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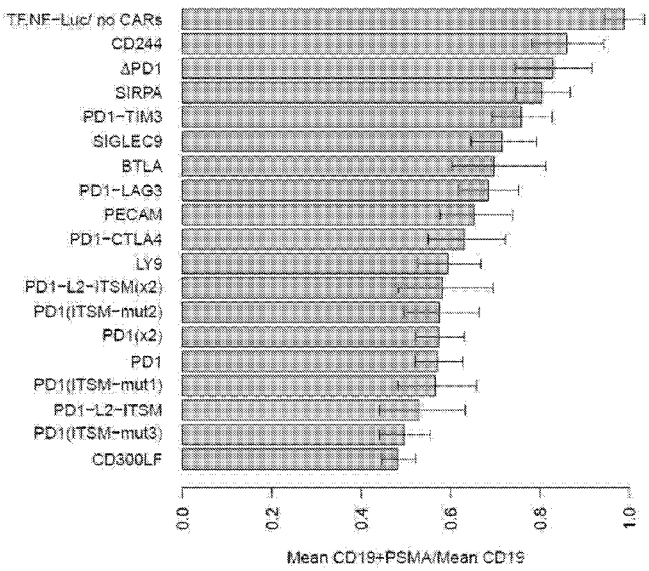
[Continued on next page]

(54) Title: INHIBITORY CHIMERIC ANTIGEN RECEPTORS

FIG 5A



(57) Abstract: The invention relates to an inhibitory chimeric antigen receptor (N-CAR) comprising an extracellular domain comprising an antigen binding domain, a transmembrane domain, and, an intracellular domain wherein the intracellular domain comprises an Immunoreceptor Tyrosine-based Switch Motif ITSM, wherein said ITSM is a sequence of amino acid $TX_1YX_2X_3X_4$, wherein X_1 is an amino acid X_2 is an amino acid X_3 is an amino acid and X_4 is V or I.

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— *as to the identity of the inventor (Rule 4.17(i))*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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INHIBITORY CHIMERIC ANTIGEN RECEPTORS

Field of the invention

The invention relates to negative T-cell signal inducing chimeric antigen receptor (N-CAR or ICAR) and to T-cells comprising such N-CAR as well as a positive T-cell signal inducing CAR (P-CAR) as well as their use in therapy.

Background

T-cell therapies based on redirected T-cell targeting using chimeric antigen receptor (CAR) are beginning to show great promise in the clinic, particularly in the oncology setting (see Hutchinson L., *Nat Rev Clin Oncol.* 2014 Oct 28; Lee DW et al., *Lancet.* 2014 Oct 10. pii: S0140-6736(14)61403-3 or Grupp SA et al., *N Engl J Med.* 2013 Apr 18;368(16):1509-18). Given the growing enthusiasm of the field, there is a significant effort being made to identify appropriate targets for CAR T-cell therapy. Given the potency of such therapeutics, the field's ability to identify novel targets for such therapy is hindered by concerns about on-target off-tissue (meaning off-tumor) activity. Such events not only mitigate efficacy but also present tremendous safety challenges as demonstrated by recent clinical events (see Morgan RA et al., *Mol Ther.* 2010 Apr;18(4):843-51; Morgan RA et al., *J Immunother.* 2013 Feb;36(2):133-51 or Linette GP et al., *Blood.* 2013 Aug 8;122(6):863-71). Clinical approaches to mitigate these safety concerns while effective also act directly or indirectly on the infused CAR T-cell therapeutic entities.

In order to address these safety issues pertaining to on-target off-tissue activity of CAR T-cells, and expand the target space amenable to this mode of therapeutics, there is growing emphasis in creating logic gates to modulate T-cell signaling (see Federov VD et al., *Sci Transl Med.* 2013 Dec 11;5(215):215ra172).

One such approach involves using a NOT gate, wherein the T-cell expresses two or more CARs on its cell surface. CARs that provide positive T-cell signals (P-CARs) bind to tumor antigens to enable T-cell activation and/or proliferation and/or cytokine secretion, and/or cytotoxicity mediated by CD3zeta or other immunoreceptor tyrosine-based activation motif (ITAM) containing motifs; while CARs that provide a negative T-cell signal (N-CARs) bind to the off-tissue antigens and attenuate or abrogate the positive signals.

Therefore under the on-tissue (on-tumor) scenario the T-cell only receives the P-CAR signal and subsequent activation and cytotoxicity and in the off-tissue (off-tumor) scenario the T-cell receives both the P-CAR and N-CAR signals, whereby the latter attenuates or terminates downstream signaling leading to impaired or no activation and cytotoxicity.

Therefore, there is a need for negative or inhibitory CAR (N-CAR) that can be used to generate a negative signal suitable to prevent off target activation of P-CAR T-cells (T-cells comprising a P-CAR). It would be an additional benefit if such negative signal is short-termed, reversible and sufficient to attenuate or prevent on-target off-tissue activity of CAR T-cells comprising such N-CAR.

Detailed description of the invention

General Techniques

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, Molecular Cloning: A Laboratory Manual, second edition (Sambrook et al., 1989) Cold Spring Harbor Press; Oligonucleotide Synthesis (M.J. Gait, ed., 1984); Methods in Molecular Biology, Humana Press; Cell Biology: A Laboratory Notebook (J.E. Cellis, ed., 1998) Academic Press; Animal Cell Culture (R.I. Freshney, ed., 1987); Introduction to Cell and Tissue Culture (J.P. Mather and P.E. Roberts, 1998) Plenum Press; Cell and Tissue Culture: Laboratory Procedures (A. Doyle, J.B. Griffiths, and D.G. Newell, eds., 1993-1998) J. Wiley and Sons; Methods in Enzymology (Academic Press, Inc.); Handbook of Experimental Immunology (D.M. Weir and C.C. Blackwell, eds.); Gene Transfer Vectors for Mammalian Cells (J.M. Miller and M.P. Calos, eds., 1987); Current Protocols in Molecular Biology (F.M. Ausubel et al., eds., 1987); PCR: The Polymerase Chain Reaction, (Mullis et al., eds., 1994); Current Protocols in Immunology (J.E. Coligan et al., eds., 1991); Short Protocols in Molecular Biology (Wiley and Sons, 1999); Immunobiology (C.A. Janeway and P. Travers, 1997); Antibodies (P. Finch, 1997); Antibodies: a practical approach (D. Catty., ed., IRL Press, 1988-1989); Monoclonal antibodies: a practical approach (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); Using antibodies: a laboratory manual (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, 1999); The Antibodies (M. Zanetti and J.D. Capra, eds., Harwood Academic Publishers, 1995).

Definitions

The following terms, unless otherwise indicated, shall be understood to have the following meanings: the term "isolated molecule" as referring to a molecule (where the molecule is, for example, a polypeptide, a polynucleotide, or an antibody) that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is substantially free of other molecules from the same source, e.g., species, cell from which it is expressed, library, etc., (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a molecule that is chemically synthesized, or expressed in a cellular system different from the system from which it naturally originates, will be "isolated" from its naturally associated components. A molecule also may be rendered substantially free of naturally associated components by isolation, using purification techniques well known in the art. Molecule purity or homogeneity may be assayed by a number of means well known in the art. For example, the purity of a polypeptide sample may be assayed using polyacrylamide gel electrophoresis and staining of the gel to visualize the polypeptide using techniques well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

An “antibody” is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, but also, unless otherwise specified, any antigen binding portion thereof that competes with the antibody for specific binding, fusion proteins comprising an antigen binding portion, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site. Antigen binding portions include, for example, Fab, Fab’, F(ab’)2, Fd, Fv, domain antibodies (dAbs, e.g., shark and camelid antibodies), fragments including complementarity determining regions (CDRs), single chain variable fragment antibodies (scFv), maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide. An antibody includes an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant region of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1

and IgA2. The heavy-chain constant regions that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

A "variable region" of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. As known in the art, the variable regions of the heavy and light chains each consist of four framework regions (FRs) connected by three complementarity determining regions (CDRs) also known as hypervariable regions, and contribute to the formation of the antigen binding site of antibodies. If variants of a subject variable region are desired, particularly with substitution in amino acid residues outside of a CDR region (e.g., in the framework region), appropriate amino acid substitution, preferably, conservative amino acid substitution, can be identified by comparing the subject variable region to the variable regions of other antibodies which contain CDR1 and CDR2 sequences in the same canonincal class as the subject variable region (Chothia and Lesk, J Mol Biol 196(4): 901-917, 1987).

In certain embodiments, definitive delineation of a CDR and identification of residues comprising the binding site of an antibody is accomplished by solving the structure of the antibody and/or solving the structure of the antibody-ligand complex. In certain embodiments, that can be accomplished by any of a variety of techniques known to those skilled in the art, such as X-ray crystallography. In certain embodiments, various methods of analysis can be employed to identify or approximate the CDR regions. In certain embodiments, various methods of analysis can be employed to identify or approximate the CDR regions. Examples of such methods include, but are not limited to, the Kabat definition, the Chothia definition, the AbM definition, the contact definition, and the conformational definition.

The Kabat definition is a standard for numbering the residues in an antibody and is typically used to identify CDR regions. See, e.g., Johnson & Wu, 2000, Nucleic Acids Res., 28: 214-8. The Chothia definition is similar to the Kabat definition, but the Chothia definition takes into account positions of certain structural loop regions. See, e.g., Chothia et al., 1986, J. Mol. Biol., 196: 901-17; Chothia et al., 1989, Nature, 342: 877-83. The AbM definition uses an integrated suite of computer programs produced by Oxford Molecular Group that model antibody structure. See, e.g., Martin et al., 1989, Proc Natl Acad Sci (USA), 86:9268-9272; "AbM™, A Computer Program for Modeling Variable Regions of Antibodies," Oxford, UK; Oxford Molecular, Ltd. The AbM definition models the tertiary structure of an antibody from positive sequence using a combination of knowledge databases and ab initio methods, such

as those described by Samudrala et al., 1999, “Ab Initio Protein Structure Prediction Using a Combined Hierarchical Approach,” in PROTEINS, Structure, Function and Genetics Suppl., 3:194-198. The contact definition is based on an analysis of the available complex crystal structures. See, e.g., MacCallum et al., 1996, J. Mol. Biol., 5:732-45. In another approach, referred to herein as the “conformational definition” of CDRs, the positions of the CDRs may be identified as the residues that make enthalpic contributions to antigen binding. See, e.g., Makabe et al., 2008, Journal of Biological Chemistry, 283:1156-1166. Still other CDR boundary definitions may not strictly follow one of the above approaches, but will nonetheless overlap with at least a portion of the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues do not significantly impact antigen binding. As used herein, a CDR may refer to CDRs defined by any approach known in the art, including combinations of approaches. The methods used herein may utilize CDRs defined according to any of these approaches. For any given embodiment containing more than one CDR, the CDRs may be defined in accordance with any of Kabat, Chothia, extended, AbM, contact, and/or conformational definitions.

As known in the art, a “constant region” of an antibody refers to the constant region of the antibody light chain or the constant region of the antibody heavy chain, either alone or in combination.

As used herein, "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler and Milstein, 1975, Nature 256:495, or may be made by recombinant DNA methods such as described in U.S. Pat. No. 4,816,567. The monoclonal antibodies may also be isolated from phage libraries generated using the techniques described in McCafferty et al., 1990, Nature 348:552-554, for example. As used herein, "humanized" antibody refers to forms of non-human (e.g. murine) antibodies that are chimeric immunoglobulins,

immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. Preferably, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. . The humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance.

A “human antibody” is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies as disclosed herein. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen binding residues.

The term “chimeric antibody” is intended to refer to antibodies in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

The term "epitope" refers to that portion of a molecule capable of being recognized by and bound by an antibody at one or more of the antibody's antigen-binding regions. Epitopes often consist of a surface grouping of molecules such as amino acids or sugar side chains and have specific three-dimensional structural characteristics as well as specific charge characteristics. In some embodiments, the epitope can be a protein epitope. Protein epitopes can be linear or conformational. In a linear epitope, all of the points of interaction between the protein and the interacting molecule (such as an antibody) occur linearly along the positive amino acid sequence of the protein. A "nonlinear epitope" or "conformational epitope" comprises noncontiguous polypeptides (or amino acids) within the antigenic protein to which an antibody specific to the epitope binds. The term "antigenic epitope" as used herein, is defined as a portion of an antigen to which an antibody can specifically bind as determined by any method well known in the art, for example, by conventional immunoassays. Once a desired epitope on an antigen is determined, it is possible to generate antibodies to that epitope, e.g., using the techniques described in the present specification. Alternatively, during the discovery process, the generation and characterization of antibodies may elucidate information about desirable epitopes. From this information, it is then possible to competitively screen antibodies for binding to the same epitope. An

approach to achieve this is to conduct competition and cross-competition studies to find antibodies that compete or cross-compete with one another for binding to the antigen.

The term "signaling domain" refers to the functional portion of a protein which acts by transmitting information within the cell to regulate cellular activity via defined signaling pathways by generating second messengers or functioning as effectors by responding to such messengers.

The term “off-tissue antigen” (or off-tumor antigen) refers to an antigen which is present on non-tumor tissue and not present on the tumor of interest (tumor to be treated by the cells of the invention comprising a P-CAR directed to a tumor antigen and a N-CAR directed to an off-tissue antigen), or only present on the tumor of interest at much lower levels compared to levels of tumor antigen (i.e. the antigen present on the tumor of interest and targeted by the P-CAR).

The term "anti-tumor effect" refers to a biological effect which can be manifested by various means, including but not limited to, e.g., a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in the number of metastases, an increase in life expectancy, decrease in tumor cell proliferation, decrease in tumor cell survival, or amelioration of various physiological symptoms associated with the cancerous condition. An "anti-tumor effect" can also be manifested by the ability of the cells of the invention in prevention of the occurrence of tumor in the first place.

The term "autologous" refers to any material derived from the same individual to whom it is later to be re-introduced into the individual.

The term "allogeneic" refers to any material derived from a different animal of the same species as the individual to whom the material is introduced. Two or more individuals are said to be allogeneic to one another when the genes at one or more loci are not identical. In some aspects, allogeneic material from individuals of the same species may be sufficiently unlike genetically to interact antigenically

The term "xenogeneic" refers to a graft derived from an animal of a different species.

The term "cancer" refers to a disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers are described herein and include but are not limited to, breast cancer, prostate cancer, ovarian cancer, cervical cancer,

skin cancer, pancreatic cancer, colorectal cancer, renal cell cancer, liver cancer, brain cancer, lymphoma, leukemia, lung cancer and the like.

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

In some embodiments, the “fragment” of a sequence of amino acids is shorter than said sequence of amino acid. In some embodiments, the fragment of a sequence of amino acids is at least 1%, 5% 10%, 20%, 40%, 50%, 60%, 70%, 80% or 90% shorter than said sequence of amino acids. In some embodiments, the fragment of a sequence of amino acids is shorter by at least 1, 5, 10, 20, 50, 100, 200, 300 amino acids as compared to said sequence of amino acids.

Unless otherwise specified, the left to right orientation of amino acid sequences or formula representing amino acid sequences are disclosed using the conventional left to right orientation N-Term to C-term.

N-terminal flanking region of a domain refers to the sequence of amino acid which is directly adjacent to the N-terminal amino acid of said domain. C-terminal flanking region of a domain refers to the sequence of amino acid which is directly adjacent to the C-terminal amino acid of said domain. For example, in the sequence seq1-ITIM-seq2, seq1 is the N-terminal flanking region of the ITIM intracellular domain and seq2 N-terminal flanking region of the

ITIM intracellular domain. In another example, the naturally occurring N-terminal flanking region of ITIM.*ITSM intracellular domains is the sequence of amino acid which is directly adjacent to the N-terminal amino acid of the ITIM motif of the ITIM.*ITSM intracellular domain. In another example, the naturally occurring C-terminal flanking region of ITIM.*ITSM intracellular domain is the sequence of amino acid which is directly adjacent to the C-terminal amino acid of the ITSM motif of the ITIM.*ITSM intracellular domain.

In another example, the naturally occurring N-terminal flanking region of an ITIM only intracellular domain is the sequence of amino acid which is directly adjacent to the N-terminal amino acid of the ITIM of the ITIM only intracellular domain. In another example, the naturally occurring C-terminal flanking region of an ITIM only intracellular domain is the sequence of amino acid which is directly adjacent to the C-terminal amino acid of the ITIM of the ITIM only intracellular domain.

In another example, the naturally occurring N-terminal flanking region of an ITSM only intracellular domain is the sequence of amino acid which is directly adjacent to the N-terminal amino acid of the ITSM of the ITSM only intracellular domain. In another example, the naturally occurring C-terminal flanking region of an ITSM only intracellular domain is the sequence of amino acid which is directly adjacent to the C-terminal amino acid of the ITSM of the ITSM only intracellular domain.

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

The term "antigen presenting cell" or "APC" refers to an immune system cell such as an accessory cell (e.g., a B-cell, a dendritic cell, and the like) that displays a foreign antigen complexed with major histocompatibility complexes (MHC's) on its surface. T-cells may recognize these complexes using their T-cell receptors (TCRs). APCs process antigens and present them to T-cells.

An "intracellular signaling domain," as the term is used herein, refers to an intracellular portion of a molecule.

The term "encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (e.g., rRNA, tRNA and mRNA) or a defined sequence of amino

acids and the biological properties resulting therefrom. Thus, a gene, cDNA, or RNA, encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

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

The term "effective amount" or "therapeutically effective amount" are used interchangeably herein, and refer to an amount of a compound, formulation, material, or composition, as described herein effective to achieve a particular biological result.

The term "endogenous" refers to any material from or produced inside an organism, cell, tissue or system.

The term "exogenous" refers to any material introduced from or produced outside an organism, cell, tissue or system.

The term "expression" refers to the transcription and/or translation of a particular nucleotide sequence driven by a promoter.

The term "transfer vector" refers to a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term "transfer vector" includes an autonomously replicating plasmid or a virus. The term should also be construed to further include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, a polylysine compound, liposome, and the like. Examples of viral transfer vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like.

The term "expression vector" refers to a vector comprising a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an in vitro expression system. Expression vectors include all those known in the art, including cosmids, plasmids (e.g., naked or contained in liposomes) and viruses (e.g., lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses) that incorporate the recombinant polynucleotide.

The term "lentivirus" refers to a genus of the Retroviridae family. Lentiviruses are unique among the retroviruses in being able to infect non-dividing cells; they can deliver a significant amount of genetic information into the DNA of the host cell, so they are one of the most efficient methods of a gene delivery vector. HIV, SIV, and FIV are all examples of lentiviruses.

The term "lentiviral vector" refers to a vector derived from at least a portion of a lentivirus genome, including especially a self-inactivating lentiviral vector as provided in Milone et al., Mol. Ther. 17(8): 1453-1464 (2009). Other examples of lentivirus vectors that may be used in the clinic, include but are not limited to, e.g., the LENTIVECTOR® gene delivery technology from Oxford BioMedica, the LENTIMAX™ vector system from Lentigen and the like. Nonclinical types of lentiviral vectors are also available and would be known to one skilled in the art.

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

The term "operably linked" or "transcriptional control" refers to functional linkage between a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the

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

The terms “polypeptide”, “oligopeptide”, “peptide” and “protein” are used interchangeably herein to refer to chains of amino acids of any length. The chain may be linear or branched, it may comprise modified amino acids, and/or may be interrupted by non-amino acids. The terms also encompass an amino acid chain that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that the polypeptides can occur as single chains or associated chains.

As known in the art, “polynucleotide,” or “nucleic acid,” as used interchangeably herein, refer to chains of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a chain by DNA or RNA polymerase. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the chain. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. Other types of modifications include, for example, “caps”, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups,

phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-allyl, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, alpha- or beta-anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S("thioate"), P(S)S ("dithioate"), (O)NR_2 ("amidate"), P(O)R, P(O)OR', CO or CH_2 ("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (-O-) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

An antibody that "preferentially binds" or "specifically binds" (used interchangeably herein) to an epitope is a term well understood in the art, and methods to determine such specific or preferential binding are also well known in the art. A molecule is said to exhibit "specific binding" or "preferential binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular cell or substance than it does with alternative cells or substances. An antibody "specifically binds" or "preferentially binds" to a target if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances.

A "host cell" includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a polynucleotide(s) of this invention.

The term "compete", as used herein with regard to an antibody, means that a first antibody, or an antigen-binding portion thereof, binds to an epitope in a manner sufficiently similar to the binding of a second antibody, or an antigen-binding portion thereof, such that the result of

binding of the first antibody with its cognate epitope is detectably decreased in the presence of the second antibody compared to the binding of the first antibody in the absence of the second antibody. The alternative, where the binding of the second antibody to its epitope is also detectably decreased in the presence of the first antibody, can, but need not be the case. That is, a first antibody can inhibit the binding of a second antibody to its epitope without that second antibody inhibiting the binding of the first antibody to its respective epitope. However, where each antibody detectably inhibits the binding of the other antibody with its cognate epitope or ligand, whether to the same, greater, or lesser extent, the antibodies are said to "cross-compete" with each other for binding of their respective epitope(s). Both competing and cross-competing antibodies are encompassed by the present invention. Regardless of the mechanism by which such competition or cross-competition occurs (e.g., steric hindrance, conformational change, or binding to a common epitope, or portion thereof), the skilled artisan would appreciate, based upon the teachings provided herein, that such competing and/or cross-competing antibodies are encompassed and can be useful for the methods disclosed herein.

As used herein, "treatment" is an approach for obtaining beneficial or desired clinical results.

As used herein, an "effective dosage" or "effective amount" of drug, compound, or pharmaceutical composition is an amount sufficient to effect any one or more beneficial or desired results. For prophylactic use, beneficial or desired results include eliminating or reducing the risk, lessening the severity, or delaying the outset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as reducing incidence or amelioration of one or more symptoms of various diseases or conditions (such as, for example without limitation, renal cell, gastric, head and neck, lung, ovarian, and pancreatic cancers), decreasing the dose of other medications required to treat the disease, enhancing the effect of another medication, and/or delaying the progression of the disease. An effective dosage can be administered in one or more administrations. For purposes of this invention, an effective dosage of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective dosage of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an "effective dosage" may be considered in the context of administering one or more therapeutic agents, and a single agent may be

considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

An “individual” or a “subject” is a mammal, more preferably, a human. Mammals also include, but are not limited to, farm animals, sport animals, pets, primates, horses, dogs, cats, mice and rats.

As used herein, “vector” means a construct, which is capable of delivering, and, preferably, expressing, one or more gene(s) or sequence(s) of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, DNA or RNA expression vectors encapsulated in liposomes, and certain eukaryotic cells, such as producer cells.

As used herein, “expression control sequence” means a nucleic acid sequence that directs transcription of a nucleic acid. An expression control sequence can be a promoter, such as a constitutive or an inducible promoter, or an enhancer. The expression control sequence is operably linked to the nucleic acid sequence to be transcribed.

The term "promoter" refers to a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a polynucleotide sequence.

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

The term "constitutive" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell under most or all physiological conditions of the cell.

The term "inducible" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to

be produced in a cell substantially only when an inducer which corresponds to the promoter is present in the cell.

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

The term "flexible polypeptide linker" or "linker" as used in the context of a scFv refers to a peptide linker that consists of amino acids such as glycine and/or serine residues used alone or in combination, to link variable heavy and variable light chain regions together. In one embodiment, the flexible polypeptide linker is a Glycine/Serine linker and comprises the amino acid sequence $(Gly\text{-}Gly\text{-}Gly\text{-}Ser)_n$ or $(Gly\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Ser)_n$, where n is a positive integer equal to or greater than 1. For example, n=1, n=2, n=3, n=4, n=5, n=6, n=7, n=8, n=9 and n=10. In one embodiment, the flexible polypeptide linkers include, but are not limited to, $(Gly_4Ser)_4$ or $(Gly_4Ser)_3$. In another embodiment, the linkers include multiple repeats of $(Gly_xSer)_n$, where x=1, 2, 3, 4 or 5 and n is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, such as multiple repeat of (GlySer), (Gly_2Ser) or (Gly_5Ser). Also included within the scope of the invention are linkers described in WO2012/138475, incorporated herein by reference.

As used herein, a 5' cap (also termed an RNA cap, an RNA 7-methylguanosine cap or an RNA m G cap) is a modified guanine nucleotide that has been added to the "front" or 5' end of a eukaryotic messenger RNA shortly after the start of transcription. The 5' cap consists of a terminal group which is linked to the first transcribed nucleotide. Its presence is critical for recognition by the ribosome and protection from RNases. Cap addition is coupled to transcription, and occurs co-transcriptionally, such that each influences the other. Shortly after the start of transcription, the 5' end of the mRNA being synthesized is bound by a cap-synthesizing complex associated with RNA polymerase. This enzymatic complex catalyzes the chemical reactions that are required for mRNA capping. Synthesis proceeds as a multi-step biochemical reaction. The capping moiety can be modified to modulate functionality of mRNA such as its stability or efficiency of translation.

As used herein, "in vitro transcribed RNA" refers to RNA, preferably mRNA, that has been synthesized in vitro. Generally, the in vitro transcribed RNA is generated from an in vitro transcription vector. The in vitro transcription vector comprises a template that is used to generate the in vitro transcribed RNA.

As used herein, a "poly(A)" is a series of adenosines attached by polyadenylation to the mRNA. In the preferred embodiment of a construct for transient expression, the polyA is between 50 and 5000, preferably greater than 64, more preferably greater than 100, most preferably greater than 300 or 400. poly(A) sequences can be modified chemically or enzymatically to modulate mRNA functionality such as localization, stability or efficiency of translation.

As used herein, "polyadenylation" refers to the covalent linkage of a polyadenylyl moiety, or its modified variant, to a messenger RNA molecule. In eukaryotic organisms, most messenger RNA (mRNA) molecules are polyadenylated at the 3' end. The 3' poly(A) tail is a long sequence of adenine nucleotides (often several hundred) added to the pre-mRNA through the action of an enzyme, polyadenylate polymerase. In higher eukaryotes, the poly(A) tail is added onto transcripts that contain a specific sequence, the polyadenylation signal. The poly(A) tail and the protein bound to it aid in protecting mRNA from degradation by exonucleases. Polyadenylation is also important for transcription termination, export of the mRNA from the nucleus, and translation. Polyadenylation occurs in the nucleus immediately after transcription of DNA into RNA, but additionally can also occur later in the cytoplasm. After transcription has been terminated, the mRNA chain is cleaved through the action of an endonuclease complex associated with RNA polymerase. The cleavage site is usually characterized by the presence of the base sequence AAUAAA near the cleavage site. After the mRNA has been cleaved, adenosine residues are added to the free 3' end at the cleavage site.

As used herein, "transient" refers to expression of a non-integrated transgene for a period of hours, days or weeks, wherein the period of time of expression is less than the period of time for expression of the gene if integrated into the genome or contained within a stable plasmid replicon in the host cell.

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

Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X.” Numeric ranges are inclusive of the numbers defining the range.

It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided.

Where aspects or embodiments of the invention are described in terms of a Markush group or other grouping of alternatives, the present invention encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group, but also the main group absent one or more of the group members. The present invention also envisages the explicit exclusion of one or more of any of the group members in the claimed invention.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In case of conflict, the present specification, including definitions, will control. Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Any example(s) following the term "e.g." or "for example" is not meant to be exhaustive or limiting.

Exemplary methods and materials are described herein, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention. The materials, methods, and examples are illustrative only and not intended to be limiting.

Description of Figures

Figures 1 and 2 show the dual cell surface expression of P-CAR1 and various N-CARs assessed by multicolor flow cytometry in transduced NFAT-luciferase reporter Jurkat cells.

Figures 3 and 4 show the dual cell surface expression of P-CAR1 and various N-CARs assessed by multicolor flow cytometry in transduced NFkB-luciferase reporter Jurkat cells.

In Figures 1 to 4, P-CAR expression was detected using a recombinant human CD19-mouse IgG Fc fusion protein followed by APC-conjugated F(ab')2 goat anti-mouse Fcγ (shown on x axis), and N-CAR expression was detected with a biotinylated recombinant human PSMA-human IgG1 Fc fusion protein followed by PE-conjugated streptavidin (y axis).

Figures 5A, 5B and 5C show the inhibitory effect of various N-CARs on P-CAR1 induced T cell activation. Control ΔPD1- or test N-CAR-transduced luciferase reporter Jurkat cells

expressing P-CAR1 were incubated with either CD19-expressing AAPCs or dual CD19+PSMA-expressing AAPCs, and luciferase activity was assessed 16h later. Data are expressed as a ratio of the mean RLU from co-culture with CD19+PSMA AAPCs/CD19 AAPCs. n=6 replicates per sample; data shown are the means+/- 95%CI). Figures 5A/5C and 5B show results using NFAT-luciferase reporter and NFkB-luciferase reporter Jurkat cells, respectively.

Figures 6 and 7 show the dual cell surface expression of P-CAR2 and and N-CARs listed in Table 10 assessed by multicolor flow cytometry in transduced NFAT-luciferase reporter Jurkat cells. Figures 8 and 9 show the dual cell surface expression of P-CAR2 and N-CARs listed in Table 10 assessed by multicolor flow cytometry in transduced NFkB-luciferase reporter Jurkat cells. In Figures 6 to 9, P-CAR expression was detected using a recombinant human CD19-mouse IgG Fc fusion protein followed by APC-conjugated F(ab')2 goat anti-mouse Fcγ (shown on x axis), and N-CAR expression was detected with a biotinylated recombinant human PSMA-human IgG1 Fc fusion protein followed by PE-conjugated streptavidin (y axis).

Figures 10A and 10B show the inhibitory effect of various N-CARs on P-CAR2 induced T cell activation. Control ΔPD1- or test N-CAR-transduced luciferase reporter Jurkat cells expressing P-CAR2 were incubated with either CD19-expressing or dual PSMA/CD19-expressing AAPCs, and luciferase activity was assessed 16h later. Data are expressed as a ratio of the mean RLU from co-culture with CD19+PSMA AAPCs/CD19 AAPCs. n=6 replicates per sample; data shown are the means +/- 95%CI. Figures 10A and 10B show results using NFAT-luciferase reporter and NFkB-luciferase reporter Jurkat cells, respectively.

Detailed description

The invention relates to a negative signal (or inhibitory) chimeric antigen receptor (N-CAR) comprising

an extracellular domain comprising an antigen binding domain,

a transmembrane domain, and,

an intracellular domain

wherein the intracellular domain comprises an Immunoreceptor Tyrosine-based Switch Motif ITSM, wherein said ITSM is a sequence of amino acid $TX_1YX_2X_3X_4$, wherein

X_1 is an amino acid,

X_2 is an amino acid,

X_3 is an amino acid, and,

X_4 is V or I.

In some embodiments the term amino acid refers to a natural amino acid. In some embodiments, the term amino acid refer to an amino acid selected from glycine, alanine, valine, leucine, isoleucine, phenylalanine, proline, serine, threonine, tyrosine, cysteine, methionine, lysine, arginine, histidine, tryptophan, aspartic acid, glutamic acid, asparagine or glutamine.

In some embodiments, when the extracellular domain is a scFv against PSMA, then the intracellular domain is not the intracellular domain of human PD-1.

In some embodiments, the intracellular domain is not the intracellular domain of human PD-1.

In some embodiments, the intracellular domain is not the intracellular domain of human BTLA.

In some embodiments, the intracellular domain is not the intracellular domain of human CD244.

In some embodiments, the intracellular domain is not SEQ ID No 2000, SEQ ID No 2001 or SEQ ID No 2002.

In some embodiments, the extracellular domain does not bind to PMSA.

In some embodiments, the intracellular domain does not comprise the full intracellular domain of PD-1.

In some embodiments, the ITSM is not TEYATI.

The intracellular domain or region of the N-CAR includes an inhibitory intracellular signaling domain. An inhibitory intracellular signaling domain is generally responsible for inactivation of the signal from a positive intracellular signaling domain from a P-CAR on the same immune cell in which the N-CAR has been introduced, thereby blocking activation of a normal effector function of the immune cell. The term "effector function" refers to a specialized function of a cell. Effector function of a T-cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines.

Intracellular domain of the N-CAR

In some embodiments, the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein

n is 0, 1 or an integer greater than 1;

m is 1 or an integer greater than 1;

p is 1 or an integer greater than 1;

L1 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(a) a naturally occurring N-terminal flanking region of an ITIM only intracellular domain or a fragment thereof such as, for example, any of the sequences shown in Table 3 below or a fragment thereof;

(b) a naturally occurring N-terminal flanking region of an ITIM.*ITSM intracellular domain or a fragment thereof, such as, for example, any of the sequences shown in Table 1 below or a fragment thereof;

(c) a naturally occurring intracellular domain from a known inhibitory receptor such as any of the sequences shown in table 2 or a fragment thereof, wherein said intracellular domain is N-terminally flanking to a sequence in (b) above; and

(d) a non-naturally occurring sequence comprising between 1 and 500 amino acids;

each of L2 and L3 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(e) a naturally occurring C-terminal flanking region of an ITIM only intracellular domain, such as, for example, any of the sequences shown in Table 4 below or a fragment thereof;

(f) a naturally occurring N-terminal flanking region of an ITSM only intracellular domain such as, for example, any of the sequences shown in Table 6 below or a fragment thereof;

(g) a naturally occurring intracellular domain between ITIM and ITSM from proteins that have ITIM.*ITSM motif such as, for example, any of the sequences shown in Table 5 below or a fragment thereof;

(h) a naturally occurring intracellular domain from a known inhibitory receptor such as any of the sequences shown in table 2 or a fragment thereof, wherein said intracellular domain is N-terminally flanking to a sequence in (f) or (g) above; and

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids; and

L4 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(j) a naturally occurring C-terminal flanking region of an ITIM.*ITSM intracellular domain or a fragment thereof such as, for example, any of the sequences shown in Table 7 below or a fragment thereof;

(k) a naturally occurring C-terminal flanking region of an ITSM only intracellular domain such as, for example, any of the sequences shown in Table 8 below or a fragment thereof;

(l) a naturally occurring intracellular domain from a known inhibitory receptor such as any of the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (j) or (k) above; and

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids, and, wherein,

the ITIM is the sequence $X_5X_6YX_7X_8X_9$, wherein
X_5 is S, V, I or L,
X_6 is an amino acid,
X_7 is an amino acid,
X_8 is an amino acid, and,
X_9 is V, I or L, and,

the ITSM is the sequence $TX_1YX_2X_3X_4$, wherein
X_1 is an amino acid,
X_2 is an amino acid,
X_3 is an amino acid, and,
X_4 is V or I,
or a variant thereof.

In some embodiments, the known inhibitory receptor refers to an inhibitory receptor comprising an extracellular domain, a transmembrane domain and an intracellular domain which do not comprise any ITIM or ITSM and which provides a negative signal able to reduce the activation signal provided by the TCR/CD3 complex in a T-cell.
In some embodiments, the known inhibitory receptor refers to an inhibitory receptor comprising an extracellular domain, a transmembrane domain and an intracellular domain which provide a negative signal able to reduce the activation signal provided by the TCR/CD3 complex in a T-cell.

In some embodiments, the known inhibitory receptor is selected from CTLA4, LAG3 HAVCR2 (TIM3), KIR2DL2, LILRB1, TIGIT, CEACAM1, CSF1R, CD5, CD96, CD22 and LAIR1. In a preferred embodiment, the known inhibitory receptor is KIR2DL2.

ITIM.*ITSM intracellular domain refers to a domain comprising one ITIM and one ITSM.
ITSM only intracellular domain refers to a domain comprising one ITSM and no ITIM.
ITIM only intracellular domain refers to a domain comprising one ITIM and no ITSM.

When one or more of n, m or p are greater than 1, each occurrence of L1, L2, L3, L4, ITIM and ITSM is selected independently from the other. For example, the intracellular domain of the N-CAR may comprise several ITSM having different sequences.

In some embodiments, L1 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(a) a naturally occurring N-terminal flanking region of ITIM only intracellular domains selected from

YKMYGSEMLHKRDPLDEDEDTD
DHWALTQRTARAVSPQSTKPMAES
CSRAARGTIGARRTGQPLKEDPSAVPVFS
HRQNQIKQGPPRSKDEEQKPQQRPDLAVDVLERTADKATVNGLPEKDRETDTSALAAGSSQE
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPTVEMDEE
LTRKKKALRIHSVEGDLRRKSAGQEEWSPSAPSPPGSCVQAEAAPAGLCGEQRGEDCAELHDYFNV
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPINDNKEPLNSD
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEENKPG
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKED
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKLEDVVIDRNLLILGKILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNSSQREIEEFLSEAACMKDFSHPNVIRLLGVCIEMSSQGIPKPMVILPFMKYGDLHTY

(b) a naturally occurring N-terminal flanking region of ITIM.*ITSM intracellular domains selected from

YKMYGSEMLHKRDPLDEDEDTD
WRMMKYQQKAAGMSPEQVLQPLEGD
CSRAARGTIGARRTGQPLKEDPSAVPVFS
RIRQKKAQGSTSSTRLHEPEKNAREITQDTND
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPTVEMDEE
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPINDNKEPLNSD
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEG

SEVYSNPCLEENKPG
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKLEDVVIDRNLLILG KILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNSSQREIEEFLSEAACMKDFSHPNVIRL LGVCIEMSSQGIPKPMVILPFMKYGDLHTY

(c) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2, wherein said intracellular domain is N-terminally flanking to a sequence in (b) above; and

(d) a non-naturally occurring sequence comprising between 1 and 500 amino acids.

In some embodiments, each of L2 and L3 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(e) a naturally occurring C-terminal flanking region of ITIM only intracellular domains selected from;

GNCSFFTETG
NFHGMNPSKDTSTEYSEVRTQ
KEEEMADTSYGTVKAENIIMMETAQTSL
NHSVIGPNSRLARNVKEAPTEYASICVRS
DHWALTQRTARAVSPQSTKPMAESITYAAVARH
QVSSAESHKDLGKKDTETVYSEVRKAVPDAVESRYSRTEGSLDGT
DFQWREKTPEPPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCS WPL
NLPKGKKPAPQAAEPNNHTEYASIQTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSF SEYASVQVPRK
TLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKEDISYASLTLGAEDQEPTYCNMGHL SSHLPGRGPEEPTEYSTISRP
ETGPKHIPLQTLLKFMVDIALGMEYLSNRNFLHRDLAARNCMLRDDMTVCVADFGLSKKIYS GDYYRQGRIAKMPVKWIAIESLADRVYTSKSDVWAFGVTMWEIATRGMTPYPGVQNHEMY DYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVRNQADVIY VNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGRYILNGGSE EWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFADDSSEGSE VLM

(f) a naturally occurring N-terminal flanking region of ITSM only intracellular domains selected from;

YKMYGSEMLHKRDPLDEDEDTDISYKKLKEEEMAD
CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQ
RIRQKKAQGSTSSTRLHEPEKNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNH
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPTVEMDEELHYAS LNFHGMNPSKDTS
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPIND NKEPLNSDVQYTEVQVSSAESHKDLGKKDTE
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEG SEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVKEAP
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEY VTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGRGPEEP
WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQE PAYTLYSLIQPSRKSGSRKRNHSPSFNS
VRSCRKKSARPAAGVGDTGIEDANAVRGSASQGPLTEPWAEDSPPDQPPPASARSSVGE GELQYASLSFQMVKPWDSRGQEATD
NKCGRRNKFGINRPAVLAPEDGLAMSLHFMTLGGSSLSPTEGKGSGLQGHIIENPQYFSDA CVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPEQDKMLVAVKALKEASESARQDFQREA ELLTMLQHQHIVRFFGVCTEGRPLLMVFEYMRHGDLNRFLRSHGPDAKLLAGGEDVAPGPL GLGQLLAVASQVAAGMVYLAGLHFVHRDLATRNCLVGQGLVVKIGDFGMSRDIYS
KLARHSKFGMKGPASVISNDDDSASPLHHISNGSNTPSSSEGGPDAVIIGMTKIPVIENPQYF GITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFLAECYNLCPEQDKILVAVKTLKDASDN ARKDFHREAELLTNLQHEHIVKFYGVCVEGDPLIMVFEYMKHGDLNKFLRAHGPDAVLMAE GNPPTELTQSQMLHIAQQIAAGMVYLASQHFVHRDLATRNCLVGENLLVKIGDFGMSRDVY S
KRKGRCSVPAFCSSQAEAPADTPEPTAGHTLYSVLSQGYEKLDTPLRPARQQPTPTSDSSS DSNLTTEEDEDRPEVHKPISGRYEVFDQVTQEGAGHDPAPEGQADYDPVTPYVTEVESVV GENTMYAQVFNLQGKTPVSQKEESSA
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKLEDVVIDRNLLILG KILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNSSQREIEEFLSEAACMKDFSHPNVIRL LGVCIEMSSQGIPKPMVILPFMKYGDLHTYLLYSRLETGPKHIPLQTLLKFMVDIALGMEYLS NRNFLHRDLAARNCMLRDDMTVCVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADRV YTSKSDVWAFGVTMWEIATRGM

(g) a naturally occurring intracellular domain between ITIM and ITSM from proteins that have ITIM.*ITSM motif selected from;

KEEEMAD
NFHGMNPSKDTS
QVSSAESHKDLGKKDTE
NLPKGKKPAPQAAEPNNH
NHSVIGPNSRLARNVKEAP
DFQWREKTPEPPVPCVPEQ
TLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKEDISYASLTLGAEDQEPTYCNMGHL SSHLPGRGPEEP
ETGPKHIPLQTLLKFMVDIALGMEYLSNRNFLHRDLAARNCMLRDDMTVCVADFGLSKKIYS GDYYRQGRIAKMPVKWIAIESLADRVYTSKSDVWAFGVTMWEIATRGM

(h) a naturally occurring intracellular domain from known inhibitory receptors selected from the sequences shown in table 2 wherein said intracellular domain is N-terminally flanking to a sequence in (f) or (g) above; and

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids.

In some embodiments, L4 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(j) a naturally occurring C-terminal flanking region of ITIM.*ITSM intracellular domains selected from:

SRP
RTQ
CVRS
KAENIIMMETAQTSL
RKAVPDAVESRYSRTEGSLDGT
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVR NQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGR YILNGGSEEWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFAD DSSEGSEVLM

(k) a naturally occurring C-terminal flanking region of ITSM only intracellular domain selected from

RTQ
SRP
KIHR
CVRS
KAENIIMMETAQTSL
RKAVPDAVESRYSRTEGSLDGT
RKPQVVPPPQQNDLEIPESPTYENFT
GKSQPKAQNPARLSRKELENFDVYS
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
FNLQGKTPVSQKEESSATIYCSIRKPQVVPPPQQNDLEIPESPTYENFT
GGRTMLPIRWMPPESILYRKFTTESDVWSFGVVLWEIFTYGKQPWYQLSNTEAIDCITQGRE LERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARLQALAQAPPVYLDVLG
GGHTMLPIRWMPPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNEVIECITQGR VLQRPRTCPQEVYELMLGCWQREPHMRKNIKGIHTLLQNLAKASPVYLDILG
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVR NQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGR YILNGGSEEWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFAD DSSEGSEVLM
KDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQEPAYTLYSLIQPSRKSGSRKRNHSP SFNSTIYEVIGKSQPKAQNPARLSRKELENFDVYS

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2 wherein said intracellular domain is C-terminally flanking to a sequence in (j) or (k) above; and

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids.

In some embodiments the intracellular domain comprises the sequence $(L3\text{-}ITSM\text{-}L4)^m$ (i.e, n is 0 and p is 1).

In some embodiments, the intracellular domain comprises the sequence L3-ITSM-L4 (i.e, n is 0, m is 1 and p is 1).

In some embodiments, the intracellular domain comprises the sequence L3-ITSM-L4-L3-ITSM-L4 (i.e, n is 0, m is 2 and p is 1).

In some embodiments, the intracellular domain comprises the following sequence:
$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein
n is 0;
m is 1;
p is 1;
L3 comprises one sequence selected from

(f) a naturally occurring N-terminal flanking region of an ITSM only intracellular domain such as, for example, any of the sequences shown in Table 6 below or a fragment thereof; or,

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids; and

L4 comprises one or more, preferably one or two, sequences selected from the group consisting of:

(k) a naturally occurring C-terminal flanking region of an ITSM only intracellular domain such as, for example, any of the sequences shown in Table 8 below or a fragment thereof;

(l) a naturally occurring intracellular domain from a known inhibitory receptor such as any of the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above; and

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids, and, wherein,

the ITSM is the sequence $TX_1YX_2X_3X_4$, wherein
X_1 is an amino acid,
X_2 is an amino acid,
X_3 is an amino acid, and,
X_4 is V or I,
or a variant thereof.

In some embodiments, the intracellular domain comprises the following sequence:
$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein
n is 0;
m is 1;
p is 1;
L3 is selected from

YKMYGSEMLHKRDPLDEDEDTDISYKKLKEEEMAD
CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQ
RIRQKKAQGSTSSTRLHEPEKNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNH
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPTVEMDEELHYAS LNFHGMNPSKDTS
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPIND NKEPLNSDVQYTEVQVSSAESHKDLGKKDTE
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEG SEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVKEAP
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEY VTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGRGPEEP
WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQE PAYTLYSLIQPSRKSGSRKRNHSPSFNS
VRSCRKKSARPAAGVGDTGIEDANAVRGSASQGPLTEPWAEDSPPDQPPPASARSSVGE GELQYASLSFQMVKPWDSRGQEATD
NKCGRRNKFGINRPAVLAPEDGLAMSLHFMTLGGSSLSPTEGKGSGLQGHIIENPQYFSDA CVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPEQDKMLVAVKALKEASESARQDFQREA ELLTMLQHQHIVRFFGVCTEGRPLLMVFEYMRHGDLNRFLRSHGPDAKLLAGGEDVAPGPL GLGQLLAVASQVAAGMVYLAGLHFVHRDLATRNCLVGQGLVVKIGDFGMSRDIYS
KLARHSKFGMKGPASVISNDDDSASPLHHISNGSNTPSSSEGGPDAVIIGMTKIPVIENPQYF GITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFLAECYNLCPEQDKILVAVKTLKDASDN ARKDFHREAELLTNLQHEHIVKFYGVCVEGDPLIMVFEYMKHGDLNKFLRAHGPDAVLMAE GNPPTELTQSQMLHIAQQIAAGMVYLASQHFVHRDLATRNCLVGENLLVKIGDFGMSRDVY S
KRKGRCSVPAFCSSQAEAPADTPEPTAGHTLYSVLSQGYEKLDTPLRPARQQPTPTSDSSS DSNLTTEEDEDRPEVHKPISGRYEVFDQVTQEGAGHDPAPEGQADYDPVTPYVTEVESVV GENTMYAQVFNLQGKTPVSQKEESSA
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKLEDVVIDRNLLILG KILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNSSQREIEEFLSEAACMKDFSHPNVIRL LGVCIEMSSQGIPKPMVILPFMKYGDLHTYLLYSRLETGPKHIPLQTLLKFMVDIALGMEYLS NRNFLHRDLAARNCMLRDDMTVCVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADRV YTSKSDVWAFGVTMWEIATRGM

and L4 comprises one sequence selected from the group consisting of

(k)

RTQ
SRP
KIHR
CVRS
KAENIIMMETAQTSL
RKAVPDAVESRYSRTEGSLDGT
RKPQVVPPPQQNDLEIPESPTYENFT
GKSQPKAQNPARLSRKELENFDVYS
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
FNLQGKTPVSQKEESSATIYCSIRKPQVVPPPQQNDLEIPESPTYENFT
GGRTMLPIRWMPPESILYRKFTTESDVWSFGVVLWEIFTYGKQPWYQLSNTEAIDCITQGRE LERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARLQALAQAPPVYLDVLG
GGHTMLPIRWMPPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNEVIECITQGR VLQRPRTCPQEVYELMLGCWQREPHMRKNIKGIHTLLQNLAKASPVYLDILG
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVR NQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGR YILNGGSEEWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFAD DSSEGSEVLM
KDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQEPAYTLYSLIQPSRKSGSRKRNHSP SFNSTIYEVIGKSQPKAQNPARLSRKELENFDVYS

and optionally

(l) a naturally occurring intracellular domain from a known inhibitory receptor such as any of the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above;

and the ITSM is the sequence $TX_1YX_2X_3X_4$, wherein

X_1 is an amino acid,

X_2 is an amino acid,

X_3 is an amino acid, and,

X_4 is V or I,

or a variant thereof.

In some embodiments, the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^{n}\text{-}(L3\text{-}ITSM\text{-}L4)^{m})^{p}$, wherein

n is 0;

m is 1;

p is 1;

L3 is selected from

CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQ
RIRQKKAQGSTSSTRLHEPEKNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNH
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPIND NKEPLNSDVQYTEVQVSSAESHKDLGKKDTE
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEG SEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVKEAP
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEY VTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGRGPEEP
WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQE PAYTLYSLIQPSRKSGSRKRNHSPSFNS
VRSCRKKSARPAAGVGDTGIEDANAVRGSASQGPLTEPWAEDSPPDQPPPASARSSVGE GELQYASLSFQMVKPWDSRGQEATD
KRKGRCSVPAFCSSQAEAPADTPEPTAGHTLYSVLSQGYEKLDTPLRPARQQPTPTSDSSS DSNLTTEEDEDRPEVHKPISGRYEVFDQVTQEGAGHDPAPEGQADYDPVTPYVTEVESVV GENTMYAQVFNLQGKTPVSQKEESSA

L4 comprises one sequence selected from the group consisting of

(k)

SRP
KIHR
CVRS
RKAVPDAVESRYSRTEGSLDGT
RKPQVVPPPQQNDLEIPESPTYENFT
GKSQPKAQNPARLSRKELENFDVYS
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK

and optionally

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above;

and the ITSM is the sequence $TX_1YX_2X_3X_4$, wherein

X_1 is an amino acid,

X_2 is an amino acid,

X_3 is an amino acid, and,

X_4 is V or I,

or a variant thereof.

In some embodiments, the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein

n is 0;

m is 1;

p is 1;

L3 is selected from

CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQ

and L4 comprises

(k)

VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL

and

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above;

and the ITSM is the sequence $TX_1YX_2X_3X_4$, wherein

X_1 is an amino acid,

X_2 is an amino acid,

X_3 is an amino acid, and,

X_4 is V or I,

or a variant thereof.

In some embodiments, the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein

n is 0;

m is 1;

p is 1;

L3 is selected from

WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEY VTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGRGPEEP

L4 comprises

(k)

SRP

and optionally

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above;

and the ITSM is the sequence $TX_1YX_2X_3X_4$, wherein

X_1 is an amino acid,

X_2 is an amino acid,

X_3 is an amino acid, and,

X_4 is V or I,

or a variant thereof.

In some embodiments, the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein

n is 0;

m is 1;

p is 1 or 2;

L3 comprises one sequence selected from

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids; and

L4 comprises one or more, preferably one or two, sequences selected from:

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids, and, wherein,

the ITSM is the sequence $TX_1YX_2X_3X_4$, wherein

X_1 is an amino acid,

X_2 is an amino acid,

X_3 is an amino acid, and,

X_4 is V or I.

In some embodiments, the intracellular domain comprises the sequence $(L1\text{-}ITIM\text{-}L2\text{-}L3\text{-}ITSM\text{-}L4)^p$ wherein

p is 1, 2, 3, 4 or 5;

L1 is a naturally occurring N-terminal flanking region of an ITIM only intracellular domain or a fragment thereof such as, for example, any of the sequences shown in Table 3 below or a fragment thereof;

L2 is absent;

L3 is a naturally occurring intracellular domain between ITIM and ITSM from proteins that have ITIM.*ITSM motif or a fragment thereof such as, for example, any of the sequences shown in Table 5 below or a fragment thereof;

L4 is a naturally occurring C-terminal flanking region of an ITIM.*ITSM intracellular domain or a fragment thereof such as, for example, any of the sequences shown in Table 7 below or a fragment thereof; or a naturally occurring C-terminal flanking region of ITSM only intracellular domain or a fragment thereof such as, for example, any of the sequences shown in Table 8 below or a fragment thereof.

In some embodiments, the intracellular domain comprises the sequence $(L1\text{-}ITIM\text{-}L2\text{-}L3\text{-}ITSM\text{-}L4)^p$ wherein

p is 1, 2, 3, 4 or 5;

L1 is a naturally occurring N-terminal flanking region of ITIM only intracellular domains selected from the following sequences;

YKMYGSEMLHKRDPLDEDEDTD
DHWALTQRTARAVSPQSTKPMAES
CSRAARGTIGARRTGQPLKEDPSAVPVFS
HRQNQIKQGPPRSKDEEQKPQQRPDLAVDVLERTADKATVNGLPEKDRETDTSALAAGSSQE
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPTVEMDEE
LTRKKKALRIHSVEGDLRRKSAGQEEWSPSAPSPPGSCVQAEAAPAGLCGEQRGEDCAELHDYFNV
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPINDNKEPLNSD
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEENKPG
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKED
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKLEDVVIDRNLLILGKILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNSSQREIEEFLSEAACMKDFSHPNVIRLLGVCIEMSSQGIPKPMVILPFMKYGDLHTY

L2 is absent;

L3 is a naturally occurring intracellular domain between ITIM and ITSM from proteins that have ITIM.*ITSM motif selected from the following sequences:

KEEEMAD
NFHGMNPSKDTS
QVSSAESHKDLGKKDTE
NLPKGKKPAPQAAEPNNH
NHSVIGPNSRLARNVKEAP
DFQWREKTPEPPVPCVPEQ
TLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKEDISYASLTLGAEDQEPTYCNMGHL SSHLPGRGPEEP
ETGPKHIPLQTLLKFMVDIALGMEYLSNRNFLHRDLAARNCMLRDDMTVCVADFGLSKKIYS GDYYRQGRIAKMPVKWIAIESLADRVYTSKSDVWAFGVTMWEIATRGM

L4 is a naturally occurring C-terminal flanking region of ITIM.*ITSM intracellular domains selected from the following sequences:

SRP
RTQ
CVRS
KAENIIMMETAQTSL
RKAVPDAVESRYSRTEGSLDGT
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVR NQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGR YILNGGSEEWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFAD DSSEGSEVLM

or a naturally occurring C-terminal flanking region of ITSM only intracellular domains selected from the following sequences:

RTQ
SRP
CVRS
KAENIIMMETAQTSL
RKAVPDAVESRYSRTEGSLDGT

VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
FNLQGKTPVSQKEESSATIYCSIRKPQVVPPPQQNDLEIPESPTYENFT
GGRTMLPIRWMPPESILYRKFTTESDVWSFGVVLWEIFTYGKQPWYQLSNTEAIDCITQGRE LERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARLQALAQAPPVYLDVLG
GGHTMLPIRWMPPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNEVIECITQGR VLQRPRTCPQEVYELMLGCWQREPHMRKNIKGIHTLLQNLAKASPVYLDILG
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVR NQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGR YILNGGSEEWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFAD DSSEGSEVLM
KDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQEPAYTLYSLIQPSRKSGSRKRNHSP SFNSTIYEVIGKSQPKAQNPARLSRKELENFDVYS.

or a variant thereof.

In some embodiments, the non-naturally occurring sequence of (d), (i) and (m) comprises between 1 and 500 amino acids, preferably 1 to 400, 1 to 300, 1 to 200, 1 to 100, 10 to 100, 10 to 80, 10 to 60, 10 to 40, 100 to 200, 100 to 300 or 100 to 400.

