMRF35-like molecule 8	2,29	4,23
CD68	Macrosialin	4,02	8,92
CD74	HLA class II histocompatibility antigen gamma chain	9,1	13,44
CD86	T-lymphocyte activation antigen CD86	2,93	5,04
CHRNA3	Neuronal acetylcholine receptor subunit alpha-3	2,54	4,62
CHRNA3	Neuronal acetylcholine receptor subunit alpha-3	2	4,62
CKAP4	Cytoskeleton-associated protein 4	6,15	11,94
CLCA2	Calcium-activated chloride channel regulator 2, 35 kDa form	2,99	9,81
CLDN5	Claudin-5	3,66	7,73
CLSTN1	CTF1-alpha	8,26	12,51
CNIH3	Protein cornichon homolog 3	2,7	6,09
COMT	Catechol O-methyltransferase	7,78	12,13
CSPG5	Chondroitin sulfate proteoglycan 5	2,84	5,69
CXCR6	C-X-C chemokine receptor type 6	3,16	3,91
CXCR7	Atypical chemokine receptor 3	2,5	8,95
DCHS1	Protocadherin-16	4,29	2,28
DSC3	Desmocollin-2	2,82	8,95
DSG3	Desmoglein-3	2,23	10,73
EGFR	Epidermal growth factor receptor	3,8	10,92

FAT2	Protocadherin Fat 2	2,25	9,29
FCER1G	High affinity immunoglobulin epsilon receptor subunit gamma	3,13	8,96
FCGR1A	High affinity immunoglobulin gamma Fc receptor I	2,09	9,65
FLT4	Vascular endothelial growth factor receptor 3	3,19	3,36
FPR2	N-formyl peptide receptor 2	2,9	7,14
FURIN	Furin	6,42	7,5
FZD6	Frizzled-6	2,64	10,45
GABBR2	Gamma-aminobutyric acid type B receptor subunit 2	3,79	9,19
GABRB3	Gamma-aminobutyric acid receptor subunit beta-3	2,46	8,83
GABRD	Gamma-aminobutyric acid receptor subunit delta	1,72	1,67
GABRE	Gamma-aminobutyric acid receptor subunit epsilon	1,85	9,18
GIPR	Gastric inhibitory polypeptide receptor	3,43	5,37
GJA1	Gap junction alpha-1 protein	2,84	12,65
GJB3	Gap junction beta-3 protein	3,72	3,79
GJB5	Gap junction beta-5 protein	1,77	6,69
GLRA2	Glycine receptor subunit alpha-2	2,26	6,15
GPR109B	Hydroxycarboxylic acid receptor 3	1,77	2,91
GPR12	G-protein coupled receptor 12	2	1,76
GPR176	Probable G-protein coupled receptor 176	2,05	3,86
GPR50	Melatonin-related receptor	2,26	3,16
GRIK1	Glutamate receptor ionotropic, kainate 1	4,66	5,65
GRIN2D	Glutamate receptor ionotropic, NMDA 2D	2,17	2,32
HCRTR1	Orexin receptor type 1	2,34	3,56
HLA-DPA1	HLA class II histocompatibility antigen, DP alpha 1 chain	8,31	12,86
HLA-DQA1	HLA class II histocompatibility antigen, DQ alpha 1 chain	2,35	11,44
HLA-DQB1	HLA class II histocompatibility antigen, DQ beta 1 chain	7,4	12,71
HLA-DRA	HLA class II histocompatibility antigen, DR alpha chain	6,42	14,18
HLA-DRB4	HLA class II histocompatibility antigen, DR beta 4 chain	2,72	11,24
IGSF9B	Protein turtle homolog B	3,92	2,81
IL1RAP	Interleukin-1 receptor accessory protein	3,99	11,4
IL1RL1	Interleukin-1 receptor-like 1	2,55	5,15
IL4R	Soluble interleukin-4 receptor subunit alpha	4,15	9,56
IL7R	Interleukin-7 receptor subunit alpha	11,62	11,26
ITGA6	Integrin alpha-6 light chain	7,99	12,76
JPH3	Junctophilin-3	2,34	2,5
KCNS3	Potassium voltage-gated channel subfamily S member 3	2,45	8,91
KIT	Mast/stem cell growth factor receptor Kit	2,85	8,67
KITLG	Soluble KIT ligand	2,58	7,27
LILRB3	Leukocyte immunoglobulin-like receptor subfamily B member 3	5,65	8,03
LILRB4	Leukocyte immunoglobulin-like receptor subfamily B member 4	3,12	10,44
LPAR1	Lysophosphatidic acid receptor 1	4,12	5,47
LPHN3	Latrophilin-3	2,85	6,43
MMP24	Processed matrix metalloproteinase-24	5,19	5,73
MPZ	Myelin protein P0	2,56	3,63
MUC4	Mucin-4 beta chain	3,04	10,34
NCKAP1L	Nck-associated protein 1-like	6,69	7,51
NKG7	Protein NKG7	10,92	3,66
NOTCH2	Notch 2 intracellular domain	6,62	6,22
NRCAM	Neuronal cell adhesion molecule	2,78	8,16

NRG2	Neuregulin-2	3,55	9,22
NRXN1	Neurexin-1	2,56	5,33
NTRK2	BDNF/NT-3 growth factors receptor	2,56	10,7
NTSR1	Neurotensin receptor type 1	1,74	9,74
P2RY1	P2Y purinoceptor 1	2,34	7,62
P2RY6	P2Y purinoceptor 6	4,27	5,79
PCDH8	Protocadherin-8	2,67	9,29
PCDHA3	Protocadherin alpha-3	2,14	3,54
PIK3IP1	Phosphoinositide-3-kinase-interacting protein 1	8,68	3,47
PLXNA2	Plexin-A2	2,88	7,3
PRR4	Processed poliovirus receptor-related protein 4	3,24	8,02
PTPRE	Receptor-type tyrosine-protein phosphatase epsilon	6,03	7,92
PTPRO	Receptor-type tyrosine-protein phosphatase U	10,46	9,01
PTPRU	Receptor-type tyrosine-protein phosphatase U	3,72	6,18
RABAC1	Prenylated Rab acceptor protein 1	7,54	8,82
SCTR	Secretin receptor	2,2	2,48
SECTM1	Secreted and transmembrane protein 1	2,42	6,9
SGCE	Epsilon-sarcoglycan	2,15	9,65
SGCG	Gamma-sarcoglycan	2,56	5,74
SLC16A3	Monocarboxylate transporter 4	5,89	12,72
SLC16A7	Monocarboxylate transporter 2	5,39	6,97
SLC20A2	Sodium-dependent phosphate transporter 2	2,51	12,69
SLC26A4	Pendrin	3,57	9,39
SLC2A1	Solute carrier family 2, facilitated glucose transporter member 1	5,1	5,83
SLC4A7	Sodium bicarbonate cotransporter 3	4,89	8,7
SLCO3A1	Solute carrier organic anion transporter family member 3A1	4,87	7,91
SYNE2	Nesprin-2	9,43	10,43
TACR2	Substance-K receptor	2,23	6,68
TFRC	Transferrin receptor protein 1, serum form	7,32	14,31
TMEFF1	Tomoregulin-1	3,22	5,05
TMPRSS11D	Transmembrane protease serine 11D catalytic chain	2,35	8,32

Table 11: antigen markers expressed on the surface of both ovary tumor cells and T-cells;

Antigen	Protein Name	Relative expression in T-Cell	Relative Expression in colon cancer cells
ACVR2B	Activin receptor type-2B	2,1	4,26
ADAM28	Disintegrin and metalloproteinase domain-containing protein 28	2,83	9,22
ADRA2C	Alpha-2C adrenergic receptor	4,6	5,13
ATP2B1	Plasma membrane calcium-transporting ATPase 1	5,3	11,49
ATP2B4	Plasma membrane calcium-transporting ATPase 4	8,21	10,1
ATP7A	Copper-transporting ATPase 1	3,91	7,31
CD200	OX-2 membrane glycoprotein	2,83	10,51
CD47	Leukocyte surface antigen CD47	9,88	10,42
CDH12	Cadherin-12	2,31	5,91
CDH18	Cadherin-18	2,28	4,79
CDH2	Cadherin-2	3,72	11,97
CDH6	Cadherin-6	2,77	8,68
CDIPT	CDP-diacylglycerol--inositol 3-phosphatidyltransferase	8,88	10,73
CELSR2	Cadherin EGF LAG seven-pass G-type receptor 2	2,66	8,38
CHRNA1	Acetylcholine receptor subunit alpha	2,42	5,71
CLSTN3	Calsyntenin-3	3,87	4,54
CX3CR1	CX3C chemokine receptor 1	9	11,42
DDR1	Epithelial discoidin domain-containing receptor 1	3,83	12,36
EPHA1	Ephrin type-A receptor 1	2,02	5,96
EPHA4	Ephrin type-A receptor 4	2,39	8,56
ERBB4	ERBB4 intracellular domain	2,29	9,76
FGFR1	Fibroblast growth factor receptor 1	5,42	11,4
FGFR3	Fibroblast growth factor receptor 3	2,95	11,35
FZD2	Frizzled-2	1,91	8,06
FZD7	Frizzled-7	2,55	10,24
GJA4	Gap junction alpha-4 protein	2,04	6,7
GPR125	Probable G-protein coupled receptor 125	2,35	7,88
GPR56	GPR56 C-terminal fragment	8,6	11,27
GPR64	G-protein coupled receptor 64	2,04	8,57
GPRC5B	G-protein coupled receptor family C group 5 member B	1,96	10,29
GRIA2	Glutamate receptor 2	1,96	11,78
GRIK5	Glutamate receptor ionotropic, kainate 5	5,79	3,36
GRIN2A	Glutamate receptor ionotropic, NMDA 2A	1,68	2,96
HEG1	Protein HEG homolog 1	4,8	10,1
HRH1	Histamine H1 receptor	2,31	6,26
HTR3A	5-hydroxytryptamine receptor 3A	2,1	9,35
IFITM2	Interferon-induced transmembrane protein 2	10,27	11,36
IFITM3	Interferon-induced transmembrane protein 3	8,55	13,48
KCNH2	Potassium voltage-gated channel subfamily H member 2	2,09	5,36
KCNJ12	ATP-sensitive inward rectifier potassium channel 12	2,29	2,21
L1CAM	Neural cell adhesion molecule L1	2,61	8,73
LGR5	Leucine-rich repeat-containing G-protein coupled receptor 5	2,45	12,12
LPHN1	Latrophilin-1	4,5	5,56

LPHN1	Latrophilin-1	1,63	5,56
LPHN2	Latrophilin-2	1,93	7,14
MGA	Glucoamylase	5,15	5,65
NEO1	Neogenin	1,85	10,31
NPTN	Neuroplastin	8,46	13,14
NRG1	Neuregulin-1	2,61	6,53
NTRK1	High affinity nerve growth factor receptor	2,09	2,49
PCDH7	Protocadherin-7	2,89	8,52
PCDH9	Protocadherin-9	2,99	6,15
PDGFRA	Platelet-derived growth factor receptor alpha	3,69	8,44
PDGFRA	Platelet-derived growth factor receptor alpha	2,26	8,44
PLXNB1	Plexin-B1	2,26	6,71
PLXNB2	Plexin-B2	3,1	10,68
PODXL	Podocalyxin	2,73	11,41
PRSS8	Prostasin heavy chain	2,07	10,77
PTH2R	Parathyroid hormone 2 receptor	1,85	8,67
PVRL3	Poliovirus receptor-related protein 3	2,56	10,15
SCNN1A	Amiloride-sensitive sodium channel subunit alpha	5,97	10,63
SLC29A2	Equilibrative nucleoside transporter 2	2,93	1,89
SSPN	Sarcospan	3,49	9,16
STAR	Heat-stable enterotoxin receptor	2,36	7,13
TGFA	Transforming growth factor alpha	2,64	1,71
TMED1	Transmembrane emp24 domain-containing protein 1	4,79	9,3
TMEM59	Transmembrane protein 59	8,83	12,74
TNFRSF25	Tumor necrosis factor receptor superfamily member 25	7,53	4,27
TYRO3	Tyrosine-protein kinase receptor TYRO3	4,11	10,27
UPK2	Uroplakin-2	2,29	7,49

Table 12: antigen markers expressed on the surface of both pancreas tumor cells and T-cells

Antigen	Protein Name	Relative expression in T-Cell	Relative Expression in colon cancer cells
ADAM9	Disintegrin and metalloproteinase domain-containing protein 9	3,49	10,99
B4GALT1	Processed beta-1,4-galactosyltransferase 1	7,44	8,99
BDKRB2	B2 bradykinin receptor	2,52	4,44
CA9	Carbonic anhydrase 9	3,34	11,9
CACNA1C	Voltage-dependent L-type calcium channel subunit alpha-1C	2,36	4,54
CD58	Lymphocyte function-associated antigen 3	6,51	8,16
CDH11	Cadherin-11	2,85	10,38
CDH3	Cadherin-3	1,96	10,91
CFTR	Cystic fibrosis transmembrane conductance regulator	3,12	11,45
CHRNA4	Neuronal acetylcholine receptor subunit beta-4	2,38	0,66
CLDN10	Claudin-10	2,36	11,5
CXCR4	C-X-C chemokine receptor type 4	11,74	10,98
DAG1	Beta-dystroglycan	5,65	10,98
DDR2	Discoidin domain-containing receptor 2	2,34	8
DMPK	Myotonic-protein kinase	3,7	4,21
FAT1	Protocadherin Fat 1, nuclear form	3,3	12,45
HTR2B	5-hydroxytryptamine receptor 2B	2,22	7,73
LDLR	Low-density lipoprotein receptor	2,93	12,14
NCKAP1	Nck-associated protein 1	3,34	11,99
PMP22	Peripheral myelin protein 22	2,09	10,66
PNPLA2	Patatin-like phospholipase domain-containing protein 2	5,46	3,45
PNPLA2	Patatin-like phospholipase domain-containing protein 2	2,35	3,45
TEK	Angiopoietin-1 receptor	3,87	8,52
TGFBR1	TGF-beta receptor type-1	2,17	4,3

Table 13: antigen markers expressed on the surface of both prostate tumor cells and T-cells

Antigen	Protein Name	Relative expression in T-Cell	Relative Expression in colon cancer cells
ACCN3	Acid-sensing ion channel 3	2,47	2,03
ADRB1	Beta-1 adrenergic receptor	2,85	5,09
ADRB2	Beta-2 adrenergic receptor	5,74	9,43
AGTR1	Type-1 angiotensin II receptor	2,81	11,62
APLP2	Amyloid-like protein 2	7,06	13,06
ATP1A2	Sodium/potassium-transporting ATPase subunit alpha-2	3,07	7,55
ATP8A1	Probable phospholipid-transporting ATPase IA	7,23	9,16
CADM1	Cell adhesion molecule 1	4,42	12,28
CHRM3	Muscarinic acetylcholine receptor M3	1,85	9,23
CHRNA2	Neuronal acetylcholine receptor subunit alpha-2	2,83	5,34
CXADR	Coxsackievirus and adenovirus receptor	3,31	12,74
DPP4	Dipeptidyl peptidase 4 soluble form	6,42	11,22
ECE1	Endothelin-converting enzyme 1	7,14	4,7
ENPP4	Bis(5'-adenosyl)-triphosphatase ENPP4	6,57	7,49
EPHA3	Ephrin type-A receptor 3	2,84	7,85
ERG	Potassium voltage-gated channel subfamily H member 2	2,72	11,3
FAM38A	Piezo-type mechanosensitive ion channel component 1	8,4	9,57
FOLH1	Glutamate carboxypeptidase 2	2,96	13,18
GABRA2	Gamma-aminobutyric acid receptor subunit alpha-2	3	6,42
GHR	Growth hormone-binding protein	2,52	6,84
GPM6B	Neuronal membrane glycoprotein M6-b	3,22	6,56
GPR116	Probable G-protein coupled receptor 116	3,69	10,09
HBEGF	Heparin-binding EGF-like growth factor	2,87	8,12
JAM3	Junctional adhesion molecule C	4,29	7,26
KCND3	Potassium voltage-gated channel subfamily D member 3	3,09	9,77
LIFR	Leukemia inhibitory factor receptor	2,71	6,8
LRBA	Lipopolysaccharide-responsive and beige-like anchor protein	5,35	9,26
MME	Neprilysin	2,62	8,05
NOV	Plexin-A1	2,43	10,41
NRP1	Neuropilin-1	3,17	7,85
OPRK1	Kappa-type opioid receptor	2,07	4,92
PLXNB3	Plexin-B3	2,57	3,59
PPAP2A	Lipid phosphate phosphohydrolase 1	3,6	11,55
SCAMP5	Secretory carrier-associated membrane protein 5	3,03	8,43
SLC23A2	Solute carrier family 23 member 2	3,55	7,04
SLC2A4	Solute carrier family 2, facilitated glucose transporter member 4	2,67	5,96
SLC36A1	Proton-coupled amino acid transporter 1	3,38	9,28
SLC4A4	Electrogenic sodium bicarbonate cotransporter 1	3,14	11,29
STIM1	Stromal interaction molecule 1	3,68	6,51
TMPRSS2	Transmembrane protease serine 2 catalytic chain	2,67	9,63
TRPV6	Transient receptor potential cation channel subfamily V member 6	4,84	8,09
VIPR1	Vasoactive intestinal polypeptide receptor 1	4,41	7,73
YIPF3	Protein YIPF3, 36 kDa form III	4	4,3

Table 14: antigen markers expressed on the surface of T-cells and overexpressed in liquid tumor cells (ALL, AML, CML, MDS, CLL, CTRL)

Antigen	Protein Name	Relative expression on T cell
CD63	CD63 antigen	0.83
CXCR4	C-X-C chemokine receptor type 4	0.82
IFITM2	Interferon-induced transmembrane protein 2	0.82
ITM2B	Bri23 peptide	0.81
BTF3	Butyrophilin subfamily 3 member A2	0.8
HLA-DRB1	HLA class II histocompatibility antigen, DRB1-12 beta chain	0.79
HLA-DRA	HLA class II histocompatibility antigen, DR alpha chain	0.78
IFITM3	Interferon-induced transmembrane protein 3	0.78
NKG7	Protein NKG7	0.78
FCER1G	High affinity immunoglobulin epsilon receptor subunit gamma	0.78
IFITM1	Interferon-induced transmembrane protein 1	0.76
NPTN	Neuroplastin	0.76
GYPC	Glycophorin-C	0.76
GPR160	Probable G-protein coupled receptor 160	0.76
HLA-DPB1	HLA class II histocompatibility antigen, DP beta 1 chain	0.75
BRI3	CT-BRI3	0.75
SLC38A2	Sodium-coupled neutral amino acid transporter 2	0.74
C5AR1	C5a anaphylatoxin chemotactic receptor 1	0.74
CDIPT	CDP-diacylglycerol--inositol 3-phosphatidyltransferase	0.73
TNFSF13B	Tumor necrosis factor ligand superfamily member 13b, soluble form	0.73
CSF3R	Granulocyte colony-stimulating factor receptor	0.73
HLA-DPA1	HLA class II histocompatibility antigen, DP alpha 1 chain	0.71
CD164	Sialomucin core protein 24	0.71
CD97	CD97 antigen subunit beta	0.7
C3AR1	C3a anaphylatoxin chemotactic receptor	0.69
P2RY8	P2Y purinoceptor 8	0.68
BSG	Basigin	0.68
APLP2	Amyloid-like protein 2	0.67
TFRC	Transferrin receptor protein 1, serum form	0.67
MGAM	Glucoamylase	0.67
GYPA	Glycophorin-A	0.67
TMED10	Transmembrane emp24 domain-containing protein 10	0.66
FCGRT	IgG receptor FcRn large subunit p51	0.66
CKAP4	Cytoskeleton-associated protein 4	0.66
DYSF	Dysferlin	0.66
SPPL2A	Signal peptide peptidase-like 2A	0.65
LAMP2	Lysosome-associated membrane glycoprotein 2	0.65
SLC7A5	Large neutral amino acids transporter small subunit 1	0.65
TNFRSF1B	Tumor necrosis factor-binding protein 2	0.64
TREM1	Triggering receptor expressed on myeloid cells 1	0.64

GPR183	G-protein coupled receptor 183	0.63
SERINC3	Serine incorporator 3	0.63
CD58	Lymphocyte function-associated antigen 3	0.63
GYPB	Glycophorin-B	0.63
RABAC1	Prenylated Rab acceptor protein 1	0.62
KCNH2	Potassium voltage-gated channel subfamily H member 2	0.62
FPR1	fMet-Leu-Phe receptor	0.62
P2RY13	P2Y purinoceptor 13	0.62
CLEC5A	C-type lectin domain family 5 member A	0.62
SLC7A7	Y+L amino acid transporter 1	0.61
MICB	MHC class I polypeptide-related sequence B	0.61
CD300LF	CMRF35-like molecule 1	0.61
GJB6	Gap junction beta-6 protein	0.61
ATP1A1	Sodium/potassium-transporting ATPase subunit alpha-1	0.6
PTGER4	Prostaglandin E2 receptor EP4 subtype	0.6
CD8A	T-cell surface glycoprotein CD8 alpha chain	0.6
PTGER2	Prostaglandin E2 receptor EP2 subtype	0.6
GPR97	Probable G-protein coupled receptor 97	0.6
IMP3	Signal peptide peptidase-like 2A	0.59
LAMP1	Lysosome-associated membrane glycoprotein 1	0.59
LILRB3	Leukocyte immunoglobulin-like receptor subfamily B member 3	0.59
GPR109B	Hydroxycarboxylic acid receptor 3	0.59
SAT2	Sodium-coupled neutral amino acid transporter 2	0.58
GPR65	Psychosine receptor	0.58
AMICA1	Junctional adhesion molecule-like	0.58
PAG1	Phosphoprotein associated with glycosphingolipid-enriched microdomains 1	0.58
ENPP4	Bis(5'-adenosyl)-triphosphatase ENPP4	0.57
SLC40A1	Solute carrier family 40 member 1	0.57
OLR1	Oxidized low-density lipoprotein receptor 1, soluble form	0.57
LRRC33	Negative regulator of reactive oxygen species	0.56
IL7R	Interleukin-7 receptor subunit alpha	0.56
LAIR1	Leukocyte-associated immunoglobulin-like receptor 1	0.56
ITM2C	CT-BRI3	0.56
GPR84	G-protein coupled receptor 84	0.56
SLC12A7	Solute carrier family 12 member 7	0.55
PTAFR	Platelet-activating factor receptor	0.55
CD33	Myeloid cell surface antigen CD33	0.55
SLC22A16	Solute carrier family 22 member 16	0.55
CCR7	C-C chemokine receptor type 7	0.54
TLR1	Toll-like receptor 1	0.54
TGOLN2	Trans-Golgi network integral membrane protein 2	0.54
YIPF3	Protein YIPF3, 36 kDa form III	0.54
BST2	Bone marrow stromal antigen 2	0.54
MAGT1	Magnesium transporter protein 1	0.54

TMEM173	Stimulator of interferon genes protein	0.54
ERMAP	Erythroid membrane-associated protein	0.54
CEACAM1	Carcinoembryonic antigen-related cell adhesion molecule 1	0.54
NIPA2	Magnesium transporter NIPA2	0.53
PECAM1	Platelet endothelial cell adhesion molecule	0.53
CD1D	Antigen-presenting glycoprotein CD1d	0.53
TMEM59	Transmembrane protein 59	0.53
NCKAP1L	Nck-associated protein 1-like	0.53
FAS	Tumor necrosis factor receptor superfamily member 6	0.53
IL6R	Interleukin-6 receptor subunit alpha	0.53
TNFRSF1A	Tumor necrosis factor-binding protein 1	0.53
KEL	Kell blood group glycoprotein	0.53
TMEM149	IGF-like family receptor 1	0.52
SLC3A2	4F2 cell-surface antigen heavy chain	0.52
ORAI1	Calcium release-activated calcium channel protein 1	0.52
XKR8	XK-related protein 8, processed form	0.52
C9orf46	Plasminogen receptor (KT)	0.52
TMEM127	Transmembrane protein 127	0.52
SLC2A1	Solute carrier family 2, facilitated glucose transporter member 1	0.52
FCGR1B	High affinity immunoglobulin gamma Fc receptor IB	0.52
CXCR2	C-X-C chemokine receptor type 2	0.52
IL4R	Soluble interleukin-4 receptor subunit alpha	0.51
HSD17B7	3-keto-steroid reductase	0.51
SEMA4D	Semaphorin-4D	0.51
ZDHHC5	Palmitoyltransferase ZDHHC5	0.51
ADRB2	Beta-2 adrenergic receptor	0.51
S1PR4	Sphingosine 1-phosphate receptor 4	0.51
PILRA	Paired immunoglobulin-like type 2 receptor alpha	0.51
LTB4R	Leukotriene B4 receptor 1	0.51
SORT1	Sortilin	0.51
SLCO4C1	Solute carrier organic anion transporter family member 4C1	0.51
ANO10	Anoctamin-10	0.51
CLSTN1	CTF1-alpha	0.5
RHBDF2	Inactive rhomboid protein 2	0.5
CCR1	C-C chemokine receptor type 1	0.5
EPCAM	Epithelial cell adhesion molecule	0.5
PNPLA2	Patatin-like phospholipase domain-containing protein 2	0.49
SLC12A6	Solute carrier family 12 member 6	0.49
SLC30A1	Zinc transporter 1	0.49
GPR27	Probable G-protein coupled receptor 27	0.49
EPOR	Erythropoietin receptor	0.49
CD79A	B-cell antigen receptor complex-associated protein alpha chain	0.48
HLA-DQB1	HLA class II histocompatibility antigen, DQ beta 1 chain	0.48
HBP1	Glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1	0.48

ABCA7	ATP-binding cassette sub-family A member 7	0.48
RAG1AP1	Sugar transporter SWEET1	0.48
CD47	Leukocyte surface antigen CD47	0.48
CXCL16	C-X-C motif chemokine 16	0.48
SLC14A1	Urea transporter 1	0.48
TGFBR2	TGF-beta receptor type-2	0.47
LRBA	Lipopolysaccharide-responsive and beige-like anchor protein	0.47
MFSD5	Molybdate-anion transporter	0.47
RELT	Tumor necrosis factor receptor superfamily member 19L	0.47
ATP2B4	Plasma membrane calcium-transporting ATPase 4	0.47
FURIN	Furin	0.47
GAPT	Protein GAPT	0.47
NFAM1	NFAT activation molecule 1	0.47
ATP2B1	Plasma membrane calcium-transporting ATPase 1	0.46
SLC26A11	Sodium-independent sulfate anion transporter	0.46
STX4	Syntaxin-4	0.46
NAT1	Sodium-coupled neutral amino acid transporter 3	0.46
STIM1	Stromal interaction molecule 1	0.46
SLC39A4	Zinc transporter ZIP4	0.46
ESYT2	Extended synaptotagmin-2	0.46
TM7SF3	Transmembrane 7 superfamily member 3	0.46
SEMA4A	Semaphorin-4A	0.46
CYBB	Cytochrome b-245 heavy chain	0.46
FCAR	Immunoglobulin alpha Fc receptor	0.46
GABBR1	Gamma-aminobutyric acid type B receptor subunit 1	0.45
CD53	Leukocyte surface antigen CD53	0.45
SIGLEC10	Sialic acid-binding Ig-like lectin 10	0.45
S1PR1	Sphingosine 1-phosphate receptor 1	0.45
BTN3A2	Butyrophilin subfamily 3 member A2	0.45
NOTCH2	Notch 2 intracellular domain	0.45
PIK3IP1	Phosphoinositide-3-kinase-interacting protein 1	0.45
FAM168B	Myelin-associated neurite-outgrowth inhibitor	0.45
LPAR2	Lysophosphatidic acid receptor 2	0.45
ATP1B3	Sodium/potassium-transporting ATPase subunit beta-3	0.45
FLVCR1	Feline leukemia virus subgroup C receptor-related protein 1	0.45
SECTM1	Secreted and transmembrane protein 1	0.45
SLC38A5	Sodium-coupled neutral amino acid transporter 5	0.45
GPR18	N-arachidonyl glycine receptor	0.44
LMBR1L	Protein LMBR1L	0.44
ABCC1	Multidrug resistance-associated protein 1	0.44
SLC22A18	Solute carrier family 22 member 18	0.44
CSF1R	Macrophage colony-stimulating factor 1 receptor	0.44
EMR1	EGF-like module-containing mucin-like hormone receptor-like 1	0.44
FPR2	N-formyl peptide receptor 2	0.44

KIT	Mast/stem cell growth factor receptor Kit	0.44
MS4A1	B-lymphocyte antigen CD20	0.43
MICA	MHC class I polypeptide-related sequence A	0.43
GPR172A	Solute carrier family 52, riboflavin transporter, member 2	0.43
F11R	Junctional adhesion molecule A	0.43
ADAM10	Disintegrin and metalloproteinase domain-containing protein 10	0.43
FAM38A	Piezo-type mechanosensitive ion channel component 1	0.43
CD68	Macrosialin	0.43
SLC26A6	Solute carrier family 26 member 6	0.43
MCOLN1	Mucolipin-1	0.43
SLCO3A1	Solute carrier organic anion transporter family member 3A1	0.43
PPAP2B	Lipid phosphate phosphohydrolase 3	0.43
ICAM4	Intercellular adhesion molecule 4	0.43
CXCR1	C-X-C chemokine receptor type 1	0.43
CD300A	CMRF35-like molecule 8	0.43
RELL1	RELT-like protein 1	0.43
TAPBPL	Tapasin-related protein	0.42
FCGR2C	Low affinity immunoglobulin gamma Fc region receptor II-c	0.42
SLC16A6	Monocarboxylate transporter 7	0.42
TMED1	Transmembrane emp24 domain-containing protein 1	0.42
CD86	T-lymphocyte activation antigen CD86	0.42
SLC16A3	Monocarboxylate transporter 4	0.42
SLC2A5	Solute carrier family 2, facilitated glucose transporter member 5	0.42
SLC29A1	Equilibrative nucleoside transporter 1	0.42
SLC16A14	Monocarboxylate transporter 14	0.42
P2RY2	P2Y purinoceptor 2	0.42
SUCNR1	Succinate receptor 1	0.42
BTN3A1	Butyrophilin subfamily 3 member A1	0.41
LAT2	Linker for activation of T-cells family member 2	0.41
PLXND1	Plexin-D1	0.41
ECE1	Endothelin-converting enzyme 1	0.41
TGFBR1	TGF-beta receptor type-1	0.41
CCRL2	C-C chemokine receptor-like 2	0.41
TFR2	Transferrin receptor protein 2	0.41
SLC44A1	Choline transporter-like protein 1	0.41
ITGA6	Integrin alpha-6 light chain	0.41
PMP22	Peripheral myelin protein 22	0.41
LAX1	Lymphocyte transmembrane adapter 1	0.4
AMIGO2	Amphoterin-induced protein 2	0.4
SLC38A1	Sodium-coupled neutral amino acid transporter 1	0.4
SLC41A1	Solute carrier family 41 member 1	0.4
C2orf89	Metalloprotease TIK1	0.4
ABCC10	Multidrug resistance-associated protein 7	0.4
CLDN15	Claudin-15	0.4

SLC39A6	Zinc transporter ZIP6	0.4
SLC16A5	Monocarboxylate transporter 6	0.4
TTYH3	Protein tweety homolog 3	0.4
ATP7A	Copper-transporting ATPase 1	0.4
COMT	Catechol O-methyltransferase	0.4
SLC17A5	Sialin	0.4
TMIGD2	Transmembrane and immunoglobulin domain-containing protein 2	0.4
CLEC7A	C-type lectin domain family 7 member A	0.4
SLC31A1	High affinity copper uptake protein 1	0.4
LRRC4	Leucine-rich repeat-containing protein 4	0.4
P2RY10	Putative P2Y purinoceptor 10	0.39
ATP10D	Probable phospholipid-transporting ATPase VD	0.39
BTN3A3	Butyrophilin subfamily 3 member A3	0.39
LIME1	Lck-interacting transmembrane adapter 1	0.39
TNF	Tumor necrosis factor, soluble form	0.39
PAQR8	Membrane progesterin receptor beta	0.39
OXER1	Oxoeicosanoid receptor 1	0.39
TRAT1	T-cell receptor-associated transmembrane adapter 1	0.39
GPBAR1	G-protein coupled bile acid receptor 1	0.39
SLC36A1	Proton-coupled amino acid transporter 1	0.39
PTPRE	Receptor-type tyrosine-protein phosphatase epsilon	0.39
PROM1	Prominin-1	0.39
CD74	HLA class II histocompatibility antigen gamma chain	0.38
CNST	Consortin	0.38
TMEM49	Vacuole membrane protein 1	0.38
CLIC4	Chloride intracellular channel protein 4	0.38
NAALADL1	N-acetylated-alpha-linked acidic dipeptidase-like protein	0.38
ANTXR2	Anthrax toxin receptor 2	0.38
FGFR1	Fibroblast growth factor receptor 1	0.38
IL1RAP	Interleukin-1 receptor accessory protein	0.38
ATP1B2	Sodium/potassium-transporting ATPase subunit beta-2	0.38
ABCG2	ATP-binding cassette sub-family G member 2	0.38
CLEC12A	C-type lectin domain family 12 member A	0.38
HLA-DQA1	HLA class II histocompatibility antigen, DQ alpha 1 chain	0.37
B4GALT1	Processed beta-1,4-galactosyltransferase 1	0.37
CNNM3	Metal transporter CNNM3	0.37
ATP1B1	Sodium/potassium-transporting ATPase subunit beta-1	0.37
SLC39A1	Zinc transporter ZIP1	0.37
ATRN	Attractin	0.37
CYSLTR1	Cysteinyl leukotriene receptor 1	0.37
TRPV2	Transient receptor potential cation channel subfamily V member 2	0.37
SLC27A1	Long-chain fatty acid transport protein 1	0.37
GPR171	Probable G-protein coupled receptor 171	0.37
DAGLB	Sn1-specific diacylglycerol lipase beta	0.37

KCNQ1	Potassium voltage-gated channel subfamily KQT member 1	0.37
FZD6	Frizzled-6	0.37
CSF2RA	Granulocyte-macrophage colony-stimulating factor receptor subunit alpha	0.37
PTH2R	Parathyroid hormone 2 receptor	0.37
MARCH1	E3 ubiquitin-protein ligase MARCH1	0.36
BACE2	Beta-secretase 2	0.36
CD5	T-cell surface glycoprotein CD5	0.36
TMEM219	Insulin-like growth factor-binding protein 3 receptor	0.36
XPR1	Xenotropic and polytropic retrovirus receptor 1	0.36
CD1C	T-cell surface glycoprotein CD1c	0.36
CNNM2	Metal transporter CNNM2	0.36
TMEM88	Transmembrane protein 88	0.36
ICOS	Inducible T-cell costimulator	0.36
KLRG1	Killer cell lectin-like receptor subfamily G member 1	0.36
LRP8	Low-density lipoprotein receptor-related protein 8	0.36
F2R	Proteinase-activated receptor 1	0.36
HM13	Minor histocompatibility antigen H13	0.36
EMR2	EGF-like module-containing mucin-like hormone receptor-like 2	0.36
TREML1	Trem-like transcript 1 protein	0.36
C17orf60	Allergin-1	0.36
GPR146	Probable G-protein coupled receptor 146	0.36
SLAMF6	SLAM family member 6	0.35
SLC7A6	Y+L amino acid transporter 2	0.35
RELL2	RELT-like protein 2	0.35
LGR6	Leucine-rich repeat-containing G-protein coupled receptor 6	0.35
PANX1	Pannexin-1	0.35
C18orf1	Low-density lipoprotein receptor class A domain-containing protein 4	0.35
SLMAP	Sarcolemmal membrane-associated protein	0.35
CCR5	C-C chemokine receptor type 5	0.35
MUC1	Mucin-1 subunit beta	0.35
EMR3	EGF-like module-containing mucin-like hormone receptor-like 3 subunit beta	0.35
COL23A1	Collagen alpha-1(XXIII) chain	0.35
OR2W3	Olfactory receptor 2W3	0.35
LNPEP	Leucyl-cystinyl aminopeptidase, pregnancy serum form	0.34
PRR7	Proline-rich protein 7	0.34
NOTCH1	Notch 1 intracellular domain	0.34
RFT1	Solute carrier family 52, riboflavin transporter, member 1	0.34
TNFRSF25	Tumor necrosis factor receptor superfamily member 25	0.34
ANO6	Anoctamin-6	0.34
AQP3	Aquaporin-3	0.34
ADAM9	Disintegrin and metalloproteinase domain-containing protein 9	0.34
INSR	Insulin receptor subunit beta	0.34

