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(71) Applicant(s)
Cellectis

(72) Inventor(s)
Busser, Brian;Duchateau, Philippe;Juillerat, Alexandre;Poirot, Laurent;Valton, Julien

(74) Agent / Attorney
Spruson & Ferguson, GPO Box 3898, Sydney, NSW, 2001, AU

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(71) Applicant: **CELLECTIS** [FR/FR]; 8, rue de la Croix Jarry, 75013 Paris (FR).

(72) Inventors: **BUSSER, Brian**; 295 Park Avenue South, NEW YORK, New York 100010 (US). **DUCHATEAU, Philippe**; Bateau Fawen Quai des Dames, 91210 Draveil (FR). **JUILLERAT, Alexandre**; 444 East, 82nd Street, NEW YORK, New York 10028 (US). **POIROT, Laurent**; 10, rue de la Réunion, 75020 Paris (FR). **VALTON, Julien**; 533 East 12th Street Apt #5D, NEW YORK, New York 10009 (US).

(74) Agent: **ZACCO DENMARK A/S**; Arne Jacobsens Allé 15, 2300 København S (DK).

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(54) Title: TARGETED GENE INSERTION FOR IMPROVED IMMUNE CELLS THERAPY

(57) Abstract: The invention pertains to the field of adaptive cell immunotherapy. It provides with the genetic insertion of exogenous coding sequence(s) that help the immune cells to direct their immune response against infected or malignant cells. These exogenous coding sequences are more particularly inserted under the transcriptional control of endogenous gene promoters that are sensitive to immune cells activation. Such method allows the production of safer immune primary cells of higher therapeutic potential.

TARGETED GENE INSERTION FOR IMPROVED IMMUNE CELLS THERAPY

Field of the invention

The invention pertains to the field of adaptive cell immunotherapy. It aims to enhance the functionality of primary immune cells against pathologies that develop immune resistance, such as tumors, thereby improving the therapeutic potential of these immune cells. The method of the invention provides with the genetic insertion of exogenous coding sequence(s) that help the immune cells to direct their immune response against infected or malignant cells. These exogenous coding sequences are more particularly inserted under the transcriptional control of endogenous gene promoters that are up or downregulated upon immune cells activation, upon tumor microenvironment or life threatening inflammatory conditions or promoters that are insensitive to immune cells activation. The invention also provides with sequence-specific endonuclease reagents and donor DNA vectors, such as AAV vectors, to perform such targeted insertions at said particular loci. The method of the invention contributes to improving the therapeutic potential and safety of engineered primary immune cells for their efficient use in cell therapy

Background of the invention

Effective clinical application of primary immune cell populations including hematopoietic cell lineages has been established by a number of clinical trials over a decade against a range of pathologies, in particular HIV infection and Leukemia (Tristen S.J. et al. (2011) Treating cancer with genetically engineered T cells. *Trends in Biotechnology*. 29(11):550-557).

However, most of these clinical trials have used immune cells, mainly NK and T-cells, obtained from the patients themselves or from compatible donors, bringing some limitations with respect to the number of available immune cells, their fitness, and their efficiency to overcome diseases that have already developed strategies to get around or reduce patient's immune system.

As a primary advance into the procurement of allogeneic immune cells, universal immune cells, available as "off-the-shelf" therapeutic products, have been produced by

gene editing (Poirot et *al.* (2015) Multiplex Genome-Edited T-cell Manufacturing Platform for "Off-the-Shelf" Adoptive T-cell Immunotherapies *Cancer Res.* 75: 3853-64). These universal immune cells are obtainable by expressing specific rare-cutting endonuclease into immune cells originating from donors, with the effect of disrupting, by double strand-break, their self-recognition genetic determinants.

Since the emergence of the first programmable sequence-specific reagents by the turn of the century, initially referred to as Meganucleases (Smith et al. (2006) A combinatorial approach to create artificial homing endonucleases cleaving chosen sequences. *Nucl. Acids Res.* 34 (22):e149.), different types of sequence-specific endonucleases reagents have been developed offering improved specificity, safety and reliability.

TALE-nucleases (WO2011072246), which are fusions of a TALE binding domain with a cleavage catalytic domain have been successfully applied to primary immune cells, in particular T-cells from peripheral blood mononuclear cell (PBMC). Such TALE-nucleases, marketed under the name TALEN®, are those currently used to simultaneously inactivate gene sequences in T-cells originating from donors, in particular to produce allogeneic therapeutic T-Cells in which the genes encoding TCR (T-cell receptor) and CD52 are disrupted. These cells can be endowed with chimeric antigen receptors (CAR) for treating cancer patients (US2013/0315884). TALE-nucleases are very specific reagents because they need to bind DNA by pairs under obligatory heterodimeric form to obtain dimerization of the cleavage domain Fok-1. Left and right heterodimer members each recognizes a different nucleic sequences of about 14 to 20 bp, together spanning target sequences of 30 to 50 bp overall specificity.

Other endonucleases reagents have been developed based on the components of the type II prokaryotic CRISPR (Clustered Regularly Interspaced Short palindromic Repeats) adaptive immune system of the bacteria *S. pyogenes*. This multi-component system referred to as RNA-guided nuclease system (Gasiunas, Barrangou et al. 2012; Jinek, Chylinski et al. 2012), involves members of Cas9 or Cpf1 endonuclease families coupled with a guide RNA molecules that have the ability to drive said nuclease to some specific genome sequences (Zetsche et al. (2015). Cpf1 is a single RNA-guided endonuclease that provides immunity in bacteria and can be adapted for genome editing in mammalian cells. *Cell* 163:759-771). Such programmable RNA-guided endonucleases are easy to produce because the cleavage specificity is determined by the sequence of the RNA guide, which can be easily designed and cheaply produced. The specificity of CRISPR/Cas9 although stands on shorter sequences than TAL-nucleases of about 10 pb,

which must be located near a particular motif (PAM) in the targeted genetic sequence. Similar systems have been described using a DNA single strand oligonucleotide (DNA guide) in combination with Argonaute proteins (Gao, F. et *al*. DNA-guided genome editing using the *Natronobacterium gregoryi* Argonaute (2016) doi:10.1038/nbt.3547).

Other endonuclease systems derived from homing endonucleases (ex: I-OnuI, or I-CreI), combined or not with TAL-nuclease (ex: MegaTAL) or zing-finger nucleases have also proven specificity, but to a lesser extend so far.

In parallel, novel specificities can be conferred to immune cells through the genetic transfer of transgenic T-cell receptors or so-called chimeric antigen receptors (CARs) (Jena et *al*. (2010) Redirecting T-cell specificity by introducing a tumor-specific chimeric antigen receptor. *Blood*. 116:1035-1044). CARs are recombinant receptors comprising a targeting moiety that is associated with one or more signaling domains in a single fusion molecule. In general, the binding moiety of a CAR consists of an antigen-binding domain of a single-chain antibody (scFv), comprising the light and heavy variable fragments of a monoclonal antibody joined by a flexible linker. Binding moieties based on receptor or ligand domains have also been used successfully. The signaling domains for first generation CARs are derived from the cytoplasmic region of the CD3zeta or the Fc receptor gamma chains. First generation CARs have been shown to successfully redirect T cell cytotoxicity, however, they failed to provide prolonged expansion and anti-tumor activity in vivo. Signaling domains from co-stimulatory molecules including CD28, OX-40 (CD134), ICOS and 4-1BB (CD137) have been added alone (second generation) or in combination (third generation) to enhance survival and increase proliferation of CAR modified T cells. CARs have successfully allowed T cells to be redirected against antigens expressed at the surface of tumor cells from various malignancies including lymphomas and solid tumors.

Recently engineered T-cells disrupted in their T-cell receptor (TCR) using TALE-nucleases, endowed with chimeric antigen receptor (CAR) targeting CD19 malignant antigen, referred to as “UCART19” product, have shown therapeutic potential in at least two infants who had refractory leukemia (Leukaemia success heralds wave of gene-editing therapies (2015) *Nature* 527:146–147). To obtain such UCART19 cells, the TALE-nuclease was transiently expressed into the cells upon electroporation of capped mRNA to operate TCR gene disruption, whereas a cassette encoding the chimeric antigen receptor (CAR CD19) was introduced randomly into the genome using a retroviral vector.

In this later approach, the steps of gene inactivation and of expressing the chimeric antigen receptor are independently performed after inducing activation of the T-Cell “ex-vivo”.

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However, engineering primary immune cells is not without any consequences on the growth/physiology of such cells. In particular one major challenge is to ovoid cells exhaustion/anergy that significantly reduces their immune reaction and life span. This is more likely to happen when the cells are artificially activated ahead of their infusion into the patient. It is also the case when a cell is endowed with a CAR that is too reactive.

To avoid these pitfalls, the inventors have thought about taking advantage of the transcriptional regulation of some key genes during T-cell activation to express exogenous genetic sequences increasing the therapeutic potential of the immune cells. The exogenous genetic sequences to be expressed or co-expressed upon immune cell activation are introduced by gene targeted insertion using sequence-specific endonuclease reagents, so that their coding sequences are transcribed under the control of the endogenous promoters present at said loci. Alternatively, loci that are not expressed during immune cell activation can be used as “safe-harbor loci” for the integration of expression cassettes without any adverse consequences on the genome.

These cell engineering strategies, as per the present invention, tend to reinforce the therapeutic potential of primary immune cells in general, in particular by increasing their life span, persistence and immune activity, as well as by limiting cell exhaustion. The invention may be carried out on primary cells originating from patients as part of autologous treatment strategies, as well as from donors, as part of allogeneic treatment strategies.

Summary of the invention

In a first aspect, the present invention provides a method for preparing engineered immune cells for cell immunotherapy, said method comprising:

- providing a population of primary immune cells;
- introducing into a proportion of said primary immune cells:

i) at least one nucleic acid comprising an exogenous nucleotide or polynucleotide sequence to be integrated at a selected endogenous locus to encode at least one molecule improving the therapeutic potential of said immune cells population;

ii) at least one sequence-specific reagent that specifically targets said selected endogenous locus,

wherein said exogenous nucleotide or polynucleotide sequence is inserted by targeted gene integration into said endogenous locus, so that said exogenous nucleotide or polynucleotide sequence forms an exogenous coding sequence under transcriptional control of an endogenous promoter present at said locus.

wherein the transcriptional activity of said endogenous promoter is upregulated upon immune cell activation.

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In a second aspect, the present invention provides an engineered immune cell obtained by the method of the first aspect.

In a third aspect, the present invention provides an engineered immune cell, which comprises an exogenous coding sequence under transcriptional control of an endogenous gene promoter, wherein said endogenous gene promoter is responsive to the activation of said immune cell, preferably up-regulated, and wherein said engineered immune cell is a primary cell endowed with a chimeric antigen receptor.

In a fourth aspect, the present invention provides a therapeutically effective population of immune cells, comprising at least 30 %, preferably 50 %, more preferably 80 % of cells according to the second or third aspect.

In a fifth aspect, the present invention provides a pharmaceutical composition comprising an engineered immune cell according to the second and third aspect or the immune cell population according to the fourth aspect.

In a sixth aspect, the present invention provides use of an engineered immune cell according to the second or third aspect or immune cell population according to the fourth aspect or the pharmaceutical composition according to the fifth aspect in the manufacture of a medicament for the treatment of cancer.

In a seventh aspect, the present invention provides a method for the treatment of cancer comprising administering a therapeutically effective dose of an engineered immune cell according to the second or third aspect or immune cell population according to the fourth aspect or the pharmaceutical composition according to the fifth aspect to a patient in need thereof.