In some embodiments, the non-naturally occurring sequence of (d) or (i) is a Glycine/Serine linker $(Gly_xSer)_n$ where x=1, 2, 3, 4 or 5 and n is 1 to 100. Preferably the Glycine/Serine linker comprises the amino acid sequence $(Gly\text{-}Gly\text{-}Gly\text{-}Ser)_n$ or $(Gly\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Ser)_n$, where n is a positive integer equal to or greater than 1, preferably between 1 to 100, 1 to 80, 1 to 50, 1 to 20 or 1 to 10. For example, n=1, n=2, n=3, n=4, n=5, n=6, n=7, n=8, n=9 and n=10. In one embodiment, the glycine/serine linkers include, but are not limited to, $(Gly_4Ser)_4$ or $(Gly_4Ser)_3$.

In some embodiments, X_1 is E, V or I.
In some embodiments, X_1 is E.

In some embodiments, X_2 is S or A.
In some embodiments, X_2 is A.

In some embodiments, X_3 is E, S, T, Q or V.
In some embodiments, X_3 is E.
In some embodiments, X_3 is T.

In some embodiments, X_2 is I.

In some embodiments, X_5 is L, V or I.
In some embodiments, X_5 is L.
In some embodiments, X_5 is V.
In some embodiments, X_5 is I.

In some embodiments, X_6 is A, H, Q, T, D, V, L or E.
In some embodiments, X_6 is H.
In some embodiments, X_6 is D.

In some embodiments, X_7 is A, G, T, V or E.
In some embodiments, X_7 is A.
In some embodiments, X_7 is G.

In some embodiments, X_8 is V, S, D or E.
In some embodiments, X_8 is S or E.
In some embodiments, X_8 is E.

In some embodiments, X_9 is L or V.
In some embodiments, X_9 is L.

In some embodiments, X_5 is L or V, X_8 is E and X_9 is L.

In some embodiments, the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain, is selected from SEQ ID No 926 to SEQ ID No 1015 (see below table).

TAYELV	SEQ ID No 926	TIYEVI	SEQ ID No 956	TQYGRV	SEQ ID No 986
TAYGLI	SEQ ID No 927	TIYHVI	SEQ ID No 957	TQYNQV	SEQ ID No 987
TAYNAV	SEQ ID No 928	TIYIGV	SEQ ID No 958	TRYAYV	SEQ ID No 988
TCYGLV	SEQ ID No 929	TIYLKV	SEQ ID No 959	TRYGEV	SEQ ID No 989
TCYPDI	SEQ ID No 930	TIYSMI	SEQ ID No 960	TRYHSV	SEQ ID No 990
TDYASI	SEQ ID No 931	TIYSTI	SEQ ID No 961	TRYKTI	SEQ ID No 991
TDYDLV	SEQ ID No 932	TIYTYI	SEQ ID No 962	TRYLAI	SEQ ID No 992

TDYLSI	SEQ ID No 933	TKYFHI	SEQ ID No 963	TRYMAI	SEQ ID No 993
TDYQQV	SEQ ID No 934	TKYMEI	SEQ ID No 964	TRYQKI	SEQ ID No 994
TDYYRV	SEQ ID No 935	TKYQSV	SEQ ID No 965	TRYQQI	SEQ ID No 995
TEYASI	SEQ ID No 936	TKYSNI	SEQ ID No 966	TRYSNI	SEQ ID No 996
TEYATI	SEQ ID No 937	TKYSTV	SEQ ID No 967	TRYSPI	SEQ ID No 997
TEYDTI	SEQ ID No 938	TLYASV	SEQ ID No 968	TSYGTV	SEQ ID No 998
TEYPLV	SEQ ID No 939	TLYAVV	SEQ ID No 969	TSYMEV	SEQ ID No 999
TEYSEI	SEQ ID No 940	TLYFWV	SEQ ID No 970	TSYQGV	SEQ ID No 1000
TEYSEV	SEQ ID No 941	TLYHLV	SEQ ID No 971	TSYTTI	SEQ ID No 1001
TEYSTI	SEQ ID No 942	TLYPMV	SEQ ID No 972	TTYRSI	SEQ ID No 1002
TEYTKV	SEQ ID No 943	TLYPPI	SEQ ID No 973	TTYSDV	SEQ ID No 1003
TFYHVV	SEQ ID No 944	TLYRDI	SEQ ID No 974	TTYVTI	SEQ ID No 1004
TFYLLI	SEQ ID No 945	TLYRDV	SEQ ID No 975	TVYAQI	SEQ ID No 1005
TFYNKI	SEQ ID No 946	TLYSKI	SEQ ID No 976	TVYASV	SEQ ID No 1006
TFYPDI	SEQ ID No 947	TLYSLI	SEQ ID No 977	TVYEVI	SEQ ID No 1007
TGYEDV	SEQ ID No 948	TLYSPV	SEQ ID No 978	TVYGDV	SEQ ID No 1008
TGYLSI	SEQ ID No 949	TMYAQV	SEQ ID No 979	TVYKGI	SEQ ID No 1009
THYKEI	SEQ ID No 950	TMYCQV	SEQ ID No 980	TVYQRV	SEQ ID No 1010
TIYAQV	SEQ ID No 951	TNYKAV	SEQ ID No 981	TVYSEV	SEQ ID No 1011
TIYAVV	SEQ ID No 952	TNYNLV	SEQ ID No 982	TVYSTV	SEQ ID No 1012
TIYCSI	SEQ ID No 953	TPYAGI	SEQ ID No 983	TYYHSI	SEQ ID No 1013
TIYEDV	SEQ ID No 954	TPYPGV	SEQ ID No 984	TYYLQI	SEQ ID No 1014
TIYERI	SEQ ID No 955	TPYVDI	SEQ ID No 985	TYYYSV	SEQ ID No 1015
TAYELV	SEQ ID No 86	TAYELV	SEQ ID No 86	TAYELV	SEQ ID No 86

In some embodiments, the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain is TEYASI.

In some embodiments, the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain is TEYSEI.

In some embodiments, the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain is TVYSEV.

In some embodiments, the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain is TEYSTI.

In some embodiments, the ITIM, or at least one of the ITIMs when several ITIMs are present in the intracellular domain is selected from SEQ ID No 1016 to SEQ ID 1998 (see below table).

LLYEMV	SEQ ID No 1016	IGYDVL	SEQ ID No 1050	INYKDI	SEQ ID No 1084
ITYFAL	SEQ ID No 1017	IGYICL	SEQ ID No 1051	INYTTV	SEQ ID No 1085
ISYKGL	SEQ ID No 1018	IGYKAI	SEQ ID No 1052	INYVLL	SEQ ID No 1086
LAYHTV	SEQ ID No 1019	IGYLEL	SEQ ID No 1053	IPYDVL	SEQ ID No 1087
VQYLRL	SEQ ID No 1020	IGYLPL	SEQ ID No 1054	IPYLLV	SEQ ID No 1088
LTYVLL	SEQ ID No 1021	IGYLRL	SEQ ID No 1055	IPYRTV	SEQ ID No 1089
VRYSIV	SEQ ID No 1022	IGYPFL	SEQ ID No 1056	IPYSQL	SEQ ID No 1090
LLYLLL	SEQ ID No 1023	IGYSDL	SEQ ID No 1057	IPYSRI	SEQ ID No 1091
IAYGDI	SEQ ID No 1024	IHYRQI	SEQ ID No 1058	IPYTQI	SEQ ID No 1092
IAYRDL	SEQ ID No 1025	IHYSEL	SEQ ID No 1059	IQYAPL	SEQ ID No 1093
IAYSLL	SEQ ID No 1026	IIYAFL	SEQ ID No 1060	IQYASL	SEQ ID No 1094
IAYSRL	SEQ ID No 1027	IIYHVI	SEQ ID No 1061	IQYERL	SEQ ID No 1095
ICYALL	SEQ ID No 1028	IIYMFL	SEQ ID No 1062	IQYGII	SEQ ID No 1096
ICYDAL	SEQ ID No 1029	IIYNLL	SEQ ID No 1063	IQYGNV	SEQ ID No 1097
ICYPLL	SEQ ID No 1030	IIYNNL	SEQ ID No 1064	IQYGRV	SEQ ID No 1098
ICYQLI	SEQ ID No 1031	IIYSEV	SEQ ID No 1065	IQYNVV	SEQ ID No 1099
IDYILV	SEQ ID No 1032	IKYCLV	SEQ ID No 1066	IQYRSI	SEQ ID No 1100
IDYKTL	SEQ ID No 1033	IKYKEL	SEQ ID No 1067	IQYTEL	SEQ ID No 1101
IDYTQL	SEQ ID No 1034	IKYLAL	SEQ ID No 1068	IQYWGI	SEQ ID No 1102
IDYYNL	SEQ ID No 1035	IKYTCI	SEQ ID No 1069	IRYANL	SEQ ID No 1103
IEYCKL	SEQ ID No 1036	ILYADI	SEQ ID No 1070	IRYLDL	SEQ ID No 1104
IEYDQI	SEQ ID No 1037	ILYAFL	SEQ ID No 1071	IRYPLL	SEQ ID No 1105
IEYGPL	SEQ ID No 1038	ILYCSV	SEQ ID No 1072	IRYRLL	SEQ ID No 1106
IEYIRV	SEQ ID No 1039	ILYEGL	SEQ ID No 1073	IRYRTI	SEQ ID No 1107
IEYKSL	SEQ ID No 1040	ILYELL	SEQ ID No 1074	ISYASL	SEQ ID No 1108
IEYKTL	SEQ ID No 1041	ILYFQI	SEQ ID No 1075	ISYCGV	SEQ ID No 1109
IEYSVL	SEQ ID No 1042	ILYHTV	SEQ ID No 1076	ISYEPI	SEQ ID No 1110
IEYWGI	SEQ ID No 1043	ILYLQV	SEQ ID No 1077	ISYFQI	SEQ ID No 1111
IFYGNV	SEQ ID No 1044	ILYSIL	SEQ ID No 1078	ISYGLI	SEQ ID No 1112
IFYHNL	SEQ ID No 1045	ILYSVL	SEQ ID No 1079	ISYKKL	SEQ ID No 1113
IFYKDI	SEQ ID No 1046	ILYTEL	SEQ ID No 1080	ISYLPL	SEQ ID No 1114
IFYQNV	SEQ ID No 1047	ILYTIL	SEQ ID No 1081	ISYPML	SEQ ID No 1115
IFYRLI	SEQ ID No 1048	IMYTLV	SEQ ID No 1082	ISYTTL	SEQ ID No 1116
IGYDIL	SEQ ID No 1049	INYCSV	SEQ ID No 1083	ITYAAV	SEQ ID No 1117

ITYADL	SEQ ID No 1118	LAYRLL	SEQ ID No 1153	LEYLQI	SEQ ID No 1188
ITYAEL	SEQ ID No 1119	LAYSQL	SEQ ID No 1154	LEYLQL	SEQ ID No 1189
ITYAEV	SEQ ID No 1120	LAYSSV	SEQ ID No 1155	LEYQRL	SEQ ID No 1190
ITYASV	SEQ ID No 1121	LAYTLL	SEQ ID No 1156	LEYVDL	SEQ ID No 1191
ITYDLI	SEQ ID No 1122	LAYWGI	SEQ ID No 1157	LEYVSV	SEQ ID No 1192
ITYENV	SEQ ID No 1123	LAYYTV	SEQ ID No 1158	LEYYQI	SEQ ID No 1193
ITYQLL	SEQ ID No 1124	LCYADL	SEQ ID No 1159	LFYAQL	SEQ ID No 1194
ITYSLL	SEQ ID No 1125	LCYAIL	SEQ ID No 1160	LFYCSV	SEQ ID No 1195
IVYAEL	SEQ ID No 1126	LCYFHL	SEQ ID No 1161	LFYERV	SEQ ID No 1196
IVYALV	SEQ ID No 1127	LCYHPI	SEQ ID No 1162	LFYGFL	SEQ ID No 1197
IVYASL	SEQ ID No 1128	LCYKEI	SEQ ID No 1163	LFYKYV	SEQ ID No 1198
IVYEIL	SEQ ID No 1129	LCYKFL	SEQ ID No 1164	LFYLLL	SEQ ID No 1199
IVYFIL	SEQ ID No 1130	LCYMII	SEQ ID No 1165	LFYNKV	SEQ ID No 1200
IVYHML	SEQ ID No 1131	LCYRKI	SEQ ID No 1166	LFYRHL	SEQ ID No 1201
IVYLCI	SEQ ID No 1132	LCYRVL	SEQ ID No 1167	LFYTLL	SEQ ID No 1202
IVYRLL	SEQ ID No 1133	LCYSTV	SEQ ID No 1168	LFYWDV	SEQ ID No 1203
IVYSAL	SEQ ID No 1134	LCYTLV	SEQ ID No 1169	LFYWKL	SEQ ID No 1204
IVYSWV	SEQ ID No 1135	LDYASI	SEQ ID No 1170	LGYGNV	SEQ ID No 1205
IVYTEL	SEQ ID No 1136	LDYCEL	SEQ ID No 1171	LGYKEL	SEQ ID No 1206
IVYYIL	SEQ ID No 1137	LDYDKI	SEQ ID No 1172	LGYLQL	SEQ ID No 1207
IWYENL	SEQ ID No 1138	LDYDKL	SEQ ID No 1173	LGYPLI	SEQ ID No 1208
IWYFVV	SEQ ID No 1139	LDYDYL	SEQ ID No 1174	LGYPWV	SEQ ID No 1209
IWYNIL	SEQ ID No 1140	LDYDYV	SEQ ID No 1175	LGYSAL	SEQ ID No 1210
IYYLGV	SEQ ID No 1141	LDYEFL	SEQ ID No 1176	LGYSDL	SEQ ID No 1211
LAYALL	SEQ ID No 1142	LDYINV	SEQ ID No 1177	LGYVTL	SEQ ID No 1212
LAYARI	SEQ ID No 1143	LDYNNL	SEQ ID No 1178	LHYAKI	SEQ ID No 1213
LAYDSV	SEQ ID No 1144	LDYPHV	SEQ ID No 1179	LHYALV	SEQ ID No 1214
LAYFGV	SEQ ID No 1145	LDYSPV	SEQ ID No 1180	LHYANL	SEQ ID No 1215
LAYHRL	SEQ ID No 1146	LDYVEI	SEQ ID No 1181	LHYARL	SEQ ID No 1216
LAYKDL	SEQ ID No 1147	LDYWGI	SEQ ID No 1182	LHYASI	SEQ ID No 1217
LAYKRI	SEQ ID No 1148	LEYAPV	SEQ ID No 1183	LHYASL	SEQ ID No 1218
LAYPPL	SEQ ID No 1149	LEYIPL	SEQ ID No 1184	LHYASV	SEQ ID No 1219
LAYQTL	SEQ ID No 1150	LEYKTI	SEQ ID No 1185	LHYATI	SEQ ID No 1220
LAYREV	SEQ ID No 1151	LEYLCL	SEQ ID No 1186	LHYATL	SEQ ID No 1221
LAYRII	SEQ ID No 1152	LEYLKL	SEQ ID No 1187	LHYAVL	SEQ ID No 1222

LHYDVV	SEQ ID No 1223	LHYRTI	SEQ ID No 1258	LKYKHV	SEQ ID No 1293
LHYEGL	SEQ ID No 1224	LHYSII	SEQ ID No 1259	LKYLYL	SEQ ID No 1294
LHYETI	SEQ ID No 1225	LHYSSI	SEQ ID No 1260	LKYMEV	SEQ ID No 1295
LHYFEI	SEQ ID No 1226	LHYSTI	SEQ ID No 1261	LKYMTL	SEQ ID No 1296
LHYFVV	SEQ ID No 1227	LHYSTL	SEQ ID No 1262	LKYPAI	SEQ ID No 1297
LHYGAI	SEQ ID No 1228	LHYSVI	SEQ ID No 1263	LKYPDV	SEQ ID No 1298
LHYILI	SEQ ID No 1229	LHYTAI	SEQ ID No 1264	LKYPEL	SEQ ID No 1299
LHYINL	SEQ ID No 1230	LHYTAL	SEQ ID No 1265	LKYQPI	SEQ ID No 1300
LHYKRI	SEQ ID No 1231	LHYTII	SEQ ID No 1266	LKYRGL	SEQ ID No 1301
LHYLDL	SEQ ID No 1232	LHYTKV	SEQ ID No 1267	LKYRLL	SEQ ID No 1302
LHYLNI	SEQ ID No 1233	LHYTLI	SEQ ID No 1268	LLYADL	SEQ ID No 1303
LHYLTI	SEQ ID No 1234	LHYTSI	SEQ ID No 1269	LLYAPL	SEQ ID No 1304
LHYLVI	SEQ ID No 1235	LHYTTI	SEQ ID No 1270	LLYAVV	SEQ ID No 1305
LHYMAI	SEQ ID No 1236	LHYTTV	SEQ ID No 1271	LLYCAI	SEQ ID No 1306
LHYMII	SEQ ID No 1237	LHYTVI	SEQ ID No 1272	LLYEHV	SEQ ID No 1307
LHYMNI	SEQ ID No 1238	LHYTVL	SEQ ID No 1273	LLYELL	SEQ ID No 1308
LHYMTI	SEQ ID No 1239	LHYTVV	SEQ ID No 1274	LLYEQL	SEQ ID No 1309
LHYMTL	SEQ ID No 1240	LHYVSI	SEQ ID No 1275	LLYGQI	SEQ ID No 1310
LHYMTV	SEQ ID No 1241	LHYVTI	SEQ ID No 1276	LLYIRL	SEQ ID No 1311
LHYMVI	SEQ ID No 1242	LHYVVI	SEQ ID No 1277	LLYKAL	SEQ ID No 1312
LHYNML	SEQ ID No 1243	LIYEKL	SEQ ID No 1278	LLYKFL	SEQ ID No 1313
LHYPAL	SEQ ID No 1244	LIYENV	SEQ ID No 1279	LLYKLL	SEQ ID No 1314
LHYPDL	SEQ ID No 1245	LIYKDL	SEQ ID No 1280	LLYKTV	SEQ ID No 1315
LHYPII	SEQ ID No 1246	LIYNSL	SEQ ID No 1281	LLYMVV	SEQ ID No 1316
LHYPIL	SEQ ID No 1247	LIYSGL	SEQ ID No 1282	LLYNAI	SEQ ID No 1317
LHYPLL	SEQ ID No 1248	LIYTLL	SEQ ID No 1283	LLYNIV	SEQ ID No 1318
LHYPML	SEQ ID No 1249	LIYTVL	SEQ ID No 1284	LLYNVI	SEQ ID No 1319
LHYPNV	SEQ ID No 1250	LIYWEI	SEQ ID No 1285	LLYPAI	SEQ ID No 1320
LHYPSI	SEQ ID No 1251	LKYCEL	SEQ ID No 1286	LLYPLI	SEQ ID No 1321
LHYPTI	SEQ ID No 1252	LKYDKL	SEQ ID No 1287	LLYPNI	SEQ ID No 1322
LHYPTL	SEQ ID No 1253	LKYESL	SEQ ID No 1288	LLYPSL	SEQ ID No 1323
LHYPTV	SEQ ID No 1254	LKYFTI	SEQ ID No 1289	LLYPTI	SEQ ID No 1324
LHYPVI	SEQ ID No 1255	LKYHTV	SEQ ID No 1290	LLYPVI	SEQ ID No 1325
LHYPVL	SEQ ID No 1256	LKYILL	SEQ ID No 1291	LLYPVV	SEQ ID No 1326
LHYRII	SEQ ID No 1257	LKYIPI	SEQ ID No 1292	LLYQIL	SEQ ID No 1327

LLYQNI	SEQ ID No 1328	LNYTTI	SEQ ID No 1363	LQYTIL	SEQ ID No 1398
LLYRLL	SEQ ID No 1329	LNYVPI	SEQ ID No 1364	LQYTLI	SEQ ID No 1399
LLYRVI	SEQ ID No 1330	LPYADL	SEQ ID No 1365	LQYTMI	SEQ ID No 1400
LLYSII	SEQ ID No 1331	LPYALL	SEQ ID No 1366	LQYYQV	SEQ ID No 1401
LLYSLI	SEQ ID No 1332	LPYFNI	SEQ ID No 1367	LRYAAV	SEQ ID No 1402
LLYSPV	SEQ ID No 1333	LPYFNV	SEQ ID No 1368	LRYAGL	SEQ ID No 1403
LLYSRL	SEQ ID No 1334	LPYHDL	SEQ ID No 1369	LRYAPL	SEQ ID No 1404
LLYSTI	SEQ ID No 1335	LPYKLI	SEQ ID No 1370	LRYASI	SEQ ID No 1405
LLYSVI	SEQ ID No 1336	LPYKTL	SEQ ID No 1371	LRYATI	SEQ ID No 1406
LLYSVV	SEQ ID No 1337	LPYLGV	SEQ ID No 1372	LRYATV	SEQ ID No 1407
LLYTTI	SEQ ID No 1338	LPYLKV	SEQ ID No 1373	LRYAVL	SEQ ID No 1408
LLYTVI	SEQ ID No 1339	LPYPAL	SEQ ID No 1374	LRYCGI	SEQ ID No 1409
LLYTVV	SEQ ID No 1340	LPYQVV	SEQ ID No 1375	LRYELL	SEQ ID No 1410
LLYVII	SEQ ID No 1341	LPYRTV	SEQ ID No 1376	LRYETL	SEQ ID No 1411
LLYVIL	SEQ ID No 1342	LPYVEI	SEQ ID No 1377	LRYGAL	SEQ ID No 1412
LLYVTI	SEQ ID No 1343	LPYYDL	SEQ ID No 1378	LRYGPI	SEQ ID No 1413
LLYWGI	SEQ ID No 1344	LQYASL	SEQ ID No 1379	LRYGTL	SEQ ID No 1414
LLYYLL	SEQ ID No 1345	LQYERI	SEQ ID No 1380	LRYHHI	SEQ ID No 1415
LLYYVI	SEQ ID No 1346	LQYFAV	SEQ ID No 1381	LRYHSI	SEQ ID No 1416
LMYDNV	SEQ ID No 1347	LQYFSI	SEQ ID No 1382	LRYHVL	SEQ ID No 1417
LMYMVV	SEQ ID No 1348	LQYHNI	SEQ ID No 1383	LRYIAI	SEQ ID No 1418
LMYQEL	SEQ ID No 1349	LQYIGL	SEQ ID No 1384	LRYIFV	SEQ ID No 1419
LMYRGI	SEQ ID No 1350	LQYIKI	SEQ ID No 1385	LRYITV	SEQ ID No 1420
LNYACL	SEQ ID No 1351	LQYLSL	SEQ ID No 1386	LRYKEV	SEQ ID No 1421
LNYATI	SEQ ID No 1352	LQYMIV	SEQ ID No 1387	LRYKKL	SEQ ID No 1422
LNYEVI	SEQ ID No 1353	LQYPAI	SEQ ID No 1388	LRYKMV	SEQ ID No 1423
LNYGDL	SEQ ID No 1354	LQYPLL	SEQ ID No 1389	LRYKSL	SEQ ID No 1424
LNYHKL	SEQ ID No 1355	LQYPLV	SEQ ID No 1390	LRYKVI	SEQ ID No 1425
LNYMVL	SEQ ID No 1356	LQYPSI	SEQ ID No 1391	LRYLAI	SEQ ID No 1426
LNYNIV	SEQ ID No 1357	LQYPTL	SEQ ID No 1392	LRYLDL	SEQ ID No 1427
LNYPVI	SEQ ID No 1358	LQYPVL	SEQ ID No 1393	LRYLTI	SEQ ID No 1428
LNYQMI	SEQ ID No 1359	LQYRAV	SEQ ID No 1394	LRYLTV	SEQ ID No 1429
LNYSGV	SEQ ID No 1360	LQYSAI	SEQ ID No 1395	LRYMSI	SEQ ID No 1430
LNYSVI	SEQ ID No 1361	LQYSSI	SEQ ID No 1396	LRYMVI	SEQ ID No 1431
LNYTIL	SEQ ID No 1362	LQYSVI	SEQ ID No 1397	LRYNCI	SEQ ID No 1432

LRYNGL	SEQ ID No 1433	LRYTMI	SEQ ID No 1468	LSYTTI	SEQ ID No 1503
LRYNII	SEQ ID No 1434	LRYTNL	SEQ ID No 1469	LSYVLI	SEQ ID No 1504
LRYNIL	SEQ ID No 1435	LRYTPV	SEQ ID No 1470	LTYADL	SEQ ID No 1505
LRYNKI	SEQ ID No 1436	LRYTSI	SEQ ID No 1471	LTYAEL	SEQ ID No 1506
LRYNSL	SEQ ID No 1437	LRYTSV	SEQ ID No 1472	LTYAQV	SEQ ID No 1507
LRYNVI	SEQ ID No 1438	LRYTTI	SEQ ID No 1473	LTYARL	SEQ ID No 1508
LRYNVL	SEQ ID No 1439	LRYTTV	SEQ ID No 1474	LTYCDL	SEQ ID No 1509
LRYPFL	SEQ ID No 1440	LRYTVI	SEQ ID No 1475	LTYCGL	SEQ ID No 1510
LRYPII	SEQ ID No 1441	LRYVEV	SEQ ID No 1476	LTYCVL	SEQ ID No 1511
LRYPIL	SEQ ID No 1442	LRYVTI	SEQ ID No 1477	LTYEEL	SEQ ID No 1512
LRYPLL	SEQ ID No 1443	LRYVTV	SEQ ID No 1478	LTYEFL	SEQ ID No 1513
LRYPNI	SEQ ID No 1444	LSYDSL	SEQ ID No 1479	LTYGEV	SEQ ID No 1514
LRYPSI	SEQ ID No 1445	LSYEDV	SEQ ID No 1480	LTYGRL	SEQ ID No 1515
LRYPTI	SEQ ID No 1446	LSYFGV	SEQ ID No 1481	LTYKAL	SEQ ID No 1516
LRYPTL	SEQ ID No 1447	LSYILI	SEQ ID No 1482	LTYLRL	SEQ ID No 1517
LRYPVI	SEQ ID No 1448	LSYISV	SEQ ID No 1483	LTYMTL	SEQ ID No 1518
LRYPVL	SEQ ID No 1449	LSYKQV	SEQ ID No 1484	LTYNTL	SEQ ID No 1519
LRYQKL	SEQ ID No 1450	LSYKRL	SEQ ID No 1485	LTYPGI	SEQ ID No 1520
LRYQMI	SEQ ID No 1451	LSYLDV	SEQ ID No 1486	LTYQSV	SEQ ID No 1521
LRYQNL	SEQ ID No 1452	LSYMDL	SEQ ID No 1487	LTYSSV	SEQ ID No 1522
LRYRLI	SEQ ID No 1453	LSYNAL	SEQ ID No 1488	LTYTTV	SEQ ID No 1523
LRYRVI	SEQ ID No 1454	LSYNDL	SEQ ID No 1489	LVYDAI	SEQ ID No 1524
LRYSAI	SEQ ID No 1455	LSYNKL	SEQ ID No 1490	LVYDKL	SEQ ID No 1525
LRYSDL	SEQ ID No 1456	LSYNQL	SEQ ID No 1491	LVYDLV	SEQ ID No 1526
LRYSII	SEQ ID No 1457	LSYPVL	SEQ ID No 1492	LVYENL	SEQ ID No 1527
LRYSMI	SEQ ID No 1458	LSYQEV	SEQ ID No 1493	LVYGQL	SEQ ID No 1528
LRYSSI	SEQ ID No 1459	LSYQPV	SEQ ID No 1494	LVYHKL	SEQ ID No 1529
LRYSTI	SEQ ID No 1460	LSYQTI	SEQ ID No 1495	LVYQEV	SEQ ID No 1530
LRYSTL	SEQ ID No 1461	LSYRSL	SEQ ID No 1496	LVYRKV	SEQ ID No 1531
LRYSVI	SEQ ID No 1462	LSYRSV	SEQ ID No 1497	LVYRNL	SEQ ID No 1532
LRYSVL	SEQ ID No 1463	LSYSII	SEQ ID No 1498	LVYSEI	SEQ ID No 1533
LRYSVV	SEQ ID No 1464	LSYSSL	SEQ ID No 1499	LVYTNV	SEQ ID No 1534
LRYTAI	SEQ ID No 1465	LSYSTL	SEQ ID No 1500	LVYWEI	SEQ ID No 1535
LRYTIL	SEQ ID No 1466	LSYTKV	SEQ ID No 1501	LVYWKL	SEQ ID No 1536
LRYTLI	SEQ ID No 1467	LSYTSI	SEQ ID No 1502	LVYWRL	SEQ ID No 1537

LWYEGL	SEQ ID No 1538	SDYESV	SEQ ID No 1573	SFYSAL	SEQ ID No 1608
LWYKYI	SEQ ID No 1539	SDYFIV	SEQ ID No 1574	SFYSDI	SEQ ID No 1609
LWYNHI	SEQ ID No 1540	SDYHTL	SEQ ID No 1575	SFYSKL	SEQ ID No 1610
LWYTMI	SEQ ID No 1541	SDYLAI	SEQ ID No 1576	SFYSRV	SEQ ID No 1611
LYYCQL	SEQ ID No 1542	SDYLDI	SEQ ID No 1577	SFYWNV	SEQ ID No 1612
LYYGDL	SEQ ID No 1543	SDYLEL	SEQ ID No 1578	SFYYLI	SEQ ID No 1613
LYYKKV	SEQ ID No 1544	SDYQDL	SEQ ID No 1579	SGYAQL	SEQ ID No 1614
LYYLLI	SEQ ID No 1545	SDYQRL	SEQ ID No 1580	SGYATL	SEQ ID No 1615
LYYPKV	SEQ ID No 1546	SDYSVI	SEQ ID No 1581	SGYEKL	SEQ ID No 1616
LYYRRV	SEQ ID No 1547	SDYTHL	SEQ ID No 1582	SGYQLV	SEQ ID No 1617
LYYSTI	SEQ ID No 1548	SEYASV	SEQ ID No 1583	SGYQRI	SEQ ID No 1618
LYYVRI	SEQ ID No 1549	SEYEEL	SEQ ID No 1584	SGYRRL	SEQ ID No 1619
LYYVVI	SEQ ID No 1550	SEYFEL	SEQ ID No 1585	SGYSHL	SEQ ID No 1620
SAYATL	SEQ ID No 1551	SEYGEL	SEQ ID No 1586	SGYSQL	SEQ ID No 1621
SAYCPL	SEQ ID No 1552	SEYITL	SEQ ID No 1587	SGYTLI	SEQ ID No 1622
SAYPAL	SEQ ID No 1553	SEYKAL	SEQ ID No 1588	SGYTRI	SEQ ID No 1623
SAYQAL	SEQ ID No 1554	SEYKEL	SEQ ID No 1589	SGYYRV	SEQ ID No 1624
SAYQTI	SEQ ID No 1555	SEYKGI	SEQ ID No 1590	SHYADV	SEQ ID No 1625
SAYRSV	SEQ ID No 1556	SEYLAI	SEQ ID No 1591	SHYFPL	SEQ ID No 1626
SAYTAL	SEQ ID No 1557	SEYLEI	SEQ ID No 1592	SHYIDI	SEQ ID No 1627
SAYTPL	SEQ ID No 1558	SEYMVI	SEQ ID No 1593	SHYKRL	SEQ ID No 1628
SAYVVL	SEQ ID No 1559	SEYQSI	SEQ ID No 1594	SHYQVV	SEQ ID No 1629
SCYAAV	SEQ ID No 1560	SEYRPI	SEQ ID No 1595	SIYAPL	SEQ ID No 1630
SCYCII	SEQ ID No 1561	SEYSEI	SEQ ID No 1596	SIYATL	SEQ ID No 1631
SCYCLL	SEQ ID No 1562	SEYSSI	SEQ ID No 1597	SIYEEL	SEQ ID No 1632
SCYDFL	SEQ ID No 1563	SEYTPI	SEQ ID No 1598	SIYEEV	SEQ ID No 1633
SCYEEL	SEQ ID No 1564	SEYTYV	SEQ ID No 1599	SIYELL	SEQ ID No 1634
SCYEKI	SEQ ID No 1565	SFYAAL	SEQ ID No 1600	SIYEVL	SEQ ID No 1635
SCYHIL	SEQ ID No 1566	SFYDSL	SEQ ID No 1601	SIYGDL	SEQ ID No 1636
SCYPYI	SEQ ID No 1567	SFYKGL	SEQ ID No 1602	SIYKKL	SEQ ID No 1637
SCYRIL	SEQ ID No 1568	SFYLYV	SEQ ID No 1603	SIYLNI	SEQ ID No 1638
SCYRTL	SEQ ID No 1569	SFYNAV	SEQ ID No 1604	SIYLVI	SEQ ID No 1639
SDYCNL	SEQ ID No 1570	SFYPSV	SEQ ID No 1605	SIYRYI	SEQ ID No 1640
SDYEDL	SEQ ID No 1571	SFYQQI	SEQ ID No 1606	SIYSWI	SEQ ID No 1641
SDYENV	SEQ ID No 1572	SFYQQL	SEQ ID No 1607	SKYKEI	SEQ ID No 1642

SKYKIL	SEQ ID No 1643	SLYVDV	SEQ ID No 1678	SQYEAL	SEQ ID No 1713
SKYKSL	SEQ ID No 1644	SLYVSI	SEQ ID No 1679	SQYKRL	SEQ ID No 1714
SKYLAV	SEQ ID No 1645	SLYYAL	SEQ ID No 1680	SQYLAL	SEQ ID No 1715
SKYLGV	SEQ ID No 1646	SLYYNI	SEQ ID No 1681	SQYLRL	SEQ ID No 1716
SKYNIL	SEQ ID No 1647	SLYYPI	SEQ ID No 1682	SQYMHV	SEQ ID No 1717
SKYQAV	SEQ ID No 1648	SMYDGL	SEQ ID No 1683	SQYSAV	SEQ ID No 1718
SKYSDI	SEQ ID No 1649	SMYEDI	SEQ ID No 1684	SQYTSI	SEQ ID No 1719
SKYSSL	SEQ ID No 1650	SMYNEI	SEQ ID No 1685	SQYWRL	SEQ ID No 1720
SKYVGL	SEQ ID No 1651	SMYQSV	SEQ ID No 1686	SRYAEL	SEQ ID No 1721
SKYVSL	SEQ ID No 1652	SMYTWL	SEQ ID No 1687	SRYATL	SEQ ID No 1722
SLYANI	SEQ ID No 1653	SMYVSI	SEQ ID No 1688	SRYESL	SEQ ID No 1723
SLYAQV	SEQ ID No 1654	SNYENL	SEQ ID No 1689	SRYGLL	SEQ ID No 1724
SLYAYI	SEQ ID No 1655	SNYGSL	SEQ ID No 1690	SRYLSL	SEQ ID No 1725
SLYDDL	SEQ ID No 1656	SNYGTI	SEQ ID No 1691	SRYMEL	SEQ ID No 1726
SLYDFL	SEQ ID No 1657	SNYLVL	SEQ ID No 1692	SRYMRI	SEQ ID No 1727
SLYDNL	SEQ ID No 1658	SNYQEI	SEQ ID No 1693	SRYPPV	SEQ ID No 1728
SLYDSI	SEQ ID No 1659	SNYRLL	SEQ ID No 1694	SRYQAL	SEQ ID No 1729
SLYDYL	SEQ ID No 1660	SNYRTL	SEQ ID No 1695	SRYQQL	SEQ ID No 1730
SLYEGL	SEQ ID No 1661	SNYSDI	SEQ ID No 1696	SRYRFI	SEQ ID No 1731
SLYEHI	SEQ ID No 1662	SNYSLL	SEQ ID No 1697	SRYRFV	SEQ ID No 1732
SLYELL	SEQ ID No 1663	SPYAEI	SEQ ID No 1698	SRYSAL	SEQ ID No 1733
SLYHCL	SEQ ID No 1664	SPYATL	SEQ ID No 1699	SRYSDL	SEQ ID No 1734
SLYHKL	SEQ ID No 1665	SPYEKV	SEQ ID No 1700	SRYTGL	SEQ ID No 1735
SLYIGI	SEQ ID No 1666	SPYGDI	SEQ ID No 1701	SRYVRL	SEQ ID No 1736
SLYKKL	SEQ ID No 1667	SPYGGL	SEQ ID No 1702	SSYDEL	SEQ ID No 1737
SLYKNL	SEQ ID No 1668	SPYNTL	SEQ ID No 1703	SSYEAL	SEQ ID No 1738
SLYLAI	SEQ ID No 1669	SPYPGI	SEQ ID No 1704	SSYEIV	SEQ ID No 1739
SLYLGI	SEQ ID No 1670	SPYPGV	SEQ ID No 1705	SSYEPL	SEQ ID No 1740
SLYNAL	SEQ ID No 1671	SPYQEL	SEQ ID No 1706	SSYGRL	SEQ ID No 1741
SLYNLL	SEQ ID No 1672	SPYRSV	SEQ ID No 1707	SSYGSI	SEQ ID No 1742
SLYRNI	SEQ ID No 1673	SPYSRL	SEQ ID No 1708	SSYGSL	SEQ ID No 1743
SLYSDV	SEQ ID No 1674	SPYTDV	SEQ ID No 1709	SSYHII	SEQ ID No 1744
SLYTCV	SEQ ID No 1675	SPYTSV	SEQ ID No 1710	SSYHIL	SEQ ID No 1745
SLYTTL	SEQ ID No 1676	SPYVVI	SEQ ID No 1711	SSYHKL	SEQ ID No 1746
SLYVAI	SEQ ID No 1677	SQYCVL	SEQ ID No 1712	SSYHNI	SEQ ID No 1747

SSYIKV	SEQ ID No 1748	SVYEKV	SEQ ID No 1783	VDYFTI	SEQ ID No 1818
SSYNSV	SEQ ID No 1749	SVYEML	SEQ ID No 1784	VDYFVL	SEQ ID No 1819
SSYQEI	SEQ ID No 1750	SVYGSV	SEQ ID No 1785	VDYGEL	SEQ ID No 1820
SSYRKV	SEQ ID No 1751	SVYPII	SEQ ID No 1786	VDYILV	SEQ ID No 1821
SSYRRV	SEQ ID No 1752	SVYQPI	SEQ ID No 1787	VDYIQV	SEQ ID No 1822
SSYSDI	SEQ ID No 1753	SVYRKV	SEQ ID No 1788	VDYKNI	SEQ ID No 1823
SSYTPL	SEQ ID No 1754	SVYSHL	SEQ ID No 1789	VDYMSI	SEQ ID No 1824
SSYTRL	SEQ ID No 1755	SVYSRV	SEQ ID No 1790	VDYNLV	SEQ ID No 1825
SSYTSV	SEQ ID No 1756	SVYTAL	SEQ ID No 1791	VDYPDV	SEQ ID No 1826
SSYTTI	SEQ ID No 1757	SVYTEL	SEQ ID No 1792	VDYSDL	SEQ ID No 1827
SSYVKL	SEQ ID No 1758	SVYWKV	SEQ ID No 1793	VDYSSV	SEQ ID No 1828
STYAEV	SEQ ID No 1759	SWYDSI	SEQ ID No 1794	VDYTTL	SEQ ID No 1829
STYAGI	SEQ ID No 1760	SWYFTV	SEQ ID No 1795	VDYVDV	SEQ ID No 1830
STYAHL	SEQ ID No 1761	SYYKAI	SEQ ID No 1796	VDYVGV	SEQ ID No 1831
STYALV	SEQ ID No 1762	SYYLKL	SEQ ID No 1797	VDYVIL	SEQ ID No 1832
STYAPI	SEQ ID No 1763	SYYSFV	SEQ ID No 1798	VDYVQV	SEQ ID No 1833
STYDHV	SEQ ID No 1764	SYYVTI	SEQ ID No 1799	VEYAPL	SEQ ID No 1834
STYDKV	SEQ ID No 1765	VAYADL	SEQ ID No 1800	VEYDPL	SEQ ID No 1835
STYDQV	SEQ ID No 1766	VAYARI	SEQ ID No 1801	VEYGTI	SEQ ID No 1836
STYDRI	SEQ ID No 1767	VAYARV	SEQ ID No 1802	VEYHRL	SEQ ID No 1837
STYEEL	SEQ ID No 1768	VAYDQL	SEQ ID No 1803	VEYLEV	SEQ ID No 1838
STYEYL	SEQ ID No 1769	VAYGHV	SEQ ID No 1804	VEYQLL	SEQ ID No 1839
STYILV	SEQ ID No 1770	VAYKQV	SEQ ID No 1805	VEYRPL	SEQ ID No 1840
STYLPL	SEQ ID No 1771	VAYKRL	SEQ ID No 1806	VEYSSI	SEQ ID No 1841
STYMAV	SEQ ID No 1772	VAYNLL	SEQ ID No 1807	VEYSTV	SEQ ID No 1842
STYQTL	SEQ ID No 1773	VAYQRV	SEQ ID No 1808	VFYAEI	SEQ ID No 1843
STYRKL	SEQ ID No 1774	VAYSGV	SEQ ID No 1809	VFYLAV	SEQ ID No 1844
STYSQL	SEQ ID No 1775	VAYSQV	SEQ ID No 1810	VFYRQV	SEQ ID No 1845
STYTSI	SEQ ID No 1776	VCYCIV	SEQ ID No 1811	VFYVGV	SEQ ID No 1846
STYYQV	SEQ ID No 1777	VCYGLV	SEQ ID No 1812	VFYYVI	SEQ ID No 1847
SVYATL	SEQ ID No 1778	VCYGRL	SEQ ID No 1813	VFYYVL	SEQ ID No 1848
SVYCFL	SEQ ID No 1779	VCYIVV	SEQ ID No 1814	VGYETI	SEQ ID No 1849
SVYCNL	SEQ ID No 1780	VCYLLV	SEQ ID No 1815	VHYALL	SEQ ID No 1850
SVYDSV	SEQ ID No 1781	VDYDCI	SEQ ID No 1816	VHYARL	SEQ ID No 1851
SVYDTI	SEQ ID No 1782	VDYDFL	SEQ ID No 1817	VHYETL	SEQ ID No 1852

VHYGGV	SEQ ID No 1853	VKYSRL	SEQ ID No 1888	VPYRLL	SEQ ID No 1923
VHYHSL	SEQ ID No 1854	VKYSTL	SEQ ID No 1889	VPYSEL	SEQ ID No 1924
VHYIPV	SEQ ID No 1855	VKYVDL	SEQ ID No 1890	VPYTLL	SEQ ID No 1925
VHYKEI	SEQ ID No 1856	VLYADI	SEQ ID No 1891	VPYTPL	SEQ ID No 1926
VHYLQV	SEQ ID No 1857	VLYAML	SEQ ID No 1892	VPYTTL	SEQ ID No 1927
VHYNSL	SEQ ID No 1858	VLYASV	SEQ ID No 1893	VPYVEL	SEQ ID No 1928
VHYQSV	SEQ ID No 1859	VLYCLL	SEQ ID No 1894	VPYVMV	SEQ ID No 1929
VHYRSL	SEQ ID No 1860	VLYCLV	SEQ ID No 1895	VPYVSL	SEQ ID No 1930
VIYAQL	SEQ ID No 1861	VLYCVL	SEQ ID No 1896	VQYKAV	SEQ ID No 1931
VIYDRL	SEQ ID No 1862	VLYDCL	SEQ ID No 1897	VQYKEI	SEQ ID No 1932
VIYENV	SEQ ID No 1863	VLYFHI	SEQ ID No 1898	VQYNIV	SEQ ID No 1933
VIYEPL	SEQ ID No 1864	VLYFTV	SEQ ID No 1899	VQYRPV	SEQ ID No 1934
VIYERL	SEQ ID No 1865	VLYGDL	SEQ ID No 1900	VQYSQI	SEQ ID No 1935
VIYIDV	SEQ ID No 1866	VLYGQL	SEQ ID No 1901	VQYSTV	SEQ ID No 1936
VIYKKI	SEQ ID No 1867	VLYPMV	SEQ ID No 1902	VQYTEV	SEQ ID No 1937
VIYKRI	SEQ ID No 1868	VLYPRL	SEQ ID No 1903	VQYYNI	SEQ ID No 1938
VIYPFL	SEQ ID No 1869	VLYPRV	SEQ ID No 1904	VRYARL	SEQ ID No 1939
VIYPNI	SEQ ID No 1870	VLYSEL	SEQ ID No 1905	VRYDNL	SEQ ID No 1940
VIYSDL	SEQ ID No 1871	VLYSRV	SEQ ID No 1906	VRYGRI	SEQ ID No 1941
VIYSML	SEQ ID No 1872	VLYTAV	SEQ ID No 1907	VRYKKL	SEQ ID No 1942
VIYSSV	SEQ ID No 1873	VLYTIL	SEQ ID No 1908	VRYKRV	SEQ ID No 1943
VIYSWI	SEQ ID No 1874	VMYDAV	SEQ ID No 1909	VRYLDV	SEQ ID No 1944
VKYADI	SEQ ID No 1875	VNYESI	SEQ ID No 1910	VRYRTI	SEQ ID No 1945
VKYARL	SEQ ID No 1876	VNYSAL	SEQ ID No 1911	VRYSDI	SEQ ID No 1946
VKYATL	SEQ ID No 1877	VNYSKI	SEQ ID No 1912	VRYTQL	SEQ ID No 1947
VKYEGL	SEQ ID No 1878	VNYSSI	SEQ ID No 1913	VRYVCL	SEQ ID No 1948
VKYGDL	SEQ ID No 1879	VPYALL	SEQ ID No 1914	VSYAEL	SEQ ID No 1949
VKYGSV	SEQ ID No 1880	VPYDTL	SEQ ID No 1915	VSYASV	SEQ ID No 1950
VKYLLV	SEQ ID No 1881	VPYEDV	SEQ ID No 1916	VSYEPI	SEQ ID No 1951
VKYNPV	SEQ ID No 1882	VPYEEL	SEQ ID No 1917	VSYGDI	SEQ ID No 1952
VKYPPI	SEQ ID No 1883	VPYKTI	SEQ ID No 1918	VSYIGL	SEQ ID No 1953
VKYQRL	SEQ ID No 1884	VPYLRV	SEQ ID No 1919	VSYILV	SEQ ID No 1954
VKYQVI	SEQ ID No 1885	VPYNDL	SEQ ID No 1920	VSYMML	SEQ ID No 1955
VKYSEV	SEQ ID No 1886	VPYPAL	SEQ ID No 1921	VSYNNI	SEQ ID No 1956
VKYSNV	SEQ ID No 1887	VPYQEL	SEQ ID No 1922	VSYNNL	SEQ ID No 1957

VSYQEI	SEQ ID No 1958	VTYAKV	SEQ ID No 1972	VTYVNL	SEQ ID No 1986
VSYQPI	SEQ ID No 1959	VTYAPV	SEQ ID No 1973	VVYADI	SEQ ID No 1987
VSYSAV	SEQ ID No 1960	VTYAQL	SEQ ID No 1974	VVYEDV	SEQ ID No 1988
VSYSFL	SEQ ID No 1961	VTYATL	SEQ ID No 1975	VVYFCL	SEQ ID No 1989
VSYSLV	SEQ ID No 1962	VTYATV	SEQ ID No 1976	VVYKTL	SEQ ID No 1990
VSYSPV	SEQ ID No 1963	VTYGNI	SEQ ID No 1977	VVYQKL	SEQ ID No 1991
VSYTML	SEQ ID No 1964	VTYITI	SEQ ID No 1978	VVYSEV	SEQ ID No 1992
VSYTNL	SEQ ID No 1965	VTYQII	SEQ ID No 1979	VVYSQV	SEQ ID No 1993
VSYTPL	SEQ ID No 1966	VTYQIL	SEQ ID No 1980	VVYSVV	SEQ ID No 1994
VSYVKI	SEQ ID No 1967	VTYQLL	SEQ ID No 1981	VVYTVL	SEQ ID No 1995
VSYVLL	SEQ ID No 1968	VTYSAL	SEQ ID No 1982	VVYYRI	SEQ ID No 1996
VTYADL	SEQ ID No 1969	VTYSTL	SEQ ID No 1983	VYYHWL	SEQ ID No 1997
VTYAEL	SEQ ID No 1970	VTYTLL	SEQ ID No 1984	VYYLPL	SEQ ID No 1998
VTYAEV	SEQ ID No 1971	VTYTQL	SEQ ID No 1985		

In some embodiments, the ITIM, or at least one of the ITIMs when several ITIMs are present in the intracellular domain is selected from LSYRSL, LPYYDL, LLYSRL, LIYTLL, LLYADL, ISYTTL, VTYSAL, IHYSEL, VDYVIL, LHYASL, LDYDYL, VDYDFL, VTYSTL, IIYSEV, LEYLCL, VLYGQL, VPYTPL, ISYPML, VSYTNL, LLYEMV, VDYNLV, ITYFAL, VHYQSV, VPYVMV, IPYRTV, IAYSLL, VCYGRL, LKYLYL, LLYEHV, ITYSLL, VLYSEL, IWYNIL, ISYKGL, IDYYNL, LEYLQL, LKYRGL, VLYASV, LQYLSL, LFYRHL, VQYKAV, LSYSSL, LSYTKV, VQYSTV, VKYNPV, VVYSEV, LEYVSV, LAYHTV, VQYLRL, VTYTQL, IVYTEL, IVYAEL, VTYAQL, ILYTEL, ITYAAV, VIYIDV, VTYAEV, VTYAPV, VTYAKV, VTYARL, ILYHTV, VLYAML, VIYAQL, LVYENL, LCYADL, ISYASL, LTYVLL, VTYVNL, VRYSIV, VFYRQV, LKYMEV, VDYGEL, LSYMDL, VLYTAV, VQYTEV, IVYASL, VEYLEV, LEYVDL, ITYADL, LTYADL, VIYENV, LAYYTV, VSYSAV, LVYDKL, LNYMVL, LNYACL, LDYINV, LHYATL, LHYAVL, IQYAPL, IQYASL, LLYLLL, VVYSQV, VIYSSV, VVYYRV, VPYVEL, LDYDKL, LSYPVL, VAYSQV, LFYWDV, LIYSQV, or LDYEFL.

In some embodiments, p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. In some embodiments, p is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, p is 1, 2, 3, 4 or 5. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5.

In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, n is 1, 2, 3, 4 or 5. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3.

In some embodiments, m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. In some embodiments, m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, m is 1, 2, 3, 4 or 5. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4. In some embodiments, m is 5.

In some embodiments, n is 1 and m is 1.
In some embodiments, n is 1 and m is 1 and p is 1 to 10.
In some embodiments, n is 1 and m is 1 and p is 1.
In some embodiments, n is 0 and m is 1 and p is 1 to 20.
In some embodiments, n is 0, m is 1 to 6 and p is 1.
In some embodiments, n is 0, m is 1 and p is 1.
In some embodiments, n is 0, m is 2 and p is 1.
In some embodiments, n is 0, m is 3 and p is 1.
In some embodiments, n is 0, m is 4 and p is 1.
In some embodiments, n is 0, m is 5 and p is 1.
In some embodiments, n is 0, m is 6 and p is 1.
In some embodiments, n is 0, m is 1 to 6 and p is 1 and ITSM is TEYATI.
In some embodiments, n is 0, m is 1 to 6 and p is 1 and ITSM is TEYSEI.
In some embodiments, n is 0, m is 1 to 6 and p is 1 and ITSM is TVYSEV.
In some embodiments, n is 1, m is 1 and p is 1 to 5.
In some embodiments, n is 1, m is 1 and p is 1.
In some embodiments, n is 1, m is 1 and p is 2.
In some embodiments, n is 1, m is 1 and p is 3.
In some embodiments, n is 1, m is 1 and p is 4.
In some embodiments, n is 1, m is 1 and p is 5.
In some embodiments, n is 1, m is 1 and p is 1 to 5 and ITIM is VDYGEL and ITSM is TEYATI.
In some embodiments, n is 1, m is 1 and p is 1 to 5 and ITIM is LX_6YAX_8L wherein X_6 is selected from H or Q and X_8 is V or S, and ITSM is TEYSEI.
In some embodiments, n is 1, m is 1 and p is 1 to 5 and ITIM is LX_6YAX_8L wherein X_6 is selected from H or Q and X_8 is V or S, and ITSM is TEYASI.
In some embodiments, n is 1, m is 1 and p is 1 to 5 and ITIM is LX_6YAX_8L wherein X_6 is selected from H or Q and X_8 is V or S, and ITSM is TVYSEV.

In some embodiments, the intracellular domain comprises several ITSMs having the same amino acid sequence.

In some embodiments, the intracellular domain comprises several ITSMs having different amino acid sequences.

In some embodiments, the intracellular domain comprises several ITIMs having the same amino acid sequence.

In some embodiments, the intracellular domain comprises several ITIMs having different amino acid sequences.

In some embodiments, the intracellular domain of the NCAR is selected from SEQ ID No 2000, SEQ ID No 2001, SEQ ID No 2002, SEQ ID No 2003, SEQ ID No 2004, SEQ ID No 2005, SEQ ID No 2006, SEQ ID No 2007, SEQ ID No 2008, SEQ ID No 2009, SEQ ID No 2010, SEQ ID No 2011, SEQ ID No 2012, SEQ ID No 2013, SEQ ID No 2014, SEQ ID No 2015, SEQ ID No 2016 and SEQ ID No 2017.