FZD5	Frizzled-5	0.34
ERG	Potassium voltage-gated channel subfamily H member 2	0.34
MME	Neprilysin	0.34
FCGR2B	Low affinity immunoglobulin gamma Fc region receptor II-b	0.33
LSR	Lipolysis-stimulated lipoprotein receptor	0.33
DDR1	Epithelial discoidin domain-containing receptor 1	0.33
CNR2	Cannabinoid receptor 2	0.33
ATR	Anthrax toxin receptor 1	0.33
P2RY14	P2Y purinoceptor 14	0.33
VEZT	Vezatin	0.33
ALG10B	Putative Dol-P-Glc:Glc(2)Man(9)GlcNAc(2)-PP-Dol alpha-1,2-glucosyltransferase	0.33
PAQR7	Membrane progesterin receptor alpha	0.33
FLT3LG	Fms-related tyrosine kinase 3 ligand	0.33
CD40LG	CD40 ligand, soluble form	0.33
FCGR2A	Low affinity immunoglobulin gamma Fc region receptor II-a	0.33
CLDN12	Claudin-12	0.33
GP6	Platelet glycoprotein VI	0.33
EPHB4	Ephrin type-B receptor 4	0.33
SEMA4C	Semaphorin-4C	0.33
CD300C	CMRF35-like molecule 6	0.33
PEAR1	Platelet endothelial aggregation receptor 1	0.33
FFAR2	Free fatty acid receptor 2	0.33
SLC2A6	Solute carrier family 2, facilitated glucose transporter member 6	0.32
TMEM150A	Transmembrane protein 150A	0.32
ANO8	Anoctamin-8	0.32
CD200R1	Cell surface glycoprotein CD200 receptor 1	0.32
FCER1A	High affinity immunoglobulin epsilon receptor subunit alpha	0.32
BEST1	Bestrophin-1	0.32
CLDN5	Claudin-5	0.32
SLC47A1	Multidrug and toxin extrusion protein 1	0.32
SLC5A10	Sodium/glucose cotransporter 5	0.32
CD40	Tumor necrosis factor receptor superfamily member 5	0.31
ANO9	Anoctamin-9	0.31
CLEC2D	C-type lectin domain family 2 member D	0.31
VIPR1	Vasoactive intestinal polypeptide receptor 1	0.31
SLC16A7	Monocarboxylate transporter 2	0.31
UTS2R	Urotensin-2 receptor	0.31
CLSTN3	Calsyntenin-3	0.31
GPR35	G-protein coupled receptor 35	0.31
SYT15	Synaptotagmin-15	0.31
FAM57A	Protein FAM57A	0.31
CD8B	T-cell surface glycoprotein CD8 beta chain	0.31
IL17RC	Interleukin-17 receptor C	0.31
GLDN	Gliomedin	0.31

FZD2	Frizzled-2	0.31
KCNA3	Potassium voltage-gated channel subfamily A member 3	0.3
MGA	Glucoamylase	0.3
GPR1	G-protein coupled receptor 1	0.3
IL6ST	Interleukin-6 receptor subunit beta	0.3
PCDHGB5	Protocadherin gamma-B5	0.3
OR1I1	Olfactory receptor 111	0.3
PTH1R	Parathyroid hormone/parathyroid hormone-related peptide receptor	0.3
NLGN2	Neurologin-2	0.3
MMP24	Processed matrix metalloproteinase-24	0.3
CDH22	Cadherin-22	0.3
TNFRSF8	Tumor necrosis factor receptor superfamily member 8	0.3
CHRNA2	Acetylcholine receptor subunit gamma	0.3
PSEN1	Presenilin-1 CTF12	0.3
GPR114	Probable G-protein coupled receptor 114	0.3
PLXNB2	Plexin-B2	0.3
CHRNA2	Neuronal acetylcholine receptor subunit alpha-2	0.3
GPR34	Probable G-protein coupled receptor 34	0.3
LPAR6	Lysophosphatidic acid receptor 6	0.3
ATP8A1	Probable phospholipid-transporting ATPase IA	0.3
FZD1	Frizzled-1	0.3
CCR2	C-C chemokine receptor type 2	0.3
P2RY1	P2Y purinoceptor 1	0.3
SLC16A9	Monocarboxylate transporter 9	0.3
C20orf103	Lysosome-associated membrane glycoprotein 5	0.3
ADORA2B	Adenosine receptor A2b	0.3
CLEC12B	C-type lectin domain family 12 member B	0.3
FCRL3	Fc receptor-like protein 3	0.29
CD180	CD180 antigen	0.29
TIGIT	T-cell immunoreceptor with Ig and ITIM domains	0.29
PPAP2A	Lipid phosphate phosphohydrolase 1	0.29
ATP11C	Probable phospholipid-transporting ATPase IG	0.29
TNFRSF17	Tumor necrosis factor receptor superfamily member 17	0.29
TNFSF12	Tumor necrosis factor ligand superfamily member 12, secreted form	0.29
TBXA2R	Thromboxane A2 receptor	0.29
OR3A3	Olfactory receptor 3A3	0.29
GPR153	Probable G-protein coupled receptor 153	0.29
ATP11A	Probable phospholipid-transporting ATPase IH	0.29
LRFN1	Leucine-rich repeat and fibronectin type III domain-containing protein 1	0.29
OR51B2	Olfactory receptor 51B2	0.29
KCNS1	Potassium voltage-gated channel subfamily S member 1	0.29
OR12D2	Olfactory receptor 12D2	0.29
GRM4	Metabotropic glutamate receptor 4	0.29
NEO1	Neogenin	0.29

DRD5	D(1B) dopamine receptor	0.29
PLXDC1	Plexin domain-containing protein 1	0.29
GPR157	Probable G-protein coupled receptor 157	0.29
CD300LB	CMRF35-like molecule 7	0.29
MARVELD1	MARVEL domain-containing protein 1	0.29
MFAP3	Microfibril-associated glycoprotein 3	0.29
CHRNA1	Acetylcholine receptor subunit beta	0.29
PVRL2	Poliovirus receptor-related protein 2	0.29
F2RL1	Proteinase-activated receptor 2, alternate cleaved 2	0.29
GPR124	G-protein coupled receptor 124	0.29
BACE1	Beta-secretase 1	0.29
C6orf105	Androgen-dependent TFPI-regulating protein	0.28
CXCR3	C-X-C chemokine receptor type 3	0.28
IGSF8	Immunoglobulin superfamily member 8	0.28
ATP8B1	Probable phospholipid-transporting ATPase 1C	0.28
TP53I13	Tumor protein p53-inducible protein 13	0.28
MC1R	Melanocyte-stimulating hormone receptor	0.28
CD84	SLAM family member 5	0.28
CALHM1	Calcium homeostasis modulator protein 1	0.28
CHRNA6	Neuronal acetylcholine receptor subunit alpha-6	0.28
CDH10	Cadherin-10	0.28
SLC16A1	Monocarboxylate transporter 1	0.28
GPRC5D	G-protein coupled receptor family C group 5 member D	0.28
AGER	Advanced glycosylation end product-specific receptor	0.28
FASLG	FasL intracellular domain	0.28
GPR56	GPR56 C-terminal fragment	0.28
SIGLEC1	Sialoadhesin	0.28
KIR2DL5A	Killer cell immunoglobulin-like receptor 2DL5A	0.28
PLB1	Lysophospholipase	0.28
CD200	OX-2 membrane glycoprotein	0.27
ADAM28	Disintegrin and metalloproteinase domain-containing protein 28	0.27
SIT1	Sodium- and chloride-dependent transporter XTRP3	0.27
SLC23A2	Solute carrier family 23 member 2	0.27
CCR10	C-C chemokine receptor type 10	0.27
PRR4	Processed poliovirus receptor-related protein 4	0.27
GJD2	Gap junction delta-2 protein	0.27
SLC2A8	Solute carrier family 2, facilitated glucose transporter member 8	0.27
CD209	CD209 antigen	0.27
CD274	Programmed cell death 1 ligand 1	0.27
PROM2	Prominin-2	0.27
ATP6V0A2	V-type proton ATPase 116 kDa subunit a isoform 2	0.27
MPZ	Myelin protein P0	0.27
TNFRSF18	Tumor necrosis factor receptor superfamily member 18	0.27
MFSD2A	Major facilitator superfamily domain-containing protein 2A	0.27

HEG1	Protein HEG homolog 1	0.27
OXTR	Oxytocin receptor	0.27
CD99L2	CD99 antigen-like protein 2	0.27
LILRB4	Leukocyte immunoglobulin-like receptor subfamily B member 4	0.27
SMAGP	Small cell adhesion glycoprotein	0.27
OR51I2	Olfactory receptor 51I2	0.27
LY6G6D	Lymphocyte antigen 6 complex locus protein G6f	0.27
KCNQ4	Potassium voltage-gated channel subfamily KQT member 4	0.27
HRH2	Histamine H2 receptor	0.27
SLC39A2	Zinc transporter ZIP2	0.27
CLDN10	Claudin-10	0.27
GPM6B	Neuronal membrane glycoprotein M6-b	0.27
STEAP4	Metalloreductase STEAP4	0.27
APOLD1	Apolipoprotein L domain-containing protein 1	0.27
S1PR3	Sphingosine 1-phosphate receptor 3	0.27
SGMS2	Phosphatidylcholine:ceramide cholinephosphotransferase 2	0.27
KIR2DS5	Killer cell immunoglobulin-like receptor 2DS5	0.27
STAR	Heat-stable enterotoxin receptor	0.27
NIPA1	Magnesium transporter NIPA1	0.26
CNNM4	Metal transporter CNNM4	0.26
SLAMF1	Signaling lymphocytic activation molecule	0.26
KIAA1919	Sodium-dependent glucose transporter 1	0.26
TLR6	Toll-like receptor 6	0.26
CRB3	Protein crumbs homolog 3	0.26
SLC12A9	Solute carrier family 12 member 9	0.26
GPR68	Ovarian cancer G-protein coupled receptor 1	0.26
OR51J1	Olfactory receptor 51J1	0.26
TREML2	Trem-like transcript 2 protein	0.26
GPR176	Probable G-protein coupled receptor 176	0.26
FLVCR2	Feline leukemia virus subgroup C receptor-related protein 2	0.26
LPAR1	Lysophosphatidic acid receptor 1	0.26
PANX2	Pannexin-2	0.26
SLC6A6	Sodium- and chloride-dependent taurine transporter	0.26
PROKR2	Prokineticin receptor 2	0.26
CLDN9	Claudin-9	0.26
MYOF	Myoferlin	0.26
LY6G6F	Lymphocyte antigen 6 complex locus protein G6f	0.26
ESAM	Endothelial cell-selective adhesion molecule	0.26
NCR3	Natural cytotoxicity triggering receptor 3	0.25
HLA-DQB2	HLA class II histocompatibility antigen, DQ beta 2 chain	0.25
SLC4A5	Electrogenic sodium bicarbonate cotransporter 4	0.25
P2RY4	P2Y purinoceptor 4	0.25
ABCB1	Multidrug resistance protein 1	0.25
SLC9A1	Sodium/hydrogen exchanger 1	0.25

CELSR2	Cadherin EGF LAG seven-pass G-type receptor 2	0.25
SYT8	Synaptotagmin-8	0.25
PCDHA9	Protocadherin alpha-9	0.25
TMEM204	Transmembrane protein 204	0.25
PTPRJ	Receptor-type tyrosine-protein phosphatase eta	0.25
GRPR	Gastrin-releasing peptide receptor	0.25
SEMA6B	Semaphorin-6B	0.25
CLCN5	H(+)/Cl(-) exchange transporter 5	0.25
GLRA2	Glycine receptor subunit alpha-2	0.25
PLVAP	Plasmalemma vesicle-associated protein	0.25
ACVR1B	Activin receptor type-1B	0.25
JAM3	Junctional adhesion molecule C	0.25
LDLRAD3	Low-density lipoprotein receptor class A domain-containing protein 3	0.25
XG	Glycoprotein Xg	0.25
SLC2A11	Solute carrier family 2, facilitated glucose transporter member 11	0.24
PCDH9	Protocadherin-9	0.24
VAMP5	Vesicle-associated membrane protein 5	0.24
CDHR2	Cadherin-related family member 2	0.24
DRD2	D(2) dopamine receptor	0.24
LRIG2	Leucine-rich repeats and immunoglobulin-like domains protein 2	0.24
RAMP3	Receptor activity-modifying protein 3	0.24
SLC39A14	Zinc transporter ZIP14	0.24
STRA6	Stimulated by retinoic acid gene 6 protein homolog	0.24
ADRA2C	Alpha-2C adrenergic receptor	0.24
CLDN19	Claudin-19	0.24
CX3CR1	CX3C chemokine receptor 1	0.24
CD79B	B-cell antigen receptor complex-associated protein beta chain	0.24
KIR2DL2	Killer cell immunoglobulin-like receptor 2DL2	0.24
CXCR7	Atypical chemokine receptor 3	0.24
OR5L2	Olfactory receptor 5L2	0.24
LRRC52	Leucine-rich repeat-containing protein 52	0.24
JPH1	Junctophilin-1	0.24
ADORA1	Adenosine receptor A1	0.24
GPRC5C	G-protein coupled receptor family C group 5 member C	0.24
RET	Extracellular cell-membrane anchored RET cadherin 120 kDa fragment	0.24
PVR	Poliovirus receptor	0.24
ITGB3	Integrin beta-3	0.24
PTGIR	Prostacyclin receptor	0.24
LPHN1	Latrophilin-1	0.24
OR10J1	Olfactory receptor 10J1	0.24
MFAP3L	Microfibrillar-associated protein 3-like	0.24
GNPMB	Transmembrane glycoprotein NMB	0.24
CELSR3	Cadherin EGF LAG seven-pass G-type receptor 3	0.23

CCR6	C-C chemokine receptor-like 2	0.23
DMPK	Myotonin-protein kinase	0.23
UPK3B	Uroplakin-3b	0.23
OR1D2	Olfactory receptor 1D2	0.23
OR7D2	Olfactory receptor 7D2	0.23
ITGB1	Integrin beta-1	0.23
HRH3	Histamine H3 receptor	0.23
GRIN2C	Glutamate receptor ionotropic, NMDA 2C	0.23
KIR3DL1	Killer cell immunoglobulin-like receptor 3DL1	0.23
EPHB2	Ephrin type-B receptor 2	0.23
OR2S2	Olfactory receptor 2S2	0.23
KIR2DL4	Killer cell immunoglobulin-like receptor 2DL4	0.23
CNNM1	Metal transporter CNNM1	0.23
MARVELD2	MARVEL domain-containing protein 2	0.23
CXCR6	C-X-C chemokine receptor type 6	0.23
NOV	Plexin-A1	0.23
ABCB6	ATP-binding cassette sub-family B member 6, mitochondrial	0.23
PVRL1	Poliovirus receptor-related protein 1	0.23
SLC46A2	Thymic stromal cotransporter homolog	0.23
ADORA3	Adenosine receptor A3	0.23
GPR125	Probable G-protein coupled receptor 125	0.23
CD22	B-cell receptor CD22	0.22
FZD3	Frizzled-3	0.22
LPAR5	Lysophosphatidic acid receptor 5	0.22
TMEM8B	Transmembrane protein 8B	0.22
PLXNA1	Plexin-A1	0.22
NPFFR1	Neuropeptide FF receptor 1	0.22
SEZ6L2	Seizure 6-like protein 2	0.22
LRRTM2	Leucine-rich repeat transmembrane neuronal protein 2	0.22
SLC16A11	Monocarboxylate transporter 11	0.22
GRIK5	Glutamate receptor ionotropic, kainate 5	0.22
SYT6	Synaptotagmin-6	0.22
TMEM102	Transmembrane protein 102	0.22
OR8B8	Olfactory receptor 8B8	0.22
GJB1	Gap junction beta-1 protein	0.22
GRM6	Metabotropic glutamate receptor 6	0.22
C20orf54	Solute carrier family 52, riboflavin transporter, member 3	0.22
OR52D1	Olfactory receptor 52D1	0.22
SLC46A1	Proton-coupled folate transporter	0.22
DSC2	Desmocollin-2	0.22
FAT1	Protocadherin Fat 1, nuclear form	0.22
GCGR	Glucagon receptor	0.22
POP1	Blood vessel epicardial substance	0.22
CXADR	Coxsackievirus and adenovirus receptor	0.22

ABCC6	Multidrug resistance-associated protein 6	0.22
GJA1	Gap junction alpha-1 protein	0.22
CXCR5	C-X-C chemokine receptor type 5	0.21
ABCB4	Multidrug resistance protein 3	0.21
CTLA4	Cytotoxic T-lymphocyte protein 4	0.21
TRPV1	Transient receptor potential cation channel subfamily V member 1	0.21
MRGPRX4	Mas-related G-protein coupled receptor member X4	0.21
SIGLEC6	Sialic acid-binding Ig-like lectin 6	0.21
IL9R	Interleukin-9 receptor	0.21
CHRNA2	Neuronal acetylcholine receptor subunit beta-2	0.21
PDGFRB	Platelet-derived growth factor receptor beta	0.21
TMPRSS11D	Transmembrane protease serine 11D catalytic chain	0.21
CDH24	Cadherin-24	0.21
PRRT2	Proline-rich transmembrane protein 2	0.21
GALR3	Galanin receptor type 3	0.21
OR51I1	Olfactory receptor 51I1	0.21
PTPRU	Receptor-type tyrosine-protein phosphatase U	0.21
LPAR4	Lysophosphatidic acid receptor 4	0.21
ZNRF3	E3 ubiquitin-protein ligase ZNRF3	0.21
P2RY6	P2Y purinoceptor 6	0.21
AGTR1	Type-1 angiotensin II receptor	0.21
GPR182	G-protein coupled receptor 182	0.21
PODXL	Podocalyxin	0.21
BDKRB1	B1 bradykinin receptor	0.21
DCHS1	Protocadherin-16	0.21
GRIN3B	Glutamate receptor ionotropic, NMDA 3B	0.21
PTGDR	Prostaglandin D2 receptor	0.21
PVRL4	Processed poliovirus receptor-related protein 4	0.21
GPR77	C5a anaphylatoxin chemotactic receptor 2	0.21
PARM1	Prostate androgen-regulated mucin-like protein 1	0.21
OR10H1	Olfactory receptor 10H1	0.21
OR10D3	Putative olfactory receptor 10D3	0.21
TNFSF14	Tumor necrosis factor ligand superfamily member 14, soluble form	0.21
FCRL5	Fc receptor-like protein 5	0.2
RNF43	E3 ubiquitin-protein ligase RNF43	0.2
AMIGO1	Amphoterin-induced protein 1	0.2
OR1F1	Olfactory receptor 1F1	0.2
SLCO4A1	Solute carrier organic anion transporter family member 4A1	0.2
TTYH2	Protein tweety homolog 2	0.2
GABRR2	Gamma-aminobutyric acid receptor subunit rho-2	0.2
GJD3	Gap junction delta-3 protein	0.2
GRID1	Glutamate receptor ionotropic, delta-1	0.2
CLDN1	Claudin-1	0.2
SLC6A13	Sodium- and chloride-dependent GABA transporter 2	0.2

SLC30A8	Zinc transporter 8	0.2
KIR2DL3	Killer cell immunoglobulin-like receptor 2DL3	0.2
GPR78	G-protein coupled receptor 78	0.2
UPK2	Uroplakin-2	0.2
CLDN14	Claudin-14	0.2
EDA	Ectodysplasin-A, secreted form	0.2
PTGER1	Prostaglandin E2 receptor EP1 subtype	0.2
TRPV5	Transient receptor potential cation channel subfamily V member 5	0.2
PRIMA1	Proline-rich membrane anchor 1	0.2
GJA9	Gap junction alpha-9 protein	0.2
SLC7A3	Cationic amino acid transporter 3	0.2
SSTR2	Somatostatin receptor type 2	0.2
CD1A	T-cell surface glycoprotein CD1a	0.2
SLC7A8	Large neutral amino acids transporter small subunit 2	0.2
CLIC6	Chloride intracellular channel protein 6	0.2
EPHA8	Ephrin type-A receptor 8	0.2
SLC20A2	Sodium-dependent phosphate transporter 2	0.2
SCNN1A	Amiloride-sensitive sodium channel subunit alpha	0.2
OR51B6	Olfactory receptor 51B6	0.2
OR14J1	Olfactory receptor 14J1	0.2
OR10C1	Olfactory receptor 10C1	0.2
OPRL1	Nociceptin receptor	0.2
CCR9	C-C chemokine receptor type 9	0.2
JPH4	Junctophilin-4	0.2
HTR1E	5-hydroxytryptamine receptor 1E	0.2
MC3R	Melanocortin receptor 3	0.2
CD163L1	Scavenger receptor cysteine-rich type 1 protein M160	0.2
SEZ6	Seizure protein 6 homolog	0.2
PRSS8	Prostasin heavy chain	0.2
CDH26	Cadherin-like protein 26	0.2
ODZ1	Teneurin C-terminal-associated peptide	0.2
FGFR3	Fibroblast growth factor receptor 3	0.2

EXAMPLE 1 - KNOCK OUT (KO) ON CD38 GENE & EXPRESSION OF ANTI-CD38 CAR**Presentation of the CD38 target** -cyclic ADP ribose hydrolase

CD38 is a glycoprotein found on the surface of many immune cells, including multiple myeloma (MM) cells that express a high level of CD38 in a large majority of patients. CD38 is a validated target for MM as many studies have shown efficient killing of CD38+ MM cells from patients and CD38+ MM cell lines using anti-CD38 mAbs by CDC and ADCC (Ellis, J. H. K. et al, Journal of Immunology, 1995, 155 (2), 925–937). Daratumumab is a therapeutic human CD38 monoclonal antibody which induces killing of multiple myeloma and other hematological tumors (De Weers, M. et al, *J Immunol* 2011 186:1840-1848). In some studies, it has been shown that CD38 is also highly expressed by activated T cells (Sandoval-Montes CJ et al, 2005, *Leukoc Biol.* 77(4):513-21).

Expression of CD38 by T-cells

The CD38 expression by T cells after CD3/CD28 beads and IL-2 stimulation was analyzed by FACS every 3-4 days during 17 days. It was observed that more than 90% T cells express between day 6 and day 17 after activation (Figure 10B).

Thus, in order to avoid killing of activated T cells by anti-CD38 CAR+ T cells CD38 surface expression in T cells needs to be prevented. This may be accomplished by the inactivation of the CD38 gene using TALE-nucleases. TALEN is a trademark owned by the applicant (Cellestis, 8 rue de la Croix Jarry, 75013 PARIS) designating customized format of TAL nucleases.

Strategy for the CD38 knock-out (KO)

Heterodimeric TALE-nuclease targeting two 17-pb long sequences separated by a 13–pb spacer within the CD38 gene were designed and produced. Each half target is recognized by repeats of the half TALE-nucleases listed in the following Table 15 and Figure 10A.

The repeats sequence of the left TALEN for the CD38ex1_T2 target was NN-NI-NN-NN-NG-NN-NN-NN-NG-NG-NN-NN-HD-NN-NI-NG, and the one for the right TALEN was NN-NG-HD-HD-HD-HD-NN-HD-NI-NN-NG-NN-HD-HD-HD-NG.

Table 15: Sequences of the tested CD38 target and TALENs for inactivation of the CD38 antigen

Name	TALEN L/R	SEQ ID #	Nucleic acid sequence or polypeptide sequence
CD38 target	N/A	1	TGAGGTGGGTTGGCGAC taaggcgaccgg TGGGCACTGCGGGGACA
CD38ex 1_T2- L1 TALEN	L	2	MGDPKKKRKVIDYPYDVPDYAIDIADLRTLGYSSQQQKEIKPKVIRSTV AQHHEALVGHGFTAHIVALSQHPAALGTAVVKYQDMIAALPEATHE AIVGVGKQWSGARALEALLTVAGELRGPPQLQDGTGQLLKIAGRGGVTA VEAVHAWRNALTGAPLNLTQQVVAIASNNGGKQALETVQRLLPVL CQAHGLTPEQVVAIASNIGGKQALETVQALLPVLCQAHGLTPQQVVAI ASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALET VQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHG LTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNN GGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLL PVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQ QVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGK QALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVL CQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVV AIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALET VQALLPVLCQAHGLTPQQVVAIASNNGGGRPALESIVAQLSRDPALAA LTNDHLVALACLGGRPALDAVKKGLGDPISRSQVLKSELEKKSELRHK LKYVPHEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRKP DGAIYTVGSPIDYGVIVDTKAYSGGYNLPIGQADEMQRYVEENQTRN KHINPNEWWKVYPSSVTEFKFLVSGHFKGNYKAQLTRLNHITNCNG AVLSVEELLIGGEMIKAGTLTLEEVRKFNNGEINFAAD
CD38ex 1_T2- R1 TALEN	R	3	MGDPKKKRKVIDKETAAAKFERQHMSIDIADLRTLGYSSQQQKEIKP KVRSTVAQHHEALVGHGFTAHIVALSQHPAALGTAVVKYQDMIAAL PEATHEAIVGVGKQWSGARALEALLTVAGELRGPPQLQDGTGQLLKIAG RGGVTAVEAVHAWRNALTGAPLNLTQQVVAIASNNGGKQALETV QRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGL TPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDG GKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLP VLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQV VAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQAL ETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQALLPVLCQAH GLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASN GGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQR LLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPE QVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQ ALETVQRLLPVLCQAHGLTPQQVVAIASNNGGGRPALESIVAQLSRDP ALAAALTNDHLVALACLGGRPALDAVKKGLGDPISRSQVLKSELEKKSE LRHKLKYVPHEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGG SRKPDGAIYTVGSPIDYGVIVDTKAYSGGYNLPIGQADEMQRYVEENQ TRNKHINPNEWWKVYPSSVTEFKFLVSGHFKGNYKAQLTRLNHITNC NGAVLSVEELLIGGEMIKAGTLTLEEVRKFNNGEINFAAD

Each TALE-nuclease construct was subcloned using restriction enzyme digestion in a mammalian expression vector under the control of the T7 promoter. mRNA encoding TALE-nuclease cleaving CD38 were synthesized from plasmids carrying the coding sequence downstream from the T7 promoter.

5 Purified T cells activated during 72 hours with anti CD3/CD28 coated beads and recombinant IL-2 were transfected by electroporation (Cytopulse) with each of the 2 mRNAs (10µg each) encoding both half CD38ex1_T2 TALE-nucleases. To investigate, the CD38 KO, the percentage of CD38 negative T cells was assessed by flow cytometry at day 3, 6, 10 and 13 after TALEN mRNA transfection. It was observed that 15% of transfected T cells were CD38 deficient
10 (Figure 10 C) and this deficiency was stable during 13 days after transfection.

In addition two alternative TALE-nucleases targeting the CD38 gene have been designed. Each half target is recognized by repeats of the half TALE-nucleases listed in the following Table 16 and Figure 10A. The repeats sequence of the left TALEN for the CD38ex1_T4 target was NG-NN-HD-NN-NI-NN-NG-NG-HD-NI-NN-HD-HD-HD-NN-NN-NG, and the one for the right TALEN was NG-NN-HD-NG-NN-HD-HD-NN-NN-HD-NG-HD-NG-HD-NG-NI. The repeats sequence of the left TALEN
15 for the CD38ex1_T5 target was NG-NN-NI-NG-HD-HD-NG-HD-NN-NG-HD-NN-NG-NN-NN-NG, and the one for the right TALEN was HD-NN-NI-NN-NN-NG-NN-NN-HD-NN-HD-HD-NI-NN-HD-NI.

Table 16: Sequences of two other CD38 targets and the corresponding TALENs for their
20 inactivation

Name	TALEN L/R	SEQ ID #	Nucleic acid sequence or repeats sequence
CD38ex 1_T4 target	N/A	4	TGCGAGTTCAGCCCGGtggtccggggacaaacccTGCTGCCGGCTCTCTA
CD38ex 1_T4-L TALEN	L	5	MGDPKKKRKVIDYPYDVPDYAIDIADLRTLGYSSQQQKEIKPKVRSTVA QHHEALVGHGFTAHIVALSQHPAALGTVAVKYQDMIAALPEATHEA IVGVGKQWSGARALEALLTVAGELRGPPLQLDTGQLLKIARGGVTAV EAVHAWRNALTGAPLNLTQQVVAIASNNGGKQALETVQRLLPVLCQ AHGLTPEQVVAIASNNGGKQALETVQALLPVLCQAHGLTPQQVVAIA SHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQ RLLPVLCQAHGLTPQQVVAIASNIGGKQALETVQRLLPVLCQAHGLTP QQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGK QALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLC QAHGLTPQQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAI ASNIGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETV QRLLPVLCQAHGLTPQQVVAIASHDGGKQALETVQRLLPVLCQAHGL TPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASHDG

[illegible]

			WKVYPSSVTEFKFLFVSGHFKGNYKAQLTRLNHITNCNGAVLSVEELLI GGEMIKAGTLTLEEVRKFNNGEINFAAD
CD38ex 1_T5-R TALEN	R	9	MGDPKKKRKVIDKETAAAKFERQHMDSIDIADLRTLGYSSQQQKEIKP KVRSTVAQHHEALVGHGFTHAHIVALSQHPAALGTVAVKYQDMIAAL PEATHEAIVGVGKQWSGARALEALLTVAGELRGPPLQLDTGQLLIAK RGGVTAVEAVHAWRNALTGAPLNLTQQVVAIASHDGGKQALETVQ RLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTP EQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQ ALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQ AHGLTPEQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIAS NNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNNGGKQALETVQR LLPVLCQAHGLTPEQVVAIASHDGGKQALETVQALLPVLCQAHGLTPQ QVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASHDGGKQ ALETVQRLLPVLCQAHGLTPQQVVAIASHDGGKQALETVQRLLPVLCQ AHGLTPEQVVAIASNIGGKQALETVQRLLPVLCQAHGLTPEQVVAIAS NNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQR LLPVLCQAHGLTPQQVVAIASNIGGRPALESIVAQLSRPDPALAALTND HLVALACLGGRPALDAVKKGLGDPISRSQVLKSELEKKSELRHKLKYVP HEYELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIY TVGSPIDYGVIVDTKAYSGGYNLPIGQADEMQRYVEENQTRNKHINPN EWWKVYPSSVTEFKFLFVSGHFKGNYKAQLTRLNHITNCNGAVLSVEE LLIGGEMIKAGTLTLEEVRKFNNGEINFAAD

Strategy for the expression of the CAR anti-CD38

Structure and composition of CARs anti-CD38

5 In Table 17 are presented VH and VL chain of scFv anti-CD38. SEQ ID NO:10-11 correspond to the humanized anti-CD38 antibody daratumumab (Genmab) and SEQ ID NO: 12-13 to the MOR202 (or MOR03087) such as described in the US 8,263,746B patent.

10 SEQ ID NO:14-20 and SEQ ID NO:21-26 correspond to the CDR sequence for respectively the VH chain (HCDR) and the VL chain (LCDR) such as described in the WO 2008/047242 application.

Table 17: Sequences of VH and VL chains of the scFv anti-CD38 antibodies daratumumab, MOR202 and of specific CDRs for VH and VL chains.

Name	VH or VL chain	SEQ ID #	Polypeptide or nucleic acid sequence
Daratumumab	VH	10	EVQLLESGGGLVQPGGSLRLSCAVSGFTFNSFAMSWVRQAPGK GLEWVSAISGSGGGTYADSVKGRFTISRDNKNTLYLQMNSLR AEDTAVYFCAKDILWFGEVPFDYWGQGLTVTVSSASTKGPSV

			FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
	VL	11	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIIYDASNRATGIPARFSGSGSGTDFTLTISLEPEDFAVYYCQQRSNWPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
MOR202 (or MOR03087)	VH	12	QVQLVESGGGLVQPGGSLRLSCAASGFTSSYYMNWVRQAPGKGLEWVSGISGDPSTNTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAWGGTLVTVSS
	VL	13	DIELTQPPSVSVAPGQTARISCSGDNLRHYVYVYQQKPGQAPVLVIYGDSCRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTGASLVFGGGTKLTVLGQ
HCDR1-1	VH	14	GFTSSYYMN
HCDR1-2	VH	15	SYMMN
HCDR2	VH	16	GISGDPSTNTYYADSVKG
HCDR3	VH	17	DLPLVYTGFA
HCDR4	VH	18	DYWMQ
HCDR5	VH	19	TIYPGDGDTGYAQKFK
HCDR6	VH	20	GDYYGSNSLDY
LCDR1	VL	21	SGDNLRHYVY
LCDR2	VL	22	GDSKRPS
LCDR3	VL	23	QTYTGASL
LCDR4	VL	24	KASQDVSTVVA
LCDR5	VL	25	SASYRYI
LCDR6	VL	26	QQHSPPYT

For the daratumumab scFv 3 different CARs constructs (GMB005-V1&V2&V3) have been designed such as presented in Figure 11A and their sequence displayed in the following Table 18.

- 5 All three constructs share the same components, in terms of signal peptide (CD8 α), GS linker (between the scFv VH and VL chains), transmembrane domain (TM), 4-1BB costimulatory domain, and CD3 ζ activation domain (sequences displayed in the following Table 18). Their differences come from the choice of the hinge (Table 18):

V1 : FcRIIa hinge

- 10 - V2 : CD8a hinge
- V3 : IgG1 hinge

Table 18: Polypeptide sequence of the 3 different structures of scFv daratumumab-based anti-CD38 CARs and of the individual components used

Name of CAR	SEQ ID #	
CD8 α -Signal peptide (SP)	27	MALPVTALLPLALLHAARP
GS linker	28	GGGSGGGSGGGGS
FCRII α hinge	29	GLAVSTISSFFPPGYQ
CD8 α hinge	30	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
IgG1 hinge	31	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
TM domain	32	IYIWAPLAGTCGVLLLSLVITLYC
4-1 BB co-stimulatory domain	33	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL
CD3 ζ activation domain	34	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR
GMB005-V1 CAR	35	PLALLHAARPEVQLLESGGGLVQPGGSLRLSCAVSGFTFNSFAMSWVRQAPGKGLEWVSAISGSGGGTYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYFCAKDILWFGEVPFDYWGGQTLVTVSSASGGGSGGGSGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGGTDFLTISSELPEDFAVYYCQQRSNWPPTFGQGTKEIKGLAVSTISSFFPPGYQYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDA
GMB005-V2 CAR	36	PLALLHAARPEVQLLESGGGLVQPGGSLRLSCAVSGFTFNSFAMSWVRQAPGKGLEWVSAISGSGGGTYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYFCAKDILWFGEVPFDYWGGQTLVTVSSASGGGSGGGSGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGGTDFLTISSELPEDFAVYYCQQRSNWPPTFGQGTKEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDA
GMB005-V3 CAR	37	PLALLHAARPEVQLLESGGGLVQPGGSLRLSCAVSGFTFNSFAMSWVRQAPGKGLEWVSAISGSGGGTYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYFCAKDILWFGEVPFDYWGGQTLVTVSSASGGGSGGGSGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGGTDFLTISSELPEDFAVYYCQQRSNWPPTFGQGTKEIKEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQ

		EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDV LDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG HDGLYQGLSTATKDTYDA
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Screening

CD38 TALENs will be transfected at day 4 after activation. 3 days after the CD38 deficient cells will be sorted by negative selection and transfected 3 days after with anti-CD38 CAR mRNAs. The CAR molecules generated will then be screened for expression and degranulation activity toward target cell lines expression CD38 upon CAR mRNA transient transfection. Target cell lines expressing different expression levels of CD38 (Figure 11B) will be used for activity testing:

- U266 CD38+ and U266 CD38- obtained by magnetic separation using anti-CD38 microbeads
- L363, a multiple myeloma cell line expressing intermediate levels of CD38
- Daudi, a cell line derived from Burkitt lymphoma expressing high levels of CD38
- K562, a cell line CD38 negative cell line derived from chronic myelogenous leukemia.

This first screening will be followed by a second screening step in which a number of selected candidates will be tested for their ability to induce degranulation, IFN γ release and specific cytotoxic activity towards the selected target cell lines. Candidate selection will then be narrowed and some candidates selected for lentivirus vector production and CAR activity will be assessed in CD38 KO T-cells stably expressing the CARs.

EXAMPLE 2 ACTIVITY OF ANTI-CS1 CAR IN THE CONTEXT OF CS1 KO

Presentation of CS1 target

Multiple myeloma (MM) is a B-cell malignancy characterized by the aberrant clonal expansion of plasma cells (PCs) within the bone marrow, with an estimated 21,700 new cases and 10,710 deaths from MM identified in the United States in 2012 (Siegel R, et al. Cancer J Clin 2012 62:10–29). In 2013, it has been estimated that 22,350 individuals will be newly diagnosed with MM in the United States and 10,710 people will die from it, accounting for 20% of the deaths from all hematologic malignancies. Despite the use of proteasome inhibitors and immune-modulating drugs, which have improved overall survival (Palumbo A, et al. *Leukemia* 2009

23:449–456), MM remains an incurable malignancy (Podar K, et al. *Leukemia* 2009 23:10–24) for which novel therapeutic approaches are urgently needed.