Non-homologous end-joining (NHEJ) and homology-directed repair (HDR) are the two major pathways used to repair in vivo DNA breaks. The latter pathway repairs the break in a template-dependent manner (HDR naturally utilizes the sister chromatid as a DNA repair template). Homologous recombination has been used for decades to precisely edit genomes with targeted DNA modifications using exogenously supplied donor template. The artificial generation of a double strand break (DSB) at the target location using rare-cutting endonucleases considerably enhances the efficiency of homologous recombination (e.g. US 8,921,332). Also the co-delivery of a rare-cutting endonuclease along with a donor template containing DNA sequences homologous to the break site enables HDR-based gene editing such as gene correction or gene insertion. However, such techniques have not been widely used in primary immune cells, especially CAR T-cells, due to several technical limitations: difficulty of transfecting DNA into such types of cells leading to apoptosis, immune cells have a limited life span and number of generations, homologous recombination occurs at a low frequency in general.

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So far, sequence specific endonuclease reagents have been mainly used in primary immune cells for gene inactivation (e.g. WO2013176915) using the NHEJ pathway.

In a general aspect, the present invention relies on performing site directed gene editing, in particular gene insertion (or multi gene insertions) in a target cell in order to have the integrated gene transcription be under the control of an endogenous promoter.

In a general aspect the invention relies on performing gene editing in primary immune cells to have integrated genes transcription be under the control of an endogenous promoter while maintaining the expression of the native gene through the use of cis-regulatory elements (e.g. 2A cis-acting hydrolase elements) or of internal ribosome entry site (IRES) in the donor template.

In a general aspect the invention relies, as non-limiting examples, on controlling the expression, in primary T-cells, of chimeric antigen receptors (CAR), of critical cytokines to drive an anti-tumor response, of stimulatory cytokines to increase proliferative potential, of chemokine receptors to encourage trafficking to the tumor, or of different protective or inhibitory genes to block the immune inhibition provided by the tumor. Indeed, one major advantage of the present invention is to place such exogenous sequences under control of endogenous promoters, which transcriptional activity is not reduced by the effects of the immune cells activation.

By contrast to previous method for engineering therapeutic immune cells, where for instance an exogenous coding sequence was integrated and expressed at the TCR locus for constitutive gene expression, the inventors have integrated coding sequence at loci, which are specifically transcribed during T-cells activation, preferably on a CAR dependent fashion.

In another aspect, the invention relies on expressing a chimeric antigen receptor (CAR) at selected gene loci that are upregulated upon immune cells activation. The exogenous sequence(s) encoding the CAR and the endogenous gene coding sequence (s) may be co-transcribed, for instance by being separated by cis-regulatory elements (e.g. 2A cis-acting hydrolase elements) or by an internal ribosome entry site (IRES), which are also introduced. For instance, the exogenous sequences encoding a CAR can be placed under transcriptional control of the promoter of endogenous genes that are activated by the tumor microenvironment, such as HIF1a, transcription factor hypoxia-inducible factor, or the aryl hydrocarbon receptor (AhR), which are gene sensors respectively induced by hypoxia and xenobiotics in the close environment of tumors.

The present invention is thus useful to improve the therapeutic outcome of CAR T-cell therapies by integrating exogenous genetic attributes/circuits under the control of

endogenous T-cell promoters influenced by tumor microenvironment (TME). TME features, including as non-limiting examples, arginine, cysteine, tryptophan and oxygen deprivation as well as extracellular acidosis (lactate build up), are known to upregulate specific endogenous genes. Pursuant to the invention, upregulation of endogenous genes can be “hijacked” to re-express relevant exogenous coding sequences to improve the antitumor activity of CAR T-cells in certain tumor microenvironment.

In preferred embodiments, the method of the invention comprises the step of generating a double-strand break at a locus highly transcribed under tumor microenvironment, by expressing sequence-specific nuclease reagents, such as TALEN, ZFN or RNA-guided endonucleases as non-limiting examples, in the presence of a DNA repair matrix preferably set into an AAV6 based vector. This DNA donor template generally includes two homology arms embedding unique or multiple Open Reading Frames and regulatory genetic elements (stop codon and polyA sequences) referred to herein as exogenous coding sequences.

In another aspect, said exogenous sequence is introduced into the genome by deleting or modifying the endogenous coding sequence(s) present at said locus (knock-out by knock-in), so that a gene inactivation is combined with transgenesis.

Depending on the locus targeted and its involvement in immune cells activity, the targeted endogenous gene may be inactivated or maintained in its original function. Should the targeted gene be essential for immune cells activity, this insertion procedure can generate a single knock-in (KI) without gene inactivation. In the opposite, if the targeted gene is deemed involved in immune cells inhibition/exhaustion, the insertion procedure is designed to prevent expression of the endogenous gene, preferably by knocking-out the endogenous sequence, while enabling expression of the introduced exogenous coding sequence(s).

In more specific aspects, the invention relies on up-regulating, with various kinetics, the target gene expression upon activation of the CAR signalling pathway by targeted integration (with or without the native gene disruption) at the specific loci such as, as non-limiting example, PD1, PDL1, CTLA-4, TIM3, LAG3, TNFa or IFNg.

In an even more specific aspect, it is herein described engineered immune cells, and preferably primary immune cells for infusion into patients, comprising exogenous sequences encoding IL-15 or IL-12 polypeptide(s), which are integrated at the PD1, CD25 or CD69 endogenous locus for their expression under the control of the endogenous promoters present at these loci.

The immune cells according to the present invention can be $[CAR]^{positive}$,$[CAR]^{negative}$,$[TCR]^{positive}$,or $[TCR]^{negative}$, depending on the therapeutic

indications and recipient patients. In one preferred aspect, the immune cells are further made $[TCR]^{negative}$ for allogeneic transplantation. This can be achieved especially by genetic disruption of at least one endogenous sequence encoding at least one component of TCR, such as TRAC (locus encoding TCRalpha), preferably by integration of an exogenous sequence encoding a chimeric antigen receptor (CAR) or a recombinant TCR, or component(s) thereof.

According to a further aspect of the invention, the immune cells are transfected with an exogenous sequence coding for a polypeptide which can associate and preferably interfere with a cytokine receptor of the IL-6 receptor family, such as a mutated GP130, In particular, the invention provides immune cells, preferably T-cells, which secrete soluble mutated GP130, aiming at reducing cytokine release syndrome (CRS) by interfering, and ideally block, interleukine-6 (IL-6) signal transduction. CRS is a well-known complication of cell immunotherapy leading to auto immunity that appears when the transduced immune cells start to be active in-vivo. Following binding of IL-6 to its receptor IL-6R, the complex associate with the GP130 subunit, initiating signal transduction and a cascade of inflammatory responses. According to a particular aspect, a dimeric protein comprising the extracellular domain of GP130 fused to the Fc portion of an IgG1 antibody (sgp130Fc) is expressed in the engineered immune cells to bind specifically soluble IL-R/IL-6 complex to achieve partial or complete blockade of IL-6 trans signaling. The present invention thus refers to a method for limiting CRS in immunotherapy, wherein immune cells are genetically modified to express a soluble polypeptide which can associate and preferably interfere with a cytokine receptor of the IL-6 receptor family, such as sgp130Fc. According to a preferred aspect, this sequence encoding said soluble polypeptide which can associate and preferably interfere with a cytokine receptor of the IL-6 receptor family, is integrated under control of an endogenous promoter, preferably at one locus responsive to T-cells activation, such as one selected from Tables 6, 8 or 9, more especially PD1, CD25 or CD69. Polynucleotide sequences of the vectors, donor templates comprising the exogenous coding sequences and/or sequences homologous to the endogenous loci, the sequences pertaining to the resulting engineered cells, as well as those permitting the detection of said engineered cells are all part of the present disclosure.

In a general aspect the invention relies, as non-limiting examples, on controlling the expression of components of biological “logic gates” (“AND” or “OR” or “NOT” or any combination of these) by targeted integration of genes. Similar to the electronic logic gates, cellular components expressed at different loci can exchange negative and positive signals that rule, for instance, the conditions of activation of an immune cell. Such component encompasses as non-limiting examples positive and negative chimeric antigen

receptors that may be used to control T-cell activation and the resulting cytotoxicity of the engineered T-cells in which they are expressed.

According to a preferred embodiment, the invention relies on introducing the sequence specific endonuclease reagent and/or the donor template containing the gene of interest and sequences homologous to the target gene by transfecting ssDNA (oligonucleotides as non-limiting example), dsDNA (plasmid DNA as non-limiting example), and more particularly adeno-associated virus (AAV) as non-limiting example.

The invention also relates to the vectors, donor templates, reagents and resulting engineered cells pertaining to the above methods, as well as their use in therapy.

Brief description of the figures and Tables:

Figure 1: Strategies for engineering hematopoietic stem cells (HSCs) by introducing exogenous sequences at specific loci under transcriptional control of endogenous promoters specifically activated in specific immune cell types. The figure lists examples of specific endogenous genes, at which loci the exogenous coding sequence(s) can be inserted for expression in the desired hematopoietic lineages as per the present invention. The goal is to produce ex-vivo engineered HSCs to be engrafted into patients, in order for them to produce immune cells in-vivo, which will express selected transgenes while they get differentiated into a desired lineage.

Figure 2: Schematic representation of the donor sequences used in the experimental section to insert IL-15 exogenous coding sequence at the CD25 and PD1 loci and also the anti-CD22 CAR exogenous coding sequence at the TRAC locus. **A:** donor template (designated IL-15m-CD25) designed for site directed insertion of IL-15 at the CD25 locus for obtaining co-transcription of CD25 and IL-15 polypeptides by the immune cell. Sequences are detailed in the examples. **B:** donor template (designated IL-15m-PD1) designed for site directed insertion of IL-15 at the PD1 locus for obtaining transcription of IL-15 under the transcriptional activity of the promoter of PD1 endogenous gene. The PD1 right and Left border sequences can be selected so as to keep the PD1 endogenous coding sequence intact or disrupted. In this later case, PD1 is knocked-out while IL-15 is Knocked-in and transcribed. **C:** donor template designed for site directed insertion of a chimeric antigen receptor (ex: anti-CD22 CAR) into the TCR locus (ex: TRAC). In general, the left and right borders are chosen so as to disrupt the TCR in order to obtain $[TCR]^{neg}[CAR]^{pos}$ engineered immune cells suitable for allogeneic transplant into patients.

Figure 3: Flow cytometry measures of the frequency of targeted integration of IL-15m at either the PD1 or CD25 locus by using respectively PD1 or CD25 TALEN®, in a context where an anti-CD22 CAR is also integrated at the TRAC locus using TRAC TALEN®. These results show efficient targeted integration of both the CAR anti-CD22 at the TRAC locus together and the IL-15 coding sequence at the PD1 or CD25 loci. **A:** mock transfected primary T-cells. **B:** primary T-cells transfected with the donor sequences described in figure 1 (B and C) and specific TALEN® for the double integration at the TCR and PDI loci. **C:** primary T-cells transfected with the donor sequences described in figure 1 (A and C) and specific TALEN® for the double integration at the TCR and CD25 loci.

Figure 4: Schematic representation of the exogenous sequences used in the experimental section to transfect the primary immune cells to obtain the results shown in figures 5 and 6.

Figure 5 and 6: Flow cytometry measures for LNGFR expression among viable T-cells transfected with donor templates of figure 4 and specific TALEN® (TCR and CD25), upon antiCD3/CD28 non-specific activation (Dynabeads®) and upon CAR dependent tumor cell activation (raji tumor cells). As shown in figure 6, LNGFR expression was specifically induced in [CAR anti-CD22] ^{positive} cells upon CAR/tumor engagement.

Figure 7 and 8: Flow cytometry measures for CD25 expression among viable T-cells transfected with donor templates of figure 4 and specific TALEN® (TCR and CD25) upon antiCD3/CD28 non-specific activation (Dynabeads®) and Tumor cell activation (raji tumor cells). As shown in figure 8, CD25 expression was specifically induced in [CAR anti-CD22] ^{positive} cells upon CAR/tumor engagement.

Figure 9: Schematic representation of the exogenous sequences used in the experimental section to transfect the primary immune cells to obtain the results shown in figures 11 and 12.