Table 1: Naturally occurring N-terminal flanking region of ITIM.*ITSM intracellular domains varying in length from 1-520 (Table 1 comprises SEQ ID No 1 to SEQ ID No 36)

N	
ELFANKRKYT	SEQ ID No 1
RKRNNSRLGNG	SEQ ID No 2
YRHRKKRNGLT	SEQ ID No 3
YKMYGSEMLHKRDPLDEDEDTD	SEQ ID No 4
LRKRRDSLSLSTQRTQGPAESARN	SEQ ID No 5
WRMMKYQQKAAGMSPEQVLQPLEGD	SEQ ID No 6
CSRAARGTIGARRTGQPLKEDPSAVPVFS	SEQ ID No 7
RIRQKKAQGSTSSTRLHEPEKNAREITQDTND	SEQ ID No 8
NNSYQEIEEDADVEWKFARAKLWLSYFDEGRTLPAPFNLVPSPK	SEQ ID No 9
WLHRRLPPQPIRPLPRFAPLVKTEPQRPVKEEEPKIPGDLDQEPS	SEQ ID No 10
SNKCDVVVVGGGISGMAAAKLLHDSGLNVVVLEARDRVGGRTYTLRNQK	SEQ ID No 11
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPT VEMDEE	SEQ ID No 12
RVKTRRKKAAQPVQNTDDVNPVMVSGSRGHQHQFQTGIVSDHPAEAGPI SEDEQE	SEQ ID No 13
KARRKQAAGRPEKMDDEDPIMGTITSGSRKKPWPDSPGDQASPPGDAP PLEEQKE	SEQ ID No 14

KICRKEARKRAAAEQDVPSTLGPISQGHQHECSAGSSQDHPPPGAATYT PGKGEEQE	SEQ ID No 15
MENQEKASIAGHMFDVVVIGGGISGLSAAKLLTEYGVSVLVLEARDRVGG RTYTIRNEH	SEQ ID No 16
VRSCRKKSARPAAGVGDTGIEDANAVRGSASQGPLTEPWAEDSPPDQP PPASARSSVGEGE	SEQ ID No 17
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDD VRNHAMKPINDNKEPLNSD	SEQ ID No 18
VRLRLQKHRPPADPCRGETETMNNLANCQREKDISVSIIGATQIKNTNKKA DFHGDHSADKNGFKARYPA	SEQ ID No 19
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDN DPDLCFRMQEGSEVYSNPCLEENKPG	SEQ ID No 20
QSVFNKRKSRVRHYLVKCPQNSSGETVTSVTSLAPLQPKKGKRQKEKPDI PPAVPAKAPIAPTFHKPKLLKPQRKVTLPKIAEEN	SEQ ID No 21
MSDKMSSFLHIGDICSLYAEGSTNGFISTLGLVDDRCVVQPETGDLNNPP KKFRDCLFKLCPMNRYSAQKQFWKAAKPGANSTTDAVLLNKLHHAADLE KKQNETENRKLLGTV	SEQ ID No 22
MTEKMSSFLYIGDIVSLYAEGSVNGFISTLGLVDDRCVVHPEAGDLANPPK KFRDCLFKVCPMNRYSAQKQYWKAKQAKQGNHTEAALLKKLQHAAELE QKQNESENKKLLGEI	SEQ ID No 23
MSEMSSFLHIGDIVSLYAEGSVNGFISTLGLVDDRCVVEPAAGDLDNPPKK FRDCLFKVCPMNRYSAQKQYWKAKQTKQDKEKIADVVLLQKLQHAAQME QKQNDTENKKVHGDV	SEQ ID No 24
NCVSCCKDPEIDFKEFEDNFDDEIDFTPPAEDTPSVQSPAEVFTLSVPNIS LPAPSQFQPSVEGLKSQVARHSLNYIQEIGNGWFGKVLLGEIYTGTSVAR VIVKELKASANPKEQDTFLKNGEPYYILQHPNILQCVGQCVEA	SEQ ID No 25
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKL EDVVIDRNLLILGKILGEGEF GSVMEGNLKQEDGTSLKVAVKTMKLDNSSQREIEEFLSEAACMKDFSHP NVIRLLGVCIEMSSQGIPKPMVILPFMKYGDLHTY	SEQ ID No 26
HRRKKETRYGEVFEPTVERGELVVRYRVRKSYSRRTTEATLNSLGISEEL KEKLRDVMVDRHKVALGKTLGEGEFGAVMEGQLNQDDSILKVAVKTMKIA ICTRSELEDFLSEAVCMKEFDHPNVMRLIGVCFQGSERESFPAPVVILPFM KHGDLHSF	SEQ ID No 27
MSGGASATGPRRGPPGLEDTTSKKKQKDRANQESKDGDPRKETGSRYV	SEQ ID No 28

AQAGLEPLASGDPSASASHAAGITGSRHRTRLFFPSSSGSASTPQEEQTK EGACEDPHDLLATPTPELLLDWRQSAEEVIVKLRVGVGPLQLEDVDAAFT DTDCVVRFAGGQQWGG	
AYKRKSRESDLTLKRLQMQMDNLESRVALECKEAFAELQTDIHELTSDLD GAGIPFLDYRTYTMRVLFPGIEDHPVLRDLEVPGYRQERVEKGLKLFAQLI NNKVFLLSFIRTLESQRSFSMRDRGNVASLIMTVLQSKLEYATDVLKQLLA DLIDKNLESKNHPKLLLRRTESVAEKMLTNWFTF	SEQ ID No 29
YKRKTQDADRTLKRLQLQMDNLESRVALECKEAFAELQTDINELTNHMDE VQIPFLDYRTYAVRVLFPGIEAHPVLKELDTPPNVEKALRLFGQLLHSRAFV LTFIHTLEAQSSFSMRDRGTVASLTMVALQSRLDYATGLLKQLLADLIEKNL ESKNHPKLLLRRTESVAEKMLTNWFTFLLHKFLKECAGEPLF	SEQ ID No 30
RWHCPRRLLGACWTLNGQEEPVSQPTPQLENEVSRQHLPATLPEMVAF YQELHTPTQGQTMVRQLMHKLLVFSAREVDHRGGCLMLQDTGISLLIPPG AVAVGRQERVSLILVWDLSDAPSLSQAQGLVSPVVACGPHGASFLKPCTL TFKHCAEQPSHARTYSSNTTLLDAKVWRPLGRPGAHASRDECRIHLSHF	SEQ ID No 31
KQKPRYEIRWRVIESISPDGHEYIYVDPMQLPYDSRWEFPRDGLVLGRVL GSGAFGKVVEGTAYGLSRSQPVMKVAVKMLKPTARSSEKQALMSELKIM THLGPHLNIVNLLGACTKSGPIYIITEYCFYGDLVNYLHKNRDSFLSHHPEK PKKELDIFGLNPADESTRSYVILSFENNGDYMDMKQADTTQYVPMLERKE V	SEQ ID No 32
MFNYTFQQVQEHTDQIWKFQRHDLIEEYHGRPAAPPPFILLSHLQLFIKRV VLKTPAKRHKQLKNKLEKNEEAALLSWEIYLKENYLQNRQFQQKQRPEQK IEDISNKVDAMVDLLDLDPLKRSGSMEQRLASLEEQVAQTAQALHWIVRTL RASGFSSEADVPTLASQKAAEEPDAEPGGRKKTEEPGDSYHVNARHLLY PNCPVTRFPVPNEKVPWETEFLIYDPPFYTAERKDAAAMDPMGDTLEPLS T	SEQ ID No 33
CCDCGGAPRSAAGFEPVPECSDGAIHSWAVEGPQPEPRDITTVIPQIPPD NANIIECIDNSGVYTNEYGGREMQDLGGGERMTGFELTEGVKTSGMPEIC QEYSGTLRRNSMRECREGGLNMNFMESYFCQKAYAYADEDEGRPSNDC LLIYDIEGVGSPAGSVGCCSFIGEDLDDSFLDTLGPKFKKLADISLGKESYP DLDPSWPPQSTEPVCLPQETEPVVSGHPPISPHFGTTTVISESTYPSGPG VLHPKPILDP	SEQ ID No 34
MADGGEGEDEIQFLRTDDEVVLQCTATIHKEQQKLCLAAEGFGNRLCFLE STSNSKNVPPDLSICTFVLEQSLSVRALQEMLANTVEKSEGQVDVEKWKF MMKTAQGGGHRTLLYGHAILLRHSYSGMYLCCLSTSRSSTDKLAFDVGL QEDTTGEACWWTIHPASKQRSEGEKVRVGDDLILVSVSSERYLHLSYGN	SEQ ID No 35

GSLHVDAAFQQTLWSVAPISSGSEAAQGYLIGGDVLRLLHGHMDECLTVP SGEHGEEQRRTVHYEGGAVSVHARSLWRLETLRVAWSGSHIRWGQPFR LRHVTTGKYLSLMEDKNLLLMDKEKADVKSTAFTFRSSKEKLDVGVRKEV DGMGTSEIKYGDSVCYIQHVDTGLW	
MGDAEGEDEVQFLRTDDEVVLQCSATVLKEQLKLCLAAEGFGNRLCFLE PTSNAQNVPPDLAICCFVLEQSLSVRALQEMLANTVEAGVESSQGGGHR TLLYGHAILLRHAHSRMYLSCLTTSRSMTDKLAFDVGLQEDATGEACWWT MHPASKQRSEGEKVRVGDDIILVSVSSERYLHLSTASGELQVDASFMQTL WNMNPICSRCEEGFVTGGHVLRLFHGHMDECLTISPADSDDQRRLVYYE GGAVCTHARSLWRLEPLRISWSGSHLRWGQPLRVRHVTTGQYLALTEDQ GLVVVDASKAHTKATSFCFRISKEKLDVAPKRDVEGMGPPEIKYGESLCF VQHVASGLWLTYAAPDPKALRLGVLKKKAMLHQEGHMDDALSLTRCQQE ESQAARMIHSTNGLYNQFIKSLDSFSGKPRGSGPPAGTALPIEGVILSLQD LIIYFEPPSEDLQHEEKQSKLRSLRNRQSLFQEEGMLSMVLNCIDRLNVYT TAAHFAEFAGEEAAESWKEIVN	SEQ ID No 36

Table 2: Examples of intracellular domains of known inhibitory receptors

CTLA4	AVSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPIN (SEQ ID No 37)
LAG3	HLWRRQWRPRRFSALEQGIHPPQAQSKIEELEQEPEPEPEPEPEPEPEPEPE QL (SEQ ID No 38)
HAVCR2 (TIM3)	FKWYSHSKEKIQNLSLISLANLPPSGLANAVAEGIRSEENIYTIEENVYEVEEPNE YYCYVSSRQQPSQPLGCRFAMP (SEQ ID No 39)
LAIR1	HRQNQIKQGPPRSKDEEQKPQQRPDLAVDVLERTADKATVNGLPEKDRETDT SALAAGSSQEVTYAQLDHWALTQRTARAVSPQSTKPMAESITYAAVARH (SEQ ID No 40)
KIR2DL2	HRWCSNKKNAAVMDQESAGNRTANSEDSDEQDPQEVTYTQLNHCVFTQRKI TRPSQRPKTPPTDIIVYAELPNAESRSKVVSCP (SEQ ID No 41)
LILRB1	LRHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGLQWRSSPAADAQEENLY AAVKHTQPEDGVEMDTRSPHDEDPQAVTYAEVKHSRPRREMASPPSPLSGEF LDTKDRQAEEDRQMDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGPS PAVPSIYATLAIH (SEQ ID No 2021)
TIGIT	LTRKKKALRIHSVEGDLRRKSAGQEEWSPSAPSPPGSCVQAEAAPAGLCGEQ RGEDCAELHDYFNVLSYRSLGNCSFFTETG (SEQ ID No 2022)
CEACAM 1	HFGKTGRASDQRDLTEHKPSVSNHTQDHSNDPPNKMNEVTYSTLNFEAQQPT QPTSASPSLTATEIIYSEVKKQ (SEQ ID No 2023)
CSF1R	KYKQKPKYQVRWKIIESYEGNSYTFIDPTQLPYNEKWEFPRNNLQFGKTLGAG

	AFGKVVEATAFGLGKEDAVLKVAVKMLKSTAHADEKEALMSELKIMSHLGQHE NIVNLLGACTHGGPVLVITEYCCYGDLLNFLRRKAEAMLGPSLSPGQDPEGGV DYKNIHLEKKYVRRDSGFSSQGVDTYVEMRPVSTSSNDSFSEQDLDKEDGRP LELRDLLHFSSQVAQGMAFLASKNCIHRDVAARNVLLTNGHVAKIGDFGLARDI MNDSNYIVKGNARLPVKWMAPESIFDCVYTVQSDVWSYGILLWEIFSLGLNPY PGILVNSKFYKLVKDGYQMAQPAFAPKNIYSIMQACWALEPTHRPTFQQICSFL QEQAQEDRRERDYTNLPSSSRSGGSGSSSSELEEESSSEHLTCCEQGDIAQP LLQPNNYQFC ((SEQ ID No 2024)
CD5	KKLVKKFRQKKQRQWIGPTGMNQNMSFHRNHTATVRSHAENPTASHVDNEY SQPPRNSHLSAYPALEGALHRSSMQPDNSSDSDYDLHGAQRL ((SEQ ID No 2025)
CD96	RKWCQYQKEIMERPPPFKPPPPPIKYTCIQEPNESDLPYHEMETL (SEQ ID No 2026)
CD22	KLQRRWKRTQSQQGLQENSSGQSFFVRNKKVRRAPLSEGPHSLGCYNPMME DGISYTTLRFPEMNIPRTGDAESSEMQRPPPDCDDTVTYSALHKRQVGDYENV IPDFPEDEGIHYSELIQFGVGERPQAQENVDYVILKH (SEQ ID No 2027)

Table 3: Examples of naturally occurring N-terminal flanking regions of ITIM only intracellular domains varying in length from 0 to 4211 (Table 3 comprises SEQ ID No 42 to SEQ ID No 351)

K	
V	
Q	
V	
T	
F	
Y	
LL	
QP	
EH	
NL	
KW	
LV	
NP	
TF	
RL	

LNP	
KCP	
ETL	
RRA	
MAQ	
RRRP	SEQ ID No 42
MSEE	SEQ ID No 43
MTSE	SEQ ID No 44
DRYL	SEQ ID No 45
MTDS	SEQ ID No 46
AAKP	SEQ ID No 47
QHFS	SEQ ID No 48
MKPK	SEQ ID No 49
IAAL	SEQ ID No 50
CLNP	SEQ ID No 51
QKVL	SEQ ID No 52
DRYQS	SEQ ID No 53
LKAKD	SEQ ID No 54
DRYYA	SEQ ID No 55
MSYYG	SEQ ID No 56
SSSKP	SEQ ID No 57
LKIRH	SEQ ID No 58
DVRHV	SEQ ID No 59
DRFYA	SEQ ID No 60
EGWRI	SEQ ID No 61
SDIKR	SEQ ID No 62
LHHKKY	SEQ ID No 63
TVDRYL	SEQ ID No 64
SSPTFR	SEQ ID No 65
WRRAGH	SEQ ID No 66
YRVDLV	SEQ ID No 67
NSFDLA	SEQ ID No 68
YRSGIT	SEQ ID No 69
YRLGLT	SEQ ID No 70
QHIMAI	SEQ ID No 71

NSCANP	SEQ ID No 72
RRFCAT	SEQ ID No 73
GDMANNS	SEQ ID No 74
MAYQSLR	SEQ ID No 75
TARNLTV	SEQ ID No 76
MERAEEP	SEQ ID No 77
SMDRFLA	SEQ ID No 78
LRLAAAP	SEQ ID No 79
LRLFAAP	SEQ ID No 80
KRLIALS	SEQ ID No 81
YSNSSVNP	SEQ ID No 82
YANSCVNP	SEQ ID No 83
KLSPRVKR	SEQ ID No 84
KIRLRCQS	SEQ ID No 85
SCDLLTAF	SEQ ID No 86
MASESSPL	SEQ ID No 87
KTANEGGS	SEQ ID No 88
DFAKEGHS	SEQ ID No 89
DHVRRKDS	SEQ ID No 90
DNVKKENS	SEQ ID No 91
VMWKHRYQ	SEQ ID No 92
KMYYSRRG	SEQ ID No 93
DRYIAIRIP	SEQ ID No 94
DRYLAICVP	SEQ ID No 95
DRYLRVKLT	SEQ ID No 96
DRYIGVSYP	SEQ ID No 97
DRYIGVRYS	SEQ ID No 98
DRYVGVRHS	SEQ ID No 99
DRYLAVTNP	SEQ ID No 100
MPFHPVTAA	SEQ ID No 101
DRYISIHRP	SEQ ID No 102
MQLKILVSA	SEQ ID No 103
WKQRRAKEK	SEQ ID No 104
DRFIAVVHP	SEQ ID No 105
DRYIAITKP	SEQ ID No 106

NRYCYICHS	SEQ ID No 107
DRYLAITKP	SEQ ID No 108
DRYCAVMDP	SEQ ID No 109
DRYISIFYA	SEQ ID No 110
DRYITIFHA	SEQ ID No 111
NRYCYICHS	SEQ ID No 112
WKKICNKSS	SEQ ID No 113
WCYRKRYFV	SEQ ID No 114
AHSNSCLNP	SEQ ID No 115
PVFYKLGIT	SEQ ID No 116
KFHRSRRLLG	SEQ ID No 117
VDRYLRVKIP	SEQ ID No 118
FERSCRKENM	SEQ ID No 119
LPSIYLVFLI	SEQ ID No 120
SSKTFQTWQS	SEQ ID No 121
IDRYIAVCHP	SEQ ID No 122
SFCLRNLFFP	SEQ ID No 123
LLKTAKEGGS	SEQ ID No 124
MWRNSKVMNI	SEQ ID No 125
VEKKLFIHEYI	SEQ ID No 126
RKRNNSRLGNG	SEQ ID No 127
QRITVHVTRRP	SEQ ID No 128
MEAAHAKTTEEC	SEQ ID No 129
MARISFSYLCPA	SEQ ID No 130
CCKRQKGKPKRK	SEQ ID No 131
MTGDKGPQRLSG	SEQ ID No 132
PDIPQSVKNKVLE	SEQ ID No 133
KIFKIDIVLWYRD	SEQ ID No 134
TEYVVRLWSAGCR	SEQ ID No 135
QSKSELSHYTFYF	SEQ ID No 136
SIVAYKQVPL	SEQ ID No 137
SLDFFGSQNTQDD	SEQ ID No 138
LWLHNGRSCFGVNR	SEQ ID No 139
RFLRLNLKPDLSDT	SEQ ID No 140
REHQRSGSYHVREE	SEQ ID No 141

MITLTELKCLADAQ	SEQ ID No 142
YNLTRLCRWDKRLL	SEQ ID No 143
AFMNENFKKNVLSA	SEQ ID No 144
MIYRLAQAEERQQLE	SEQ ID No 145
KFRKNFWKLVKDIGC	SEQ ID No 146
ALALAALAAVEPACG	SEQ ID No 147
KKIAAATETAAQENA	SEQ ID No 148
YRKVSKAEEAAQENA	SEQ ID No 149
LKDFSILLMEGVPKS	SEQ ID No 150
TVATAVEQYVPSEKL	SEQ ID No 151
MGRQKELVSRCGEMLH	SEQ ID No 152
CKRRRGQSPQSSPDLP	SEQ ID No 153
LLEGVHLFLTARNLTV	SEQ ID No 154
EERERKHHLKHGPNAP	SEQ ID No 155
PLTHRLLCSEEPPRLH	SEQ ID No 156
LYLLVRKHINRAHTAL	SEQ ID No 157
KLPLWGQPSDQNCYDD	SEQ ID No 158
MYRLKVLQMRLRSAITG	SEQ ID No 159
SMRGTICNPGPRKSMSK	SEQ ID No 160
RILVRKLEPAQGSLHTQ	SEQ ID No 161
SRYATLMQKDSSQETT	SEQ ID No 162
SSHFGCQLVCCQSSNVS	SEQ ID No 163
RILMRKLRTQETRGNEV	SEQ ID No 164
RILLQKLRPPDIRKSDS	SEQ ID No 165
RILLQKLTSPDVGGNDQ	SEQ ID No 166
RSVRPCFTQAAFLKSKYW	SEQ ID No 167
RSGRGRKLSGDQITLPTT	SEQ ID No 168
MAAENEASQESALGAYSP	SEQ ID No 169
TAHVFSCLSLRLRAAFFY	SEQ ID No 170
NPFIYSRNSAGLRRKVLWC	SEQ ID No 171
NNESSNNPSSIASFLSSITY	SEQ ID No 172
TPQLFINYKLKSVAHLPWRM	SEQ ID No 173
WRLKPSADCGPFRGLPLFIH	SEQ ID No 174
NIPLLFYHLWRYFHRPADGSE	SEQ ID No 175
SQVTKSSPEQSYQGDMYPTRG	SEQ ID No 176

CCSALQKRCRKCFNKDSTEAT	SEQ ID No 177
CQRLAARLGVVTGKDLGEVCH	SEQ ID No 178
QVFRNISGKQSSLPAMSKVRR	SEQ ID No 179
GGRREGESWNWAWVLSTRLARH	SEQ ID No 180
YKMYGSEMLHKRDPLDEDEDTD	SEQ ID No 181
HMYRERGGELLVHTGFLGSSQDR	SEQ ID No 182
RKWCQYQKEIMERPPPFKPPPPP	SEQ ID No 183
HNKRKIFLLVQSRKWRDGLCSKT	SEQ ID No 184
RAARRRPEHLDTPDTPPRSQAQE	SEQ ID No 185
NGTCFTAGRLIYVAGREGHMLKV	SEQ ID No 186
DANYEMPGETLKVRYWPRDSWPVG	SEQ ID No 187
ARSQMARNIWYFVVS	SEQ ID No 188
LRKRRDSLSLSTQRTQGPAESARN	SEQ ID No 189
DAASEIPEQGPVIKFWPNEKWAFIG	SEQ ID No 190
WGYKNYREQRQLPQGDYVKKPGDGD	SEQ ID No 191
TSYYSFVSHLRKIRTCTSIMEKD	SEQ ID No 192
LIVRALIYKDLDNSPLRRK	SEQ ID No 193
DHWALTQRTARAVSPQSTKPMAES	SEQ ID No 194
HHNKRKIIAFVLEGKRSKVTRRPKA	SEQ ID No 195
EWKSPFGLTPKGRNRSKVFSFSSALN	SEQ ID No 196
YFLGRLVPRGRGAAEAATRKQRITETE	SEQ ID No 197
QATACRTCHRQQQPAACRGFARVARTIL	SEQ ID No 198
NKFSKYYQKQKDIDVDQCSEDAPEKCHE	SEQ ID No 199
SKCSREVLWHCHLCPSSTEHASASANGH	SEQ ID No 200
DMGSSDGETTHDSQITQEAVPKSLGASE	SEQ ID No 201
CSRAARGTIGARRTGQPLKEDPSAVPVFS	SEQ ID No 202
SVQKLSEFLSSAEIREEQCAPHEPTPQGPA	SEQ ID No 203
KCYKIEIMLFYRNHFGAEELDGDNKDYDAY	SEQ ID No 204
KCYNIELMLFYRQHFGADETNDDNKEYDAY	SEQ ID No 205
GWKLRSYKTLFDAAETMVSLQLGIFNYEEV	SEQ ID No 206
SSFSSCKDVTAEENNEAKNLQLAVARIKKG	SEQ ID No 207
MRTKAAGCAERRPLQPRTEAAAAPAGRAMP	SEQ ID No 208
RKRWQNEKLGLDAGDEYEDENLYEGLNLDDC	SEQ ID No 209
MASHEVDNAELGSASAHGTPGSEAGPEELNT	SEQ ID No 210
NGHPTSNAALFFIERRPHHWPAMKFRSHPDH	SEQ ID No 211

ALLNNIIEIRLDAKKFVTELRRPVAVRAKDIG	SEQ ID No 212
PETKGQSLAEIDQQFQKRRFTLSFGHRQNSTG	SEQ ID No 213
PETKGKKLEEIESLFDNRLCTCGTSDSDEGRY	SEQ ID No 214
YNLMSQKFRAAFRKLCNCKQKPTEKPANYSVA	SEQ ID No 215
NYIFFGRGPQRQKKAAEKAASANNEKMRLDVNK	SEQ ID No 216
DLNESANSTAQYASNAWFAAASSEPEEGISVFE	SEQ ID No 217
DLNESANSTAQYASNAWFAAASSEPEEGISVFE	SEQ ID No 218
SYQQKKFCFSIQQGLNADYVKGENLEAVVCEEPQ	SEQ ID No 219
MDGSGERSLPEPGSQSSAASDDIEIVVNVGGVRQ	SEQ ID No 220
RWCSKKKDAAVMNQEPAGHRTVNREDSDEQDPQE	SEQ ID No 221
MFCSEKKLREVERIVKANDREYNEKFQYADNRIHT	SEQ ID No 222
TQFSETKQRESQLMREQRVRFLSNASTLASFSEPG	SEQ ID No 223
NWLNPPRLQMGSMTSTTLYNSMWFVYGSFVQQGGE	SEQ ID No 224
CFYIKKINPLKEKSIILPKSLISVVRSATLETKPE	SEQ ID No 225
HRWCANKKNAVVMDQEPAGNRTVNREDSDEQDPQE	SEQ ID No 226
NYYSSCRKPTTTKKTTSLLHPDSSRWIPERISLQAP	SEQ ID No 227
HLTALFLTVYEWRSPYGLTPRGRNRSTVFSYSSALN	SEQ ID No 228
YFFIRTLQAHHDRSERESPFSGSSRQPDSLSSIENA	SEQ ID No 229
LHCCCSNKKNAAVMDQEPAGDRTVNREDSDDQDPQE	SEQ ID No 230
HYLRFQRKSIDGSFGSNDGSGNMVASHPIAASTPEG	SEQ ID No 231
RWWNQYENLPWPDRLMSLVSGFVEGKDEQGRLLRRTL	SEQ ID No 232
DVDVDDTTEEQGYGMAYTVHKWSELSWASHWVTFGCW	SEQ ID No 233
RYCWLRRQAALQRRLSAMEKGKLHKPGKDASKRGRQTP	SEQ ID No 234
MKKAEMGRFSISPDEDSSSYSSNSDFNYSYPTKQAALK	SEQ ID No 235
LKCLIVALPKIILAVKSKGKFYLVIEELSQLFRSLVPIQ	SEQ ID No 236
ETLLNAPRAMGTSSSPPSPASVVAPGTTLFEESRLPVFT	SEQ ID No 237
YVRSWRKAGPLPSQIPPTAPGGEQCPLYANVHHQKGKDEG	SEQ ID No 238
TYLSEPLVRGYTTAAAVQVFVSQLKYVFGLHLSSHSGPLS	SEQ ID No 239
RWWSQYTSIPLPDQLMCVISASVHGVDQRGRLLRRTL	SEQ ID No 240
RRFRQACLETCARCCPRPPRARPRALPDEDPPTPSIASLSR	SEQ ID No 241
MAEAITYADLRFVKAPLKKSISSRLGQDPGADDDGE	SEQ ID No 242
MQTSEREGSGPELSPSVMPEAPLESPPFPTKSPAFDLFNLV	SEQ ID No 243
SKEKQFRGLQSRIEQEQKFTVIRGGQVIQIPVADITVGDIAQ	SEQ ID No 244
SKEKQFRGLQSRIEQEQKFTVVRAGQVVQIPVAEIVVGDIAQ	SEQ ID No 245
SKEKQFRGLQCRIEQEQKFSIIRNGQLIQLPVAEIVVGDIAQ	SEQ ID No 246

KCLQGNADGDGGGGQCCRRQDSPSPDFYKQSSPNLQVSSDGT	SEQ ID No 247
SSECQRYVYSILCCKESSDPSSYNSSGQLMASKMDTCSSNLNN	SEQ ID No 248
MDNQGVIYSDLNLPPNPKRQQRKPKGNKNSILATEQE	SEQ ID No 249
WWGDIWWKTMMELRSLDTQKATCHLQQVTDLPWTSVSSPVERE	SEQ ID No 250
RLLFSKTYKLQERSDLTVKEKEELIEEWQPEPLVPPVPKDHPA	SEQ ID No 251
KYYPINMDFKPNFITTYKCECVAPDTVNTTVFNASAPLAPDTNA	SEQ ID No 252
CIRRSCLHRRRTFTYQSGSGEETILQFSSGTLTLTRRPKLQPEP	SEQ ID No 253
MTNPSDRVLPANSMAESREGDFGCTVMELRKLMELRSRDALTQIN	SEQ ID No 254
WLHRRLPPQPIRPLPRFAPLVKTEPQRPVKEEEPKIPGDLDQEPS	SEQ ID No 255
WCQCCPHTCCCYVRCPCCPDKCCCPEALYAAGKAATSGVPSIYAP	SEQ ID No 256
AVCQCRRKNYGQLDIFPARDTYHPMSEYPTYHTHGRYVPPSSTDR	SEQ ID No 257
TVVLRVQFPSWNGLGSIPSTDIYKSTKNYKNIEEPQGVKILRFSSP	SEQ ID No 258
DNTVPGSPEERGLIQWKAGAHANSDMSSSLKSYDFPIGMGIVKRITF	SEQ ID No 259
YRCSQHSSSSEESTKRTSHSKLPEQEAAEADLSNMERVSLSTADPQG	SEQ ID No 260
GLKGIRSALKRPVEQPLGEIPEKSLHSIAVSSIQKAKGYQLLEEEKIV	SEQ ID No 261
RWRRRKGQQRTKATTPAREPFQNTEEPYENIRNEGQNTDPKLNPKDD G	SEQ ID No 262
RFTGHPGAYLRLINRWRLEECHPSGCLIDLCMQMGIIMVLKQTWNNFME	SEQ ID No 263
VVALIYCRKKRISALPGYPECREMGETLPEKPANPTNPDEADKVGAENT	SEQ ID No 264
SYRYVTKPPAPPNSLNVQRVLTFQPLRFIQEHVLIPVFDLSGPSSLAQP	SEQ ID No 265
SNKCDVVVVGGGISGMAAAKLLHDSGLNVVVLEARDRVGGRTYTLRNQ K	SEQ ID No 266
TLRNATQQKDMVEVADFDFSPMSDKNPEPPSGVRCCCQMCCGPFLLE TP	SEQ ID No 267
HRQNQIKQGPPRSKDEEQKPQQRPDLAVDVLERTADKATVNGLPEKDR ETDTSALAAGSSQE	SEQ ID No 268
MDEEEDGAGAEESGQPRSFMRLNDLSGAGGRPGPGSAEKDPGSADSE AEG	SEQ ID No 269
EMLHLGFGTIRDSLNSKRRELEDPGAYNYPFTWNTPSAPPGYNIAVKPD Q	SEQ ID No 270
AKTGRTSIQRDLKEQQPQALAPGRGPSHSSAFSMSPLSTAQAPLPNPRT AA	SEQ ID No 271
LCLRKQSNGREAEYSDKHGQYLIGHGTKVYIDPFTYEDPNEAVREFAKEI D	SEQ ID No 272
KNFRRDFFILLSKCGCYEMQAQIYRTETSSTVHNTHPRNGHCSSAPRVT NG	SEQ ID No 273

QDIGYFLKVAAVGRRVRSYGKRRPARTILRAFLEKARQTPHKPFLLFRDE T	SEQ ID No 274
MSAARPQFSIDDAFELSLEDGGPGPESSGVARFGPLHFERRARFEVAD EDKQSR	SEQ ID No 275
YAATSRQLKRLESVSRSPIYSHFSETVTGASVIRAYNRSRDFEIISDTKVD ANQR	SEQ ID No 276
MTVPKEMPEKWARAQAPPSWSRKKPSWGTEEERRARANDREYNEKF QYASNCIKT	SEQ ID No 277
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAP TVEMDEE	SEQ ID No 278
KARRKQAAGRPEKMDDEDPIMGTITSGSRKKPWPDSPGDQASPPGDA PPLEEQKE	SEQ ID No 279
RVKTRRKKAAQPVQNTDDVNPVMVSGSRGHQHQFQTGIVSDHPAEAG PISEDEQE	SEQ ID No 280
MKFEEKCGDNGSIVGRNQSYPGEKHQPKGKPIANGEAEVYAKQEANGK CSTPRKSL	SEQ ID No 281
DIKINQYIIKKCSPCCACLAKAMERSEQQPLMGWEDEGQPFIRRQSRTD SGIFYED	SEQ ID No 282
MAEPQAESEPLLGGARGGGGDWPAGLTTYRSIQVGPGAAARWDLCID QAVVFIEDA	SEQ ID No 283
AVTISLAYSVKKMMKDNNLVRHLDACETMGNATAICSDKTGTLTTNRMT VVQAYVGD	SEQ ID No 284
AVTISLAYSVKKMMKDNNLVRHLDACETMGNATAICSDKTGTLTMNRMT VVQAYIGG	SEQ ID No 285
SNMKSRSAGKLWELQHEIEVYRKTVIAQWRALDLDVVLTPMLAPALDLN APGRATGA	SEQ ID No 286
HPELNVQKRKRSFKAVVTAATMSSRLSHKPSDRPNGEAKTELCENVDP NSPAAKKKY	SEQ ID No 287
RKSNFIFDKLHKVGIKTRRQWRRSQFCDINILAMFCNENRDHIKSLNRLD FITNESD	SEQ ID No 288
KICRKEARKRAAAEQDVPSTLGPISQGHQHECSAGSSQDHPPPGAATY TPGKGEEQE	SEQ ID No 289
SGKTLESWRSLCTRCCWASKGAAVGGGAGATAAGGGGGPGGGGGGG GPGGGGGPGGGGG	SEQ ID No 290
RSCRKKSARPAADVGDIGMKDANTIRGSASQGNLTESWADDNPRHHGL AAHSSGEERE	SEQ ID No 291

MKSKMRQALGFAKEARESPDTQALLTCAEKEEENQENLDWVPLTTLSH CKSLRTMTAI	SEQ ID No 292
AILFAVVARGTTILAKHAWCGGNFLEVTEQILAKIPSENNKLTYSHGNYLF HYICQDR	SEQ ID No 293
MDHAEENEILAATQRYYVERPIFSHPVLQERLHTKDKVPDSIADKLKQAF TCTPKKIRN	SEQ ID No 294
KKLVKKFRQKKQRQWIGPTGMNQNMSFHRNHTATVRSHAENPTASHV DNEYSQPPRNSHL	SEQ ID No 295
MPRRLQPRGAGTKGPPAPAPAASGAARNSHSAASRDPPASAKPLLRW DEVPDDFVECFIL	SEQ ID No 296
RSCRKKSARPAVGVGDTGMEDANAVRGSASQGPLIESPADDSPPHHAP PALATPSPEEGE	SEQ ID No 297
DNFEYLTRDSSILGPHHLDEFIRVWAEYDPAACGRISYNDMFEMLKHMS PPLGLGKKCPAR	SEQ ID No 298
SKRWTHLPCGCIINCRQNAYAVASDGKKIKRKGFEFNLSFQKSYGIYKIA HEDYYDDDENS	SEQ ID No 299
NFNYFYHRETEGEEQSQYMHVGSCQHLSSSAEELRKARSNSTLSK	SEQ ID No 300
VRSCRKKSARPAAGVGDTGIEDANAVRGSASQGPLTEPWAEDSPPDQP PPASARSSVGEGE	SEQ ID No 301
LKLANEETIKNITHWTLFNYYNSSGWNESVPRPPLHPADVPRGSCWETA VGIEFMRLTVSDML	SEQ ID No 302
MCHSRSCHPTMTILQAPTPAPSTIPGPRRGSGPEIFTFDPLPEPAAAPAG RPSASRGHRKRSRR	SEQ ID No 303
ASSAASSEHFEKLHEIFRGLHEDLQGVPERLLGTAGTEEKKKLIRDFDEK QQEANETLAEMEEE	SEQ ID No 304
MADQIPLYPVRSAAAAAANRKRAAYYSAAGPRPGADRHSRYQLEDESA HLDEMPLMMSEEGFENEE	SEQ ID No 305
SMILSASVIRVRDGLPLSASTDYEQSTGMQECRKYFKMLSRKLAQLPDR CTLKTGHYNINFISSLG	SEQ ID No 306
LTRKKKALRIHSVEGDLRRKSAGQEEWSPSAPSPPGSCVQAEAAPAGL CGEQRGEDCAELHDYFNV	SEQ ID No 307
TIPTSRLKFLKEAGRLTQKEEIPEEELNEDVEEIDHAERELRRGQILWFRG LNRIQTQIRVVKAFRS	SEQ ID No 308
TIPTSQLKCLKEAGHGPGKDEMTDEELAEGEEEIDHAERELRRGQILWF RGLNRIQTQIRVVKAFRS	SEQ ID No 309
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHND	SEQ ID No 310

DVRNHAMKPINDNKEPLNSD	
MGDTHWRVAQERDELWRAQVVATTVMLERKLPRCLWPRSGICGCEFG LGDRWFLRVENHNDQNPLRV	SEQ ID No 311
YSPGDYICKKGDIGREMYIIKEGKLAVVADDGVTQFVVLSDGSYFGEISIL NIKGSKAGNRRTANIKS	SEQ ID No 312
FSPGDYICRKGDIGKEMYIIKEGKLAVVADDGVTQYALLSAGSCFGEISIL NIKGSKMGNRRTANIRS	SEQ ID No 313
CLKIIKEYERAVVFRLGRIQADKAKGPGLILVLPCIDVFVKVDLRTVTCNIP PQEILTRDSVTTQVDG	SEQ ID No 314
MTEGARAADEVRVPLGAPPPGPAALVGASPESPGAPGREAERGSELGV SPSESPAAERGAELGADEEQR	SEQ ID No 315
VRLRLQKHRPPADPCRGETETMNNLANCQREKDISVSIIGATQIKNTNKK ADFHGDHSADKNGFKARYPA	SEQ ID No 316
VITTCLALGTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSV CRMFILDRVEGDTCSLNEFTITG	SEQ ID No 317
MEAVLNELVSVEDLLKFEKKFQSEKAAGSVSKSTQFEYAWCLVRSKYND DIRKGIVLLEELLPKGSKEEQRDY	SEQ ID No 318
TRPKPLKPPCDLSMQSVEVAGSGGARRSALLDSDEPLVYFYDDVTTLYE GFQRGIQVSNNGPCLGSRKPDQPYEW	SEQ ID No 319
HRPKALQPPCNLLMQSEEVEDSGGARRSVIGSGPQLLTHYYDDARTMY QVFRRGLSISGNGPCLGFRKPKQPYQW	SEQ ID No 320
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYD NDPDLCFRMQEGSEVYSNPCLEENKPG	SEQ ID No 321
WSCERYRADVRTVWEQCVAIMSEEDGDDDGGCDDYAEGRVCKVRFD ANGATGPGSRDPAQVKLLPGRHMLFPPLER	SEQ ID No 322
GPLVRYLDVKKTNKKESINEELHIRLMDHLKAGIEDVCGHWSHYQVRDK FKKFDHRYLRKILIRKNLPKSSIV	SEQ ID No 323
KYPTLLHQRKKQRFLSKHISHRGGAGENLENTMAAFQHAVKIGTDMLEL DCHITKDEQVVVSHDENLKRATGVNVNISD	SEQ ID No 324
AHDHYTVDVVVAYYITTRLFWWYHTMANQQVLKEASQMNLLARVWWY RPFQYFEKNVQGIVPRSYHWPFPWPVVHLSRQ	SEQ ID No 325
SKASRAPRAHRDINVPRALVDILRHQAGPGTRPDRARSSSLTPGIGGPD SMPPRTPKNLYNTVKTPNLDWRALPPPSPS	SEQ ID No 326
FKVYKWKQSRDLYRAPVSSLYRTPGPSLHADAVRGGLMSPHLYHQVYL TTDSRRSDPLLKKPGAASPLASRQNTLRSCDP	SEQ ID No 327
MLCRKTSQQEHVYEAARAHAREANDSGETMRVAIFASGCSSDEPTSQN	SEQ ID No 328

LGNNYSDEPCIGQEYQIIAQINGNYARLLDTVP	
KQKNEHHHGHSHYASESLPSKKDQEEGVMEKLQNGDLDHMIPQHCSS ELDGKAPMVDEKVIVGSLSVQDLQASQSACYWLKG	SEQ ID No 329
HKALMERALRATFREALSSLHSRRRLDTEKKHQEHLLLSILPAYLAREMK AEIMARLQAGQGSRPESTNNFHSLYVKRHQGVS	SEQ ID No 330
HKHQMQDASRDLFTYTVKCIQIRRKLRIEKRQQENLLLSVLPAHISMGMK LAIIERLKEHGDRRCMPDNNFHSLYVKRHQNVS	SEQ ID No 331
ERFVAKPCAIALNIQANGPQIAPPNAILEKVFTAITKHPDEKRLEGLSKQLD WDVRSIQRWFRQRRNQEKPSTLTRFCESMWRF	SEQ ID No 332
AWRLWRCRVARSRELNKPWAAQDGPKPGLGLQPRYGSRSAPKPQVA VPSCPSTPDYENMFVGQPAAEHQWDEQGAHPSEDNDFY	SEQ ID No 333
HLSQWTRGRSRSHPGQGRSGESVEEVPLYGNLHYLQTGRLSQDPEPD QQDPTLGGPARAAEEVMCYTSLQLRPPQGRIPGPGTP	SEQ ID No 334
KKRHCGYSKAFQDSDEEKMHYQNGQAPPPVFLPLHHPPGKLPEPQFYA EPHTYEEPGRAGRSFTREIEASRIHIEKIIGSGDSGE	SEQ ID No 335
QSVFNKRKSRVRHYLVKCPQNSSGETVTSVTSLAPLQPKKGKRQKEKP DIPPAVPAKAPIAPTFHKPKLLKPQRKVTLPKIAEEN	SEQ ID No 336
MASPGAGRAPPELPERNCGYREVEYWDQRYQGAADSAPYDWFGDFS SFRALLEPELRPEDRILVLGCGNSALSYELFLGGFPNVTS	SEQ ID No 337
MPHFTVVPVDGPRRGDYDNLEGLSWVDYGERAELDDSDGHGNHRESS PFLSPLEASRGIDYYDRNLALFEEELDIRPKVSSLLGKL	SEQ ID No 338
AIPTRSLKFLKEAGHGTTKEEITKDAEGLDEIDHAEMELRRGQILWFRGL NRIQTQIDVINTFQTGASFKGVLRRQNMGQHLDVKLVPS	SEQ ID No 339
IFMKTAQAHRRAETLIFSKHAVIALRHGRLCFMLRVGDLRKSMIISATIHM QVVRKTTSPEGEVVPLHQVDIPMENGVGGNSIFLVAPL	SEQ ID No 340
SWKRYPASMKQLQQRSLMRRHRKKKRQSLKQMTPSTQEFYVDYKPTN TETSEMLLNGTGPCTYNKSGSRECEIPLSMNVSTFLAYDQPT	SEQ ID No 341
MANVSKKVSWSGRDRDDEEAAPLLRRTARPGGGTPLLNGAGPGAARQ SPRSALFRVGHMSSVELDDELLDPDMDPPHPFPKEIPHNEKLLS	SEQ ID No 342
RLFKRRQGRIFPEGSCLNTFTKNPYAASKKTIYTYIMASRNTQPAESRIYD EILQSKVLPSKEEPVNTVYSEVQFADKMGKASTQDSKPPGT	SEQ ID No 343
AMCLWKNRQQNTIQKYDPPGYLYQGSDMNGQMVDYTTLSGASQINGN VHGGFLTNGGLS	SEQ ID No 344
LGSGFALKVQEQHRQKHFEKRRMPAANLIQAAWRLYSTDMSRAYLTAT WYYYDSILPSFRELALLFEHVQRARNGGLRPLEVRRAPVPDGAP	SEQ ID No 345
MSSHKGSVVAQGNGAPASNREADTVELAELGPLLEEKGKRVIANPPKAE	SEQ ID No 346

EEQTCPVPQEEEEEVRVLTLPLQAHHAMEKMEEFVYKVWEGRWRV	
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLS SAQVDQVEVEYVTMASLPKED	SEQ ID No 347
HYARARRKPGGLSATGTSSHSPSECQEPSSSRPSRIDPQEPTHSKPLAP MELEPMYSNVNPGDSNPIYSQIWSIQHTKENSANCPMMHQEHEELT	SEQ ID No 348
MAKRKQGNRLGVCGRFLSSRVSGMNPSSVVHHVSDSGPAAELPLDVP HIRLDSPPSFDNTTYTSLPLDSPSGKPSLPAPSSLPPLPPKVLVCSKP	SEQ ID No 349
SPNRKNPLWPSVPDPAHSSLGSWVPTIMEEDAFQLPGLGTPPITKLTVL EEDEKKPVPWESHNSSETCGLPTLVQTYVLQGDPRAVSTQPQSQSGTS DQ	SEQ ID No 350
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNK LEDVVIDRNLLILGKILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNS SQREIEEFLSEAACMKDFSHPNVIRLLGVCIEMSSQGIPKPMVILPFMKY GDLHTY	SEQ ID No 351

Table 4: Examples of naturally occurring C-terminal flanking regions of ITIM only intracellular domains (Table 4 comprises SEQ ID No 352 to SEQ ID No 685)

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QI	
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VI	
VLT	
KVS	
ARS	
IFR	
TFL	
QGVQ	SEQ ID No 352
FSVR	SEQ ID No 353
YSSK	SEQ ID No 354
PKTR	SEQ ID No 355
VNDT	SEQ ID No 356
GMQQ	SEQ ID No 357
PDLL	SEQ ID No 358
HKSL	SEQ ID No 359
RQPLN	SEQ ID No 360
RTPTN	SEQ ID No 361
RNLTN	SEQ ID No 362
TVFSP	SEQ ID No 363
NRFMK	SEQ ID No 364
LNAIA	SEQ ID No 365
LFTML	SEQ ID No 366
MYVMG	SEQ ID No 367
VTGTR	SEQ ID No 368
TTHRR	SEQ ID No 369
VTRRK	SEQ ID No 370
VTPVR	SEQ ID No 371
MTVRK	SEQ ID No 372
MTVKR	SEQ ID No 373
VTPRR	SEQ ID No 374
KPWWD	SEQ ID No 375
NRLMK	SEQ ID No 376

FKETV	SEQ ID No 377
PFLKNT	SEQ ID No 378
VTQRRG	SEQ ID No 379
MTERKA	SEQ ID No 380
VTMRRT	SEQ ID No 381
RQALAE	SEQ ID No 382
APDSNT	SEQ ID No 383
SKKRGG	SEQ ID No 384
EISAAS	SEQ ID No 385
STLGPG	SEQ ID No 386
NSLSFL	SEQ ID No 387
AHLVQY	SEQ ID No 388
DEHDAII	SEQ ID No 389
VTKRCAR	SEQ ID No 390
KRIEHAK	SEQ ID No 391
VTPWRLR	SEQ ID No 392
VTPCRLR	SEQ ID No 393
RWGFSKQ	SEQ ID No 394
RGDDKDC	SEQ ID No 395
ATRMMMG	SEQ ID No 396
GPSRDPD	SEQ ID No 397
VTLPRARR	SEQ ID No 398
RLPYQLAQ	SEQ ID No 399
LGSFLIGS	SEQ ID No 400
MGDDSSNS	SEQ ID No 401
PLSHLAQN	SEQ ID No 402
ATEGKSVC	SEQ ID No 403
HNNCEKDSV	SEQ ID No 404
RTMKPLPRH	SEQ ID No 405
SQRRNPWQA	SEQ ID No 406
YPMKITGNR	SEQ ID No 407
VSHLRSPRK	SEQ ID No 408
SYPARTRKV	SEQ ID No 409
WGRLRFARK	SEQ ID No 410
VFLNKVMRG	SEQ ID No 411

SGSGYQLV	SEQ ID No 412
HSDSLGSAS	SEQ ID No 413
KATVHLAYL	SEQ ID No 414
CAEDYHWQWR	SEQ ID No 415
QRLLVKAKTQ	SEQ ID No 416
EDFLEESRNQ	SEQ ID No 417
GEKAFGWPGK	SEQ ID No 418
PTVSPFLRQR	SEQ ID No 419
PRTVLWLTIE	SEQ ID No 420
EVCWKLPQSK	SEQ ID No 421
ISNRWLSIGV	SEQ ID No 422
GNCSFFTETG	SEQ ID No 423
DSIRGYFGET	SEQ ID No 424
LHSNSFIRNNY	SEQ ID No 425
TYYSETTVTRT	SEQ ID No 426
TYYSRRTLLGV	SEQ ID No 427
SSYFLGKLLSD	SEQ ID No 428
QARLRQHYQTI	SEQ ID No 429
LVFHHMAQHLMM	SEQ ID No 430
YSTKITIPVIKR	SEQ ID No 431
TYHSERTVTFTY	SEQ ID No 432
PGSNYSEGWHIS	SEQ ID No 433
LCANKKSSVKIT	SEQ ID No 434
DGSPDYQKAKLQ	SEQ ID No 435
VRRQLPVEEPNP	SEQ ID No 436
KLNQVVRKVSAL	SEQ ID No 437
ILRDYKQSSSTL	SEQ ID No 438
DPAKYARWKPWLK	SEQ ID No 439
QLRFNKPVRYAAT	SEQ ID No 440
ELRFNKCVRLCGT	SEQ ID No 441
GLKDQVNTVGIPI	SEQ ID No 442
YKTSQNALDFNTKV	SEQ ID No 443
PSENKENSAVPVEE	SEQ ID No 444
ARTKISDDDDEHTL	SEQ ID No 445
PITKWLPAYKFKEY	SEQ ID No 446

SNLDEVGQQVERLD	SEQ ID No 447
RATASLNANEVEWF	SEQ ID No 448
EMRFSRAVRLCGTLQ	SEQ ID No 449
RICSLTASEGPQQKI	SEQ ID No 450
PLSPYGDIIEK	SEQ ID No 451
TSESKENCTGVQVAE	SEQ ID No 452
SQMNPRSPPATMCSP	SEQ ID No 453
MHPDALEEPDDQNRI	SEQ ID No 454
LSRMQHQSQECKSEE	SEQ ID No 455
QEPNESDLPYHEMETL	SEQ ID No 456
SRENSSSQDPQTEGTR	SEQ ID No 457
EPSGHEKEGFMEAEQC	SEQ ID No 458
KGSNYHLSDNDASDVE	SEQ ID No 459
HTQSAEPPPPPEPARI	SEQ ID No 460
CLISEERNECVIATEV	SEQ ID No 461
ASWATNLKSSIRKANK	SEQ ID No 462
TSMQPTEAMGEEPSRAE	SEQ ID No 463
LSQEHRLLRHSSMADKK	SEQ ID No 464
YSQKPPKRASSQLSWFS	SEQ ID No 465
PRRPGEPREVHIGRALGR	SEQ ID No 466
DTLSTRPGYLWVVWIYRN	SEQ ID No 467
SIMNADILNYCQKESWCK	SEQ ID No 468
NRGPPLDRAEVYSSKLQD	SEQ ID No 469
ISKLSHSKGHQKRKALKTT	SEQ ID No 470
DQNVNEAMPSLKITNDYIF	SEQ ID No 471
DNSPLRRKSIYLVIIV	SEQ ID No 472
QGQRSDVYSDLNTQRPYYK	SEQ ID No 473
EIYLEPLKDAGDGVRYLLR	SEQ ID No 474
LKHDTNIYCRMDHKAEVAS	SEQ ID No 475
QWPALKEKYPKSVYLGRIV	SEQ ID No 476
GKIFSSCFHNTILCMQKESE	SEQ ID No 477
LDDHDYGSWGNYNNPLYDDS	SEQ ID No 478
VRENHGLLPPLYKSVKTYTV	SEQ ID No 479
PCTAQECLASVLKPTNETLN	SEQ ID No 480
PNCNKPRWEKWFMVTFASST	SEQ ID No 481

GYKAFGLVGKLAASGSITMQN	SEQ ID No 482
FGRTVAIKPPKCWTGRFLMNL	SEQ ID No 483
FRRTVSSKTPKCPTGRLLMNL	SEQ ID No 484
NFHGMNPSKDTSTEYSEVRTQ	SEQ ID No 485
HNPTLQVFRKTALLGANGAQP	SEQ ID No 486
GELSLASLHIPFVETQHQTQV	SEQ ID No 487
GEEGVALPANGAGGPGGASARK	SEQ ID No 488
DRRSNQVARALHDHLGLRQGDC	SEQ ID No 489
NHRVDASSMWLYRRYYSNVCQR	SEQ ID No 490
QKMDSLDAMEGDVELEWEETTM	SEQ ID No 491
FHTLRGKGQAAEPPDFNPRDSYS	SEQ ID No 492
SVYQYGSALAHFFYSSDQAWYDR	SEQ ID No 493
DSAEAPADPFAVPEGRSQDARGY	SEQ ID No 494
SAGNGGSSLSYTNPAVAATSANL	SEQ ID No 495
KAKLQSSPDYLQVLEEQTALNKI	SEQ ID No 496
LLKGLGRRQACGYCVFWLLNPLPM	SEQ ID No 497
SRGLQGTYQDVGSLNIGDVQLEKP	SEQ ID No 498
APVVFFYLSQDSRPRSWCLRTVCN	SEQ ID No 499
HFHKVQPQEPKVTDTEYSEIKIHK	SEQ ID No 500
SISLHGLSQVSEDPPSVFNMPEAD	SEQ ID No 501
VNNCEHFVTLLRYGEGVSEQANRA	SEQ ID No 502
QNWGPRFKKLADLYGSKDTFDDDS	SEQ ID No 503
KLRSDCSRPSLQWYTRAQSKMRRPS	SEQ ID No 504
DHSRSTKAVSEKKAKGLGESRKDKK	SEQ ID No 505
STGLTWRSGTASSVSYPKQMPLSQV	SEQ ID No 506
AATVFFCLGQTTRPRSWCLRLVCNP	SEQ ID No 507
YAANPVITPEPVTSPPSYSSEIQANK	SEQ ID No 508
NHCVFTQRKITRPSQRPKTPPTDTSV	SEQ ID No 509
TQGAKEHEEAESGEGTRRRAAEAPSM	SEQ ID No 510
DHLALSRPRRLSTADPADASTIYAVVV	SEQ ID No 511
STSALSEAASDTTQEPPGSHEYAALKV	SEQ ID No 512
SFHKGEPQDLSGQEATNNEYSEIKIPK	SEQ ID No 513
EGALHRSSMQPDNSSDSDYDLHGAQRL	SEQ ID No 514
SFHKARPQYPQEQEAIGYEYSEINIPK	SEQ ID No 515
SFQMVKPWDSRGQEATDTEYSEIKIHR	SEQ ID No 516

IFPGGNKGGGTSCGPAQNPPNNQTPSS	SEQ ID No 517
ELPTATQAQNDYGPQQKSSSSRPSCSCL	SEQ ID No 518
KVPAEEPANELPMNEIEAWKAAEKKARW	SEQ ID No 519
SHQWKSSEDNSKTFSASHNVEATSMFQL	SEQ ID No 520
KEEEMADTSYGTVKAENIIMMETAQTSL	SEQ ID No 521
NLTALDWSLLSKKECLSYGGRLLGNSCK	SEQ ID No 522
SFSEMKSREPKDQEAPSTTEYSEIKTSK	SEQ ID No 523
ELIKPHRAAKGAPTSTVYAQILFEENKL	SEQ ID No 524
NHSVIGPNSRLARNVKEAPTEYASICVRS	SEQ ID No 525
DLASQPVYCNLQSLGQAPMDEEEYVIPGH	SEQ ID No 526
DYDNSENQLFLEEERRINHTAFRTVEIKR	SEQ ID No 527
DHSGGHHSDKINKSESVVYADIRKN	SEQ ID No 528
DHWALTQRTARAVSPQSTKPMAESITYAAVARH	SEQ ID No 529
ENLIYENVAAIQAHKLEV	SEQ ID No 530
SETTGLTPDQVKRNLEKYGLNELPAEEGKT	SEQ ID No 531
SLCYKFLSYFRASSTMRY	SEQ ID No 532
KLEKLVSSLREEDEYSIHPPSSRWKRFYRA	SEQ ID No 533
SHLRKIRTCTSIMEKDLTYSSVKRHL	SEQ ID No 534
ALSSSTSPRAPPSHRPLKSPQNETLYSVLKA	SEQ ID No 535
DPENQNFLLESNLGKKKYETEFHPGTTSFGMS	SEQ ID No 536
FTYGVRFLKKTPWLWNTRHCWYNYPYQPLTTD	SEQ ID No 537
KTLRSLEATDSAFDNPDYWHSRLFPKANAQRT	SEQ ID No 538
QFQNSSEMEKIPEIGKFGEKAPPAPSHVWRPAA	SEQ ID No 539
TFQDSAGARNNRDGNNLRKRGHPAPSPIWRHAA	SEQ ID No 540
LALSSGSRKASAVGDVVNLVSVDVQRLTESVLY	SEQ ID No 541
DILRPYFDVEPAQVRSRLLESMIPIKMVNFPQK	SEQ ID No 542
TCQFEGLLRPYIQHAMYDEEKGTPIFICPVSWG	SEQ ID No 543
LQLDKVDVIPVTAINLYPDGPEKRAENLEDKTCI	SEQ ID No 544
CPVFKGFSSSSKDQIAIPEDTPENTETASVCTKV	SEQ ID No 545
NFEAQQPTQPTSASPSLTATEIIYSEVKKQ	SEQ ID No 546
WSMQQPESSANIRTLLENKDSQVIYSSVKKS	SEQ ID No 547
GRQPGKREPLRSVLRRALGEGAELGARGQSLPMGLL	SEQ ID No 548
PDWLKDNDYLLHGHRPPMPSFRACFKSIFRIHTETG	SEQ ID No 549
DGSHIHTFLDVSFSEALYPVFRILTLEPTALTICPA	SEQ ID No 550
DHWALTQRTARAVSPQSTKPMAESITYAAVARH	SEQ ID No 551