The cell surface glycoprotein CS1 (also referred in the literature as SLAMF7, CD319 or CRACC - NCBI Reference Sequence: NP_067004.3) is highly and ubiquitously expressed on the surface of myeloma cells (Hsi ED, et al. *Clin Cancer Res* 2008 14:2775–84). CS1 is expressed at very low levels in the majority of immune effector cells, including natural killer (NK) cells, some subsets of T cells, and normal B cells, and is almost undetectable on myeloid cells (Hsi ED, et al. *Clin Cancer Res* 2008 14:2775–84). Notably, CS1 is negligibly expressed in human hematopoietic stem cells (Hsi ED, et al. *Clin Cancer Res* 2008 14:2775–84), which can be used for stem cell transplantation to treat hematologic malignancies, including MM. The functions of CS1 in MM remain incompletely understood, and it has been documented that CS1 may play a role in myeloma cell adhesion, clonogenic growth, and tumorigenicity (Benson DM Jr, et al. *J Clin Oncol* 2012 30:2013–5; Tai YT, et al. *Blood* 2009 113:4309–18).

Structure of the CAR anti-CS1

The same structures V1, V2 and V3 are designed such as in the Example 1 for the anti-CD38 antigen target single-chain CAR, with the same components in terms of hinge, transmembrane domain, co-activation and transduction domains (such as depicted in the Figure 11A and sequences shown in Table 18).

In Table 19 are presented the VH and VL chains of scFv anti-CS1. SEQ ID NO:38-40-42-44-46 and SEQ ID NO:39-41-43-45-47 correspond to respectively the VH chain and the VL chain of the murine scFv Luc63, Luc90, Luc34, LucX1 and LucX2 .

In Table 20 are presented anti-CS1 CARs with the above scFv; these CARs being based on the versions V1, V2 and V3 of Figure 11A, wherein respectively the short FcERy hinge, the medium hinge CD8 α hinge and the long IgG1 hinge are used. The underlined parts correspond to the scFv VH and VL chains bound by a linker.

Table 19: Sequences of VH and VL chains of the scFv anti-CS1 antibodies

Name	VH or VL chain	SEQ ID NO :	Polypeptide sequence
Luc63	VH	38	EVKLLSEGGGLVQPGGSLKLSAASGFDFSRYWMSWVRQAPGKGLEWIG EINPDSSTINYTPSLKDKFIISRDNAKNTLYLQMSKVRSEDTALYYCARPDGN YWYFDVWGAGTTVTVSS
	VL	39	DIVMTQSHKFMSTSVGDRVSITCKASQDVGIABAWYQQKPGQSPKLLIY WASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPYTFGG GTKLEIK
Luc90	VH	40	QVQLQQPGAELVRPGASVKLSCKASGYSFTTYWMNWWKQRPQGQLEWI GMIHPDSETRLNQKFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCARS TMIATRAMDYWGQGTSTVTVSS
	VL	41	DIVMTQSQKSMSTSVGDRVSITCKASQDVITGVAWYQQKPGQSPKLLIYS ASYRYTGVPDRFTGSGSGTDFTFTISNVQAEDLAVYYCQQHYSTPLTFGAG TKLEIK
Luc34	VH	42	QVQLQQSGAELARPGASVKLSCKASGYTFTSYWMQWVKQRPQGQLEWI GAIYPGDGDTTRYTQKFKGKATLTADKSSSTAYMQLSSLASEDSAVYYCARG KVYYGSNPFAYWGQGTSLTVSA
	VL	43	DIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPGNAPRLISG ATSLETGVPSRFSGSGSGKDYTLTSLQTEDVATYYCQQYWSTPWTFGGG TKLEIK
LucX1	VH	44	QVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKQRPQGQLEWI GRIYPGDGDTKYNGKFKGKATLTADKSSSTAYMQLSSLTSVDSAVYFCARS TMIATGAMDYWGQGTSTVTVSS
	VL	45	ETTVTQSPASLSMAIGKVTIRCITSTDIDDDMNWYQQKPGEPKLLISEGN TLRPGVPSRFSSSGYGTDFVFTIENMLSEDVADYYCLQSDNLPLTFGGGTKL EIK
LucX2	VH	46	QVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKQRPQGQLEWI GRIYPGDGDTKYNGKFKGKATLTADKSSSTAYMQLSSLTSVDSAVYFCARS TMIATGAMDYWGQGTSTVTVSS
	VL	47	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYS ASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPPYTFGG GTKLEIK

Table 20: Polypeptide sequence of anti-CS1 CARs based on the V1, V2 and V3 versions in Figure 11A

Name of CAR	SEQ ID #	Polypeptide sequence
Luc63-V1 CAR	48	<u>MALPVTALLPLALLLHAARPEVKLLES</u> <u>GGGLVQPGGSLKLS</u> <u>CAASGFDFSRYWMSWVRQAPGKGL</u> <u>EWIGEINPDSSTINYTPSLKDKFIISRDNAKNTLYLQMSKVRSEDTALYYCARPDGNYWYFDVWGAG</u> <u>TTVTVSSGGGGSGGGSGGGSGGGSDIVMTQSHKFMSTSVGDRVSITCKASQDVGIABAWYQQKPGQ</u> <u>SPKLLIYWASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPYTFGGGTKEIKGLAV</u> <u>STISSFFPPGYQKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQ</u> <u>QQQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKG</u> <u>ERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR</u>
Luc63-V2 CAR	49	<u>MALPVTALLPLALLLHAARPEVKLLES</u> <u>GGGLVQPGGSLKLS</u> <u>CAASGFDFSRYWMSWVRQAPGKGL</u> <u>EWIGEINPDSSTINYTPSLKDKFIISRDNAKNTLYLQMSKVRSEDTALYYCARPDGNYWYFDVWGAG</u> <u>TTVTVSSGGGGSGGGSGGGSGGGSDIVMTQSHKFMSTSVGDRVSITCKASQDVGIABAWYQQKPGQ</u> <u>SPKLLIYWASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPYTFGGGTKEIKTTTP</u> <u>APRPPTPAPTASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAFLAGTCGVLLSLVITLYCKRGR</u> <u>KLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQQNQLYNELNLGR</u> <u>REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQG</u> <u>LSTATKDTYDALHMQALPPR</u>
Luc63-V3 CAR	50	<u>MALPVTALLPLALLLHAARPEVKLLES</u> <u>GGGLVQPGGSLKLS</u> <u>CAASGFDFSRYWMSWVRQAPGKGL</u> <u>EWIGEINPDSSTINYTPSLKDKFIISRDNAKNTLYLQMSKVRSEDTALYYCARPDGNYWYFDVWGAG</u> <u>TTVTVSSGGGGSGGGSGGGSGGGSDIVMTQSHKFMSTSVGDRVSITCKASQDVGIABAWYQQKPGQ</u> <u>SPKLLIYWASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPYTFGGGTKEIKEPKS</u> <u>PKDTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN</u> <u>AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS</u> <u>RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG</u> <u>NVFSCSVMEALHNHYTQKSLSLSPGKKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC</u> <u>ELRVKFSRSADAPAYQQQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ</u> <u>KDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR</u>
Luc90-V1 CAR	51	<u>MALPVTALLPLALLLHAARPQVQLQPGAE</u> <u>LRPGASVKLSCKASGYSFTTYWMN</u> <u>WVKQRPQGQ</u> <u>GLEWIGMIHPDSETRLNQKFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCARSTMIATRAMDY</u> <u>WGQGTSTVTVSSGGGGSGGGSGGGSGGGSDIVMTQSQKSMSTSVGDRVSITCKASQDVITGVAWYQ</u> <u>QKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFFTISNVQAEDLAVYYCQHYSTPLTFGAGTKLEL</u> <u>KGLAVSTISSFFPPGYQKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSAD</u> <u>APAYQQQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE</u> <u>IGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR</u>
Luc90-V2 CAR	52	<u>MALPVTALLPLALLLHAARPQVQLQPGAE</u> <u>LRPGASVKLSCKASGYSFTTYWMN</u> <u>WVKQRPQGQ</u> <u>GLEWIGMIHPDSETRLNQKFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCARSTMIATRAMDY</u> <u>WGQGTSTVTVSSGGGGSGGGSGGGSGGGSDIVMTQSQKSMSTSVGDRVSITCKASQDVITGVAWYQ</u> <u>QKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFFTISNVQAEDLAVYYCQHYSTPLTFGAGTKLEL</u> <u>KTTPAPRPPTPAPTASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAFLAGTCGVLLSLVITLYC</u> <u>KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQQNQLYNEL</u> <u>NLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDG</u> <u>LYQGLSTATKDTYDALHMQALPPR</u>
Luc90-V3 CAR	53	<u>MALPVTALLPLALLLHAARPQVQLQPGAE</u> <u>LRPGASVKLSCKASGYSFTTYWMN</u> <u>WVKQRPQGQ</u> <u>GLEWIGMIHPDSETRLNQKFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCARSTMIATRAMDY</u> <u>WGQGTSTVTVSSGGGGSGGGSGGGSGGGSDIVMTQSQKSMSTSVGDRVSITCKASQDVITGVAWYQ</u> <u>QKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFFTISNVQAEDLAVYYCQHYSTPLTFGAGTKLEL</u> <u>KEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWYVDG</u> <u>VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQV</u> <u>YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSR</u> <u>WQQGNVFSCSVMEALHNHYTQKSLSLSPGKKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE</u> <u>EEGGCELRVKFSRSADAPAYQQQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG</u> <u>LYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR</u>
Luc34-V1 CAR	54	<u>MALPVTALLPLALLLHAARPQVQLQSGAE</u> <u>LARPGASVKLSCKASGYFTSYWMQWVKQRPQGQ</u> <u>LEWIGAIYPGDGTRYTQKFKGKATLTADKSSSTAYMQLSSLASEDSAVYYCARGKVVYGSNPFIYW</u>

		<u>GQGT</u> <u>LV</u> <u>TV</u> <u>SAGGGG</u> <u>SGGGG</u> <u>SGGGG</u> <u>SDIQ</u> <u>MTQ</u> <u>SSSY</u> <u>LSV</u> <u>SLG</u> <u>GRV</u> <u>TIT</u> <u>CKAS</u> <u>DHIN</u> <u>NW</u> <u>LAWY</u> <u>QQK</u> <u>PG</u> <u>NAP</u> <u>RL</u> <u>IS</u> <u>GAT</u> <u>S</u> <u>LET</u> <u>GV</u> <u>PS</u> <u>RF</u> <u>SG</u> <u>SG</u> <u>GK</u> <u>DY</u> <u>LS</u> <u>IT</u> <u>SL</u> <u>Q</u> <u>T</u> <u>ED</u> <u>VAT</u> <u>Y</u> <u>Y</u> <u>CQ</u> <u>Q</u> <u>Y</u> <u>W</u> <u>S</u> <u>T</u> <u>P</u> <u>W</u> <u>T</u> <u>F</u> <u>G</u> <u>G</u> <u>G</u> <u>T</u> <u>K</u> <u>L</u> <u>E</u> <u>I</u> <u>K</u> <u>GL</u> <u>AV</u> <u>ST</u> <u>IS</u> <u>S</u> <u>F</u> <u>P</u> <u>P</u> <u>G</u> <u>Y</u> <u>Q</u> <u>K</u> <u>R</u> <u>G</u> <u>R</u> <u>K</u> <u>L</u> <u>L</u> <u>Y</u> <u>I</u> <u>F</u> <u>K</u> <u>Q</u> <u>P</u> <u>F</u> <u>M</u> <u>R</u> <u>P</u> <u>V</u> <u>Q</u> <u>T</u> <u>T</u> <u>Q</u> <u>E</u> <u>E</u> <u>D</u> <u>G</u> <u>C</u> <u>S</u> <u>C</u> <u>R</u> <u>F</u> <u>E</u> <u>E</u> <u>E</u> <u>E</u> <u>G</u> <u>G</u> <u>C</u> <u>E</u> <u>L</u> <u>R</u> <u>V</u> <u>K</u> <u>F</u> <u>S</u> <u>R</u> <u>S</u> <u>A</u> <u>D</u> <u>A</u> <u>P</u> <u>A</u> <u>Y</u> <u>Q</u> <u>Q</u> <u>G</u> <u>N</u> <u>Q</u> <u>L</u> <u>Y</u> <u>N</u> <u>E</u> <u>L</u> <u>N</u> <u>L</u> <u>G</u> <u>R</u> <u>R</u> <u>E</u> <u>E</u> <u>D</u> <u>V</u> <u>L</u> <u>D</u> <u>K</u> <u>R</u> <u>R</u> <u>G</u> <u>R</u> <u>D</u> <u>P</u> <u>E</u> <u>M</u> <u>G</u> <u>G</u> <u>K</u> <u>P</u> <u>R</u> <u>R</u> <u>K</u> <u>N</u> <u>P</u> <u>Q</u> <u>E</u> <u>G</u> <u>L</u> <u>Y</u> <u>N</u> <u>E</u> <u>L</u> <u>Q</u> <u>K</u> <u>D</u> <u>K</u> <u>M</u> <u>A</u> <u>E</u> <u>A</u> <u>Y</u> <u>S</u> <u>E</u> <u>I</u> <u>G</u> <u>M</u> <u>K</u> <u>G</u> <u>E</u> <u>R</u> <u>R</u> <u>R</u> <u>G</u> <u>K</u> <u>G</u> <u>H</u> <u>D</u> <u>G</u> <u>L</u> <u>Y</u> <u>Q</u> <u>G</u> <u>L</u> <u>S</u> <u>T</u> <u>A</u> <u>T</u> <u>K</u> <u>D</u> <u>T</u> <u>Y</u> <u>D</u> <u>A</u> <u>L</u> <u>H</u> <u>M</u> <u>Q</u> <u>A</u> <u>L</u> <u>P</u> <u>P</u> <u>R</u>
Luc34- V2 CAR	55	<u>MALP</u> <u>VT</u> <u>ALL</u> <u>PL</u> <u>ALL</u> <u>HA</u> <u>ARP</u> <u>QV</u> <u>Q</u> <u>L</u> <u>Q</u> <u>S</u> <u>G</u> <u>A</u> <u>E</u> <u>L</u> <u>A</u> <u>R</u> <u>P</u> <u>G</u> <u>A</u> <u>S</u> <u>V</u> <u>K</u> <u>L</u> <u>S</u> <u>C</u> <u>K</u> <u>A</u> <u>S</u> <u>G</u> <u>Y</u> <u>T</u> <u>F</u> <u>T</u> <u>S</u> <u>Y</u> <u>W</u> <u>M</u> <u>Q</u> <u>W</u> <u>V</u> <u>K</u> <u>O</u> <u>R</u> <u>P</u> <u>G</u> <u>Q</u> <u>G</u> <u>LE</u> <u>W</u> <u>I</u> <u>G</u> <u>A</u> <u>I</u> <u>P</u> <u>G</u> <u>D</u> <u>G</u> <u>D</u> <u>T</u> <u>R</u> <u>Y</u> <u>T</u> <u>Q</u> <u>K</u> <u>F</u> <u>G</u> <u>K</u> <u>A</u> <u>T</u> <u>L</u> <u>T</u> <u>A</u> <u>D</u> <u>K</u> <u>S</u> <u>S</u> <u>T</u> <u>A</u> <u>Y</u> <u>M</u> <u>Q</u> <u>L</u> <u>S</u> <u>S</u> <u>L</u> <u>A</u> <u>S</u> <u>E</u> <u>D</u> <u>S</u> <u>A</u> <u>V</u> <u>Y</u> <u>C</u> <u>A</u> <u>R</u> <u>G</u> <u>K</u> <u>V</u> <u>Y</u> <u>G</u> <u>S</u> <u>N</u> <u>P</u> <u>F</u> <u>A</u> <u>Y</u> <u>W</u> <u>GQGT</u> <u>LV</u> <u>TV</u> <u>SAGGGG</u> <u>SGGGG</u> <u>SGGGG</u> <u>SDIQ</u> <u>MTQ</u> <u>SSSY</u> <u>LSV</u> <u>SLG</u> <u>GRV</u> <u>TIT</u> <u>CKAS</u> <u>DHIN</u> <u>NW</u> <u>LAWY</u> <u>QQK</u> <u>PG</u> <u>NAP</u> <u>RL</u> <u>IS</u> <u>GAT</u> <u>S</u> <u>LET</u> <u>GV</u> <u>PS</u> <u>RF</u> <u>SG</u> <u>SG</u> <u>GK</u> <u>DY</u> <u>LS</u> <u>IT</u> <u>SL</u> <u>Q</u> <u>T</u> <u>ED</u> <u>VAT</u> <u>Y</u> <u>Y</u> <u>CQ</u> <u>Q</u> <u>Y</u> <u>W</u> <u>S</u> <u>T</u> <u>P</u> <u>W</u> <u>T</u> <u>F</u> <u>G</u> <u>G</u> <u>G</u> <u>T</u> <u>K</u> <u>L</u> <u>E</u> <u>I</u> <u>K</u> <u>TT</u> <u>T</u> <u>P</u> <u>A</u> <u>P</u> <u>R</u> <u>P</u> <u>T</u> <u>P</u> <u>A</u> <u>P</u> <u>T</u> <u>I</u> <u>A</u> <u>S</u> <u>Q</u> <u>P</u> <u>L</u> <u>S</u> <u>R</u> <u>P</u> <u>E</u> <u>A</u> <u>C</u> <u>R</u> <u>P</u> <u>A</u> <u>A</u> <u>G</u> <u>G</u> <u>A</u> <u>V</u> <u>H</u> <u>T</u> <u>R</u> <u>G</u> <u>L</u> <u>D</u> <u>F</u> <u>A</u> <u>C</u> <u>D</u> <u>I</u> <u>Y</u> <u>I</u> <u>W</u> <u>A</u> <u>P</u> <u>L</u> <u>A</u> <u>G</u> <u>T</u> <u>C</u> <u>G</u> <u>V</u> <u>L</u> <u>L</u> <u>S</u> <u>L</u> <u>V</u> <u>I</u> <u>T</u> <u>L</u> <u>Y</u> <u>C</u> <u>K</u> <u>R</u> <u>G</u> <u>R</u> <u>K</u> <u>L</u> <u>L</u> <u>Y</u> <u>I</u> <u>F</u> <u>K</u> <u>Q</u> <u>P</u> <u>F</u> <u>M</u> <u>R</u> <u>P</u> <u>V</u> <u>Q</u> <u>T</u> <u>T</u> <u>Q</u> <u>E</u> <u>E</u> <u>D</u> <u>G</u> <u>C</u> <u>S</u> <u>C</u> <u>R</u> <u>F</u> <u>E</u> <u>E</u> <u>E</u> <u>E</u> <u>G</u> <u>G</u> <u>C</u> <u>E</u> <u>L</u> <u>R</u> <u>V</u> <u>K</u> <u>F</u> <u>S</u> <u>R</u> <u>S</u> <u>A</u> <u>D</u> <u>A</u> <u>P</u> <u>A</u> <u>Y</u> <u>Q</u> <u>Q</u> <u>G</u> <u>N</u> <u>Q</u> <u>L</u> <u>Y</u> <u>N</u> <u>E</u> <u>L</u> <u>N</u> <u>L</u> <u>G</u> <u>R</u> <u>R</u> <u>E</u> <u>E</u> <u>D</u> <u>V</u> <u>L</u> <u>D</u> <u>K</u> <u>R</u> <u>R</u> <u>G</u> <u>R</u> <u>D</u> <u>P</u> <u>E</u> <u>M</u> <u>G</u> <u>G</u> <u>K</u> <u>P</u> <u>R</u> <u>R</u> <u>K</u> <u>N</u> <u>P</u> <u>Q</u> <u>E</u> <u>G</u> <u>L</u> <u>Y</u> <u>N</u> <u>E</u> <u>L</u> <u>Q</u> <u>K</u> <u>D</u> <u>K</u> <u>M</u> <u>A</u> <u>E</u> <u>A</u> <u>Y</u> <u>S</u> <u>E</u> <u>I</u> <u>G</u> <u>M</u> <u>K</u> <u>G</u> <u>E</u> <u>R</u> <u>R</u> <u>R</u> <u>G</u> <u>K</u> <u>G</u> <u>H</u> <u>D</u> <u>G</u> <u>L</u> <u>Y</u> <u>Q</u> <u>G</u> <u>L</u> <u>S</u> <u>T</u> <u>A</u> <u>T</u> <u>K</u> <u>D</u> <u>T</u> <u>Y</u> <u>D</u> <u>A</u> <u>L</u> <u>H</u> <u>M</u> <u>Q</u> <u>A</u> <u>L</u> <u>P</u> <u>P</u> <u>R</u>
Luc34- V3 CAR	56	<u>MALP</u> <u>VT</u> <u>ALL</u> <u>PL</u> <u>ALL</u> <u>HA</u> <u>ARP</u> <u>QV</u> <u>Q</u> <u>L</u> <u>Q</u> <u>S</u> <u>G</u> <u>A</u> <u>E</u> <u>L</u> <u>A</u> <u>R</u> <u>P</u> <u>G</u> <u>A</u> <u>S</u> <u>V</u> <u>K</u> <u>L</u> <u>S</u> <u>C</u> <u>K</u> <u>A</u> <u>S</u> <u>G</u> <u>Y</u> <u>T</u> <u>F</u> <u>T</u> <u>S</u> <u>Y</u> <u>W</u> <u>M</u> <u>Q</u> <u>W</u> <u>V</u> <u>K</u> <u>O</u> <u>R</u> <u>P</u> <u>G</u> <u>Q</u> <u>G</u> <u>LE</u> <u>W</u> <u>I</u> <u>G</u> <u>A</u> <u>I</u> <u>P</u> <u>G</u> <u>D</u> <u>G</u> <u>D</u> <u>T</u> <u>R</u> <u>Y</u> <u>T</u> <u>Q</u> <u>K</u> <u>F</u> <u>G</u> <u>K</u> <u>A</u> <u>T</u> <u>L</u> <u>T</u> <u>A</u> <u>D</u> <u>K</u> <u>S</u> <u>S</u> <u>T</u> <u>A</u> <u>Y</u> <u>M</u> <u>Q</u> <u>L</u> <u>S</u> <u>S</u> <u>L</u> <u>A</u> <u>S</u> <u>E</u> <u>D</u> <u>S</u> <u>A</u> <u>V</u> <u>Y</u> <u>C</u> <u>A</u> <u>R</u> <u>G</u> <u>K</u> <u>V</u> <u>Y</u> <u>G</u> <u>S</u> <u>N</u> <u>P</u> <u>F</u> <u>A</u> <u>Y</u> <u>W</u> <u>GQGT</u> <u>LV</u> <u>TV</u> <u>SAGGGG</u> <u>SGGGG</u> <u>SGGGG</u> <u>SDIQ</u> <u>MTQ</u> <u>SSSY</u> <u>LSV</u> <u>SLG</u> <u>GRV</u> <u>TIT</u> <u>CKAS</u> <u>DHIN</u> <u>NW</u> <u>LAWY</u> <u>QQK</u> <u>PG</u> <u>NAP</u> <u>RL</u> <u>IS</u> <u>GAT</u> <u>S</u> <u>LET</u> <u>GV</u> <u>PS</u> <u>RF</u> <u>SG</u> <u>SG</u> <u>GK</u> <u>DY</u> <u>LS</u> <u>IT</u> <u>SL</u> <u>Q</u> <u>T</u> <u>ED</u> <u>VAT</u> <u>Y</u> <u>Y</u> <u>CQ</u> <u>Q</u> <u>Y</u> <u>W</u> <u>S</u> <u>T</u> <u>P</u> <u>W</u> <u>T</u> <u>F</u> <u>G</u> <u>G</u> <u>G</u> <u>T</u> <u>K</u> <u>L</u> <u>E</u> <u>I</u> <u>K</u> <u>EP</u> <u>K</u> <u>S</u> <u>P</u> <u>D</u> <u>K</u> <u>T</u> <u>H</u> <u>T</u> <u>C</u> <u>P</u> <u>P</u> <u>C</u> <u>A</u> <u>P</u> <u>P</u> <u>V</u> <u>A</u> <u>G</u> <u>P</u> <u>S</u> <u>V</u> <u>L</u> <u>F</u> <u>P</u> <u>P</u> <u>K</u> <u>P</u> <u>K</u> <u>D</u> <u>T</u> <u>L</u> <u>M</u> <u>I</u> <u>A</u> <u>R</u> <u>T</u> <u>P</u> <u>E</u> <u>V</u> <u>T</u> <u>C</u> <u>V</u> <u>V</u> <u>D</u> <u>V</u> <u>S</u> <u>H</u> <u>E</u> <u>D</u> <u>P</u> <u>E</u> <u>V</u> <u>K</u> <u>F</u> <u>N</u> <u>W</u> <u>Y</u> <u>V</u> <u>D</u> <u>G</u> <u>V</u> <u>E</u> <u>V</u> <u>H</u> <u>N</u> <u>A</u> <u>K</u> <u>T</u> <u>P</u> <u>R</u> <u>E</u> <u>E</u> <u>Q</u> <u>Y</u> <u>N</u> <u>S</u> <u>T</u> <u>Y</u> <u>R</u> <u>V</u> <u>V</u> <u>S</u> <u>V</u> <u>L</u> <u>T</u> <u>V</u> <u>L</u> <u>H</u> <u>Q</u> <u>D</u> <u>W</u> <u>L</u> <u>N</u> <u>G</u> <u>K</u> <u>E</u> <u>Y</u> <u>K</u> <u>C</u> <u>K</u> <u>V</u> <u>S</u> <u>N</u> <u>K</u> <u>A</u> <u>L</u> <u>P</u> <u>A</u> <u>P</u> <u>I</u> <u>E</u> <u>K</u> <u>T</u> <u>I</u> <u>S</u> <u>K</u> <u>A</u> <u>G</u> <u>Q</u> <u>P</u> <u>R</u> <u>E</u> <u>P</u> <u>Q</u> <u>V</u> <u>Y</u> <u>T</u> <u>L</u> <u>P</u> <u>S</u> <u>R</u> <u>D</u> <u>E</u> <u>L</u> <u>T</u> <u>K</u> <u>N</u> <u>Q</u> <u>V</u> <u>S</u> <u>L</u> <u>T</u> <u>C</u> <u>L</u> <u>V</u> <u>K</u> <u>G</u> <u>F</u> <u>Y</u> <u>P</u> <u>S</u> <u>D</u> <u>I</u> <u>A</u> <u>V</u> <u>E</u> <u>S</u> <u>N</u> <u>G</u> <u>Q</u> <u>P</u> <u>E</u> <u>N</u> <u>N</u> <u>Y</u> <u>K</u> <u>T</u> <u>T</u> <u>P</u> <u>P</u> <u>V</u> <u>L</u> <u>D</u> <u>S</u> <u>D</u> <u>G</u> <u>S</u> <u>F</u> <u>F</u> <u>L</u> <u>Y</u> <u>S</u> <u>K</u> <u>L</u> <u>T</u> <u>V</u> <u>D</u> <u>K</u> <u>S</u> <u>R</u> <u>W</u> <u>Q</u> <u>Q</u> <u>G</u> <u>N</u> <u>V</u> <u>F</u> <u>S</u> <u>C</u> <u>S</u> <u>V</u> <u>M</u> <u>H</u> <u>E</u> <u>A</u> <u>L</u> <u>H</u> <u>N</u> <u>H</u> <u>Y</u> <u>T</u> <u>Q</u> <u>K</u> <u>S</u> <u>L</u> <u>S</u> <u>L</u> <u>S</u> <u>P</u> <u>G</u> <u>K</u> <u>R</u> <u>G</u> <u>R</u> <u>K</u> <u>L</u> <u>L</u> <u>Y</u> <u>I</u> <u>F</u> <u>K</u> <u>Q</u> <u>P</u> <u>F</u> <u>M</u> <u>R</u> <u>P</u> <u>V</u> <u>Q</u> <u>T</u> <u>T</u> <u>Q</u> <u>E</u> <u>E</u> <u>D</u> <u>G</u> <u>C</u> <u>S</u> <u>C</u> <u>R</u> <u>F</u> <u>E</u> <u>E</u> <u>E</u> <u>E</u> <u>G</u> <u>G</u> <u>C</u> <u>E</u> <u>L</u> <u>R</u> <u>V</u> <u>K</u> <u>F</u> <u>S</u> <u>R</u> <u>S</u> <u>A</u> <u>D</u> <u>A</u> <u>P</u> <u>A</u> <u>Y</u> <u>Q</u> <u>Q</u> <u>G</u> <u>N</u> <u>Q</u> <u>L</u> <u>Y</u> <u>N</u> <u>E</u> <u>L</u> <u>N</u> <u>L</u> <u>G</u> <u>R</u> <u>R</u> <u>E</u> <u>E</u> <u>D</u> <u>V</u> <u>L</u> <u>D</u> <u>K</u> <u>R</u> <u>R</u> <u>G</u> <u>R</u> <u>D</u> <u>P</u> <u>E</u> <u>M</u> <u>G</u> <u>G</u> <u>K</u> <u>P</u> <u>R</u> <u>R</u> <u>K</u> <u>N</u> <u>P</u> <u>Q</u> <u>E</u> <u>G</u> <u>L</u> <u>Y</u> <u>N</u> <u>E</u> <u>L</u> <u>Q</u> <u>K</u> <u>D</u> <u>K</u> <u>M</u> <u>A</u> <u>E</u> <u>A</u> <u>Y</u> <u>S</u> <u>E</u> <u>I</u> <u>G</u> <u>M</u> <u>K</u> <u>G</u> <u>E</u> <u>R</u> <u>R</u> <u>R</u> <u>G</u> <u>K</u> <u>G</u> <u>H</u> <u>D</u> <u>G</u> <u>L</u> <u>Y</u> <u>Q</u> <u>G</u> <u>L</u> <u>S</u> <u>T</u> <u>A</u> <u>T</u> <u>K</u> <u>D</u> <u>T</u> <u>Y</u> <u>D</u> <u>A</u> <u>L</u> <u>H</u> <u>M</u> <u>Q</u> <u>A</u> <u>L</u> <u>P</u> <u>P</u> <u>R</u>
LucX1- V1 CAR	57	<u>MALP</u> <u>VT</u> <u>ALL</u> <u>PL</u> <u>ALL</u> <u>HA</u> <u>ARP</u> <u>QV</u> <u>Q</u> <u>L</u> <u>Q</u> <u>S</u> <u>G</u> <u>P</u> <u>E</u> <u>L</u> <u>V</u> <u>K</u> <u>P</u> <u>G</u> <u>A</u> <u>S</u> <u>V</u> <u>K</u> <u>I</u> <u>S</u> <u>C</u> <u>K</u> <u>A</u> <u>S</u> <u>G</u> <u>Y</u> <u>A</u> <u>F</u> <u>S</u> <u>S</u> <u>S</u> <u>W</u> <u>M</u> <u>N</u> <u>W</u> <u>V</u> <u>K</u> <u>O</u> <u>R</u> <u>P</u> <u>G</u> <u>Q</u> <u>G</u> <u>LE</u> <u>W</u> <u>I</u> <u>G</u> <u>R</u> <u>I</u> <u>P</u> <u>G</u> <u>D</u> <u>G</u> <u>D</u> <u>T</u> <u>K</u> <u>Y</u> <u>N</u> <u>G</u> <u>K</u> <u>F</u> <u>G</u> <u>K</u> <u>A</u> <u>T</u> <u>L</u> <u>T</u> <u>A</u> <u>D</u> <u>K</u> <u>S</u> <u>S</u> <u>T</u> <u>A</u> <u>Y</u> <u>M</u> <u>Q</u> <u>L</u> <u>S</u> <u>S</u> <u>L</u> <u>T</u> <u>S</u> <u>V</u> <u>D</u> <u>S</u> <u>A</u> <u>V</u> <u>Y</u> <u>F</u> <u>C</u> <u>A</u> <u>R</u> <u>S</u> <u>T</u> <u>M</u> <u>I</u> <u>A</u> <u>T</u> <u>G</u> <u>A</u> <u>M</u> <u>D</u> <u>Y</u> <u>W</u> <u>GQGT</u> <u>SV</u> <u>TV</u> <u>S</u> <u>S</u> <u>G</u> <u>G</u> <u>G</u> <u>G</u> <u>SGGGG</u> <u>SGGGG</u> <u>SGGGG</u> <u>S</u> <u>E</u> <u>T</u> <u>T</u> <u>V</u> <u>T</u> <u>Q</u> <u>S</u> <u>P</u> <u>A</u> <u>S</u> <u>L</u> <u>S</u> <u>M</u> <u>A</u> <u>I</u> <u>G</u> <u>E</u> <u>K</u> <u>V</u> <u>T</u> <u>I</u> <u>R</u> <u>C</u> <u>I</u> <u>T</u> <u>S</u> <u>T</u> <u>D</u> <u>I</u> <u>D</u> <u>D</u> <u>D</u> <u>M</u> <u>N</u> <u>W</u> <u>Y</u> <u>Q</u> <u>Q</u> <u>K</u> <u>P</u> <u>GE</u> <u>PP</u> <u>K</u> <u>L</u> <u>I</u> <u>S</u> <u>E</u> <u>G</u> <u>N</u> <u>T</u> <u>L</u> <u>R</u> <u>P</u> <u>G</u> <u>V</u> <u>P</u> <u>S</u> <u>R</u> <u>F</u> <u>S</u> <u>S</u> <u>S</u> <u>G</u> <u>Y</u> <u>G</u> <u>T</u> <u>D</u> <u>F</u> <u>V</u> <u>T</u> <u>I</u> <u>E</u> <u>N</u> <u>M</u> <u>L</u> <u>S</u> <u>E</u> <u>D</u> <u>V</u> <u>A</u> <u>D</u> <u>Y</u> <u>C</u> <u>L</u> <u>O</u> <u>S</u> <u>D</u> <u>N</u> <u>L</u> <u>P</u> <u>L</u> <u>T</u> <u>F</u> <u>G</u> <u>G</u> <u>G</u> <u>T</u> <u>K</u> <u>L</u> <u>E</u> <u>I</u> <u>K</u> <u>L</u> <u>A</u> <u>V</u> <u>S</u> <u>T</u> <u>IS</u> <u>S</u> <u>F</u> <u>P</u> <u>P</u> <u>G</u> <u>Y</u> <u>Q</u> <u>K</u> <u>R</u> <u>G</u> <u>R</u> <u>K</u> <u>L</u> <u>L</u> <u>Y</u> <u>I</u> <u>F</u> <u>K</u> <u>Q</u> <u>P</u> <u>F</u> <u>M</u> <u>R</u> <u>P</u> <u>V</u> <u>Q</u> <u>T</u> <u>T</u> <u>Q</u> <u>E</u> <u>E</u> <u>D</u> <u>G</u> <u>C</u> <u>S</u> <u>C</u> <u>R</u> <u>F</u> <u>E</u> <u>E</u> <u>E</u> <u>E</u> <u>G</u> <u>G</u> <u>C</u> <u>E</u> <u>L</u> <u>R</u> <u>V</u> <u>K</u> <u>F</u> <u>S</u> <u>R</u> <u>S</u> <u>A</u> <u>D</u> <u>A</u> <u>Y</u> <u>Q</u> <u>Q</u> <u>G</u> <u>N</u> <u>Q</u> <u>L</u> <u>Y</u> <u>N</u> <u>E</u> <u>L</u> <u>N</u> <u>L</u> <u>G</u> <u>R</u> <u>R</u> <u>E</u> <u>E</u> <u>D</u> <u>V</u> <u>L</u> <u>D</u> <u>K</u> <u>R</u> <u>R</u> <u>G</u> <u>R</u> <u>D</u> <u>P</u> <u>E</u> <u>M</u> <u>G</u> <u>G</u> <u>K</u> <u>P</u> <u>R</u> <u>R</u> <u>K</u> <u>N</u> <u>P</u> <u>Q</u> <u>E</u> <u>G</u> <u>L</u> <u>Y</u> <u>N</u> <u>E</u> <u>L</u> <u>Q</u> <u>K</u> <u>D</u> <u>K</u> <u>M</u> <u>A</u> <u>E</u> <u>A</u> <u>Y</u> <u>S</u> <u>E</u> <u>I</u> <u>G</u> <u>M</u> <u>K</u> <u>G</u> <u>E</u> <u>R</u> <u>R</u> <u>R</u> <u>G</u> <u>K</u> <u>G</u> <u>H</u> <u>D</u> <u>G</u> <u>L</u> <u>Y</u> <u>Q</u> <u>G</u> <u>L</u> <u>S</u> <u>T</u> <u>A</u> <u>T</u> <u>K</u> <u>D</u> <u>T</u> <u>Y</u> <u>D</u> <u>A</u> <u>L</u> <u>H</u> <u>M</u> <u>Q</u> <u>A</u> <u>L</u> <u>P</u> <u>P</u> <u>R</u>
LucX1- V2 CAR	58	<u>MALP</u> <u>VT</u> <u>ALL</u> <u>PL</u> <u>ALL</u> <u>HA</u> <u>ARP</u> <u>QV</u> <u>Q</u> <u>L</u> <u>Q</u> <u>S</u> <u>G</u> <u>A</u> <u>E</u> <u>L</u> <u>A</u> <u>R</u> <u>P</u> <u>G</u> <u>A</u> <u>S</u> <u>V</u> <u>K</u> <u>L</u> <u>S</u> <u>C</u> <u>K</u> <u>A</u> <u>S</u> <u>G</u> <u>Y</u> <u>T</u> <u>F</u> <u>T</u> <u>S</u> <u>Y</u> <u>W</u> <u>M</u> <u>Q</u> <u>W</u> <u>V</u> <u>K</u> <u>O</u> <u>R</u> <u>P</u> <u>G</u> <u>Q</u> <u>G</u> <u>LE</u> <u>W</u> <u>I</u> <u>G</u> <u>A</u> <u>I</u> <u>P</u> <u>G</u> <u>D</u> <u>G</u> <u>D</u> <u>T</u> <u>R</u> <u>Y</u> <u>T</u> <u>Q</u> <u>K</u> <u>F</u> <u>G</u> <u>K</u> <u>A</u> <u>T</u> <u>L</u> <u>T</u> <u>A</u> <u>D</u> <u>K</u> <u>S</u> <u>S</u> <u>T</u> <u>A</u> <u>Y</u> <u>M</u> <u>Q</u> <u>L</u> <u>S</u> <u>S</u> <u>L</u> <u>A</u> <u>S</u> <u>E</u> <u>D</u> <u>S</u> <u>A</u> <u>V</u> <u>Y</u> <u>C</u> <u>A</u> <u>R</u> <u>G</u> <u>K</u> <u>V</u> <u>Y</u> <u>G</u> <u>S</u> <u>N</u> <u>P</u> <u>F</u> <u>A</u> <u>Y</u> <u>W</u> <u>GQGT</u> <u>LV</u> <u>TV</u> <u>SAGGGG</u> <u>SGGGG</u> <u>SGGGG</u> <u>SDIQ</u> <u>MTQ</u> <u>SSSY</u> <u>LSV</u> <u>SLG</u> <u>GRV</u> <u>TIT</u> <u>CKAS</u> <u>DHIN</u> <u>NW</u> <u>LAWY</u> <u>QQK</u> <u>PG</u> <u>NAP</u> <u>RL</u> <u>IS</u> <u>GAT</u> <u>S</u> <u>LET</u> <u>GV</u> <u>PS</u> <u>RF</u> <u>SG</u> <u>SG</u> <u>GK</u> <u>DY</u> <u>LS</u> <u>IT</u> <u>SL</u> <u>Q</u> <u>T</u> <u>ED</u> <u>VAT</u> <u>Y</u> <u>Y</u> <u>CQ</u> <u>Q</u> <u>Y</u> <u>W</u> <u>S</u> <u>T</u> <u>P</u> <u>W</u> <u>T</u> <u>F</u> <u>G</u> <u>G</u> <u>G</u> <u>T</u> <u>K</u> <u>L</u> <u>E</u> <u>I</u> <u>K</u> <u>TT</u> <u>T</u> <u>P</u> <u>A</u> <u>P</u> <u>R</u> <u>P</u> <u>T</u> <u>P</u> <u>A</u> <u>P</u> <u>T</u> <u>I</u> <u>A</u> <u>S</u> <u>Q</u> <u>P</u> <u>L</u> <u>S</u> <u>R</u> <u>P</u> <u>E</u> <u>A</u> <u>C</u> <u>R</u> <u>P</u> <u>A</u> <u>A</u> <u>G</u> <u>G</u> <u>A</u> <u>V</u> <u>H</u> <u>T</u> <u>R</u> <u>G</u> <u>L</u> <u>D</u> <u>F</u> <u>A</u> <u>C</u> <u>D</u> <u>I</u> <u>Y</u> <u>I</u> <u>W</u> <u>A</u> <u>P</u> <u>L</u> <u>A</u> <u>G</u> <u>T</u> <u>C</u> <u>G</u> <u>V</u> <u>L</u> <u>L</u> <u>S</u> <u>L</u> <u>V</u> <u>I</u> <u>T</u> <u>L</u> <u>Y</u> <u>C</u> <u>K</u> <u>R</u> <u>G</u> <u>R</u> <u>K</u> <u>L</u> <u>L</u> <u>Y</u> <u>I</u> <u>F</u> <u>K</u> <u>Q</u> <u>P</u> <u>F</u> <u>M</u> <u>R</u> <u>P</u> <u>V</u> <u>Q</u> <u>T</u> <u>T</u> <u>Q</u> <u>E</u> <u>E</u> <u>D</u> <u>G</u> <u>C</u> <u>S</u> <u>C</u> <u>R</u> <u>F</u> <u>E</u> <u>E</u> <u>E</u> <u>E</u> <u>G</u> <u>G</u> <u>C</u> <u>E</u> <u>L</u> <u>R</u> <u>V</u> <u>K</u> <u>F</u> <u>S</u> <u>R</u> <u>S</u> <u>A</u> <u>D</u> <u>A</u> <u>P</u> <u>A</u> <u>Y</u> <u>Q</u> <u>Q</u> <u>G</u> <u>N</u> <u>Q</u> <u>L</u> <u>Y</u> <u>N</u> <u>E</u> <u>L</u> <u>N</u> <u>L</u> <u>G</u> <u>R</u> <u>R</u> <u>E</u> <u>E</u> <u>D</u> <u>V</u> <u>L</u> <u>D</u> <u>K</u> <u>R</u> <u>R</u> <u>G</u> <u>R</u> <u>D</u> <u>P</u> <u>E</u> <u>M</u> <u>G</u> <u>G</u> <u>K</u> <u>P</u> <u>R</u> <u>R</u> <u>K</u> <u>N</u> <u>P</u> <u>Q</u> <u>E</u> <u>G</u> <u>L</u> <u>Y</u> <u>N</u> <u>E</u> <u>L</u> <u>Q</u> <u>K</u> <u>D</u> <u>K</u> <u>M</u> <u>A</u> <u>E</u> <u>A</u> <u>Y</u> <u>S</u> <u>E</u> <u>I</u> <u>G</u> <u>M</u> <u>K</u> <u>G</u> <u>E</u> <u>R</u> <u>R</u> <u>R</u> <u>G</u> <u>K</u> <u>G</u> <u>H</u> <u>D</u> <u>G</u> <u>L</u> <u>Y</u> <u>Q</u> <u>G</u> <u>L</u> <u>S</u> <u>T</u> <u>A</u> <u>T</u> <u>K</u> <u>D</u> <u>T</u> <u>Y</u> <u>D</u> <u>A</u> <u>L</u> <u>H</u> <u>M</u> <u>Q</u> <u>A</u> <u>L</u> <u>P</u> <u>P</u> <u>R</u>
LucX1- V3 CAR	59	<u>MALP</u> <u>VT</u> <u>ALL</u> <u>PL</u> <u>ALL</u> <u>HA</u> <u>ARP</u> <u>QV</u> <u>Q</u> <u>L</u> <u>Q</u> <u>S</u> <u>G</u> <u>P</u> <u>E</u> <u>L</u> <u>V</u> <u>K</u> <u>P</u> <u>G</u> <u>A</u> <u>S</u> <u>V</u> <u>K</u> <u>I</u> <u>S</u> <u>C</u> <u>K</u> <u>A</u> <u>S</u> <u>G</u> <u>Y</u> <u>A</u> <u>F</u> <u>S</u> <u>S</u> <u>S</u> <u>W</u> <u>M</u> <u>N</u> <u>W</u> <u>V</u> <u>K</u> <u>O</u> <u>R</u> <u>P</u> <u>G</u> <u>Q</u> <u>G</u> <u>LE</u> <u>W</u> <u>I</u> <u>G</u> <u>R</u> <u>I</u> <u>P</u> <u>G</u> <u>D</u> <u>G</u> <u>D</u> <u>T</u> <u>K</u> <u>Y</u> <u>N</u> <u>G</u> <u>K</u> <u>F</u> <u>G</u> <u>K</u> <u>A</u> <u>T</u> <u>L</u> <u>T</u> <u>A</u> <u>D</u> <u>K</u> <u>S</u> <u>S</u> <u>T</u> <u>A</u> <u>Y</u> <u>M</u> <u>Q</u> <u>L</u> <u>S</u> <u>S</u> <u>L</u> <u>T</u> <u>S</u> <u>V</u> <u>D</u> <u>S</u> <u>A</u> <u>V</u> <u>Y</u> <u>F</u> <u>C</u> <u>A</u> <u>R</u> <u>S</u> <u>T</u> <u>M</u> <u>I</u> <u>A</u> <u>T</u> <u>G</u> <u>A</u> <u>M</u> <u>D</u> <u>Y</u> <u>W</u> <u>GQGT</u> <u>SV</u> <u>TV</u> <u>S</u> <u>S</u> <u>G</u> <u>G</u> <u>G</u> <u>G</u> <u>SGGGG</u> <u>SGGGG</u> <u>SGGGG</u> <u>S</u> <u>E</u> <u>T</u> <u>T</u> <u>V</u> <u>T</u> <u>Q</u> <u>S</u> <u>P</u> <u>A</u> <u>S</u> <u>L</u> <u>S</u> <u>M</u> <u>A</u> <u>I</u> <u>G</u> <u>E</u> <u>K</u> <u>V</u> <u>T</u> <u>I</u> <u>R</u> <u>C</u> <u>I</u> <u>T</u> <u>S</u> <u>T</u> <u>D</u> <u>I</u> <u>D</u> <u>D</u> <u>D</u> <u>M</u> <u>N</u> <u>W</u> <u>Y</u> <u>Q</u> <u>Q</u> <u>K</u> <u>P</u> <u>GE</u> <u>PP</u> <u>K</u> <u>L</u> <u>I</u> <u>S</u> <u>E</u> <u>G</u> <u>N</u> <u>T</u> <u>L</u> <u>R</u> <u>P</u> <u>G</u> <u>V</u> <u>P</u> <u>S</u> <u>R</u> <u>F</u> <u>S</u> <u>S</u> <u>S</u> <u>G</u> <u>Y</u> <u>G</u> <u>T</u> <u>D</u> <u>F</u> <u>V</u> <u>T</u> <u>I</u> <u>E</u> <u>N</u> <u>M</u> <u>L</u> <u>S</u> <u>E</u> <u>D</u> <u>V</u> <u>A</u> <u>D</u> <u>Y</u> <u>C</u> <u>L</u> <u>O</u> <u>S</u> <u>D</u> <u>N</u> <u>L</u> <u>P</u> <u>L</u> <u>T</u> <u>F</u> <u>G</u> <u>G</u> <u>G</u> <u>T</u> <u>K</u> <u>L</u> <u>E</u> <u>I</u> <u>K</u> <u>E</u> <u>P</u> <u>K</u> <u>S</u> <u>P</u> <u>D</u> <u>K</u> <u>T</u> <u>H</u> <u>T</u> <u>C</u> <u>P</u> <u>P</u> <u>C</u> <u>A</u> <u>P</u> <u>P</u> <u>V</u> <u>A</u> <u>G</u> <u>P</u> <u>S</u> <u>V</u> <u>L</u> <u>F</u> <u>P</u> <u>P</u> <u>K</u> <u>P</u> <u>K</u> <u>D</u> <u>T</u> <u>L</u> <u>M</u> <u>I</u> <u>A</u> <u>R</u> <u>T</u> <u>P</u> <u>E</u> <u>V</u> <u>T</u> <u>C</u> <u>V</u> <u>V</u> <u>D</u> <u>V</u> <u>S</u> <u>H</u> <u>E</u> <u>D</u> <u>P</u> <u>E</u> <u>V</u> <u>K</u> <u>F</u> <u>N</u> <u>W</u> <u>Y</u> <u>V</u> <u>D</u> <u>G</u> <u>V</u> <u>E</u> <u>V</u> <u>H</u> <u>N</u> <u>A</u> <u>K</u> <u>T</u> <u>K</u> <u>P</u> <u>R</u> <u>E</u> <u>E</u> <u>Q</u> <u>Y</u> <u>N</u> <u>S</u> <u>T</u> <u>Y</u> <u>R</u> <u>V</u> <u>V</u> <u>S</u> <u>V</u> <u>L</u> <u>T</u> <u>V</u> <u>L</u> <u>H</u> <u>Q</u> <u>D</u> <u>W</u> <u>L</u> <u>N</u> <u>G</u> <u>K</u> <u>E</u> <u>Y</u> <u>K</u> <u>C</u> <u>K</u> <u>V</u> <u>S</u> <u>N</u> <u>K</u> <u>A</u> <u>L</u> <u>P</u> <u>A</u> <u>P</u> <u>I</u> <u>E</u> <u>K</u> <u>T</u> <u>I</u> <u>S</u> <u>K</u> <u>A</u> <u>G</u> <u>Q</u> <u>P</u> <u>R</u> <u>E</u> <u>P</u> <u>Q</u> <u>V</u> <u>Y</u> <u>T</u> <u>L</u> <u>P</u> <u>P</u> <u>S</u> <u>R</u> <u>D</u> <u>E</u> <u>L</u> <u>T</u> <u>K</u> <u>N</u>