Figure 10 and 11: Flow cytometry measures for LNGFR expression among viable T-cells transfected with donor templates of figure 9 and specific TALEN® (TCR and PD1) upon antiCD3/CD28 non-specific activation (Dynabeads®) and Tumor cell activation (raji tumor cells). As shown in figure 11, LNGFR expression was specifically induced in [CAR anti-CD22] ^{positive} cells upon CAR/tumor engagement.

Figure 12: Flow cytometry measures for endogenous PD1 expression among viable T-cells transfected with donor templates of figure 9 upon antiCD3/CD28 non-specific activation (Dynabeads®) and Tumor cell activation (raji tumor cells) with and

without using TALEN® (TCR and PD1). PD1 was efficiently Knocked-out by TALEN treatment (8% remaining expression of PD1 out of 54 %).

Figure 13: Diagram showing IL-15 production in $[CAR]^{positive}$ (CARm) and $[CAR]^{negative}$ engineered immune cells according to the invention transfected with the donor template described in Figure 2 (B) and TALEN® for insertion of IL-15 exogenous coding sequences into the PD1 locus. IL15, which transcription was under control of endogenous PD1 promoter, was efficiently induced upon antiCD3/CD28 non-specific activation (Dynabeads®) and Tumor cell activation (raji tumor cells) and secreted in the culture media.

Figure 14: Graph showing the amount of IL-15 secreted over time (days) post activation by the immune cells engineered according to the invention. **A**: Cells engineered by integration of the IL-15 coding sequence at the CD25 locus using the DNA donor templates described in Figures 2A (IL-15m_CD25) and/or 2C (CARm). **B**: Cells engineered by integration of the IL-15 coding sequence at the PD1 locus using the DNA donor templates described in Figures 2B (IL-15m_PD1) and/or 2C (CARm). Integrations at both loci show similar IL-15 secretion profiles. Secretion of IL-15 is significant increased by tumor specific activation of CAR.

Figure 15: Graph reporting number of Raji-Luc tumor cells expressing CD22 antigen (luciferase signal) over time in a survival assay (serial killing assay) as described in Example 2. The immune cells (PBMCs) have been engineered to integrate IL-15 coding sequences at the PD1 (**A**) or CD25 locus (**B**) and to express anti-CD22-CAR at the TCR locus (thereby disrupting TCR expression). In this assay, tumor cells are regularly added to the culture medium, while being partially or totally eliminated by the CAR positive cells. The re-expression of IL-15 at either PD1 or CD25 cells dramatically helps the elimination of the tumor cells by the CAR positive cells.

Figure 16: Schematic representation of the donor sequences used in the experimental section to insert at the PD1 locus the exogenous sequences encoding IL-12 and gp130Fc. **A**: donor template (designated IL-12m-PD1) designed for site directed insertion of IL-12a and IL-12b coding sequences (SEQ ID NO:47 and 48) at the PD1 locus for obtaining co-transcription of IL-12a and IL-12b, while disrupting PD1 endogenous coding sequence. The right and left border sequences homologous to the PD1 locus sequences are at least 100pb long, preferably at least 200 pb long, and more preferably at least 300 pb long and comprising SEQ ID NO:45 and 46. Sequences are detailed in Table 5. **B**: donor template (designated gp130Fcm-PD1) designed for site directed insertion of

gp130Fc coding sequences (SEQ ID NO:51) for obtaining transcription at the PD1 locus under PD1 promoter, while disrupting PD1 endogenous coding sequence. The right and left border sequences homologous to the PD1 locus sequences are at least 100pb long, preferably at least 200 pb long, and more preferably at least 300 pb long and comprising SEQ ID NO:45 and 46. Sequences are detailed in Table 5.

Table 1: ISU domain variants from diverse viruses.

Table 2: Aminoacid sequences of FP polypeptide from natural and artificial origins.

Table 3: List of genes involved into immune cells inhibitory pathways, which can be advantageously modified or inactivated by inserting exogenous coding sequence according to the invention.

Table 4: sequences referred to in example 1.

Table 5: sequences referred to in example 2.

Table 6: List of human genes that are up-regulated upon T-cell activation (CAR activation sensitive promoters), in which gene targeted insertion is sought according to the present invention to improve immune cells therapeutic potential.

Table 7: Selection of genes that are steadily transcribed during immune cell activation (dependent or independent from T-cell activation).

Table 8: Selection of genes that are transiently upregulated upon T-cell activation.

Table 9: Selection of genes that are upregulated over more than 24 hours upon T-cell activation.

Table 10: Selection of genes that are down-regulated upon immune cell activation.

Table 11:.Selection of genes that are silent upon T-cell activation (safe harbor gene targeted integration loci).

Table 12: List of gene loci upregulated in tumor exhausted infiltrating lymphocytes (compiled from multiple tumors) useful for gene integration of exogenous coding sequences as per the present invention.

Table 13: List of gene loci upregulated in hypoxic tumor conditions useful for gene integration of exogenous coding sequences as per the present invention.

Detailed description of the invention

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

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

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

The present invention is drawn to a general method of preparing primary immune cells for cell immunotherapy involving gene targeted integration of an exogenous coding

sequence into the chromosomal DNA of said immune cells. According to some aspects, this integration is performed in such a way that said coding sequence is placed under the transcriptional control of at least one promoter endogenous to said cells, said endogenous promoter being preferably not a constitutive promoter, such as the one transcribing T-cell receptor alpha constant (TRAC - NCBI Gene ID #28755) A constitutive promoter as per the present invention is for instance a promoter that is active independently from CAR activation – ex: when T-cells are not yet activated.

Improving the therapeutic potential of immune cells by gene targeted integration

Gene editing techniques using polynucleotide sequence-specific reagents, such as rare-cutting endonucleases, have become the state of the art for the introduction of genetic modifications into primary cells. However, they have not been used so far in immune cells to introduce exogenous coding sequences under the transcriptional control of endogenous promoters.

The present invention aims to improve the therapeutic potential of immune cells through gene editing techniques, especially by gene targeted integration.

By “gene targeting integration” is meant any known site-specific methods allowing to insert, replace or correct a genomic sequence into a living cell. According to a preferred aspect of the present invention, said gene targeted integration involves homologous gene recombination at the locus of the targeted gene to result the insertion or replacement of at least one exogenous nucleotide, preferably a sequence of several nucleotides (i.e. polynucleotide), and more preferably a coding sequence.

By “sequence-specific reagent” is meant any active molecule that has the ability to specifically recognize a selected polynucleotide sequence at a genomic locus, preferably of at least 9 bp, more preferably of at least 10 bp and even more preferably of at least 12 pb in length, in view of modifying said genomic locus. According to a preferred aspect of the invention, said sequence-specific reagent is preferably a sequence-specific nuclease reagent.

By “immune cell” is meant a cell of hematopoietic origin functionally involved in the initiation and/or execution of innate and/or adaptative immune response, such as typically CD3 or CD4 positive cells. The immune cell according to the present invention can be a dendritic cell, killer dendritic cell, a mast cell, a NK-cell, a B-cell or a T-cell selected from the group consisting of inflammatory T-lymphocytes, cytotoxic T-lymphocytes, regulatory T-lymphocytes or helper T-lymphocytes. Cells can be obtained from a number of non-limiting sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion,

spleen tissue, and from tumors, such as tumor infiltrating lymphocytes. In some embodiments, said immune cell can be derived from a healthy donor, from a patient diagnosed with cancer or from a patient diagnosed with an infection. In another embodiment, said cell is part of a mixed population of immune cells which present different phenotypic characteristics, such as comprising CD4, CD8 and CD56 positive cells.

By "primary cell" or "primary cells" are intended cells taken directly from living tissue (e.g. biopsy material) and established for growth in vitro for a limited amount of time, meaning that they can undergo a limited number of population doublings. Primary cells are opposed to continuous tumorigenic or artificially immortalized cell lines. Non-limiting examples of such cell lines are CHO-K1 cells; HEK293 cells; Caco2 cells; U2-OS cells; NIH 3T3 cells; NSO cells; SP2 cells; CHO-S cells; DG44 cells; K-562 cells, U-937 cells; MRC5 cells; IMR90 cells; Jurkat cells; HepG2 cells; HeLa cells; HT-1080 cells; HCT-116 cells; Hu-h7 cells; Huvec cells; Molt 4 cells. Primary cells are generally used in cell therapy as they are deemed more functional and less tumorigenic.

In general, primary immune cells are provided from donors or patients through a variety of methods known in the art, as for instance by leukapheresis techniques as reviewed by Schwartz J.et *al.* (Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue (2013) *J Clin Apher*. 28(3):145-284).

The primary immune cells according to the present invention can also be differentiated from stem cells, such as cord blood stem cells, progenitor cells, bone marrow stem cells, hematopoietic stem cells (HSC) and induced pluripotent stem cells (iPS).

By "nuclease reagent" is meant a nucleic acid molecule that contributes to an nuclease catalytic reaction in the target cell, preferably an endonuclease reaction, by itself or as a subunit of a complex such as a guide RNA/Cas9, preferably leading to the cleavage of a nucleic acid sequence target.

The nuclease reagents of the invention are generally "sequence-specific reagents", meaning that they can induce DNA cleavage in the cells at predetermined loci, referred to by extension as "targeted gene". The nucleic acid sequence which is recognized by the sequence specific reagents is referred to as "target sequence". Said target sequence is usually selected to be rare or unique in the cell's genome, and more extensively in the human genome, as can be determined using software and data available from human genome databases, such as http://www.ensembl.org/index.html.

"Rare-cutting endonucleases" are sequence-specific endonuclease reagents of choice, insofar as their recognition sequences generally range from 10 to 50 successive base pairs, preferably from 12 to 30 bp, and more preferably from 14 to 20 bp.

According to a preferred aspect of the invention, said endonuclease reagent is a nucleic acid encoding an "engineered" or "programmable" rare-cutting endonuclease, such as a homing endonuclease as described for instance by Arnould S., et *al.* (WO2004067736), a zing finger nuclease (ZFN) as described, for instance, by Urnov F., et *al.* (Highly efficient endogenous human gene correction using designed zinc-finger nucleases (2005) *Nature* 435:646-651), a TALE-Nuclease as described, for instance, by Mussolino et *al.* (A novel TALE nuclease scaffold enables high genome editing activity in combination with low toxicity (2011) *Nucl. Acids Res.* 39(21):9283-9293), or a MegaTAL nuclease as described, for instance by Boissel et al. (MegaTALs: a rare-cleaving nuclease architecture for therapeutic genome engineering (2013) Nucleic Acids Research 42 (4):2591-2601).

According to another embodiment, the endonuclease reagent is a RNA-guide to be used in conjunction with a RNA guided endonuclease, such as Cas9 or Cpf1, as per, *inter alia*, the teaching by Doudna, J., and Chapentier, E., (The new frontier of genome engineering with CRISPR-Cas9 (2014) *Science* 346 (6213):1077), which is incorporated herein by reference.

According to a preferred aspect of the invention, the endonuclease reagent is transiently expressed into the cells, meaning that said reagent is not supposed to integrate into the genome or persist over a long period of time, such as be the case of RNA, more particularly mRNA, proteins or complexes mixing proteins and nucleic acids (eg: Ribonucleoproteins).

In general, 80% the endonuclease reagent is degraded by 30 hours, preferably by 24, more preferably by 20 hours after transfection.

An endonuclease under mRNA form is preferably synthetized with a cap to enhance its stability according to techniques well known in the art, as described, for instance, by Kore A.L., et *al.* (Locked nucleic acid (LNA)-modified dinucleotide mRNA cap analogue: synthesis, enzymatic incorporation, and utilization (2009) *J Am Chem Soc.* 131(18):6364-5).