HSLTLRREATEPPPSQEREPPAEPSIYAPLAIH	SEQ ID No 552
RFKNEFKSSGINTASSAASKERTAPHKSNTGFPKLLCA	SEQ ID No 553
REKMWHGRQRLGGVGAGSRPPMPAHPTPASIFSARSTDV	SEQ ID No 554
KKTHPDDSAGEASSRGRAHEEDDEENYENVPRVLLASDH	SEQ ID No 555
GSAQGRRLPLRLVLQRALGDEAELGAVRETSRRGLVDIAA	SEQ ID No 556
SSPTSPTSPGPQQAPPRETYLSEKIPIPDTKPGTFSLRKL	SEQ ID No 557
AGFPKTRLGRLATSTSRSRQLSLCDDYEEQTDEYFFDRDP	SEQ ID No 558
KSLMARRTYLEWPKEKSKRGLFWANLRAAINIKLTEQAKK	SEQ ID No 559
LPWEPSLESEEEVEEEETSEALVLNPRRHQDSSRNKAGGLP	SEQ ID No 560
KESDHFSTELDDITVTDTYLSATKVSFDDTCLASEVSFSQS	SEQ ID No 561
QNLCSRLKTSPVEGLSGNPADLEKRRQVFGHNVIPPKKPKT	SEQ ID No 562
NHCVFTQRKITRPSQRPKTPPTDIIVYTELPNAEP	SEQ ID No 563
TMKTSDKFKFVFREKMGRIVDYFTIQNPSNVDH	SEQ ID No 564
SENFRKAYKQVFKCHIRKDSHLSDTKESKSRIDTPPSTNCTHV	SEQ ID No 565
EFMNEQKLNRYPASSLVVVRSKTEDHEEAGPLPTKVNLAHSEI	SEQ ID No 566
GNYRLKEYEKALKYVRGLLQTEPQNNQAKELERLIDKAMKKDG	SEQ ID No 567
PAGEEDEEEEEDLGWGCPDVAGPTRPTAPPDLHNYMRRIKEIA	SEQ ID No 568
SGLREQTIAIKCLVVLVVALGLPFLAIGYWIAPCSRLGKILRS	SEQ ID No 569
SGLRQQTMAVKFLVVLAVAIGLPFLALIYWFAPCSKMGKIMRG	SEQ ID No 570
SGLRQQTMAVKFLVVLAVAIGLPFLALIYWFAPCSKMGKIMRG	SEQ ID No 571
PPVSRAYTTACVLTTAAVQLELITPFQLYFNPELIFKHFQIWRL	SEQ ID No 572
GNVLILRSVSTAVYKRFPSAQHLVQAGFMTPAEHKQLEKLSLPH	SEQ ID No 573
QNWWTRRKVRQEHGPERKISFPQWEKDYNLQPMNAYGLFDEYLE	SEQ ID No 574
DSNIAFSVNASDKGEASCCDPVSAAFEGCLRRLFTRWGSFCVRNP	SEQ ID No 575
QVSSAESHKDLGKKDTETVYSEVRKAVPDAVESRYSRTEGSLDGT	SEQ ID No 576
VLDSEPKSQASGPEPELYASVCAQTRRARASFPDQAYANSQPAAS	SEQ ID No 577
ETGINLRGALLAMIYNKILRLSTSNLSMGEMTLGQINNLVAIETNQ	SEQ ID No 578
AAGRARAKACRAPGSYGRGTHCHYKAPTVVLHMTKTDPSLENPTHL	SEQ ID No 579
HHELLSHKSFETNAQEDTMETHLETELDLSTITTAGRISDHKQQLA	SEQ ID No 580
DQKYVLILNVFPAPPKRSFLPQVLTEWYIPLEKDERHQWIVLLSFQL	SEQ ID No 581
LQTVYLGKNSEAQPARQILVLDNAAIVCNFGSELSLVYVPSVLEKLD	SEQ ID No 582
RKDSEEEVSLLGSQDIEEGNHQVEDGCREMACEEFNFGEILMTQVIHS	SEQ ID No 583
QRRETEVYACIENEDGSSPTAKQSPLSQERPHRFEDDGELNLVYENL	SEQ ID No 584
APCAKVRPYIAEGESDTDSDLCTPCGPPPRSATGEGPFGDVGWAGPRK	SEQ ID No 585
ERLGYSEDGLEELSRHSVSEADRLLSARSSVDFQAFGVKGGRRINEYFC	SEQ ID No 586

RQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNHHFYNRNFCQGPTAE	SEQ ID No 587
LHRDYDRTVTLLSPPRPGRLPDLQEIGVPLYQSPPGRYLSPKKGANENV	SEQ ID No 588
RSPFYDRFSEARILFLLQLLADHVPGVGLVTRPLMDYLPTWQKIYFYSWG	SEQ ID No 589
NPSPDTRIELNDVVYLIRPDPLAYLPNSEPSRRNSICNVTGQDSREETQL	SEQ ID No 590
RDIYAQRMHTFITSLSSVGIVVSDPDSTDASSIEDNEDICNTTSLENCTAK	SEQ ID No 591
SFQGLRLWEPADQEAPSTTEYSEIKIHTGQPLRGPGFGLQLEREMSGMVPK	SEQ ID No 592
LVSSVADVLAQGGGPRSSQHCGEGSQLVAADHRGGLDGWEQPGAGQPPSDT	SEQ ID No 593
VVSDSGISTDYSSGDSQGAQGGLSDGPYSNPYENSLIPAAEPLPPSYVACS	SEQ ID No 594
NPPPDTRLEPSDIVYLIRSDPLAHVASSSQSRKSSCSHKLSSCNPETRDETQL	SEQ ID No 595
HPSCCWKPDPDQVDGARSLLSPEGYQLPQNRRMTHLAQKFFPKAKDEAASPVKG	SEQ ID No 596
GKKFKRYFLQLLKYIPPKAKSHSNLSTKMSTLSYRPSDNVSSSTKKPAPCFEVE	SEQ ID No 597
SDNFKKSFQNVLCLVKVSGTDDGERSDSKQDKSRLNETTETQRTLLNGDLQTSI	SEQ ID No 598
SPTNNTVYASVTHSNRETEIWTPRENDTITIYSTINHSKESKPTFSRATALDNV	SEQ ID No 599
LGGAAYVNTFHNIALETSDEHREFAMAATCISDTLGISLSGLLALPLHDFLCQLS	SEQ ID No 600
MQKDSSQETTSCYEKIFYGHLLKKFRQPNFARKLC	SEQ ID No 601
ALATSKALVKFDPEIIGPRDIIKIIEEIGFHASLAQRNPNAHHLDHKMEIKQWKKS	SEQ ID No 602
NHCVFTQRKITRPSQRPKTPPTDIIVYTELPNAESRSKVVSCP	SEQ ID No 603
DHCVFTQRKITRPSQRPKTPPTDTILYTELPNAKPRSKVVSCP	SEQ ID No 604
ERKRIQYLHAKLLKKRSKQPLGEVKRRLSLYLTKIHFWLPVLKMIRKKQMDMASADKS	SEQ ID No 605
SEWLESIRMKRYILHFHSAGLDTMECVLELTAEDLTQMGITLPGHQKRILCSIQGFKD	SEQ ID No 606
NADAKYPGYPPEHIIAEKRRARRRLLHKDGSCNVYFKHIFGEWGSYVVDIFTTLVDTKW	SEQ ID No 607

HRTSKRSEARSAEFTVGRKDSSIICAEVRCLQPSEVSSTEVNMRSRTLQ EPLSDCEEVLC	SEQ ID No 608
IKYWFHTPPSIPLQIEEYLKDPTQPILEALDKDSSPKDDVWDSVSIISFPEK EQEDVLQTL	SEQ ID No 609
RREPRQALAGTFRDLRLRLWPQGGGWVQQVALKQVGRRWVASNPRE SRPSTLLTNLDRGTPG	SEQ ID No 610
DFQWREKTPEPPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSA QPLRPEDGHCSWPL	SEQ ID No 611
ENDEDGAQASPEPDGGVGTRDSSRTSIRSSQWSFSTISSSTQRSYNTC CSWTQHPLIQKNRR	SEQ ID No 612
DEIYLESCCQARYHQKKEQMNEELKREAETLREREGEEFDNTCCAEKR KKLWDLLEKPNSSV	SEQ ID No 613
DMRPPPTAMITLNNSVYWQEFEDTCVYECLDGKDCQSFFCCYEECKSG SWRKGRIHIDILELDS	SEQ ID No 614
GTLAWMITLSDGLHNFIDGLAIGASFTVSVFQGISTSVAILCEEFPHELGD FVILLNAGMSIQQ	SEQ ID No 615
GHNEVIGVCRVGPDAADPHGREHWAEMLANPRKPVEHWHQLVEEKTV TSFTKGSKGLSEKENSE	SEQ ID No 616
PSLSTSNKNIYEVEPTVSVVQEGCGHNSSYIQNAYDLPRNSHIPGHYDLL PVRQSPANGPSQDKQS	SEQ ID No 617
DEARLERCCLRRLRRREEEAAEARAGPTERGAQGSPARALGPRGRLQ RGRRRLRDVVDNPHSGLAGK	SEQ ID No 618
DELSIDSCCRDRYFRRKELSETLDFKKDTEDQESQHESEQDFSQGPCPT VRQKLWNILEKPGSSTAAR	SEQ ID No 619
KETKVKELKRAKTVLTVIKWKGEKSKYPQGRFWKQLQVAMPVKKSPRR SSSDEQGLSYSSLKNV	SEQ ID No 620
LSYNHHRLEEHEAETYEDGFTGNPSSLSQIPETNSEETTVIFEQLHSFVV DDDGFIEDKYIDIHELCEEN	SEQ ID No 621
DESSSSPGRQMSSSDGGPPGQSDTDSSVEESDFDTMPDIESDKNIIRTK MFLYLSDLSRKDRRIVSKKYK	SEQ ID No 622
RIIQEKKKHAVASDPRHLRNKGSPIIYSEVKVASTPVSGSLFLASSAPHR	SEQ ID No 623
AEDHLDGCCKRRYLQKIEEFAEMVEREEEDDALDSEGRDSEGPAEGEG RLGRCMRRLRDMVERPHSGLPGK	SEQ ID No 624
EDPWIGSESDKFILLGYLDQLRKDPALLSSEAVLPDLTDELAPVFLLRWF YSASDYISDCWDSIFHNNWRE	SEQ ID No 625
MDRKWYFLCNSWLSINVGDCVLDKVFPVATEQDRKQFSHLFFMKTSAG	SEQ ID No 626

FQDGHIWYSIFSRCARSSFTRVQR	
VPSDPSVEEMRKVVCEQKLRPNIPNRWQSCEALRVMAKIMRECWYAN GAARLTALRIKKTLSQLSQQEGIKM	SEQ ID No 627
CSDFQEDIVFPFSLGWSSLVHRFLGPRNAQRVLLGLSEPIFQLPRSLAST PTAPTTPATPDNASQEELMITL	SEQ ID No 628
RIPLLGDEEEGSEDEGESTHLLPENENELEKFIHSVIISKRSKNIKKKLKEE QNSVTENKTKNASHNGKMEDL	SEQ ID No 629
SKIPQITLNFVDLKGDPFLASPTSDREIIAPKIKERTHNVTEKVTQVLSLGA DVLPEYKLQAPRIHRWTILHY	SEQ ID No 630
DHCIFTQRKITGPSQRSKRPSTDTSVCIELPNAEPRALSPAHEHHSQALM GSSRETTALSQTQLASSNVPAAGI	SEQ ID No 631
PRARIMQRKRGLEWFVCDGWKFLCTSCCGWLINICRRKKELKARTVWL GCPEKCEEKHPRNSIKNQKYNVFTFI	SEQ ID No 632
SPRHYYSGYSSSPEYSSESTHKIWERFRPYKKHHREEVYMAAGHALRK KVQFAKDEDLHDILDYWKGVSAQQKL	SEQ ID No 633
SPQYHSLSYSSSPEYTCRASQSIWERFRLSRRRHKEEEEFMAAGHALR KKVQFAKDEDLHDILDYWKGVSAQHKS	SEQ ID No 634
MAFNAKVSDPLIGGTYMTLLNTVSNLGGNWPSTVALWLVDPLTVKECVG ASNQNCRTPDAVELCKKLGGSCVTALD	SEQ ID No 635
YYPHGHSHSLGLDLNLGLGSGTFHSLGNALVHGGELEMGHGGTHGFG YGVGHGLSHIHGDGYGVNHGGHYGHGGGH	SEQ ID No 636
SFHKVKPQDPQGQEATDSEYSEIKIHKRETAETQACLRNHNPSSKEVRG	SEQ ID No 637
NNSTSANRNVYEVEPTVSVVQGVFSNNGRLSQDPYDLPKNSHIPCHYD LLPVRDSSSSPKQEDSGGSSSNSSSSSE	SEQ ID No 638
RREFRKALKSLLWRIASPSITSMRPFTATTKPEHEDQGLQAPAPPHAAAE PDLLYYPPGVVVYSGGRYDLLPSSSAY	SEQ ID No 639
NELFIDSCCSNRYQERKEENHEKDWDQKSHDVSTDSSFEESSLFEKELE KFDTLRFGQLRKKIWIRMENPAYCLSAK	SEQ ID No 640
NEFFIDSCCSYSYHGRKVEPEQEKWDEQSDQESTTSSFDEILAFYNDAS KFDGQPLGNFRRQLWLALDNPGYSVLSR	SEQ ID No 641
DATDQESLELKPTSRAGIKQKGLLLSSSLMHSESELDSDDAIFTWPDREK GKLLHGQNGSVPNGQTPLKARSPREEIL	SEQ ID No 642
SRGASIPGTPPTAGRVVSLSPEDAPGPSLRRSGGCSPSSDTVFGPGAP AAAGAEACRRENRGTLYGTRSFTVSVAQKR	SEQ ID No 643
NKTFSPAQRHGNSGITMMRKKAKFSLRENPVEETKGEAFSDGNIEVKLC EQTEEKKKLKRHLALFRSELAENSPLDSGH	SEQ ID No 644

YESHRAGCEKYEGPYPQHPFYSSASGDVIGGLSREEIRQMYESSELSREEIQERMRVLELYANDPEFAAFVREQQVEEV	SEQ ID No 645
FKNSDKEDDQEHPSEKQPSGAESGTLARASLALPTSSLSRTASQSSSHRGWEILRQNTLGHLNLGLNLSEGDGEEVYHF	SEQ ID No 646
QDLKGDDTAVRDAHSKRDTKCQPQGSSGEEKGTPTTLRGGEASERKRPDSGCSTSKDTKYQSVYVISEEKDECVIATEV	SEQ ID No 647
DHCVFIQRKISRPSQRPKTPLTDTSVYTELPNAEPRSKVVSCPRAPQSGLEGVF	SEQ ID No 648
RDLPPLSSSEMEEFLTQESKKHENEFNEEVALTEIYKYIVKYFDEILNKLERERGLEEAQKQLLHVKVLFDEKKKCKWM	SEQ ID No 649
LGSPTSPGPGHYLRCDSTQPLLAGLTPSPKSYENLWFQASPLGTLVTPAPSQEDDCVFGPLLNFPLLQGIRVHGMEALGSF	SEQ ID No 650
LSQPGPTLPKTHVKTASLGLAGKARSPLLPVSVPTAPEVSEESHKPTEDSANVYEQDDLSEQMASLEGLMKQLNAITGSAF	SEQ ID No 651
ATECGQGEEKSEGPLGSQESESCGLRKEEKEPHADKDFCQEKQVAYCPSGKPEGLNYACLTHSGYGDGSD	SEQ ID No 652
KELILAVDGVLSVHSLHIWSLTMNQVILSAHVATAASRDSQVVRREIAKALSKSFTMHSLTIQMESPVDQDPDCLFCEDPCD	SEQ ID No 653
TSFPRLPEDEPAPAAPLRGRKDEDAFLGDPDTDPDSFLKSARLQRLPSSSSEMGSQDGSPLRETRKDPFSAAAAECSCRQDG	SEQ ID No 654
LEKERELQQLGITEYLRKNIAQLQPDMEAHYPGAHEELKLMETLMYSRPRKVLVEQTKNEYFELKANLHAEPDYLEVLEQQT	SEQ ID No 655
KNSLKEANHDGDFGITLAELRALMELRSTDALRKIQESYGDVYGICTKLKTSPNEGLSGNPADLERREAVFGKNFIPPKKPKT	SEQ ID No 656
YNCLDFPAGVVPVTTVTAEDEAQMEHYRGYFGDIWDKMLQKGMKKSVGLPVAVQCVALPWQEELCLRFMREVERLMTPEKQSS	SEQ ID No 657
PAFDLLSRKMLGCPINDLNVILLFLRANISELISFSWLSVLCVLKDTTTQKHNIDTVVDFMTLLAGLEPSKPKHLTNSACDEHP	SEQ ID No 658
SRRFQAAFQNVISSFHKQWHSQHDPQLPPAQRNIFLTECHFVELTEDIGPQFPCQSSMHNSHLPAALSSEQMSRTNYQSFHFNKT	SEQ ID No 659
ELKTTRFHPNRQSSMYTVTRMESMTVVFDPNDADTTRSSRKKRATPRDPSFNGCSRRNSKSASATSSFISSPYTSVDEYS	SEQ ID No 660
SRQCKQFAKDLLDQTRSSRELEIILNYRDDNSLIEEQSGNDLARLKLAIKYRQKEFVAQPNCQQLLASRWYDEFPGWRRRHWAVK	SEQ ID No 661
VRKKQKAQHRCMRRVGRTGSRRSGYAFSHQEGFGELIMSGKNMRLSSLALSSFTTRSSSSWIESLRRKKSDSASSPSGGADKPLKG	SEQ ID No 662

LLKLMFVNPPELPEQTTKALPVRFLFTDYNRLSSVGGETSLAEMIATLSD ACEREFGFLATRLFRVFKTEDTQGKKKWKKTCCLPS	SEQ ID No 663
PPYLGKLDVSFQRACQCEGKDNRIPLLKEVFEAFPNTPINIDIKVNNNVLI KKVSELVKRYNREHLTVWGNANYEIVEKCYKENSD	SEQ ID No 664
VVAAMQARHAHVPQLRWETMDVRKLDFPSASFDVVLEKGTLDALLAGE RDPWTVSSEGVHTVDQVLSEVGFQKGTRQLLGSRTQLE	SEQ ID No 665
SAEVQAVLRKFDELDAVMSRLPHHSESRQEHERISRIHEEFKKKKNDPT FLEKKERCDYLKNKLSHIKQRIQEYDKVMNWDVQGYS	SEQ ID No 666
AERVKELPSAGLVHYNFCTLPKRQFAPSYESRRQNQDRINKTVLYGTPR KCFVGQSKPNHPLLQAKPQSEPDYLEVLEKQTAISQL	SEQ ID No 667
NLPPNPKRQQRKPKGNKNSILATEQEITYAELNLQKASQDFQGNDKTYH CKDLPSAPEK	SEQ ID No 668
EKPESRTSIHNFMAHPEFRIEDSQPHIPLIDDTDLEEDAALKQNSSPPSSL NKNNSAIDSGINLTTDTSKSATSSSPGSPIHSLETSL	SEQ ID No 669
EKPESRSSIHNFMTHPEFRIEDSEPHIPLIDDTDAEDDAPTKRNSSPPPSP NKNNNAVDSGIHLTIEMNKSATSSSPGSPLHSLETSL	SEQ ID No 670
QGDPQRSPSSCNDLYATVKDFEKTPNSTLPPAGRPSEEPEPDYEAIQTL NREEEKATLGTNGHHGLVPKENDYESISDLQQGRDITRL	SEQ ID No 671
KVAMIEPGYFKTAVTSKERFLKSFLEIWDRSSPEVKEAYGEKFVADYKKS AEQMEQKCTQDLSLVTNCMEHALIACHPRTRYSAGWDAK	SEQ ID No 672
EKPESKTSIHNFMATPEFLINDYTHNIPLIDDTDVDENEERLRAPPPPSPN QNNNAIDSGIYLTTHVTKSATSSVFSSSPGSPLHSVETSL	SEQ ID No 673
PAAPLAGPALPARRLSRASRPLSASQPSLPHGAPGPAASTRPASSSTPR LGPTPAARAAAPSPDRRDSASPGAAGGLDPQDSARSRLSSNL	SEQ ID No 674
SKHFRKGFRTICAGLLGRAPGRASGRVCAAARGTHSGSVLERESSDLLH MSEAAGALRPCPGASQPCILEPCPGPSWQGPKAGDSILTVDVA	SEQ ID No 675
SNAKIAYKQNKANTAQEQQYGSHEENLPADLEALQREIRMAQERLDLAV QAYSHQNNPHGPREKKAKVGSKAGSNKSTASSKSGDGKTSVWI	SEQ ID No 676
QNEEESGEPEQAAGDAPPPYSSISAESAAYFDYKDESGFPKPPSYNVAT TLPSYDEAERTKAEATIPLVPGRDEDFVGRDDFDDADQLRIGNDG	SEQ ID No 677
EGDPQTQLQDDKDPMLILRGRVPEGRALDSEVDPDPEGDLGVRGPVFG EPSAPPHTSGVSLGESRSSEVDVSDLGSRNYSARTDFYCLVSKDDM	SEQ ID No 678
LLGDFLRACFVRFMNYCWCWDLEAGFPSYAEFDISGNVLGLIFNQGMIW MGSFYAPGLVGINVLRLLTSMYFQCWAVMSSNVPHERVFKASRSNN	SEQ ID No 679
TIEPVQQAGCSATRLPGDGQTSAGDASLQDPPSYPPVQVIRARVSSGSS SEVSSINSDLEWDPEDVNLEGSKENVELLGSQVHQDSVRTAHLSDDD	SEQ ID No 680

RRTLKQAFADCTVILCEHRIEAMLECQQFLVIEENKVRQYDSIQKLLNERS LFRQAISPSDRVKLFPHRNSSKCKSKPQIAALKEETEEEVQDTRL	SEQ ID No 681
VKAFHSSLHESIQKPYNQKSIHSFMTHPEFAIEEELPRTPLLDEEEEENPD KASKFGTRVLLLDGEVTPYANTNNNAVDCNQVQLPQSDSSLQSLETSV	SEQ ID No 682
NLPKGKKPAPQAAEPNNHTEYASIQTSPQPASEDTLTYADLDMVHLNRT PKQPAPKPEPSFSEYASVQVPRK	SEQ ID No 683
TLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKEDISYASLTLGAED QEPTYCNMGHLSSHLPGRGPEEPTEYSTISRP	SEQ ID No 684
ETGPKHIPLQTLLKFMVDIALGMEYLSNRNFLHRDLAARNCMLRDDMTV CVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADRVYTSKSDVWAF GVTMWEIATRGMTPYPGVQNHEMYDYLLHGHRLKQPEDCLDELYEIMY SCWRTDPLDRPTFSVLRLQLEKLLESLPDVRNQADVIYVNTQLLESSEGL AQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGRYILNGGS EEWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPD ELLFADDSSEGSEVLM	SEQ ID No 685

Table 5: Examples of naturally occurring intracellular domains between ITIM and ITSM from proteins that have ITIM.*ITSM motif and vary in length from 7-1882 (Table 4 comprises SEQ ID No 686 to SEQ ID No 717)

KEEEMAD	SEQ ID No 686
NFHGMNPSKDTS	SEQ ID No 687
HFHKVQPQEPKVTD	SEQ ID No 688
ELIKPHRAAKGAPTS	SEQ ID No 689
SFQMVKPWDSRGQEATD	SEQ ID No 690
QVSSAESHKDLGKKDTE	SEQ ID No 691
SFSEMKSREPKDQEAPST	SEQ ID No 692
SFQGLRLWEPADQEAPST	SEQ ID No 693
NLPKGKKPAPQAAEPNNH	SEQ ID No 694
NHSVIGPNSRLARNVKEAP	SEQ ID No 695
DFQWREKTPEPPVPCVPEQ	SEQ ID No 696
DHLALSRPRRLSTADPADAS	SEQ ID No 697
SPTNNTVYASVTHSNRETEIWTPRENDTI	SEQ ID No 698
DGLRDRRSFHGPYTVQAGLPLNPMGRTGLRGRGSLSCFGPNH	SEQ ID No 699
MRIKMCLIKLCKSKAKSCENDLEMGMLNSKFKKTRYQAGMRNSENLTAN NTLSKP	SEQ ID No 700
QDLKGDDTAVRDAHSKRDTKCQPQGSSGEEKGTPTTLRGGEASERKR	SEQ ID No 701

PDSGCSTSKD	
KQQMEKGPIDAITGEARYSLSEDKLIRQQIDYKTLTLHCVCPENEGSAQV PVKVLNCDSITQAKDKLLD	SEQ ID No 702
TLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKEDISYASLTLGAED QEPTYCNMGHLSSHLPGRGPEEP	SEQ ID No 703
EDDSDVEWKFARSKLWLSYFDDGKTLPPPFSLVPSPKSFVYFIMRIVNFP KCRRRRLQKDIEMGMGNSKSRLNLFTQSNSRVFESHSFNSILNQP	SEQ ID No 704
RKVPSFTFTPTVTYQRGGEAVSSGGRPGLLNISEPAAQPWLADTWPNT GNNHNDCSISCCTAGNGNSDSNLTTYSRPADCIANYNNQLDNKQTNLM LPES	SEQ ID No 705
GDQPVYLPTQMLVKFMADIASGMEYLSTKRFIHRDLAARNCMLNENMSV CVADFGLSKKIYNGDYYRQGRIAKMPVKWIAIESLADRVYTSKSDVWSF GVTMWEIATRGQ	SEQ ID No 706
ETGPKHIPLQTLLKFMVDIALGMEYLSNRNFLHRDLAARNCMLRDDMTV CVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADRVYTSKSDVWAF GVTMWEIATRGM	SEQ ID No 707
FEFCDLGDLKAYLRSEQEHMRGDSQTMLLQRMACEVAAGLAAMHKLHF LHSDLALRNCFLTSDLNVKVGDYGIGFSRYKEDYIETDDKKVFPLRWTAP ELVTSFQDRLLTADQ	SEQ ID No 708
LEAPVGREARKWLQLAVFCSPLVPGQSHLQLRIYFLNNTPCALQWALTN EQPHGGRLRGPCQLFDFNGARGDQCLKLTYISEGWENVDDSSCQLVP HLHIWHGKCPFRSFCFRRKAADENEDCSALTNEIIVTMHTFQDGLE	SEQ ID No 709
QRSLYDRPASYKKKSMLDSEVKNLLSDDNSEGLTLLDLLSFTYQVARGM EFLASKNCVHRDLAARNVLLAQGKIVKICDFGLARDIMHDSNYVSKGSTF LPVKWMAPESIFDNLYTTLSDVWSYGILLWEIFSLGGTPYPGMMVDS	SEQ ID No 710
KECAGEPLFSLFCAIKQQMEKGPIDAITGEARYSLSEDKLIRQQIDYKTLV LSCVSPDNANSPEVPVKILNCDTITQVKEKILDAIFKNVPCSHRPKAADMD LEWRQGSGARMILQDEDITTKIENDWKRLNTLAHYQVPDGSVVALVSKQ V	SEQ ID No 711
TVTESYTTSDTLKPSVHVHDNRPASNVVVTERVVGPISGADLHGMLEMP DLRDGSNVIVTERVIAPSSSLPTSLTIHHPRESSNVVVTERVIQPTSGMIG SLSMHPELANAHNVIVTERVVSGAGVTGISGTTGISGGIGSSGLVGTSMG AGSGALSGAGISGGGIGLSSLGGTASIGHMRSSSDHHFNQTIGSASPST ARSRI	SEQ ID No 712
NPEYFSAADVYVPDEWEVAREKITMSRELGQGSFGMVYEGVAKGVVKD EPETRVAIKTVNEAASMRERIEFLNEASVMKEFNCHHVVRLLGVVSQGQ	SEQ ID No 713

PTLVIMELMTRGDLKSYLRSLRPEMENNPVLAPPSLSKMIQMAGEIADG MAYLNANKFVHRDLAARNCMVAEDFTVKIGDFGMTRDIYETDYYRKGG KGLLPVRWMSPESLKDGVF	
GGAYVGPTQNRILRLSKELGIETYKVNVSERLVQYVKGKTYPFRGAFPP VWNPIAYLDYNNLWRTIDNMGKEIPTDAPWEAQHADKWDKMTMKELID KICWTKTARRFAYLFVNINVTSEPHEVSALWFLWYVKQCGGTTRIFSVTN GGQERKFVGGSGQVSERIMDLLGDQVKLNHPVTHVDQSSDNIIIETLNH EHYECKYVINAIPPTLTAKIHFRPELPAERNQLIQRLPMGAVIKCMMYYKE AFWKKKDYCGCMIIEDEDAPISITLDDTKPDGSLPAIMGFILARKADRLAK LHKEIRKKKICELYAKVLGSQEALHPVHYEEKNWCEEQYSGGCYTAYFP PGIM	SEQ ID No 714
GGSYVGPTQNRILRLAKELGLETYKVNEVERLIHHVKGKSYPFRGPFPPV WNPITYLDHNNFWRTMDDMGREIPSDAPWKAPLAEEWDNMTMKELLD KLCWTESAKQLATLFVNLCVTAETHEVSALWFLWYVKQCGGTTRIISTTN GGQERKFVGGSGQVSERIMDLLGDRVKLERPVIYIDQTRENVLVETLNH EMYEAKYVISAIPPTLGMKIHFNPPLPMMRNQMITRVPLGSVIKCIVYYKE PFWRKKDYCGTMIIDGEEAPVAYTLDDTKPEGNYAAIMGFILAHKARKLA RLTKEERLKKLCELYAKVLGSLEALEPVHYEEKNWCEEQYSGGCYTTYF PPGIL	SEQ ID No 715
KGKKFIVVCGNITVDSVTAFLRNFLRDKSGEINTEIVFLGETPPSLELETIF KCYLAYTTFISGSAMKWEDLRRVAVESAEACLIIANPLCSDSHAEDISNIM RVLSIKNYDSTTRIIIQILQSHNKVYLPKIPSWNWDTGDNIICFAELKLGFIA QGCLVPGLCTFLTSLFVEQNKKVMPKQTWKKHFLNSMKNKILTQRLSDD FAGMSFPEVARLCFLKMHLLLIAIEYKSLFTDGFCGLILNPPPQVRIRKNTL GFFIAETPKDVRRALFYCSVCHDDVFIPELITNCGCKSRSRQHITVPSVKR MKKCLKGISSRISGQDSPPRVSASTSSISNFTTRTLQHDVEQDSDQLDSS GMFHWCKPTSLDKVTLKRTGKSKYKFRNHIVACVFGDAHSAPMGLRNF VMPLRASNYTRKELKDIVFIGSLDYLQREWRFLWNFPQIYILPGCALYSG DLHAANIEQCSMCAVLSPPPQPSSNQTLVDTEAIMATLTIGSLQIDSSSD PSPSVSEETPGYTNGHNEKSNCRKVPILTELKNPSNIHFIEQLGGLEGSL QETNLHLSTAFSTGTVFSGSFLDSLLATAFYNYHVLELLQMLVTGGVSSQ LEQHLDKDKVYGVADSCTSLLSGRNRCKLGLLSLHETILSDVNPRNTFG QLFCGSLDLFGILCVGLYRIIDEEELNPENKRFVITRPANEFKLLPSDLVFC AIPFSTACYKRNEEFSLQKSYEIVNKASQTTETHSDTNCPPTIDSVTE	SEQ ID No 716
ASLIRGNRSNCALFSTNLDWLVSKLDRLEASSGILEVLYCVLIESPEVLNII QENHIKSIISLLDKHGRNHKVLDVLCSLCVCNGVAVRSNQDLITENLLPGR	SEQ ID No 717

ELLLQTNLINYVTSIRPNIFVGRAEGTTQYSKWYFEVMVDEVTPFLTAQA THLRVGWALTEGYTPYPGAGEGWGGNGVGDDLYSYGFDGLHLWTGH VARPVTSPGQHLLAPEDVISCCLDLSVPSISFRINGCPVQGVFESFNLDG LFFPVVSFSAGVKVRFLLGGRHGEFKFLPPPGYAPCHEAVLPRERLHLE PIKEYRREGPRGPHLVGPSRCLSHTDFVPCPVDTVQIVLPPHLERIREKL AENIHELWALTRIEQGWTYGPVRDDNKRLHPCLVDFHSLPEPERNYNLQ MSGETLKTLLALGCHVGMADEKAEDNLKKTKLPKTYMMSNGYKPAPLD LSHVRLTPAQTTLVDRLAENGHNVWARDRVGQGWSYSAVQDIPARRNP RLVPYRLLDEATKRSNRDSLCQAVRTLLGYGYNIEPPDQEPSQVENQSR CDRVRIFRAEKSYTVQSGRWYFEFEAVTTGEMRVGWARPELRPDVELG ADELAYVFNGHRGQRWHLGSEPFGRPWQPGDVVGCMIDLTENTIIFTLN GEVLMSDSGSETAFREIEIGDGFLPVCSLGPGQVGHLNLGQDVSSLRFF AICGLQEGFEPFAINMQRPVTTWFSKGLPQFEPVPLEHPHYEVSRVDGT VDTPPCLRLTHRTWGSQNSLVEMLFLRLSLPVQFHQHFRCTAGATPLAP PGLQPPAEDEARAAEPDPDYENLRRSAGGWSEAENGKEGTAKEGAPG GTPQAGGEAQPARAENEKDATTEKNKKRGFLFKAKKVAMMTQPPATPT LPRLPHDVVPADNRDDPEIILNTT	

Table 6: Examples of naturally occurring N-terminal flanking regions of ITSM only intracellular domains that could vary in length from 0-2002 (Table 6 comprises SEQ ID No 718 to SEQ ID No 805)

V	
AM	
NLMSY	SEQ ID No 718
SRFKRQ	SEQ ID No 719
MDDSDTP	SEQ ID No 720
YGKKRNR	SEQ ID No 721
KSQWIKE	SEQ ID No 722
CRGLAPEE	SEQ ID No 723
RLCSAMKQ	SEQ ID No 724
YRKREWIKE	SEQ ID No 725
RKMKRSSSEIK	SEQ ID No 726
FCNMRRPAHADIK	SEQ ID No 727
LRTVKRANGGELK	SEQ ID No 728
MEQHVGIDVLKRDP	SEQ ID No 729
LEQHVDPHVLQNKP	SEQ ID No 730

RNKDVKDAIRKIIN	SEQ ID No 731
VDFRPPPQGPSGPEV	SEQ ID No 732
DRYFALVQPFRLTRWR	SEQ ID No 733
VRMTSEIETNIVAVERI	SEQ ID No 734
MERLWGLFQRAQQLSPRSSQ	SEQ ID No 735
MAEPQAESEPLLGGARGGGGDWPAGL	SEQ ID No 736
PETKGVALPETMKDAENLGRKAKPKEN	SEQ ID No 737
MEDEAVLDRGASFLKHVCDEEEVEGHH	SEQ ID No 738
YKMYGSEMLHKRDPLDEDEDTDISYKKLKEEEMAD	SEQ ID No 739
RHVSDLHGLTELILLPPPCPASFNADEDDRVDILGPQPESHQQLSASSH	SEQ ID No 740
CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPV PCVPEQ	SEQ ID No 741
RRKSIKKKRALRRFLETELVEPLTPSGTAPNQAQLRILKETELKRVKVLGS GAFG	SEQ ID No 742
RIRQKKAQGSTSSTRLHEPEKNAREITQDTNDITYADLNLPKGKKPAPQA AEPNNH	SEQ ID No 743
AVTISLAYSVKKMMKDNNLVRHLDACETMGNATAICSDKTGTLTTNRMT VVQSYLGD	SEQ ID No 744
CCRKKRREEKYEKEVHHDIREDVPPPKSRTSTARSYIGSNHSSLGSMSP SNMEGYSK	SEQ ID No 745
KRRQQKIRKYTMRRLLQETELVEPLTPSGAMPNQAQMRILKETELRKVK VLGSGAFG	SEQ ID No 746
KYLQKPMYEVQWKVVEEINGNNYVYIDPTQLPYDHKWEFPRNRLSFGK TLGAGAFGKVVEA	SEQ ID No 747
YTTYPLLKESALILLQTVPKQIDIRNLIKELRNVEGVEEVHELHVWQLAGS RIIATAHIKCEDP	SEQ ID No 748
AANAIAQSCQPSFYDGTIIVKKLPYLPRILGRNIGSHHVRVEHFMNHSITTL AKDTPLEEVVKVVTSTDV	SEQ ID No 749
WLHRRLPPQPIRPLPRFAPLVKTEPQRPVKEEEPKIPGDLDQEPSLLYAD LDHLALSRPRRLSTADPADAS	SEQ ID No 750
KKYQPYKVIKQKLEGRPETEYRKAQTFSGHEDALDDFGIYEFVAFPDVS GVSRIPSRSVPASDCVSGQDLHS	SEQ ID No 751
MDEINNKIEEEKLVKANITLWEANMIKAYNASFSENSTGPPFFVHPADVP RGPCWETMVGQEFVRLTVSDVL	SEQ ID No 752
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAP TVEMDEELHYASLNFHGMNPSKDTS	SEQ ID No 753

RVKTRRKKAAQPVQNTDDVNPVMVSGSRGHQHQFQTGIVSDHPAEAG PISEDEQELHYAVLHFHKVQPQEPKVTD	SEQ ID No 754
IVLRRRRKRVNTKRSSRAFRAHLRAPLKGNCTHPEDMKLCTVIMKSNGS FPVNRRRVEAARRAQELEMEMLSSTSPPER	SEQ ID No 755
KARRKQAAGRPEKMDDEDPIMGTITSGSRKKPWPDSPGDQASPPGDA PPLEEQKELHYASLSFSEMKSREPKDQEAPST	SEQ ID No 756
KICRKEARKRAAAEQDVPSTLGPISQGHQHECSAGSSQDHPPPGAATY TPGKGEEQELHYASLSFQGLRLWEPADQEAPST	SEQ ID No 757
QRVVCQRYAGANGPFPHEYVSGTPHVPLNFIAPGGSQHGPFTGIACGK SMMSSVSLMGGRGGVPLYDRNHVTGASSSSSSSTKA	SEQ ID No 758
VRSCRKKSARPAAGVGDTGIEDANAVRGSASQGPLTEPWAEDSPPDQP PPASARSSVGEGELQYASLSFQMVKPWDSRGQEATD	SEQ ID No 759
FVAKIARPKNRAFSIRFTDTAVVAHMDGKPNLIFQVANTRPSPLTSVRVS AVLYQERENGKLYQTSVDFHLDGISSDECPFFIFPL	SEQ ID No 760
QLRRRGKTNHYQTTVEKKSLTIYAQVQKPGPLQKKLDSFPAQDPCTTIY VAATEPVPESVQETNSI	SEQ ID No 761
ILAKISRPKKRAKTITFSKNAVISKRGGKLCLLIRVANLRKSLLIGSHIYGKL LKTTVTPEGETIILDQININFVVDAGNENLFFISPL	SEQ ID No 762
FLAKIARPKKRAETIRFSQHAVVASHNGKPCLMIRVANMRKSLLIGCQVT GKLLQTHQTKEGENIRLNQVNVTFQVDTASDSPFLILPL	SEQ ID No 763
WFLKRERQEEYIEEKKRVDICRETPNICPHSGENTEYDTIPHTNRTILKED PAN	SEQ ID No 764
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHND DVRNHAMKPINDNKEPLNSDVQYTEVQVSSAESHKDLGKKDTE	SEQ ID No 765
LRKRRDSLSLSTQRTQGPAESARNLEYVSVSPTNNTVYASVTHSNRETE IWTPRENDTI	SEQ ID No 766
RLFKRRQGRIFPEGSCLNTFTKNPYAASKKTIYTYIMASRNTQPAESRIYD EILQSKVLPSKEEPVN	SEQ ID No 767
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYD NDPDLCFRMQEGSEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVK EAP	SEQ ID No 768
KYRHKRFAVSEQGNIPHSHDWVWLGNEVELLENPVDITLPSEECTTMID RGLQFEERNFLLNGSSQKTFHSQLLRPSDYVYEKEIKNEPMNSSGPKRK RVKF	SEQ ID No 769
NSSYQEIEDDSDVEWKFARSKLWLSYFDDGKTLPPPFSLVPSPKSFVYFI MRIVNFPKCRRRRLQKDIEMGMGNSKSRLNLFTQSNSRVFESHSFNSIL	SEQ ID No 770

NQP	
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLS SAQVDQVEVEYVTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLP GRGPEEP	SEQ ID No 771
NNSYQEIEEDADVEWKFARAKLWLSYFDEGRTLPAPFNLVPSPKSFYYLI MRIKMCLIKLCKSKAKSCENDLEMGMLNSKFKKTRYQAGMRNSENLTAN NTLSKP	SEQ ID No 772
QSVFNKRKSRVRHYLVKCPQNSSGETVTSVTSLAPLQPKKGKRQKEKP DIPPAVPAKAPIAPTFHKPKLLKPQRKVTLPKIAEENLTYAELELIKPHRAA KGAPTS	SEQ ID No 773
YRHRKKRNGLTSTYAGIRKVPSFTFTPTVTYQRGGEAVSSGGRPGLLNI SEPAAQPWLADTWPNTGNNHNDCSISCCTAGNGNSDSNLTTYSRPAD CIANYNNQLDNKQTNLMLPES	SEQ ID No 774
RYQRWKSKLYSIVCGKSTPEKEGELEGTTTKPLAPNPSFSPTPGFTPTL GFSPVPSSTFTSSSTYTPGDCPNFAAPRREVAPPYQGADPILATALASD PIPNPLQKWEDSAHKPQSLDTDDPA	SEQ ID No 775
VRLRLQKHRPPADPCRGETETMNNLANCQREKDISVSIIGATQIKNTNKK ADFHGDHSADKNGFKARYPAVDYNLVQDLKGDDTAVRDAHSKRDTKC QPQGSSGEEKGTPTTLRGGEASERKRPDSGCSTSKD	SEQ ID No 776
RAWVVFKLSSAPRLHEQRVRDIQKQVREWKEQGSKTFMCTGRPGWLT VSLRVGKYKKTHKNIMINLMDILEVDTKKQIVRVEPLVTMGQVTALLTSIG WTLPVLPELDDLTVGGLIMGTGIESSSHKYGLFQHIC	SEQ ID No 777
TRDLVDDMGRHKSDRAINNRPCQILMGKSFKQKKWQDLCVGDVVCLRK DNIVPADMLLLASTEPSSLCYVETVDIDGETNLKFRQALMVTHKELATIKK MASFQGTVTCEAPNSRMHHFVGCLEWNDKKYSLDIGNLLLRGCRIRNT D	SEQ ID No 778
VFDPLGGKMAPYSSAGPSHLDSHDSSQLLNGLKTAATSVWETRIKLLCC CIGKDDHTRVAFSSTAELFSTYFSDTDLVPSDIAAGLALLHQQQDNIRNN QEPAQVVCHAPGSSQEADLDAELENCHHYMQFAAAAYGWPLYIYRNPL TGLCRIGGDCCRSRT	SEQ ID No 779
WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTFPGGGSTIYSM IQSQSSAPTSQEPAYTLYSLIQPSRKSGSRKRNHSPSFNS	SEQ ID No 780
RKRNNSRLGNGVLYASVNPEYFSAADVYVPDEWEVAREKITMSRELGQ GSFGMVYEGVAKGVVKDEPETRVAIKTVNEAASMRERIEFLNEASVMKE FNCHHVVRLLGVVSQGQPTLVIMELMTRGDLKSYLRSLRPEMENNPVLA PPSLSKMIQMAGEIADGMAYLNANKFVHRDLAARNCMVAEDFTVKIGDF	SEQ ID No 781

GMTRDIYETDYYRKGGKGLLPVRWMSPESLKDGVF	
NKCGRRNKFGINRPAVLAPEDGLAMSLHFMTLGGSSLSPTEGKGSGLQ GHIIENPQYFSDACVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPEQD KMLVAVKALKEASESARQDFQREAELLTMLQHQHIVRFFGVCTEGRPLL MVFEYMRHGDLNRFLRSHGPDAKLLAGGEDVAPGPLGLGQLLAVASQV AAGMVYLAGLHFVHRDLATRNCLVGQGLVVKIGDFGMSRDIYS	SEQ ID No 782
KLARHSKFGMKGPASVISNDDDSASPLHHISNGSNTPSSSEGGPDAVIIG MTKIPVIENPQYFGITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFLA ECYNLCPEQDKILVAVKTLKDASDNARKDFHREAELLTNLQHEHIVKFYG VCVEGDPLIMVFEYMKHGDLNKFLRAHGPDAVLMAEGNPPTELTQSQM LHIAQQIAAGMVYLASQHFVHRDLATRNCLVGENLLVKIGDFGMSRDVY S	SEQ ID No 783
NCVSCCKDPEIDFKEFEDNFDDEIDFTPPAEDTPSVQSPAEVFTLSVPNI SLPAPSQFQPSVEGLKSQVARHSLNYIQEIGNGWFGKVLLGEIYTGTSVA RVIVKELKASANPKEQDTFLKNGEPYYILQHPNILQCVGQCVEAIPYLLVF EFCDLGDLKAYLRSEQEHMRGDSQTMLLQRMACEVAAGLAAMHKLHFL HSDLALRNCFLTSDLNVKVGDYGIGFSRYKEDYIETDDKKVFPLRWTAPE LVTSFQDRLLTADQ	SEQ ID No 784
YKRKTQDADRTLKRLQLQMDNLESRVALECKEAFAELQTDINELTNHMD EVQIPFLDYRTYAVRVLFPGIEAHPVLKELDTPPNVEKALRLFGQLLHSRA FVLTFIHTLEAQSSFSMRDRGTVASLTMVALQSRLDYATGLLKQLLADLIE KNLESKNHPKLLLRRTESVAEKMLTNWFTFLLHKFLKECAGEPLFLLYCA IKQQMEKGPIDAITGEARYSLSEDKLIRQQIDYKTLTLHCVCPENEGSAQV PVKVLNCDSITQAKDKLLD	SEQ ID No 785
KRKGRCSVPAFCSSQAEAPADTPEPTAGHTLYSVLSQGYEKLDTPLRPA RQQPTPTSDSSSDSNLTTEEDEDRPEVHKPISGRYEVFDQVTQEGAGH DPAPEGQADYDPVTPYVTEVESVVGENTMYAQVFNLQGKTPVSQKEES SA	SEQ ID No 786
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNK LEDVVIDRNLLILGKILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNS SQREIEEFLSEAACMKDFSHPNVIRLLGVCIEMSSQGIPKPMVILPFMKY GDLHTYLLYSRLETGPKHIPLQTLLKFMVDIALGMEYLSNRNFLHRDLAA RNCMLRDDMTVCVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADR VYTSKSDVWAFGVTMWEIATRGM	SEQ ID No 787
SRQQRRREARGRGDASGLKRNSERKTPEGRASPAPGSGHPEGPGAHL	SEQ ID No 788

DMNSLDRAQAAKNKGNKYFKAGKYEQAIQCYTEAISLCPTEKNVDLSTF YQNRAAAFEQLQKWKEVAQDCTKAVELNPKYVKALFRRAKAHEKLDNK KECLEDVTAVCILEGFQNQQSMLLADKVLKLLGKEKAKEKYKNREPLMP SPQFIKSYFSSFTDDIISQPMLKGEKSDEDKDKEGEALEVKENSGYLKAK QYMEEENYDKIISECSKEIDAEGKYMAEALLLRA	
LRKRRKETRFGQAFDSVMARGEPAVHFRAARSFNRERPERIEATLDSLG ISDELKEKLEDVLIPEQQFTLGRMLGKGEFGSVREAQLKQEDGSFVKVA VKMLKADIIASSDIEEFLREAACMKEFDHPHVAKLVGVSLRSRAKGRLPIP MVILPFMKHGDLHAFLLASRIGENPFNLPLQTLIRFMVDIACGMEYLSSRN FIHRDLAARNCMLAEDMTVCVADFGLSRKIYSGDYYRQGCASKLPVKWL ALESLADNLYTVQSDVWAFGVTMWEIMTRGQ	SEQ ID No 789
HRRKKETRYGEVFEPTVERGELVVRYRVRKSYSRRTTEATLNSLGISEE LKEKLRDVMVDRHKVALGKTLGEGEFGAVMEGQLNQDDSILKVAVKTM KIAICTRSELEDFLSEAVCMKEFDHPNVMRLIGVCFQGSERESFPAPVVIL PFMKHGDLHSFLLYSRLGDQPVYLPTQMLVKFMADIASGMEYLSTKRFI HRDLAARNCMLNENMSVCVADFGLSKKIYNGDYYRQGRIAKMPVKWIAI ESLADRVYTSKSDVWSFGVTMWEIATRGQ	SEQ ID No 790
KRIELDDSISASSSSQGLSQPSTQTTQYLRADTPNNATPITSYPTLRIEKN DLRSVTLLEAKGKVKDIAISRERITLKDVLQEGTFGRIFHGILIDEKDPNKE KQAFVKTVKDQASEIQVTMMLTESCKLRGLHHRNLLPITHVCIEEGEKPM VILPYMNWGNLKLFLRQCKLVEANNPQAISQQDLVHMAIQIACGMSYLA RREVIHKDLAARNCVIDDTLQVKITDNALSRDLFPMDYHCLGDNENRPVR WMALESLVNNEFSSASDVWAFGVTLWELMTLGQ	SEQ ID No 791
NCRTWWQVLDSLLNSQRKRLHNAASKLHKLKSEGFMKVLKCEVELMAR MAKTIDSFTQNQTRLVVIIDGLDACEQDKVLQMLDTVRVLFSKGPFIAIFA SDPHIIIKAINQNLNSVLRDSNINGHDYMRNIVHLPVFLNSRGLSNARKFL VTSATNGDVPCSDTTGIQEDADRRVSQNSLGEMTKLGSKTALNRRDTY RRRQMQRTITRQMSFDLTKLLVTEDWFSDISPQTMRRLLNIVSVTGRLLR ANQISFNWDRLASWINLTEQWPYRTSWLILYLEETEGIPDQMTLK	SEQ ID No 792
MFNYTFQQVQEHTDQIWKFQRHDLIEEYHGRPAAPPPFILLSHLQLFIKR VVLKTPAKRHKQLKNKLEKNEEAALLSWEIYLKENYLQNRQFQQKQRPE QKIEDISNKVDAMVDLLDLDPLKRSGSMEQRLASLEEQVAQTAQALHWI VRTLRASGFSSEADVPTLASQKAAEEPDAEPGGRKKTEEPGDSYHVNA RHLLYPNCPVTRFPVPNEKVPWETEFLIYDPPFYTAERKDAAAMDPMGD TLEPLSTIQYNVVDGLRDRRSFHGPYTVQAGLPLNPMGRTGLRGRGSLS CFGPNH	SEQ ID No 793

AYKRKSRESDLTLKRLQMQMDNLESRVALECKEAFAELQTDIHELTSDL DGAGIPFLDYRTYTMRVLFPGIEDHPVLRDLEVPGYRQERVEKGLKLFA QLINNKVFLLSFIRTLESQRSFSMRDRGNVASLIMTVLQSKLEYATDVLKQ LLADLIDKNLESKNHPKLLLRRTESVAEKMLTNWFTFLLYKFLKECAGEPL FSLFCAIKQQMEKGPIDAITGEARYSLSEDKLIRQQIDYKTLVLSCVSPDN ANSPEVPVKILNCDTITQVKEKILDAIFKNVPCSHRPKAADMDLEWRQGS GARMILQDEDITTKIENDWKRLNTLAHYQVPDGSVVALVSKQV	SEQ ID No 794
RWHCPRRLLGACWTLNGQEEPVSQPTPQLENEVSRQHLPATLPEMVA FYQELHTPTQGQTMVRQLMHKLLVFSAREVDHRGGCLMLQDTGISLLIP PGAVAVGRQERVSLILVWDLSDAPSLSQAQGLVSPVVACGPHGASFLK PCTLTFKHCAEQPSHARTYSSNTTLLDAKVWRPLGRPGAHASRDECRIH LSHFSLYTCVLEAPVGREARKWLQLAVFCSPLVPGQSHLQLRIYFLNNTP CALQWALTNEQPHGGRLRGPCQLFDFNGARGDQCLKLTYISEGWENV DDSSCQLVPHLHIWHGKCPFRSFCFRRKAADENEDCSALTNEIIVTMHT FQDGLE	SEQ ID No 795
KQKPRYEIRWRVIESISPDGHEYIYVDPMQLPYDSRWEFPRDGLVLGRV LGSGAFGKVVEGTAYGLSRSQPVMKVAVKMLKPTARSSEKQALMSELKI MTHLGPHLNIVNLLGACTKSGPIYIITEYCFYGDLVNYLHKNRDSFLSHHP EKPKKELDIFGLNPADESTRSYVILSFENNGDYMDMKQADTTQYVPMLE RKEVSKYSDIQRSLYDRPASYKKKSMLDSEVKNLLSDDNSEGLTLLDLLS FTYQVARGMEFLASKNCVHRDLAARNVLLAQGKIVKICDFGLARDIMHD SNYVSKGSTFLPVKWMAPESIFDNLYTTLSDVWSYGILLWEIFSLGGTPY PGMMVDS	SEQ ID No 796
CCCKQRQPEGLGTRFAPVPEGGEGVMQSWRIEGAHPEDRDVSNICAP MTASNTQDRMDSSEIYTNTYAAGGTVEGGVSGVELNTGMGTAVGLMAA GAAGASGAARKRSSTMGTLRDYADADINMAFLDSYFSEKAYAYADEDE GRPANDCLLIYDHEGVGSPVGSIGCCSWIVDDLDESCMETLDPKFRTLA EICLNTEIEPFPSHQACIPISTDLPLLGPNYFVNESSGLTPSEVEFQEEMA ASEPVVHGDIIVTETYGNADPCVQPTTIIFDPQLAPNVVVTEAVMAPVYDI QGNICVPAELADYNNVIYAERVLASPGVPDMSNSSTTEGCMGPVMSGNI LVGPEIQVMQMMSPDLPIGQTVGSTSPMTSRHRV	SEQ ID No 797
SNKCDVVVVGGGISGMAAAKLLHDSGLNVVVLEARDRVGGRTYTLRNQ KVKYVDLGGSYVGPTQNRILRLAKELGLETYKVNEVERLIHHVKGKSYPF RGPFPPVWNPITYLDHNNFWRTMDDMGREIPSDAPWKAPLAEEWDNM TMKELLDKLCWTESAKQLATLFVNLCVTAETHEVSALWFLWYVKQCGG TTRIISTTNGGQERKFVGGSGQVSERIMDLLGDRVKLERPVIYIDQTREN	SEQ ID No 798