V2 CAR		<u>LEWIGRIYPGDGDTKYNGKFKGKATLTADKSSSTAYMQLSSLTSVDSAVYFCARSTMIATGAMDYW</u> <u>GQGTSTVTVSSGGGGSGGGGSGGGGSDIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQ</u> <u>KPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPPYTFGGGKLEI</u> <u>KTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYC</u> KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNEL NLGRREEYDVLDKRRGRDPGEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHG LYQGLSTATKDTYDALHMQALPPR
LucX2- V3 CAR	62	MALPVTALLPLALLHAARPQVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKQRPQGQ <u>LEWIGRIYPGDGDTKYNGKFKGKATLTADKSSSTAYMQLSSLTSVDSAVYFCARSTMIATGAMDYW</u> <u>GQGTSTVTVSSGGGGSGGGGSGGGGSDIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQ</u> <u>KPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPPYTFGGGKLEI</u> <u>KEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWYVDG</u> <u>VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV</u> <u>YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSR</u> <u>WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE</u> EEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPGEMGGKPRRKNPQEG LYNELQKDKMAEAYSEIGMKGERRRGKGHGGLYQGLSTATKDTYDALHMQALPPR

Strategy for CAR CS1+ and KO CS1 engineering

CS1 is expressed at high levels in plasmacytoid cells from patients with Multiple Myeloma, making this an interesting target for CAR development. T-cells, especially the CD8 subset, express low levels of CS1, which is a drawback for T-cell CAR development, since they could be killed when expressing an anti-CS1 CAR.

In this example we assessed the activity of the Luc90-v2 CAR (sequence shown in Table 20) in human T-cells that were either mock transfected, or transfected with a TALEN targeting the CS1 (SLAMF7) gene, to see if the CAR activity was enhanced when the CS1 gene was disrupted in CAR+ T-cells. The course of the experiment is shown in the Figure 12.

T-cells were purified from buffy-coat samples and activated using CD3/CD28-coated beads. Cells were co-transfected 72h after activation with 10 µg of mRNA encoding the T01_left TAL and 10 µg of the mRNA encoding the T01_right TAL. Sequences of the TALs are shown in the following Table 21 and the plasmid constructs (T01, T02 and T03) with the TAL repeats shown in Figure 13.

Figure 14 shows the target location for the TALs T01, T02 and T03 within the CS1 (SLAMF7) gene: T01 and T02 target the exon 1 (Figure 14A), whereas T03 targets the exon 2 (Figure 14B).

Table 21: Sequences of the CS1 target and TALENs for its inactivation

Name	TALEN L/R	SEQ ID #	Nucleic acid sequence
Target of T01		63	TGACTTCCAGAGAGCAATATGGCTGGTTCCTCCCAACATGCCTC ACCCTCA
	L	64	TGACTTCCAGAGAGCAA
	R	65	AACATGCCTCACCCTCA
Target of T02		66	TTCCAGAGAGCAATATGGCTGGTTCCTCCCAACATGCCTCACCC TCATCTA
	L	67	TTCCAGAGAGCAATATG
	R	68	TGCCTCACCTCATCTA
Target of T03		69	TTGACTCTATTGTCTGGACCTTCAACACAACCCCTCTTGTCAC CATACA
	L	70	TTGACTCTATTGTCTGG
	R	71	CCTCTTGTCACCATACA

3 days after TALEn transfection, cells were transduced with a recombinant lentiviral vector driving expression of the L90-v2 CAR off an EF1a promoter. The lentiviral vector is built in a way that CAR expression is coupled with BFP expression (Blue Fluorescent Protein) through a ribosomal skip peptide. The L90-v2 CAR is constituted by an extracellular binding domain recognizing the CS1 target (scFv L90) followed by hinge and transmembrane regions derived from the hCD8 α protein. The intracellular portion of the molecule contains a 41BB-derived costimulatory domain, followed by the CD3 γ signaling domain (sequences displayed in previous Table 18-19-20 for individual components, scFv and CAR sequences respectively).

Transduction efficiency was assessed 6 days after transduction by flow cytometry, by following BFP expression. Cells were also stained with anti-CD8 and anti-CS1 antibodies.

Results

CAR CS1+ expression

The results from Figure 16 show that the transduction efficiencies are higher in mock transfected cells than in cells that have been transfected with TALEn targeting the CS1 gene. This is probably due to specific cell killing of non-transduced CS1-expressing T-cells, while this population is not affected when the cells no longer express CS1 as a consequence of TALEN-driven gene disruption.

No significant differences in CS1 levels are observed at this timepoint between TALEN or mock transfected cells (negative control- transfection without plasmid), since CS1 levels decrease over time after initial activation of T-cells. On the other hand, a significant decrease in the % of CD8+ cells is observed in mock transfected CAR expressing cells compared to TALEN transfected CAR+ cells, indicating that a high proportion of CD8+ cells has been eliminated by the CAR+ T-cells.

Cytotoxic activity assessment

The cytotoxic activity of these cells was evaluated 8 days after CAR transduction, by co-culturing the same amount of T-cells either with a cell line expressing CS1 (L363 cells) or a negative control cell line lacking expression of CS1 (MOLM13). The viability of the target cell lines was measured by flow cytometry 4h after starting cell co-cultures. The results shown in Figure 15A show reduced cell viability of CS1(+) cells when they were co-cultured with CAR+ T-cells, while no impact on CS1(-) cell viability was observed. The specific cell lysis was calculated using the flow cytometry data, and it was 2-times higher when T-cells have been transfected with TALEn targeting the CS1 gene prior to CAR transduction (Figure 15B). It should be considered that the impact might be even higher, since the amount of CAR+ T-cells present in the co-cultures is higher when the cells were mock transfected (see flow cytometry data from Figure 16). The results from the experiment are the following:

- for the Mock/NTD sample, the % of BFP+ cells is 0.1% and the amount of CD8+ cells is 53.9%;
- for the TALEn/NTD sample, the % of BFP+ cells is 0.2% and the amount of CD8+ cells is 49.5%;
- for the Mock /L90-2 sample, the % of BFP+ cells is 94% and the amount of CD8+ cells is 1.8%;

- for the TALEn /L90-2 sample, the % of BFP+ cells is 61% and the amount of CD8+ cells is 8.3%.

Transduction efficiencies are higher in mock transfected cells than in cells that have been transfected with TALEn targeting the CS1 gene (NTD: not transduced).

5

Reactivation after transduction

In order to confirm that the CS1 gene has been disrupted in TALEn transfected T-cells, the different samples were reactivated with CD3/CD28 beads at D11 after transduction. 72h after reactivation cells were stained with anti-CD8 and anti-CS1 antibodies and expression analyzed by flow cytometry.

10

Figure 17 shows the transduction efficiencies and CD8/CS1 expression levels in each sample. As shown in the lower panel, an increase in CS1 levels upon re-activation is observed in mock transfected cells, while a low amount of cells are able to express CS1 in the TALEn transfected populations.

15

The results from the experiment are the following:

- for the Mock/NTD sample, the % of BFP+ cells is 0.01%, CS1 is expressed in 65.2% of cells, and the amount of CD8+ cells is 80.7%;
- for the TALEn/NTD sample, the % of BFP+ cells is 0.2%, the CS1 is expressed in 9.7% of cells and the amount of CD8+ cells is 78.8%;
- for the Mock /L90-2 sample, the % of BFP+ cells is 94%, the CS1 is expressed in 37.5% of cells and the amount of CD8+ cells is 16%.
- for the TALEn /L90-2 sample, the BFP intensity is 61%, the CS1 expression is 8.5% and the CD8 expression is 68.5%.

20

An increase in CS1 levels upon re-activation is observed in mock transfected cells, while a low amount of cells are able to express CS1 in the TALEn transfected populations.

25

Altogether, these results indicate that the CS1 gene is disrupted in TALEn transfected T-cells, and that this enhances the cytotoxic activity of anti-CS1 CAR+ cells, mainly by preserving the cytotoxic CD8+ T-cells.

30

EXAMPLE 3: CD70 TARGET

Presentation of CD70 target

The CD70 is a cytokine that binds to CD27 and is part of the TNF family (Goodwin R.G. et al, 1993, Cell 73:447-456). This protein has a role in adaptive T cell responses, induces the proliferation of costimulated T-cells and enhances the generation of cytolytic T-cells. Its accession number is P32970 (Uniprot). Some studies such as in Schürch, C. *et al.* (J. Clin. Invest., 2012; doi:10.1172/JCI45977) suggest that blocking CD27-CD70 interactions could help treat chronic myelogenous leukemia (CML).

Strategy for CD70 KO

The same strategy for the KO of CD70 gene will be performed such as in Example 1 and Example 2. Heterodimeric TALE-nuclease targeting two 49-pb long sequences separated by a 15pb spacer within the CD70 gene and one TALE-nuclease targeting a 57-pb long sequence separated by a 23pb spacer were designed and produced. Each half target is recognized by repeats of the half TALE-nucleases listed in the following Table 22.

Table 22: Sequences of the CD70 target and TALENs for its inactivation

Name	TALEN L/R	SEQ ID #	Nucleic acid sequence
Target 1 TALEN 1		72	TGGTCTTTTCTTCCAGTgggacgtagctgagcTGCAGCTGAATCACACA
	L	73	TGGTCTTTTCTTCCAGT
	R	74	TGCAGCTGAATCACACA
Target 2 TALEN 2		75	TGGTGATCTGCCTCGTGgtgtgcatccagcgcTTCGCACAGGCTCAGCA
	L	76	TGGTGATCTGCCTCGTG
	R	77	TTCGCACAGGCTCAGCA
Target 3 TALEN 3		78	TGCGGGCTGCTTTGGTCccattggtcgcggttggtgatCTGCCTCGTGGTG TGCA
	L	79	TGCGGGCTGCTTTGGTC
	R	80	CTGCCTCGTGGTGTGCA

Strategy for the expression of anti-CD70 CAR

The same strategy for expressing a CAR anti-CD70 will be performed such as in Example 1 and in Example 2.

The same structures V1, V2 and V3 are designed such as in the Example 1-2 with the same components in terms of signal peptide, linker between the VH and VL chains, transmembrane domain, co-activation and transduction domains (general architectures shown in Figure 11A, and sequences for individual components shown in Table 18). Only the hinge differs between the 3 versions V1, V2 and V3, wherein respectively the short FcE γ hinge, the medium hinge CD8 α hinge and the long IgG1 hinge are used.

In Table 23 are presented VH and VL chain of scFv anti-CD70. SEQ ID NO:81-82, 85-86, 89-90 and SEQ ID NO:83-84,87-88,91-92 correspond to respectively the VH chain and the VL chain of the scFv Ab4, Ab8 from AMGEN and 1F6 from Seattle Genetics.

In Table 24 are presented the anti-CD70 CARs with the above scFv; these CARs being based on the versions V1, V2 and V3 according to Figure 11A, wherein respectively a short FcE γ hinge, a medium hinge CD8 and a long IgG1 hinge are used.

Table 23: Polynucleotide and nucleic acid sequences of VH and VL chains for the scFv anti-CD70 Ab4, Ab8 and 1F6 antibodies

Name	VH or VL chain	SEQ ID #	Polypeptide and nucleic acid sequence
Ab4	VH	81	QVQLVESGGGVVQPGRSRLRLSCAASGFTFSNYGIHWVRQAPGKGLE WVAVIWDGNSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV YYCARDGGYSGYDSGFDYWGGQGLTVTVSS
	VH	82	cagggtgcagctggtggagctctgggggaggcgtggtccagcctgggagggtccctgagactctctgt gcagcgtctggattcaccttcagtaactatggcatacactgggtccgccaggctccaggcaaggg gctggagtggtggcagttatatggtatgatggaagtaataaatactatgcagactccgtgaagg gccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgaga gccgaggacacggctgtgtattactgtgcgagagatggaggatagatggctacgattcggggttt gactactggggccagggaaccctggtcaccgtctcctcagctagaccaaggggccatccgtcttc ccctggcaccctctccaagagcacctctgggggacacggccctgggctgctcgttgcaagga ctacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacacctt cccggctgtctacagtcctcaggactctactcctcagcagcgtggtgaccgtgcccctccagcag cttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaaacaccaaggtggacaag aaagttgagcccaaatctgtgacaaaactcacacatgccaccgtgcccagcacctgaactcct ggggggaccgtcagttctctctcccccaaaacccaaggacacctcatgatctccggacccc tgagggtcacatgcgtggtggtggacgtgagccacgaagacctgagggtcaagttcaactggtacg tgacggcgtggagggtgcataatgccaagacaaagccgaggaggagcagtagacaacagcacgt accgtgtggtcagcgtcctcaccgtcctgcaccaggactgggtgaatggcaaggagtacaagtgc aaggtctccaacaaagccctccagccccatcgagaaaacatctccaagccaaagggcagc cccgagaaccacaggtgtacacctgcccccatcccgaggagagatgaccaagaaccagggtcag cctgacctgctggtcaaaggcttctatccagcgacatcgccgtggagtgggagagcaatgggc agccggagaacaactacaagaccagcctcccgctgctggactccgacggctccttctctctata gcaagctcacgtggacaagagcaggtggcagcagggggaacgtcttctcatgtctccgtgatgc gaggctctgcacaaccactacacgcagaagagcctctcctgtctccgggtaaatga
	VL	83	DIVMTQSPSLPVTGPGEASISCRSSQSLNSNGYNYLDWYLQKPGQS PQFLIYLGSYRASGVPDRFSGSGSGTDFTLRISRVEAEDVGVYCIQTLQ TPFTFGPGTKVDIK
	VL	84	Gatattgtgatgactcagctctccactctccctgcccgtcaccctggagagcggcctccatctcct gcagggtcagtcagagcctcctgaatagtaatggatacaactatttggttggtacgtgcagaagc cagggcagctctccacagttcctgatctatttgggttcttatcgggcctccggggtcctgacaggttc agtggcagtgatcaggcacagattttactgagaatcagcagagtgagggtgaggtggttg ggtttattactgtatacaaaactctaaaaactccattcatttccggccctgggaccaaagtggatc aaacgtacgggtggctgaccatctgtcttcatcttccgcatctgatgagcagttgaaatctggaa ctgcctctgtgtgtcctgctgaataacttctatccagagaggccaaagtacagtggaaggtgg ataacgccctccaatcgggtaactccaggagagtgacacagagcaggacagcaaggacagcac ctacagcctcagcagcaccctgacgtgagcaagcagactacgagaaacacaaagtctacgcc tgcaagtcacccatcagggcctgagctcgccgtcacaaagagcttcaacaggggagagtgta gtcctca53ggactctactcctcagcagcgtggtgaccgtgcccctcagcagcttgggacccag acctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaagaaagttgagccca aatcttgtgacaaaactcacacatgccaccgtgcccagcacctgaactcctggggggaccgtca gtcttctcttcccccaaaacccaaggacacctcatgatctccggaccctgaggtcacatgc gtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgga ggtgcataatgccaagacaaagccgaggaggagcagtagacaacagcacgtaccgtgtggtcagc gtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaa agccctccagccccatcgagaaaacatctccaagccaaagggcagccccgagaaccacag

			gtgtacacctgcccccatccgggaggagatgaccaagaaccagggtcagcctgacctgcctggt caaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaac tacaagaccacgctcccgtgctgactccgacggctccttctctctatagcaagctcaccgtgg acaagagcaggtggcagcaggggaaacgtcttctcatgctccgtgatgcatgaggctctgcacaac cactacacgcagaagagcctctccctgtctccgggtaaa
Ab8	VH	85	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLE WVAVIWDGSDKYFADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAV YYCARDGIAGARYVYFDYWGGT LVTVSS
		86	cagggtgcagctggtggagtctggggaggcgtggtccagcctgggagggtccctgagactctctgt gcagcgtctggattcaccttcagtagctatggcatgcactgggtccgccaggctccaggcaaggg gctggagtgggtggcagttatatggtatgatggaagtataaatactttgcagactccgtgaaggg ccgattcaccatctccagagacaattccaagaacacgctgtatctgaaaataacagcctgagag ccgaggacacggctgtgtattactgtgcgagagatgggtagcaggagctcgtactactttg actactggggccagggaacccgtgtaccgtctcctcagtagcaccaagggccatccgtcttc ccctggcacctcctcaagagcacctctggggcacagcgccctgggtgctgctgtaaggac tacttccccgaaccggtgacgggtcgtggaactcaggcgccctgaccagcggtgcacaccttc cgggtgtctctacagctcctcaggactctactccct
	VL	87	DIQMTQSPSSLSASVGRVTITCRASQGISNYLAWFQQKPKAPKSLIY AASSLQGGVPSKFSGSGSGTDFTLTISLQPEDFATYYCQYINYPFTF GPGTTVDIK
		88	gacatccagatgaccagctccatcctccctgtctgcatctgtaggagacagagtcaccatcatt gtcgggagcagtcaggcattagcaattatttagcctggttcagcagaaaccagggaagccct aagtcctgatctatgtctgcatccagtttgaagggtgggtcccatcaaaagttcagcggtgga tctgggacagatttactctcaccatcagcagcctgcagcctgaagattttgcaacttattactgc aacaatattataattaccatttactttcgccctgggaccacagtggtatcaaacgtacggtgg ctgcacatctgtcttactcttccgccatctgatgagcagttgaaatctggaactgcctctgttg tgctgctgaataacttctatccagagaggccaaagtacagtggaagggtgataacgcctcca atcggtgaactccaggagagtggtcacagagcaggacagcaaggacagcacctacagcctcagc agcacctgacgctgagcaaaagcagactacgagaaacacaaagtctacgctggaagtcaccc atcagggcctgagctgcccgtcacaagagcttcaacaggggagagtgtag
1F6	VH	89	QIQLVQSGPEVKKPGETVKISKASGYFTNYGMNWVKQAPGKGLK WMGINTYTGEPTYADAFKGRFAFSLETSASTAYLQINNLK NEDTATYF CARDYGDYGM DYWGQTSVTVSS
		90	atggcttgggtgtggacctgtctattcctgatggcagctgccccaaagtgcccaagcacagatccag ttggtgcagctctggacctgaggtgaagaagcctggagagacagtcagatctcctgaaggcttc tgggtataccttcacaaactatggaatgaactgggtgaagcaggtccaggaaagggtttaaagt ggatgggctggataaacacctacactggagagccaacatatgctgatgccttcaaggacggttt gccttctcttggaaacctctgccagactgcctatttgcatatcaaacctcaaaaatgaggac acggctacatatcttctgtgcaagagactacggcgactatggtatggactactgggtcaaggaaac ctcagtcaccgtctcctca
	VL	91	DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSFMHWYQQKPGQPP KLLIYLASNLESVGP ARFSGSGSGTDFTLN IHPVEEEDAATYYCQHSREV PWTFGGG TKLEIKR
		92	atggagacagacacactcctgttatgggtactgtgctctgggttcagggtccactggtgacattg tgctgacacagctctcctgcttcttagctgtatctctggggcagagggccaccatctcatgcagggc cagcaaaagtgcagtacatctggctatagttttatgactggtatcaacagaaaccaggacagc caccctcctcctatctatctgtcatcaacctaagaatctgggtccctgccagggtcagtggtgag tgggtctgggacagacttcacctcaacatcctcctgtggaggaggaggtgctgcaacctatta ctgtcagcacagtagggaggttcgtggacgttcgggtggaggaccaagctggaaatcaaacgg

Table 24: Polypeptide sequences of anti-CD70 CARs based on the V1, V2 and V3 versions according to Figure 11A

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Name of CAR	SEQ ID NO:	Polypeptide sequence
Ab4-V1 CAR	93	MALPVTALLPLALLHAARPQVQLVESGGGVVQPGRSRLSCAASGFTFSNYGIHWVR QAPGKGLEWVAVIWDGSDNYKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVY YCARDGGYSGYDSGFDYWGGTLTVTVSSGGGGSGGGSGGGGSDIVMTQSPLSLPVT PGEPASISCRSSQSLNSNGYNYLDWYLQKPGQSPQFLIYLGSYRASGVPDRFSGSGS GTDFTLRISRVEAEDVGVYYCIQTLQTPFTFGPGTKVDIKGLAVSTISSFFPPGYQIYIWAPL AGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRS ADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR
Ab4-V2 CAR	94	MALPVTALLPLALLHAARPQVQLVESGGGVVQPGRSRLSCAASGFTFSNYGIHWVR QAPGKGLEWVAVIWDGSDNYKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVY YCARDGGYSGYDSGFDYWGGTLTVTVSSGGGGSGGGSGGGGSDIVMTQSPLSLPVT PGEPASISCRSSQSLNSNGYNYLDWYLQKPGQSPQFLIYLGSYRASGVPDRFSGSGS GTDFTLRISRVEAEDVGVYYCIQTLQTPFTFGPGTKVDIKTTTPAPRPPTAPTASQPLSL RPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRP VQTTQEEDGCSCRFEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATK DTYDALHMQALPPR
Ab4-V3 CAR	95	MALPVTALLPLALLHAARPQVQLVESGGGVVQPGRSRLSCAASGFTFSNYGIHWVR QAPGKGLEWVAVIWDGSDNYKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVY YCARDGGYSGYDSGFDYWGGTLTVTVSSGGGGSGGGSGGGGSDIVMTQSPLSLPVT PGEPASISCRSSQSLNSNGYNYLDWYLQKPGQSPQFLIYLGSYRASGVPDRFSGSGS GTDFTLRISRVEAEDVGVYYCIQTLQTPFTFGPGTKVDIKEPKSPDKTHTCPPCPAPPVAG PSVFLFPPKPKDTLMIAARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSV MHEALHNHYTQKSLSLSPGKIYIWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ TQEEDGCSCRFEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGR DPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYD ALHMQALPPR
Ab8-V1 CAR	96	MALPVTALLPLALLHAARPQVQLVESGGGVVQPGRSRLSCAASGFTFSYGMHWV RQAPGKGLEWVAVIWDGSDKYFADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV YYCARDGIAGARYVYFDYWGGTLTVTVSSGGGGSGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCRASQGISNYLAWFQQKPGKAPKSLIYAASSLQGGVPSKFSGSGSGTDF TLTISSLQPEDFATYYCQYYNYPFTFGPGTTVDIKGLAVSTISSFFPPGYQIYIWAPLAGTC GVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRSADAP AYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAY SEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR
Ab8-V2 CAR	97	MALPVTALLPLALLHAARPQVQLVESGGGVVQPGRSRLSCAASGFTFSYGMHWV RQAPGKGLEWVAVIWDGSDKYFADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV YYCARDGIAGARYVYFDYWGGTLTVTVSSGGGGSGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCRASQGISNYLAWFQQKPGKAPKSLIYAASSLQGGVPSKFSGSGSGTDF TLTISSLQPEDFATYYCQYYNYPFTFGPGTTVDIKTTTPAPRPPTAPTASQPLSLRPEAC RPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQ

		EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR
Ab8-V3 CAR	98	MALPVTALLPLALLHAARPQVQLVESGGGVVQPGRSRLSCAASGFTFSSYGMHWV RQAPGKGLEWVAVIWDGSDKYFADSVKGRFTISRDNKNTLYLQMNSLRAEDTAV YYCARDGIAGARYVYFDYWGGTTLVTVSSGGGGSGGGSGGGGSDIQTQSPSSLSA SVGDRVTITCRASQGISNYLAWFQQKPGKAPKSLIYAASSLQGGVPSKFSGSGSGTDF TLTISSLQPEDFATYYCQQYNYNPTFTGPGTTVDIKEPKSPDKTHTCPPCPAPPVAGPSVFL FPPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHE ALHNHYTQKSLSLSPGKIYIWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
1F6 V1 CAR	99	MALPVTALLPLALLHAARPQIQLVQSGPEVKKPGETVKISCKASGYTFTNYGMNWVK QAPGKGLKWMGINTYTGEPTYADAFKGRFAFSLETSASTAYLQINNKNEDTATYFC ARDYGDYGMMDYWGGTSTVTSSGGGGSGGGSGGGGSDIVLTQSPASLAVSLGQRA TISCRASKSVSTSGYSFMHWYQQKPGQPPKLLIYASNLESVGPAPARFSGSGSGTDFTL NIHPVEEEDAATYYCQHSREVPWTFGGGKLEIKRGLAVSTISSFFPPGYQIYIWAPLAGT CGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEEDGCSCRFPEEEEGGCELRVKFSRSADA PAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMALPPR
1F6 V2 CAR	100	MALPVTALLPLALLHAARPQIQLVQSGPEVKKPGETVKISCKASGYTFTNYGMNWVK QAPGKGLKWMGINTYTGEPTYADAFKGRFAFSLETSASTAYLQINNKNEDTATYFC ARDYGDYGMMDYWGGTSTVTSSGGGGSGGGSGGGGSDIVLTQSPASLAVSLGQRA TISCRASKSVSTSGYSFMHWYQQKPGQPPKLLIYASNLESVGPAPARFSGSGSGTDFTL NIHPVEEEDAATYYCQHSREVPWTFGGGKLEIKRTTTPAPRPPTAPTIASQPLSLRPEA CRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT QEEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRD PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDA LHMALPPR
1F6 V3 CAR	101	MALPVTALLPLALLHAARPQIQLVQSGPEVKKPGETVKISCKASGYTFTNYGMNWVK QAPGKGLKWMGINTYTGEPTYADAFKGRFAFSLETSASTAYLQINNKNEDTATYFC ARDYGDYGMMDYWGGTSTVTSSGGGGSGGGSGGGGSDIVLTQSPASLAVSLGQRA TISCRASKSVSTSGYSFMHWYQQKPGQPPKLLIYASNLESVGPAPARFSGSGSGTDFTL NIHPVEEEDAATYYCQHSREVPWTFGGGKLEIKREPSPDKTHTCPPCPAPPVAGPSVF LFPPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHE ALHNHYTQKSLSLSPGKIYIWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR

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Yam, P., M. Jensen, et al. (2006). "Ex vivo selection and expansion of cells based on expression of a mutated inosine monophosphate dehydrogenase 2 after HIV vector transduction: effects on lymphocytes, monocytes, and CD34+ stem cells." Mol Ther **14**(2): 236-44.