In general, electroporation steps that are used to transfect immune cells are typically performed in closed chambers comprising parallel plate electrodes producing a pulse electric field between said parallel plate electrodes greater than 100 volts/cm and less than 5,000 volts/cm, substantially uniform throughout the treatment volume such as described in WO/2004/083379, which is incorporated by reference, especially from page

23, line 25 to page 29, line 11. One such electroporation chamber preferably has a geometric factor (cm^{-1}) defined by the quotient of the electrode gap squared (cm2) divided by the chamber volume (cm^3), wherein the geometric factor is less than or equal to 0.1 cm^{-1}, wherein the suspension of the cells and the sequence-specific reagent is in a medium which is adjusted such that the medium has conductivity in a range spanning 0.01 to 1.0 milliSiemens. In general, the suspension of cells undergoes one or more pulsed electric fields. With the method, the treatment volume of the suspension is scalable, and the time of treatment of the cells in the chamber is substantially uniform.

Due to their higher specificity, TALE-nuclease have proven to be particularly appropriate sequence specific nuclease reagents for therapeutic applications, especially under heterodimeric forms – i.e. working by pairs with a "right" monomer (also referred to as "5'" or "forward") and 'left" monomer (also referred to as "3'"" or "reverse") as reported for instance by Mussolino et *al.* (TALEN® facilitate targeted genome editing in human cells with high specificity and low cytotoxicity (2014) *Nucl. Acids Res.* 42(10): 6762-6773).

As previously stated, the sequence specific reagent is preferably under the form of nucleic acids, such as under DNA or RNA form encoding a rare cutting endonuclease a subunit thereof, but they can also be part of conjugates involving polynucleotide(s) and polypeptide(s) such as so-called "ribonucleoproteins". Such conjugates can be formed with reagents as Cas9 or Cpf1 (RNA-guided endonucleases) or Argonaute (DNA-guided endonucleases) as recently respectively described by Zetsche, B. et *al*. (Cpf1 Is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System (2015) *Cell* 163(3): 759–771) and by Gao F. et *al*. (DNA-guided genome editing using the *Natronobacterium gregoryi* Argonaute (2016) *Nature Biotech*), which involve RNA or DNA guides that can be complexed with their respective nucleases.

"Exogenous sequence" refers to any nucleotide or nucleic acid sequence that was not initially present at the selected locus. This sequence may be homologous to, or a copy of, a genomic sequence, or be a foreign sequence introduced into the cell. By opposition "endogenous sequence" means a cell genomic sequence initially present at a locus. The exogenous sequence preferably codes for a polypeptide which expression confers a therapeutic advantage over sister cells that have not integrated this exogenous sequence at the locus. A endogenous sequence that is gene edited by the insertion of a nucleotide or polynucleotide as per the method of the present invention, in order to express a different polypeptide is broadly referred to as an exogenous coding sequence

The method of the present invention can be associated with other methods involving physical of genetic transformations, such as a viral transduction or transfection

using nanoparticles, and also may be combined with other gene inactivation and/or transgene insertions.

According to one aspect, the method according to the invention comprises the steps of:

- providing a population of primary immune cells;
- introducing into a proportion of said primary immune cells:

i) At least one nucleic acid comprising an exogenous nucleotide or polynucleotide sequence to be integrated at a selected endogenous locus to encode at least one molecule improving the therapeutic potential of said immune cells population;

ii) At least one sequence-specific reagent that specifically targets said selected endogenous locus,

wherein said exogenous nucleotide or polynucleotide sequence is inserted by targeted gene integration into said endogenous locus, so that said exogenous nucleotide or polynucleotide sequence forms an exogenous coding sequence under transcriptional control of an endogenous promoter present at said locus.

According to one aspect of the method, the sequence specific reagent is a nuclease and the targeted gene integration is operated by homologous recombination or NHEJ into said immune cells.

According to a further aspect of the invention, said endogenous promoter is selected to be active during immune cell activation and preferably up-regulated.

More specifically, the invention is drawn to a method for preparing engineered primary immune cells for cell immunotherapy, said method comprising:

- providing a population of primary immune cells;
- introducing into a proportion of said primary immune cells:

i) At least one exogenous nucleic acid comprising an exogenous coding sequence encoding at least one molecule improving the therapeutic potential of said immune cells population;

ii) At least one sequence-specific nuclease reagent that specifically targets a gene which is under control of an endogenous promoter active during immune cell activation;

wherein said coding sequence is introduced into the primary immune cells genome by targeted homologous recombination, so that said coding sequence is placed under the transcriptional control of at least one endogenous promoter of said gene.

By “improving therapeutic potential” is meant that the engineered immune cells gain at least one advantageous property for their use in cell therapy by comparison to

their sister non-engineered immune cells. The therapeutic properties sought by the invention maybe any measurable one as referred to in the relevant scientific literature.

Improved therapeutic potential can be more particularly reflected by a resistance of the immune cells to a drug, an increase in their persistence *in-vitro* or *in-vivo*, or a safer/more convenient handling during manufacturing of therapeutic compositions and treatments.

In general said molecule improving the therapeutic potential is a polypeptide, but it can also be a nucleic acid able to direct or repress expression of other genes, such as interference RNAs or guide-RNAs. The polypeptides may act directly or indirectly, such as signal transducers or transcriptional regulators.

According to one embodiment of the present method, the exogenous sequence is introduced into the endogenous chromosomal DNA by targeted homologous recombination. Accordingly, the exogenous nucleic acid introduced into the immune cell comprises at least one coding sequence(s), along with sequences that can hybridize endogenous chromosomal sequences under physiological conditions. In general, such homologous sequences show at least 70 %, preferably 80% and more preferably 90% sequence identity with the endogenous gene sequences located at the insertion locus. These homologous sequences may flank the coding sequence to improve the precision of recombination as already taught for instance in US 6,528,313. Using available software and on-line genome databases, it is possible to design vectors that includes said coding sequence (s), in such a way that said sequence(s) is (are) introduced at a precise locus, under transcriptional control of at least one endogenous promoter, which is a promoter of an endogenous gene. The exogenous coding sequence(s) is (are) then preferably inserted “in frame” with said endogenous gene. The sequences resulting from the integration of the exogenous polynucleotide sequence(s) can encode many different types of proteins, including fusion proteins, tagged protein or mutated proteins. Fusion proteins allow adding new functional domains to the proteins expressed in the cell, such as a dimerization domain that can be used to switch-on or switch-off the activity of said protein, such as caspase-9 switch. Tagged proteins can be advantageous for the detection of the engineered immune cells and the follow-up of the patients treated with said cells. Introducing mutation into proteins can confer resistance to drugs or immune depletion agents as further described below.

Conferring resistance to drugs or immune depletion agents

According to one aspect of the present method, the exogenous sequence that is integrated into the immune cells genomic locus encodes a molecule that confers resistance of said immune cells to a drug.

Examples of preferred exogenous sequences are variants of dihydrofolate reductase (DHFR) conferring resistance to folate analogs such as methotrexate, variants of inosine monophosphate dehydrogenase 2 (IMPDH2) conferring resistance to IMPDH inhibitors such as mycophenolic acid (MPA) or its prodrug mycophenolate mofetil (MMF), variants of calcineurin or methylguanine transferase (MGMT) conferring resistance to calcineurin inhibitor such as FK506 and/or CsA, variants of mTOR such as mTORmut conferring resistance to rapamycin) and variants of Lck, such as Lckmut conferring resistance to Imatinib and Gleevec.

The term “drug” is used herein as referring to a compound or a derivative thereof, preferably a standard chemotherapy agent that is generally used for interacting with a cancer cell, thereby reducing the proliferative or living status of the cell. Examples of chemotherapeutic agents include, but are not limited to, alkylating agents (e.g., cyclophosphamide, ifosamide), metabolic antagonists (e.g., purine nucleoside antimetabolite such as clofarabine, fludarabine or 2’-deoxyadenosine, methotrexate (MTX), 5-fluorouracil or derivatives thereof), antitumor antibiotics (e.g., mitomycin, adriamycin), plant-derived antitumor agents (e.g., vincristine, vindesine, Taxol), cisplatin, carboplatin, etoposide, and the like. Such agents may further include, but are not limited to, the anti-cancer agents TRIMETHOTRIXATE™ (TMTX), TEMOZOLOMIDE™, RALTRITREXED™, S-(4-Nitrobenzyl)-6-thioinosine (NBMPR),6-benzyguanidine (6-BG), bis-chloronitrosourea (BCNU) and CAMPTOTHECIN™, or a therapeutic derivative of any thereof.

As used herein, an immune cell is made "resistant or tolerant" to a drug when said cell, or population of cells is modified so that it can proliferate, at least in-vitro, in a culture medium containing half maximal inhibitory concentration (IC50) of said drug (said IC50 being determined with respect to an unmodified cell(s) or population of cells).

In a particular embodiment, said drug resistance can be conferred to the immune cells by the expression of at least one “drug resistance coding sequence”. Said drug resistance coding sequence refers to a nucleic acid sequence that confers "resistance" to an agent, such as one of the chemotherapeutic agents referred to above. A drug resistance coding sequence of the invention can encode resistance to anti-metabolite, methotrexate, vinblastine, cisplatin, alkylating agents, anthracyclines, cytotoxic antibiotics, anti-immunophilins, their analogs or derivatives, and the like (Takebe, N., S. C. Zhao, et *al*. (2001) "Generation of dual resistance to 4-hydroperoxycyclophosphamide and

methotrexate by retroviral transfer of the human aldehyde dehydrogenase class 1 gene and a mutated dihydrofolate reductase gene". *Mol. Ther.* 3(1): 88-96), (Zielske, S. P., J. S. Reese, et al. (2003) "In vivo selection of MGMT(P140K) lentivirus-transduced human NOD/SCID repopulating cells without pretransplant irradiation conditioning." *J. Clin. Invest.* 112(10): 1561-70) (Nivens, M. C., T. Felder, et *al.* (2004) "Engineered resistance to camptothecin and antifolates by retroviral coexpression of tyrosyl DNA phosphodiesterase-I and thymidylate synthase" Cancer Chemother Pharmacol 53(2): 107-15), (Bardenheuer, W., K. Lehmberg, et *al.* (2005). "Resistance to cytarabine and gemcitabine and in vitro selection of transduced cells after retroviral expression of cytidine deaminase in human hematopoietic progenitor cells". *Leukemia* 19(12): 2281-8), (Kushman, M. E., S. L. Kabler, et *al.* (2007) "Expression of human glutathione S-transferase P1 confers resistance to benzo[a]pyrene or benzo[a]pyrene-7,8-dihydrodiol mutagenesis, macromolecular alkylation and formation of stable N2-Gua-BPDE adducts in stably transfected V79MZ cells co-expressing hCYP1A1" *Carcinogenesis* 28(1): 207-14).

The expression of such drug resistance exogenous sequences in the immune cells as per the present invention more particularly allows the use of said immune cells in cell therapy treatment schemes where cell therapy is combined with chemotherapy or into patients previously treated with these drugs.

Several drug resistance coding sequences have been identified that can potentially be used to confer drug resistance according to the invention. One example of drug resistance coding sequence can be for instance a mutant or modified form of Dihydrofolate reductase (DHFR). DHFR is an enzyme involved in regulating the amount of tetrahydrofolate in the cell and is essential to DNA synthesis. Folate analogs such as methotrexate (MTX) inhibit DHFR and are thus used as anti-neoplastic agents in clinic. Different mutant forms of DHFR which have increased resistance to inhibition by anti-folates used in therapy have been described. In a particular embodiment, the drug resistance coding sequence according to the present invention can be a nucleic acid sequence encoding a mutant form of human wild type DHFR (GenBank: AAH71996.1), which comprises at least one mutation conferring resistance to an anti-folate treatment, such as methotrexate. In particular embodiment, mutant form of DHFR comprises at least one mutated amino acid at position G15, L22, F31 or F34, preferably at positions L22 or F31 (Schweitzer et al. (1990) "Dihydrofolate reductase as a therapeutic target" *Faseb J* 4(8): 2441-52; International application WO94/24277; and US patent US 6,642,043). In a particular embodiment, said DHFR mutant form comprises two mutated amino acids at position L22 and F31. Correspondence of amino acid positions described herein is frequently expressed in terms of the positions of the amino acids of the form of wild-type

DHFR polypeptide. In a particular embodiment, the serine residue at position 15 is preferably replaced with a tryptophan residue. In another particular embodiment, the leucine residue at position 22 is preferably replaced with an amino acid which will disrupt binding of the mutant DHFR to antifolates, preferably with uncharged amino acid residues such as phenylalanine or tyrosine. In another particular embodiment, the phenylalanine residue at positions 31 or 34 is preferably replaced with a small hydrophilic amino acid such as alanine, serine or glycine.