VLVETLNHEMYEAKYVISAIPPTLGMKIHFNPPLPMMRNQMITRVPLGSVI KCIVYYKEPFWRKKDYCGTMIIDGEEAPVAYTLDDTKPEGNYAAIMGFIL AHKARKLARLTKEERLKKLCELYAKVLGSLEALEPVHYEEKNWCEEQYS GGCYTTYFPPGIL	
MENQEKASIAGHMFDVVVIGGGISGLSAAKLLTEYGVSVLVLEARDRVG GRTYTIRNEHVDYVDVGGAYVGPTQNRILRLSKELGIETYKVNVSERLVQ YVKGKTYPFRGAFPPVWNPIAYLDYNNLWRTIDNMGKEIPTDAPWEAQH ADKWDKMTMKELIDKICWTKTARRFAYLFVNINVTSEPHEVSALWFLWY VKQCGGTTRIFSVTNGGQERKFVGGSGQVSERIMDLLGDQVKLNHPVT HVDQSSDNIIIETLNHEHYECKYVINAIPPTLTAKIHFRPELPAERNQLIQRL PMGAVIKCMMYYKEAFWKKKDYCGCMIIEDEDAPISITLDDTKPDGSLPA IMGFILARKADRLAKLHKEIRKKKICELYAKVLGSQEALHPVHYEEKNWC EEQYSGGCYTAYFPPGIM	SEQ ID No 799
CCDCGGAPRSAAGFEPVPECSDGAIHSWAVEGPQPEPRDITTVIPQIPP DNANIIECIDNSGVYTNEYGGREMQDLGGGERMTGFELTEGVKTSGMP EICQEYSGTLRRNSMRECREGGLNMNFMESYFCQKAYAYADEDEGRP SNDCLLIYDIEGVGSPAGSVGCCSFIGEDLDDSFLDTLGPKFKKLADISLG KESYPDLDPSWPPQSTEPVCLPQETEPVVSGHPPISPHFGTTTVISESTY PSGPGVLHPKPILDPLGYGNVTVTESYTTSDTLKPSVHVHDNRPASNVV VTERVVGPISGADLHGMLEMPDLRDGSNVIVTERVIAPSSSLPTSLTIHHP RESSNVVVTERVIQPTSGMIGSLSMHPELANAHNVIVTERVVSGAGVTGI SGTTGISGGIGSSGLVGTSMGAGSGALSGAGISGGGIGLSSLGGTASIG HMRSSSDHHFNQTIGSASPSTARSRI	SEQ ID No 800
NLEGVMNQADAPRPLNWTIRKLCHAAFLPSVRLLKAQKSWIERAFYKRE CVHIIPSTKDPHRCCCGRLIGQHVGLTPSISVLQNEKNESRLSRNDIQSE KWSISKHTQLSPTDAFGTIEFQGGGHSNKAMYVRVSFDTKPDLLLHLMT KEWQLELPKLLISVHGGLQNFELQPKLKQVFGKGLIKAAMTTGAWIFTGG VNTGVIRHVGDALKDHASKSRGKICTIGIAPWGIVENQEDLIGRDVVRPY QTMSNPMSKLTVLNSMHSHFILADNGTTGKYGAEVKLRRQLEKHISLQKI NTRCLPFFSLDSRLFYSFWGSCQLDSVGIGQGVPVVALIVEGGPNVISIV LEYLRDTPPVPVVVCDGSGRASDILAFGHKYSEEGGLINESLRDQLLVTI QKTFTYTRTQAQHLFIILMECMKKKELITVFRMGSEGHQDIDLAILTALLK GANASAPDQLSLALAWNRVDIARSQIFIYGQQWPVGSLEQAMLDALVLD RVDFVKLLIENGVSMHRFLTISRLEELYNTRHGPSN	SEQ ID No 801
ELFANKRKYTSSYEALKGKKFIVVCGNITVDSVTAFLRNFLRDKSGEINTE IVFLGETPPSLELETIFKCYLAYTTFISGSAMKWEDLRRVAVESAEACLIIA	SEQ ID No 802

NPLCSDSHAEDISNIMRVLSIKNYDSTTRIIIQILQSHNKVYLPKIPSWNWD TGDNIICFAELKLGFIAQGCLVPGLCTFLTSLFVEQNKKVMPKQTWKKHF LNSMKNKILTQRLSDDFAGMSFPEVARLCFLKMHLLLIAIEYKSLFTDGFC GLILNPPPQVRIRKNTLGFFIAETPKDVRRALFYCSVCHDDVFIPELITNCG CKSRSRQHITVPSVKRMKKCLKGISSRISGQDSPPRVSASTSSISNFTTR TLQHDVEQDSDQLDSSGMFHWCKPTSLDKVTLKRTGKSKYKFRNHIVA CVFGDAHSAPMGLRNFVMPLRASNYTRKELKDIVFIGSLDYLQREWRFL WNFPQIYILPGCALYSGDLHAANIEQCSMCAVLSPPPQPSSNQTLVDTE AIMATLTIGSLQIDSSSDPSPSVSEETPGYTNGHNEKSNCRKVPILTELKN PSNIHFIEQLGGLEGSLQETNLHLSTAFSTGTVFSGSFLDSLLATAFYNYH VLELLQMLVTGGVSSQLEQHLDKDKVYGVADSCTSLLSGRNRCKLGLLS LHETILSDVNPRNTFGQLFCGSLDLFGILCVGLYRIIDEEELNPENKRFVIT RPANEFKLLPSDLVFCAIPFSTACYKRNEEFSLQKSYEIVNKASQTTETH SDTNCPPTIDSVTE	
QFEELVYLWMERQKSGGNYSRHRAQTEKHVVLCVSSLKIDLLMDFLNEF YAHPRLQDYYVVILCPTEMDVQVRRVLQIPLWSQRVIYLQGSALKDQDL MRAKMDNGEACFILSSRNEVDRTAADHQTILRAWAVKDFAPNCPLYVQI LKPENKFHVKFADHVVCEEECKYAMLALNCICPATSTLITLLVHTSRGQE GQESPEQWQRMYGRCSGNEVYHIRMGDSKFFREYEGKSFTYAAFHAH KKYGVCLIGLKREDNKSILLNPGPRHILAASDTCFYINITKEENSAFIFKQE EKRKKRAFSGQGLHEGPARLPVHSIIASMGTVAMDLQGTEHRPTQSGG GGGGSKLALPTENGSGSRRPSIAPVLELADSSALLPCDLLSDQSEDEVT PSDDEGLSVVEYVKGYPPNSPYIGSSPTLCHLLPVKAPFCCLRLDKGCK HNSYEDAKAYGFKNKLIIVSAETAGNGLYNFIVPLRAYYRSRKELNPIVLL LDNKPDHHFLEAICCFPMVYYMEGSVDNLDSLLQCGIIYADNLVVVDKES TMSAEEDYMADAKTIVNVQTMFRLFPSLSITTELTHPSNMRFMQFRAKD SYSLALSKLEKRERENGSNLAFMFRLPFAAGRVFSISMLDTLLYQSFVKD YMITITRLLLGLDTTPGSGYLCAMKITEGDLWIRTYGRLFQKLCSSSAEIPI GIYRTESHVFSTSESQISVNVEDCEDTREVKGPWGSRAGTGGSSQGRH TGGGDPAEHPLLRRKSLQWARRLSRKAPKQAGRAAAAEWISQQRLSLY RRSERQELSELVKNRMKHLGLPT	SEQ ID No 803
MSGGASATGPRRGPPGLEDTTSKKKQKDRANQESKDGDPRKETGSRY VAQAGLEPLASGDPSASASHAAGITGSRHRTRLFFPSSSGSASTPQEEQ TKEGACEDPHDLLATPTPELLLDWRQSAEEVIVKLRVGVGPLQLEDVDA AFTDTDCVVRFAGGQQWGGVFYAEIKSSCAKVQTRKGSLLHLTLPKKVP MLTWPSLLVEADEQLCIPPLNSQTCLLGSEENLAPLAGEKAVPPGNDPV	SEQ ID No 804

SPAMVRSRNPGKDDCAKEEMAVAADAATLVDEPESMVNLAFVKNDSYE KGPDSVVVHVYVKEICRDTSRVLFREQDFTLIFQTRDGNFLRLHPGCGP HTTFRWQVKLRNLIEPEQCTFCFTASRIDICLRKRQSQRWGGLEAPAAR VGGAKVAVPTGPTPLDSTPPGGAPHPLTGQEEARAVEKDKSKARSEDT GLDSVATRTPMEHVTPKPETHLASPKPTCMVPPMPHSPVSGDSVEEEE EEEKKVCLPGFTGLVNLGNTCFMNSVIQSLSNTRELRDFFHDRSFEAEIN YNNPLGTGGRLAIGFAVLLRALWKGTHHAFQPSKLKAIVASKASQFTGY AQHDAQEFMAFLLDGLHEDLNRIQNKPYTETVDSDGRPDEVVAEEAWQ RHKMRNDSFIVDLFQGQYKSKLVCPVCAKVSITFDPFLYLPVPLPQKQKV LPVFYFAREPHSKPIKFLVSVSKENSTASEVLDSLSQSVHVKPENLRLAE VIKNRFHRVFLPSHSLDTVSPSDTLLCFELLSSELAKERVVVLEVQQRPQ VPSVPISKCAACQRKQQSEDEKLKRCTRCYRVGYCNQLCQKTHWPDH KGLCRPENIGYPFLVSVPASRLTYARLAQLLEGYARYSVSVFQPPFQPG RMALESQSPGCTTLLSTGSLEAGDSERDPIQPPELQLVTPMAEGDTGLP RVWAAPDRGPVPSTSGISSEMLASGPIEVGSLPAGERVSRPEAAVPGY QHPSEAMNAHTPQFFIYKIDSSNREQRLEDKGDTPLELGDDCSLALVWR NNERLQEFVLVASKELECAEDPGSAGEAARAGHFTLDQCLNLFTRPEVL APEEAWYCPQCKQHREASKQLLLWRLPNVLIVQLKRFSFRSFIWRDKIN DLVEFPVRNLDLSKFCIGQKEEQLPSYDLYAVINHYGGMIGGHYTACARL PNDRSSQRSDVGWRLFDDSTVTTVDESQVV	
MADGGEGEDEIQFLRTDDEVVLQCTATIHKEQQKLCLAAEGFGNRLCFL ESTSNSKNVPPDLSICTFVLEQSLSVRALQEMLANTVEKSEGQVDVEKW KFMMKTAQGGGHRTLLYGHAILLRHSYSGMYLCCLSTSRSSTDKLAFDV GLQEDTTGEACWWTIHPASKQRSEGEKVRVGDDLILVSVSSERYLHLSY GNGSLHVDAAFQQTLWSVAPISSGSEAAQGYLIGGDVLRLLHGHMDEC LTVPSGEHGEEQRRTVHYEGGAVSVHARSLWRLETLRVAWSGSHIRW GQPFRLRHVTTGKYLSLMEDKNLLLMDKEKADVKSTAFTFRSSKEKLDV GVRKEVDGMGTSEIKYGDSVCYIQHVDTGLWLTYQSVDVKSVRMGSIQ RKAIMHHEGHMDDGISLSRSQHEESRTARVIRSTVFLFNRFIRGLDALSK KAKASTVDLPIESVSLSLQDLIGYFHPPDEHLEHEDKQNRLRALKNRQNL FQEEGMINLVLECIDRLHVYSSAAHFADVAGREAGESWKSILNSLYELLA ALIRGNRKNCAQFSGSLDWLISRLERLEASSGILEVLHCVLVESPEALNIIK EGHIKSIISLLDKHGRNHKVLDVLCSLCVCHGVAVRSNQHLICDNLLPGR DLLLQTRLVNHVSSMRPNIFLGVSEGSAQYKKWYYELMVDHTEPFVTAE ATHLRVGWASTEGYSPYPGGGEEWGGNGVGDDLFSYGFDGLHLWSG CIARTVSSPNQHLLRTDDVISCCLDLSAPSISFRINGQPVQGMFENFNIDG	SEQ ID No 805

LFFPVVSFSAGIKVRFLLGGRHGEFKFLPPPGYAPCYEAVLPKEKLKVEH SREYKQERTYTRDLLGPTVSLTQAAFTPIPVDTSQIVLPPHLERIREKLAE NIHELWVMNKIELGWQYGPVRDDNKRQHPCLVEFSKLPEQERNYNLQM SLETLKTLLALGCHVGISDEHAEDKVKKMKLPKNYQLTSGYKPAPMDLSF IKLTPSQEAMVDKLAENAHNVWARDRIRQGWTYGIQQDVKNRRNPRLV PYTLLDDRTKKSNKDSLREAVRTLLGYGYNLEAPDQDHAARAEVCSGT GERFRIFRAEKTYAVKAGRWYFEFETVTAGDMRVGWSRPGCQPDQEL GSDERAFAFDGFKAQRWHQGNEHYGRSWQAGDVVGCMVDMNEHTM MFTLNGEILLDDSGSELAFKDFDVGDGFIPVCSLGVAQVGRMNFGKDVS TLKYFTICGLQEGYEPFAVNTNRDITMWLSKRLPQFLQVPSNHEHIEVTRI DGTIDSSPCLKVTQKSFGSQNSNTDIMFYRLSMPIECAEVFSKTVAGGLP GAGLFGPKNDLEDYDADSDFEVLMKTAHGHLVPDRVDKDKEATKPEFN NHKDYAQEKPSRLKQRFLLRRTKPDYSTSHSARLTEDVLADDRDDYDFL MQTS	

Table 7: Naturally occurring C-terminal flanking regions of ITIM.*ITSM intracellular domains varying in length from 1-2890 (Table 7 comprises SEQ ID No 806 to SEQ ID No 836)

V	
SRP	
RTQ	
KIHK	SEQ ID No 806
KTSK	SEQ ID No 807
KIHR	SEQ ID No 808
CVRS	SEQ ID No 809
QYSK	SEQ ID No 810
LFEENKL	SEQ ID No 811
KAENIIMMETAQTSL	SEQ ID No 812
YVISEEKDECVIATEV	SEQ ID No 813
NHSKESKPTFSRATALDNV	SEQ ID No 814
RKAVPDAVESRYSRTEGSLDGT	SEQ ID No 815
KIHTGQPLRGPGFGLQLEREMSGMVPK	SEQ ID No 816
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL	SEQ ID No 817
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK	SEQ ID No 818
YSYQPRTNSLSFPKQIAWNQSRTNSIISSQIPLGDNAKENERKTSDEVYD EDPFAYSEPL	SEQ ID No 819

MKRLIKRYVLKAQVDKENDEVNEGELKEIKQDISSLRYELLEDKSQATEE LAILIHKLSEKLNPSMLRCE	SEQ ID No 820
IRQPVGRIFFAGTETATKWSGYMEGAVEAGERAAREVLNGLGKVTEKDI WVQEPESKDVPAVEITHTFWERNLPS	SEQ ID No 821
LRQPVDRIYFAGTETATHWSGYMEGAVEAGERAAREILHAMGKIPEDEI WQSEPESVDVPAQPITTTFLERHLPSV	SEQ ID No 822
MKRLIKRYVLKAQVDRENDEVNEGELKEIKQDISSLRYELLEEKSQATGE LADLIQQLSEKFGKNLNKDHLRVNKGKDI	SEQ ID No 823
LFYRRRNSPVERPPRAGHSEHHPDLGPAAEAAASQASRIWQELEAEEE PVPEGSGPLGPWGPQDWVGPLPRGPTTPDEGCLRY	SEQ ID No 824
LRFQASEEESWAAPPPVSQPPPCNRLPPELFEQLRMLLEPNSITGNDW RRLASHLGLCGMKIRFLSCQRSPAAAILELFEEQNGSLQELHYLMTVME RLDCASAIQNYLSGTHGGSPGPERGGARDNQGLELDEKL	SEQ ID No 825
ENSEIYDYLRQGNRLKQPADCLDGLYALMSRCWELNPQDRPSFTELRE DLENTLKALPPAQEPDEILYVNMDEGGGYPEPPGAAGGADPPTQPDPK DSCSCLTAAEVHPAGRYVLCPSTTPSPAQPADRGSPAAPGQEDGA	SEQ ID No 826
TRWRRNEDGAICRKSIKKMLEVLVVKLPLSEHWALPGGSREPGEMLPR KLKRILRQEHWPSFENLLKCGMEVYKGYMDDPRNTDNAWIETVAVSVH FQDQNDVELNRLNSNLHACDSGASIRWQVVDRRIPLYANHKTLLQKAAA EFGAHY	SEQ ID No 827
WSFGVVLWEIATLAEQPYQGLSNEQVLRFVMEGGLLDKPDNCPDMLFE LMRMCWQYNPKMRPSFLEIISSIKEEMEPGFREVSFYYSEENKLPEPEE LDLEPENMESVPLDPSASSSSLPLPDRHSGHKAENGPGPGVLVLRASFD ERQPYAHMNGGRKNERALPLPQSSTC	SEQ ID No 828
KSGYRMAKPDHATSEVYEIMVKCWNSEPEKRPSFYHLSEIVENLLPGQY KKSYEKIHLDFLKSDHPAVARMRVDSDNAYIGVTYKNEEDKLKDWEGGL DEQRLSADSGYIIPLPDIDPVPEEEDLGKRNRHSSQTSEESAIETGSSSS TFIKREDETIEDIDMMDDIGIDSSDLVEDSFL	SEQ ID No 829
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRL QLEKLLESLPDVRNQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSII ASCTPRAAISVVTAEVHDSKPHEGRYILNGGSEEWEDLTSAPSAAVTAE KNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFADDSSEGSEVLM	SEQ ID No 830
CETLQFLDCICGSTTGGLGLLGLYINEKNVALINQTLESLTEYCQGPCHE NQNCIATHESNGIDIITALILNDINPLGKKRMDLVLELKNNASKLLLAIMESR HDSENAERILYNMRPKELVEVIKKAYMQGEVEFEDGENGEDGAASPRN VGHNIYILAHQLARHNKELQSMLKPGGQVDGDEALEFYAKHTAQIEIVRL	SEQ ID No 831

DRTMEQIVFPVPSICEFLTKESKLRIYYTTERDEQGSKINDFFLRSEDLFN EMNWQKKLRAQPVLYWCARNMS	
CETLQFLDCICGSTTGGLGLLGLYINEKNVALVNQNLESLTEYCQGPCHE NQTCIATHESNGIDIIIALILNDINPLGKYRMDLVLQLKNNASKLLLAIMESR HDSENAERILFNMRPRELVDVMKNAYNQGLECDHGDDEGGDDGVSPK DVGHNIYILAHQLARHNKLLQQMLKPGSDPDEGDEALKYYANHTAQIEIV RHDRTMEQIVFPVPNICEYLTRESKCRVFNTTERDEQGSKVNDFFQQTE DLYNEMKWQKKIRNNPALFWFSRHIS	SEQ ID No 832
NNSTVSRTSASKYENMIRYTGSPDSLRSRTPMITPDLESGVKMWHLVKN HEHGDQKEGDRGSKMVSEIYLTRLLATKGTLQKFVDDLFETIFSTAHRG SALPLAIKYMFDFLDEQADKHGIHDPHVRHTWKSNCLPLRFWVNMIKNP QFVFDIHKNSITDACLSVVAQTFMDSCSTSEHRLGKDSPSNKLLYAKDIP SYKNWVERYYSDIGKMPAISDQDMNAYLAEQSRMHMNEFNTMSALSEI FSYVGKYSEEILGPLDHDDQCGKQKLAYKLEQVITLMSLDS	SEQ ID No 833
CETLQFLDIMCGSTTGGLGLLGLYINEDNVGLVIQTLETLTEYCQGPCHE NQTCIVTHESNGIDIITALILNDISPLCKYRMDLVLQLKDNASKLLLALMES RHDSENAERILISLRPQELVDVIKKAYLQEEERENSEVSPREVGHNIYILA LQLSRHNKQLQHLLKPVKRIQEEEAEGISSMLSLNNKQLSQMLKSSAPA QEEEEDPLAYYENHTSQIEIVRQDRSMEQIVFPVPGICQFLTEETKHRLF TTTEQDEQGSKVSDFFDQSSFLHNEMEWQRKLRSMPLIYWFSRRMT	SEQ ID No 834
PYSQRPKAEDMDLEWRQGRMTRIILQDEDVTTKIECDWKRLNSLAHYQ VTDGSLVALVPKQVSAYNMANSFTFTRSLSRYESLLRTASSPDSLRSRA PMITPDQETGTKLWHLVKNHDHADHREGDRGSKMVSEIYLTRLLATKGT LQKFVDDLFETVFSTAHRGSALPLAIKYMFDFLDEQADQRQISDPDVRHT WKSNCLPLRFWVNVIKNPQFVFDIHKNSITDACLSVVAQTFMDSCSTSE HRLGKDSPSNKLLYAKDIPNYKSWVERYYRDIAKMASISDQDMDAYLVE QSRLHASDFSVLSALNELYFYVTKYRQEILTALDRDASCRKHKLRQKLEQ IISLVSSDS	SEQ ID No 835
DLSNKINEMKTFNSPNLKDGRFVNPSGQPTPYATTQLIQSNLSNNMNNG SGDSGEKHWKPLGQQKQEVAPVQYNIVEQNKLNKDYRANDTVPPTIPY NQSYDQNTGGSYNSSDRGSSTSGSQGHKKGARTPKVPKQGGMNWAD LLPPPPAHPPPHSNSEEYNISVDESYDQEMPCPVPPARMYLQQDELEEE EDERGPTPPVRGAASSPAAVSYSHQSTATLTPSPQEELQPMLQDCPEE TGHMQHQPDRRRQPVSPPPPPRPISPPHTYGYISGPLVSDMDTDAPEE EEDEADMEVAKMQTRRLLLRGLEQTPASSVGDLESSVTGSMINGWGSA SEEDNISSGRSSVSSSDGSFFTDADFAQAVAAAAEYAGLKVARRQMQD	SEQ ID No 836

AAGRRHFHASQCPRPTSPVSTDSNMSAAVMQKTRPAKKLKHQPGHLR RETYTDDLPPPPVPPPAIKSPTAQSKTQLEVRPVVVPKLPSMDARTDRS SDRKGSSYKGREVLDGRQVVDMRTNPGDPREAQEQQNDGKGRGNKA AKRDLPPAKTHLIQEDILPYCRPTFPTSNNPRDPSSSSSMSSRGSGSRQ REQANVGRRNIAEMQVLGGYERGEDNNEELEETES	

Table 8: Examples of naturally occurring C-terminal flanking regions of ITSM only intracellular domains that could vary in length from 1-2890 (Table 8 comprises SEQ ID No 837 to SEQ ID No 925)

L	
V	
PR	
RIN	
RTQ	
SRP	
KIHK	SEQ ID No 837
KTSK	SEQ ID No 838
KIHR	SEQ ID No 839
CVRS	SEQ ID No 840
QYSK	SEQ ID No 841
HYTQQ	SEQ ID No 842
LGPKPQG	SEQ ID No 843
LFEENKL	SEQ ID No 844
VKADTYCA	SEQ ID No 845
QTSEPSGT	SEQ ID No 846
QSCALPTDAL	SEQ ID No 847
AKNALLRWRV	SEQ ID No 848
SKNRLLSIKT	SEQ ID No 849
QHIPAQQQDHPE	SEQ ID No 850
AHHRFYTKRLTFWT	SEQ ID No 851
AHHRFYAKRMTLWT	SEQ ID No 852
KHRHWYPFNFVIEQ	SEQ ID No 853
AHHRFYAERLAGWPC	SEQ ID No 854
KAENIIMMETAQTSL	SEQ ID No 855
YVISEEKDECVIATEV	SEQ ID No 856

RKAVPDAVESRYSRTEGSLDGT	SEQ ID No 857
RKPQVVPPPQQNDLEIPESPTYENFT	SEQ ID No 2028
GKSQPKAQNPARLSRKELENFDVYS	SEQ ID No 2029
KIHTGQPLRGPGFGLQLEREMSGMVPK	SEQ ID No 858
IYAGFDTKIMKNCGKIHLKRTKLDLLMNKL	SEQ ID No 859
ASALKSHRTRGHGRGDCCGRSLGDSCCFSAK	SEQ ID No 860
FTLVLEEIRQGFFTDEDTHLVKKFTLYVGDNWNKCD	SEQ ID No 861
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL	SEQ ID No 862
PSEDFERTPQSPTLPPAKVAAPNLSRMGAIPVMIPAQSKDGSIV	SEQ ID No 863
LPEDGGPYTNSILFDSDDNIKWVCQDMGLGDSQDFRDYMESLQDQM	SEQ ID No 864
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK	SEQ ID No 865
SYHASGHSVAYKPGGFKASTGFGSNTKNKKIYDGGARTEDEVQSYPSK HDYV	SEQ ID No 866
QVGPGAAARWDLCIDQAVVFIEDAIQYRSINHRVDASSMWLYRRYYSNV CQR	SEQ ID No 867
EGPRKGHLEEEEEDGEEGAETLAHFCPMELRGPEPLGSRPRQPNLIPW AAAGRRAAP	SEQ ID No 868
QKPGPLQKKLDSFPAQDPCTTIYVAATEPVPESVQETNSITVYASVTLPE S	SEQ ID No 869
YSYQPRTNSLSFPKQIAWNQSRTNSIISSQIPLGDNAKENERKTSDEVYD EDPFAYSEPL	SEQ ID No 870
DPFEMAAYLKDGYRIAQPINCPDELFAVMACCWALDPEERPKFQQLVQ CLTEFHAALGAYV	SEQ ID No 871
THSNRETEIWTPRENDTITIYSTINHSKESKPTFSRATALDNV	SEQ ID No 872
MKRLIKRYVLKAQVDKENDEVNEGELKEIKQDISSLRYELLEDKSQATEE LAILIHKLSEKLNPSMLRCE	SEQ ID No 873
PPSHHQLTLPDPSHHGLHSTPDSPAKPEKNGHAKDHPKIAKIFEIQTMPN GKTRTSLKTMSRRKLSQQKEKKATQ	SEQ ID No 874
IRQPVGRIFFAGTETATKWSGYMEGAVEAGERAAREVLNGLGKVTEKDI WVQEPESKDVPAVEITHTFWERNLPS	SEQ ID No 875
FNLQGKTPVSQKEESSATIYCSIRKPQVVPPPQQNDLEIPESPTYENFT	SEQ ID No 876
LRQPVDRIYFAGTETATHWSGYMEGAVEAGERAAREILHAMGKIPEDEI WQSEPESVDVPAQPITTTFLERHLPSV	SEQ ID No 877
PHTNRTILKEDPANTVYSTVEIPKKMENPHSLLTMPDTPRLFAYENVI	SEQ ID No 878

MKRLIKRYVLKAQVDRENDEVNEGELKEIKQDISSLRYELLEEKSQATGE LADLIQQLSEKFGKNLNKDHLRVNKGKDI	SEQ ID No 879
LFYRRRNSPVERPPRAGHSEHHPDLGPAAEAAASQASRIWQELEAEEE PVPEGSGPLGPWGPQDWVGPLPRGPTTPDEGCLRY	SEQ ID No 880
ANLTASDVMNRVNLGYLQDEMNDHQNTLSYVLINPPPDTRLEPSDIVYLI RSDPLAHVASSSQSRKSSCSHKLSSCNPETRDETQL	SEQ ID No 881
MASRNTQPAESRIYDEILQSKVLPSKEEPVNTVYSEVQFADKMGKASTQ DSKPPGTSSYEIVI	SEQ ID No 882
ENVPPLRWKEFVRRLGLSDHEIDRLELQNGRCLREAQYSMLATWRRRT PRREATLELLGRVLRDMDLLGCLEDIEEALCGPAALPPAPSLLR	SEQ ID No 883
LIGDFLRACFVRFCNYCWCWDLEYGYPSYTEFDISGNVLALIFNQGMIW MGSFFAPSLPGINILRLHTSMYFQCWAVMCCNVPEARVFKASRSNN	SEQ ID No 884
ESTESQILVGIVQRAQLVQALQAEPPSRAPGHQQCLQDILARGCPTEPV TLTLFSETTLHQAQNLFKLLNLQSLFVTSRGRAVGCVSWVEMKKAISNLT NPPAPK	SEQ ID No 885
AKTIKDVFHNHGIHATTIQPEFASVGSKSSVVPCELACRTQCALKQCCGT LPQAPSGKDAEKTPAVSISCLELSNNLEKKPRRTKAENIPAVVIEIKNMPN KQPESSL	SEQ ID No 886
TPSSPLATLLQHENPSHFELVVFLSAMQEGTGEICQRRTSYLPSEIMLHH CFASLLTRGSKGEYQIKMENFDKTVPEFPTPLVSKSPNRTDLDIHINGQSI DNFQISETGLTE	SEQ ID No 887
GGRTMLPIRWMPPESILYRKFTTESDVWSFGVVLWEIFTYGKQPWYQLS NTEAIDCITQGRELERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARL QALAQAPPVYLDVLG	SEQ ID No 888
GGHTMLPIRWMPPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQL SNNEVIECITQGRVLQRPRTCPQEVYELMLGCWQREPHMRKNIKGIHTL LQNLAKASPVYLDILG	SEQ ID No 889
LNPPPSPATDPSLYNMDMFYSSNIPATARPYRPYIIRGMAPPTTPCSTDV CDSDYSASRWKASKYYLDLNSDSDPYPPPPTPHSQYLSAEDSCPPSPA TERSYFHLFPPPPSPCTDSS	SEQ ID No 890
DHNSPFFHMAAETLLQQDFELVVFLDGTVESTSATCQVRTSYVPEEVLW GYRFAPIVSKTKEGKYRVDFHNFSKTVEVETPHCAMCLYNEKDVRARM KRGYDNPNFILSEVNETDDTKM	SEQ ID No 891
DETSPLKDLPLRSGEGDFELVLILSGTVESTSATCQVRTSYLPEEILWGY EFTPAISLSASGKYIADFSLFDQVVKVASPSGLRDSTVRYGDPEKLKLEE	SEQ ID No 892

SLREQAEKEGSALSVRISNV	
LRFQASEEESWAAPPPVSQPPPCNRLPPELFEQLRMLLEPNSITGNDW RRLASHLGLCGMKIRFLSCQRSPAAAILELFEEQNGSLQELHYLMTVME RLDCASAIQNYLSGTHGGSPGPERGGARDNQGLELDEKL	SEQ ID No 893
TRWRRNEDGAICRKSIKKMLEVLVVKLPLSEHWALPGGSREPGEMLPR KLKRILRQEHWPSFENLLKCGMEVYKGYMDDPRNTDNAWIETVAVSVH FQDQNDVELNRLNSNLHACDSGASIRWQVVDRRIPLYANHKTLLQKAAA EFGAHY	SEQ ID No 894
ENAEIYNYLIGGNRLKQPPECMEDVYDLMYQCWSADPKQRPSFTCLRM ELENILGQLSVLSASQDPLYINIERAEEPTAGGSLELPGRDQPYSGAGDG SGMGAVGGTPSDCRYILTPGGLAEQPGQAEHQPESPLNETQRLLLLQQ GLLPHSSC	SEQ ID No 895
WSFGVVLWEIATLAEQPYQGLSNEQVLRFVMEGGLLDKPDNCPDMLFE LMRMCWQYNPKMRPSFLEIISSIKEEMEPGFREVSFYYSEENKLPEPEE LDLEPENMESVPLDPSASSSSLPLPDRHSGHKAENGPGPGVLVLRASFD ERQPYAHMNGGRKNERALPLPQSSTC	SEQ ID No 896
KSGYRMAKPDHATSEVYEIMVKCWNSEPEKRPSFYHLSEIVENLLPGQY KKSYEKIHLDFLKSDHPAVARMRVDSDNAYIGVTYKNEEDKLKDWEGGL DEQRLSADSGYIIPLPDIDPVPEEEDLGKRNRHSSQTSEESAIETGSSSS TFIKREDETIEDIDMMDDIGIDSSDLVEDSFL	SEQ ID No 897
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRL QLEKLLESLPDVRNQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSII ASCTPRAAISVVTAEVHDSKPHEGRYILNGGSEEWEDLTSAPSAAVTAE KNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFADDSSEGSEVLM	SEQ ID No 898
PDPYKSSILSLIKFKENPHLIIMNVSDCIPDAIEVVSKPEGTKIQFLGTRKSL TETELTKPNYLYLLPTEKNHSGPGPCICFENLTYNQAASDSGSCGHVPV SPKAPSMLGLMTSPENVLKALEKNYMNSLGEIPAGETSLNYVSQLASPM FGDKDSLPTNPVEAPHCSEYKMQMAVSLRLALPPPTENSSLSSITLLDP GEHYC	SEQ ID No 899
PNPENCKALQFQKSVCEGSSALKTLEMNPCTPNNVEVLETRSAFPKIED TEIISPVAERPEDRSDAEPENHVVVSYCPPIIEEEIPNPAADEAGGTAQVI YIDVQSMYQPQAKPEEEQENDPVGGAGYKPQMHLPINSTVEDIAAEEDL DKTAGYRPQANVNTWNLVSPDSPRSIDSNSEIVSFGSPCSINSRQFLIPP KDEDSPKSNGGGWSFTNFFQNKPND	SEQ ID No 900
RDVKKGNLPPDYRISLIDIGLVIEYLMGGAYRCNYTRKRFRTLYHNLFGP KRPKALKLLGMEDDIPLRRGRKTTKKREEEVDIDLDDPEINHFPFPFHEL	SEQ ID No 901

MVWAVLMKRQKMALFFWQHGEEAMAKALVACKLCKAMAHEASENDM VDDISQELNHNSRDFGQLAVELLDQSYKQDEQLAMKLLTYELKNWSNAT CLQLAVAAKHRDFIAHTCSQMLLTDMWMGRLRMRK	
KDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQEPAYTLYSLIQPSR KSGSRKRNHSPSFNSTIYEVIGKSQPKAQNPARLSRKELENFDVYS	SEQ ID No 902
GNANAAKPDLDKVISLKEANVKLRANALIKRGSMYMQQQQPLLSTQDFN MAADIDPQNADVYHHRGQLKILLDQVEEAVADFDECIRLRPESALAQAQ KCFALYRQAYTGNNSSQIQAAMKGFEEVIKKFPRCAEGYALYAQALTDQ QQFGKADEMYDKCIDLEPDNATTYVHKGLLQLQWKQDLDRGLELISKAI EIDNKCDFAYETMGTIEVQRGNMEKAIDMFNKAINLAKSEMEMAHLYSLC DAAHAQTEVAKKYGLKPPTL	SEQ ID No 903
ENEAPWVTDKRPPPDWPSKGKIQFNNYQVRYRPELDLVLRGITCDIGSM EKIGVVGRTGAGKSSLTNCLFRILEAAGGQIIIDGVDIASIGLHDLREKLTII PQDPILFSGSLRMNLDPFNNYSDEEIWKALELAHLKSFVASLQLGLSHEV TEAGGNLSIGQRQLLCLGRALLRKSKILVLDEATAAVDLETDNLIQTTIQN EFAHCTVITIAHRLHTIMDSDKVMVLDNGKIIECGSPEELLQIPGPFYFMA KEAGIENVNSTKF	SEQ ID No 904
CETLQFLDCICGSTTGGLGLLGLYINEKNVALINQTLESLTEYCQGPCHE NQNCIATHESNGIDIITALILNDINPLGKKRMDLVLELKNNASKLLLAIMESR HDSENAERILYNMRPKELVEVIKKAYMQGEVEFEDGENGEDGAASPRN VGHNIYILAHQLARHNKELQSMLKPGGQVDGDEALEFYAKHTAQIEIVRL DRTMEQIVFPVPSICEFLTKESKLRIYYTTERDEQGSKINDFFLRSEDLFN EMNWQKKLRAQPVLYWCARNMS	SEQ ID No 905
CETLQFLDCICGSTTGGLGLLGLYINEKNVALVNQNLESLTEYCQGPCHE NQTCIATHESNGIDIIIALILNDINPLGKYRMDLVLQLKNNASKLLLAIMESR HDSENAERILFNMRPRELVDVMKNAYNQGLECDHGDDEGGDDGVSPK DVGHNIYILAHQLARHNKLLQQMLKPGSDPDEGDEALKYYANHTAQIEIV RHDRTMEQIVFPVPNICEYLTRESKCRVFNTTERDEQGSKVNDFFQQTE DLYNEMKWQKKIRNNPALFWFSRHIS	SEQ ID No 906
NNSTVSRTSASKYENMIRYTGSPDSLRSRTPMITPDLESGVKMWHLVKN HEHGDQKEGDRGSKMVSEIYLTRLLATKGTLQKFVDDLFETIFSTAHRG SALPLAIKYMFDFLDEQADKHGIHDPHVRHTWKSNCLPLRFWVNMIKNP QFVFDIHKNSITDACLSVVAQTFMDSCSTSEHRLGKDSPSNKLLYAKDIP SYKNWVERYYSDIGKMPAISDQDMNAYLAEQSRMHMNEFNTMSALSEI FSYVGKYSEEILGPLDHDDQCGKQKLAYKLEQVITLMSLDS	SEQ ID No 907
CETLQFLDIMCGSTTGGLGLLGLYINEDNVGLVIQTLETLTEYCQGPCHE	SEQ ID No 908

NQTCIVTHESNGIDIITALILNDISPLCKYRMDLVLQLKDNASKLLLALMES RHDSENAERILISLRPQELVDVIKKAYLQEEERENSEVSPREVGHNIYILA LQLSRHNKQLQHLLKPVKRIQEEEAEGISSMLSLNNKQLSQMLKSSAPA QEEEEDPLAYYENHTSQIEIVRQDRSMEQIVFPVPGICQFLTEETKHRLF TTTEQDEQGSKVSDFFDQSSFLHNEMEWQRKLRSMPLIYWFSRRMT	
LADGSFVRCTPSENSDLFYAVPWSCGTLGFLVAAEIRIIPAKKYVKLRFEP VRGLEAICAKFTHESQRQENHFVEGLLYSLDEAVIMTGVMTDEAEPSKL NSIGNYYKPWFFKHVENYLKTNREGLEYIPLRHYYHRHTRSIFWELQDIIP FGNNPIFRYLFGWMVPPKISLLKLTQGETLRKLYEQHHVVQDMLVPMKC LQQALHTFQNDIHVYPIWLCPFILPSQPGLVHPKGNEAELYIDIGAYGEPR VKHFEARSCMRQLEKFVRSVHGFQMLYADCYMNREEFWEMFDGSLYH KLREKLGCQDAFPEVYDKICKAARH	SEQ ID No 909
NPEYFSASDMYVPDEWEVPREQISIIRELGQGSFGMVYEGLARGLEAGE ESTPVALKTVNELASPRECIEFLKEASVMKAFKCHHVVRLLGVVSQGQP TLVIMELMTRGDLKSHLRSLRPEAENNPGLPQPALGEMIQMAGEIADGM AYLAANKFVHRDLAARNCMVSQDFTVKIGDFGMTRDVYETDYYRKGGK GLLPVRWMAPESLKDGIFTTHSDVWSFGVVLWEIVTLAEQPYQGLSNEQ VLKFVMDGGVLEELEGCPLQLQELMSRCWQPNPRLRPSFTHILDSIQEE LRPSFRLLSFYYSPECRGARGSLPTTDAEPDSSPTPRDCSPQNGGPGH	SEQ ID No 910
PAPSALTPKILDLLVHAISINSAYTTKILPPEKEGALPRQVGNKTECALLGF VLDLKRDFQPVREQIPEDKLYKVYTFNSVRKSMSTVIRMPDGGFRLFSK GASEILLKKCTNILNSNGELRGFRPRDRDDMVRKIIEPMACDGLRTICIAY RDFSAGQEPDWDNENEVVGDLTCIAVVGIEDPVRPEVPEAIRKCQRAGI TVRMVTGDNINTARAIAAKCGIIQPGEDFLCLEGKEFNRRIRNEKGEIEQE RLDKVWPKLRVLARSSPTDKHTLVKGIIDSTTGEQRQVVAVTGDGTNDG PALKKADVGFAMGIAGTDVAKEASDIILTDDNFTSIVKAVMWGRNVYDSI	SEQ ID No 911
GGDQLNCHFGSILHTTGLQYRDFIHVSFHDKVYELPFLVALDHRKESVVV AVRGTMSLQDVLTDLSAESEVLDVECEVQDRLAHKGISQAARYVYQRLI NDGILSQAFSIAPEYRLVIVGHSLGGGAAALLATMLRAAYPQVRCYAFSP PRGLWSKALQEYSQSFIVSLVLGKDVIPRLSVTNLEDLKRRILRVVAHCN KPKYKILLHGLWYELFGGNPNNLPTELDGGDQEVLTQPLLGEQSLLTRW SPAYSFSSDSPLDSSPKYPPLYPPGRIIHLQEEGASGRFGCCSAAHYSA KWSHEAEFSKILIGPKMLTDHMPDILMRALDSVVSDRAACVSCPAQGVS SVDVA	SEQ ID No 912
PYSQRPKAEDMDLEWRQGRMTRIILQDEDVTTKIECDWKRLNSLAHYQ VTDGSLVALVPKQVSAYNMANSFTFTRSLSRYESLLRTASSPDSLRSRA	SEQ ID No 913

PMITPDQETGTKLWHLVKNHDHADHREGDRGSKMVSEIYLTRLLATKGT LQKFVDDLFETVFSTAHRGSALPLAIKYMFDFLDEQADQRQISDPDVRHT WKSNCLPLRFWVNVIKNPQFVFDIHKNSITDACLSVVAQTFMDSCSTSE HRLGKDSPSNKLLYAKDIPNYKSWVERYYRDIAKMASISDQDMDAYLVE QSRLHASDFSVLSALNELYFYVTKYRQEILTALDRDASCRKHKLRQKLEQ IISLVSSDS	
KSDAAMTVAVKMLKPSAHLTEREALMSELKVLSYLGNHMNIVNLLGACTI GGPTLVITEYCCYGDLLNFLRRKRDSFICSKQEDHAEAALYKNLLHSKES SCSDSTNEYMDMKPGVSYVVPTKADKRRSVRIGSYIERDVTPAIMEDDE LALDLEDLLSFSYQVAKGMAFLASKNCIHRDLAARNILLTHGRITKICDFG LARDIKNDSNYVVKGNARLPVKWMAPESIFNCVYTFESDVWSYGIFLWE LFSLGSSPYPGMPVDSKFYKMIKEGFRMLSPEHAPAEMYDIMKTCWDA DPLKRPTFKQIVQLIEKQISESTNHIYSNLANCSPNRQKPVVDHSVRINSV GSTASSSQPLLVHDDV	SEQ ID No 914
HVPKSYRRRRRHKRKTGHKEKKEKERISENYSDKSDIENADESSSSILKP LISPAAERIRFILGEEDDSPAPPQLFTELDELLAVDGQEMEWKETARWIK FEEKVEQGGERWSKPHVATLSLHSLFELRTCMEKGSIMLDREASSLPQL VEMIVDHQIETGLLKPELKDKVTYTLLRKHRHQTKKSNLRSLADIGKTVSS ASRMFTNPDNGSPAMTHRNLTSSSLNDISDKPEKDQLKNKFMKKLPRD AEASNVLVGEVDFLDTPFIAFVRLQQAVMLGALTEVPVPTRFLFILLGPKG KAKSYHEIGRAIATLMSDEVFHDIAYKAKDRHDLIAGIDEFLDEVIVLPPGE WDPAIRIEPPKSLPSSDKRKNMYSGGENVQMNGDTPHDGGHGGGGHG DCEELQRTGRFCGGLIKDIKRKAPFFASDFYDALNIQ	SEQ ID No 915
WIPDGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGVGSPYVSRLLGIC LTSTVQLVTQLMPYGCLLDHVRENRGRLGSQDLLNWCMQIAKGMSYLE DVRLVHRDLAARNVLVKSPNHVKITDFGLARLLDIDETEYHADGGKVPIK WMALESILRRRFTHQSDVWSYGVTVWELMTFGAKPYDGIPAREIPDLLE KGERLPQPPICTIDVYMIMVKCWMIDSECRPRFRELVSEFSRMARDPQR FVVIQNEDLGPASPLDSTFYRSLLEDDDMGDLVDAEEYLVPQQGFFCPD PAPGAGGMVHHRHRSSSTRSGGGDLTLGLEPSEEEAPRSPLAPSEGA GSDVFDGDLGMGAAKGLQSLPTHDPSPLQRYSEDPTVPLPSETDGYVA PLTCSPQPEYVNQPDVRPQPPSPREGPLPAARPAGATLERPKTLSPGK NGVVKDVFAFGGAVENPEYLTPQGGAAPQPHPPPAFSPAFDNLYYWD QDPPERGAPPSTFKGTPTAENPEYLGLDVPV	SEQ ID No 916
IMDPDEVPLDEQCERLPYDASKWEFARERLKLGKSLGRGAFGKVVQAS AFGIKKSPTCRTVAVKMLKEGATASEYKALMTELKILTHIGHHLNVVNLLG	SEQ ID No 917

ACTKQGGPLMVIVEYCKYGNLSNYLKSKRDLFFLNKDAALHMEPKKEKM EPGLEQGKKPRLDSVTSSESFASSGFQEDKSLSDVEEEEDSDGFYKEPI TMEDLISYSFQVARGMEFLSSRKCIHRDLAARNILLSENNVVKICDFGLAR DIYKNPDYVRKGDTRLPLKWMAPESIFDKIYSTKSDVWSYGVLLWEIFSL GGSPYPGVQMDEDFCSRLREGMRMRAPEYSTPEIYQIMLDCWHRDPK ERPRFAELVEKLGDLLQANVQQDGKDYIPINAILTGNSGFTYSTPAFSED FFKESISAPKFNSGSSDDVRYVNAFKFMSLERIKTFEELLPNATSMFDDY QGDSSTLLASPMLKRFTWTDSKPKASLKIDLRVTSKSKESGLSDVSRPS FCHSSCGHVSEGKRRFTYDHAELERKIACCSPPPDYNSVVLYSTPPI	
IMDPGEVPLEEQCEYLSYDASQWEFPRERLHLGRVLGYGAFGKVVEAS AFGIHKGSSCDTVAVKMLKEGATASEHRALMSELKILIHIGNHLNVVNLLG ACTKPQGPLMVIVEFCKYGNLSNFLRAKRDAFSPCAEKSPEQRGRFRA MVELARLDRRRPGSSDRVLFARFSKTEGGARRASPDQEAEDLWLSPLT MEDLVCYSFQVARGMEFLASRKCIHRDLAARNILLSESDVVKICDFGLAR DIYKDPDYVRKGSARLPLKWMAPESIFDKVYTTQSDVWSFGVLLWEIFS LGASPYPGVQINEEFCQRLRDGTRMRAPELATPAIRRIMLNCWSGDPKA RPAFSELVEILGDLLQGRGLQEEEEVCMAPRSSQSSEEGSFSQVSTMAL HIAQADAEDSPPSLQRHSLAARYYNWVSFPGCLARGAETRGSSRMKTF EEFPMTPTTYKGSVDNQTDSGMVLASEEFEQIESRHRQESGFSCKGPG QNVAVTRAHPDSQGRRRRPERGARGGQVFYNSEYGELSEPSEEDHCS PSARVTFFTDNSY	SEQ ID No 918
VMDPDELPLDEHCERLPYDASKWEFPRDRLKLGKPLGRGAFGQVIEAD AFGIDKTATCRTVAVKMLKEGATHSEHRALMSELKILIHIGHHLNVVNLLG ACTKPGGPLMVIVEFCKFGNLSTYLRSKRNEFVPYKTKGARFRQGKDYV GAIPVDLKRRLDSITSSQSSASSGFVEEKSLSDVEEEEAPEDLYKDFLTL EHLICYSFQVAKGMEFLASRKCIHRDLAARNILLSEKNVVKICDFGLARDI YKDPDYVRKGDARLPLKWMAPETIFDRVYTIQSDVWSFGVLLWEIFSLG ASPYPGVKIDEEFCRRLKEGTRMRAPDYTTPEMYQTMLDCWHGEPSQ RPTFSELVEHLGNLLQANAQQDGKDYIVLPISETLSMEEDSGLSLPTSPV SCMEEEEVCDPKFHYDNTAGISQYLQNSKRKSRPVSVKTFEDIPLEEPE VKVIPDDNQTDSGMVLASEELKTLEDRTKLSPSFGGMVPSKSRESVASE GSNQTSGYQSGYHSDDTDTTVYSSEEAELLKLIEIGVQTGSTAQILQPDS GTTLSSPPV	SEQ ID No 919
FEPTVERGELVVRYRVRKSYSRRTTEATLNSLGISEELKEKLRDVMVDR HKVALGKTLGEGEFGAVMEGQLNQDDSILKVAVKTMKIAICTRSELEDFL SEAVCMKEFDHPNVMRLIGVCFQGSERESFPAPVVILPFMKHGDLHSFL	SEQ ID No 920

LYSRLGDQPVYLPTQMLVKFMADIASGMEYLSTKRFIHRDLAARNCMLN ENMSVCVADFGLSKKIYNGDYYRQGRIAKMPVKWIAIESLADRVYTSKS DVWSFGVTMWEIATRGQTPYPGVENSEIYDYLRQGNRLKQPADCLDGL YALMSRCWELNPQDRPSFTELREDLENTLKALPPAQEPDEILYVNMDEG GGYPEPPGAAGGADPPTQPDPKDSCSCLTAAEVHPAGRYVLCPSTTPS PAQPADRGSPAAPGQEDGA	
WVPEGETVKIPVAIKILNETTGPKANVEFMDEALIMASMDHPHLVRLLGV CLSPTIQLVTQLMPHGCLLEYVHEHKDNIGSQLLLNWCVQIAKGMMYLE ERRLVHRDLAARNVLVKSPNHVKITDFGLARLLEGDEKEYNADGGKMPI KWMALECIHYRKFTHQSDVWSYGVTIWELMTFGGKPYDGIPTREIPDLL EKGERLPQPPICTIDVYMVMVKCWMIDADSRPKFKELAAEFSRMARDPQ RYLVIQGDDRMKLPSPNDSKFFQNLLDEEDLEDMMDAEEYLVPQAFNIP PPIYTSRARIDSNRSEIGHSPPPAYTPMSGNQFVYRDGGFAAEQGVSVP YRAPTSTIPEAPVAQGATAEIFDDSCCNGTLRKPVAPHVQEDSSTQRYS ADPTVFAPERSPRGELDEEGYMTPMRDKPKQEYLNPVEENPFVSRRKN GDLQALDNPEYHNASNGPPKAEDEYVNEPLYLNTFANTLGKAEYLKNNI LSMPEKAKKAFDNPDYWNHSLPPRSTLQHPDYLQEYSTKYFYKQNGRI RPIVAENPEYLSEFSLKPGTVLPPPPYRHRNTVV	SEQ ID No 921
DLSNKINEMKTFNSPNLKDGRFVNPSGQPTPYATTQLIQSNLSNNMNNG SGDSGEKHWKPLGQQKQEVAPVQYNIVEQNKLNKDYRANDTVPPTIPY NQSYDQNTGGSYNSSDRGSSTSGSQGHKKGARTPKVPKQGGMNWAD LLPPPPAHPPPHSNSEEYNISVDESYDQEMPCPVPPARMYLQQDELEEE EDERGPTPPVRGAASSPAAVSYSHQSTATLTPSPQEELQPMLQDCPEE TGHMQHQPDRRRQPVSPPPPPRPISPPHTYGYISGPLVSDMDTDAPEE EEDEADMEVAKMQTRRLLLRGLEQTPASSVGDLESSVTGSMINGWGSA SEEDNISSGRSSVSSSDGSFFTDADFAQAVAAAAEYAGLKVARRQMQD AAGRRHFHASQCPRPTSPVSTDSNMSAAVMQKTRPAKKLKHQPGHLR RETYTDDLPPPPVPPPAIKSPTAQSKTQLEVRPVVVPKLPSMDARTDRS SDRKGSSYKGREVLDGRQVVDMRTNPGDPREAQEQQNDGKGRGNKA AKRDLPPAKTHLIQEDILPYCRPTFPTSNNPRDPSSSSSMSSRGSGSRQ REQANVGRRNIAEMQVLGGYERGEDNNEELEETES	SEQ ID No 922
EPQDGCHPGDSVERSVTCLPSASDENENQLDGDGHEHLTSSDSAMGK PQVSEQDSLNNNESCTLSCEVAAGENLQNTLCEASRDEQAFLGKDKKIP GKRSPRSKKGTAKKIPPGLFSGDIAPLMQEKVLSAVTYAVDDEEAAEVN ANEQPEAPKLVLQSLFSLIRGEVEQLDSRALPLCLHQIAESYFQEEDYEK AMKFIQLERLYHEQLLANLSAIQEQWETKWKTVQPHTVTALRNSEKGFN	SEQ ID No 923

GEDFERLTKICATHQDPLLSKHKIAAVEKSQERKCSTQLLVSEDPKEGGA TTKESESKTCLGTESSKESQHTVEPLGSSPCCHQMDVQTDSPSLSVTA GKDHMEELLCSAEATLALHTQSSETAGSPSGPDSSEDACEDDSRLQLA QTEACQDVARIEGIAEDPKVFLSSKSKTEPLISPGCDRIPPALISEGKYSQ AQRKELRLPLRDASEALPTDQLENNELNELQQPDLTDSDGKSPQAQAD SDGSENVLCGNNQISDLGILLPEVCMAPEEKGDKDDQLNKETEDYLNSL LEGCLKDTEDSLSYEDNQDDDSDLLQDLSPEEASYSLQENLPSDESCLS LDDLAKRIEIAEVVPTEGLVSILKKRNDTVGDHPAQMQHKPSKRRVRFQE IDDSLDQDEVGGGS	
SKNIPTTKDVEPLLEIDGDIRNFEVFLSSRTPVLVARDVKVFLPCTVNLDP KLREIIADVRAAREQISIGGLAYPPLPLHEGPPRAPSGYSQPPSVCSSTSF NGPFAGGVVSPQPHSSYYSGMTGPQHPFYNRPFFAPYLYTPRYYPGG SQHLISRPSVKTSLPRDQNNGLEVIKEDAAEGLSSPTDSSRGSGPAPGP VVLLNSLNVDAVCEKLKQIEGLDQSMLPQYCTTIKKANINGRVLAQCNID ELKKEMNMNFGDWHLFRSTVLEMRNAESHVVPEDPRFLSESSSGPAPH GEPARRASHNELPHTELSSQTPYTLNFSFEELNTLGLDEGAPRHSNLSW QSQTRRTPSLSSLNSQDSSIEISKLTDKVQAEYRDAYREYIAQMSQLEG GPGSTTISGRSSPHSTYYMGQSSSGGSIHSNLEQEKGKDSEPKPDDGR KSFLMKRGDVIDYSSSGVSTNDASPLDPITEEDEKSDQSGSKLLPGKKS SERSSLFQTDLKLKGSGLRYQKLPSDEDESGTEESDNTPLLKDDKDRKA EGKVERVPKSPEHSAEPIRTFIKAKEYLSDALLDKKDSSDSGVRSSESSP NHSLHNEVADDSQLEKANLIELEDDSHSGKRGIPHSLSGLQDPIIARMSIC SEDKKSPSECSLIASSPEENWPACQKAYNLNRTPSTVTLNNNSAPANRA NQNFDEMEGIRETSQVILRPSSSPNPTTIQNENLKSMTHKRSQRSSYTR LSKDPPELHAAASSESTGFGEERESIL	SEQ ID No 924
WSLGVTLWELFDNAAQPYSNLSNLDVLNQVIRERDTKLPKPQLEQPYSD RWYEVLQFCWLSPEKRPAAEDVHRLLTYLRLQSQRDSEVDFEQQWNA LKPNTNSRDSSNNAAFPILDHFARDRLGREMEEVLTVTETSQGLSFEYV WEAAKHDHFDERSRGHLDEGLSYTSIFYPVEVFESSLSDPGPGKQDDS GQDVPLRVPGVVPVFDAHNLSVGSDYYIQLEEKSGSNLELDYPPALLTT DMDNPERTGPELSQLTALRSVELEESSTDEDFFQSSTDPKDSSLPGDLH VTSGPESPFNNIFNDVDKSEDLPSHQKIFDLMELNGVQADFKPATLSSSL DNPKESVITGHFEKEKPRKIFDSEPLCLSDNLMHQDNFDPLNVQELSENF LFLQEKNLLKGSLSSKEHINDLQTELKNAGFTEAMLETSCRNSLDTELQF AENKPGLSLLQENVSTKGDDTDVMLTGDTLSTSLQSSPEVQVPPTSFET EETPRRVPPDSLPTQGETQPTCLDVIVPEDCLHQDISPDAVTVPVEILST	SEQ ID No 925

DARTHSLDNRSQDSPGESEETLRLTESDSVLADDILASRVSVGSSLPEL GQELHNKPFSEDHHSHRRLEKNLEAVETLNQLNSKDAAKEAGLVSALSS DSTSQDSLLEDSLSAPFPASEPSLETPDSLESVDVHEALLDSLGSHTPQK LVPPDKPADSGYETENLESPEWTLHPAPEGTADSEPATTGDGGHSGLP PNPVIVISDAGDGHRGTEVTPETFTAGSQGSYRDSAYFSDNDSEPEKRS EEVPGTSPSALVLVQEQPLPEPVLPEQSPAAQDSCLEARKSQPDESCLS ALHNSSDLELRATPEPAQTGVPQQVHPTEDEASSPWSVLNAELSSGDD FETQDDRPCTLASTGTNTNELLAYTNSALDKSLSSHSEGPKLKEPDIEGK YLGKLGVSGMLDLSEDGMDADEEDENSDDSDEDLRAFNLHSLSSESED ETEHPVPIILSNEDGRHLRSLLKPTAANAPDPLPEDWKKEKKAVTFFDDV TVYLFDQETPTKELGPCGGEACGPDLSGPAPASGSPYLSRCINSESSTD EEGGGFEWDDDFSPDPFMSKTTSNLLSSKPSLQTSKYFSPPPPARSTE QSWPHSAPYSRFSISPANIASFSLTHLTDSDIEQGGSSEDGEKD	

In some embodiments, variants of the sequence $((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$ have at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% amino acid sequence identity with said sequence.