Zielske, S. P., J. S. Reese, et al. (2003). "In vivo selection of MGMT(P140K) lentivirus-transduced human NOD/SCID repopulating cells without pretransplant irradiation conditioning." J Clin Invest **112**(10): 1561-70.

CLAIMS:

- 1) A method of preparing T-cells for immunotherapy against pathological cells comprising the step of:
 - (a) Genetically inactivating a gene in a T-cell, which encodes an antigen marker, said antigen marker being present both on the surface of said T-cell and the pathological cell, resulting in the absence of said antigen marker on the surface of said T-cell;
 - (b) Expressing into said T-cell a transgene encoding a chimeric antigen receptor directed against said antigen marker present at the surface of said pathological cell.
- 2) The method according to claim 1, wherein said antigen marker is selected from CD1a, CD1b, CD1c, CD1d, CD3 gamma, CD3 delta, CD3 epsilon, CD4, CD5, CD7, CD8a, CD8b, CD9, CD10, CD11a, CD11b, CD11c, CD13, CD14, CD15, CD16a, CD16b, CD20, CD21, CD22, CD23, CD24, CD25, CD31, CD33, CD37, CD38, CD40, CD43, CD44, CD45, CD45RA, CD45RB, CD45RO, CD46, CD47, CD48, CD52, CD53, CD55, CD56, CD57, CD58, CD59, CD60a, CD63, CD68, CD69, CD70, CD74, CD79a, CD79b, CD81, CD82, CD83, CDw84, CD86, CD87, CD90, CD94, CD95, CD96, CD97, CD98, CD99, CD100, CD103, CD107a, CD107b, CD109, CD123, CD146, CD154, CD158a, CD158b, CD163, CD164, CD168, CD171, CD177, CD178, CD180, CD182, CD185, CD191, CD193, CD196, CD197, CD200, CD209, CD227, CD231, CD246, CD254, CD263, CD272, CD273, CD276, CD277, CD279, CD298, CD300a, CD300c, CD304, CD305, CD314, CD317, and CD319.
- 3) The method according to claim 1, wherein said antigen marker is CD38, CD70 or CS1.
- 4) The method according to any one of claims 1 to 3, wherein step a) is performed using a rare-cutting endonuclease.
- 5) The method according to any one of claims 1 to 4, wherein said method includes a further step of inactivating a gene encoding a component of the T-cell receptor (TCR).
- 6) The method according to any one of claims 1 to 5, wherein said method includes a further step of inactivating a gene encoding a component of HLA.
- 7) The method according to any one of claims 1 to 6, wherein said method includes a further step of inactivating a gene encoding $\beta 2m$.

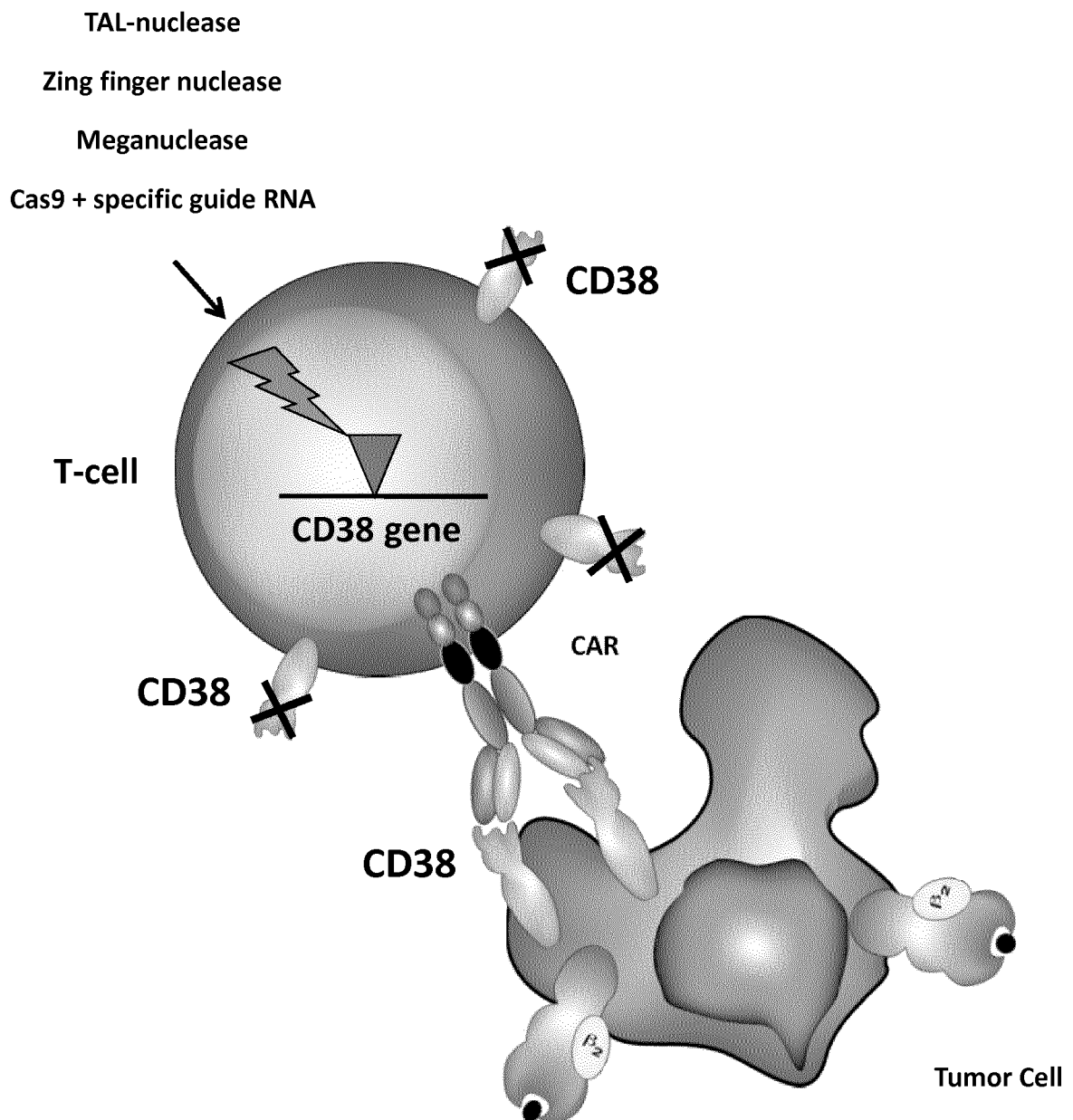
- 8) The method according to any one of claims 1 to 7, wherein said method includes a further step of inactivating a gene encoding an immune checkpoint protein selected from CTLA4, PPP2CA, PPP2CB, PTPN6, PTPN22, PDCD1, LAG3, HAVCR2, BTLA, CD160, TIGIT, CD96, CRTAM, LAIR1, SIGLEC7, SIGLEC9, CD244, TNFRSF10B, TNFRSF10A, CASP8, CASP10, CASP3, CASP6, CASP7, FADD, FAS, TGFBRII, TGFRBRI, SMAD2, SMAD3, SMAD4, SMAD10, SKI, SKIL, TGIF1, IL10RA, IL10RB, HMOX2, IL6R, IL6ST, EIF2AK4, CSK, PAG1, SIT1, FOXP3, PRDM1, BATF, GUCY1A2, GUCY1A3, GUCY1B2 and GUCY1B3.
- 9) The method according to any one of claims 1 to 8, wherein said method includes a further step of inactivating a gene conferring sensitivity of the T-cells to chemotherapy or immunosuppressive drugs.
- 10) The method according to any one of claims 1 to 9, wherein said T-cells are derived from CD4+ T-lymphocytes and/or CD8+ T-lymphocytes.
- 11) A population of T cells prepared according to the method of any one of claims 1 to 10.
- 12) Use of a population of T cells according to claim 11 in the manufacture of a medicament for the treatment of a cancer, an immune disease or an infection in a patient in need thereof.
- 13) A method for treating a cancer, an immune disease or an infection in a patient in need thereof, comprising administering to said patient a population of T cells according to claim 11.
- 14) The use according to claim 12 or the method according to claim 13, wherein said cancer is lymphoma.
- 15) The use according to claim 12 or the method according to claim 13, wherein said cancer is leukemia.
- 16) The use or method according to claim 15, wherein said leukemia is chronic lymphocytic leukemia (CLL).
- 17) An engineered T-cell wherein a gene encoding an antigen marker, which is present both on the surface of said T-cell and a pathological cell, is genetically inactivated thereby resulting in the absence of said antigen marker on the surface of said T-cell; and wherein said T-cell expresses a chimeric antigen receptor directed against said antigen marker present at the surface of said pathological cell.

- 18) The engineered immune cell according to claim 17 comprising the phenotype [CAR CD38]⁺[CD38]⁻.
- 19) The engineered immune cell according to claim 17 comprising the phenotype [CAR CD70]⁺[CD70]⁻.
- 20) The engineered immune cell according to claim 17 comprising the phenotype [CAR CS1]⁺[CS1]⁻.
- 21) A method for treating a patient comprising:
- (a) Diagnosing said patient for the presence of pathological cells presenting specific antigen markers in common with T-cells;
 - (b) preparing a population of engineered T-cells according to any one of claims 17 to 20 or according to the method of any one of claims 1 to 10; and
 - (c) administering said engineered T-cells to said patient diagnosed for said pathological cells.

Collectis

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON

**Figure 1**

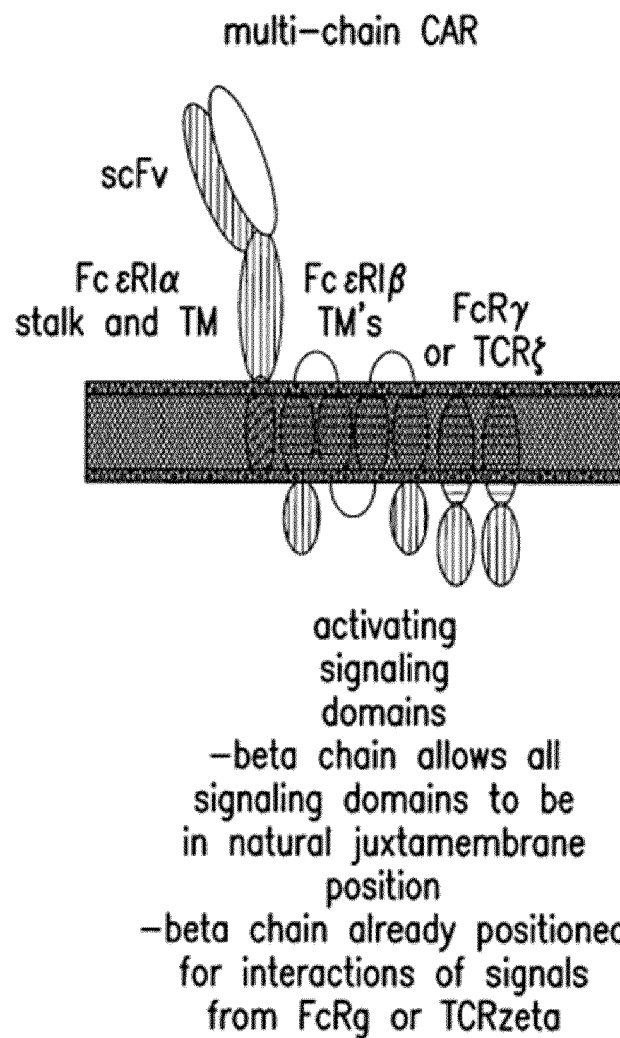


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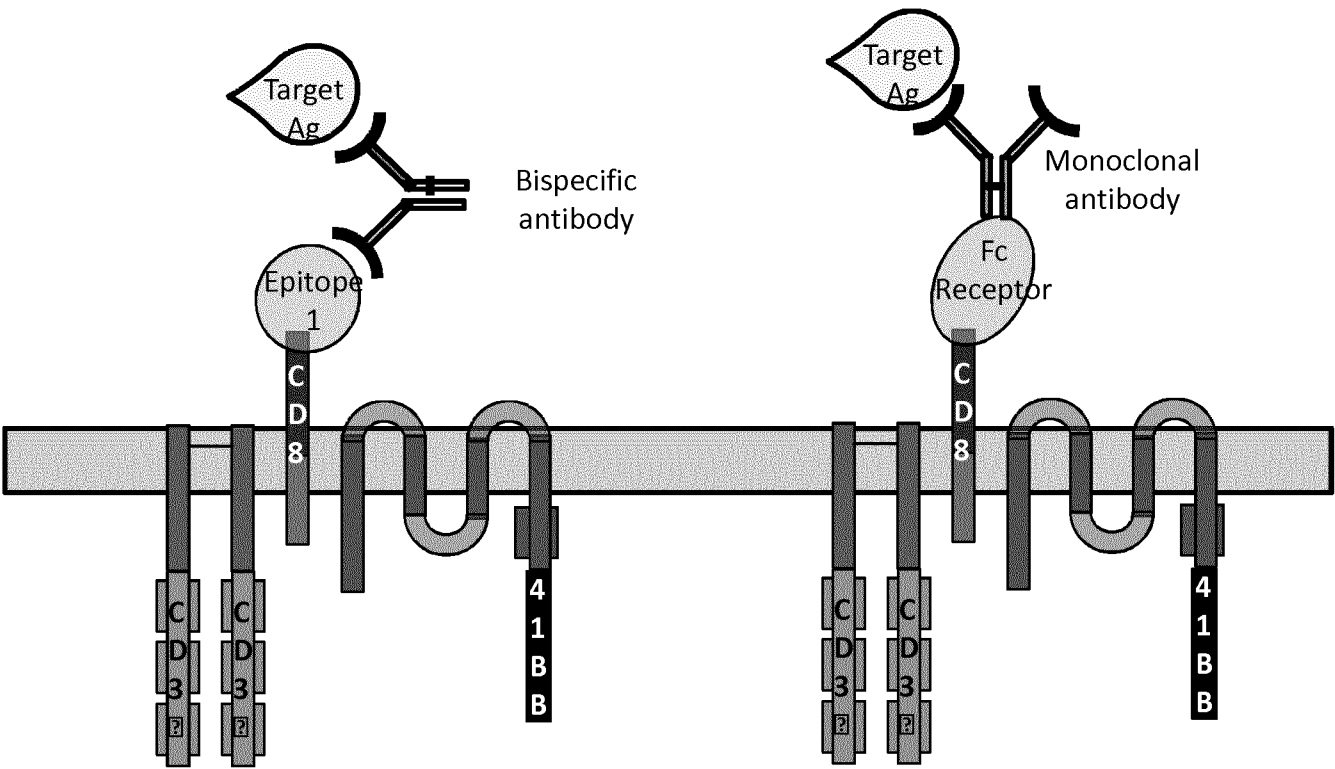


Fig. 3

Fig. 4

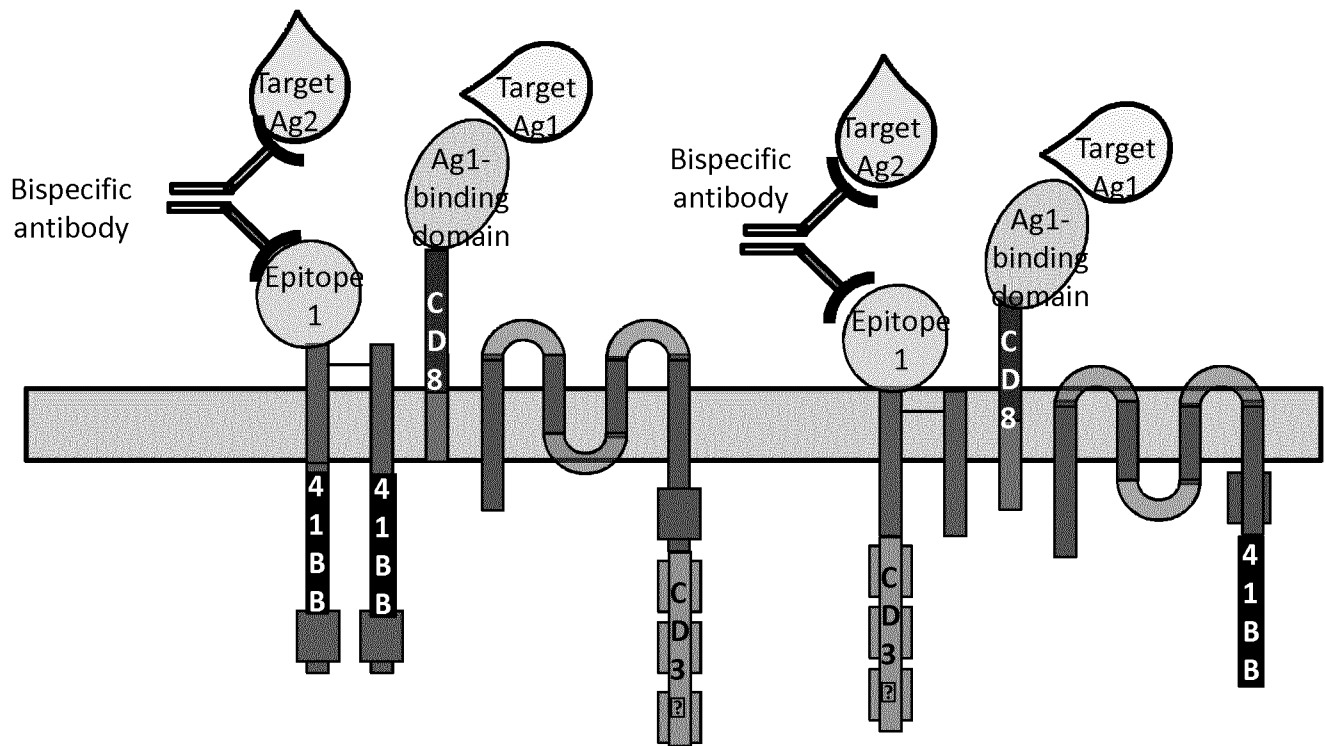


Fig. 5

Fig. 6

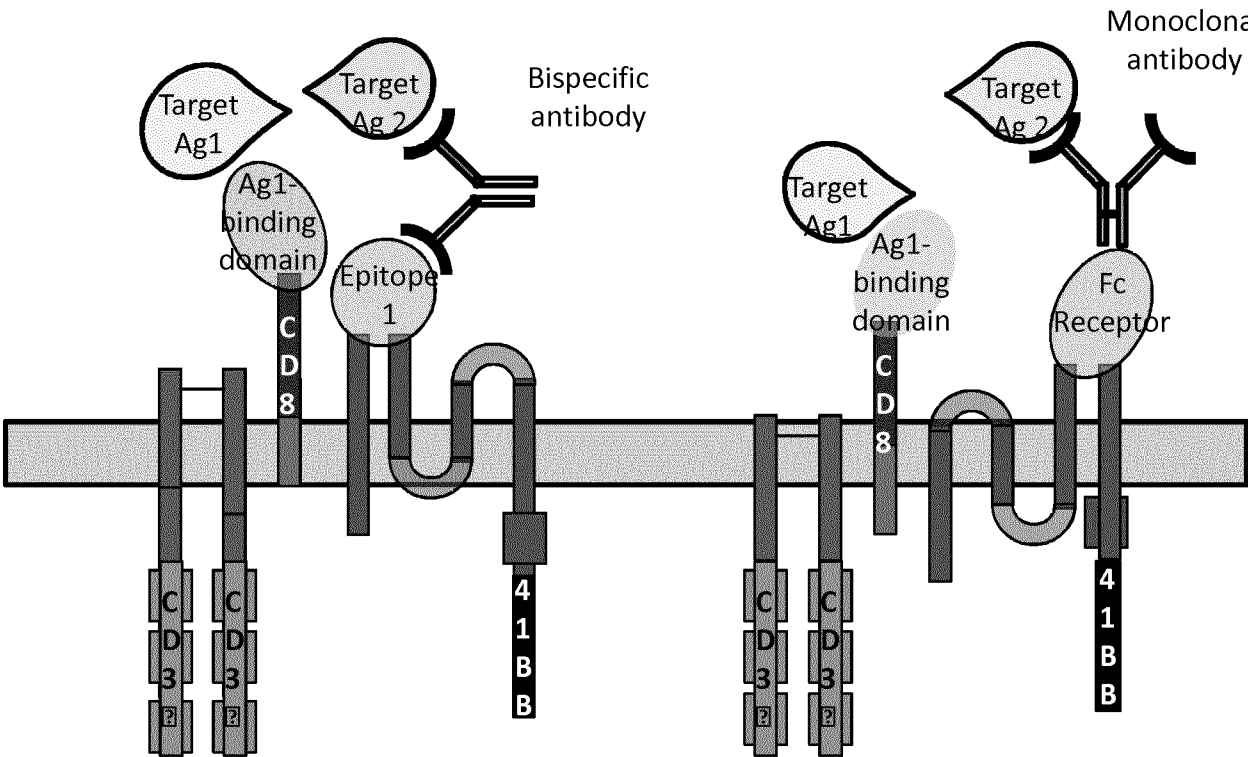


Fig. 7

Fig. 8

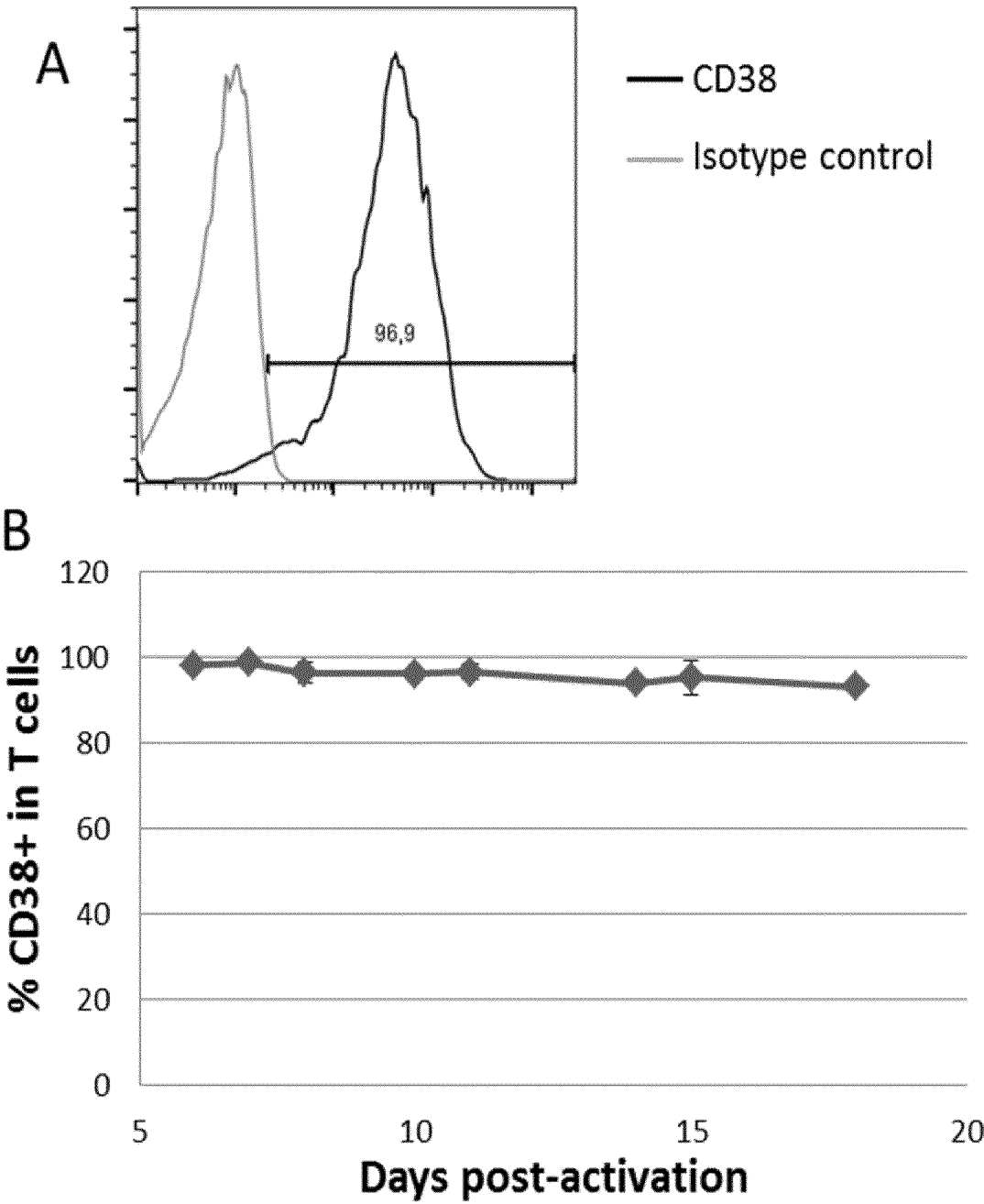
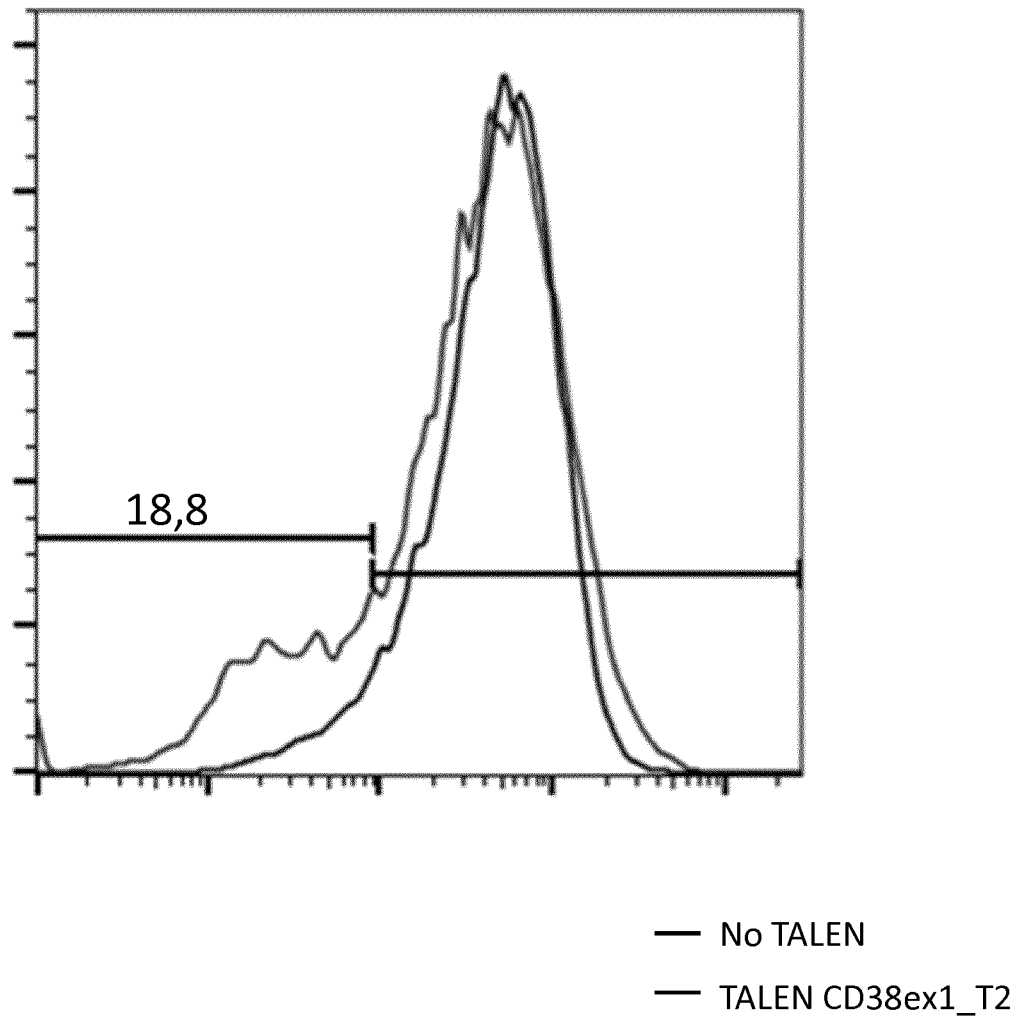


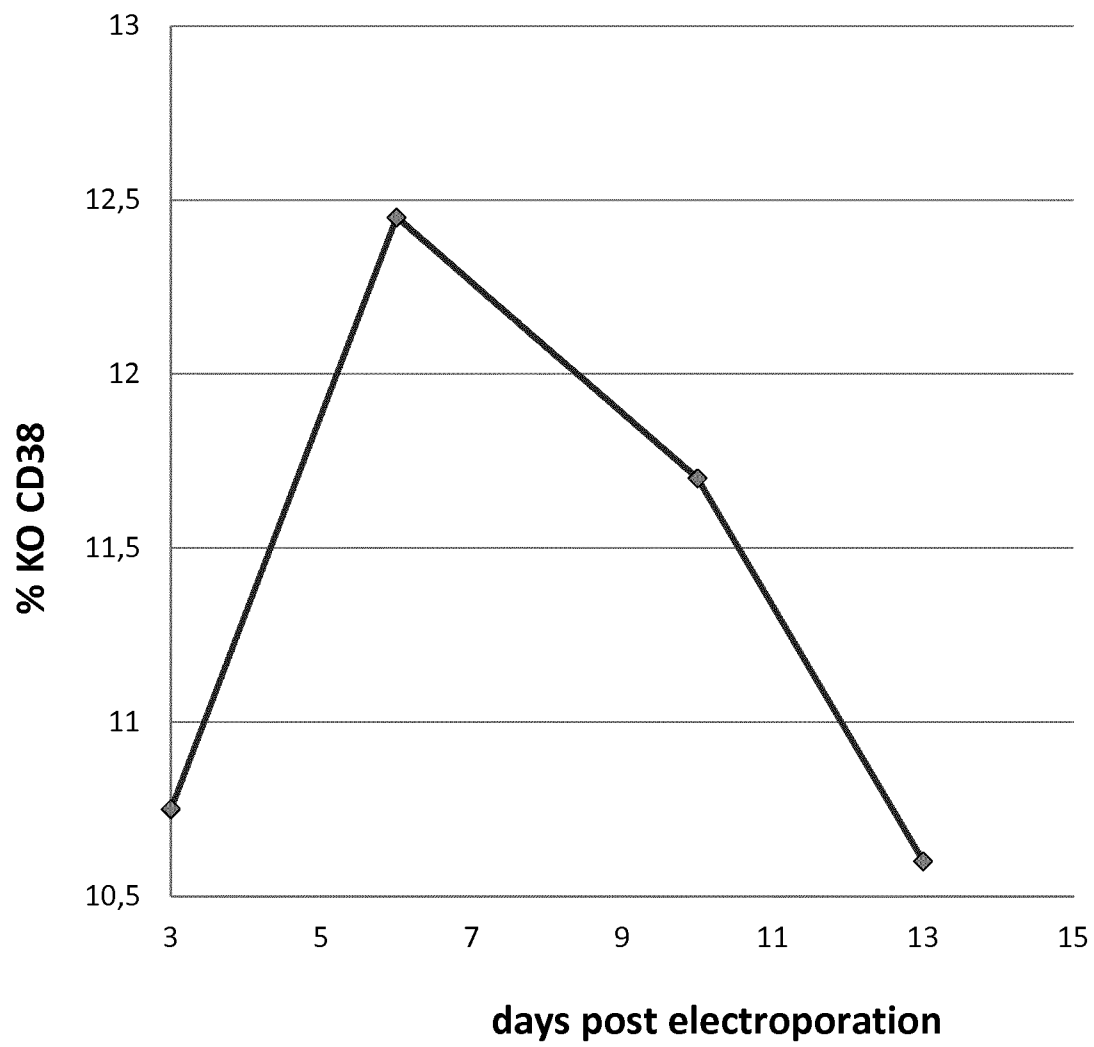
Figure 9

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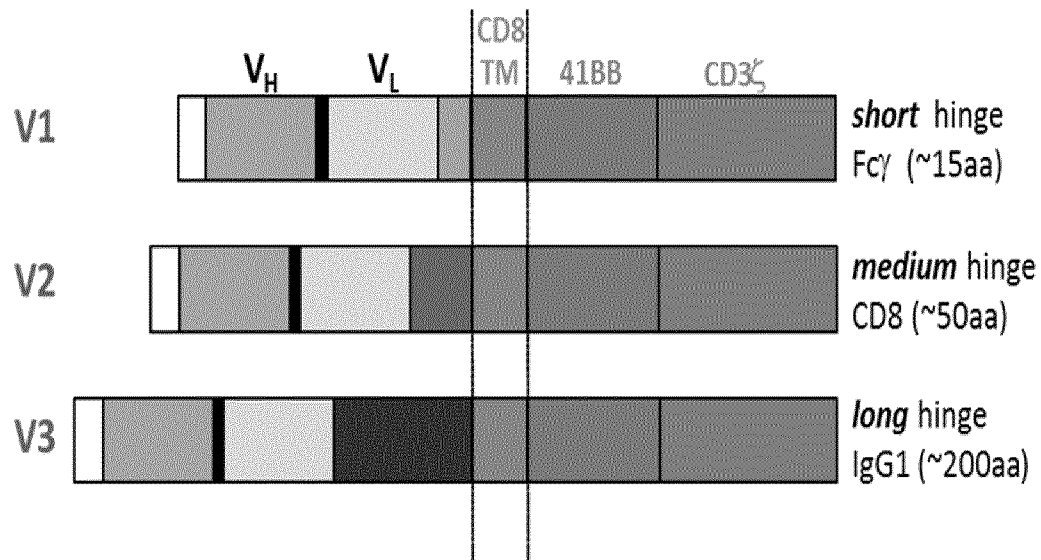
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	CGGSCCTAG	CGG								

Figure 10 A

B**Figure 10 B**

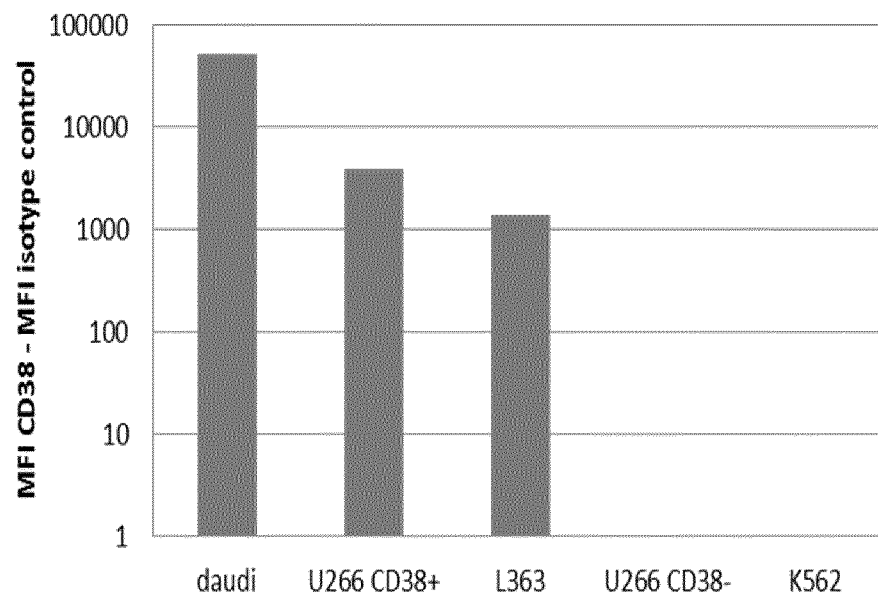
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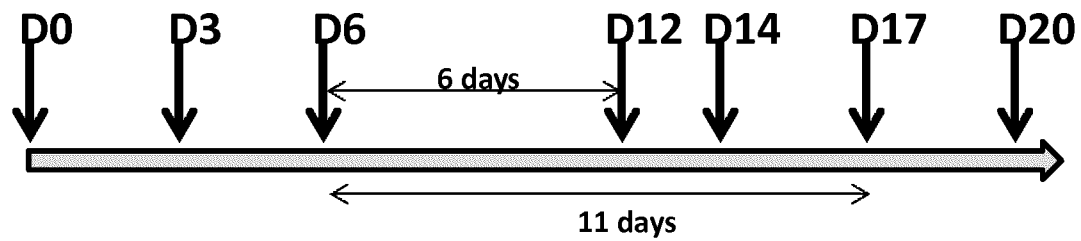
A