Another example of drug resistance coding sequence can also be a mutant or modified form of ionisine-5'- monophosphate dehydrogenase II (IMPDH2), a rate-limiting enzyme in the de novo synthesis of guanosine nucleotides. The mutant or modified form of IMPDH2 is a IMPDH inhibitor resistance gene. IMPDH inhibitors can be mycophenolic acid (MPA) or its prodrug mycophenolate mofetil (MMF). The mutant IMPDH2 can comprises at least one, preferably two mutations in the MAP binding site of the wild type human IMPDH2 (Genebank: NP_000875.2) leading to a significantly increased resistance to IMPDH inhibitor. Mutations in these variants are preferably at positions T333 and/or S351 (Yam, P., M. Jensen, et *al.* (2006) "Ex vivo selection and expansion of cells based on expression of a mutated inosine monophosphate dehydrogenase 2 after HIV vector transduction: effects on lymphocytes, monocytes, and CD34+ stem cells" *Mol. Ther.* 14(2): 236-44)(Jonnalagadda, M., et *al.* (2013) "Engineering human T cells for resistance to methotrexate and mycophenolate mofetil as an in vivo cell selection strategy." *PLoS One* 8(6): e65519).

Another drug resistance coding sequence is the mutant form of calcineurin. Calcineurin (PP2B - NCBI: ACX34092.1) is an ubiquitously expressed serine/threonine protein phosphatase that is involved in many biological processes and which is central to T-cell activation. Calcineurin is a heterodimer composed of a catalytic subunit (CnA; three isoforms) and a regulatory subunit (CnB; two isoforms). After engagement of the T-cell receptor, calcineurin dephosphorylates the transcription factor NFAT, allowing it to translocate to the nucleus and active key target gene such as IL2. FK506 in complex with FKBP12, or cyclosporine A (CsA) in complex with CyPA block NFAT access to calcineurin's active site, preventing its dephosphorylation and thereby inhibiting T-cell activation (Brewin et *al.* (2009) "Generation of EBV-specific cytotoxic T cells that are resistant to calcineurin inhibitors for the treatment of posttransplantation lymphoproliferative disease" *Blood* 114(23): 4792-803). In a particular embodiment, said mutant form can comprise at least one mutated amino acid of the wild type calcineurin heterodimer a at positions: V314, Y341, M347, T351, W352, L354, K360, preferably double mutations at positions T351 and L354 or V314 and Y341. In a particular

embodiment, the valine residue at position 341 can be replaced with a lysine or an arginine residue, the tyrosine residue at position 341 can be replaced with a phenylalanine residue; the methionine at position 347 can be replaced with the glutamic acid, arginine or tryptophane residue; the threonine at position 351 can be replaced with the glutamic acid residue; the tryptophane residue at position 352 can be replaced with a cysteine, glutamic acid or alanine residue, the serine at position 353 can be replaced with the histidine or asparagines residue, the leucine at position 354 can be replaced with an alanine residue; the lysine at position 360 can be replaced with an alanine or phenylalanine residue. In another particular embodiment, said mutant form can comprise at least one mutated amino acid of the wild type calcineurin heterodimer b at positions: V120, N123, L124 or K125, preferably double mutations at positions L124 and K125. In a particular embodiment, the valine at position 120 can be replaced with a serine, an aspartic acid, phenylalanine or leucine residue; the asparagines at position 123 can be replaced with a tryptophan, lysine, phenylalanine, arginine, histidine or serine; the leucine at position 124 can be replaced with a threonine residue; the lysine at position 125 can be replaced with an alanine, a glutamic acid, tryptophan, or two residues such as leucine-arginine or isoleucine-glutamic acid can be added after the lysine at position 125 in the amino acid sequence. Correspondence of amino acid positions described herein is frequently expressed in terms of the positions of the amino acids of the form of wild-type human calcineurin heterodimer b polypeptide (NCBI: ACX34095.1).

Another drug resistance coding sequence is 0(6)-methylguanine methyltransferase (MGMT - UniProtKB: P16455) encoding human alkyl guanine transferase (hAGT). AGT is a DNA repair protein that confers resistance to the cytotoxic effects of alkylating agents, such as nitrosoureas and temozolomide (TMZ). 6-benzylguanine (6-BG) is an inhibitor of AGT that potentiates nitrosourea toxicity and is co-administered with TMZ to potentiate the cytotoxic effects of this agent. Several mutant forms of MGMT that encode variants of AGT are highly resistant to inactivation by 6-BG, but retain their ability to repair DNA damage (Maze, R. et al. (1999) "Retroviral-mediated expression of the P140A, but not P140A/G156A, mutant form of O6-methylguanine DNA methyltransferase protects hematopoietic cells against O6-benzylguanine sensitization to chloroethylnitrosourea treatment" *J. Pharmacol. Exp. Ther.* 290(3): 1467-74). In a particular embodiment, AGT mutant form can comprise a mutated amino acid of the wild type AGT position P140. In a preferred embodiment, said proline at position 140 is replaced with a lysine residue.

Another drug resistance coding sequence can be multidrug resistance protein (MDR1) gene. This gene encodes a membrane glycoprotein, known as P-glycoprotein (P-GP) involved in the transport of metabolic byproducts across the cell membrane. The P-

Gp protein displays broad specificity towards several structurally unrelated chemotherapy agents. Thus, drug resistance can be conferred to cells by the expression of nucleic acid sequence that encodes MDR-1 (Genebank NP_000918).

Another drug resistance coding sequence can contribute to the production of cytotoxic antibiotics, such as those from *ble* or *mcrA* genes. Ectopic expression of *ble* gene or *mcrA* in an immune cell gives a selective advantage when exposed to the respective chemotherapeutic agents bleomycine and mitomycin C (Belcourt, M.F. (1999) "Mitomycin resistance in mammalian cells expressing the bacterial mitomycin C resistance protein MCRA". *PNAS*. 96(18):10489-94).

Another drug resistance coding sequence can come from genes encoded mutated version of drug targets, such as mutated variants of mTOR (mTOR mut) conferring resistance to rapamycin such as described by Lorenz M.C. et al. (1995) "TOR Mutations Confer Rapamycin Resistance by Preventing Interaction with FKBP12-Rapamycin" *The Journal of Biological Chemistry* 270, 27531-27537, or certain mutated variants of Lck (Lckmut) conferring resistance to Gleevec as described by Lee K.C. et al. (2010) "Lck is a key target of imatinib and dasatinib in T-cell activation", *Leukemia,* 24: 896–900.

As described above, the genetic modification step of the method can comprise a step of introduction into cells of an exogeneous nucleic acid comprising at least a sequence encoding the drug resistance coding sequence and a portion of an endogenous gene such that homologous recombination occurs between the endogenous gene and the exogeneous nucleic acid. In a particular embodiment, said endogenous gene can be the wild type "drug resistance" gene, such that after homologous recombination, the wild type gene is replaced by the mutant form of the gene which confers resistance to the drug.

Enhancing persistence of the immune cells in-vivo

According to one aspect of the present method, the exogenous sequence that is integrated into the immune cells genomic locus encodes a molecule that enhances persistence of the immune cells, especially *in-vivo* persistence in a tumor environment.

By "enhancing persistence" is meant extending the survival of the immune cells in terms of life span, especially once the engineered immune cells are injected into the patient. For instance, persistence is enhanced, if the mean survival of the modified cells is significantly longer than that of non-modified cells, by at least 10%, preferably 20%, more preferably 30%, even more preferably 50%.

This especially relevant when the immune cells are allogeneic. This may be done by creating a local immune protection by introducing coding sequences that ectopically express and/or secrete immunosuppressive polypeptides at, or through, the cell

membrane. A various panel of such polypeptides in particular antagonists of immune checkpoints, immunosuppressive peptides derived from viral envelope or NKG2D ligand can enhance persistence and/or an engraftment of allogeneic immune cells into patients.

According to one embodiment, the immunosuppressive polypeptide to be encoded by said exogenous coding sequence is a ligand of Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4 also known as CD152, GenBank accession number AF414120.1). Said ligand polypeptide is preferably an anti-CTLA-4 immunoglobulin, such as CTLA-4a Ig and CTLA-4b Ig or a functional variant thereof.

According to one embodiment, the immunosuppressive polypeptide to be encoded by said exogenous coding sequence is an antagonist of PD1, such as PD-L1 (other names: CD274, Programmed cell death 1 ligand; ref. UniProt for the human polypeptide sequence Q9NZQ7), which encodes a type I transmembrane protein of 290 amino acids consisting of a Ig V-like domain, a Ig C-like domain, a hydrophobic transmembrane domain and a cytoplasmic tail of 30 amino acids. Such membrane-bound form of PD-L1 ligand is meant in the present invention under a native form (wild-type) or under a truncated form such as, for instance, by removing the intracellular domain, or with one or more mutation(s) (Wang S et *al*., 2003, *J Exp Med*. 2003; 197(9): 1083–1091). Of note, PD1 is not considered as being a membrane-bound form of PD-L1 ligand according to the present invention. According to another embodiment, said immunosuppressive polypeptide is under a secreted form. Such recombinant secreted PD-L1 (or soluble PD-L1) may be generated by fusing the extracellular domain of PD-L1 to the Fc portion of an immunoglobulin (Haile ST et *al*., 2014, *Cancer Immunol*. Res. 2(7): 610–615; Song MY et *al*., 2015, *Gut*. 64(2):260-71). This recombinant PD-L1 can neutralize PD-1 and abrogate PD-1-mediated T-cell inhibition. PD-L1 ligand may be co-expressed with CTLA4 Ig for an even enhanced persistence of both.

According to another embodiment, the exogenous sequence encodes a polypeptide comprising a viral env immusuppressive domain (ISU), which is derived for instance from HIV-1, HIV-2, SIV, MoMuLV, HTLV-I, -II, MPMV, SRV-1, Syncitin 1 or 2, HERV-K or FELV.

The following Table 1 shows variants of ISU domain from diverse virus which can be expressed within the present invention.

Table 1: ISU domain variants from diverse viruses

ISU Amino acids sequences														
Amino acid positions														Virus origin
1	2	3	4	5	6	7	8	9	10	11	12	13	14	Origin

L	Q	A	R	I/V	L	A	V	E	R	Y	L	K/R/Q	D	HIV-1
L	Q	A	R	V	T	A	I	E	K	Y	L	K/A/Q	D/H	HIV-2
L	Q	A	R	L	L	A	V	E	R	Y	L	K	D	SIV
L	Q	N	R	R	G	L	D	L	L	F	L	K	E	MoMuLV
A	Q	N	R	R	G	L	D	L	L	F	W	E	Q	HTLV-I, -II
L	Q	N	R	R	G	L	D	L	L	T	A	E	Q	MPMV, SRV-1
L	Q	N	R	R	A	L	D	L	L	T	A	E	R	Syncitin 1
L	Q	N	R	R	G	L	D	M	L	T	A	A	Q	Syncitin 2
L	A	N	Q	I	N	D	L	R	Q	T	V	I	W	HERV-K
L	Q	N	R	R	G	L	D	I	L	F	L	Q	E	FELV

According to another embodiment, the exogenous sequence encodes a FP polypeptide such as gp41. The following Table 2 represents several FP polypeptide from natural and artificial origins.