In some embodiments, variants of the sequence $((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$ have at least 95% amino acid sequence identity with said sequence.

In some embodiments, variants of the sequence $((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$ have at least 99% amino acid sequence identity with said sequence.

In some embodiments, variants of the sequence $((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$ have substantially the same activity as the non-variant sequence. In some embodiments, substantially the same activity refers to at least 80%, 85%, 90%, 95% of the activity of the non-variant sequence.

In some embodiments, substantially the same activity refers to at least 80%, 85%, 90%, 95% of the activity of the non-variant sequence as measured by monitoring the luciferase activity in reporter cells comprising a P-CAR and an N-CAR comprising the intracellular domain to be tested and incorporating inducible NFAT- or NfkB-regulated luciferase expression, such as for example as disclosed in Example 3 below.

Transmembrane domain of the N-CAR

With respect to the transmembrane domain, in various embodiments, a N-CAR can be designed to comprise a transmembrane domain that is attached to the extracellular domain of the N-CAR. A transmembrane domain can include one or more additional amino acids adjacent to the transmembrane region, e.g., one or more amino acid associated with the

extracellular region of the protein from which the transmembrane was derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the extracellular region) and/or one or more additional amino acids associated with the intracellular region of the protein from which the transmembrane protein is derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the intracellular region). In one aspect, the transmembrane domain is one that is associated with one of the other domains of the N-CAR. In some instances, the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins, e.g., to minimize interactions with other members of the receptor complex. In one aspect, the transmembrane domain is capable of homodimerization with another CAR on the CAR T-cell surface. In a different aspect the amino acid sequence of the transmembrane domain may be modified or substituted so as to minimize interactions with the binding domains of the native binding partner present in the same CAR T-Cell.

The transmembrane domain may be derived either from a natural or from a recombinant source. Where the source is natural, the domain may be derived from any membrane-bound or transmembrane protein. In one aspect the transmembrane domain is capable of signaling to the intracellular domain(s) whenever the N-CAR has bound to a target. A transmembrane domain of particular use in this invention may include at least the transmembrane region(s) of e.g., the alpha, beta or zeta chain of the T-cell receptor, PD-1, 4-1BB, OX40, ICOS, CTLA-4, LAG3, 2B4, BTLA4, TIM-3, TIGIT, SIRPA, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154.

In some embodiment, the transmembrane domain of the N-CAR includes at least the transmembrane region(s) of PD-1 or CD28alpha.

In some embodiments, the transmembrane domain can be attached to the extracellular domain of the N-CAR, via a hinge, e.g., a hinge from a human protein. For example, in one embodiment, the hinge can be a human Ig (immunoglobulin) hinge, e.g., a PD-1 hinge, an IgG4 hinge, or a CD8alpha hinge.

In some embodiments, the transmembrane domain may be recombinant, in which case it will comprise predominantly hydrophobic residues such as leucine and valine. In one aspect a triplet of phenylalanine, tryptophan and valine can be found at each end of a recombinant transmembrane domain.

Optionally, a short oligo- or polypeptide linker, between 2 and 10 amino acids in length may form the linkage between the transmembrane domain and the cytoplasmic region of the N-CAR. A glycine-serine doublet provides a particularly suitable linker. For example, in one aspect, the linker comprises the amino acid sequence of GGGGSGGGGS. In some embodiments, the linker is encoded by a nucleotide sequence of GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC.

Extracellular domain of the N-CAR

The antigen binding domain can be any domain that binds to the off-tissue antigen including but not limited to a monoclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, and a functional fragment thereof, including but not limited to a single-domain antibody such as a heavy chain variable domain (VH), a light chain variable domain (VL) and a variable domain (VHH) of camelid derived nanobody, and to an alternative scaffold known in the art to function as antigen binding domain, such as a recombinant fibronectin domain, and the like. In some instances, it is beneficial for the antigen binding domain to be derived from the same species in which the N-CAR will ultimately be used in. For example, for use in humans, it may be beneficial for the antigen binding domain of the N-CAR to comprise human or humanized residues for the antigen binding domain of an antibody or antibody fragment.

A humanized antibody can be produced using a variety of techniques known in the art, including but not limited to, CDR-grafting (see, e.g., European Patent No. EP 239,400; International Publication No. WO 91/09967; and U.S. Pat. Nos. 5,225,539, 5,530,101, and 5,585,089, each of which is incorporated herein in its entirety by reference), veneering or resurfacing (see, e.g., European Patent Nos. EP 592,106 and EP 519,596; Padlan, 1991, Molecular Immunology, 28(4/5):489-498; Studnicka et al., 1994, Protein Engineering, 7(6):805-814; and Roguska et al., 1994, PNAS, 91:969-973, each of which is incorporated herein by its entirety by reference), chain shuffling (see, e.g., U.S. Pat. No. 5,565,332, which is incorporated herein in its entirety by reference), and techniques disclosed in, e.g., U.S. Patent Application Publication No. US2005/0042664, U.S. Patent Application Publication No. US2005/0048617, U.S. Pat. No. 6,407,213, U.S. Pat. No. 5,766,886, International Publication No. WO 9317105, Tan et al., J. Immunol., 169: 1119-25 (2002), Caldas et al., Protein Eng., 13(5):353-60 (2000), Morea et al., Methods, 20(3):267-79 (2000), Baca et al., J. Biol. Chem., 272(16): 10678-84 (1997), Roguska et al., Protein Eng., 9(10):895-904 (1996), Couto et al., Cancer Res., 55 (23 Supp):5973s-5977s (1995), Couto et al., Cancer Res., 55(8): 1717-22 (1995), Sandhu J S, Gene, 150(2):409-10 (1994), and Pedersen et al.,

J. Mol. Biol., 235(3):959- 73 (1994), each of which is incorporated herein in its entirety by reference. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, for example improve, antigen binding. These framework substitutions are identified by methods well-known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Pat. No. 5,585,089; and Riechmann et al., 1988, Nature, 332:323, which are incorporated herein by reference in their entireties.).

In some aspects, the portion of an N-CAR that comprises an antibody fragment is humanized with retention of high affinity for the target antigen and other favorable biological properties. According to one aspect of the invention, humanized antibodies and antibody fragments are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, e.g., the analysis of residues that influence the ability of the candidate immunoglobulin to bind the target antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody or antibody fragment characteristic, such as increased affinity for the target antigen, is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding.

In some embodiments, the antibody binding domain is a fragment, e.g., a single chain variable fragment (scFv). In some embodiments, the antibody binding domain is a Fv, a Fab, a (Fab')2, or a bi-functional (e.g. bi-specific) hybrid antibody (e.g., Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). In some embodiments, the antigen binding domain of the N-CAR of the invention binds an off-tissue antigen with wild-type or enhanced affinity.

In some instances, scFvs can be prepared according to method known in the art (see, for example, Bird et al., (1988) Science 242:423-426 and Huston et al., (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). ScFv molecules can be produced by linking VH and VL regions together using flexible polypeptide linkers. The scFv molecules comprise a linker (e.g., a Ser-Gly linker) with an optimized length and/or amino acid composition. The linker length can

greatly affect how the variable regions of a scFv fold and interact. In fact, if a short polypeptide linker is employed (e.g., between 5-10 amino acids) intrachain folding is prevented. Interchain folding is also required to bring the two variable regions together to form a functional epitope binding site. For examples of linker orientation and size see, e.g., Hollinger et al. 1993 Proc Natl Acad. Sci. U.S.A. 90:6444-6448, U.S. Patent Application Publication Nos. 2005/0100543, 2005/0175606, 2007/0014794, and PCT publication Nos. WO2006/020258 and WO2007/024715, is incorporated herein by reference.

An scFv can comprise a linker of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, or more amino acid residues between its VL and VH regions. The linker sequence may comprise any naturally occurring amino acid. In some embodiments, the linker sequence comprises amino acids glycine and serine. In another embodiment, the linker sequence comprises sets of glycine and serine repeats such as $(Gly_4Ser)_n$, where n is a positive integer equal to or greater than 1. In one embodiment, the linker can be $(Gly_4Ser)_4$ or $(Gly_4Ser)_3$. Variation in the linker length may retain or enhance activity, giving rise to superior efficacy in activity studies.

In a preferred embodiment, the antigen binding domain of the N-CAR comprises an scFv.

The off-tissue antigen recognized by the antigen binding domain of the N-CAR is preferably an antigen that is not present or present at low level on the tumour cells targeted by the P-CAR.

The below table provide examples of combinations of N-CAR and P-CAR antigens.

P-CAR Antigen	N-CAR Antigen
CD33	Antigens specifically expressed in dendritic cells and/or haematopoetic stem cells such as ITGAX, CD1E, CD34, CD1C, CD123, CD141
FLT3	Antigens specifically expressed in haematopoetic stem cells such as CD34 or specifically expressed in Brain cerebellum such as ZP2, GABRA6, CRTAM, GRM4, MDGA1
MSLN	Antigens specifically expressed in lung such as SFTPC, ROS1, SLC6A4, AGTR2
MUC16	Antigens specifically expressed in salivary gland such as LRRC26, HTR3A, TMEM211, MRGPRX3
MUC17	Antigens specifically expressed in colon & small intestine such as MEP1B, TMIGD1, CEACAM20, ALPI

N-CAR antigens could also include antigens that are independent of the antigen that the P-CAR is targeting and that are down-regulated in tumor of interest, but present in all normal tissues of concern. Examples of such antigens for pancreatic ductal adenocarcinoma are TMPRSS11B, CYP17A1 and ATP4B and examples of such antigens for kidney clear cell carcinoma are GP2, MUC21, CLCA4 and SLC27A6.

The present invention encompasses a recombinant DNA construct comprising sequences encoding an N-CAR as defined above, wherein the N-CAR comprises an extracellular domain such as an antibody fragment that binds specifically to an off-tumor antigen, and wherein the sequence of the extracellular domain is contiguous with and in the same reading frame as a nucleic acid sequence encoding a transmembrane domain and an intracellular domain. In some embodiments, an exemplary N-CAR construct comprises an optional leader sequence, an extracellular off-tissue antigen binding domain, a hinge, a transmembrane domain, and an intracellular inhibitory signaling domain.

The present invention includes retroviral and lentiviral vector constructs expressing an N-CAR that can be directly transduced into a cell.

The present invention also includes an RNA construct that can be directly transfected into a cell. A method for generating mRNA for use in transfection involves in vitro transcription (IVT) of a template with specially designed primers, followed by polyA addition, to produce a construct containing 3' and 5' untranslated sequence ("UTR"), a 5' cap and/or Internal Ribosome Entry Site (IRES), the nucleic acid to be expressed, and a polyA tail, typically 50-2000 bases in length. RNA so produced can efficiently transfect different kinds of cells. In one embodiment, the template includes sequences for the N-CAR. In an embodiment, an RNA N-CAR vector is transduced into a T-cell by electroporation.

In some embodiments, the invention relates to an isolated immune cell comprising an N-CAR as defined herein. In some embodiments, the invention further relates to immune cells comprising an N-CAR as defined herein and a P-CAR. In some embodiments, said immune cell is a T-cell. In some embodiments, said T-cell is a human T-cell.

The term “positive signaling Chimeric Antigen Receptor" or alternatively a "P-CAR" refers to a recombinant polypeptide construct comprising at least an extracellular domain comprising an antigen binding domain, a transmembrane domain and an intracellular domain (also referred to herein as a “cytoplasmic signaling domain” or "an intracellular signaling domain") comprising a functional signaling domain derived from a stimulatory molecule as defined

below. In some embodiments, the stimulatory molecule is the zeta chain associated with the T-cell receptor complex. In some embodiments, the cytoplasmic signaling domain further comprises one or more functional signaling domains derived from at least one costimulatory molecule as defined below. In some embodiments, the costimulatory molecule is chosen from 4-1BB (i.e., CD137), CD27 and/or CD28. In some embodiments, the P-CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a stimulatory molecule. In some embodiments, the P-CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a co- stimulatory molecule and a functional signaling domain derived from a stimulatory molecule. In some embodiments, the P-CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising two functional signaling domains derived from one or more co- stimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. In some embodiments, the P-CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising at least two functional signaling domains derived from one or more co-stimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. In some embodiments the P-CAR comprises an optional leader sequence at the amino-terminus (N-ter) of the P-CAR fusion protein. In some embodiments, the P-CAR further comprises a leader sequence at the N-terminus of the extracellular antigen recognition domain, wherein the leader sequence is optionally cleaved from the antigen recognition domain (e.g., aa scFv) during cellular processing and localization of the P-CAR to the cellular membrane.

The extracellular portion of a P-CAR comprising an antibody or antibody fragment thereof may exist in a variety of forms where the antigen binding domain is expressed as part of a contiguous polypeptide chain including, for example, a single domain antibody fragment (sdAb), a single chain antibody (scFv) and a humanized antibody (Harlow et al., 1999, In: Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, NY; Harlow et al., 1989, In: Antibodies: A Laboratory Manual, Cold Spring Harbor, New York; Houston et al, 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; Bird et al., 1988, Science 242:423-426).

The term "stimulatory molecule," refers to a molecule expressed by a T-cell that provides the positive cytoplasmic signaling sequence(s) that regulate positive activation of the TCR complex in a stimulatory way for at least some aspect of the T-cell signaling pathway. In

some embodiments, the positive signal is initiated by, for instance, binding of a TCR/CD3 complex with an MHC molecule loaded with peptide, and which leads to mediation of a T-cell response, including, but not limited to, proliferation, activation, differentiation, and the like. A positive cytoplasmic signaling sequence (also referred to as a "positive signaling domain" or positive intracellular signaling domain) that acts in a stimulatory manner may contain a signaling motif which is known as immunoreceptor tyrosine- based activation motif or ITAM. Examples of an ITAM containing positive cytoplasmic signaling sequence includes, but is not limited to, those derived from TCR zeta (or CD3zeta), FcR gamma, FcR beta, CD3 gamma, CD3 delta , CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (also known as "ICOS") and CD66d.

In some aspect, the intracellular signaling domain of the P-CAR can comprise a positive intracellular signaling domain. The positive intracellular signaling domain generates a signal that promotes an immune effector function of the P-CAR containing cell, e.g., a P-CAR T-cell. Examples of immune effector function, e.g., in a P-CAR T-cell, include cytolytic activity and helper activity, including the secretion of cytokines.

The term "costimulatory molecule" refers to the cognate binding partner on a T-cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T-cell, such as, but not limited to, proliferation. Costimulatory molecules are cell surface molecules other than antigen receptors or their ligands that are required for an efficient immune response. Costimulatory molecules include, but are not limited to an MHC class I molecule, BTLA and a Toll ligand receptor, as well as OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18) and 4-IBB (CD137).

A costimulatory intracellular signaling domain can be the intracellular portion of a costimulatory molecule. A costimulatory molecule can be represented in the following protein families: TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), and activating NK cell receptors. Examples of such molecules include CD27, CD28, 4-1BB (CD137), OX40, GITR, CD30, CD40, ICOS, BAFFR, HVEM, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, and a ligand that specifically binds with CD83, and the like.

P-CARs and immune cells comprising them have been extensively disclosed and can be prepared by the skilled person according to known methods. For example, methodologies to prepare P-CAR and cells comprising such P-CARs are disclosed in US7446190,

WO2008/121420, US8252592, US20140024809, WO2012/079000, WO2014153270, WO2012/099973, WO2014/011988, WO2014/011987, WO2013/067492, WO2013/070468, WO2013/040557, WO2013/126712, WO2013/126729, WO 2013/126726, WO2013/126733, US8399645, US20130266551, US20140023674, WO2014039523, US7514537, US8324353, WO2010/025177, US7446179, WO2010/025177, WO2012/031744, WO2012/136231A1, WO2012/050374A2, WO2013074916, WO2009/091826A3, WO2013/176915 or WO/2013/059593 which are all incorporated herein in their entirety by reference. Immune cells comprising a P-CAR and a N-CAR can be prepared by the skilled person according to the methodologies disclosed in the above mentioned references. In a preferred embodiment, immune cells comprising a P-CAR and a N-CAR can be prepared by the skilled person according to the methodologies disclosed in WO2013/176915.

In some embodiments, the method of engineering T-cells of invention can comprise:
(a) modifying T-cells by inactivating at least:
- A first gene expressing a target for an immunosuppressive agent, and
- A second gene encoding a component of the T-cell receptor (TCR)
(b) Expanding said cells, optionally in presence of said immunosuppressive agent.

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 u-chain blocker, an inhibitor of inosine monophosphate dehydrogenase, an inhibitor of dihydrofolic acid reductase, a corticosteroid or an immunosuppressive antimetabolite.

In a particular embodiment, the genetic modification step of the method relies on the inactivation of one gene selected from the group consisting of CD52, GR, TCR alpha and TCR beta. In another embodiment, 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.

In some embodiments, the method of engineering T-cells of invention can comprise
(a) Providing a T-cell, preferably from a cell culture or from a blood sample;
(b) Selecting a gene in said T-cell expressing a target for an immunosuppressive agent;

(c) Transforming said T cell with nucleic acid encoding a rare-cutting endonuclease able to selectively inactivate by DNA cleavage, preferably by double-strand break respectively:
said gene encoding a target for said immunosuppressive agent, and
at least one gene encoding a component of the T-cell receptor (TCR);
(d) Expressing said rare-cutting endonucleases into said T-cells;
(e) Sorting the transformed T-cells, which do not express TCR on their cell surface;
(f) Expanding said cells, optionally in presence of said immunosuppressive agent.

In some embodiment, the method to engineer cell of the invention further comprises one or more additional genomic modification step. By additional genomic modification step, can be intended the introduction into cells to engineer of one or more protein of interest. Said protein of interest can be a P-CAR and/or an N-CAR.

In some embodiment the P-CAR is a Multi-chain Chimeric Antigen Receptor particularly adapted to the production and expansion of engineered T-cells, the multi-chain CAR comprising at least two of the following components:
a) one polypeptide comprising the transmembrane domain of FcsRI 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 FccRI beta chain and/or
c) two polypeptide s comprising each a part of intracytoplasmic tail and the transmembrane domain of FccRI gamma chain, whereby different polypeptides multimerize together spontaneously to form dimeric, trimeric or tetrameric CAR.
Example of tetrameric P-CARs are illustrated in Figure 3 of WO2013176915 and different versions of multichain P-CARs are represented in Figure 4 of WO2013176915. Such P-CAR can be expressed in a T-Cell obtained using the above disclosed method together with a N-CAR according to the present disclosure to obtain a T-cell according to the invention.

In some embodiment the invention relates to an immune cell comprising a N-CAR as defined herein and a P-CAR as defined in any of US7446190, WO2008/121420, US8252592, US20140024809, WO2012/079000, WO2014153270, WO2012/099973, WO2014/011988, WO2014/011987, WO2013/067492, WO2013/070468, WO2013/040557, WO2013/126712, WO2013/126729, WO 2013/126726, WO2013/126733, US8399645, US20130266551, US20140023674, WO2014039523, US7514537, US8324353, WO2010/025177, US7446179, WO2010/025177, WO2012/031744, WO2012/136231A1, WO2012/050374A2, WO2013074916, WO/2009/091826A3, WO2013/176915 or WO/2013/059593.

In some embodiments, the immune cell comprises an N-CAR as defined herein and a multi-chain P-CAR as defined in WO2014/039523.

In some embodiments, the immune cell of the invention is activated when the P-CAR antigen binding domain binds to its antigen. In some embodiments, such activation is reduced when the N-CAR antigen binding domain binds to its antigen. In some embodiments such reduction of activation is increased, preferably by at least 5%, 10%, 15%, 20% or 30% in an immune cell comprising an N-CAR according to the invention as compared to the same immune cell comprising an N-CAR comprising the full intracellular domain of PD-1. In some embodiments such reduction of activation is increased, preferably by at least 5%, 10%, 15%, 20% or 30% in an immune cell comprising an N-CAR according to the invention as compared to the same immune cell comprising an N-CAR comprising the full intracellular domain of CTLA-4.

In some embodiments, the activation is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85% when the N-CAR and P-CAR antigen binding domains both binds to their respective antigens as compared to when only the CAR antigen binding domain binds to its antigen.

In some embodiments, the level of activation of the immune cell is measured by determining cytokine production. In some embodiments, the level of activation of the immune cell is measured by monitoring IFNgamma production by ELISA and/or FACS and/or luminex assay. In some embodiments, the level of activation of the immune cell is measured by monitoring TNFalpha production by ELISA and/or luminex assay.

In some embodiments, the level of activation of the immune cell is measured by monitoring degranulation, for example by measuring CD107a levels by FACS.

In some embodiments, the level of activation of the immune cell is measured by monitoring the ability of the immune cell to kill target cells.

In some embodiments, the level of activation of the immune cell is measured by monitoring the luciferase activity in reporter cells incorporating inducible NFAT- or NfkB-regulated luciferase expression, such as for example as disclosed in Example 3 below.

In some embodiments, the negative signal of the N-CAR is short-termed and reversible to ensure that the immune cells comprising a P-CAR and an N-CAR according to the invention may be activated when it encounters only P-CAR antigen, despite prior inactivation in a off-tissue setting that has both P-CAR and N-CAR antigens.

Examples

Example 1 – identification of inhibitory domains to be used in N-CARs

There are several receptors, i.e. CTLA-4, PD-1, BTLA, TIM-3, LAG3 that are known to provide a negative signal to attenuate or abrogate T-cell signaling. The intracellular signaling components of PD-1 were studied to identify motifs that may be responsible for its activity. PD-1 contains both an immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoreceptor tyrosine-based switch motif (ITSM) and data suggests that the ITSM domain plays a significant role in recruiting phosphatases (i.e. SHP2) that enable inactivation of upstream signaling components, like CD3zeta (see Riley JL., *Immunol Rev.* 2009 May;229(1):114-25; or Yokosuka T et al., *J Exp Med.* 2012 Jun 4;209(6):1201-17). Other receptors and molecules with ITSMs were identified and analyzed to help understand the functional role of this sequence motif with the intention to utilize it in providing a negative signal that attenuates or abrogates T-cell activation caused by engagement of the P-CAR. Protein sequences were downloaded from swissprot database restricting to sequences that were annotated as being cytoplasmic. Each of these cytoplasmic sequences was searched for the patterns of interest (ITIM motif, ITSM motif or ITIM and ITSM motif).

Example 2 – Design of N-CARs

N-CARs comprising at least one ITSM, alone or in combination with one or more ITIMs or other inhibitory domain such as those of TIM-3, LAG-3 or CTLA4 are prepared in an effort to generate effective NOT gates.

In particular, the following N-CARs are prepared:

- N-CARs comprising multiple tandems PD-1 ITIM-ITSM;
- N-CARs comprising multiple tandems PD-1 ITSM;
- N-CARs comprising single or multiple non-PD1 natural ITSM or ITIM-ITSM;
- N-CARs comprising synthetic ITSM or ITIM-ITSM;
- N-CARS comprising at least one ITSM and signaling domains from other inhibitory receptors such as TIM-3, LAG-3 or CTLA4.

Example 3 – Activity of T-cells comprising a P-CAR and a N-CAR in immortalized human T-cells

An experimental model is used to test the N-CARs designed according to Example 2. The model consists of a positive signaling CAR (P-CAR) construct containing from the N-terminus, a signaling domain or secretory signal domain (e.g. CD8 secretory signal sequence), anti-CD-19 single-chain antibody, hinge (e.g. CD8alpha), transmembrane (e.g CD8alpha), and positive intracellular signaling domains (e.g. 41BB and CD3zeta). The P-CAR is followed by or preceded by a fluorescent marker (e.g. EGFP) or antibiotic resistance gene separated from the P-CAR by either a P2A or IRES (see for example Table 9).

This construct is constructed using standard molecular biology methods and transduced into T-cell receptor (TCR) negative or an NFAT- or NfkB-regulated luciferase reporter Jurkat cell-line. These cells are purified using bulk FACS sorting using the fluorescent marker or by selection in the appropriate antibiotic followed by flow cytometry to confirm surface CAR expression, and tested for activity against differentially expressing CD19 cell-lines to establish activation, proliferation, and cytokine release, and degranulation/cytotoxicity thresholds. Once an appropriate P-CAR cell line has been identified, these cells are transduced with a plasmid containing the negative signaling CAR (N-CAR) construct containing from the N-terminus, a signaling domain (e.g. CD8 secretory signal sequence), anti-PSMA single-chain antibody, hinge (e.g. truncated PD-1 extracellular domain), transmembrane (e.g. PD-1), and negative intracellular signaling domains to be evaluated (native or modified ITSMs optionally in combination with ITIMs or other inhibitory signaling domains) followed by or preceded by a fluorescent marker (e.g. mCherry) or antibiotic-resistance gene separated from the N-CAR by either a P2A or IRES. Multiple versions of these N-CAR constructs are constructed, using standard site-directed and cassette mutagenesis. The T-cells comprising a P-CAR and a N-CAR (also named P-CAR$^+$/N-CAR$^+$ T-cells or NOT GATE CAR T-Cells) are purified by bulk FACS sorting on both fluorescent markers (e.g. EGFP and mCherry) or by sequential selection in appropriate antibiotics followed by dual-color flow cytometry to detect surface expression of both CARs, and tested first for retention of P-CAR activity on CD19 expressing cells and then the potency of negative signal on cells expressing both CD19 and PSMA. The N-CAR candidates are characterized by their ability to attenuate positive signal from P-CAR on varying levels of both the P-CAR and N-CAR antigens by monitoring NFAT- or NfkB-regulated luciferase reporter activity, cytokine production (IFNgamma by ELISA/FACS), degranulation (CD107a levels) and killing of target cells (by FACS). Reversibility and the kinetics of reversibility of the N-CAR signal are tested by first incubating the P-CAR$^+$/N-CAR$^+$ T-cells with cells expressing both CD19 and PSMA, purifying them followed by incubation with CD19 cells. The cytokine production and cytotoxicity of these cells are compared to cells that were directly incubated with CD19 cells.

Experiment and results

Jurkat cells (clone E6-1 ATCC# TIB-152) were maintained at a density of 0.4-2x10^6 cells/mL in RPMI 1640 (Life Technologies) containing 10% fetal bovine serum (hyclone), 1mM sodium pyruvate, 1 x glutaMAX, 1x nonessential amino acids (Mediatech), and 25mM HEPES buffer. 293T cells (clone HEK-293T/17, ATCC CRL-11268) were maintained subconfluently in DMEM containing 4.5 g/L glucose, 10% fetal bovine serum, 1mM sodium pyruvate, 1 x glutaMAX, 1x nonessential amino acids, and 25mM HEPES.

Lentiviral particles (LV) were produced by transient transfection of sub-confluent 293T cells in 6-well plates with a transfer vector (pLVX) encoding the CAR or protein of interest, an HIV-1 gag pol packaging plasmid (psPAX2), and a VSV-G expression plasmid (pMD2.G) at a 4:3:1 ratio, using Lipofectamine 2000 (Invitrogen). The following day the media was replaced, and 48 h after transfection the LV was harvested and filtered through a 0.45 um Millex-HV syringe filter (Millipore). Fresh LV supernatant was used immediately to transduce sub-confluent Jurkat or 293T cells by diluting LV sup in an equal volume of cell culture medium.

Artificial antigen-presenting cells (AAPCs) were prepared by sequential LV transduction of 293T cells. Subconfluent 293T cells were transfected with pLVX expression constructs encoding either codon-optimized full-length human CD19 (NP_001171569), full-length human PSMA (NP_004467), or empty vector. The pLVX vectors comprised a puromycin-resistance gene followed by a P2A sequence and the target antigen. Transduced 293Ts were subsequently selected in puromycin-containing media, and maintained as pools of expressing clones. Surface antigen expression was determined by flow cytometry, using APC-conjugated goat F(ab')$_2$-anti-human PSMA (clone LN1-17, BioLegend cat #342504) or BV421-conjugated mouse-anti-human CD19 (clone HIB19, BD Biosciences cat #562440). Cells were sorted by FACS into populations of CD19 low-expressing or high-expressing clones, PSMA low-expressing or high-expressing clones, and dual CD19 low/PSMA high-expressers or dual CD19 high/PSMA high-expressers.

For determination of T cell activation, a luciferase reporter assay was established in Jurkat cells. Jurkat cells were transduced to stably express a firefly luciferase gene under the control of a minimal (m)CMV promoter and tandem repeats of either the NFκB or NFAT transcriptional response element (TRE) [(Qiagen Cignal Lentivirus]. Transcription factors recognizing these TREs play important roles in T cell signal transduction pathways and are integral in the transcriptional regulation of cytokine genes and other genes critical for the

immune response. Upon T cell receptor activation, luciferase reporter activity is modulated and can be measured by quantitative luminometry.

Reporter Jurkat cells (either NFAT-Luc or NFkB-Luc) were subsequently transduced to stably express different combinations of P- and N-CARs. pLVX-CAR encoding constructs comprised an antibiotic resistance gene (puromycin resistance for P-CARS and blasticidin resistance for N-CARs) followed by a P2A sequence and the P- or N-CAR.

In particular, N-FAT-Luc and NFkB-Luc Jurkat cells expressing P-CAR1 or P-CAR2 and an N-CAR comprising an intracellular domain selected from the sequences listed in Table 10 were prepared.

P-CAR1 comprises a ScFv from anti-CD19 antibody FMC63 (see Nicholson et al, (1997), Mol. Immunol. 34: 1157-1165), a CD8 alpha hinge and transmembrane domain, and an intracellular domain comprising a 4-1BB and CD3zeta intracellular signaling domains.
P-CAR2 comprises a ScFv from anti-CD19 antibody SJ25C1 (see US2013063097), a CD28 hinge and transmembrane domain, and an intracellular domain comprising a CD28 and CD3zeta intracellular signaling domains.
The specific sequences of P-CAR1 and P-CAR2 are listed in Table 9.

Table 9

P-CAR1 (SEQ ID No 2019)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLN WYQQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFC QQGNTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQESGPGLVAPSQS LSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIK DNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSSTTT PAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC ELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP RRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPR
P-CAR2 (SEQ ID No 2020)	MALPVTALLLPLALLLHAEVKLQQSGAELVRPGSSVKISCKASGYAFSSYWMN WVKQRPGQGLEWIGQIYPGDGDTNYNGKFKGQATLTADKSSSTAYMQLSGL TSEDSAVYFCARKTISSVVDFYFDYWGQGTTVTVSSGGGGSGGGGSGGGGS

	DIELTQSPKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKPLIYSAT YRNSGVPDRFTGSGSGTDFTLTITNVQSKDLADYFCQQYNRYPYTSGGGTKL EIKRAAAIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVG GVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPR DFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR

The tested N-CARs comprise an amino acid sequence of SEQ ID No 1999 (ScFv from the anti-PSMA antibody J591 (see WO2004/098535), PD1 hinge and transmembrane domain) and an intracellular domain selected from the sequences listed in Table 10. A CAR comprising only SEQ ID No 1999 (no inhibitory intracellular domain) was used as control (ΔPD1).

Table 10

N-CAR NAME	**Intracelullar domain**
PD1	CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPC VPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL (SEQ ID No 2000)
BTLA	RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDND PDLCFRMQEGSEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVKEAPT EYASICVRS (SEQ ID No 2001)
CD244	WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTFPGGGSTIYSMIQ SQSSAPTSQEPAYTLYSLIQPSRKSGSRKRNHSPSFNSTIYEVIGKSQPKAQ NPARLSRKELENFDVYS (SEQ ID No 2002)
PD1-CTLA4	CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPC VPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPLAVS LSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPIN (SEQ ID No 2003)
PD1-LAG3	CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPC VPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPLHL WRRQWRPRRFSALEQGIHPPQAQSKIEELEQEPEPEPEPEPEPEPEPEPE QL (SEQ ID No 2004)
PD1-PD1	CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPC VPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPLCS RAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVP EQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL (SEQ

	ID No 2005)
PD1-TIM3	CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPC VPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPLFK WYSHSKEKIQNLSLISLANLPPSGLANAVAEGIRSEENIYTIEENVYEVEEPN EYYCYVSSRQQPSQPLGCRFAMP (SEQ ID No 2006)
CD300LF	WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSS AQVDQVEVEYVTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGR GPEEPTEYSTISRP (SEQ ID No 2007)
LY9	KRKGRCSVPAFCSSQAEAPADTPEPTAGHTLYSVLSQGYEKLDTPLRPAR QQPTPTSDSSSDSNLTTEEDEDRPEVHKPISGRYEVFDQVTQEGAGHDPA PEGQADYDPVTPYVTEVESVVGENTMYAQVFNLQGKTPVSQKEESSATIY CSIRKPQVVPPPQQNDLEIPESPTYENFT (SEQ ID No 2008)
PECAM	KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDV RNHAMKPINDNKEPLNSDVQYTEVQVSSAESHKDLGKKDTETVYSEVRKA VPDAVESRYSRTEGSLDGT (SEQ ID No 2009)
SIGLEC9	VRSCRKKSARPAAGVGDTGIEDANAVRGSASQGPLTEPWAEDSPPDQPP PASARSSVGEGELQYASLSFQMVKPWDSRGQEATDTEYSEIKIHR (SEQ ID No 2010)
SIRPA	RIRQKKAQGSTSSTRLHEPEKNAREITQDTNDITYADLNLPKGKKPAPQAAE PNNHTEYASIQTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYA SVQVPRK (SEQ ID No 2011)
PD1-L2-ITSM	CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPC VPEQTEYATIDFQWREKTPEPPVPCVPEQTEYATIVFPSGMGTSSPARRGS ADGPRSAQPLRPEDGHCSWPL (SEQ ID No 2012)
PD1-L2-ITSM-L2-ITSM	CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPC VPEQTEYATIDFQWREKTPEPPVPCVPEQTEYATIDFQWREKTPEPPVPCV PEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL (SEQ ID No 2013)
PD1 (ITSM mut 1)	CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPC VPEQTEYSEIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL (SEQ ID No 2014)
PD1 (ITSM mut 2)	CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPC VPEQTEYSEVVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL (SEQ ID No 2015)
PD1 (ITSM mut3)	CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPC VPEQTEYASIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL

	(SEQ ID No 2016)
PD1-KIR2DL2	CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPC VPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPLHR WCSNKKNAAVMDQESAGNRTANSEDSDEQDPQEVTYTQLNHCVFTQRKI TRPSQRPKTPPTDIIVYAELPNAESRSKVVSCP (SEQ ID No 2017)

Three days after transduction, Jurkat cells were placed into antibiotic selection media to select for pools of stable CAR-expressing clones.

Dual cell surface expression of P-CAR1 (Table 9) and N-CARs listed in Table 10 assessed by multicolor flow cytometry in transduced NFAT-luciferase reporter Jurkat cells is shown in Figures 1 and 2. Dual cell surface expression of P-CAR1 (Table 9) and N-CARs listed in Table 10 assessed by multicolor flow cytometry in transduced NFkB-luciferase reporter Jurkat cells is shown in Figure 3 and 4. Dual cell surface expression of P-CAR2 (Table 9) and N-CARs listed in Table 10 assessed by multicolor flow cytometry in transduced NFAT-luciferase reporter Jurkat cells is shown in Figures 6 and 7. Dual cell surface expression of P-CAR2 and N-CARs listed in Table 10 assessed by multicolor flow cytometry in transduced NFkB-luciferase reporter Jurkat cells is shown in Figures 8 and 9.

Cells were sequentially transduced with P-CAR and N-CAR lentivirus, and selected for antibiotic-resistant clones after each transduction. Intracellular domains of the various N-CARs are shown above each dot plot. P-CAR expression was detected using a recombinant human CD19-mouse IgG Fc fusion protein followed by APC-conjugated F(ab')2 goat anti-mouse Fcγ (shown on x axis), and N-CAR expression was detected with a biotinylated recombinant human PSMA-human IgG1 Fc fusion protein followed by PE-conjugated streptavidin (y axis).

In Vitro T Cell Activation Assay

For coculture assays, effector Jurkat cells expressing different combinations of P- and N-CARs were cocultured with AAPCs expressing either CD19 (on-target), both CD19 and PSMA (off-target), or neither antigen (empty vector transduced). AAPC target cells were plated at a density of 20,000 cells per well in tissue culture-treated flat-bottom white 96-well plates (Corning COSTAR). Plates were incubated at 37°C in 5% CO_2 for 24 hours, after which time media was removed and 100,000 Control ΔPD1- or test N-CAR-transduced luciferase reporter Jurkat cells expressing P-CAR1 or P-CAR2 were added to each well in a volume of 100uL. After a 16-hour incubation at 37°C, 100uL Bright-Glo luciferase substrate (Promega) was added per well, plates were shaken for 2 minutes, and relative luciferase

units (RLU) quantified on a Perkin Elmer EnVision Multilabel Reader. Each Jurkat cell line was tested in sextuplicate and results presented as a ratio of the mean RLU value from coculture with off-target AAPCs to the mean RLU from coculture with target AAPCs.

Figures 5A, 5B and 5C show the inhibitory effect of various N-CARs on P-CAR1 induced T cell activation. Control ΔPD1- or test N-CAR-transduced luciferase reporter Jurkat cells expressing P-CAR1 were incubated with either CD19-expressing AAPCs or dual CD19+PSMA-expressing AAPCs, and luciferase activity was assessed 16h later. Data are expressed as a ratio of the mean RLU from co-culture with CD19+PSMA AAPCs/CD19 AAPCs. n=6 replicates per sample; data shown are the means$\pm SEM$. Figures. 5A/5C and 5B show results using NFAT-luciferase reporter and NFkB-luciferase reporter Jurkat cells, respectively.

Figures 10A and 10B show the inhibitory effect of various N-CARs on P-CAR2 induced T cell activation. Control ΔPD1- or test N-CAR-transduced luciferase reporter Jurkat cells expressing P-CAR2 were incubated with either CD19-expressing or dual PSMA/CD19-expressing AAPCs, and luciferase activity was assessed 16h later. Data are expressed as a ratio of the mean RLU from co-culture with CD19+PSMA AAPCs/CD19 AAPCs. n=6 replicates per sample; data shown are the means$\pm SEM$. Figures. 10A and 10B show results using NFAT-luciferase reporter and NFkB-luciferase reporter Jurkat cells, respectively.

Example 4 – Activity of P-CAR$^+$/N-CAR$^+$ T-cells in primary human T-cells

The N-CAR designed according to example 2 are also optionally tested in primary human T-cells to ensure that the results from example 3 obtained with Jurkat T-cells translate to primary cells. This can be done by first transducing N-CAR constructs into primary human T-cells obtained according to methods known to the skilled person and monitoring the attenuation of T-cell activation by anti-CD3/CD28 stimulation in the absence and presence of N-CAR antigen. In addition, the P-CAR and N-CAR constructs disclosed in example 3 can also be transduced into primary human T-cells and tested on CD19, PSMA, and CD19/PSMA cells.

Example 5 – Activity of T-cells comprising P-CAR and N-CAR in xenograft studies

P-CAR and N-CAR constructs as disclosed in Example 3 can be transduced into primary human T-cells and tested for efficacy in xenograft studies in NSG animals transplanted with tumors expressing, either only CD19 or both CD19 and PSMA. NSG mice are transplanted

with luciferase labeled 10^5-10^6 cells expressing either CD19 or CD19 and PSMA. A few days after engraftment, these animals are infused with 10^4-10^6 P-CAR$^+$/N-CAR$^+$ T-cells intravenously. The animals are dosed with luciferin prior to imaging on the IVIS imaging system routinely to monitor tumor load.

The invention is further illustrated by the following embodiments:

1. An inhibitory chimeric antigen receptor (N-CAR) comprising
an extracellular domain comprising an antigen binding domain,
a transmembrane domain,
an intracellular domain, and,
wherein the intracellular domain comprises an Immunoreceptor Tyrosine-based Switch Motif ITSM, wherein said ITSM is a sequence of amino acid $TX_1YX_2X_3X_4$, wherein
X_1 is an amino acid
X_2 is an amino acid
X_3 is an amino acid and
X_4 is V or I.

2. The N-CAR according to embodiment 1, wherein when the extracellular domain is a scFv against PSMA, then the intracellular domain is not the intracellular domain of human PD-1.

3. The N-CAR according to embodiment 1 or 2, wherein the extracellular domain does not bind to PMSA.

4. The N-CAR according to any one of embodiments 1 to 3, wherein the intracellular domain does not comprise the full intracellular domain of PD-1.

5. The N-CAR according to any one of embodiments 1 to 4, wherein ITSM motif is not TEYATI.

5.1 The N-CAR according to any one of embodiments 1 to 5, wherein the intracellular domain is not the intracellular domain of human PD1.

5.2 The N-CAR according to any one of embodiments 1 to 5, wherein the intracellular domain is not the intracellular domain of human BTLA.

5.3 The N-CAR according to any one of embodiments 1 to 5, wherein the intracellular domain is not the intracellular domain of human CD244.

5.4 The N-CAR according to any one of embodiments 1 to 5, wherein the intracellular domain is not SEQ ID No 2000, SEQ ID No 2001 or SEQ ID No 2002.

6. The N-CAR according to any one of embodiments 1 to 5.4, wherein the intracellular domain comprises the sequence
$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein

n is 0, 1 or an integer greater than 1;

m is 1 or an integer greater than 1;

p is 1 or an integer greater than 1;

L1 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(a) a naturally occurring N-terminal flanking region of an ITIM only intracellular domains or a fragment thereof;

(b) a naturally occurring N-terminal flanking region of an ITIM.*ITSM intracellular domains or a fragment thereof;

(c) a naturally occurring intracellular domain from a known inhibitory receptor, wherein the said intracellular domain is N-terminally flanking to a sequence in (c) above, or a fragment thereof; and,

(d) a non-naturally occurring sequence comprising between 1 and 500 amino acids;

each of L2 and L3 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(e) a naturally occurring C-terminal flanking region of an ITIM only intracellular domain or a fragment thereof;

(f) a naturally occurring N-terminal flanking region of an ITSM only intracellular domain or a fragment thereof;

(g) a naturally occurring intracellular domain between ITIM and ITSM from proteins that have ITIM.*ITSM motif or a fragment thereof;

(h) a naturally occurring intracellular domain from a known inhibitory receptor wherein the said intracellular domain is N-terminally flanking to a sequence in (f) or (g) above, or a fragment thereof; and

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids; and

L4 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(j) a naturally occurring C-terminal flanking region of an ITIM.*ITSM intracellular domain or a fragment thereof;

(k) a naturally occurring C-terminal flanking region of an ITSM only intracellular domain or a fragment thereof;

(l) a naturally occurring intracellular domain from a known inhibitory receptor wherein the said intracellular domain is C-terminally flanking to a sequence in (j) or (k) above; or a fragment thereof and

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids,

the ITIM is the sequence $X_5X_6YX_7X_8X_9$, wherein
X_5 is S, V, I or L,
X_6 is an amino acid,
X_7 is an amino acid,
X_8 is an amino acid, and,
X_9 is V, I or L, and

the ITSM is the sequence $TX_1YX_2X_3X_4$, wherein
X_1 is an amino acid,
X_2 is an amino acid,
X_3 is an amino acid, and,
X_4 is V or I,
or a variant thereof.

7. The N-CAR according to embodiment 6, wherein
L1 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(a) a naturally occurring N-terminal flanking region of ITIM only intracellular domains selected from the sequences shown in Table 3 or a fragment thereof;

(b) a naturally occurring N-terminal flanking region of ITIM.*ITSM intracellular selected from the sequences shown in Table 1 or a fragment thereof;

(c) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in Table 2 or a fragment thereof, wherein said intracellular domain is N-terminally flanking to a sequence in (b) above, or a fragment thereof; and

(d) a non-naturally occurring sequence comprising between 1 and 500 amino acids;

each of L2 and L3 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(e) a naturally occurring C-terminal flanking region of ITIM only intracellular domains selected from the sequences shown in Table 4 or a fragment thereof;

(f) a naturally occurring N-terminal flanking region of ITSM only intracellular domains selected from the sequences shown in Table 6, or a fragment thereof;

(g) a naturally occurring intracellular domain between ITIM and ITSM from proteins that have ITIM.*ITSM motif selected from the sequences shown in Table 5, or a fragment thereof;

(h) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in Table 2 or a fragment thereof wherein said intracellular domain is N-terminally flanking to a sequence in (f) or (g) above, or a fragment thereof; and

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids; and

L4 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(j) a naturally occurring C-terminal flanking region of ITIM.*ITSM intracellular domains selected from the sequences shown in Table 7, or a fragment thereof;

(k) a naturally occurring C-terminal flanking region of ITSM only intracellular domains selected from the sequences shown in Table 8, or a fragment thereof;

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in Table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (l) above, or a fragment thereof; and,

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids.

8. The N-CAR according to embodiment 6 or 7 wherein the intracellular domain comprises the sequence $(L1\text{-}ITIM\text{-}L2\text{-}L3\text{-}ITSM\text{-}L4)^p$ wherein

p is 1, 2, 3, 4 or 5;

L1 is a naturally occurring N-terminal flanking region of an ITIM only intracellular domain or a fragment thereof such as, for example, any of the sequences shown in Table 3 or a fragment thereof;

L2 is absent;

L3 is a naturally occurring a naturally occurring intracellular domain between ITIM and ITSM from proteins that have ITIM.*ITSM motif or a fragment thereof such as, for example, any of the sequences shown in Table 5 or a fragment thereof;

L4 is a naturally occurring C-terminal flanking region of an ITIM.*ITSM intracellular domain or a fragment thereof such as, for example, any of the sequences shown in Table 7 or a fragment thereof; or a naturally occurring C-terminal flanking region of an ITSM only

intracellular domain such as, for example, any of the sequences shown in Table 8 or a fragment thereof.

9. The N-CAR according to any one of embodiments 6 to 8 wherein L1 is absent or comprises one or more, preferably one, sequences or selected from the group consisting of:

(a) a naturally occurring N-terminal flanking region of ITIM only intracellular domains selected from

YKMYGSEMLHKRDPLDEDEDTD
DHWALTQRTARAVSPQSTKPMAES
CSRAARGTIGARRTGQPLKEDPSAVPVFS
HRQNQIKQGPPRSKDEEQKPQQRPDLAVDVLERTADKATVNGLPEKDRETDTSALAAGSSQE
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPTVEMDEE
LTRKKKALRIHSVEGDLRRKSAGQEEWSPSAPSPPGSCVQAEAAPAGLCGEQRGEDCAELHDYFNV
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPINDNKEPLNSD
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEENKPG
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKED
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKLEDVVIDRNLLILGKILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNSSQREIEEFLSEAACMKDFSHPNVIRLLGVCIEMSSQGIPKPMVILPFMKYGDLHTY

(b) a naturally occurring N-terminal flanking region of ITIM.*ITSM intracellular domains selected from

YKMYGSEMLHKRDPLDEDEDTD
WRMMKYQQKAAGMSPEQVLQPLEGD
CSRAARGTIGARRTGQPLKEDPSAVPVFS
RIRQKKAQGSTSSTRLHEPEKNAREITQDTND
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPTVEMDEE
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPINDNKEPLNSD
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEG

SEVYSNPCLEENKPG
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKLEDVVIDRNLLILG KILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNSSQREIEEFLSEAACMKDFSHPNVIRL LGVCIEMSSQGIPKPMVILPFMKYGDLHTY

(c) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2, wherein said intracellular domain is N-terminally flanking to a sequence in (b) above; and

(d) a non-naturally occurring sequence comprising between 1 and 500 amino acids.

10. A N-CAR according to any one of embodiments 6 to 9 wherein each of L2 and L3 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(e) a naturally occurring C-terminal flanking region of ITIM only intracellular domains selected from;

GNCSFFTETG
NFHGMNPSKDTSTEYSEVRTQ
KEEEMADTSYGTVKAENIIMMETAQTSL
NHSVIGPNSRLARNVKEAPTEYASICVRS
DHWALTQRTARAVSPQSTKPMAESITYAAVARH
QVSSAESHKDLGKKDTETVYSEVRKAVPDAVESRYSRTEGSLDGT
DFQWREKTPEPPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCS WPL
NLPKGKKPAPQAAEPNNHTEYASIQTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSF SEYASVQVPRK
TLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKEDISYASLTLGAEDQEPTYCNMGHL SSHLPGRGPEEPTEYSTISRP
ETGPKHIPLQTLLKFMVDIALGMEYLSNRNFLHRDLAARNCMLRDDMTVCVADFGLSKKIYS GDYYRQGRIAKMPVKWIAIESLADRVYTSKSDVWAFGVTMWEIATRGMTPYPGVQNHEMY DYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVRNQADVIY VNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGRYILNGGSE EWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFADDSSEGSE VLM

(f) a naturally occurring N-terminal flanking region of ITSM only intracellular domains selected from;

YKMYGSEMLHKRDPLDEDEDTDISYKKLKEEEMAD

CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQ
RIRQKKAQGSTSSTRLHEPEKNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNH
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPTVEMDEELHYAS LNFHGMNPSKDTS
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPIND NKEPLNSDVQYTEVQVSSAESHKDLGKKDTE
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEG SEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVKEAP
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEY VTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGRGPEEP
WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQE PAYTLYSLIQPSRKSGSRKRNHSPSFNS
VRSCRKKSARPAAGVGDTGIEDANAVRGSASQGPLTEPWAEDSPPDQPPPASARSSVGE GELQYASLSFQMVKPWDSRGQEATD
NKCGRRNKFGINRPAVLAPEDGLAMSLHFMTLGGSSLSPTEGKGSGLQGHIIENPQYFSDA CVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPEQDKMLVAVKALKEASESARQDFQREA ELLTMLQHQHIVRFFGVCTEGRPLLMVFEYMRHGDLNRFLRSHGPDAKLLAGGEDVAPGPL GLGQLLAVASQVAAGMVYLAGLHFVHRDLATRNCLVGQGLVVKIGDFGMSRDIYS
KLARHSKFGMKGPASVISNDDDSASPLHHISNGSNTPSSSEGGPDAVIIGMTKIPVIENPQYF GITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFLAECYNLCPEQDKILVAVKTLKDASDN ARKDFHREAELLTNLQHEHIVKFYGVCVEGDPLIMVFEYMKHGDLNKFLRAHGPDAVLMAE GNPPTELTQSQMLHIAQQIAAGMVYLASQHFVHRDLATRNCLVGENLLVKIGDFGMSRDVY S
KRKGRCSVPAFCSSQAEAPADTPEPTAGHTLYSVLSQGYEKLDTPLRPARQQPTPTSDSSS DSNLTTEEDEDRPEVHKPISGRYEVFDQVTQEGAGHDPAPEGQADYDPVTPYVTEVESVV GENTMYAQVFNLQGKTPVSQKEESSA
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKLEDVVIDRNLLILG KILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNSSQREIEEFLSEAACMKDFSHPNVIRL LGVCIEMSSQGIPKPMVILPFMKYGDLHTYLLYSRLETGPKHIPLQTLLKFMVDIALGMEYLS NRNFLHRDLAARNCMLRDDMTVCVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADRV YTSKSDVWAFGVTMWEIATRGM

(g) a naturally occurring intracellular domain between ITIM and ITSM from proteins that have ITIM.*ITSM motif selected from;

KEEEMAD
NFHGMNPSKDTS

QVSSAESHKDLGKKDTE
NLPKGKKPAPQAAEPNNH
NHSVIGPNSRLARNVKEAP
DFQWREKTPEPPVPCVPEQ
TLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKEDISYASLTLGAEDQEPTYCNMGHL SSHLPGRGPEEP
ETGPKHIPLQTLLKFMVDIALGMEYLSNRNFLHRDLAARNCMLRDDMTVCVADFGLSKKIYS GDYYRQGRIAKMPVKWIAIESLADRVYTSKSDVWAFGVTMWEIATRGM

(h) a naturally occurring intracellular domain from known inhibitory receptors selected from the sequences shown in table 2 wherein said intracellular domain is N-terminally flanking to a sequence in (f) or (g) above; and

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids; and

11. The N-CAR according to according to any one of embodiments 6 to 10 wherein L4 is absent or comprises one or more, preferably one, sequences selected from the group consisting of:

(j) a naturally occurring C-terminal flanking region of ITIM.*ITSM intracellular domains selected from:

SRP
RTQ
CVRS
KAENIIMMETAQTSL
RKAVPDAVESRYSRTEGSLDGT
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVR NQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGR YILNGGSEEWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFAD DSSEGSEVLM

(k) a naturally occurring C-terminal flanking region of ITSM only intracellular domain selected from:

RTQ
SRP
KIHR

CVRS
KAENIIMMETAQTSL
RKAVPDAVESRYSRTEGSLDGT
RKPQVVPPPQQNDLEIPESPTYENFT
GKSQPKAQNPARLSRKELENFDVYS
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
FNLQGKTPVSQKEESSATIYCSIRKPQVVPPPQQNDLEIPESPTYENFT
GGRTMLPIRWMPPESILYRKFTTESDVWSFGVVLWEIFTYGKQPWYQLSNTEAIDCITQGRE LERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARLQALAQAPPVYLDVLG
GGHTMLPIRWMPPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNEVIECITQGR VLQRPRTCPQEVYELMLGCWQREPHMRKNIKGIHTLLQNLAKASPVYLDILG
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVR NQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGR YILNGGSEEWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFAD DSSEGSEVLM
KDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQEPAYTLYSLIQPSRKSGSRKRNHSP SFNSTIYEVIGKSQPKAQNPARLSRKELENFDVYS

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2 wherein said intracellular domain is C-terminally flanking to a sequence in (j) or (k) above; and

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids.

11.1. The N-CAR according to embodiment 6 wherein the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^{n}\text{-}(L3\text{-}ITSM\text{-}L4)^{m})^{p}$, wherein

n is 0;

m is 1;

p is 1;

L3 comprises one sequence selected from

(f) a naturally occurring N-terminal flanking region of an ITSM only intracellular domain such as, for example, any of the sequences shown in Table 6 below or a fragment thereof; or,

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids; and

L4 comprises one or more, preferably one or two, sequences selected from the group consisting of:

(k) a naturally occurring C-terminal flanking region of an ITSM only intracellular domain such as, for example, any of the sequences shown in Table 8 below or a fragment thereof;

(l) a naturally occurring intracellular domain from a known inhibitory receptor such as any of the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above; and

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids, and, wherein.