B

CD38 expression by target cell lines

**Figure 11**



D0: T-cell purification and activation

D3: TALEn mRNA transfection

D6: CAR transduction

D12: FACS analysis

D14: Cytotoxicity Assay

D17: Re-activation

D20: FACS analysis

Figure 12

T01: pCLS25985 / pCLS25986

pCLS25985: LEFT-NG-HD-HD-NI-NN-NI-NN-NI-NN-HD-NI-NI-NG-NI-NG-NG#-RIGHT

pCLS25986: LEFT-NI-NN-NI-NG-NN-NI-NN-NN-NN-NG-NN-NI-NN-NN-HD-NG#-RIGHT

T02: pCLS25992 / pCLS26065

pCLS25992: LEFT-NN-NI-HD-NG-NG-HD-HD-NI-NN-NI-NN-NI-NN-HD-NI-NG#-RIGHT

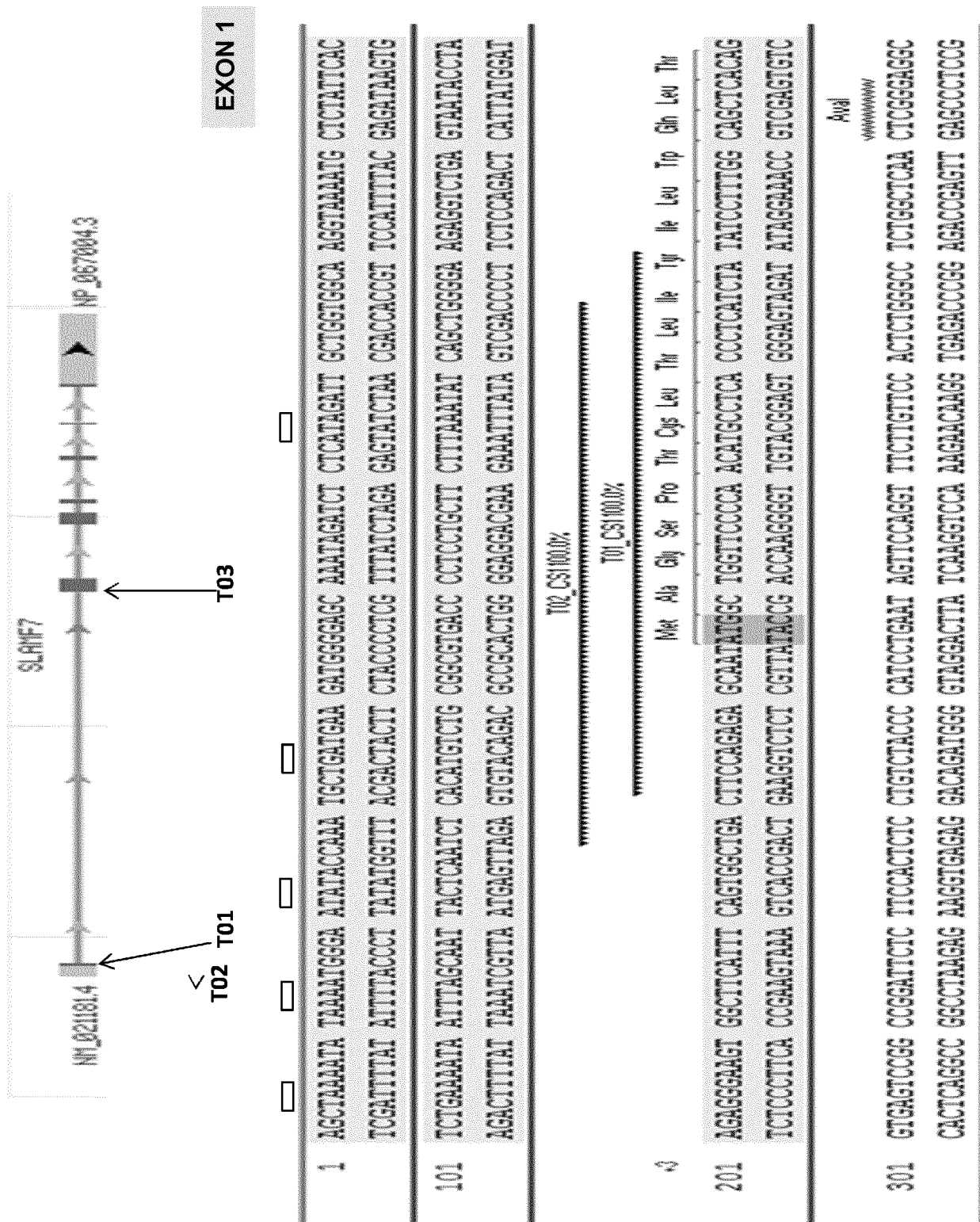
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Figure 13



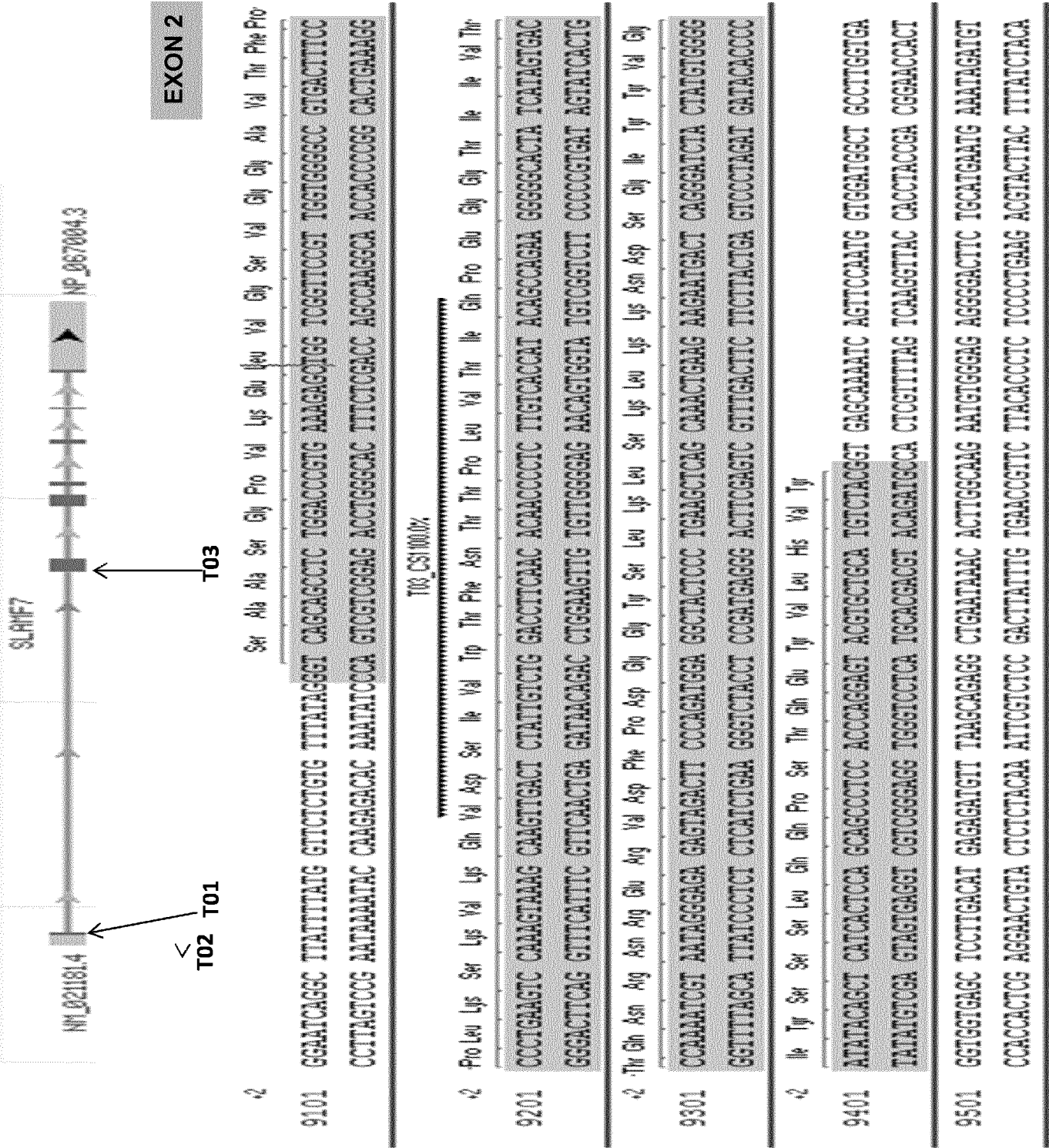


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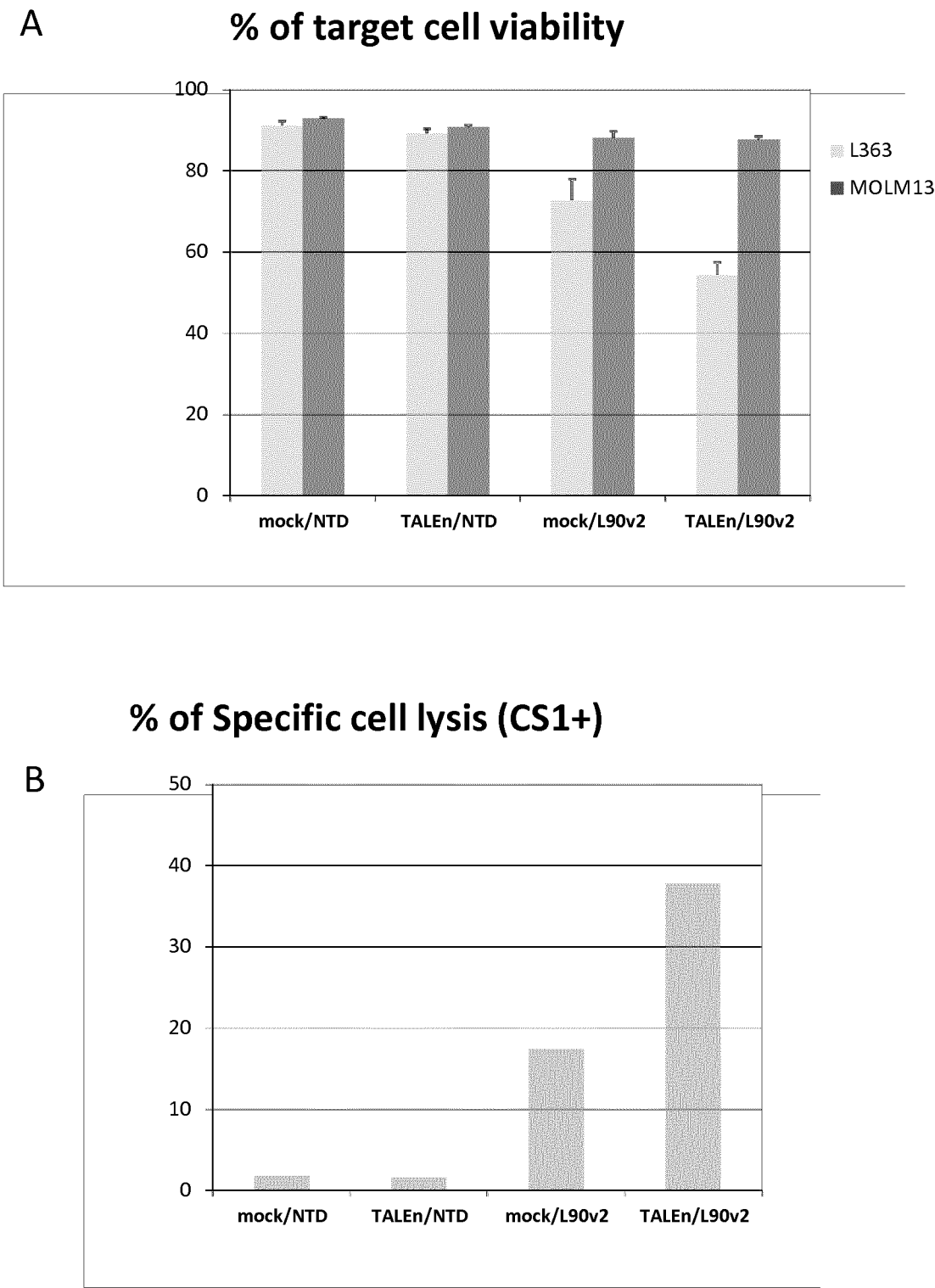


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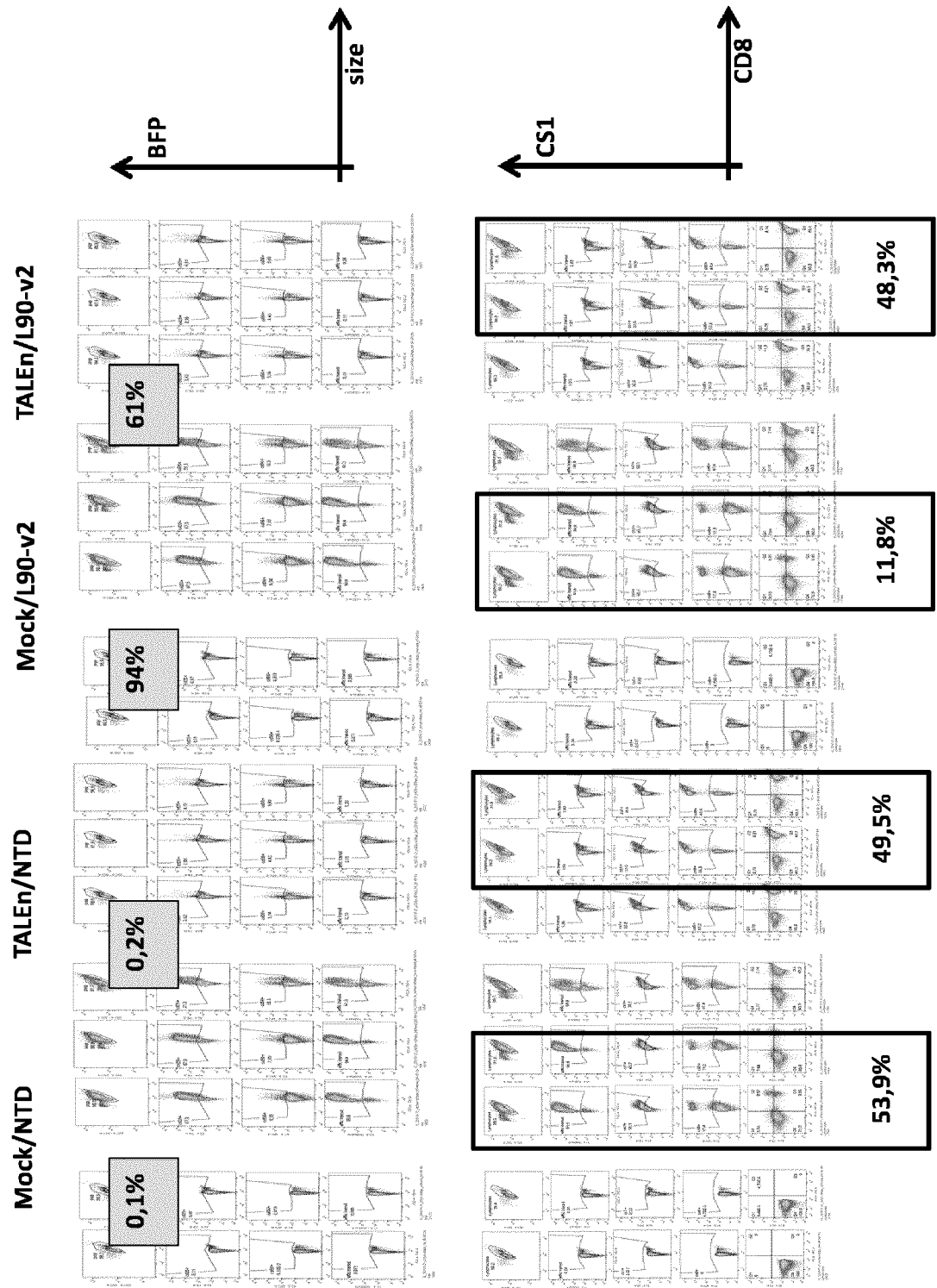


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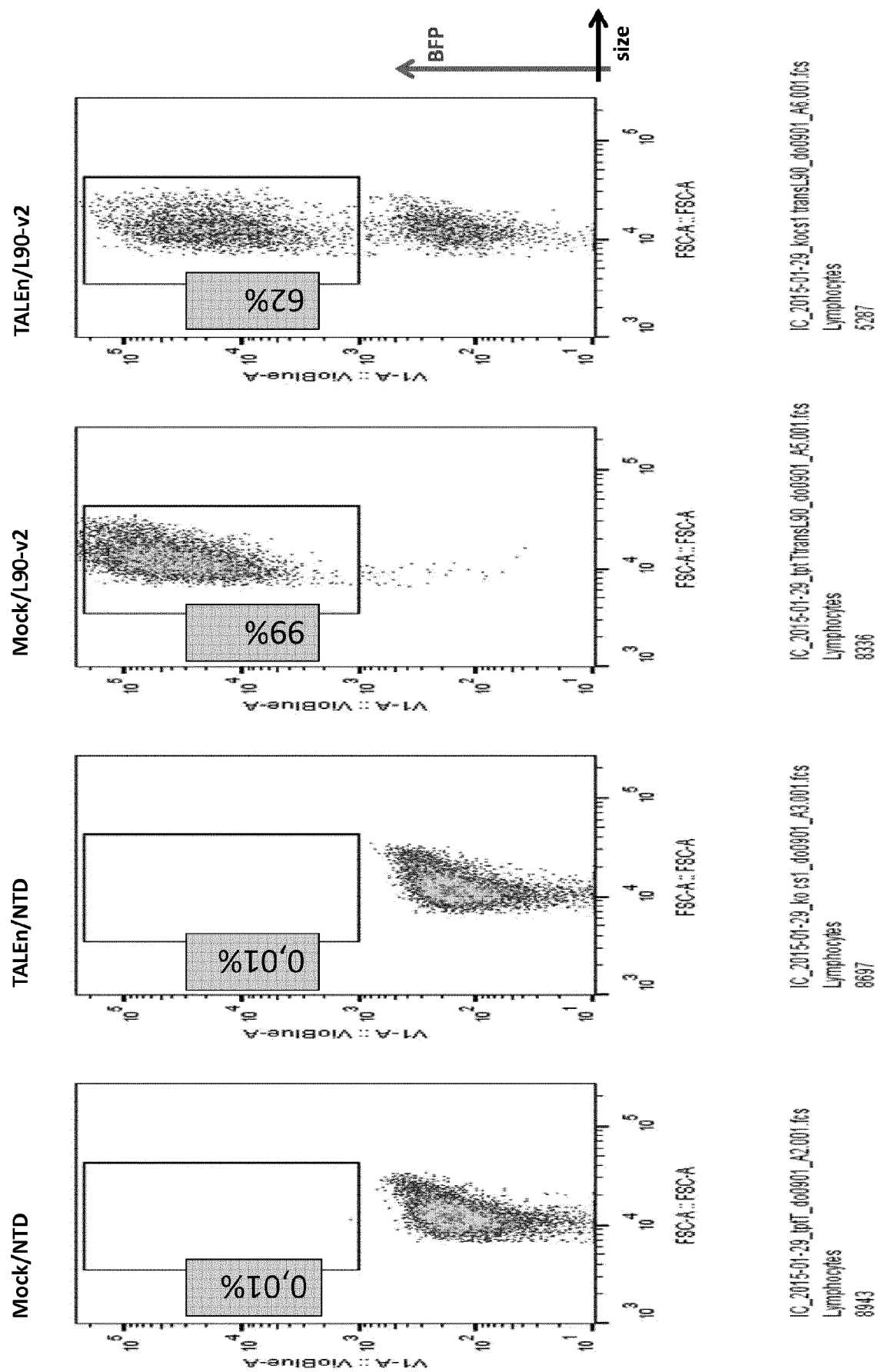


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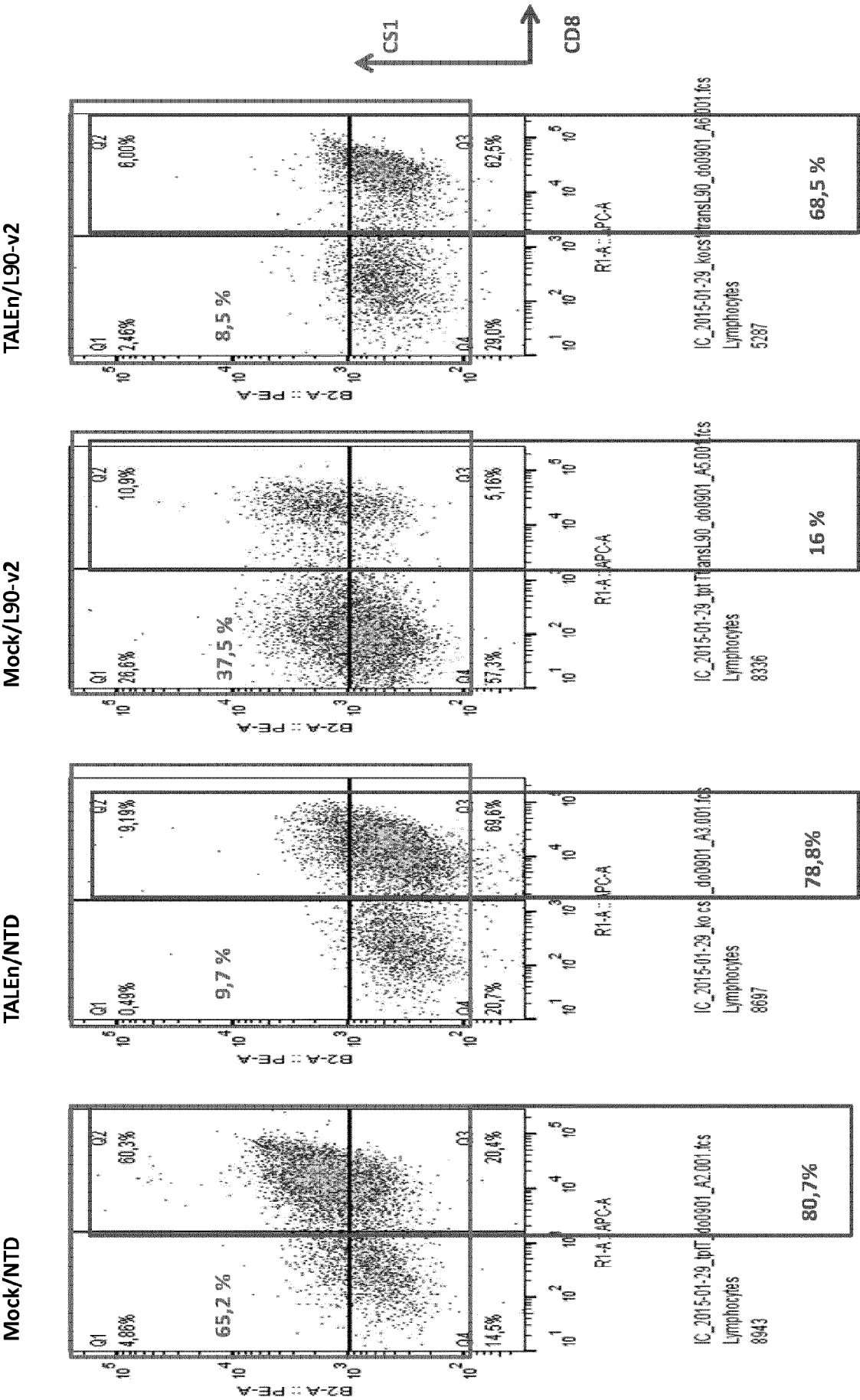


Figure 17 (cont.)

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

eo1f-seq1.txt

Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser His
225 230 235 240

Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
245 250 255

Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala
260 265 270

Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
275 280 285

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala
290 295 300

Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
305 310 315 320

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val
325 330 335

Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val
340 345 350

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
355 360 365

Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu
370 375 380

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

Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala
405 410 415

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

Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys
435 440 445

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
450 455 460

His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Ile Gly
465 470 475 480

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
485 490 495

eo1f-seq1.txt

Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn
500 505 510

Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
515 520 525

Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala
530 535 540

Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
545 550 555 560

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala
565 570 575

Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
580 585 590

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val
595 600 605

Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val
610 615 620

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu
625 630 635 640

Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu
645 650 655

Thr Val Gln Ala Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
660 665 670

Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala
675 680 685

Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly
690 695 700

Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Arg
705 710 715 720

Pro Ala Leu Glu Ser Ile Val Ala Gln Leu Ser Arg Pro Asp Pro Ala
725 730 735

Leu Ala Ala Leu Thr Asn Asp His Leu Val Ala Leu Ala Cys Leu Gly
740 745 750

Gly Arg Pro Ala Leu Asp Ala Val Lys Lys Gly Leu Gly Asp Pro Ile
755 760 765

eo1f-seq1.txt

Ser Arg Ser Gln Leu Val Lys Ser Glu Leu Glu Glu Lys Lys Ser Glu
770 775 780

Leu Arg His Lys Leu Lys Tyr Val Pro His Glu Tyr Ile Glu Leu Ile
785 790 795 800

Glu Ile Ala Arg Asn Ser Thr Gln Asp Arg Ile Leu Glu Met Lys Val
805 810 815

Met Glu Phe Phe Met Lys Val Tyr Gly Tyr Arg Gly Lys His Leu Gly
820 825 830

Gly Ser Arg Lys Pro Asp Gly Ala Ile Tyr Thr Val Gly Ser Pro Ile
835 840 845

Asp Tyr Gly Val Ile Val Asp Thr Lys Ala Tyr Ser Gly Gly Tyr Asn
850 855 860

Leu Pro Ile Gly Gln Ala Asp Glu Met Gln Arg Tyr Val Glu Glu Asn
865 870 875 880

Gln Thr Arg Asn Lys His Ile Asn Pro Asn Glu Trp Trp Lys Val Tyr
885 890 895

Pro Ser Ser Val Thr Glu Phe Lys Phe Leu Phe Val Ser Gly His Phe
900 905 910

Lys Gly Asn Tyr Lys Ala Gln Leu Thr Arg Leu Asn His Ile Thr Asn
915 920 925

Cys Asn Gly Ala Val Leu Ser Val Glu Glu Leu Leu Ile Gly Gly Glu
930 935 940

Met Ile Lys Ala Gly Thr Leu Thr Leu Glu Glu Val Arg Arg Lys Phe
945 950 955 960

Asn Asn Gly Glu Ile Asn Phe Ala Ala Asp
965 970

<210> 6

<211> 942

<212> PRT

<213> artificial sequence

<220>

<223> CD38ex1_T4-R TALEN

<400> 6

Met Gly Asp Pro Lys Lys Lys Arg Lys Val Ile Asp Lys Glu Thr Ala
1 5 10 15

eof-seq1.txt

Ala Ala Lys Phe Glu Arg Gln His Met Asp Ser Ile Asp Ile Ala Asp
20 25 30

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

Lys Val Arg Ser Thr Val Ala Gln His His Glu Ala Leu Val Gly His
50 55 60

Gly Phe Thr His Ala His Ile Val Ala Leu Ser Gln His Pro Ala Ala
65 70 75 80

Leu Gly Thr Val Ala Val Lys Tyr Gln Asp Met Ile Ala Ala Leu Pro
85 90 95

Glu Ala Thr His Glu Ala Ile Val Gly Val Gly Lys Gln Trp Ser Gly
100 105 110

Ala Arg Ala Leu Glu Ala Leu Leu Thr Val Ala Gly Glu Leu Arg Gly
115 120 125

Pro Pro Leu Gln Leu Asp Thr Gly Gln Leu Leu Lys Ile Ala Lys Arg
130 135 140

Gly Gly Val Thr Ala Val Glu Ala Val His Ala Trp Arg Asn Ala Leu
145 150 155 160

Thr Gly Ala Pro Leu Asn Leu Thr Pro Gln Gln Val Val Ala Ile Ala
165 170 175

Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
180 185 190

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

Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
210 215 220

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val
225 230 235 240

Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val
245 250 255

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu
260 265 270

Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu
275 280 285

eof-seq1.txt

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
290 295 300

Pro Glu Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala
305 310 315 320

Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly
325 330 335

Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys
340 345 350

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
355 360 365

His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser His Asp Gly
370 375 380

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

Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn
405 410 415

Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
420 425 430

Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala
435 440 445

Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Ala Leu Leu
450 455 460

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala
465 470 475 480

Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
485 490 495

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val
500 505 510

Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val
515 520 525

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
530 535 540

Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu
545 550 555 560

eo1f-seq1.txt

Thr Val Gln Arg Leu₅₆₅ Leu Pro Val Leu Cys₅₇₀ Gln Ala His Gly Leu₅₇₅ Thr

Pro Glu Gln Val₅₈₀ Val Ala Ile Ala Ser₅₈₅ Asn Gly Gly Gly Lys₅₉₀ Gln Ala

Leu Glu Thr₅₉₅ Val Gln Arg Leu Leu₆₀₀ Pro Val Leu Cys Gln₆₀₅ Ala His Gly

Leu Thr₆₁₀ Pro Glu Gln Val Val₆₁₅ Ala Ile Ala Ser His₆₂₀ Asp Gly Gly Lys

Gln Ala Leu Glu Thr Val₆₃₀ Gln Arg Leu Leu Pro₆₃₅ Val Leu Cys Gln Ala₆₄₀

His Gly Leu Thr Pro₆₄₅ Glu Gln Val Val Ala₆₅₀ Ile Ala Ser Asn Gly₆₅₅ Gly

Gly Lys Gln Ala₆₆₀ Leu Glu Thr Val Gln₆₆₅ Arg Leu Leu Pro Val₆₇₀ Leu Cys

Gln Ala His₆₇₅ Gly Leu Thr Pro Gln₆₈₀ Gln Val Val Ala Ile₆₈₅ Ala Ser Asn

Ile Gly₆₉₀ Gly Arg Pro Ala Leu₆₉₅ Glu Ser Ile Val Ala₇₀₀ Gln Leu Ser Arg

Pro Asp Pro Ala Leu Ala₇₁₀ Ala Leu Thr Asn Asp₇₁₅ His Leu Val Ala Leu₇₂₀

Ala Cys Leu Gly Gly₇₂₅ Arg Pro Ala Leu Asp₇₃₀ Ala Val Lys Lys Gly₇₃₅ Leu

Gly Asp Pro Ile₇₄₀ Ser Arg Ser Gln Leu₇₄₅ Val Lys Ser Glu Leu₇₅₀ Glu Glu

Lys Lys Ser₇₅₅ Glu Leu Arg His Lys₇₆₀ Leu Lys Tyr Val Pro₇₆₅ His Glu Tyr

Ile Glu₇₇₀ Leu Ile Glu Ile Ala₇₇₅ Arg Asn Ser Thr Gln₇₈₀ Asp Arg Ile Leu

Glu Met Lys Val Met Glu₇₉₀ Phe Phe Met Lys Val₇₉₅ Tyr Gly Tyr Arg Gly₈₀₀

Lys His Leu Gly Gly₈₀₅ Ser Arg Lys Pro Asp₈₁₀ Gly Ala Ile Tyr Thr₈₁₅ Val

Gly Ser Pro Ile₈₂₀ Asp Tyr Gly Val Ile₈₂₅ Val Asp Thr Lys Ala₈₃₀ Tyr Ser

eo1f-seq1.txt

Gly Gly Tyr Asn Leu Pro Ile Gly Gln Ala Asp Glu Met Gln Arg Tyr
835 840 845

Val Glu Glu Asn Gln Thr Arg Asn Lys His Ile Asn Pro Asn Glu Trp
850 855 860

Trp Lys Val Tyr Pro Ser Ser Val Thr Glu Phe Lys Phe Leu Phe Val
865 870 875 880

Ser Gly His Phe Lys Gly Asn Tyr Lys Ala Gln Leu Thr Arg Leu Asn
885 890 895

His Ile Thr Asn Cys Asn Gly Ala Val Leu Ser Val Glu Glu Leu Leu
900 905 910

Ile Gly Gly Glu Met Ile Lys Ala Gly Thr Leu Thr Leu Glu Glu Val
915 920 925

Arg Arg Lys Phe Asn Asn Gly Glu Ile Asn Phe Ala Ala Asp
930 935 940

<210> 7

<211> 49

<212> PRT

<213> homo sapiens

<220>

<223> CD38ex1_T5

<400> 7

Thr Gly Ala Thr Cys Cys Thr Cys Gly Thr Cys Gly Thr Gly Gly Thr
1 5 10 15

Gly Cys Thr Cys Gly Cys Gly Gly Thr Gly Gly Thr Cys Gly Thr Cys
20 25 30

Cys Cys Gly Ala Gly Gly Thr Gly Gly Cys Gly Cys Cys Ala Gly Cys
35 40 45

Ala

<210> 8

<211> 936

<212> PRT

<213> artificial sequence

<220>

<223> CD38ex1_T5-L TALEN

<400> 8

Met Gly Asp Pro Lys Lys Lys Arg Lys Val Ile Asp Tyr Pro Tyr Asp
1 5 10 15

co1f-seq1.txt

Val Pro Asp Tyr Ala Ile Asp Ile Ala Asp Leu Arg Thr Leu Gly Tyr
20 25 30

Ser Gln Gln Gln Gln Glu Lys Ile Lys Pro Lys Val Arg Ser Thr Val
35 40 45

Ala Gln His His Glu Ala Leu Val Gly His Gly Phe Thr His Ala His
50 55 60

Ile Val Ala Leu Ser Gln His Pro Ala Ala Leu Gly Thr Val Ala Val
65 70 75 80

Lys Tyr Gln Asp Met Ile Ala Ala Leu Pro Glu Ala Thr His Glu Ala
85 90 95

Ile Val Gly Val Gly Lys Gln Trp Ser Gly Ala Arg Ala Leu Glu Ala
100 105 110

Leu Leu Thr Val Ala Gly Glu Leu Arg Gly Pro Pro Leu Gln Leu Asp
115 120 125

Thr Gly Gln Leu Leu Lys Ile Ala Lys Arg Gly Gly Val Thr Ala Val
130 135 140

Glu Ala Val His Ala Trp Arg Asn Ala Leu Thr Gly Ala Pro Leu Asn
145 150 155 160

Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys
165 170 175

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
180 185 190

His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Asn Gly
195 200 205

Gly Lys Gln Ala Leu Glu Thr Val Gln Ala Leu Leu Pro Val Leu Cys
210 215 220

Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn
225 230 235 240

Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
245 250 255

Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala
260 265 270

Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
275 280 285

eof-seq1.txt

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala
290 295 300

Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
305 310 315 320

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val
325 330 335

Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val
340 345 350

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
355 360 365

Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu
370 375 380

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

Pro Gln Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala
405 410 415

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

Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys
435 440 445

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
450 455 460

His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly
465 470 475 480

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
485 490 495

Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser His
500 505 510

Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
515 520 525

Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala
530 535 540

Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
545 550 555 560

eo1f-seq1.txt

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala
565 570 575

Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
580 585 590

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val
595 600 605

Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val
610 615 620

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu
625 630 635 640

Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu
645 650 655

Thr Val Gln Ala Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
660 665 670

Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Arg Pro Ala
675 680 685

Leu Glu Ser Ile Val Ala Gln Leu Ser Arg Pro Asp Pro Ala Leu Ala
690 695 700

Ala Leu Thr Asn Asp His Leu Val Ala Leu Ala Cys Leu Gly Gly Arg
705 710 715 720

Pro Ala Leu Asp Ala Val Lys Lys Gly Leu Gly Asp Pro Ile Ser Arg
725 730 735

Ser Gln Leu Val Lys Ser Glu Leu Glu Glu Lys Lys Ser Glu Leu Arg
740 745 750

His Lys Leu Lys Tyr Val Pro His Glu Tyr Ile Glu Leu Ile Glu Ile
755 760 765

Ala Arg Asn Ser Thr Gln Asp Arg Ile Leu Glu Met Lys Val Met Glu
770 775 780

Phe Phe Met Lys Val Tyr Gly Tyr Arg Gly Lys His Leu Gly Gly Ser
785 790 795 800

Arg Lys Pro Asp Gly Ala Ile Tyr Thr Val Gly Ser Pro Ile Asp Tyr
805 810 815

Gly Val Ile Val Asp Thr Lys Ala Tyr Ser Gly Gly Tyr Asn Leu Pro
820 825 830

eof-seq1.txt

Ile Gly Gln Ala Asp Glu Met Gln Arg Tyr Val Glu Glu Asn Gln Thr
835 840 845

Arg Asn Lys His Ile Asn Pro Asn Glu Trp Trp Lys Val Tyr Pro Ser
850 855 860

Ser Val Thr Glu Phe Lys Phe Leu Phe Val Ser Gly His Phe Lys Gly
865 870 875 880

Asn Tyr Lys Ala Gln Leu Thr Arg Leu Asn His Ile Thr Asn Cys Asn
885 890 895

Gly Ala Val Leu Ser Val Glu Glu Leu Leu Ile Gly Gly Glu Met Ile
900 905 910

Lys Ala Gly Thr Leu Thr Leu Glu Glu Val Arg Arg Lys Phe Asn Asn
915 920 925

Gly Glu Ile Asn Phe Ala Ala Asp
930 935

<210> 9

<211> 942

<212> PRT

<213> artificial sequence

<220>

<223> CD38ex1_T5-R TALEN

<400> 9

Met Gly Asp Pro Lys Lys Lys Arg Lys Val Ile Asp Lys Glu Thr Ala
1 5 10 15

Ala Ala Lys Phe Glu Arg Gln His Met Asp Ser Ile Asp Ile Ala Asp
20 25 30

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

Lys Val Arg Ser Thr Val Ala Gln His His Glu Ala Leu Val Gly His
50 55 60

Gly Phe Thr His Ala His Ile Val Ala Leu Ser Gln His Pro Ala Ala
65 70 75 80

Leu Gly Thr Val Ala Val Lys Tyr Gln Asp Met Ile Ala Ala Leu Pro
85 90 95

Glu Ala Thr His Glu Ala Ile Val Gly Val Gly Lys Gln Trp Ser Gly
100 105 110

Ala Arg Ala Leu Glu Ala Leu Leu Thr Val Ala Gly Glu Leu Arg Gly
115 120 125

eo1f-seq1.txt

Pro Pro Leu Gln Leu Asp Thr Gly Gln Leu Leu Lys Ile Ala Lys Arg
130 135 140

Gly Gly Val Thr Ala Val Glu Ala Val His Ala Trp Arg Asn Ala Leu
145 150 155 160

Thr Gly Ala Pro Leu Asn Leu Thr Pro Gln Gln Val Val Ala Ile Ala
165 170 175

Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
180 185 190

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

Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
210 215 220

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val
225 230 235 240

Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val
245 250 255

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu
260 265 270

Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu
275 280 285

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
290 295 300

Pro Glu Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala
305 310 315 320

Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly
325 330 335

Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys
340 345 350

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
355 360 365

His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly
370 375 380

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

eo1f-seq1.txt

Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn
405 410 415

Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
420 425 430

Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala
435 440 445

Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Ala Leu Leu
450 455 460

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala
465 470 475 480

Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
485 490 495

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val
500 505 510

Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val
515 520 525

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
530 535 540

Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu
545 550 555 560

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
565 570 575

Pro Glu Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala
580 585 590

Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly
595 600 605

Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys
610 615 620

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
625 630 635 640

His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly
645 650 655

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
660 665 670

eo1f-seq1.txt

Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn
675 680 685

Ile Gly Gly Arg Pro Ala Leu Glu Ser Ile Val Ala Gln Leu Ser Arg
690 695 700

Pro Asp Pro Ala Leu Ala Ala Leu Thr Asn Asp His Leu Val Ala Leu
705 710 715 720

Ala Cys Leu Gly Gly Arg Pro Ala Leu Asp Ala Val Lys Lys Gly Leu
725 730 735

Gly Asp Pro Ile Ser Arg Ser Gln Leu Val Lys Ser Glu Leu Glu Glu
740 745 750

Lys Lys Ser Glu Leu Arg His Lys Leu Lys Tyr Val Pro His Glu Tyr
755 760 765

Ile Glu Leu Ile Glu Ile Ala Arg Asn Ser Thr Gln Asp Arg Ile Leu
770 775 780

Glu Met Lys Val Met Glu Phe Phe Met Lys Val Tyr Gly Tyr Arg Gly
785 790 795 800

Lys His Leu Gly Gly Ser Arg Lys Pro Asp Gly Ala Ile Tyr Thr Val
805 810 815

Gly Ser Pro Ile Asp Tyr Gly Val Ile Val Asp Thr Lys Ala Tyr Ser
820 825 830

Gly Gly Tyr Asn Leu Pro Ile Gly Gln Ala Asp Glu Met Gln Arg Tyr
835 840 845

Val Glu Glu Asn Gln Thr Arg Asn Lys His Ile Asn Pro Asn Glu Trp
850 855 860

Trp Lys Val Tyr Pro Ser Ser Val Thr Glu Phe Lys Phe Leu Phe Val
865 870 875 880

Ser Gly His Phe Lys Gly Asn Tyr Lys Ala Gln Leu Thr Arg Leu Asn
885 890 895

His Ile Thr Asn Cys Asn Gly Ala Val Leu Ser Val Glu Glu Leu Leu
900 905 910

Ile Gly Gly Glu Met Ile Lys Ala Gly Thr Leu Thr Leu Glu Glu Val
915 920 925

Arg Arg Lys Phe Asn Asn Gly Glu Ile Asn Phe Ala Ala Asp
930 935 940

eo1f-seq1.txt

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<210> 10
<211> 451
<212> PRT
<213> artificial sequence
<220>
<223> Daratumumab-VH chain
<400> 10
Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
1      5      10      15