Table 2: Amino acid sequences of FP polypeptide from natural and artificial origins

FP Amino acids sequences									
Amino acid positions									Origin
1	2	3	4	5	6	7	8	9	
G	A	L	F	L	G	F	L	G	HIV-1 gp41
A	G	F	G	L	L	L	G	F	Synthetic
A	G	L	F	L	G	F	L	G	Synthetic

According to another embodiment, the exogenous sequence encodes a non-human MHC homolog, especially a viral MHC homolog, or a chimeric β2m polypeptide such as described by Margalit A. et al. (2003) "Chimeric β2 microglobulin/CD3ζ polypeptides expressed in T cells convert MHC class I peptide ligands into T cell activation receptors: a potential tool for specific targeting of pathogenic CD8+ T cells" *Int. Immunol.* 15 (11): 1379-1387.

According to one embodiment, the exogenous sequence encodes NKG2D ligand. Some viruses such as cytomegaloviruses have acquired mechanisms to avoid NK cell mediate immune surveillance and interfere with the NKG2D pathway by secreting a protein able to bind NKG2D ligands and prevent their surface expression (Welte, S.A et al. (2003) "Selective intracellular retention of virally induced NKG2D ligands by the human cytomegalovirus UL16 glycoprotein". *Eur. J. Immunol.*, 33, 194–203). In tumors cells, some mechanisms have evolved to evade NKG2D response by secreting NKG2D ligands such as ULBP2, MICB or MICA (Salih HR, Antropius H, Gieseke F, Lutz SZ, Kanz L, et *al.*

(2003) Functional expression and release of ligands for the activating immunoreceptor NKG2D in leukemia. *Blood* 102: 1389–1396)

According to one embodiment, the exogenous sequence encodes a cytokine receptor, such as an IL-12 receptor. IL-12 is a well known activator of immune cells activation (Curtis J.H. (2008) "IL-12 Produced by Dendritic Cells Augments CD8+ T Cell Activation through the Production of the Chemokines CCL1 and CCL171". *The Journal of Immunology*. 181 (12): 8576-8584.

According to one embodiment the exogenous sequence encodes an antibody that is directed against inhibitory peptides or proteins. Said antibody is preferably be secreted under soluble form by the immune cells. Nanobodies from shark and camels are advantageous in this respect, as they are structured as single chain antibodies (Muyldermans S. (2013) "Nanobodies: Natural Single-Domain Antibodies" *Annual Review of Biochemistry* 82: 775-797). Same are also deemed more easily to fuse with secretion signal polypeptides and with soluble hydrophilic domains.

The different aspects developed above to enhance persistence of the cells are particularly preferred, when the exogenous coding sequence is introduced by disrupting an endogenous gene encoding β2m or another MHC component, as detailed further on.

Enhancing the therapeutic activity of immune cells

According to one aspect of the present method, the exogenous sequence that is integrated into the immune cells genomic locus encodes a molecule that enhances the therapeutic activity of the immune cells.

By "enhancing the therapeutic activity" is meant that the immune cells, or population of cells, engineered according to the present invention, become more aggressive than non-engineered cells or population of cells with respect to a selected type of target cells. Said target cells generally belong to a defined type of cells, or population of cells, preferably characterized by common surface marker(s). In the present specification, "therapeutic potential" reflects the therapeutic activity, as measured through *in-vitro* experiments. In general sensitive cancer cell lines, such as Daudi cells, are used to assess whether the immune cells are more or less active towards said cells by performing cell lysis or growth reduction measurements. This can also be assessed by measuring levels of degranulation of immune cells or chemokines and cytokines production. Experiments can also be performed in mice with injection of tumor cells, and by monitoring the resulting tumor expansion. Enhancement of activity is deemed significant when the number of developing cells in these experiments is reduced by the immune cells

by more than 10%, preferably more than 20%, more preferably more than 30 %, even more preferably by more than 50 %.

According to one aspect of the invention, said exogenous sequence encodes a chemokine or a cytokine, such as IL-12. It is particularly advantageous to express IL-12 as this cytokine is extensively referred to in the literature as promoting immune cell activation (Colombo M.P. et *al.* (2002) "Interleukin-12 in anti-tumor immunity and immunotherapy" *Cytokine Growth Factor Rev*. 13(2):155-68).

According to a preferred aspect of the invention the exogenous coding sequence encodes or promote secreted factors that act on other populations of immune cells, such as T-regulatory cells, to alleviate their inhibitory effect on said immune cells.

According to one aspect of the invention, said exogenous sequence encodes an inhibitor of regulatory T-cell activity is a polypeptide inhibitor of forkhead/winged helix transcription factor 3 (FoxP3), and more preferably is a cell-penetrating peptide inhibitor of FoxP3, such as that referred as P60 (Casares N. et *al*. (2010) "A peptide inhibitor of FoxP3 impairs regulatory T cell activity and improves vaccine efficacy in mice." *J Immunol* 185(9):5150-9).

By "inhibitor of regulatory T-cells activity" is meant a molecule or precursor of said molecule secreted by the T-cells and which allow T-cells to escape the down regulation activity exercised by the regulatory T-cells thereon. In general, such inhibitor of regulatory T-cell activity has the effect of reducing FoxP3 transcriptional activity in said cells.

According to one aspect of the invention, said exogenous sequence encodes a secreted inhibitor of Tumor Associated Macrophages (TAM), such as a CCR2/CCL2 neutralization agent. Tumor-associated macrophages (TAMs) are critical modulators of the tumor microenvironment. Clinicopathological studies have suggested that TAM accumulation in tumors correlates with a poor clinical outcome. Consistent with that evidence, experimental and animal studies have supported the notion that TAMs can provide a favorable microenvironment to promote tumor development and progression. (Theerawut C. et *al*. (2014) "Tumor-Associated Macrophages as Major Players in the Tumor Microenvironment" *Cancers (Basel)* 6(3): 1670–1690). Chemokine ligand 2 (CCL2), also called monocyte chemoattractant protein 1 (MCP1 - NCBI NP_002973.1), is a small cytokine that belongs to the CC chemokine family, secreted by macrophages, that produces chemoattraction on monocytes, lymphocytes and basophils. CCR2 (C-C chemokine receptor type 2 - NCBI NP_001116513.2), is the receptor of CCL2.

Enhancing specificity and safety of immune cells

Expressing chimeric antigen receptors (CAR) have become the state of the art to direct or improve the specificity of primary immune cells, such as T-Cells and NK-cells for treating tumors or infected cells. CARs expressed by these immune cells specifically target antigen markers at the surface of the pathological cells, which further help said immune cells to destroy these cells *in-vivo* (Sadelain M. et al. "The basic principles of chimeric antigen receptor design" (2013) *Cancer Discov*. 3(4):388-98). CARs are usually designed to comprise activation domains that stimulate immune cells in response to binding to a specific antigen (so-called positive CAR), but they may also comprise an inhibitory domain with the opposite effect (so-called negative CAR)(Fedorov, V. D. (2014) "Novel Approaches to Enhance the Specificity and Safety of Engineered T Cells" *Cancer Journal* 20 (2):160–165. Positive and negative CARs may be combined or co-expressed to finely tune the cells immune specificity depending of the various antigens present at the surface of the target cells.

The genetic sequences encoding CARs are generally introduced into the cells genome using retroviral vectors that have elevated transduction efficiency but integrate at random locations. Here, according to the present invention, components of chimeric antigen receptor (CAR) car be introduced at selected loci, more particularly under control of endogenous promoters by targeted gene recombination.

According to one aspect, while a positive CAR is introduced into the immune cell by a viral vector, a negative CAR can be introduced by targeted gene insertion and vice-versa, and be active preferably only during immune cells activation. Accordingly, the inhibitory (i.e. negative) CAR contributes to an improved specificity by preventing the immune cells to attack a given cell type that needs to be preserved. Still according to this aspect, said negative CAR can be an apoptosis CAR, meaning that said CAR comprise an apoptosis domain, such as FasL (CD95 - NCBI: NP_000034.1) or a functional variant thereof, that transduces a signal inducing cell death (Eberstadt M; et al. "NMR structure and mutagenesis of the FADD (Mort1) death-effector domain" (1998) *Nature*. 392 (6679): 941–5).

Accordingly, the exogenous coding sequence inserted according to the invention can encode a factor that has the capability to induce cell death, directly, in combination with, or by activating other compound(s).

As another way to enhance the safety of us of the primary immune cells, the exogenous coding sequence can encodes molecules that confer sensitivity of the immune cells to drugs or other exogenous substrates. Such molecules can be cytochrome(s), such as from the P450 family (Preissner S et *al*. (2010) "SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions".

Nucleic Acids Res 38 (Database issue): D237-43), such as CYP2D6-1 (NCBI - NP_000097.3), CYP2D6-2 (NCBI - NP_001020332.2), CYP2C9 (), CYP3A4 (NCBI - NP_000762.2), CYP2C19 (NCBI - NP_000760.1) or CYP1A2 (NCBI - NP_000752.2.), conferring hypersensitivity of the immune cells to a drug, such as cyclophosphamide and/or isophosphamide.

According to a further aspect of the invention, an exogenous sequence is introduced in the immune cells for its expression, especially in vivo, to reduce IL-6 or IL-8 trans signalling in view of controlling potential Cyokine Release Syndrome (CRS).

Such an exogenous sequence can encode for instance antibodies directed against IL-6 or IL-8 or against their receptors IL-6R or IL-8R.

According to a preferred aspect said exogenous sequence can encode soluble extracellular domain of GP130, such as one showing at least 80% identity with SEQ ID NO. 61

Such soluble extracellular domain of GP130 is described for instance by Rose-John S. [The Soluble Interleukine Receptor: Advanced Therapeutic Options in Inflammation (2017) *Clinical Pharmacology & Therapeutics*, 102(4):591-598] can be fused with fragments of immunoglobulins, such as sgp130Fc (SEQ ID NO.62). As stated before, said exogenous sequence can be stably integrated into the genome by site directed mutagenesis (i.e. using sequence specific nuclease reagents) and be placed under the transcriptional activity of an endogenous promoter at a locus which is active during immune cell activation, such as one listed in Tables 6, 8 or 9, and preferably up-regulated upon CAR activation or being CAR dependent.

According to a more preferred embodiment, the exogenous sequence is introduced into a CAR positive immune cell, such as one expressing an anti-CD22 CAR T-cell polynucleotide sequence such as SEQ ID NO:31. According to some more specific embodiments, said exogenous sequence coding for a polypeptide which can associate, and preferably interfere, with a cytokine receptor of the IL-6 receptor family, such as said soluble extracellular domain of GP130, is integrated at a PD1, CD25 or CD69 locus. As per the present invention, the endogenous sequence encoding PD1 locus is preferably disrupted by said exogenous sequence.

The invention thus provides with a method for treating or reducing CRS in cell immunotherapy, wherein cells or a therapeutic composition thereof are administered to patients, said cells being genetically modified to secrete polypeptide(s) comprising a soluble extracellular domain of GP130, sGP130Fc, an anti-IL-6 or anti-IL6R antibody,an anti-IL-8 or anti-IL8R antibody, or any fusion thereof. .

Examples of preferred genotypes of the engineered immune cells are:

- [CAR]^{positive}[GP130]^{positive}
- [CAR]^{positive}[GP130]^{positive}
- [CAR]^{positive}[TCR]^{negative} [GP130]^{positive} [PD1]^{negative}
- [CAR]^{positive}[TCR]^{negative} [GP130]^{positive} [PD1]^{negative}
- [CAR]^{positive}[GP130]^{positive} [CD25]^{negative}
- [CAR]^{positive}[TCR]^{negative} [GP130]^{positive} [CD25]^{negative}

Improving the efficiency of gene targeted insertion in primary immune cells using AAV vectors

The present specification provides with donor templates and sequence specific reagents as illustrated in the figures that are useful to perform efficient insertion of a coding sequence in frame with endogenous promoters, in particular PD1 and CD25, as well as means and sequences for detecting proper insertion of said exogenous sequences at said loci.