11.2. The N-CAR according to embodiment 6 wherein the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein

n is 0;

m is 1;

p is 1;

L3 is selected from

YKMYGSEMLHKRDPLDEDEDTDISYKKLKEEEMAD
CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQ
RIRQKKAQGSTSSTRLHEPEKNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNH
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPTVEMDEELHYAS LNFHGMNPSKDTS
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPIND NKEPLNSDVQYTEVQVSSAESHKDLGKKDTE
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEG SEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVKEAP
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEY VTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGRGPEEP
WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQE PAYTLYSLIQPSRKSGSRKRNHSPSFNS
VRSCRKKSARPAAGVGDTGIEDANAVRGSASQGPLTEPWAEDSPPDQPPPASARSSVGE GELQYASLSFQMVKPWDSRGQEATD
NKCGRRNKFGINRPAVLAPEDGLAMSLHFMTLGGSSLSPTEGKGSGLQGHIIENPQYFSDA CVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPEQDKMLVAVKALKEASESARQDFQREA ELLTMLQHQHIVRFFGVCTEGRPLLMVFEYMRHGDLNRFLRSHGPDAKLLAGGEDVAPGPL GLGQLLAVASQVAAGMVYLAGLHFVHRDLATRNCLVGQGLVVKIGDFGMSRDIYS

KLARHSKFGMKGPASVISNDDDSASPLHHISNGSNTPSSSEGGPDAVIIGMTKIPVIENPQYF GITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFLAECYNLCPEQDKILVAVKTLKDASDN ARKDFHREAELLTNLQHEHIVKFYGVCVEGDPLIMVFEYMKHGDLNKFLRAHGPDAVLMAE GNPPTELTQSQMLHIAQQIAAGMVYLASQHFVHRDLATRNCLVGENLLVKIGDFGMSRDVY S
KRKGRCSVPAFCSSQAEAPADTPEPTAGHTLYSVLSQGYEKLDTPLRPARQQPTPTSDSSS DSNLTTEEDEDRPEVHKPISGRYEVFDQVTQEGAGHDPAPEGQADYDPVTPYVTEVESVV GENTMYAQVFNLQGKTPVSQKEESSA
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKLEDVVIDRNLLILG KILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNSSQREIEEFLSEAACMKDFSHPNVIRL LGVCIEMSSQGIPKPMVILPFMKYGDLHTYLLYSRLETGPKHIPLQTLLKFMVDIALGMEYLS NRNFLHRDLAARNCMLRDDMTVCVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADRV YTSKSDVWAFGVTMWEIATRGM

and L4 comprises one sequence selected from the group consisting of

(k)

RTQ
SRP
KIHR
CVRS
KAENIIMMETAQTSL
RKAVPDAVESRYSRTEGSLDGT
RKPQVVPPPQQNDLEIPESPTYENFT
GKSQPKAQNPARLSRKELENFDVYS
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
FNLQGKTPVSQKEESSATIYCSIRKPQVVPPPQQNDLEIPESPTYENFT
GGRTMLPIRWMPPESILYRKFTTESDVWSFGVVLWEIFTYGKQPWYQLSNTEAIDCITQGRE LERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARLQALAQAPPVYLDVLG
GGHTMLPIRWMPPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNEVIECITQGR VLQRPRTCPQEVYELMLGCWQREPHMRKNIKGIHTLLQNLAKASPVYLDILG
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVR NQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGR YILNGGSEEWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFAD

DSSEGSEVLM
KDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQEPAYTLYSLIQPSRKSGSRKRNHSP SFNSTIYEVIGKSQPKAQNPARLSRKELENFDVYS

and optionally

(l) a naturally occurring intracellular domain from a known inhibitory receptor such as any of the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above.

11.3. The N-CAR according to embodiment 6 wherein the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^{n}\text{-}(L3\text{-}ITSM\text{-}L4)^{m})^{p}$, wherein

n is 0;

m is 1;

p is 1;

L3 is selected from

CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQ
RIRQKKAQGSTSSTRLHEPEKNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNH
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPIND NKEPLNSDVQYTEVQVSSAESHKDLGKKDTE
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEG SEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVKEAP
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEY VTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGRGPEEP
WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQE PAYTLYSLIQPSRKSGSRKRNHSPSFNS
VRSCRKKSARPAAGVGDTGIEDANAVRGSASQGPLTEPWAEDSPPDQPPPASARSSVGE GELQYASLSFQMVKPWDSRGQEATD
KRKGRCSVPAFCSSQAEAPADTPEPTAGHTLYSVLSQGYEKLDTPLRPARQQPTPTSDSSS DSNLTTEEDEDRPEVHKPISGRYEVFDQVTQEGAGHDPAPEGQADYDPVTPYVTEVESVV GENTMYAQVFNLQGKTPVSQKEESSA

L4 comprises one sequence selected from the group consisting of

(k)

SRP
KIHR
CVRS

RKAVPDAVESRYSRTEGSLDGT
RKPQVVPPPQQNDLEIPESPTYENFT
GKSQPKAQNPARLSRKELENFDVYS
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK

and optionally

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2, preferably KIR2DL2, or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above.

11.4. The N-CAR according to embodiment 6 wherein the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein

n is 0;

m is 1;

p is 1;

L3 is selected from

CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQ

and L4 comprises

(k)

VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL

and

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2, preferably KIR2DL2, or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above.

11.5. The N-CAR according to embodiment 6 wherein the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein

n is 0;

m is 1;

p is 1;

L3 is selected from

WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEY VTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGRGPEEP

L4 comprises a sequence selected from

(k)

SRP

and optionally

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above.

11.6. The N-CAR according to embodiment 6 wherein the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^{n}\text{-}(L3\text{-}ITSM\text{-}L4)^{m})^{p}$, wherein

n is 0;

m is 1;

p is 1 or 2;

L3 comprises one sequence selected from

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids; and

L4 comprises one or more, preferably one or two, sequences selected from:

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids.

11.7. The N-CAR according to embodiment 6 wherein the intracellular domain is selected from SEQ ID No 2000, SEQ ID No 2001, SEQ ID No 2002, SEQ ID No 2003, SEQ ID No 2004, SEQ ID No 2005, SEQ ID No 2006, SEQ ID No 2007, SEQ ID No 2008, SEQ ID No 2009, SEQ ID No 2010, SEQ ID No 2011, SEQ ID No 2012, SEQ ID No 2013, SEQ ID No 2014, SEQ ID No 2015, SEQ ID No 2016 and SEQ ID No 2017.

12. The N-CAR according to any one of embodiments 6 to 11.7 wherein the non-naturally occurring sequence of (d), (i) and (m) comprises between 1 and 400, 1 and 300, 1 and 200, 1 and 100, 10 and 100, 10 and 80, 10 and 60, 10 and 40, 100 and 200, 100 and 300 or 100 and 400.

13. The N-CAR according to any one of embodiments 6 to 11.7 wherein the non-naturally occurring sequence of (d) or (i) is a Glycine/Serine linker $(Gly_xSer)_n$ where x=1, 2, 3, 4 or 5 and n is 1 to 100.

14. The N-CAR according to embodiment 13 wherein the non-naturally occurring sequence of (d) or (i) is a Glycine/Serine linker $(Gly\text{-}Gly\text{-}Gly\text{-}Ser)_n$ or $(Gly\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Ser)_n$, where n is 1 to 100, 1 to 80, 1 to 50, 1 to 20 or 1 to 10.

15. The N-CAR according to embodiment 14 wherein the non-naturally occurring sequence of (d) or (i) is a $(Gly_4Ser)_4$ or $(Gly_4Ser)_3$.

16. The ICAR according to any one of embodiments 6 to 15 wherein the intracellular domain comprises the sequence $(L1\text{-}ITIM\text{-}L2\text{-}L3\text{-}ITSM\text{-}L4)^{p}$ wherein

p is 1, 2, 3, 4 or 5;

L1 is a naturally occurring N-terminal flanking region of ITIM only intracellular domains selected from the following sequences;

YKMYGSEMLHKRDPLDEDEDTD
DHWALTQRTARAVSPQSTKPMAES
CSRAARGTIGARRTGQPLKEDPSAVPVFS
HRQNQIKQGPPRSKDEEQKPQQRPDLAVDVLERTADKATVNGLPEKDRETDTSALAAGSSQE
KTHRRKAARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPTVEMDEE
LTRKKKALRIHSVEGDLRRKSAGQEEWSPSAPSPPGSCVQAEAAPAGLCGEQRGEDCAELHDYFNV
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPINDNKEPLNSD
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEENKPG
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKED
KRVQETKFGNAFTEEDSELVVNYIAKKSFCRRAIELTLHSLGVSEELQNKLEDVVIDRNLLILGKILGEGEFGSVMEGNLKQEDGTSLKVAVKTMKLDNSSQREIEEFLSEAACMKDFSHPNVIRLLGVCIEMSSQGIPKPMVILPFMKYGDLHTY

L2 is absent;

L3 is a naturally occurring intracellular domain between ITIM and ITSM from proteins that have ITIM.*ITSM motif selected from the following sequences:

KEEEMAD
NFHGMNPSKDTS
QVSSAESHKDLGKKDTE
NLPKGKKPAPQAAEPNNH
NHSVIGPNSRLARNVKEAP
DFQWREKTPEPPVPCVPEQ
TLQLAGTSPQKATTKLSSAQVDQVEVEYVTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGRGPEEP
ETGPKHIPLQTLLKFMVDIALGMEYLSNRNFLHRDLAARNCMLRDDMTVCVADFGLSKKIYSGDYYRQGRIAKMPVKWIAIESLADRVYTSKSDVWAFGVTMWEIATRGM

L4 is a naturally occurring C-terminal flanking region of ITIM.*ITSM intracellular domains selected from the following sequences:

SRP
RTQ
CVRS
KAENIIMMETAQTSL
RKAVPDAVESRYSRTEGSLDGT
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVR NQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGR YILNGGSEEWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFAD DSSEGSEVLM

or a naturally occurring C-terminal flanking region of ITSM only intracellular domains selected from the following sequences:

RTQ
SRP
CVRS
KAENIIMMETAQTSL
RKAVPDAVESRYSRTEGSLDGT
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
FNLQGKTPVSQKEESSATIYCSIRKPQVVPPPQQNDLEIPESPTYENFT
GGRTMLPIRWMPPESILYRKFTTESDVWSFGVVLWEIFTYGKQPWYQLSNTEAIDCITQGRE LERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARLQALAQAPPVYLDVLG
GGHTMLPIRWMPPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNEVIECITQGR VLQRPRTCPQEVYELMLGCWQREPHMRKNIKGIHTLLQNLAKASPVYLDILG
QNHEMYDYLLHGHRLKQPEDCLDELYEIMYSCWRTDPLDRPTFSVLRLQLEKLLESLPDVR NQADVIYVNTQLLESSEGLAQGSTLAPLDLNIDPDSIIASCTPRAAISVVTAEVHDSKPHEGR YILNGGSEEWEDLTSAPSAAVTAEKNSVLPGERLVRNGVSWSHSSMLPLGSSLPDELLFAD DSSEGSEVLM
KDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQEPAYTLYSLIQPSRKSGSRKRNHSP SFNSTIYEVIGKSQPKAQNPARLSRKELENFDVYS.

17. The N-CAR according to any one of the preceding embodiments wherein the term amino acid refers to glycine, alanine, valine, leucine, isoleucine, phenylalanine, proline, serine, threonine, tyrosine, cysteine, methionine, lysine, arginine, histidine, tryptophan, aspartic acid, glutamic acid, asparagine or glutamine.

18. The N-CAR according to any one of the preceding embodiments wherein X_1 is E, V or I.

19. The N-CAR any one of the preceding embodiments wherein X_1 is E.

20. The N-CAR any one of the preceding embodiments wherein X_2 is S or A.

21. The N-CAR any one of the preceding embodiments wherein X_2 is A.

22. The N-CAR any one of the preceding embodiments wherein X_3 is E, S, T, Q or V.

23. The N-CAR any one of the preceding embodiments wherein X_3 is E.

24. The N-CAR any one of the preceding embodiments wherein X_3 is T.

25. The N-CAR any one of the preceding embodiments wherein X_2 is I.

26. The N-CAR according to any one of embodiments 7 to 25 wherein X_5 is L, V or I

27. The N-CAR according to any one of embodiments 7 to 26 wherein X_5 is L.

28. The N-CAR according to any one of embodiments 7 to 26 wherein X_5 is V

29. The N-CAR according to any one of embodiments 7 to 26 wherein X_5 is I.

30. The N-CAR according to any one of embodiments 7 to 29 wherein X_6 is A, H, Q, T, D, V, L or E.

31. The N-CAR according to any one of embodiments 7 to 30 wherein X_6 is H.

32. The N-CAR according to any one of embodiments 7 to 30 wherein X_6 is D.

33. The N-CAR according to any one of embodiments 7 to 32 wherein X_7 is A, G, T, V or E.

34. The N-CAR according to any one of embodiments 7 to 33 wherein X_7 is A.

35. The N-CAR according to any one of embodiments 7 to 33 wherein X_7 is G.

36. The N-CAR according to any one of embodiments 7 to 35 wherein X_8 is V, S, D or E.

37. The N-CAR according to any one of embodiments 7 to 36 wherein X_8 is S or E.

38. The N-CAR according to any one of embodiments 7 to 37 wherein X_8 is E.

39. The N-CAR according to any one of embodiments 7 to 38 wherein X_9 is L or V.

40. The N-CAR according to any one of embodiments 7 to 38 wherein X_9 is L.

41. The N-CAR according to any one of embodiments 7 to 40 wherein X_5 is L or V, X_8 is E and X_9 is L.

42. The N-CAR any one of the preceding embodiments wherein the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain, is selected from TAYELV, TAYGLI, TAYNAV, TCYGLV, TCYPDI, TDYASI, TDYDLV, TDYLSI, TDYQQV, TDYYRV, TEYASI, TEYATI, TEYDTI, TEYPLV, TEYSEI, TEYSEV, TEYSTI, TEYTKV, TFYHVV, TFYLLI, TFYNKI, TFYPDI, TGYEDV, TGYLSI, THYKEI, TIYAQV, TIYAVV, TIYCSI, TIYEDV, TIYERI, TIYEVI, TIYHVI, TIYIGV, TIYLKV, TIYSMI, TIYSTI, TIYTYI, TKYFHI, TKYMEI, TKYQSV, TKYSNI, TKYSTV, TLYASV, TLYAVV, TLYFWV, TLYHLV,

TLYPMV, TLYPPI, TLYRDI, TLYRDV, TLYSKI, TLYSLI, TLYSPV, TMYAQV, TMYCQV, TNYKAV, TNYNLV, TPYAGI, TPYPGV, TPYVDI, TQYGRV, TQYNQV, TRYAYV, TRYGEV, TRYHSV, TRYKTI, TRYLAI, TRYMAI, TRYQKI, TRYQQI, TRYSNI, TRYSPI, TSYGTV, TSYMEV, TSYQGV, TSYTTI, TTYRSI, TTYSDV, TTYVTI, TVYAQI, TVYASV, TVYEVI, TVYGDV, TVYKGI, TVYQRV, TVYSEV, TVYSTV, TYYHSI, TYYLQI, or TYYYSV.

43. The N-CAR any one of the preceding embodiments wherein the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain is TEYASI.

44. The N-CAR any one of the preceding embodiments wherein the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain is TEYSEI.

44.1 The N-CAR any one of the preceding embodiments wherein the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain is TEYSTI.

45. The N-CAR any one of the preceding embodiments wherein the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain is TVYSEV.

46. The N-CAR according to any one of embodiments 7 to 45 wherein the ITIM, or at least one of the ITIMs when several ITSMs are present in the intracellular domain is selected from LSYRSL, LPYYDL, LPYYDL, LLYSRL, LLYSRL, LIYTLL, LLYADL, ISYTTL, VTYSAL, IHYSEL, VDYVIL, LHYASL, LDYDYL, VDYDFL, VTYSTL, IIYSEV, LEYLCL, VLYGQL, VPYTPL, ISYPML, ISYPML, ISYPML, VSYTNL, LLYEMV, VDYNLV, ITYFAL, VHYQSV, VPYVMV, IPYRTV, IAYSLL, , VCYGRL, LKYLYL, LLYEHV, ITYSLL, VLYSEL, IWYNIL, ISYKGL, IDYYNL, LEYLQL, LKYRGL, VLYASV, LQYLSL, LFYRHL, VQYKAV, LSYSSL, LSYTKV, VQYSTV, VKYNPV, VVYSEV, VVYSEV, IIYSEV, LEYVSV, LAYHTV, VQYLRL, VTYTQL, IVYTEL, VTYTQL, IVYAEL, VTYAQL, IVYTEL, VTYAQL, IVYTEL, VTYAQL, VTYAQL, VTYAQL, ILYTEL, VTYAQL, VTYAQL, ITYAAV, VTYAQL, ITYAAV, VIYIDV, VTYAEV, VTYAQL, VTYAQL, VTYAPV, VTYAQL, VTYAKV, VTYARL, VTYAQL, ILYHTV, LLYSRL, VLYAML, VIYAQL, LVYENL, LCYADL, ISYASL, LTYVLL, VTYVNL, VRYSIV, VFYRQV, VFYRQV, LKYMEV, LKYMEV, VDYGEL, LSYMDL, VLYTAV, VQYTEV, IVYASL, VEYLEV, LEYVDL, ITYADL, LTYADL, ITYADL, LTYADL, VIYENV, VIYENV, VIYENV, VIYENV, LAYYTV, VSYSAV, LVYDKL, LNYMVL, LNYACL, LDYINV, LHYATL, LHYASL, LHYASL, LHYAVL, IQYAPL, IQYASL, IQYASL, LLYLLL, VVYSQV, VIYSSV, VVYSQV, VIYSSV, VVYYRV, VPYVEL, LDYDKL, LPYYDL, LSYPVL, VAYSQV, LFYWDV, LFYWDV, LIYSQV, or LDYEFL.

47. The N-CAR according to any one of embodiments 7 to 45 wherein the ITIM, or at least one of the ITIMs when several ITSMs are present in the intracellular domain is selected IAYGDI, IAYRDL, IAYSLL, IAYSRL, ICYALL, ICYDAL, ICYPLL, ICYQLI, IDYILV, IDYKTL, IDYTQL, IDYYNL, IEYCKL, IEYDQI, IEYGPL, IEYIRV, IEYKSL, IEYKTL, IEYSVL, IEYWGI, IFYGNV, IFYHNL, IFYKDI, IFYQNV, IFYRLI, IGYDIL, IGYDVL, IGYICL, IGYKAI, IGYLEL, IGYLPL, IGYLRL, IGYPFL, IGYSDL, IHYRQI, IHYSEL, IIYAFL, IIYHVI, IIYMFL, IIYNLL,

IIYNNL, IIYSEV, IKYCLV, IKYKEL, IKYLAL, IKYTCI, ILYADI, ILYAFL, ILYCSV, ILYEGL, ILYELL, ILYFQI, ILYHTV, ILYLQV, ILYSIL, ILYSVL, ILYTEL, ILYTIL, IMYTLV, INYCSV, INYKDI, INYTTV, INYVLL, IPYDVL, IPYLLV, IPYRTV, IPYSQL, IPYSRI, IPYTQI, IQYAPL, IQYASL, IQYERL, IQYGII, IQYGNV, IQYGRV, IQYNVV, IQYRSI, IQYTEL, IQYWGI, IRYANL, IRYLDL, IRYPLL, IRYRLL, IRYRTI, ISYASL, ISYCGV, ISYEPI, ISYFQI, ISYGLI, ISYKKL, ISYLPL, ISYPML, ISYTTL, ITYAAV, ITYADL, ITYAEL, ITYAEV, ITYASV, ITYDLI, ITYENV, ITYQLL, ITYSLL, IVYAEL, IVYALV, IVYASL, IVYEIL, IVYFIL, IVYHML, IVYLCI, IVYRLL, IVYSAL, IVYSWV, IVYTEL, IVYYIL, IWYENL, IWYFVV, IWYNIL, IYYLGV, LAYALL, LAYARI, LAYDSV, LAYFGV, LAYHRL, LAYKDL, LAYKRI, LAYPPL, LAYQTL, LAYREV, LAYRII, LAYRLL, LAYSQL, LAYSSV, LAYTLL, LAYWGI, LAYYTV, LCYADL, LCYAIL, LCYFHL, LCYHPI, LCYKEI, LCYKFL, LCYMII, LCYRKI, LCYRVL, LCYSTV, LCYTLV, LDYASI, LDYCEL, LDYDKI, LDYDKL, LDYDYL, LDYDYV, LDYEFL, LDYINV, LDYNNL, LDYPHV, LDYSPV, LDYVEI, LDYWGI, LEYAPV, LEYIPL, LEYKTI, LEYLCL, LEYLKL, LEYLQI, LEYLQL, LEYQRL, LEYVDL, LEYVSV, LEYYQI, LFYAQL, LFYCSV, LFYERV, LFYGFL, LFYKYV, LFYLLL, LFYNKV, LFYRHL, LFYTLL, LFYWDV, LFYWKL, LGYGNV, LGYKEL, LGYLQL, LGYPLI, LGYPWV, LGYSAL, LGYSDL, LGYVTL, LHYAKI, LHYALV, LHYANL, LHYARL, LHYASI, LHYASL, LHYASV, LHYATI, LHYATL, LHYAVL, LHYDVV, LHYEGL, LHYETI, LHYFEI, LHYFVV, LHYGAI, LHYILI, LHYINL, LHYKRI, LHYLDL, LHYLNI, LHYLTI, LHYLVI, LHYMAI, LHYMII, LHYMNI, LHYMTI, LHYMTL, LHYMTV, LHYMVI, LHYNML, LHYPAL, LHYPDL, LHYPII, LHYPIL, LHYPLL, LHYPML, LHYPNV, LHYPSI, LHYPTI, LHYPTL, LHYPTV, LHYPVI, LHYPVL, LHYRII, LHYRTI, LHYSII, LHYSSI, LHYSTI, LHYSTL, LHYSVI, LHYTAI, LHYTAL, LHYTII, LHYTKV, LHYTLI, LHYTSI, LHYTTI, LHYTTV, LHYTVI, LHYTVL, LHYTVV, LHYVSI, LHYVTI, LHYVVI, LIYEKL, LIYENV, LIYKDL, LIYNSL, LIYSGL, LIYTLL, LIYTVL, LIYWEI, LKYCEL, LKYDKL, LKYESL, LKYFTI, LKYHTV, LKYILL, LKYIPI, LKYKHV, LKYLYL, LKYMEV, LKYMTL, LKYPAI, LKYPDV, LKYPEL, LKYQPI, LKYRGL, LKYRLL, LLYADL, LLYAPL, LLYAVV, LLYCAI, LLYEHV, LLYELL, LLYEQL, LLYGQI, LLYIRL, LLYKAL, LLYKFL, LLYKLL, LLYKTV, LLYMVV, LLYNAI, LLYNIV, LLYNVI, LLYPAI, LLYPLI, LLYPNI, LLYPSL, LLYPTI, LLYPVI, LLYPVV, LLYQIL, LLYQNI, LLYRLL, LLYRVI, LLYSII, LLYSLI, LLYSPV, LLYSRL, LLYSTI, LLYSVI, LLYSVV, LLYTTI, LLYTVI, LLYTVV, LLYVII, LLYVIL, LLYVTI, LLYWGI, LLYYLL, LLYYVI, LMYDNV, LMYMVV, LMYQEL, LMYRGI, LNYACL, LNYATI, LNYEVI, LNYGDL, LNYHKL, LNYMVL, LNYNIV, LNYPVI, LNYQMI, LNYSGV, LNYSVI, LNYTIL, LNYTTI, LNYVPI, LPYADL, LPYALL, LPYFNI, LPYFNV, LPYHDL, LPYKLI, LPYKTL, LPYLGV, LPYLKV, LPYPAL, LPYQVV, LPYRTV, LPYVEI, LPYYDL, LQYASL, LQYERI, LQYFAV, LQYFSI, LQYHNI, LQYIGL, LQYIKI, LQYLSL, LQYMIV, LQYPAI, LQYPLL, LQYPLV, LQYPSI, LQYPTL, LQYPVL, LQYRAV, LQYSAI, LQYSSI, LQYSVI, LQYTIL, LQYTLI, LQYTMI, LQYYQV, LRYAAV, LRYAGL, LRYAPL, LRYASI, LRYATI, LRYATV, LRYAVL, LRYCGI,

LRYELL, LRYETL, LRYGAL, LRYGPI, LRYGTL, LRYHHI, LRYHSI, LRYHVL, LRYIAI, LRYIFV, LRYITV, LRYKEV, LRYKKL, LRYKMV, LRYKSL, LRYKVI, LRYLAI, LRYLDL, LRYLTI, LRYLTV, LRYMSI, LRYMVI, LRYNCI, LRYNGL, LRYNII, LRYNIL, LRYNKI, LRYNSL, LRYNVI, LRYNVL, LRYPFL, LRYPII, LRYPIL, LRYPLL, LRYPNI, LRYPSI, LRYPTI, LRYPTL, LRYPVI, LRYPVL, LRYQKL, LRYQMI, LRYQNL, LRYRLI, LRYRVI, LRYSAI, LRYSDL, LRYSII, LRYSMI, LRYSSI, LRYSTI, LRYSTL, LRYSVI, LRYSVL, LRYSVV, LRYTAI, LRYTIL, LRYTLI, LRYTMI, LRYTNL, LRYTPV, LRYTSI, LRYTSV, LRYTTI, LRYTTV, LRYTVI, LRYVEV, LRYVTI, LRYVTV, LSYDSL, LSYEDV, LSYFGV, LSYILI, LSYISV, LSYKQV, LSYKRL, LSYLDV, LSYMDL, LSYNAL, LSYNDL, LSYNKL, LSYNQL, LSYPVL, LSYQEV, LSYQPV, LSYQTI, LSYRSL, LSYRSV, LSYSII, LSYSSL, LSYSTL, LSYTKV, LSYTSI, LSYTTI, LSYVLI, LTYADL, LTYAEL, LTYAQV, LTYARL, LTYCDL, LTYCGL, LTYCVL, LTYEEL, LTYEFL, LTYGEV, LTYGRL, LTYKAL, LTYLRL, LTYMTL, LTYNTL, LTYPGI, LTYQSV, LTYSSV, LTYTTV, LVYDAI, LVYDKL, LVYDLV, LVYENL, LVYGQL, LVYHKL, LVYQEV, LVYRKV, LVYRNL, LVYSEI, LVYTNV, LVYWEI, LVYWKL, LVYWRL, LWYEGL, LWYKYI, LWYNHI, LWYTMI, LYYCQL, LYYGDL, LYYKKV, LYYLLI, LYYPKV, LYYRRV, LYYSTI, LYYVRI, LYYVVI, SAYATL, SAYCPL, SAYPAL, SAYQAL, SAYQTI, SAYRSV, SAYTAL, SAYTPL, SAYVVL, SCYAAV, SCYCII, SCYCLL, SCYDFL, SCYEEL, SCYEKI, SCYHIL, SCYPYI, SCYRIL, SCYRTL, SDYCNL, SDYEDL, SDYENV, SDYESV, SDYFIV, SDYHTL, SDYLAI, SDYLDI, SDYLEL, SDYQDL, SDYQRL, SDYSVI, SDYTHL, SEYASV, SEYEEL, SEYFEL, SEYGEL, SEYITL, SEYKAL, SEYKEL, SEYKGI, SEYLAI, SEYLEI, SEYMVI, SEYQSI, SEYRPI, SEYSEI, SEYSSI, SEYTPI, SEYTYV, SFYAAL, SFYDSL, SFYKGL, SFYLYV, SFYNAV, SFYPSV, SFYQQI, SFYQQL, SFYSAL, SFYSDI, SFYSKL, SFYSRV, SFYWNV, SFYYLI, SGYAQL, SGYATL, SGYEKL, SGYQLV, SGYQRI, SGYRRL, SGYSHL, SGYSQL, SGYTLI, SGYTRI, SGYYRV, SHYADV, SHYFPL, SHYIDI, SHYKRL, SHYQVV, SIYAPL, SIYATL, SIYEEL, SIYEEV, SIYELL, SIYEVL, SIYGDL, SIYKKL, SIYLNI, SIYLVI, SIYRYI, SIYSWI, SKYKEI, SKYKIL, SKYKSL, SKYLAV, SKYLGV, SKYNIL, SKYQAV, SKYSDI, SKYSSL, SKYVGL, SKYVSL, SLYANI, SLYAQV, SLYAYI, SLYDDL, SLYDFL, SLYDNL, SLYDSI, SLYDYL, SLYEGL, SLYEHI, SLYELL, SLYHCL, SLYHKL, SLYIGI, SLYKKL, SLYKNL, SLYLAI, SLYLGI, SLYNAL, SLYNLL, SLYRNI, SLYSDV, SLYTCV, SLYTTL, SLYVAI, SLYVDV, SLYVSI, SLYYAL, SLYYNI, SLYYPI, SMYDGL, SMYEDI, SMYNEI, SMYQSV, SMYTWL, SMYVSI, SNYENL, SNYGSL, SNYGTI, SNYLVL, SNYQEI, SNYRLL, SNYRTL, SNYSDI, SNYSLL, SPYAEI, SPYATL, SPYEKV, SPYGDI, SPYGGL, SPYNTL, SPYPGI, SPYPGV, SPYQEL, SPYRSV, SPYSRL, SPYTDV, SPYTSV, SPYVVI, SQYCVL, SQYEAL, SQYKRL, SQYLAL, SQYLRL, SQYMHV, SQYSAV, SQYTSI, SQYWRL, SRYAEL, SRYATL, SRYESL, SRYGLL, SRYLSL, SRYMEL, SRYMRI, SRYPPV, SRYQAL, SRYQQL, SRYRFI, SRYRFV, SRYSAL, SRYSDL, SRYTGL, SRYVRL, SSYDEL, SSYEAL, SSYEIV, SSYEPL, SSYGRL, SSYGSI, SSYGSL,

SSYHII, SSYHIL, SSYHKL, SSYHNI, SSYIKV, SSYNSV, SSYQEI, SSYRKV, SSYRRV, SSYSDI, SSYTPL, SSYTRL, SSYTSV, SSYTTI, SSYVKL, STYAEV, STYAGI, STYAHL, STYALV, STYAPI, STYDHV, STYDKV, STYDQV, STYDRI, STYEEL, STYEYL, STYILV, STYLPL, STYMAV, STYQTL, STYRKL, STYSQL, STYTSI, STYYQV, SVYATL, SVYCFL, SVYCNL, SVYDSV, SVYDTI, SVYEKV, SVYEML, SVYGSV, SVYPII, SVYQPI, SVYRKV, SVYSHL, SVYSRV, SVYTAL, SVYTEL, SVYWKV, SWYDSI, SWYFTV, SYYKAI, SYYLKL, SYYSFV, SYYVTI, VAYADL, VAYARI, VAYARV, VAYDQL, VAYGHV, VAYKQV, VAYKRL, VAYNLL, VAYQRV, VAYSGV, VAYSQV, VCYCIV, VCYGLV, VCYGRL, VCYIVV, VCYLLV, VDYDCI, VDYDFL, VDYFTI, VDYFVL, VDYGEL, VDYILV, VDYIQV, VDYKNI, VDYMSI, VDYNLV, VDYPDV, VDYSDL, VDYSSV, VDYTTL, VDYVDV, VDYVGV, VDYVIL, VDYVQV, VEYAPL, VEYDPL, VEYGTI, VEYHRL, VEYLEV, VEYQLL, VEYRPL, VEYSSI, VEYSTV, VFYAEI, VFYLAV, VFYRQV, VFYVGV, VFYYVI, VFYYVL, VGYETI, VHYALL, VHYARL, VHYETL, VHYGGV, VHYHSL, VHYIPV, VHYKEI, VHYLQV, VHYNSL, VHYQSV, VHYRSL, VIYAQL, VIYDRL, VIYENV, VIYEPL, VIYERL, VIYIDV, VIYKKI, VIYKRI, VIYPFL, VIYPNI, VIYSDL, VIYSML, VIYSSV, VIYSWI, VKYADI, VKYARL, VKYATL, VKYEGL, VKYGDL, VKYGSV, VKYLLV, VKYNPV, VKYPPI, VKYQRL, VKYQVI, VKYSEV, VKYSNV, VKYSRL, VKYSTL, VKYVDL, VLYADI, VLYAML, VLYASV, VLYCLL, VLYCLV, VLYCVL, VLYDCL, VLYFHI, VLYFTV, VLYGDL, VLYGQL, VLYPMV, VLYPRL, VLYPRV, VLYSEL, VLYSRV, VLYTAV, VLYTIL, VMYDAV, VNYESI, VNYSAL, VNYSKI, VNYSSI, VPYALL, VPYDTL, VPYEDV, VPYEEL, VPYKTI, VPYLRV, VPYNDL, VPYPAL, VPYQEL, VPYRLL, VPYSEL, VPYTLL, VPYTPL, VPYTTL, VPYVEL, VPYVMV, VPYVSL, VQYKAV, VQYKEI, VQYNIV, VQYRPV, VQYSQI, VQYSTV, VQYTEV, VQYYNI, VRYARL, VRYDNL, VRYGRI, VRYKKL, VRYKRV, VRYLDV, VRYRTI, VRYSDI, VRYTQL, VRYVCL, VSYAEL, VSYASV, VSYEPI, VSYGDI, VSYIGL, VSYILV, VSYMML, VSYNNI, VSYNNL, VSYQEI, VSYQPI, VSYSAV, VSYSFL, VSYSLV, VSYSPV, VSYTML, VSYTNL, VSYTPL, VSYVKI, VSYVLL, VTYADL, VTYAEL, VTYAEV, VTYAKV, VTYAPV, VTYAQL, VTYATL, VTYATV, VTYGNI, VTYITI, VTYQII, VTYQIL, VTYQLL, VTYSAL, VTYSTL, VTYTLL, VTYTQL, VTYVNL, VVYADI, VVYEDV, VVYFCL, VVYKTL, VVYQKL, VVYSEV, VVYSQV, VVYSVV, VVYTVL, VVYYRI, VYYHWL or VYYLPL.

48. The N-CAR according to any one of the preceding embodiments wherein the intracellular domain comprises several ITSMs having the same amino acid sequence.

49. The N-CAR according to any one of the preceding embodiments wherein the intracellular domain comprises several ITSMs having different amino acid sequences.

50. The N-CAR any one of the preceding embodiments wherein the intracellular domain comprises several ITIMs having the same amino acid sequence.

51. The N-CAR any one of the preceding embodiments wherein the intracellular domain comprises several ITIMs having different amino acid sequences.

52. The N-CAR according to any one of embodiments 7 to 51 wherein p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

53. The N-CAR according to any one of embodiments 7 to 51 wherein p is 1.

54. The N-CAR according to any one of embodiments 7 to 51 wherein p is 2.

55. The N-CAR according to any one of embodiments 7 to 51 wherein p is 3.

56. The N-CAR according to any one of embodiments 7 to 51 wherein p is 4.

57. The N-CAR according to any one of embodiments 7 to 51 wherein p is 5.

58. The N-CAR according to any one of embodiments 7 to 57 wherein n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

59. The N-CAR according to any one of embodiments 7 to 57 wherein n is 0.

60. The N-CAR according to any one of embodiments 7 to 57 wherein n is 1.

61. The N-CAR according to any one of embodiments 7 to 57 wherein n is 2.

62. The N-CAR according to any one of embodiments 7 to 57 wherein n is 3.

63. The N-CAR according to any one of embodiments 7 to 62 wherein m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

64. The N-CAR according to any one of embodiments 7 to 62 wherein m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

65. The N-CAR according to any one of embodiments 7 to 62 wherein m is 1, 2, 3, 4 or 5.

66. The N-CAR according to any one of embodiments 7 to 62 wherein m is 1.

67. The N-CAR according to any one of embodiments 7 to 62 wherein m is 2.

68. The N-CAR according to any one of embodiments 7 to 62 wherein m is 3.

69. The N-CAR according to any one of embodiments 7 to 62 wherein m is 4.

70. The N-CAR according to any one of embodiments 7 to 62 wherein m is 5.

71. The N-CAR according to any one of embodiments 7 to 51 wherein n is 0, m is 1 to 6 and p is 1 and ITSM is TEYATI.

72. The N-CAR according to any one of embodiments 7 to 51 wherein n is 0, m is 1 to 6 and p is 1 and ITSM is TEYSEI.

73. The N-CAR according to any one of embodiments 7 to 51 wherein n is 0, m is 1 to 6 and p is 1 and ITSM is TEYASI.

74. The N-CAR according to any one of embodiments 7 to 51 wherein n is 1, m is 1 and p is 1 to 5 and ITIM is VDYGEL and ITSM is TEYATI.

75. The N-CAR according to any one of embodiments 7 to 51 wherein n is 1, m is 1 and p is 1 to 5 and ITIM is LX_6YAX_8L wherein X_6 is selected from H or Q and X_8 is V or S, and ITSM is TEYSEI.

76. The N-CAR according to any one of embodiments 1 to 75 wherein the intracellular domain comprises several ITSMs having the same amino acid sequence.

77. The N-CAR according to any one of embodiments 1 to 75 wherein the intracellular domain comprises several ITSMs having different amino acid sequences.

78. The N-CAR according to any one of embodiments 1 to 75 wherein the intracellular domain comprises several ITIMs having the same amino acid sequence.

79. The N-CAR according to any one of embodiments 1 to 75 wherein the intracellular domain comprises several ITIMs having different amino acid sequences.

80. The N-CAR according to any one of embodiments 1 to 79, wherein the antigen binding domain is a single chain variable fragment (scFv).

81. The N-CAR according to any one of embodiments 1 to 79, wherein the antigen binding domain is a Fv, a Fab, or a (Fab')2.

82. The N-CAR according to any one of embodiments 1 to 81, wherein the antigen binding domain binds to ITGAX, CD1E, CD34, CD1C, CD123 or CD141.

83. The N-CAR according to any one of embodiments 1 to 81, wherein the antigen binding domain binds to ZP2, GABRA6, CRTAM or GRM4, or MDGA1.

84. The N-CAR according to any one of embodiments 1 to 81, wherein the antigen binding domain binds to SFTPC, ROS1, SLC6A4 or AGTR2.

85. The N-CAR according to any one of embodiments 1 to 81, wherein the antigen binding domain binds to LRRC26, HTR3A, TMEM211 or MRGPRX3.

86. The N-CAR according to any one of embodiments 1 to 81, wherein the antigen binding domain binds to MEP1B, TMIGD1, CEACAM20, or ALPI.

87. The N-CAR according to any one of embodiments 1 to 81, wherein the antigen binding domain binds to TMPRSS11B, CYP17A1 or ATP4B.

88. The N-CAR according to any one of embodiments 1 to 81, wherein the antigen binding domain binds to GP2, MUC21, CLCA4 and SLC27A6.

89. The N-CAR according to any one of embodiments 1 to 81, wherein the antigen binding domain binds to a cell-surface protein present in normal tissue but not present or present at lower level on a tumor

90. The N-CAR according to any one of embodiments 1 to 81 wherein the antigen binding domain binds to an off-tissue antigen.

91. The N-CAR according to any one of embodiments 1 to 90 wherein the transmembrane domain comprises the transmembrane region(s) of the alpha, beta or zeta chain of the T-cell receptor, PD-1, 4-1BB, OX40, ICOS, CTLA-4, LAG3, 2B4, BTLA4, TIM-3, TIGIT, SIRPA, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 or CD154.

92. The N-CAR according to any one of embodiments 1 to 91 wherein the transmembrane domain comprises the transmembrane region of PD-1.

93. The N-CAR according to any one of embodiments 1 to 92 wherein the transmembrane domain comprises the transmembrane region(s) of CD8 alpha.

94. The N-CAR according to any one of embodiments 1 to 93 wherein the transmembrane domain is attached to the extracellular domain of the N-CAR via a hinge.

95. The N-CAR according to embodiment 94 wherein the hinge is a human immunoglobulin hinge.

96. The N-CAR according to embodiment 94 wherein the hinge is an IgG4 hinge, a CD8 alpha hinge or a PD-1 hinge.

96.1 The N-CAR according to embodiment 94 wherein the hinge is a PD-1 hinge.

97. An isolated immune cell comprising a P-CAR comprising,
an extracellular domain comprising an antigen binding domain ,
a transmembrane domain
an intracellular domain
and an N-CAR according to any one of embodiments 1 to 96.

98. The immune cell according to embodiment 97, wherein the antigen to which the antigen binding domain of the P-CAR binds is CD33 and the antigen to which the antigen binding domain of the N-CAR binds is ITGAX, CD1E, CD34, CD1C, CD123, or CD141.

99. The immune cell according to embodiment 97, wherein the antigen to which the antigen binding domain of the P-CAR binds is FLT3 and the antigen to which the antigen binding domain of the N-CAR binds is ZP2, GABRA6, CRTAM, GRM4 or MDGA1.

100. The immune cell according to embodiment 97, wherein the antigen to which the antigen binding domain of the P-CAR binds is MSLN and the antigen to which the antigen binding domain of the N-CAR binds is SFTPC, ROS1, SLC6A4 or AGTR2.

101. The immune cell according to embodiment 97, wherein the antigen to which the antigen binding domain of the P-CAR binds is MUC16 and the antigen to which the antigen binding domain of the N-CAR binds is LRRC26, HTR3A, TMEM211 or MRGPRX3.

102. The immune cell according to embodiment 97, wherein the antigen to which the antigen binding domain of the P-CAR binds is MUC17 and the antigen to which the antigen binding domain of the N-CAR binds is MEP1B, TMIGD1, CEACAM20 or ALPI.

103. The immune cell according to embodiment 97, wherein the antigen to which the antigen binding domain of the P-CAR binds is present in tumor cells of pancreatic ductal adenocarcinoma and the antigen to which the antigen binding domain of the N-CAR binds is TMPRSS11B, CYP17A1 or ATP4B.

104. The immune cell according to embodiment 97, wherein the antigen to which the antigen binding domain of the P-CAR binds is present in tumor cells of kidney clear cell carcinoma

and the antigen to which the antigen binding domain of the N-CAR binds is GP2, MUC21, CLCA4 and SLC27A6.

105. The immune cell according to any one of embodiments 97 to 104 wherein the immune cell is a T-cell.

106. The immune cell according to embodiment 105 wherein the T-cell is a human T-cell.

107. The immune cell according to any one of embodiments 97 to 106 for its use as a medicament.

108. The immune cell according to any one of embodiments 97 to 106 for its use for the treatment of cancer.

109. The immune cell according to any one of embodiments 97 to 106 derived from inflammatory T- lymphocytes, cytotoxic T-lymphocytes, regulatory T-lymphocytes or helper T- lymphocytes.

110. A method of engineering an immune cell according to any one of embodiments 97 to 109 comprising: (a) Providing an immune cell; (b) expressing the N-CAR and the P-CAR at the surface of said cells.

111. A method of engineering an immune cell of embodiment 110 comprising: (a) providing an immune cell; (b) introducing into said cell at least one polynucleotide encoding the N-CAR and at least one polynucleotide encoding the P-CAR; (c) expressing said polynucleotides into said cell.

112. A method for treating a patient in need thereof comprising: a) providing an immune cell according to any one of embodiments 97 to 109, and; b) administrating said T-cells to said patient.

113. The method for treating a patient of embodiment 112 wherein said immune cells are recovered from donors.

114. The method for treating a patient of embodiment 113 wherein said immune cells are recovered from patients.

115. The immune cell according to any one of embodiments 97 to 109 wherein the reduction of activation of the immune cells when both the P-CAR and N-CAR bind to their respective antigens is increased, preferably by at least 5%, 10%, 15%, 20% or 30% as compared to the same immune cell comprising an N-CAR comprising the full intracellular domain of PD-1.

116. The immune cell according to any one of embodiments 97 to 109 wherein the reduction of activation of the immune cells when both the P-CAR and N-CAR bind to their respective antigens is increased, preferably by at least 5%, 10%, 15%, 20% or 30% as compared to the same immune cell comprising an N-CAR comprising the full intracellular domain of CTLA-4.

117. The immune cell according to any one of embodiments 97 to 109 wherein the activation of the immune cells is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85% when the N-CAR and P-CAR antigen binding

domains both binds to their respective antigens as compared to when only the P-CAR antigen binding domain binds to its antigen.

118. The immune cell according to any one of embodiments 115 to 117 wherein the level of activation of the immune cell is determined by measuring cytokine production.

119. The immune cell according to embodiment 118 wherein the cytokine is IFNgamma or TNFalpha.

120. The immune cell according to embodiment 118 or 119 wherein the cytokine production is measured by ELISA and/or FACS and/or luminex.

121. The immune cell according to any one of embodiments 115 to 117 wherein the level of activation of the immune cell is determined by the level of degranulation.

122. The immune cell according to embodiment 121 wherein degranulation is measured by measuring expression of CD107a by FACS.

123. The immune cell according to embodiment 115 to 117 wherein the level of activation of the immune cell is measured by monitoring the ability of the immune cell to kill target cells.

124. The immune cell according to any one of embodiments 115 to 117 wherein the level of activation of the immune cell is determined by monitoring the luciferase activity in reporter cells incorporating inducible NFAT- or NfkB-regulated luciferase expression.

125. The immune cell according to any one of embodiments 115 to 117 wherein the level of activation of the immune cell is determined by monitoring the luciferase activity in reporter cells incorporating inducible NFAT- or NfkB-regulated luciferase expression as disclosed in Example 3.

126. A polynucleotide comprising a nucleic acid sequence encoding an N-CAR according to any one of embodiments 1 to 96.

127. A vector comprising a polynucleotide according to embodiment 124.

Claims

1. An inhibitory chimeric antigen receptor (N-CAR) comprising
an extracellular domain comprising an antigen binding domain,
a transmembrane domain
an intracellular domain
wherein the intracellular domain comprises an Immunoreceptor Tyrosine-based Switch Motif ITSM, wherein said ITSM is a sequence of amino acid $TX_1YX_2X_3X_4$, wherein
X_1 is an amino acid
X_2 is an amino acid
X_3 is an amino acid and
X_4 is V or I.

2. The N-CAR according to claim 1, wherein the intracellular domain is not the intracellular domain of human PD-1, human CD244 or human BTLA.

3. The N-CAR according to claim 1 or 2, wherein the intracellular domain comprises the sequence
$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein
n is 0, 1 or an integer greater than 1;
m is 1 or an integer greater than 1;
p is 1 or an integer greater than 1;
L1 is absent or comprises one or more sequences selected from the group consisting of:

(a) a naturally occurring N-terminal flanking region of ITIM only intracellular domains selected from the sequences shown in Table 3 or a fragment thereof;

(b) a naturally occurring N-terminal flanking region of ITIM.*ITSM intracellular selected from the sequences shown in Table 1 or a fragment thereof;

(c) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in Table 2 or a fragment thereof, wherein said intracellular domain is N-terminally flanking to a sequence in (b) above, or a fragment thereof; and

(d) a non-naturally occurring sequence comprising between 1 and 500 amino acids;

each of L2 and L3 is absent or comprises one or more sequences selected from the group consisting of:

(e) a naturally occurring C-terminal flanking region of ITIM only intracellular domains selected from the sequences shown in Table 4 or a fragment thereof;

(f) a naturally occurring N-terminal flanking region of ITSM only intracellular domains selected from the sequences shown in Table 6, or a fragment thereof;

(g) a naturally occurring intracellular domain between ITIM and ITSM from proteins that have ITIM.*ITSM motif selected from the sequences shown in Table 5, or a fragment thereof;

(h) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in Table 2 or a fragment thereof wherein said intracellular domain is N-terminally flanking to a sequence in (f) or (g) above, or a fragment thereof; and

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids; and

L4 is absent or comprises one or more sequences selected from the group consisting of:

(j) a naturally occurring C-terminal flanking region of ITIM.*ITSM intracellular domains selected from the sequences shown in Table 7, or a fragment thereof;

(k) a naturally occurring C-terminal flanking region of ITSM only intracellular domains selected from the sequences shown in Table 8, or a fragment thereof;

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in Table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (j) or (k) above, or a fragment thereof; and,

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids and,

the ITIM is the sequence $X_5X_6YX_7X_8X_9$, wherein

X_5 is S, V, I or L,

X_6 is an amino acid,

X_7 is an amino acid,

X_8 is an amino acid, and,

X_9 is V, I or L, and

the ITSM is the sequence $TX_1YX_2X_3X_4$, wherein

X_1 is an amino acid,

X_2 is an amino acid,

X_3 is an amino acid, and,

X_4 is V or I,

or a variant thereof.

4. The N-CAR according to claim 3 wherein the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein

n is 0;

m is 1;

p is 1;

L3 comprises one sequence selected from

(f) a naturally occurring N-terminal flanking region of an ITSM only intracellular domain selected from the sequences shown in Table 6 below or a fragment thereof; or,

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids; and

L4 comprises one or more, preferably one or two, sequences selected from the group consisting of:

(k) a naturally occurring C-terminal flanking region of an ITSM only intracellular domain selected from the sequences shown in Table 8 below or a fragment thereof;

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above; and

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids.

5. The N-CAR according to claim 4 wherein L3 is selected from

CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQ
RIRQKKAQGSTSSTRLHEPEKNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNH
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVRNHAMKPIND NKEPLNSDVQYTEVQVSSAESHKDLGKKDTE
RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPDLCFRMQEG SEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVKEAP
WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEY VTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGRGPEEP
WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTFPGGGSTIYSMIQSQSSAPTSQE PAYTLYSLIQPSRKSGSRKRNHSPSFNS
VRSCRKKSARPAAGVGDTGIEDANAVRGSASQGPLTEPWAEDSPPDQPPPASARSSVGE GELQYASLSFQMVKPWDSRGQEATD
KRKGRCSVPAFCSSQAEAPADTPEPTAGHTLYSVLSQGYEKLDTPLRPARQQPTPTSDSSS DSNLTTEEDEDRPEVHKPISGRYEVFDQVTQEGAGHDPAPEGQADYDPVTPYVTEVESVV GENTMYAQVFNLQGKTPVSQKEESSA

and L4 comprises one sequence selected from the group consisting of (k)

SRP
KIHR
CVRS
RKAVPDAVESRYSRTEGSLDGT
RKPQVVPPPQQNDLEIPESPTYENFT
GKSQPKAQNPARLSRKELENFDVYS
VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
QTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK

and optionally

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above.

6. The N-CAR according to claim 4 wherein L3 is selected from

CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQ

and L4 comprises (k)

VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL

and

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above.

7. The N-CAR according to claim 4 wherein L3 is

WRMMKYQQKAAGMSPEQVLQPLEGDLCYADLTLQLAGTSPQKATTKLSSAQVDQVEVEY VTMASLPKEDISYASLTLGAEDQEPTYCNMGHLSSHLPGRGPEEP

and L4 comprises one sequence selected from

(k)

SRP

and optionally

(l) a naturally occurring intracellular domain from a known inhibitory receptor selected from the sequences shown in table 2 or a fragment thereof wherein said intracellular domain is C-terminally flanking to a sequence in (k) above.

8. The N-CAR according to claim 4 wherein the intracellular domain comprises the following sequence:

$((L1\text{-}ITIM\text{-}L2)^n\text{-}(L3\text{-}ITSM\text{-}L4)^m)^p$, wherein

n is 0;

m is 1;

p is 1 or 2;

L3 comprises one sequence selected from

(i) a non-naturally occurring sequence comprising between 1 and 500 amino acids; and

L4 comprises one sequence selected from the group consisting of:

(m) a non-naturally occurring sequence comprising between 1 and 500 amino acids.

9. The N-CAR any one of the preceding claims wherein the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain, is selected from TAYELV, TAYGLI, TAYNAV, TCYGLV, TCYPDI, TDYASI, TDYDLV, TDYLSI, TDYQQV, TDYYRV, TEYASI, TEYATI, TEYDTI, TEYPLV, TEYSEI, TEYSEV, TEYSTI, TEYTKV, TFYHVV, TFYLLI, TFYNKI, TFYPDI, TGYEDV, TGYLSI, THYKEI, TIYAQV, TIYAVV, TIYCSI, TIYEDV, TIYERI, TIYEVI, TIYHVI, TIYIGV, TIYLKV, TIYSMI, TIYSTI, TIYTYI, TKYFHI, TKYMEI, TKYQSV, TKYSNI, TKYSTV, TLYASV, TLYAVV, TLYFWV, TLYHLV, TLYPMV, TLYPPI, TLYRDI, TLYRDV, TLYSKI, TLYSLI, TLYSPV, TMYAQV, TMYCQV, TNYKAV, TNYNLV, TPYAGI, TPYPGV, TPYVDI, TQYGRV, TQYNQV, TRYAYV, TRYGEV, TRYHSV, TRYKTI, TRYLAI, TRYMAI, TRYQKI, TRYQQI, TRYSNI, TRYSPI, TSYGTV, TSYMEV, TSYQGV, TSYTTI, TTYRSI, TTYSDV, TTYVTI, TVYAQI, TVYASV, TVYEVI, TVYGDV, TVYKGI, TVYQRV, TVYSEV, TVYSTV, TYYHSI, TYYLQI, or TYYYSV.

10. The N-CAR any one of the preceding claims wherein the ITSM, or at least one of the ITSMs when several ITSMs are present in the intracellular domain is selected from TEYASI, TEYSEI. TEYSTI or TVYSEV.

11. The N-CAR according to any one of claims 1 to 11, wherein the antigen binding domain is a single chain variable fragment (scFv).

12. The N-CAR according to claim 1 wherein the intracellular domain is selected from SEQ ID No 2000, SEQ ID No 2001, SEQ ID No 2002, SEQ ID No 2003, SEQ ID No 2004, SEQ ID No 2005, SEQ ID No 2006, SEQ ID No 2007, SEQ ID No 2008, SEQ ID No 2009, SEQ ID

No 2010, SEQ ID No 2011, SEQ ID No 2012, SEQ ID No 2013, SEQ ID No 2014, SEQ ID No 2015, SEQ ID No 2016 and SEQ ID No 2017 or a variant thereof.

13. The N-CAR according to any one of claims 1 to 12, wherein the antigen binding domain binds to ITGAX, CD1E, CD34, CD1C, CD123 or CD141, ZP2, GABRA6, CRTAM, GRM4, MDGA1, ZP2, GABRA6, CRTAM, GRM4, MDGA1, SFTPC, ROS1, SLC6A4, AGTR2, LRRC26, HTR3A, TMEM211, MRGPRX3, MEP1B, TMIGD1, CEACAM20, ALPI, TMPRSS11B, CYP17A1, ATP4B, GP2, MUC21, CLCA4 or SLC27A6.

14. The N-CAR according to any one of claims 1 to 13 wherein the transmembrane domain comprises the transmembrane region(s) of the alpha, beta or zeta chain of the T-cell receptor, PD-1, 4-1BB, OX40, ICOS, CTLA-4, LAG3, 2B4, BTLA4, TIM-3, TIGIT, SIRPA, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 or CD154.

15. The N-CAR according to any one of claims 1 to 14 wherein the transmembrane domain comprises the transmembrane region of PD-1 or CD8 alpha.

16. The N-CAR according to any one of claims 1 to 15 wherein the transmembrane domain is attached to the extracellular domain of the N-CAR via a hinge.

17. The N-CAR according to claim 94 wherein the hinge is an IgG4 hinge, a CD8 alpha hinge or a PD-1 hinge.

18. An isolated immune cell comprising a P-CAR comprising,
an extracellular domain comprising an antigen binding domain ,
a transmembrane domain, and,
an intracellular domain
and an N-CAR according to any one of claims 1 to 17.