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

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

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

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

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

Lys Asp Lys Ile Leu Trp Phe Gly Glu Pro Val Phe Asp Tyr Trp Gly
100     105     110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115     120     125

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

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

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165     170     175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180     185     190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195     200     205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
210     215     220

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eo1f-seq1.txt

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
 225 230 235 240
 Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 245 250 255
 Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 260 265 270
 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 275 280 285
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 290 295 300
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 305 310 315 320
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
 325 330 335
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 340 345 350
 Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
 355 360 365
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 370 375 380
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 385 390 395 400
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 405 410 415
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 420 425 430
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 435 440 445
 Pro Gly Lys
 450

<210> 11

<211> 214

<212> PRT

<213> artificial sequence

<220>

<223> Daratumumab-VL chain

eo1f-seq1.txt

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<400> 11
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1      5      10      15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
      20      25      30

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
      210

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<210> 12
<211> 120
<212> PRT
<213> artificial sequence

<220>
<223> MOR202-VH chain

<400> 12

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eof-seq1.txt

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

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

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

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

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

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

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

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 13

<211> 109

<212> PRT

<213> artificial sequence

<220>

<223> MOR202-VL chain

<400> 13

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

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

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

Gly Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

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

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105

<210> 14
 <211> 10
 <212> PRT
 <213> artificial sequence
 <220>
 <223> HCDR1-1 - VH chain
 <400> 14
 Gly Phe Thr Phe Ser Ser Tyr Tyr Met Asn
 1 5 10

<210> 15
 <211> 5
 <212> PRT
 <213> artificial sequence
 <220>
 <223> HCDR1-2 - VH chain
 <400> 15
 Ser Tyr Tyr Met Asn
 1 5

<210> 16
 <211> 17
 <212> PRT
 <213> artificial sequence
 <220>
 <223> HCDR2 - VH chain
 <400> 16
 Gly Ile Ser Gly Asp Pro Ser Asn Thr Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

Gly

<210> 17
 <211> 11
 <212> PRT
 <213> artificial sequence
 <220>
 <223> HCDR3 - VH chain
 <400> 17
 Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr
 1 5 10

<210> 18
 <211> 5
 <212> PRT
 <213> artificial sequence

<220>

<223> HCDR4 - VH chain

<400> 18

Asp Tyr Trp Met Gln
1 5

<210> 19

<211> 16

<212> PRT

<213> artificial sequence

<220>

<223> HCDR5 - VH chain

<400> 19

Thr Ile Tyr Pro Gly Asp Gly Asp Thr Gly Tyr Ala Gln Lys Phe Lys
1 5 10 15

<210> 20

<211> 11

<212> PRT

<213> artificial sequence

<220>

<223> HCDR6 - VH chain

<400> 20

Gly Asp Tyr Tyr Gly Ser Asn Ser Leu Asp Tyr
1 5 10

<210> 21

<211> 11

<212> PRT

<213> artificial sequence

<220>

<223> LCDR1 - VH chain

<400> 21

Ser Gly Asp Asn Leu Arg His Tyr Tyr Val Tyr
1 5 10

<210> 22

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> LCDR2 - VH chain

<400> 22

Gly Asp Ser Lys Arg Pro Ser
1 5

<210> 23

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> LCDR3 - VH chain

<400> 23

Gln Thr Tyr Thr Gly Gly Ala Ser Leu
1 5

<210> 24

<211> 11

<212> PRT

<213> artificial sequence

<220>

<223> LCDR4 - VH chain

<400> 24

Lys Ala Ser Gln Asp Val Ser Thr Val Val Ala
1 5 10

<210> 25

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> LCDR5 - VH chain

<400> 25

Ser Ala Ser Tyr Arg Tyr Ile
1 5

<210> 26

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> LCDR6 - VH chain

<400> 26

Gln Gln His Ser Pro Pro Tyr Thr
1 5

<210> 27

<211> 21

<212> PRT

<213> artificial sequence

<220>

<223> CD8&#945;-Signal peptide (SP)

<400> 27

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

eo1f-seq1.txt

His Ala Ala Arg Pro
20

<210> 28

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> GS linker

<400> 28

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

<210> 29

<211> 16

<212> PRT

<213> homo sapiens

<220>

<223> FCRIIα hinge

<400> 29

Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln
1 5 10 15

<210> 30

<211> 69

<212> PRT

<213> homo sapiens

<220>

<223> CD8α hinge

<400> 30

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
1 5 10 15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
20 25 30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
35 40 45

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
50 55 60

Ile Thr Leu Tyr Cys
65

<210> 31

<211> 231

<212> PRT

<213> homo sapiens

<220>

<223> IgG1 hinge

<400> 31

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

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

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

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

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

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

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

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

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

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

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

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

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

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

 Leu Ser Leu Ser Pro Gly Lys
 225 230

<210> 32

eo1f-seq1.txt

<211> 24
<212> PRT
<213> homo sapiens

<220>
<223> TM domain

<400> 32
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> 33

<211> 42
<212> PRT
<213> homo sapiens

<220>
<223> 4-1 BB co-stimulatory domain

<400> 33
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 Gly Gly Cys Glu Leu
35 40

<210> 34

<211> 112
<212> PRT
<213> homo sapiens

<220>
<223> CD3ζ activation domain

<400> 34
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln 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

eof-seq1.txt

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> 35

<211> 442

<212> PRT

<213> artificial sequence

<220>

<223> GMB005-V1 CAR

<400> 35

Pro Leu Ala Leu Leu Leu His Ala Ala Arg Pro Glu Val Gln Leu Leu
1 5 10 15

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser
20 25 30

Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Phe Ala Met Ser Trp Val
35 40 45

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly
50 55 60

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

Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser
85 90 95

Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Lys Asp Lys Ile
100 105 110

Leu Trp Phe Gly Glu Pro Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu
115 120 125

Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ala Thr
145 150 155 160

Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
165 170 175

Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
180 185 190

eo1f-seq1.txt

Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile
195 200 205

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
210 215 220

Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
225 230 235 240

Arg Ser Asn Trp Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
245 250 255

Lys Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr
260 265 270

Gln Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
275 280 285

Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu
290 295 300

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
305 310 315 320

Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
325 330 335

Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
340 345 350

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
355 360 365

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
370 375 380

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

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
405 410 415

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
420 425 430

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
435 440

<210> 36

eo1f-seq1.txt

<211> 471
 <212> PRT
 <213> artificial sequence

<220>
 <223> GMB005-V2 CAR

<400> 36
 Pro Leu Ala Leu Leu Leu His Ala Ala Arg Pro Glu Val Gln Leu Leu
 1 5 10 15
 Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser
 20 25 30
 Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Phe Ala Met Ser Trp Val
 35 40 45
 Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly
 50 55 60
 Ser Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr
 65 70 75 80
 Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser
 85 90 95
 Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Lys Asp Lys Ile
 100 105 110
 Leu Trp Phe Gly Glu Pro Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu
 115 120 125
 Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 130 135 140
 Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ala Thr
 145 150 155 160
 Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
 165 170 175
 Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 180 185 190
 Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile
 195 200 205
 Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 210 215 220
 Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
 225 230 235 240

eof-seq1.txt

Arg Ser Asn Trp Pro 245 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
255

Lys Thr Thr Thr 260 Pro Ala Pro Arg Pro 265 Thr Pro Ala Pro 270 Thr Ile

Ala Ser Gln 275 Pro Leu Ser Leu Arg 280 Pro Glu Ala Cys Arg 285 Pro Ala Ala

Gly Gly 290 Ala Val His Thr Arg 295 Gly Leu Asp Phe Ala 300 Cys Asp Ile Tyr

Ile Trp Ala Pro Leu Ala 310 Gly Thr Cys Gly Val 315 Leu Leu Leu Ser Leu 320

Val Ile Thr Leu Tyr 325 Cys Lys Arg Gly Arg 330 Lys Lys Leu Leu Tyr Ile 335

Phe Lys Gln 340 Pro Phe Met Arg Pro Val 345 Gln Thr Thr Gln Glu Glu Asp 350

Gly Cys Ser 355 Cys Arg Phe Pro Glu 360 Glu Glu Glu Gly Gly 365 Cys Glu Leu

Arg Val 370 Lys Phe Ser Arg Ser 375 Ala Asp Ala Pro Ala 380 Tyr Gln Gln Gly

Gln Asn Gln Leu Tyr Asn 390 Glu Leu Asn Leu Gly 395 Arg Arg Glu Glu Tyr 400

Asp Val Leu Asp 405 Lys Arg Arg Gly Arg Asp 410 Pro Glu Met Gly Gly 415 Lys

Pro Arg Arg 420 Lys Asn Pro Gln Glu Gly 425 Leu Tyr Asn Glu Leu Gln Lys 430

Asp Lys Met 435 Ala Glu Ala Tyr Ser 440 Glu Ile Gly Met Lys 445 Gly Glu Arg

Arg Arg 450 Gly Lys Gly His Asp 455 Gly Leu Tyr Gln Gly 460 Leu Ser Thr Ala

Thr Lys Asp Thr Tyr Asp 470 Ala

<210> 37

<211> 657

<212> PRT

<213> artificial sequence

<220>

<223> GMB005-V3 CAR

eo1f-seq1.txt

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<400> 37
Pro Leu Ala Leu Leu His Ala Ala Arg Pro Glu Val Gln Leu Leu
1      5      10      15

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser
20      25      30

Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Phe Ala Met Ser Trp Val
35      40      45

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly
50      55      60

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

Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser
85      90      95

Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Lys Asp Lys Ile
100     105     110

Leu Trp Phe Gly Glu Pro Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu
115     120     125

Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
130     135     140

Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ala Thr
145     150     155     160

Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
165     170     175

Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
180     185     190

Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile
195     200     205

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
210     215     220

Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
225     230     235     240

Arg Ser Asn Trp Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
245     250     255

Lys Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro
260     265     270

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eo1f-seq1.txt

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
275 280 285

Lys Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val
290 295 300

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
305 310 315 320

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
325 330 335

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
340 345 350

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
355 360 365

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
370 375 380

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
385 390 395 400

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
405 410 415

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
420 425 430

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
435 440 445

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
450 455 460

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
465 470 475 480

Ser Leu Ser Leu Ser Pro Gly Lys Ile Tyr Ile Trp Ala Pro Leu Ala
485 490 495

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
500 505 510

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
515 520 525

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
530 535 540

eo1f-seq1.txt

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
545 550 555 560

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
565 570 575

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
580 585 590

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
595 600 605

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
610 615 620

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
625 630 635 640

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
645 650 655

Ala

<210> 38

<211> 119

<212> PRT

<213> mus musculus

<220>

<223> Luc63-VH chain

<400> 38

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

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

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

Gly Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Thr Pro Ser Leu
50 55 60

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

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

Ala Arg Pro Asp Gly Asn Tyr Trp Tyr Phe Asp Val Trp Gly Ala Gly
Page 40

100

105

110

Thr Thr Val Thr Val Ser Ser
115

<210> 39

<211> 107

<212> PRT

<213> mus musculus

<220>

<223> Luc63-VL chain

<400> 39

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

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

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

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

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

Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Ser Ser Tyr Pro Tyr
85 90 95

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

<210> 40

<211> 120

<212> PRT

<213> mus musculus

<220>

<223> Luc90-VH chain

<400> 40

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

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

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

Gly Met Ile His Pro Ser Asp Ser Glu Thr Arg Leu Asn Gln Lys Phe
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50

55

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

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

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

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 41

<211> 107

<212> PRT

<213> mus musculus

<220>

<223> Luc90-VL chain

<400> 41

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

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

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

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

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Asn Val Gln Ala
65 70 75 80

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

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

<210> 42

<211> 121

<212> PRT

<213> mus musculus

<220>

<223> Luc34-VH chain

<400> 42

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
Page 42

eo1f-seq1.txt

1 5 10 15

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

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

Gly Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Gln Lys Phe
50 55 60

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

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

Ala Arg Gly Lys Val Tyr Tyr Gly Ser Asn Pro Phe Ala Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 43

<211> 107

<212> PRT

<213> mus musculus

<220>

<223> Luc34-VL chain

<400> 43

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

Gly Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30

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

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

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

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

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

eo1f-seq1.txt

<210> 44

<211> 120

<212> PRT

<213> mus musculus

<220>

<223> LucX1-VH chain

<400> 44

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

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Ser
20 25 30

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

Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Lys Tyr Asn Gly Lys Phe
50 55 60

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

Met Gln Leu Ser Ser Leu Thr Ser Val Asp Ser Ala Val Tyr Phe Cys
85 90 95

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

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 45

<211> 107

<212> PRT

<213> mus musculus

<220>

<223> LucX1-VL chain

<400> 45

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

Glu Lys Val Thr Ile Arg Cys Ile Thr Ser Thr Asp Ile Asp Asp Asp
20 25 30

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

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

eo1f-seq1.txt

Ser Gly Tyr Gly Thr Asp Phe Val Phe Thr Ile Glu Asn Met Leu Ser
65 70 75 80

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

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

<210> 46

<211> 120

<212> PRT

<213> mus musculus

<220>

<223> LucX2-VH chain

<400> 46

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

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Ser
20 25 30

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

Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Lys Tyr Asn Gly Lys Phe
50 55 60

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

Met Gln Leu Ser Ser Leu Thr Ser Val Asp Ser Ala Val Tyr Phe Cys
85 90 95

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

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 47

<211> 108

<212> PRT

<213> mus musculus

<220>

<223> LucX2-VL chain

<400> 47

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

eo1f-seq1.txt

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

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

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

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65 70 75 80

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

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

<210> 48

<211> 432

<212> PRT

<213> artificial sequence

<220>

<223> Luc63-V1 CAR

<400> 48

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Lys Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Asp Phe Ser Arg Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

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

Tyr Thr Pro Ser Leu Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr
100 105 110

Ala Leu Tyr Tyr Cys Ala Arg Pro Asp Gly Asn Tyr Trp Tyr Phe Asp
115 120 125

Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly

130

135

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr
145 150 155 160

Gln Ser His Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Ile
165 170 175

Thr Cys Lys Ala Ser Gln Asp Val Gly Ile Ala Val Ala Trp Tyr Gln
180 185 190

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
195 200 205

Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr
210 215 220

Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser Glu Asp Leu Ala Asp
225 230 235 240

Tyr Phe Cys Gln Gln Tyr Ser Ser Tyr Pro Tyr Thr Phe Gly Gly Gly
245 250 255

Thr Lys Leu Glu Ile Lys Gly Leu Ala Val Ser Thr Ile Ser Ser Phe
260 265 270

Phe Pro Pro Gly Tyr Gln Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
275 280 285

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
290 295 300

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
305 310 315 320

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
325 330 335

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
340 345 350

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
355 360 365

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
370 375 380

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
385 390 395 400

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
 420 425 430

<210> 49

<211> 485

<212> PRT

<213> artificial sequence

<220>

<223> Luc63-V2 CAR

<400> 49

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
 1 5 10 15

His Ala Ala Arg Pro Glu Val Lys Leu Leu Glu Ser Gly Gly Gly Leu
 20 25 30

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
 35 40 45

Asp Phe Ser Arg Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys
 50 55 60

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

Tyr Thr Pro Ser Leu Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala
 85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr
 100 105 110

Ala Leu Tyr Tyr Cys Ala Arg Pro Asp Gly Asn Tyr Trp Tyr Phe Asp
 115 120 125

Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
 130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr
 145 150 155 160

Gln Ser His Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Ile
 165 170 175

Thr Cys Lys Ala Ser Gln Asp Val Gly Ile Ala Val Ala Trp Tyr Gln
 180 185 190

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
 195 200 205

eo1f-seq1.txt

Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr
210 215 220

Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser Glu Asp Leu Ala Asp
225 230 235 240

Tyr Phe Cys Gln Gln Tyr Ser Ser Tyr Pro Tyr Thr Phe Gly Gly Gly
245 250 255

Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
260 265 270

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
275 280 285

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
290 295 300

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
305 310 315 320

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
325 330 335

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
340 345 350

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
355 360 365

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
370 375 380

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
385 390 395 400

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
405 410 415

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
420 425 430

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
435 440 445

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
450 455 460

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
465 470 475 480

eo1f-seq1.txt

Ala Leu Pro Pro Arg
485

<210> 50

<211> 647

<212> PRT

<213> artificial sequence

<220>

<223> Luc63-V3 CAR

<400> 50

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Lys Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Asp Phe Ser Arg Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

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

Tyr Thr Pro Ser Leu Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr
100 105 110

Ala Leu Tyr Tyr Cys Ala Arg Pro Asp Gly Asn Tyr Trp Tyr Phe Asp
115 120 125

Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr
145 150 155 160

Gln Ser His Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Ile
165 170 175

Thr Cys Lys Ala Ser Gln Asp Val Gly Ile Ala Val Ala Trp Tyr Gln
180 185 190

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
195 200 205

eof-seq1.txt

Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr
210 215 220

Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser Glu Asp Leu Ala Asp
225 230 235 240

Tyr Phe Cys Gln Gln Tyr Ser Ser Tyr Pro Tyr Thr Phe Gly Gly Gly
245 250 255

Thr Lys Leu Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr His Thr
260 265 270

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
275 280 285

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr Pro Glu
290 295 300

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
305 310 315 320

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
325 330 335

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
340 345 350

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
355 360 365

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
370 375 380

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
385 390 395 400

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
405 410 415

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480

eo1f-seq1.txt

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Lys Arg Gly
485 490 495

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
500 505 510

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
515 520 525

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
530 535 540

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
545 550 555 560

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
565 570 575

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
580 585 590

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
595 600 605

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
610 615 620

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
625 630 635 640

Met Gln Ala Leu Pro Pro Arg
645

<210> 51

<211> 433

<212> PRT

<213> artificial sequence

<220>

<223> Luc90-V1 CAR

<400> 51

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu
20 25 30

Val Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ser Phe Thr Thr Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

eo1f-seq1.txt

Gly Leu Glu Trp Ile Gly Met Ile His Pro Ser Asp Ser Glu Thr Arg
 65 70 75 80
 Leu Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser
 85 90 95
 Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Pro Thr Ser Glu Asp Ser
 100 105 110
 Ala Val Tyr Tyr Cys Ala Arg Ser Thr Met Ile Ala Thr Arg Ala Met
 115 120 125
 Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly
 130 135 140
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
 145 150 155 160
 Thr Gln Ser Gln Lys Ser Met Ser Thr Ser Val Gly Asp Arg Val Ser
 165 170 175
 Ile Thr Cys Lys Ala Ser Gln Asp Val Ile Thr Gly Val Ala Trp Tyr
 180 185 190
 Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Ser Ala Ser
 195 200 205
 Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly
 210 215 220
 Thr Asp Phe Thr Phe Thr Ile Ser Asn Val Gln Ala Glu Asp Leu Ala
 225 230 235 240
 Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Leu Thr Phe Gly Ala
 245 250 255
 Gly Thr Lys Leu Glu Leu Lys Gly Leu Ala Val Ser Thr Ile Ser Ser
 260 265 270
 Phe Phe Pro Pro Gly Tyr Gln Lys Arg Gly Arg Lys Lys Leu Leu Tyr
 275 280 285
 Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
 290 295 300
 Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
 305 310 315 320
 Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
 325 330 335

eo1f-seq1.txt

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
340 345 350

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
355 360 365

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
370 375 380

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
385 390 395 400

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
405 410 415

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
420 425 430

Arg

<210> 52

<211> 486

<212> PRT

<213> artificial sequence

<220>

<223> Luc90-V2 CAR

<400> 52

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu
20 25 30

Val Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ser Phe Thr Thr Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Met Ile His Pro Ser Asp Ser Glu Thr Arg
65 70 75 80

Leu Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser
85 90 95

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

eof-seq1.txt

Ala Val Tyr Tyr Cys Ala Arg Ser Thr Met Ile Ala Thr Arg Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145 150 155 160

Thr Gln Ser Gln Lys Ser Met Ser Thr Ser Val Gly Asp Arg Val Ser
165 170 175

Ile Thr Cys Lys Ala Ser Gln Asp Val Ile Thr Gly Val Ala Trp Tyr
180 185 190

Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Ser Ala Ser
195 200 205

Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly
210 215 220

Thr Asp Phe Thr Phe Thr Ile Ser Asn Val Gln Ala Glu Asp Leu Ala
225 230 235 240

Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Leu Thr Phe Gly Ala
245 250 255

Gly Thr Lys Leu Glu Leu Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

eof-seq1.txt

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 53

<211> 648

<212> PRT

<213> artificial sequence

<220>

<223> Luc90-V3 CAR

<400> 53

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu
20 25 30

Val Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ser Phe Thr Thr Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Met Ile His Pro Ser Asp Ser Glu Thr Arg
65 70 75 80

Leu Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser
85 90 95

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

Ala Val Tyr Tyr Cys Ala Arg Ser Thr Met Ile Ala Thr Arg Ala Met
115 120 125

eo1f-seq1.txt

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly
 130 135 140
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
 145 150 155 160
 Thr Gln Ser Gln Lys Ser Met Ser Thr Ser Val Gly Asp Arg Val Ser
 165 170 175
 Ile Thr Cys Lys Ala Ser Gln Asp Val Ile Thr Gly Val Ala Trp Tyr
 180 185 190
 Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Ser Ala Ser
 195 200 205
 Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly
 210 215 220
 Thr Asp Phe Thr Phe Thr Ile Ser Asn Val Gln Ala Glu Asp Leu Ala
 225 230 235 240
 Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Leu Thr Phe Gly Ala
 245 250 255
 Gly Thr Lys Leu Glu Leu Lys Glu Pro Lys Ser Pro Asp Lys Thr His
 260 265 270
 Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
 275 280 285
 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr Pro
 290 295 300
 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 305 310 315 320
 Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 325 330 335
 Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
 340 345 350
 Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 355 360 365
 Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
 370 375 380
 Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 385 390 395 400

eo1f-seq1.txt

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
405 410 415

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
420 425 430

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
435 440 445

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
450 455 460

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
465 470 475 480

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Lys Arg
485 490 495

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
500 505 510

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
515 520 525

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
530 535 540

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
545 550 555 560

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
565 570 575

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
580 585 590

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
595 600 605

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
610 615 620

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
625 630 635 640

His Met Gln Ala Leu Pro Pro Arg
645

<210> 54

eo1f-seq1.txt

<211> 434
<212> PRT
<213> artificial sequence

<220>
<223> Luc34-V1 CAR

<400> 54
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu
20 25 30

Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg
65 70 75 80

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

Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Lys Val Tyr Tyr Gly Ser Asn Pro
115 120 125

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
145 150 155 160

Met Thr Gln Ser Ser Ser Tyr Leu Ser Val Ser Leu Gly Gly Arg Val
165 170 175

Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp Leu Ala Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile Ser Gly Ala
195 200 205

Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Thr Glu Asp Val
225 230 235 240

eof-seq1.txt

Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Trp Thr Phe Gly
245 250 255

Gly Gly Thr Lys Leu Glu Ile Lys Gly Leu Ala Val Ser Thr Ile Ser
260 265 270

Ser Phe Phe Pro Pro Gly Tyr Gln Lys Arg Gly Arg Lys Lys Leu Leu
275 280 285

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
290 295 300

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
305 310 315 320

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
325 330 335

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
340 345 350

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
355 360 365

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
370 375 380

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
385 390 395 400

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
405 410 415

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
420 425 430

Pro Arg

<210> 55

<211> 487

<212> PRT

<213> artificial sequence

<220>

<223> Luc34-V2 CAR

<400> 55

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu
20 25 30

eo1f-seq1.txt

Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg
65 70 75 80

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

Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Lys Val Tyr Tyr Gly Ser Asn Pro
115 120 125

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Gln
145 150 155 160

Met Thr Gln Ser Ser Ser Tyr Leu Ser Val Ser Leu Gly Gly Arg Val
165 170 175

Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp Leu Ala Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile Ser Gly Ala
195 200 205

Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Thr Glu Asp Val
225 230 235 240

Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Trp Thr Phe Gly
245 250 255

Gly Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro
260 265 270

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
275 280 285

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
290 295 300

eo1f-seq1.txt

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
 305 310 315 320
 Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
 325 330 335
 Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
 340 345 350
 Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
 355 360 365
 Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
 370 375 380
 Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
 385 390 395 400
 Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
 405 410 415
 Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
 420 425 430
 Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
 435 440 445
 Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
 450 455 460
 Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
 465 470 475 480
 Met Gln Ala Leu Pro Pro Arg
 485
 <210> 56
 <211> 649
 <212> PRT
 <213> artificial sequence
 <220>
 <223> Luc34-V3 CAR
 <400> 56
 Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
 1 5 10 15
 His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu
 20 25 30

eof-seq1.txt

Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg
65 70 75 80

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

Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Lys Val Tyr Tyr Gly Ser Asn Pro
115 120 125

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Gln
145 150 155 160

Met Thr Gln Ser Ser Ser Tyr Leu Ser Val Ser Leu Gly Gly Arg Val
165 170 175

Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp Leu Ala Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile Ser Gly Ala
195 200 205

Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Thr Glu Asp Val
225 230 235 240

Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Trp Thr Phe Gly
245 250 255

Gly Gly Thr Lys Leu Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr
260 265 270

His Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
275 280 285

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr
290 295 300

eof-seq1.txt

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

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
325 330 335

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
340 345 350

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
355 360 365

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
370 375 380

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
385 390 395 400

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
405 410 415

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
420 425 430

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
435 440 445

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
450 455 460

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
465 470 475 480

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Lys
485 490 495

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
500 505 510

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
515 520 525

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
530 535 540

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
545 550 555 560

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
565 570 575

eof-seq1.txt

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
580 585 590

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
595 600 605

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
610 615 620

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
625 630 635 640

Leu His Met Gln Ala Leu Pro Pro Arg
645

<210> 57

<211> 433

<212> PRT

<213> artificial sequence

<220>

<223> LucX1-V1 CAR

<400> 57

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
20 25 30

Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ala Phe Ser Ser Ser Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Lys
65 70 75 80

Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser
85 90 95

Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Val Asp Ser
100 105 110

Ala Val Tyr Phe Cys Ala Arg Ser Thr Met Ile Ala Thr Gly Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Thr Thr Val
145 150 155 160

eo1f-seq1.txt

Thr Gln Ser Pro Ala Ser Leu Ser Met Ala Ile Gly Glu Lys Val Thr
 165 170 175
 Ile Arg Cys Ile Thr Ser Thr Asp Ile Asp Asp Asp Met Asn Trp Tyr
 180 185 190
 Gln Gln Lys Pro Gly Glu Pro Pro Lys Leu Leu Ile Ser Glu Gly Asn
 195 200 205
 Thr Leu Arg Pro Gly Val Pro Ser Arg Phe Ser Ser Ser Gly Tyr Gly
 210 215 220
 Thr Asp Phe Val Phe Thr Ile Glu Asn Met Leu Ser Glu Asp Val Ala
 225 230 235 240
 Asp Tyr Tyr Cys Leu Gln Ser Asp Asn Leu Pro Leu Thr Phe Gly Gly
 245 250 255
 Gly Thr Lys Leu Glu Ile Lys Gly Leu Ala Val Ser Thr Ile Ser Ser
 260 265 270
 Phe Phe Pro Pro Gly Tyr Gln Lys Arg Gly Arg Lys Lys Leu Leu Tyr
 275 285
 Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
 290 295 300
 Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
 305 310 315 320
 Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
 325 330 335
 Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
 340 345 350
 Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
 355 360 365
 Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
 370 375 380
 Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
 385 390 395 400
 Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
 405 410 415
 Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
 420 425 430

eo1f-seq1.txt

Arg

<210> 58

<211> 487

<212> PRT

<213> artificial sequence

<220>

<223> LucX1-V2 CAR

<400> 58

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu
20 25 30

Ala Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg
65 70 75 80

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

Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Lys Val Tyr Tyr Gly Ser Asn Pro
115 120 125

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Gln
145 150 155 160

Met Thr Gln Ser Ser Ser Tyr Leu Ser Val Ser Leu Gly Gly Arg Val
165 170 175

Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp Leu Ala Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile Ser Gly Ala
195 200 205

eo1f-seq1.txt

Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Thr Glu Asp Val
225 230 235 240

Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Trp Thr Phe Gly
245 250 255

Gly Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro
260 265 270

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
275 280 285

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
290 295 300

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
305 310 315 320

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
325 330 335

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
340 345 350

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
355 360 365

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
370 375 380

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385 390 395 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
405 410 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
420 425 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
435 440 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
450 455 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465 470 475 480

eo1f-seq1.txt

Met Gln Ala Leu Pro Pro Arg
485

<210> 59

<211> 648

<212> PRT

<213> artificial sequence

<220>

<223> LucX1-V3 CAR

<400> 59

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
20 25 30

Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ala Phe Ser Ser Ser Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Lys
65 70 75 80

Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser
85 90 95

Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Val Asp Ser
100 105 110

Ala Val Tyr Phe Cys Ala Arg Ser Thr Met Ile Ala Thr Gly Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Thr Thr Val
145 150 155 160

Thr Gln Ser Pro Ala Ser Leu Ser Met Ala Ile Gly Glu Lys Val Thr
165 170 175

Ile Arg Cys Ile Thr Ser Thr Asp Ile Asp Asp Asp Met Asn Trp Tyr
180 185 190

Gln Gln Lys Pro Gly Glu Pro Pro Lys Leu Leu Ile Ser Glu Gly Asn
195 200 205

Thr Leu Arg Pro Gly Val Pro Ser Arg Phe Ser Ser Ser Gly Tyr Gly
210 215 220

eo1f-seq1.txt

Thr Asp Phe Val Phe Thr Ile Glu Asn Met Leu Ser Glu Asp Val Ala
 225 230 235 240
 Asp Tyr Tyr Cys Leu Gln Ser Asp Asn Leu Pro Leu Thr Phe Gly Gly
 245 250 255
 Gly Thr Lys Leu Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr His
 260 265 270
 Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
 275 280 285
 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr Pro
 290 295 300
 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 305 310 315 320
 Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 325 330 335
 Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
 340 345 350
 Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 355 360 365
 Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
 370 375 380
 Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 385 390 395 400
 Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 405 410 415
 Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 420 425 430
 Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 435 440 445
 Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
 450 455 460
 Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 465 470 475 480
 Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Lys Arg
 485 490 495

eo1f-seq1.txt

Gly Arg Lys Lys₅₀₀ Leu Leu Tyr Ile Phe₅₀₅ Lys Gln Pro Phe Met₅₁₀ Arg Pro
Val Gln Thr₅₁₅ Thr Gln Glu Glu Asp₅₂₀ Gly Cys Ser Cys Arg₅₂₅ Phe Pro Glu
Glu Glu₅₃₀ Glu Gly Gly Cys Glu₅₃₅ Leu Arg Val Lys Phe₅₄₀ Ser Arg Ser Ala
Asp₅₄₅ Ala Pro Ala Tyr Gln₅₅₀ Gln Gly Gln Asn Gln₅₅₅ Leu Tyr Asn Glu Leu₅₆₀
Asn Leu Gly Arg Arg₅₆₅ Glu Glu Tyr Asp Val₅₇₀ Leu Asp Lys Arg Arg₅₇₅ Gly
Arg Asp Pro Glu₅₈₀ Met Gly Gly Lys Pro₅₈₅ Arg Arg Lys Asn Pro₅₉₀ Gln Glu
Gly Leu Tyr₅₉₅ Asn Glu Leu Gln Lys₆₀₀ Asp Lys Met Ala Glu₆₀₅ Ala Tyr Ser
Glu Ile₆₁₀ Gly Met Lys Gly Glu₆₁₅ Arg Arg Arg Gly Lys₆₂₀ Gly His Asp Gly
Leu Tyr Gln Gly Leu Ser₆₃₀ Thr Ala Thr Lys Asp₆₃₅ Thr Tyr Asp Ala Leu₆₄₀
His Met Gln Ala Leu₆₄₅ Pro Pro Arg