The donor templates according to the present invention are generally polynucleotide sequences which can be included into a variety of vectors described in the art prompt to deliver the donor templates into the nucleus at the time the endonuclease reagents get active to obtain their site directed insertion into the genome generally by NHEJ or homologous recombination,

Specifically, the present invention provides specific donor polynucleotides for expression of IL-15 (SEQ ID NO.59) at the PD1 locus comprising one or several of the following sequences:

- Sequence encoding IL-15, such as one presenting identity with SEQ ID NO:50;
- Upstream and downstream (also referred to left and right) sequences homologous to the PD1 locus, comprising preferably polynucleotide sequences SEQ ID NO:45 and SEQ ID NO:46;
- optionally, a sequence encoding soluble form of an IL-15 receptor (sIL-15R), such as one presenting identity with SEQ ID NO:50;
- optionally, at least one 2A peptide cleavage site such as one of SEQ ID NO:53 (F2A), SEQ ID NO:54 (P2A) and/or SEQ ID NO:55 (T2A),

Specifically, the present invention provides specific donor polynucleotides for expression of IL-12 (SEQ ID NO:58) at the PD1 locus comprising one or several of the following sequences:

- Sequence encoding IL-12a, such as one presenting identity with SEQ ID NO:47;
- Upstream and downstream (also referred to left and right) sequences homologous to the PD1 locus, comprising preferably polynucleotide sequences SEQ ID NO:45 and SEQ ID NO:46;
- optionally, a sequence encoding IL-12b, such as one presenting identity with SEQ ID NO:48;
- optionally, at least one 2A peptide cleavage site such as one of SEQ ID NO:53 (F2A), SEQ ID NO:54 (P2A) and/or SEQ ID NO:55 (T2A),

Specifically, the present invention provides specific donor polynucleotides for expression of soluble GP130 (comprising SEQ ID NO.61) at the PD1 locus comprising one or several of the following sequences:

- Sequence encoding soluble GP130, preferably a soluble gp130 fused to a Fc, such as one presenting identity with SEQ ID NO:62;
- Upstream and downstream (also referred to left and right) sequences homologous to the PD1 locus, comprising preferably polynucleotide sequences SEQ ID NO:45 and SEQ ID NO:46;
- optionally, at least one 2A peptide cleavage site such as one of SEQ ID NO:53 (F2A), SEQ ID NO:54 (P2A) and/or SEQ ID NO:55 (T2A),

Specifically, the present invention provides specific donor polynucleotides for expression of IL-15 (SEQ ID NO.59) at the CD25 locus comprising one or several of the following sequences:

- Sequence encoding IL-15, such as one presenting identity with SEQ ID NO:50;
- Upstream and downstream (also referred to left and right) sequences homologous to the CD25 locus, comprising preferably polynucleotide sequences SEQ ID NO:43 and SEQ ID NO:44;
- optionally, a sequence encoding soluble form of an IL-15 receptor (sIL-15R), such as one presenting identity with SEQ ID NO:50;
- optionally, at least one 2A peptide cleavage site such as one of SEQ ID NO:53 (F2A), SEQ ID NO:54 (P2A) and/or SEQ ID NO:55 (T2A),

Specifically, the present invention provides specific donor polynucleotides for expression of IL-12 (SEQ ID NO:58) at the CD25 locus comprising one or several of the following sequences:

- Sequence encoding IL-12a, such as one presenting identity with SEQ ID NO:47;
- Upstream and downstream (also referred to left and right) sequences homologous to the CD25 locus, comprising preferably polynucleotide sequences SEQ ID NO:43 and SEQ ID NO:44;
- optionally, a sequence encoding IL-12b, such as one presenting identity with SEQ ID NO:48;
- optionally, at least one 2A peptide cleavage site such as one of SEQ ID NO:53 (F2A), SEQ ID NO:54 (P2A) and/or SEQ ID NO:55 (T2A),

Specifically, the present invention provides specific donor polynucleotides for expression of soluble GP130 (comprising SEQ ID NO.61) at the CD25 locus comprising one or several of the following sequences:

- Sequence encoding soluble GP130, preferably a soluble gp130 fused to a Fc, such as one presenting identity with SEQ ID NO:62;
- Upstream and downstream (also referred to left and right) sequences homologous to the CD25 locus, comprising preferably polynucleotide sequences SEQ ID NO:43 and SEQ ID NO:44;
- optionally, at least one 2A peptide cleavage site such as one of SEQ ID NO:53 (F2A), SEQ ID NO:54 (P2A) and/or SEQ ID NO:55 (T2A),

As illustrated in the examples herein, the inventors have significantly improved the rate of gene targeted insertion into human cells by using AAV vectors, especially vectors from the AAV6 family.

One broad aspect of the present invention is thus the transduction of AAV vectors in human primary immune cells, in conjunction with the expression of sequence specific endonuclease reagents, such as TALE endonucleases, more preferably introduced under mRNA form, to increase homologous recombination events in these cells.

According to one aspect of this invention, sequence specific endonuclease reagents can be introduced into the cells by transfection, more preferably by electroporation of mRNA encoding said sequence specific endonuclease reagents, such as TALE nucleases.

Still according to this broad aspect, the invention more particularly provides a method of insertion of an exogenous nucleic acid sequence into an endogenous polynucleotide sequence in a cell, comprising at least the steps of:

- transducing into said cell an AAV vector comprising said exogenous nucleic acid sequence and sequences homologous to the targeted endogenous DNA sequence, and
- Inducing the expression of a sequence specific endonuclease reagent to cleave said endogenous sequence at the locus of insertion.

The obtained insertion of the exogenous nucleic acid sequence may result into the introduction of genetic material, correction or replacement of the endogenous sequence, more preferably "in frame" with respect to the endogenous gene sequences at that locus.

According to another aspect of the invention, from 10^5 to 10^7 preferably from 10^6 to 10^7, more preferably about 5.10^6 viral genomes are transduced per cell.

According to another aspect of the invention, the cells can be treated with proteasome inhibitors, such as Bortezomib to further help homologous recombination.

As one object of the present invention, the AAV vector used in the method can comprise a promoterless exogenous coding sequence as any of those referred to in this specification in order to be placed under control of an endogenous promoter at one loci selected among those listed in the present specification.

As one object of the present invention, the AAV vector used in the method can comprise a 2A peptide cleavage site followed by the cDNA (minus the start codon) forming the exogenous coding sequence.

As one object of the present invention, said AAV vector comprises an exogenous sequence coding for a chimeric antigen receptor, especially an anti-CD19 CAR, an anti-CD22 CAR, an anti-CD123 CAR, an anti-CS1 CAR, an anti-CCL1 CAR, an anti-HSP70 CAR, an anti-GD3 CAR or an anti-ROR1 CAR.

The invention thus encompasses any AAV vectors designed to perform the method herein described, especially vectors comprising a sequence homologous to a locus of insertion located in any of the endogenous gene responsive to T-cell activation referred to in Table 4.

Many other vectors known in the art, such as plasmids, episomal vectors, linear DNA matrices, etc… can also be used following the teachings to the present invention.

As stated before, the DNA vector used according to the invention preferably comprises: (1) said exogenous nucleic acid comprising the exogenous coding sequence to be inserted by homologous recombination, and (2) a sequence encoding the sequence

specific endonuclease reagent that promotes said insertion. According to a more preferred aspect, said exogenous nucleic acid under (1) does not comprise any promoter sequence, whereas the sequence under (2) has its own promoter. According to an even more preferred aspect, the nucleic acid under (1) comprises an Internal Ribosome Entry Site (IRES) or "self-cleaving" 2A peptides, such as T2A, P2A, E2A or F2A, so that the endogenous gene where the exogenous coding sequence is inserted becomes multi-cistronic. The IRES of 2A Peptide can precede or follow said exogenous coding sequence.

Preferred vectors of the present invention are vectors derived from AAV6, comprising donor polynucleotides as previously described herein or illustrated in the experimental section and figures. Examples of vectors according to the invention comprise or consist of polynucleotides having identity with sequences SEQ ID NO:37 (matrix for integration of sequence coding for IL-15 into the CD25 locus), SEQ ID NO:38 (matrix for integration of sequence coding for IL-15 into the PD1 locus) SEQ ID NO:39 (matrix for integration of sequence coding for IL-12 into the CD25 locus) and SEQ ID NO:40 (matrix for integration of sequence coding for IL-12 into the PD1 locus).

Gene targeted integration in immune cells under transcriptional control of endogenous promoters

The present invention, in one of its main aspects, is taking advantage of the endogenous transcriptional activity of the immune cells to express exogenous sequences that improve their therapeutic potential.

The invention provides with several embodiments based on the profile of transcriptional activity of the endogenous promoters and on a selection of promoter loci useful to carry out the invention. Preferred loci are those, which transcription activity is generally high upon immune cell activation, especially in response to CAR activation (CAR-sensitive promoters) when the cells are endowed with CARs.

Accordingly, the invention provides with a method for producing allogeneic therapeutic immune cells by expressing a first exogenous sequence encoding a CAR at the TCR locus, thereby disrupting TCR expression, and expressing a second exogenous coding sequence under transcriptional activity of an endogenous locus, preferably dependent from either:

- CD3/CD28 activation, such as dynabeads, which is useful for instance for promoting cells expansion;
- CAR activation, such as through the CD3zeta pathway, which is useful for instance to activate immune cells functions on-target;

- Transcriptional activity linked to the appearance of disease symptom or molecular marker. which is useful for instance for activating the cells *in-situ* in ill organs.
- Cell differentiation, which is useful for conferring therapeutic properties to cells at a given level of differentiation or to express protein into a particular lineage (see figure 1), for instance at the time hematopoietic cells gain their immune functions; or/and
- TME (Tumor microoenvironment), which is useful for redirect cells activity and their amplification to specific tumor conditions (hypoxia, low glucose…), or for preventing exhaustion and/or sustaining activation;
- CRS (cytokine release syndrome), which is useful to mitigate adverse events related to CAR T-cell activity

The inventors have established a first list of endogenous genes (Table 6) which have been found to be particularly appropriate for applying the targeted gene recombination as per the present invention. To draw this list, they have come across several transcriptome murine databases, in particular that from the Immunological Genome Project Consortium referred to in Best J.A. et *al*. (2013) "Transcriptional insights into the CD8(+) T cell response to infection and memory T cell formation" *Nat. Immunol.*. 14(4):404-12., which allows comparing transcription levels of various genes upon T-cell activation, in response to ovalbumin antigens. Also, because very few data is available with respect to human T-cell activation, they had to make some extrapolations and analysis from these data and compare with the human situation by studying available literature related to the human genes. The selected loci are particularly relevant for the insertion of sequences encoding CARs. Based on the first selection of Table 6, they made subsequent selections of genes based on their expected expression profiles (Tables 7 to 10).

On another hand, the inventors have identified a selection of transcriptional loci that are mostly inactive, which would be most appropriate to insert expression cassette(s) to express exogenous coding sequence under the transcriptional control of exogenous promoters. These loci are referred to as "safe harbor loci" as those being mostly transcriptionally inactive, especially during T-Cell activation. They are useful to integrate a coding sequence by reducing at the maximum the risk of interfering with genome expression of the immune cells.

Gene targeted insertion under control of endogenous promoters that are steadily active during immune cell activation

A selection of endogenous gene loci related to this embodiment is listed in Table 7.

Accordingly the method of the present invention provides with the step of performing gene targeted insertion under control of an endogenous promoter that is constantly active during immune cell activation, preferably from of an endogenous gene selected from *CD3G, Rn28s1, Rn18s, Rn7sk, Actg1, β2m, Rpl18a, Pabpc1, Gapdh, Rpl17, Rpl19, Rplp0, Cfl1* and *Pfn1.*

By "steadily active" means that the transcriptional activity observed for these promoters in the primary immune cell is not affected by a negative regulation upon the activation of the immune cell.