19. The immune cell according to claim 18, wherein:
- the antigen to which the antigen binding domain of the P-CAR binds is CD33 and the antigen to which the antigen binding domain of the N-CAR binds is ITGAX, CD1E, CD34, CD1C, CD123, or CD141, or,
- the antigen to which the antigen binding domain of the P-CAR binds is FLT3 and the antigen to which the antigen binding domain of the N-CAR binds is ZP2, GABRA6, CRTAM, GRM4 or MDGA1, or,

- the antigen to which the antigen binding domain of the P-CAR binds is MSLN and the antigen to which the antigen binding domain of the N-CAR binds is SFTPC, ROS1, SLC6A4 or AGTR2, or,

the antigen to which the antigen binding domain of the P-CAR binds is MUC16 and the antigen to which the antigen binding domain of the N-CAR binds is LRRC26, HTR3A, TMEM211 or MRGPRX3, or,

- the antigen to which the antigen binding domain of the P-CAR binds is MUC17 and the antigen to which the antigen binding domain of the N-CAR binds is MEP1B, TMIGD1, CEACAM20 or ALPI, or,

- the antigen to which the antigen binding domain of the P-CAR binds is present in tumor cells of pancreatic ductal adenocarcinoma and the antigen to which the antigen binding domain of the N-CAR binds is TMPRSS11B, CYP17A1 or ATP4B,

- the antigen to which the antigen binding domain of the P-CAR binds is present in tumor cells of kidney clear cell carcinoma and the antigen to which the antigen binding domain of the N-CAR binds is GP2, MUC21, CLCA4 and SLC27A6.

20. The immune cell according to claim 18 or 19 wherein the immune cell is a human T-cell.

21. The immune cell according to any one of claims 18 to 20 for its use for the treatment of cancer.

22. A method of engineering an immune cell according to any one of claims 18 to 21 comprising: (a) Providing an immune cell; (b) expressing the N-CAR and the P-CAR at the surface of said cells.

23. A method for treating a patient in need thereof comprising: a) providing an immune cell according to any one of claims 18 to 21, and; b) administrating said T-cells to said patient.

24. A polynucleotide comprising a nucleic acid sequence encoding an N-CAR according to any one of claims 1 to 17.

25. A vector comprising a polynucleotide according to claim 24.

FIG 1

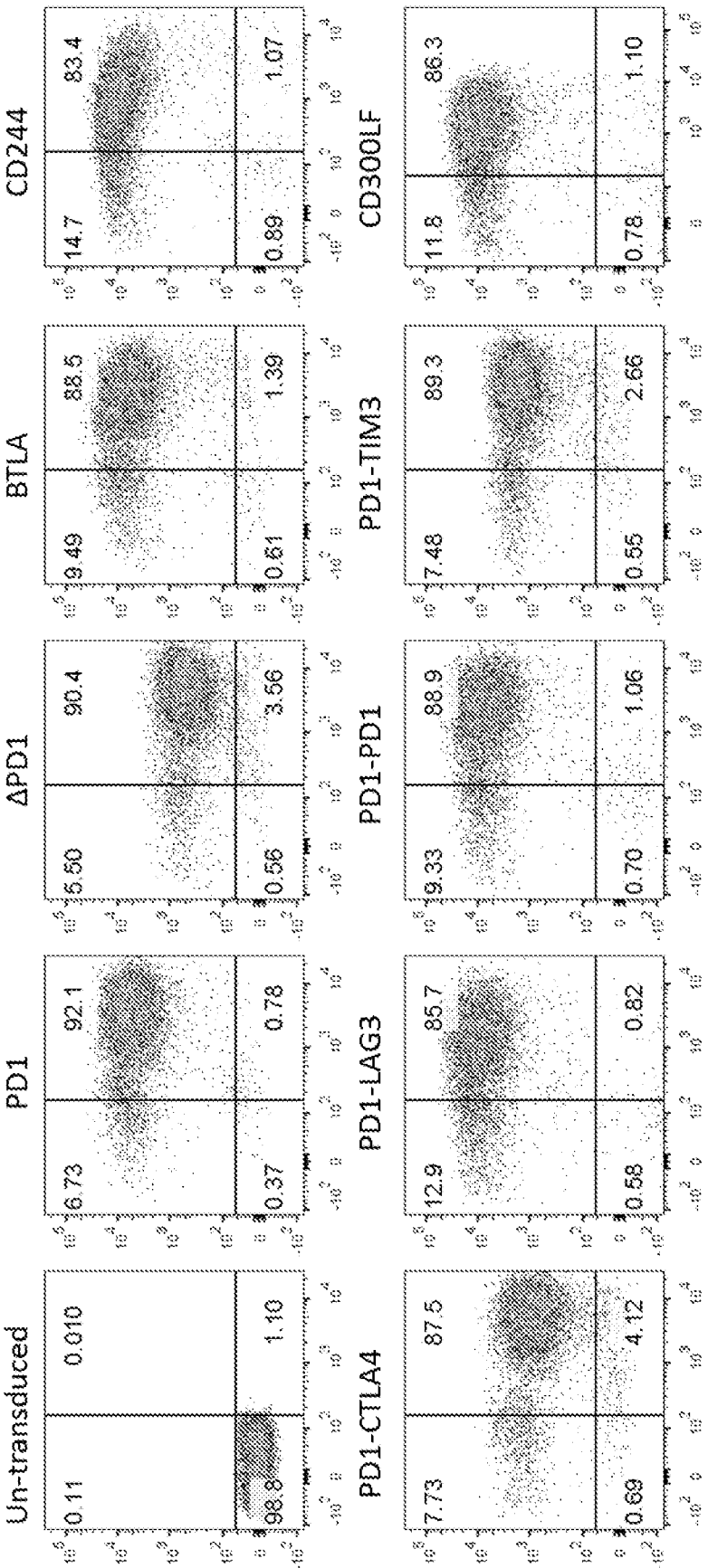

Un-transduced
PD1
ΔPD1
BTLA
CD244
0.11
0.010
98.8
1.10
6.73
92.1
0.37
0.78
6.50
90.4
0.56
3.56
9.49
88.5
0.61
1.39
14.7
83.4
0.89
1.07
PD1-CTLA4
PD1-LAG3
PD1-PD1
PD1-TIM3
CD300LF
7.73
87.5
0.69
4.12
12.9
85.7
0.58
0.82
9.33
88.9
0.70
1.06
7.48
89.3
0.55
2.66
11.8
86.3
0.78
1.10

FIG 2

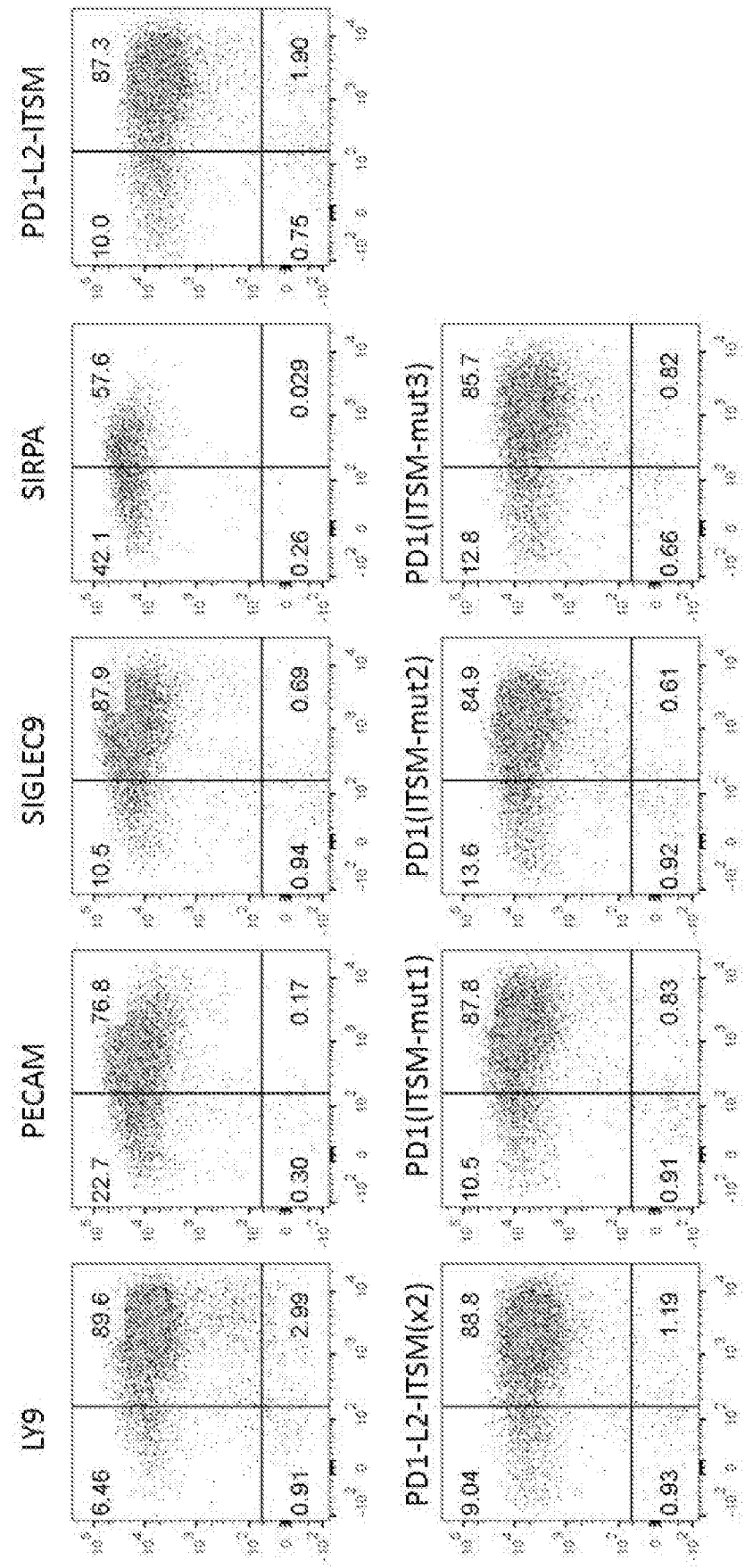

LY9
PECAM
SIGLEC9
SIRPA
PD1-L2-ITSM
PD1-L2-ITSM(x2)
PD1(ITSM-mut1)
PD1(ITSM-mut2)
PD1(ITSM-mut3)
6.46
89.6
0.91
2.99
22.7
76.8
0.30
0.17
10.5
87.9
0.94
0.69
42.1
57.6
0.26
0.029
10.0
87.3
0.75
1.90
9.04
88.8
0.93
1.19
10.5
87.8
0.91
0.83
13.6
84.9
0.92
0.61
12.8
85.7
0.66
0.82

FIG 3

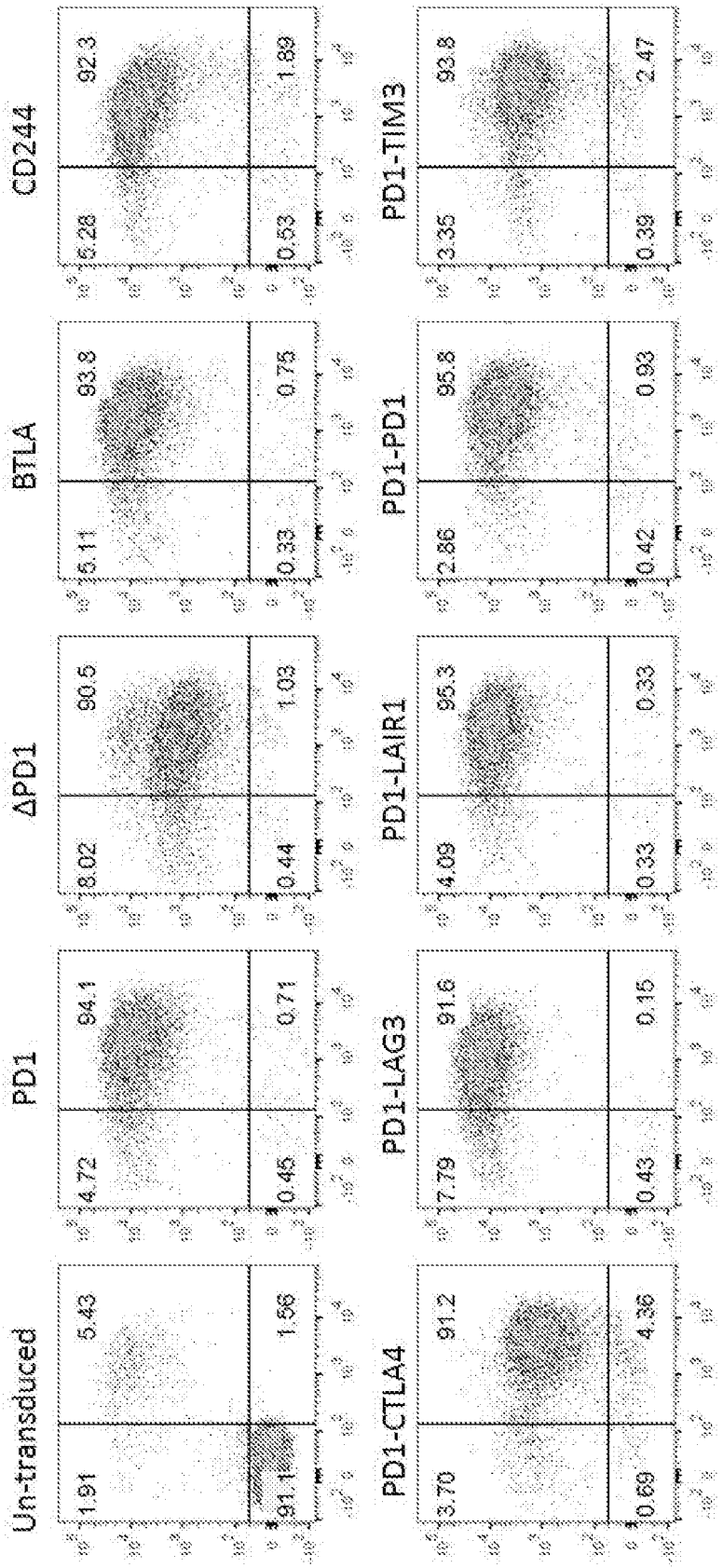

Un-transduced
PD1
ΔPD1
BTLA
CD244
1.91
5.43
91.1
1.56
4.72
94.1
0.45
0.71
8.02
90.5
0.44
1.03
5.11
93.8
0.33
0.75
16.28
92.3
0.53
1.89
PD1-CTLA4
PD1-LAG3
PD1-LAIR1
PD1-PD1
PD1-TIM3
3.70
91.2
0.69
4.36
7.79
91.6
0.43
0.15
4.09
95.3
0.33
0.33
2.86
95.8
0.42
0.93
13.35
93.8
0.39
2.47

FIG 4

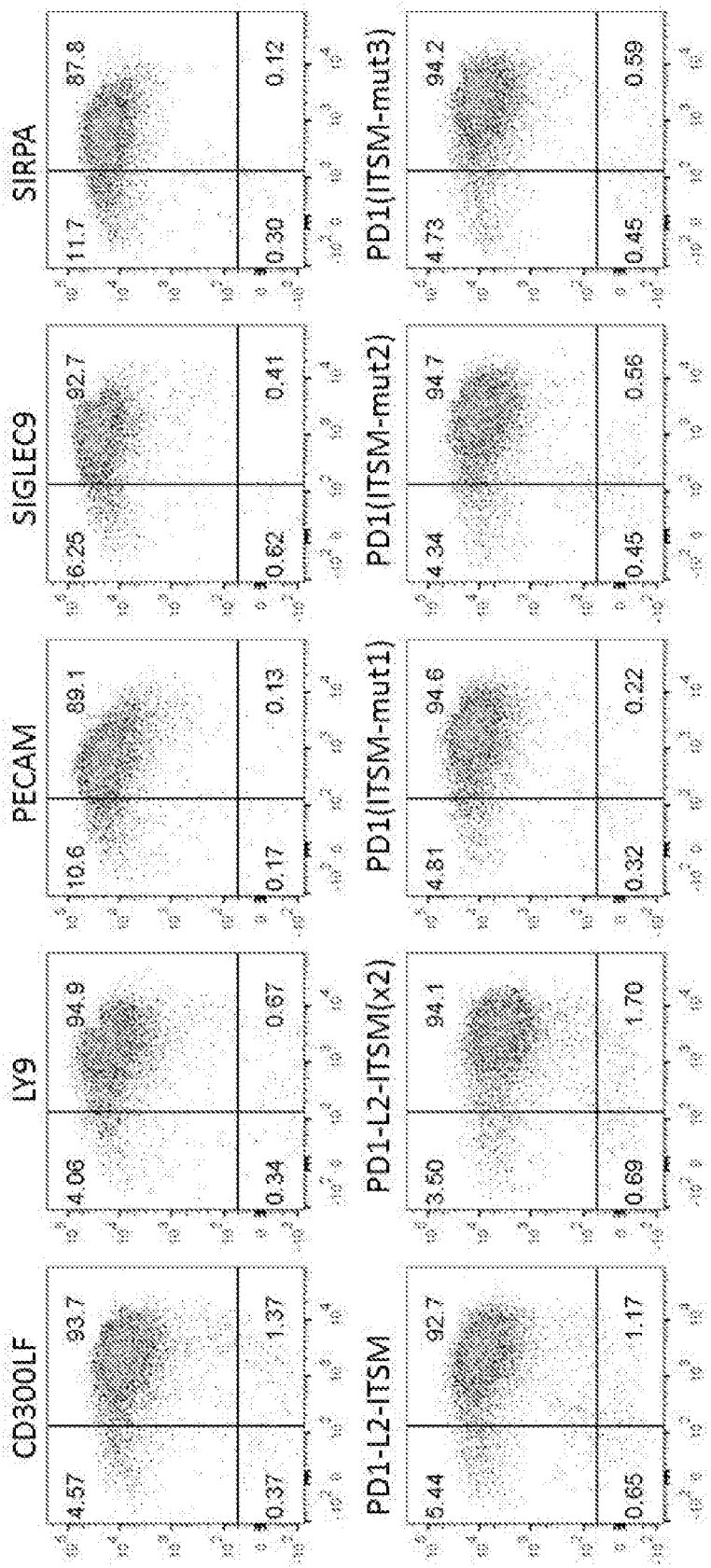

CD300LF
LY9
PECAM
SIGLEC9
SIRPA
PD1-L2-ITSM
PD1-L2-ITSM(x2)
PD1(ITSM-mut1)
PD1(ITSM-mut2)
PD1(ITSM-mut3)
4.57
93.7
0.37
1.37
4.06
94.9
0.34
0.67
10.6
89.1
0.17
0.13
6.25
92.7
0.62
0.41
11.7
87.8
0.30
0.12
5.44
92.7
0.65
1.17
3.50
94.1
0.69
1.70
4.81
94.6
0.32
0.22
4.34
94.7
0.45
0.56
4.73
94.2
0.45
0.59

FIG 5A

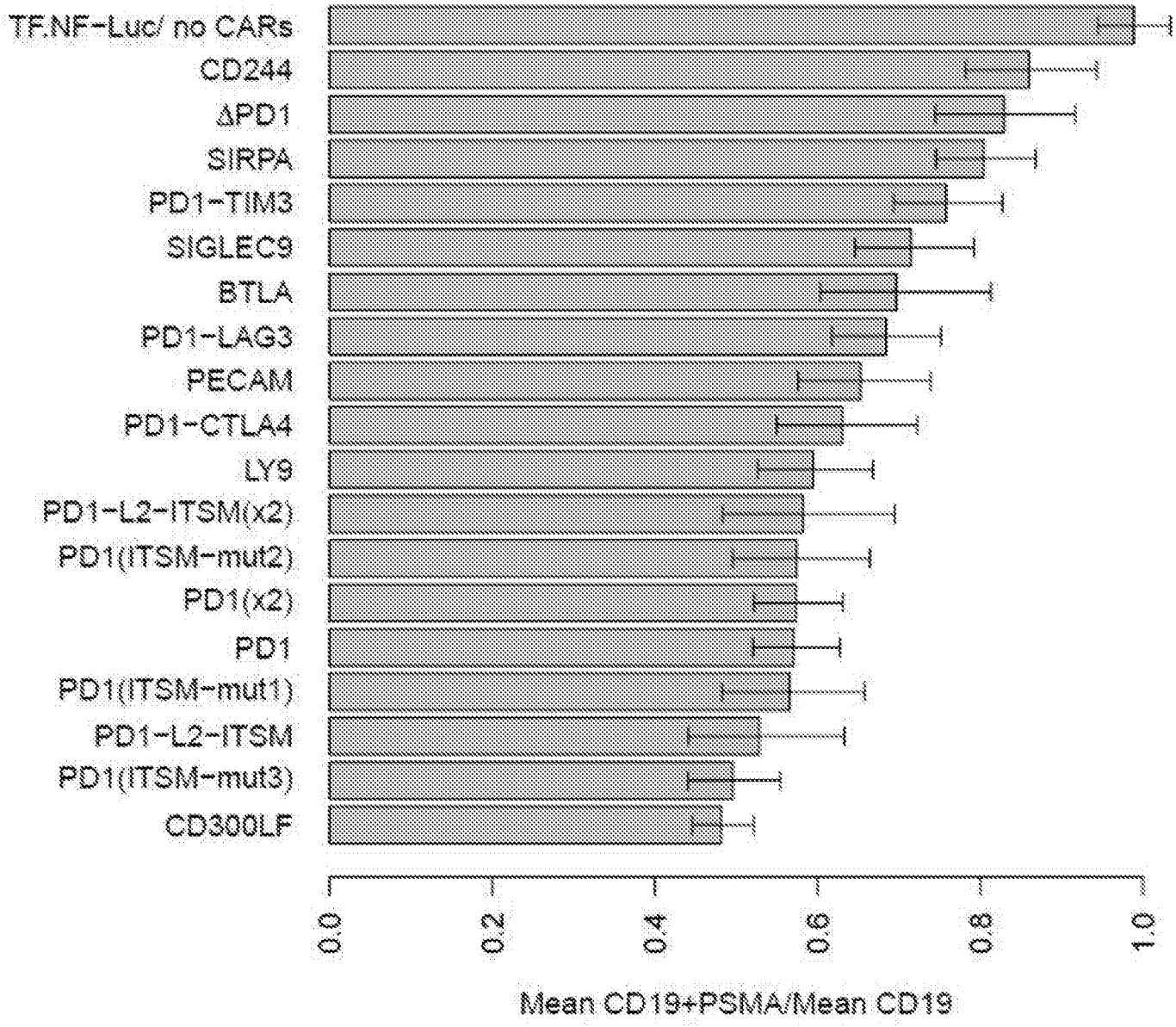

TF.NF-Luc/ no CARs
CD244
ΔPD1
SIRPA
PD1-TIM3
SIGLEC9
BTLA
PD1-LAG3
PECAM
PD1-CTLA4
LY9
PD1-L2-ITSM(x2)
PD1(ITSM-mut2)
PD1(x2)
PD1
PD1(ITSM-mut1)
PD1-L2-ITSM
PD1(ITSM-mut3)
CD300LF
0.0
0.2
0.4
0.6
0.8
1.0
Mean CD19+PSMA/Mean CD19

FIG 5B

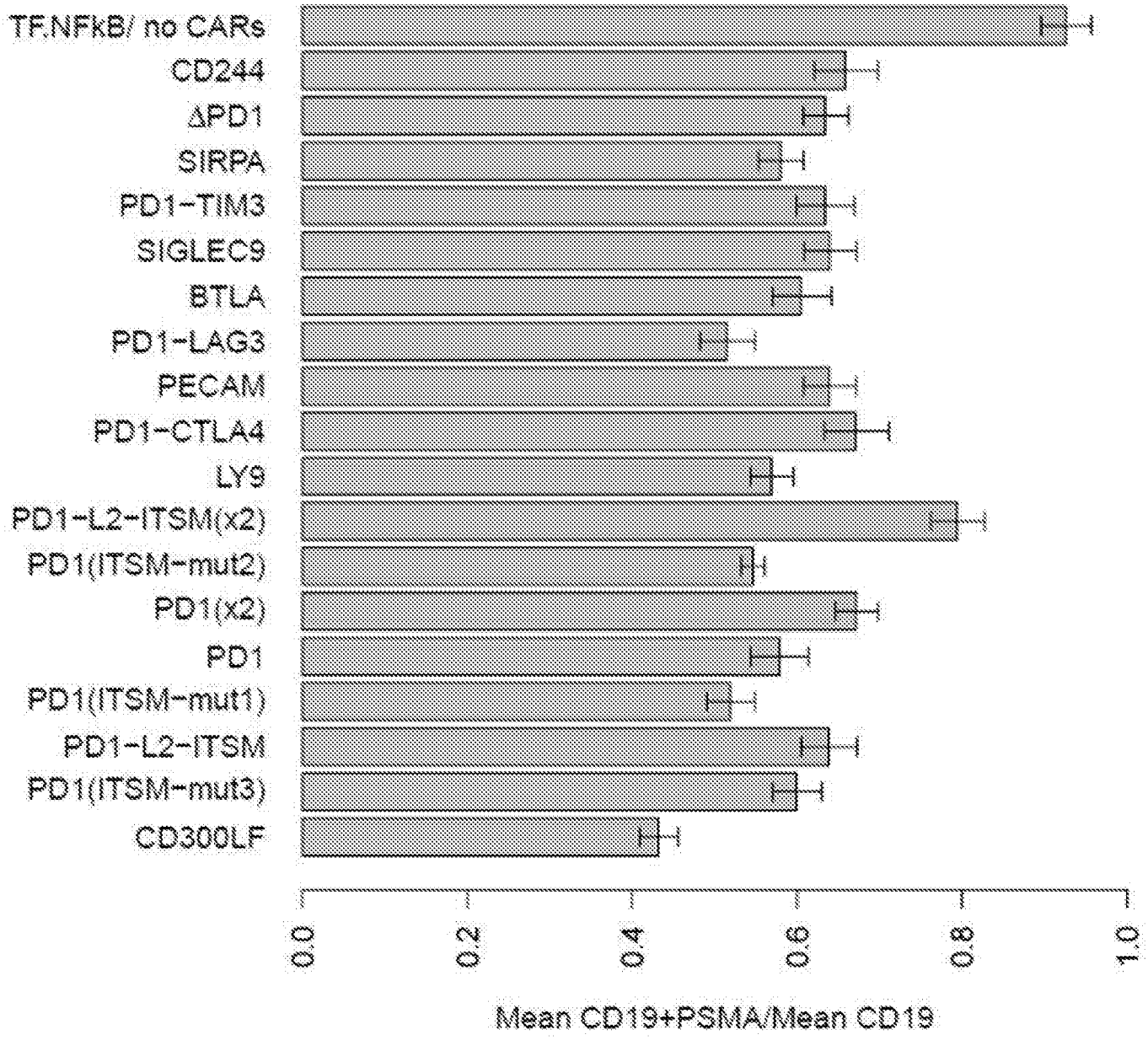

TF.NFkB/ no CARs
CD244
ΔPD1
SIRPA
PD1-TIM3
SIGLEC9
BTLA
PD1-LAG3
PECAM
PD1-CTLA4
LY9
PD1-L2-ITSM(x2)
PD1(ITSM-mut2)
PD1(x2)
PD1
PD1(ITSM-mut1)
PD1-L2-ITSM
PD1(ITSM-mut3)
CD300LF
0.0
0.2
0.4
0.6
0.8
1.0
Mean CD19+PSMA/Mean CD19

FIG 5C

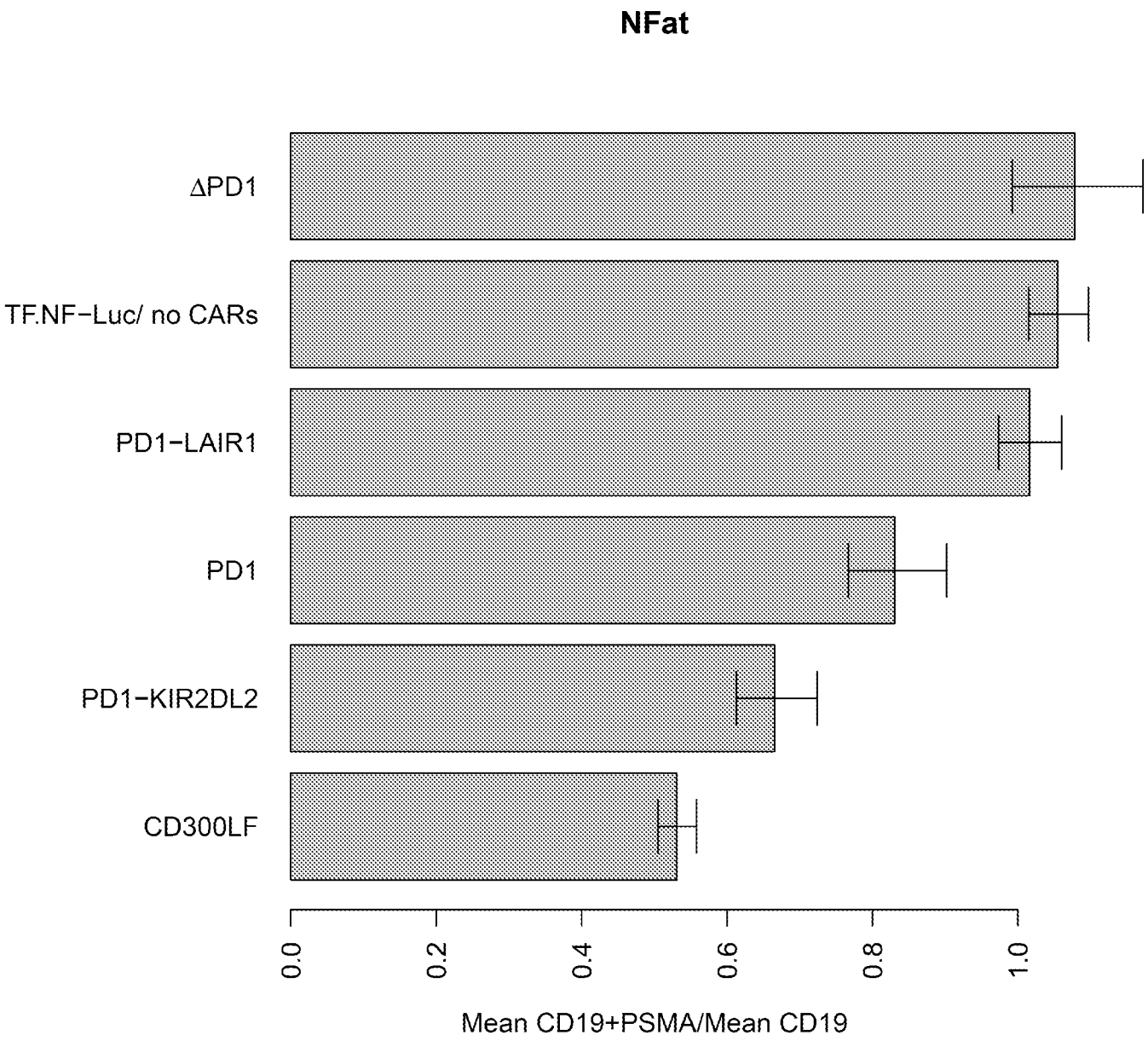

NFat
ΔPD1
TF.NF-Luc/ no CARs
PD1-LAIR1
PD1
PD1-KIR2DL2
CD300LF
0.0
0.2
0.4
0.6
0.8
1.0
Mean CD19+PSMA/Mean CD19

FIG 6

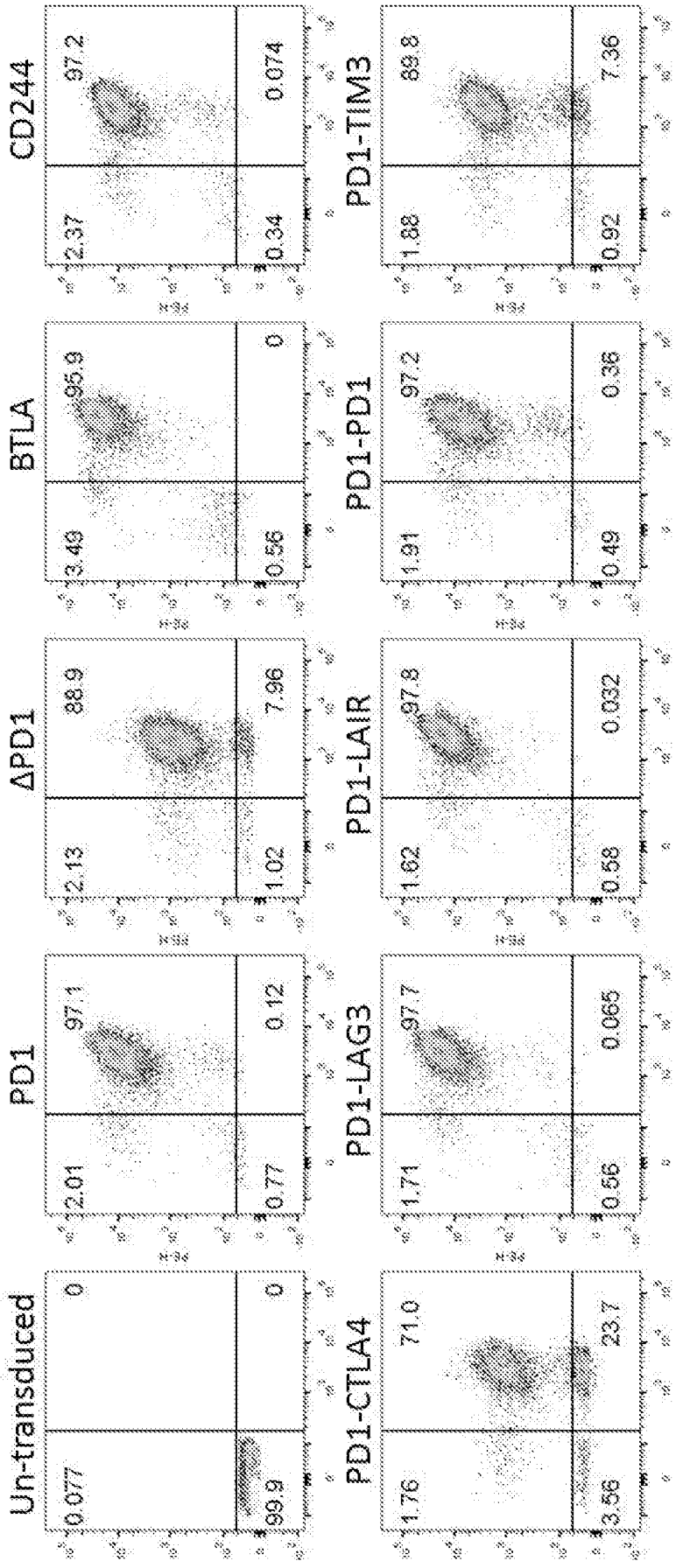

Un-transduced
0.077
99.9
0
0
PD1
2.01
0.77
97.1
0.12
ΔPD1
2.13
1.02
88.9
7.96
BTLA
3.49
0.56
95.9
0
CD244
2.37
0.34
97.2
0.074
PD1-CTLA4
1.76
3.56
71.0
23.7
PD1-LAG3
1.71
0.56
97.7
0.065
PD1-LAIR
1.62
0.58
97.8
0.032
PD1-PD1
1.91
0.49
97.2
0.36
PD1-TIM3
1.88
0.92
89.8
7.36

FIG 7

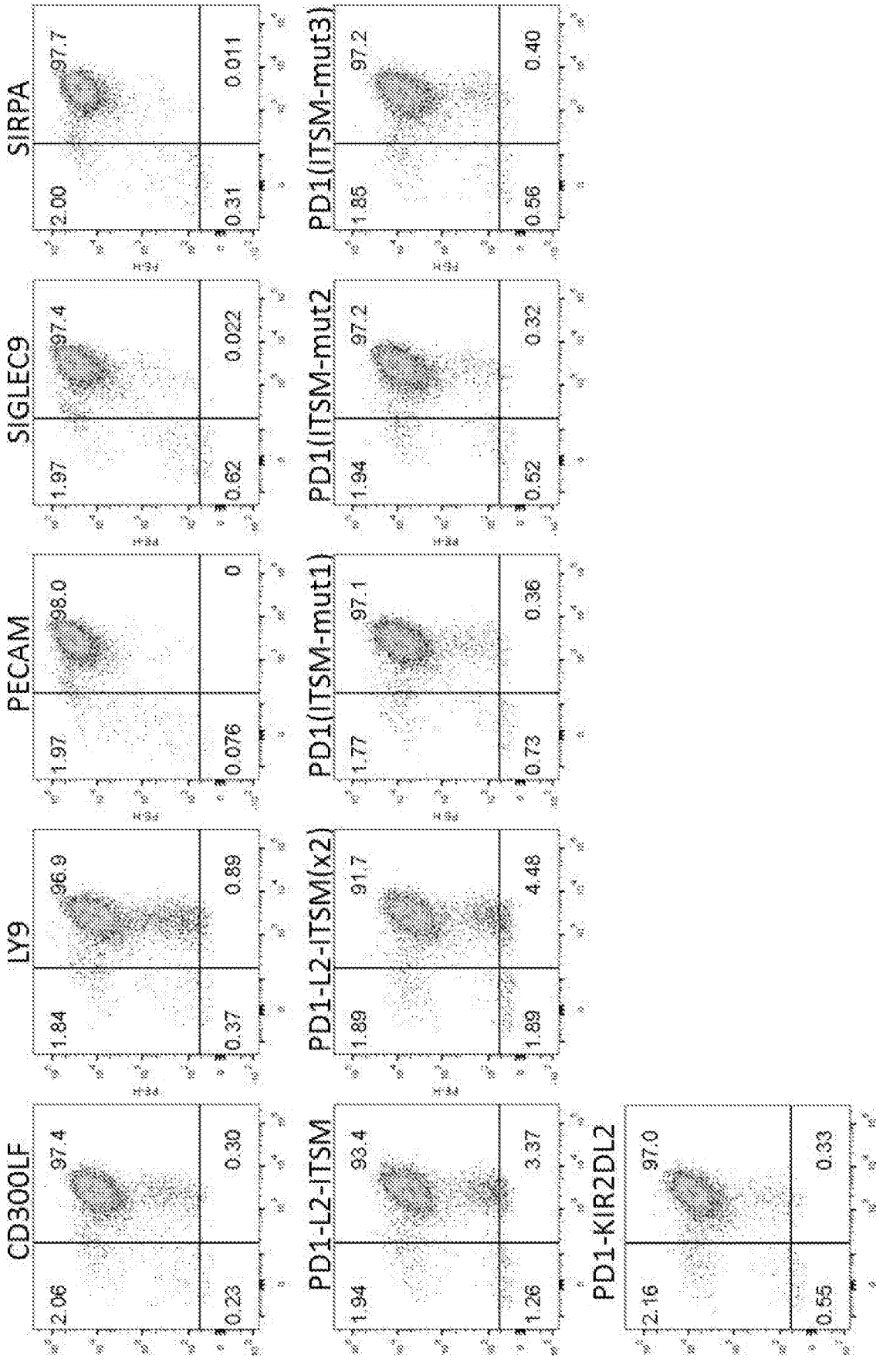

CD300LF
LY9
PECAM
SIGLEC9
SIRPA
PD1-L2-ITSM
PD1-L2-ITSM(x2)
PD1(ITSM-mut1)
PD1(ITSM-mut2)
PD1(ITSM-mut3)
PD1-KIR2DL2

FIG 8

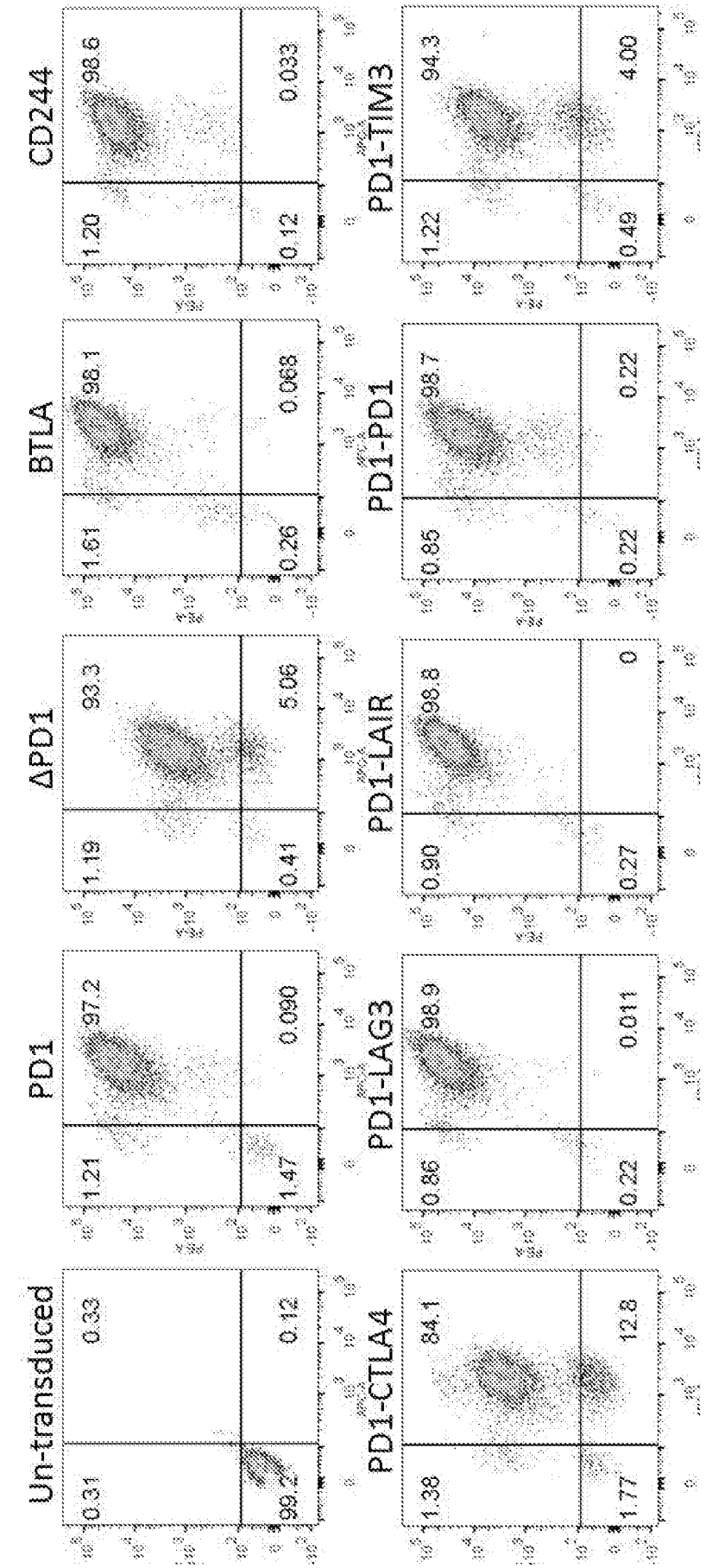

Un-transduced
0.31
0.33
99.2
0.12
PD1
1.21
97.2
1.47
0.090
ΔPD1
1.19
93.3
0.41
5.06
BTLA
1.61
98.1
0.26
0.068
CD244
1.20
98.6
0.12
0.033
PD1-CTLA4
1.38
84.1
1.77
12.8
PD1-LAG3
0.86
98.9
0.22
0.011
PD1-LAIR
0.90
98.8
0.27
0
PD1-PD1
0.85
98.7
0.22
0.22
PD1-TIM3
1.22
94.3
0.49
4.00

FIG 9

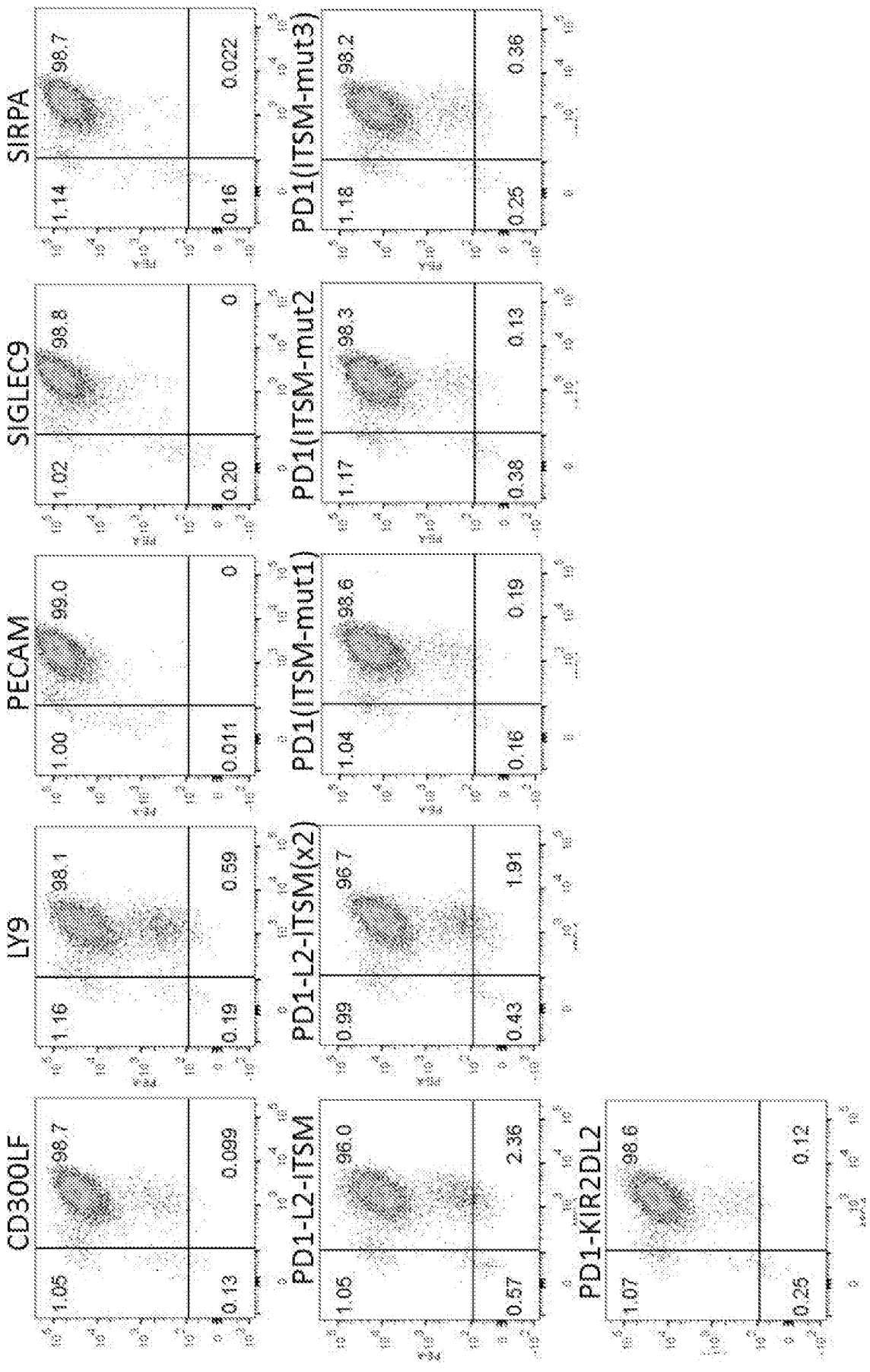

CD300LF
LY9
PECAM
SIGLEC9
SIRPA
PD1-L2-ITSM
PD1-L2-ITSM(x2)
PD1(ITSM-mut1)
PD1(ITSM-mut2)
PD1(ITSM-mut3)
PD1-KIR2DL2
1.05
98.7
0.13
0.099
1.16
98.1
0.19
0.59
1.00
99.0
0.011
0
1.02
98.8
0.20
0
1.14
98.7
0.16
0.022
1.06
96.0
0.57
2.36
0.99
96.7
0.43
1.91
1.04
98.6
0.16
0.19
1.17
98.3
0.38
0.13
1.18
98.2
0.25
0.36
1.07
98.6
0.25
0.12

FIG 10A

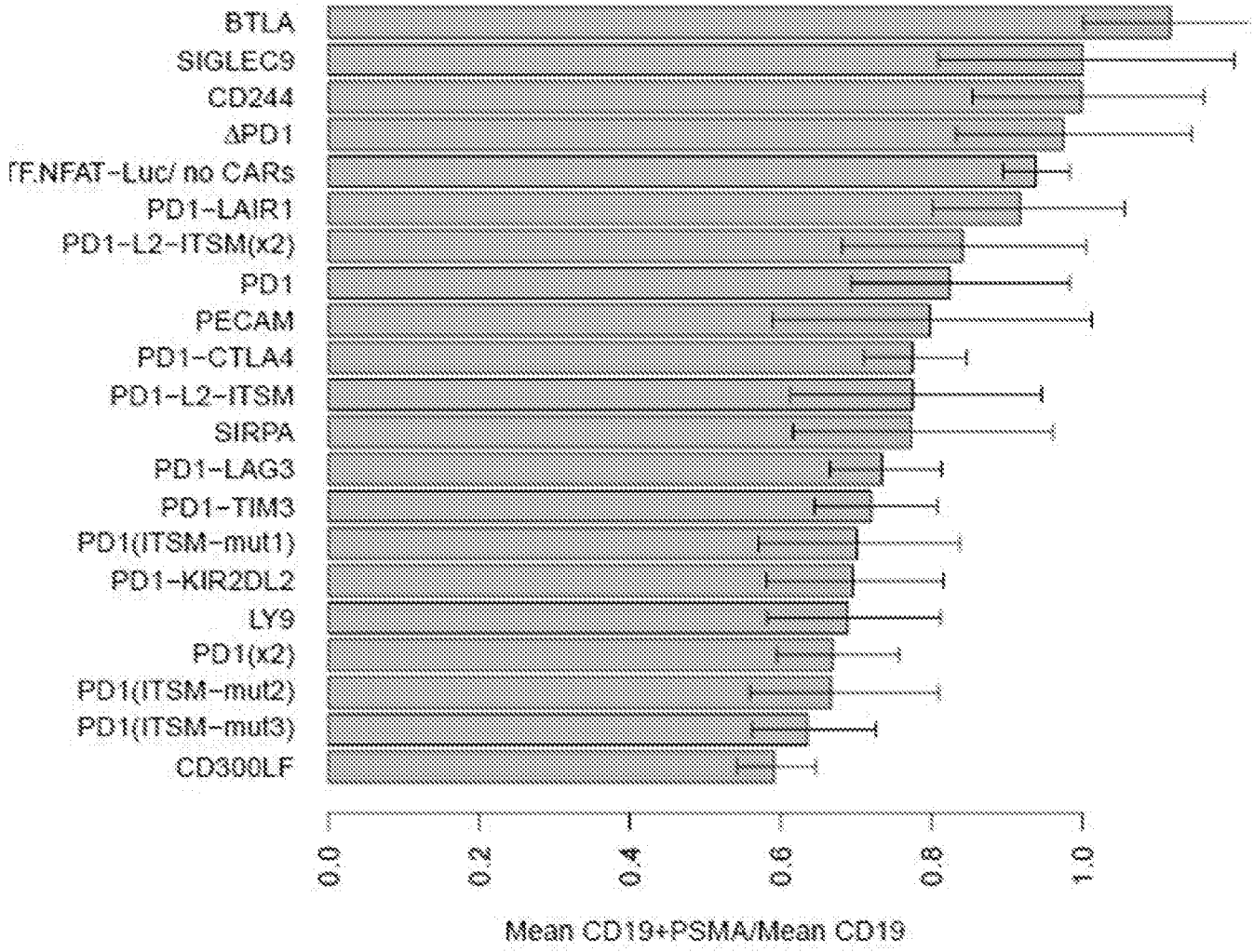
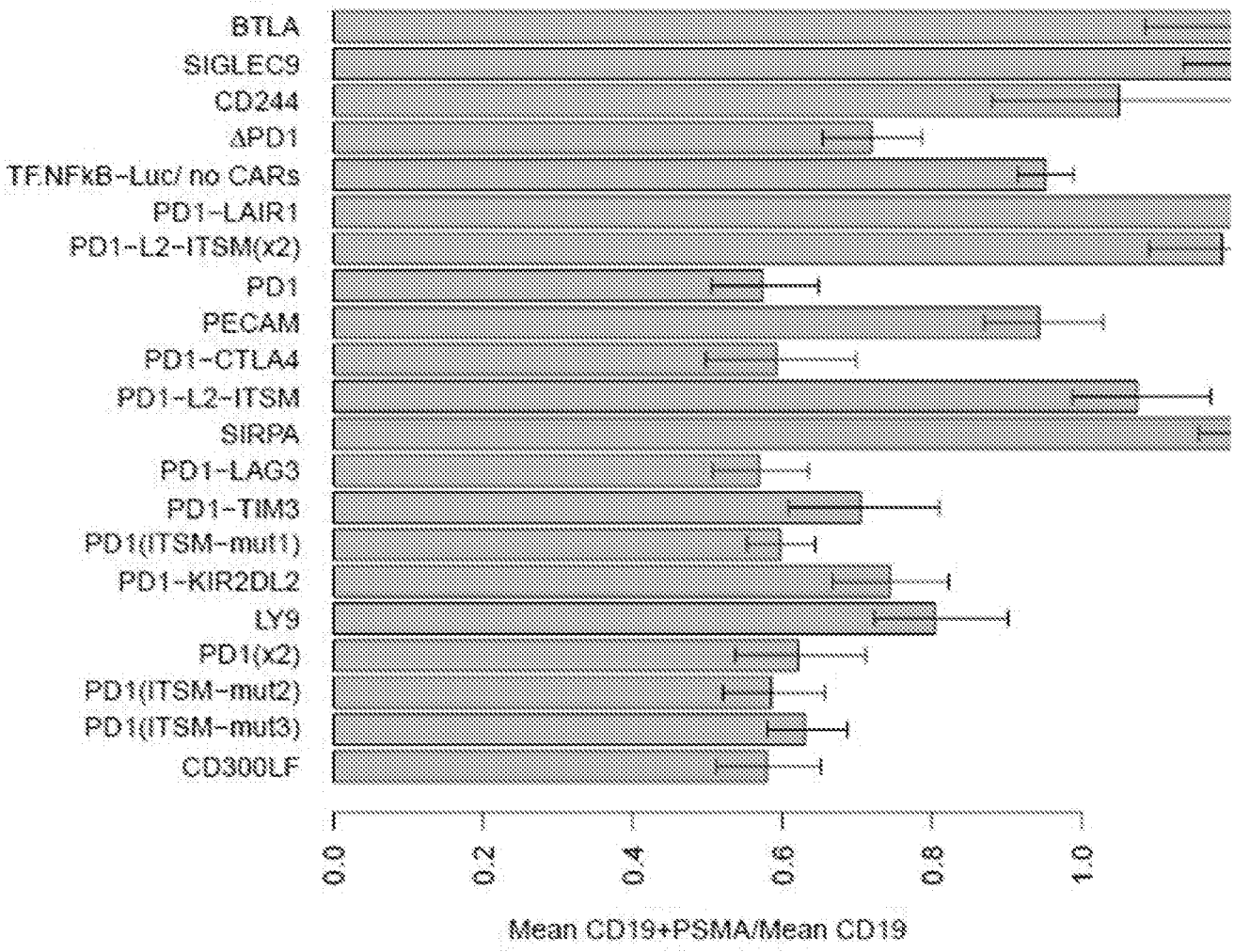

BTLA
SIGLEC9
CD244
ΔPD1
TF.NFAT-Luc/ no CARs
PD1-LAIR1
PD1-L2-ITSM(x2)
PD1
PECAM
PD1-CTLA4
PD1-L2-ITSM
SIRPA
PD1-LAG3
PD1-TIM3
PD1(ITSM-mut1)
PD1-KIR2DL2
LY9
PD1(x2)
PD1(ITSM-mut2)
PD1(ITSM-mut3)
CD300LF
0.0
0.2
0.4
0.6
0.8
1.0
Mean CD19+PSMA/Mean CD19

FIG 10B


BTLA
SIGLEC9
CD244
ΔPD1
TF.NFkB-Luc/ no CARs
PD1-LAIR1
PD1-L2-ITSM(x2)
PD1
PECAM
PD1-CTLA4
PD1-L2-ITSM
SIRPA
PD1-LAG3
PD1-TIM3
PD1(ITSM-mut1)
PD1-KIR2DL2
LY9
PD1(x2)
PD1(ITSM-mut2)
PD1(ITSM-mut3)
CD300LF
0.0
0.2
0.4
0.6
0.8
1.0
Mean CD19+PSMA/Mean CD19