<210> 60

<211> 434

<212> PRT

<213> artificial sequence

<220>

<223> LucX2-V1 CAR

<400> 60

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
20 25 30

Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ala Phe Ser Ser Ser Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

eof-seq1.txt

Gly 65 Leu Glu Trp Ile Gly 70 Arg Ile Tyr Pro Gly 75 Asp Gly Asp Thr Lys 80
 Tyr Asn Gly Lys Phe 85 Lys Gly Lys Ala Thr 90 Leu Thr Ala Asp Lys 95 Ser
 Ser Ser Thr Ala 100 Tyr Met Gln Leu Ser 105 Ser Leu Thr Ser Val 110 Asp Ser
 Ala Val Tyr 115 Phe Cys Ala Arg Ser 120 Thr Met Ile Ala Thr 125 Gly Ala Met
 Asp Tyr 130 Trp Gly Gln Gly Thr 135 Ser Val Thr Val Ser 140 Ser Gly Gly Gly
 Gly 145 Ser Gly Gly Gly Gly 150 Ser Gly Gly Gly Gly 155 Ser Asp Ile Val Met 160
 Thr Gln Ser His Lys 165 Phe Met Ser Thr Ser 170 Val Gly Asp Arg Val 175 Ser
 Ile Thr Cys Lys 180 Ala Ser Gln Asp Val 185 Ser Thr Ala Val Ala 190 Trp Tyr
 Gln Gln Lys 195 Pro Gly Gln Ser Pro 200 Lys Leu Leu Ile Tyr 205 Ser Ala Ser
 Tyr Arg 210 Tyr Thr Gly Val Pro 215 Asp Arg Phe Thr Gly 220 Ser Gly Ser Gly
 Thr 225 Asp Phe Thr Phe Thr 230 Ile Ser Ser Val Gln 235 Ala Glu Asp Leu Ala 240
 Val Tyr Tyr Cys Gln 245 Gln His Tyr Ser Thr 250 Pro Pro Tyr Thr Phe 255 Gly
 Gly Gly Thr Lys 260 Leu Glu Ile Lys Gly 265 Leu Ala Val Ser Thr 270 Ile Ser
 Ser Phe Phe 275 Pro Pro Gly Tyr Gln 280 Lys Arg Gly Arg Lys 285 Lys Leu Leu
 Tyr Ile 290 Phe Lys Gln Pro Phe 295 Met Arg Pro Val Gln 300 Thr Thr Gln Glu
 Glu 305 Asp Gly Cys Ser Cys 310 Arg Phe Pro Glu Glu 315 Glu Glu Gly Gly Cys 320
 Glu Leu Arg Val Lys 325 Phe Ser Arg Ser Ala 330 Asp Ala Pro Ala Tyr 335 Gln

eof-seq1.txt

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
340 345 350

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
355 360 365

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
370 375 380

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
385 390 395 400

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
405 410 415

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
420 425 430

Pro Arg

<210> 61

<211> 487

<212> PRT

<213> artificial sequence

<220>

<223> LucX2-V2 CAR

<400> 61

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
20 25 30

Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ala Phe Ser Ser Ser Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Lys
65 70 75 80

Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser
85 90 95

Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Val Asp Ser
100 105 110

Ala Val Tyr Phe Cys Ala Arg Ser Thr Met Ile Ala Thr Gly Ala Met
115 120 125

eo1f-seq1.txt

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly
 130 135 140
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
 145 150 155 160
 Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser
 165 170 175
 Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala Val Ala Trp Tyr
 180 185 190
 Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Ser Ala Ser
 195 200 205
 Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly
 210 215 220
 Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala
 225 230 235 240
 Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Pro Tyr Thr Phe Gly
 245 250 255
 Gly Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro
 260 265 270
 Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
 275 280 285
 Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
 290 295 300
 Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
 305 310 315 320
 Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
 325 330 335
 Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
 340 345 350
 Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
 355 360 365
 Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
 370 375 380
 Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
 385 390 395 400

eo1f-seq1.txt

Leu Gly Arg Arg Glu Gly Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
405 410 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
420 425 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
435 440 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
450 455 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465 470 475 480

Met Gln Ala Leu Pro Pro Arg
485

<210> 62

<211> 649

<212> PRT

<213> artificial sequence

<220>

<223> LucX2-V3 CAR

<400> 62

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
20 25 30

Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ala Phe Ser Ser Ser Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Lys
65 70 75 80

Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser
85 90 95

Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Val Asp Ser
100 105 110

Ala Val Tyr Phe Cys Ala Arg Ser Thr Met Ile Ala Thr Gly Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly
 130 135 140
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
 145 150 155
 Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser
 165 170 175
 Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala Val Ala Trp Tyr
 180 185 190
 Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Ser Ala Ser
 195 200 205
 Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly
 210 215 220
 Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala
 225 230 235 240
 Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Pro Tyr Thr Phe Gly
 245 250 255
 Gly Gly Thr Lys Leu Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr
 260 265 270
 His Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
 275 280 285
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr
 290 295 300
 Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
 305 310 315 320
 Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 325 330 335
 Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
 340 345 350
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 355 360 365
 Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
 370 375 380
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 385 390 395 400

eo1f-seq1.txt

Pro Ser Arg Asp Glu₄₀₅ Leu Thr Lys Asn Gln₄₁₀ Val Ser Leu Thr Cys₄₁₅ Leu
Val Lys Gly Phe₄₂₀ Tyr Pro Ser Asp Ile₄₂₅ Ala Val Glu Trp Glu₄₃₀ Ser Asn
Gly Gln Pro₄₃₅ Glu Asn Asn Tyr Lys₄₄₀ Thr Thr Pro Pro Val₄₄₅ Leu Asp Ser
Asp Gly₄₅₀ Ser Phe Phe Leu Tyr₄₅₅ Ser Lys Leu Thr Val₄₆₀ Asp Lys Ser Arg
Trp Gln Gln Gly Asn Val₄₇₀ Phe Ser Cys Ser Val₄₇₅ Met His Glu Ala Leu₄₈₀
His Asn His Tyr Thr₄₈₅ Gln Lys Ser Leu Ser₄₉₀ Leu Ser Pro Gly Lys₄₉₅ Lys
Arg Gly Arg Lys₅₀₀ Lys Leu Leu Tyr Ile₅₀₅ Phe Lys Gln Pro Phe₅₁₀ Met Arg
Pro Val Gln₅₁₅ Thr Thr Gln Glu Glu₅₂₀ Asp Gly Cys Ser Cys₅₂₅ Arg Phe Pro
Glu Glu₅₃₀ Glu Glu Gly Gly Cys₅₃₅ Glu Leu Arg Val Lys₅₄₀ Phe Ser Arg Ser
Ala Asp Ala Pro Ala Tyr₅₅₀ Gln Gln Gly Gln Asn₅₅₅ Gln Leu Tyr Asn Glu₅₆₀
Leu Asn Leu Gly₅₆₅ Arg Arg Glu Glu Tyr Asp₅₇₀ Val Leu Asp Lys Arg₅₇₅ Arg
Gly Arg Asp Pro₅₈₀ Glu Met Gly Gly Lys₅₈₅ Pro Arg Arg Lys Asn₅₉₀ Pro Gln
Glu Gly Leu₅₉₅ Tyr Asn Glu Leu Gln₆₀₀ Lys Asp Lys Met Ala₆₀₅ Glu Ala Tyr
Ser Glu₆₁₀ Ile Gly Met Lys Gly₆₁₅ Glu Arg Arg Arg Gly₆₂₀ Lys Gly His Asp
Gly Leu Tyr Gln Gly Leu₆₃₀ Ser Thr Ala Thr Lys₆₃₅ Asp Thr Tyr Asp Ala₆₄₀
Leu His Met Gln Ala₆₄₅ Leu Pro Pro Arg

<210> 64

<211> 17

<212> DNA
 <213> artificial sequence
 <220>
 <223> CS1 T01 left TALE
 <400> 64
 tgacttcag agagcaa 17

<210> 65
 <211> 17
 <212> DNA
 <213> artificial sequence
 <220>
 <223> CS1 T01 right TALE
 <400> 65
 aacatgcctc accctca 17

<210> 66
 <211> 49
 <212> DNA
 <213> homosapiens
 <220>
 <223> CS1 T02 target
 <400> 66
 ttccagagag caatatggct gggtcccca catgcctcac cctcatcta 49

<210> 67
 <211> 17
 <212> DNA
 <213> artificial sequence
 <220>
 <223> CS1 T02 left TALE
 <400> 67
 ttccagagag caatatg 17

<210> 68
 <211> 17
 <212> DNA
 <213> artificial sequence
 <220>
 <223> CS1 T02 right TALE
 <400> 68
 tgcctcacc tcata 17

<210> 69
 <211> 49
 <212> DNA
 <213> homo sapiens

<220>
 <223> CS1 T03 target
 <400> 69
 ttgactctat tgtctggacc ttcaacacaa cccctcttgt caccataca 49
 <210> 70
 <211> 17
 <212> DNA
 <213> artificial sequence
 <220>
 <223> CS1 T03 left TALE
 <400> 70
 ttgactctat tgtctgg 17
 <210> 71
 <211> 17
 <212> DNA
 <213> artificial sequence
 <220>
 <223> CS1 T03 right TALE
 <400> 71
 cctcttgtca ccataca 17
 <210> 72
 <211> 49
 <212> DNA
 <213> homo sapiens
 <220>
 <223> CD70 target 1
 <400> 72
 tggctcttttc ttccagtggg acgtagctga gctgcagctg aatcacaca 49
 <210> 73
 <211> 17
 <212> DNA
 <213> artificial sequence
 <220>
 <223> CD70 Target 1-left TALE
 <400> 73
 tggctcttttc ttccagt 17
 <210> 74
 <211> 17
 <212> DNA
 <213> artificial sequence
 <220>
 <223> CD70 Target 1-right TALE

<400> 74
 tgcagctgaa tcacaca 17

<210> 75
 <211> 49
 <212> DNA
 <213> homo sapiens
 <220>
 <223> CD70 target 2

<400> 75
 tggatgatctg cctcgtggtg tgcattccagc gcttcgcaca ggctcagca 49

<210> 76
 <211> 17
 <212> DNA
 <213> artificial sequence
 <220>
 <223> CD70 Target 2-left TALE

<400> 76
 tggatgatctg cctcgtg 17

<210> 77
 <211> 17
 <212> DNA
 <213> artificial sequence
 <220>
 <223> CD70 Target 2-right TALE

<400> 77
 ttcgcacagg ctcagca 17

<210> 78
 <211> 57
 <212> DNA
 <213> homo sapiens
 <220>
 <223> CD70 target 3

<400> 78
 tgcgggctgc tttggtccca ttggtcgcgg gcttggtgat ctgcctcgtg gtgtgca 57

<210> 79
 <211> 17
 <212> DNA
 <213> artificial sequence
 <220>
 <223> CD70 Target 3-left TALE

<400> 79
 tgcgggctgc tttggtc 17

eo1f-seq1.txt

<210> 80

<211> 17

<212> DNA

<213> artificial sequence

<220>

<223> CD70 Target 3-right TALE

<400> 80

ctgcctcgtg gtgtgca

17

<210> 81

<211> 122

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 Ab4-VH chain

<400> 81

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

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

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

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

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

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

Ala Arg Asp Gly Gly Tyr Ser Gly Tyr Asp Ser Gly Phe Asp Tyr Trp
100 105 110

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

<210> 82

<211> 1358

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD70 Ab4-VH chain

<400> 82

aggtgcagct ggtggagtct gggggaggcg tgggtccagcc tgggaggtcc ctgagactct 60
cctgtgcagc gtctggattc accttcagta actatggcat acactgggtc cgccaggctc 120

eo1f-seq1.txt

caggcaaggg	gctggagtg	gtggcagtta	tatggtatga	tggaagtaat	aaatactatg	180
cagactccgt	gaagggccga	ttcaccatct	ccagagacaa	ttccaagaac	acgctgtatc	240
tgcaaatgaa	cagcctgaga	gccgaggaca	cggctgtgta	ttactgtgcg	agagatggag	300
gatatagtgg	ctacgattcg	gggtttgact	actggggcca	gggaaccctg	gtcaccgtct	360
cctcagctag	caccaagggc	ccatccgtct	ttcccctggc	accctcctcc	aagagcacct	420
ctggggggcac	agcggccctg	ggctgcctgg	tcaaggacta	cttccccgaa	ccggtgacgg	480
tgtcgtggaa	ctcaggcgcc	ctgaccagcg	gcgtgcacac	cttcccggct	gtcctacagt	540
cctcaggact	ctactccctc	agcagcgtgg	tgaccgtgcc	ctccagcagc	ttgggcaccc	600
agacctacat	ctgcaacgtg	aatcacaaagc	ccagcaacac	caaggtggac	aagaaagtgt	660
agcccaaadc	ttgtgacaaa	actcacacat	gccaccgtg	cccagcacct	gaactcctgg	720
ggggaccgtc	agtcttcctc	ttccccccaa	aacccaagga	caccctcatg	atctcccgga	780
cccctgaggt	cacatgcgtg	gtggtggacg	tgagccacga	agaccctgag	gtcaagttca	840
actggtacgt	ggacggcgtg	gaggtgcata	atgccaaagc	aaagccgcgg	gaggagcagt	900
acaacagcac	gtaccgtgtg	gtcagcgtcc	tcaccgtcct	gcaccaggac	tggctgaatg	960
gcaaggagta	caagtgcagg	gtctccaaca	aagccctccc	agcccccatc	gagaaaacca	1020
tctccaaagc	caaagggcag	ccccgagaac	cacaggtgta	caccctgccc	ccatcccggg	1080
aggagatgac	caagaaccag	gtcagcctga	cctgcctggt	caaaggcttc	tatcccagcg	1140
acatcgccgt	ggagtgggag	agcaatgggc	agccggagaa	caactacaag	accacgcctc	1200
ccgtgctgga	ctccgacggc	tccttcttcc	tctatagcaa	gctcaccgtg	gacaagagca	1260
ggtggcagca	ggggaacgtc	ttctcatgct	ccgtgatgca	tgaggctctg	cacaaccact	1320
acacgcagaa	gagcctctcc	ctgtctccgg	gtaaataga			1358

<210> 83

<211> 112

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 Ab4-VL chain

<400> 83

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

Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	Asn	Ser
			20					25					30		

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

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

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

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

Leu	Gln	Thr	Pro	Phe	Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Asp	Ile	Lys
			100					105					110		

<210> 84

<211> 1476

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD70 Ab4-VL chain

eof-seq1.txt

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<400> 84
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atctcctgca ggtctagtca gagcctcctg aatagtaatg gatacaacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ttcctgatct atttgggttc ttatcgggcc 180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgagaatc 240
agcagagtgg aggctgagga tgttgggggt tattactgta taaaaactct aaaaactcca 300
ttcactttcg gccctgggac caaagtggat atcaaacgta cggtggctgc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420
ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480
tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540
agcagcaccg tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcaccatc agggcctgag ctgcccgtc acaaagagct tcaacagggg agagtgttag 660
tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcag cttgggcacc 720
cagacctaca tctgcaacgt gaatcacaa cccagcaaca ccaaggtgga caagaaagt 780
gagcccaaat cttgtgacaa aactcacaca tgcccaccgt gccagcacc tgaactcctg 840
gggggaccgt cagtcttctt cttcccccca aaaccaagg acaccctcat gatctcccgg 900
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 1020
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagcccccat cgagaaaacc 1140
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1200
gaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc 1260
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1320
cccgtgctgg actccgacgg ctccttcttc ctctatagca agctcaccgt ggacaagagc 1380
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1440
tacacgcaga agagcctctc cctgtctccg ggtaaa 1476

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<210> 85

<211> 122

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 Ab8-VH chain

<400> 85

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

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

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

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

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

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

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

Gly Gln Gly Thr Leu Val Thr Val Ser Ser

115

120

<210> 86

<211> 560

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD70 Ab8-VH chain

<400> 86

caggtgcagc	tggtggagtc	tgggggaggc	gtggtccagc	ctgggaggtc	cctgagactc	60
tcctgtgcag	cgctggatt	caccttcagt	agctatggca	tgactgggt	ccgccaggct	120
ccaggcaagg	ggctggagt	ggtggcagtt	atatggtatg	atggaagtga	taaatacttt	180
gcagactccg	tgaagggccg	attcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
ctgcaaata	acagcctgag	agccgaggac	acggctgtgt	attactgtgc	gagagatggg	300
atagcaggag	ctcgctacgt	ctactttgac	tactggggcc	aggaaccct	ggtcaccgtc	360
tcctcagcta	gcaccaagg	cccattccgtc	ttccccctgg	caccctcctc	caagagcacc	420
tctgggggca	cagcgccct	gggtgcctg	gtcaaggact	acttccccga	accggtgacg	480
gtgtcgtgga	actcaggcgc	cctgaccagc	ggcgtgcaca	ccttcccggc	tgctctacag	540
tcctcaggac	tctactccct					560

<210> 87

<211> 107

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 Ab8-VL chain

<400> 87

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

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

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

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

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

Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Tyr	Asn	Tyr	Pro	Phe
				85					90					95	

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

<210> 88

<211> 645

<212> DNA

<213> artificial sequence

eo1f-seq1.txt

<220>

<223> anti-CD70 Ab8-VL chain

<400> 88

gacatccaga	tgacccagtc	tccatcctcc	ctgtctgcat	ctgtaggaga	cagagtcacc	60
atcacttgtc	gggcgagtc	gggcattagc	aattatttag	cctggtttca	gcagaaacca	120
gggaaagccc	ctaagtccct	gatctatgct	gcatccagtt	tgcaagggtg	gggtcccatca	180
aagttcagcg	gcagtggatc	tgggacagat	ttcactctca	ccatcagcag	cctgcagcct	240
gaagattttg	caacttatta	ctgccaacaa	tattataatt	acccattcac	tttcggccct	300
gggaccacag	tggatatcaa	acgtacggtg	gctgcacat	ctgtcttcat	cttcccgcga	360
tctgatgagc	agttgaaatc	tggaactgcc	tctgtttgtg	gcctgctgaa	taacttctat	420
cccagagagg	ccaaagtaca	gtggaagggt	gataacgccc	tccaatcggg	taactcccag	480
gagagtgtca	cagagcagga	cagcaaggac	agcacctaca	gcctcagcag	caccctgacg	540
ctgagcaaag	cagactacga	gaaacacaaa	gtctacgcct	gcgaagtcac	ccatcagggc	600
ctgagctcgc	ccgtcacaaa	gagcttcaac	aggggagagt	gtttag		645

<210> 89

<211> 117

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 1F6-VH chain

<400> 89

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

Thr	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr
			20					25					30		

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

Gly	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Ala	Phe	Lys
	50					55					60				

Gly	Arg	Phe	Ala	Phe	Ser	Leu	Glu	Thr	Ser	Ala	Ser	Thr	Ala	Tyr	Leu
65					70					75					80

Gln	Ile	Asn	Asn	Leu	Lys	Asn	Glu	Asp	Thr	Ala	Thr	Tyr	Phe	Cys	Ala
				85					90					95	

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

Val	Thr	Val	Ser	Ser
				115

<210> 90

<211> 411

<212> DNA

<213> artificial sequence

eo1f-seq1.txt

<220>

<223> anti-CD70 1F6-VH chain

<400> 90

atggccttggg	tgtggacctt	gctattcctg	atggcagctg	cccaaagtgc	ccaagcacag	60
atccagttgg	tgcagtctgg	acctgaggtg	aagaagcctg	gagagacagt	caagatctcc	120
tgcaaggctt	ctgggtatac	cttcacaaac	tatggaatga	actgggtgaa	gcaggctcca	180
ggaaagggtt	taaagtggat	gggctggata	aacacctaca	ctggagagcc	aacatatgct	240
gatgccctca	agggacgggt	tgccttctct	ttggaaacct	ctgccagcac	tgcttatttg	300
cagatcaaca	acctcaaaaa	tgaggacacg	gctacatatt	tctgtgcaag	agactacggc	360
gactatggta	tggactactg	gggtcaagga	acctcagtca	ccgtctcctc	a	411

<210> 91

<211> 112

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 1F6-VL chain

<400> 91

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

Gln	Arg	Ala	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20					25					30		

Gly	Tyr	Ser	Phe	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
		35					40					45			

Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Asn	Leu	Glu	Ser	Gly	Val	Pro	Ala
	50					55					60				

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

Pro	Val	Glu	Glu	Glu	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
				85					90					95	

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

<210> 92

<211> 396

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD70 1F6-VL chain

<400> 92

atggagacag	acacactcct	gttatgggta	ctgctgctct	gggttccagg	ttccactggg	60
gacattgtgc	tgacacagtc	tcctgcttcc	ttagctgtat	ctctggggca	gagggccacc	120
atctcatgca	gggccagcaa	aagtgtcagt	acatctggct	atagttttat	gcactgggat	180
caacagaaac	caggacagcc	accctaaact	ctcatctatc	ttgcatccaa	cctagaatct	240
gggggtccctg	ccagggttcag	tggcagtggg	tctgggacag	acttcaccct	caacatccat	300

eof-seq1.txt

cctgtggagg aggaggatgc tgcaacctat tactgtcagc acagtaggga ggttccgtgg 360
acgttcggtg gaggaccaa gctggaaatc aaacgg 396

<210> 93

<211> 464

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 Ab4-V1 CAR

<400> 93

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val
20 25 30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Asn Tyr Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Gly Gly Tyr Ser Gly Tyr Asp Ser
115 120 125

Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile
145 150 155 160

Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro
165 170 175

Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Asn Ser Asn Gly
180 185 190

Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln
195 200 205

eof-seq1.txt

Phe Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro Asp Arg
210 215 220

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Arg
225 230 235 240

Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ile Gln Thr Leu Gln
245 250 255

Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Gly Leu
260 265 270

Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln Ile Tyr
275 280 285

Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu
290 295 300

Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
305 310 315 320

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
325 330 335

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu
340 345 350

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
355 360 365

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
370 375 380

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
385 390 395 400

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
405 410 415

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
420 425 430

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
435 440 445

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
450 455 460

eo1f-seq1.txt

<210> 94

<211> 493

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 Ab4-V2 CAR

<400> 94

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val
20 25 30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Asn Tyr Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Gly Gly Tyr Ser Gly Tyr Asp Ser
115 120 125

Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile
145 150 155 160

Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro
165 170 175

Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Asn Ser Asn Gly
180 185 190

Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln
195 200 205

Phe Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro Asp Arg
210 215 220

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Arg
225 230 235 240

eo1f-seq1.txt

Val Glu Ala Glu Asp₂₄₅ Val Gly Val Tyr Tyr₂₅₀ Cys Ile Gln Thr Leu₂₅₅ Gln
 Thr Pro Phe Thr₂₆₀ Phe Gly Pro Gly Thr₂₆₅ Lys Val Asp Ile Lys₂₇₀ Thr Thr
 Thr Pro Ala₂₇₅ Pro Arg Pro Pro Thr₂₈₀ Pro Ala Pro Thr Ile₂₈₅ Ala Ser Gln
 Pro Leu₂₉₀ Ser Leu Arg Pro Glu₂₉₅ Ala Cys Arg Pro Ala₃₀₀ Ala Gly Gly Ala
 Val₃₀₅ His Thr Arg Gly Leu₃₁₀ Asp Phe Ala Cys Asp₃₁₅ Ile Tyr Ile Trp Ala₃₂₀
 Pro Leu Ala Gly Thr₃₂₅ Cys Gly Val Leu₃₃₀ Leu Ser Leu Val Ile₃₃₅ Thr
 Leu Tyr Cys Lys₃₄₀ Arg Gly Arg Lys Lys₃₄₅ Leu Leu Tyr Ile Phe₃₅₀ Lys Gln
 Pro Phe Met₃₅₅ Arg Pro Val Gln Thr₃₆₀ Thr Gln Glu Glu Asp₃₆₅ Gly Cys Ser
 Cys Arg₃₇₀ Phe Pro Glu Glu Glu₃₇₅ Glu Gly Gly Cys Glu₃₈₀ Leu Arg Val Lys
 Phe₃₈₅ Ser Arg Ser Ala Asp₃₉₀ Ala Pro Ala Tyr Gln₃₉₅ Gln Gly Gln Asn Gln₄₀₀
 Leu Tyr Asn Glu₄₀₅ Leu Asn Leu Gly Arg Arg₄₁₀ Glu Glu Tyr Asp Val₄₁₅ Leu
 Asp Lys Arg Arg₄₂₀ Gly Arg Asp Pro Glu₄₂₅ Met Gly Gly Lys Pro₄₃₀ Arg Arg
 Lys Asn Pro₄₃₅ Gln Glu Gly Leu Tyr₄₄₀ Asn Glu Leu Gln Lys₄₄₅ Asp Lys Met
 Ala Glu₄₅₀ Ala Tyr Ser Glu Ile₄₅₅ Gly Met Lys Gly Glu₄₆₀ Arg Arg Arg Gly
 Lys₄₆₅ Gly His Asp Gly Leu₄₇₀ Tyr Gln Gly Leu Ser₄₇₅ Thr Ala Thr Lys Asp₄₈₀
 Thr Tyr Asp Ala Leu₄₈₅ His Met Gln Ala Leu₄₉₀ Pro Pro Arg

<210> 95

eo1f-seq1.txt

<211> 584
 <212> PRT
 <213> artificial sequence

<220>
 <223> anti-CD70 Ab4-V3 CAR

<400> 95
 Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
 1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val
 20 25 30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
 35 40 45

Thr Phe Ser Asn Tyr Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys
 50 55 60

Gly Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr
 65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
 85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
 100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Gly Gly Tyr Ser Gly Tyr Asp Ser
 115 120 125

Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
 130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
 145 150 155 160

Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro
 165 170 175

Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Asn Ser Asn Gly
 180 185 190

Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln
 195 200 205

Phe Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro Asp Arg
 210 215 220

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Arg
 225 230 235 240

eo1f-seq1.txt

Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ile Gln Thr Leu Gln
245 250 255

Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Glu Pro
260 265 270

Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Pro
275 280 285

Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
290 295 300

Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
305 310 315 320

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
325 330 335

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
340 345 350

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

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
370 375 380

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
385 390 395 400

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
405 410 415

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
420 425 430

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
435 440 445

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
450 455 460

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
465 470 475 480

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
485 490 495

Leu Ser Pro Gly Lys Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
500 505 510

eo1f-seq1.txt

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
515 520 525

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
530 535 540

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

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

Ala Pro Ala Tyr Gln Gln Gly Gln
580

<210> 96

<211> 459

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 Ab8-V1 CAR

<400> 96

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val
20 25 30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asp Lys Tyr
65 70 75 80

Phe Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Gly Ile Ala Gly Ala Arg Tyr Val
115 120 125

Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
145 150 155 160

eo1f-seq1.txt

Gln Met Thr Gln Ser₁₆₅ Pro Ser Ser Leu Ser₁₇₀ Ala Ser Val Gly Asp₁₇₅ Arg
Val Thr Ile Thr₁₈₀ Cys Arg Ala Ser Gln₁₈₅ Gly Ile Ser Asn Tyr₁₉₀ Leu Ala
Trp Phe Gln₁₉₅ Gln Lys Pro Gly Lys₂₀₀ Ala Pro Lys Ser Leu₂₀₅ Ile Tyr Ala
Ala Ser₂₁₀ Ser Leu Gln Gly Gly₂₁₅ Val Pro Ser Lys Phe₂₂₀ Ser Gly Ser Gly
Ser₂₂₅ Gly Thr Asp Phe Thr₂₃₀ Leu Thr Ile Ser Ser₂₃₅ Leu Gln Pro Glu Asp₂₄₀
Phe Ala Thr Tyr Tyr₂₄₅ Cys Gln Gln Tyr Tyr₂₅₀ Asn Tyr Pro Phe Thr₂₅₅ Phe
Gly Pro Gly Thr₂₆₀ Thr Val Asp Ile Lys₂₆₅ Gly Leu Ala Val Ser₂₇₀ Thr Ile
Ser Ser Phe₂₇₅ Phe Pro Pro Gly Tyr₂₈₀ Gln Ile Tyr Ile Trp₂₈₅ Ala Pro Leu
Ala Gly₂₉₀ Thr Cys Gly Val Leu₂₉₅ Leu Leu Ser Leu Val₃₀₀ Ile Thr Leu Tyr
Cys₃₀₅ Lys Arg Gly Arg Lys₃₁₀ Lys Leu Leu Tyr Ile₃₁₅ Phe Lys Gln Pro Phe₃₂₀
Met Arg Pro Val₃₂₅ Gln Thr Thr Gln Glu Glu₃₃₀ Asp Gly Cys Ser Cys₃₃₅ Arg
Phe Pro Glu Glu₃₄₀ Glu Glu Gly Gly Cys₃₄₅ Glu Leu Arg Val Lys₃₅₀ Phe Ser
Arg Ser Ala₃₅₅ Asp Ala Pro Ala Tyr₃₆₀ Gln Gln Gly Gln Asn₃₆₅ Gln Leu Tyr
Asn Glu₃₇₀ Leu Asn Leu Gly Arg₃₇₅ Arg Glu Glu Tyr Asp₃₈₀ Val Leu Asp Lys
Arg₃₈₅ Arg Gly Arg Asp Pro₃₉₀ Glu Met Gly Gly Lys₃₉₅ Pro Arg Arg Lys Asn₄₀₀
Pro Gln Glu Gly₄₀₅ Leu Tyr Asn Glu Leu Gln₄₁₀ Lys Asp Lys Met Ala Glu₄₁₅
Ala Tyr Ser Glu₄₂₀ Ile Gly Met Lys Gly₄₂₅ Glu Arg Arg Arg Gly₄₃₀ Lys Gly

eo1f-seq1.txt

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
435 440 445

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
450 455

<210> 97

<211> 488

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 Ab8-V2 CAR

<400> 97

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val
20 25 30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asp Lys Tyr
65 70 75 80

Phe Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Gly Ile Ala Gly Ala Arg Tyr Val
115 120 125

Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
145 150 155 160

Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
165 170 175

Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
180 185 190

eo1f-seq1.txt

Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile Tyr Ala
195 200 205

Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Lys Phe Ser Gly Ser Gly
210 215 220

Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp
225 230 235 240

Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asn Tyr Pro Phe Thr Phe
245 250 255

Gly Pro Gly Thr Thr Val Asp Ile Lys Thr Thr Thr Pro Ala Pro Arg
260 265 270

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
275 280 285

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
290 295 300

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
305 310 315 320

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
325 330 335

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
340 345 350

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
355 360 365

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
370 375 380

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
385 390 395 400

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
405 410 415

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
420 425 430

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
435 440 445

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
450 455 460

eo1f-seq1.txt

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
465 470 475 480

His Met Gln Ala Leu Pro Pro Arg
485

<210> 98

<211> 674

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 Ab8-V3 CAR

<400> 98

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val
20 25 30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asp Lys Tyr
65 70 75 80

Phe Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Gly Ile Ala Gly Ala Arg Tyr Val
115 120 125

Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile
145 150 155 160

Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
165 170 175

Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
180 185 190

Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile Tyr Ala
195 200 205

eo1f-seq1.txt

Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Lys Phe Ser Gly Ser Gly
210 215 220

Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp
225 230 235 240

Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asn Tyr Pro Phe Thr Phe
245 250 255

Gly Pro Gly Thr Thr Val Asp Ile Lys Glu Pro Lys Ser Pro Asp Lys
260 265 270

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
275 280 285

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ala Arg
290 295 300

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

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
325 330 335

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
340 345 350

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
355 360 365

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
370 375 380

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
385 390 395 400

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
405 410 415

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
420 425 430

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
435 440 445

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
450 455 460

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

eo1f-seq1.txt

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490 495

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
500 505 510

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
515 520 525

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
530 535 540

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys
545 550 555 560

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
565 570 575

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
580 585 590

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
595 600 605

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
610 615 620

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
625 630 635 640

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
645 650 655

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
660 665 670

Pro Arg

<210> 99

<211> 459

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 1F6-V1 CAR

<400> 99

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

eof-seq1.txt

His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Val
20 25 30

Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys
50 55 60

Gly Leu Lys Trp Met Gly Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr
65 70 75 80

Ala Asp Ala Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala
85 90 95

Ser Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala
100 105 110

Thr Tyr Phe Cys Ala Arg Asp Tyr Gly Asp Tyr Gly Met Asp Tyr Trp
115 120 125

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
145 150 155 160

Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys
165 170 175

Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Phe Met His Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala
195 200 205

Ser Asn Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala
225 230 235 240

Ala Thr Tyr Tyr Cys Gln His Ser Arg Glu Val Pro Trp Thr Phe Gly
245 250 255

Gly Gly Thr Lys Leu Glu Ile Lys Arg Gly Leu Ala Val Ser Thr Ile
260 265 270

Ser Ser Phe Phe Pro Pro Gly Tyr Gln Ile Tyr Ile Trp Ala Pro Leu
275 280 285

eo1f-seq1.txt

Ala Gly Thr Cys Gly Val Leu Leu Ser Leu Val Ile Thr Leu Tyr
290 295 300

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
305 310 315 320

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
325 330 335

Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
340 345 350

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
355 360 365

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
370 375 380

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
385 390 395 400

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
405 410 415

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
420 425 430

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
435 440 445

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
450 455

<210> 100

<211> 488

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 1F6-V2 CAR

<400> 100

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Val
20 25 30

Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys
50 55 60

eo1f-seq1.txt

Gly Leu Lys Trp Met Gly Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr
 65 70 75 80
 Ala Asp Ala Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala
 85 90 95
 Ser Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala
 100 105 110
 Thr Tyr Phe Cys Ala Arg Asp Tyr Gly Asp Tyr Gly Met Asp Tyr Trp
 115 120 125
 Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 130 135 140
 Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
 145 150 155 160
 Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys
 165 170 175
 Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Phe Met His Trp
 180 185 190
 Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala
 195 200 205
 Ser Asn Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser
 210 215 220
 Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala
 225 230 235 240
 Ala Thr Tyr Tyr Cys Gln His Ser Arg Glu Val Pro Trp Thr Phe Gly
 245 250 255
 Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Thr Thr Pro Ala Pro Arg
 260 265 270
 Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
 275 280 285
 Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
 290 295 300
 Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
 305 310 315 320
 Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
 325 330 335

eo1f-seq1.txt

Gly Arg Lys Lys₃₄₀ Leu Leu Tyr Ile Phe₃₄₅ Lys Gln Pro Phe Met₃₅₀ Arg Pro
Val Gln Thr₃₅₅ Thr Gln Glu Glu Asp₃₆₀ Gly Cys Ser Cys Arg₃₆₅ Phe Pro Glu
Glu Glu Glu Gly Gly Cys Glu₃₇₅ Leu Arg Val Lys Phe₃₈₀ Ser Arg Ser Ala
Asp₃₈₅ Ala Pro Ala Tyr Gln₃₉₀ Gln Gly Gln Asn Gln₃₉₅ Leu Tyr Asn Glu Leu₄₀₀
Asn Leu Gly Arg Arg₄₀₅ Glu Glu Tyr Asp Val₄₁₀ Leu Asp Lys Arg Arg₄₁₅ Gly
Arg Asp Pro Glu₄₂₀ Met Gly Gly Lys Pro₄₂₅ Arg Arg Lys Asn Pro₄₃₀ Gln Glu
Gly Leu Tyr₄₃₅ Asn Glu Leu Gln Lys₄₄₀ Asp Lys Met Ala Glu₄₄₅ Ala Tyr Ser
Glu Ile Gly Met Lys Gly Glu₄₅₅ Arg Arg Arg Gly Lys₄₆₀ Gly His Asp Gly
Leu Tyr Gln Gly Leu Ser₄₇₀ Thr Ala Thr Lys Asp₄₇₅ Thr Tyr Asp Ala Leu₄₈₀
His Met Gln Ala Leu₄₈₅ Pro Pro Arg

<210> 101

<211> 674

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD70 1F6-V3 CAR

<400> 101

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Val
20 25 30

Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys
50 55 60

eo1f-seq1.txt

Gly Leu Lys Trp Met Gly Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr
65 70 75 80

Ala Asp Ala Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala
85 90 95

Ser Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala
100 105 110

Thr Tyr Phe Cys Ala Arg Asp Tyr Gly Asp Tyr Gly Met Asp Tyr Trp
115 120 125

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
145 150 155 160

Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys
165 170 175

Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Phe Met His Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala
195 200 205

Ser Asn Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser
210 215 220

Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala
225 230 235 240

Ala Thr Tyr Tyr Cys Gln His Ser Arg Glu Val Pro Trp Thr Phe Gly
245 250 255

Gly Gly Thr Lys Leu Glu Ile Lys Arg Glu Pro Lys Ser Pro Asp Lys
260 265 270

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
275 280 285

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ala Arg
290 295 300

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

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
325 330 335

eof-seq1.txt

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
 340 345 350
 Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 355 360 365
 Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
 370 375 380
 Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
 385 390 395 400
 Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
 405 410 415
 Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 420 425 430
 Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
 435 440 445
 Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
 450 455 460
 Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 465 470 475 480
 Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 485 490 495
 Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
 500 505 510
 Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
 515 520 525
 Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
 530 535 540
 Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
 545 550 555 560
 Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
 565 570 575
 Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
 580 585 590
 Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
 595 600 605

eof-seq1.txt

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
610 615 620

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
625 630 635 640

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
645 650 655

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
660 665 670

Pro Arg