As reported elsewhere (Acuto, O. (2008) "Tailoring T-cell receptor signals by proximal negative feedback mechanisms". *Nature Reviews Immunology* 8:699-712), the promoters present at the TCR locus are subjected to different negative feedback mechanisms upon TCR engagement and thus may not be steadily active or up regulated during for the method of the present invention. The present invention has been designed to some extend to avoid using the TCR locus as a possible insertion site for exogenous coding sequences to be expressed during T-cell activation. Therefore, according to one aspect of the invention, the targeted insertion of the exogenous coding sequence is not performed at a TCRalpha or TCRbeta gene locus.

Examples of exogenous coding sequence that can be advantageously introduced at such loci under the control of steadily active endogenous promoters, are those encoding or positively regulating the production of a cytokine, a chemokine receptor, a molecule conferring resistance to a drug, a co-stimulation ligand, such as 4-1BRL and OX40L, or of a secreted antibody.

Gene integration under endogenous promoters that are dependent from immune cell activation or dependent from CAR activation

As stated before, the method of the present invention provides with the step of performing gene targeted insertion under control of an endogenous promoter, which transcriptional activity is preferably up-regulated upon immune cell activation, either transiently or over more than 10 days.

By "immune cell activation" is meant production of an immune response as per the mechanisms generally described and commonly established in the literature for a given type of immune cells. With respect to T-cell, for instance, T- cell activation is generally characterized by one of the changes consisting of cell surface expression by production of a variety of proteins, including CD69, CD71 and CD25 (also a marker for Treg cells), and

HLA-DR (a marker of human T cell activation), release of perforin, granzymes and granulysin (degranulation), or production of cytokine effectors IFN-γ, TNF and LT-alpha.

According to a preferred embodiment of the invention, the transcriptional activity of the endogenous gene is up-regulated in the immune cell, especially in response to an activation by a CAR. The CAR can be independently expressed in the immune cell. By "independently expressed" is meant that the CAR can be transcribed in the immune cell from an exogenous expression cassette introduced, for instance, using a retroviral vector, such as a lentiviral vector, or by transfecting capped messenger RNAs by electroporation encoding such CAR Many methods are known in the art to express a CAR into an immune cell as described for instance by (REF.)

Said endogenous gene whose transcriptional activity is up regulated are particularly appropriate for the integration of exogenous sequences to encode cytokine(s), such as IL-12 and IL-15, immunogenic peptide(s), or a secreted antibody, such as an anti-IDO1, anti-IL10, anti-PD1, anti-PDL1, anti-IL6 or anti-PGE2 antibody.

According to a preferred embodiment of the invention, the endogenous promoter is selected for its transcriptional activity being responsive to, and more preferably being dependent from CAR activation.

As shown herein, CD69, CD25 and PD1 are such loci, which are particularly appropriate for the insertion of expression of an exogenous coding sequences to be expressed when the immune cells get activated, especially into CAR positive immune cells.

The present invention thus combines any methods of expressing a CAR into an immune cell with the step of performing a site directed insertion of an exogenous coding sequence at a locus, the transcriptional activity of which is responsive to or dependent from the engagement of said CAR with a tumor antigen. Especially, the method comprises the step of introducing into a CAR positive or Recombinant TCR positive immune cell an exogenous sequence encoding IL-12 or IL-15 under transcriptional control of one promoter selected from PD1, CD25 and CD69 promoters.

In particular, CAR positive cells can obtained by following the steps of co-expressing into an immune cell, preferably a primary cell, and more preferably into a primary T- cell, at least one exogenous sequence encoding a CAR and another exogenous sequence placed under an endogenous promoter dependent, which transcriptional activity is dependent from said CAR, such a PD1, CD25 or CD71.

The expression "dependent from said CAR" means that the transcriptional activity of said endogenous promoter is necessary increased by more than 10%, preferably by more

than 20 %, more preferably by more than 50% and even more preferably more than 80 %, as a result of the engagement of the CAR with its cognate antigen, in a situation where, in general, the antigens are exceeding the number of CARs present at the cell surface and the number of CARs expressed at the cell surface is more than 10 per cell, preferably more than 100, and more preferably more than 1000 molecules per cells.

The present invention thus teaches the expression of a CAR sequence, preferably inserted at the TCR locus and constitutively expressed, whereas another exogenous sequence integrated at another locus is co-expressed, in response to, or dependent from, the engagement of said CAR with its cognate antigen. Said another locus is for instance CD25, PD1 or CD71 or any loci being specifically transcribed upon CAR activation.

In other words, the invention provides the co-expression of a CAR and at least one exogenous coding sequence, the expression of said exogenous sequence being under control of an endogenous promoter the transcriptional activity of which is influenced by the CAR activity, this being done in view of obtaining engineered immune cells offering a better immune response.

As previously described, this can be performed by transfecting the cells with sequence-specific nuclease reagents targeting the coding regions of such loci being specifically CAR dependent, along with donor templates comprising sequences homologous to said genomic regions. The sequence specific nuclease reagents help the donor templates to be integrated by homologous recombination or NHEJ.

According to a preferred embodiment, the exogenous coding sequence is integrated in frame with the endogenous gene, so that the expression of said endogenous gene is preserved. This is the case for instance with respect to CD25 and CD69 in at least one example of the experimental section herein.

According to a preferred embodiment, the exogenous sequence disrupts the endogenous coding sequence of the gene to prevent its expression of one endogenous coding sequence, especially when this expression has a negative effect on the immune cell functions, as it the case for instance with PD1 in the experimental section herein.

According to an even more preferred embodiments, the exogenous coding sequence, which disrupts the endogenous gene sequence is placed in frame with the endogenous promoter, so that its expression is made dependent from the endogenous promoter as also shown in the experimental section.

The present invention is also drawn to the polynucleotide and polypeptide sequences encoding the different TAL-nucleases exemplified in the present patent application, especially those permitting the site directed insertion at the CD25 locus (SEQ ID NO:18 and 19), as well as their respective target and RVD sequences.

The present invention also encompasses kits for immune cells transfection comprising polynucleotides encoding the sequence-specific endonuclease reagents and the donor sequences designed to integrate the exogenous sequence at the locus targeted by said reagents. Examples of such kits are a kit comprising mRNA encoding rare-cutting endonuclease targeting PD1 locus (ex: PD1 TALEN®) and an AAV vector comprising an exogenous sequence encoding IL-12, a kit comprising mRNA encoding rare-cutting endonuclease targeting PD1 locus (ex: PD1 TALEN®) and an AAV vector comprising an exogenous sequence encoding IL-15, a kit comprising mRNA encoding rare-cutting endonuclease targeting CD25 locus (ex: CD25 TALEN®) and an AAV vector comprising an exogenous sequence encoding IL-12, a kit comprising mRNA encoding rare-cutting endonuclease targeting CD25 locus (ex: CD25 TALEN®) and an AAV vector comprising an exogenous sequence encoding IL-15, a kit comprising mRNA encoding rare-cutting endonuclease targeting PD1 locus (ex: PD1 TALEN®) and an AAV vector comprising an exogenous sequence encoding soluble gp130, a kit comprising mRNA encoding rare-cutting endonuclease targeting CD25 locus (ex: CD25 TALEN®) and an AAV vector comprising an exogenous sequence encoding soluble gp130, and any kits involving endonuclease reagents targeting a gene listed in table 6, and a donor matrix for introducing a coding sequence referred to in the present specification.

According to one aspect of the invention, the endogenous gene is selected for a weak up-regulation. The exogenous coding sequence introduced into said endogenous gene whose transcriptional activity is weakly up regulated, can be advantageously a constituent of an inhibitory CAR, or of an apoptotic CAR, which expression level has generally to remain lower than that of a positive CAR. Such combination of CAR expression, for instance one transduced with a viral vector and the other introduced according to the invention, can greatly improve the specificity or safety of CAR immune cells

Some endogenous promoters are transiently up-regulated, sometimes over less than 12 hours upon immune cell activation, such as those selected from the endogenous gene loci *Spata6, Itga6, Rcbtb2, Cd1d1, St8sia4, Itgae* and *Fam214a* (Table 8). Other endogenous promoters are up-regulated over less than 24 hours upon immune cell activation, such as those selected from the endogenous gene loci *IL3, IL2, Ccl4, IL21, Gp49a, Nr4a3, Lilrb4, Cd200, Cdkn1a, Gzmc, Nr4a2, Cish, Ccr8, Lad1* and *Crabp2* (Table 9) and others over more than 24 hours, more generally over more than 10 days, upon immune cell activation. Such as those selected from *Gzmb, Tbx21, Plek, Chek1, Slamf7, Zbtb32, Tigit, Lag3, Gzma, Wee1, IL12rb2, Eea1* and *Dtl* (Table 9).

Alternatively, the inventors have found that endogenous gene under transcriptional control of promoters that are down-regulated upon immune cell activation, could also be of interest for the method according to the present invention. Indeed they have conceived that exogenous coding sequences encoding anti-apoptotic factors, such as of Bcl2 family, BclXL, NF-kB, Survivin, or anti-FAP (fibroblast activation protein), such as a constituent of a CAR anti-FAP, could be introduced at said loci. Said endogenous gene under transcriptional control of promoters that are down-regulated upon immune cell activation can be more particularly selected from *Slc6a19, Cd55, Xkrx, Mturn, H2-Ob, Cnr2, Itgae, Raver2, Zbtb20, Arrb1, Abca1, Tet1, Slc16a5* and *Ampd3* (Table 10)

Gene integration under endogenous promoters activated under tumor microenvironment (TME) conditions

One aspect of the present invention more particularly concerns methods to prevent immune cells exhaustion in tumor microenvironment (TME) conditions. Immune cells often get exhausted in response to nutrient depletion or molecular signals found in the microoenvironment of tumors, which helps tumor resistance. The method comprises the steps of engineering immune cells by integrating exogenous coding sequences under control of endogenous promoters which are up-regulated under arginine, cysteine, tryptophan and oxygen deprivation as well as extracellular acidosis (lactate build up).

Such exogenous sequences may encode chimeric antigen receptors, interleukins, or any polypeptide given elsewhere in this specification to bolster immune cells function or activation and/or confer a therapeutic advantage.

The inventors have listed a number of loci which have been found to be upregulated in a large number of exhausted tumor infiltrating lymphocytes (TIL), which are listed in tables 12 and 13. The invention provides with the step of integrating exogenous coding sequences at these preferred loci to prevent exhaustion of the immune cells, in particular T-cells, in tumor microoenvironment.

For instance, the exogenous sequences encoding a CAR can be placed under transcriptional control of the promoter of endogenous genes that are activated by the tumor microenvironment, such as HIF1a, transcription factor hypoxia-inducible factor, or the aryl hydrocarbon receptor (AhR), These gene are sensors respectively induced by hypoxia and xenobiotics in the close environment of tumors.

The present invention is thus useful to improve the therapeutic outcome of CAR T-cell therapies by integrating exogenous coding sequences, and more generally genetic

attributes/circuits, under the control of endogenous T-cell promoters influenced by tumor microenvironment (TME).

Pursuant to the invention, upregulation of endogenous genes can be "hijacked" to re-express relevant exogenous coding sequences to improve the antitumor activity of CAR T-cells in certain tumor microenvironment.

Gene targeted insertion and expression in Hematopoietic Stem Cells (HSCs)

One aspect of the present invention more particularly concerns the insertion of transgenes into hematopoietic stem cells (HSCs).

Hematopoietic stem cells (HSCs) are multipotent, self-renewing progenitor cells from which all differentiated blood cell types arise during the process of hematopoiesis. These cells include lymphocytes, granulocytes, and macrophages of the immune system as well as circulating erythrocytes and platelets. Classically, HSCs are thought to differentiate into two lineage-restricted, lymphoid and myelo-erythroid, oligopotent progenitor cells. The mechanisms controlling HSC self-renewal and differentiation are thought to be influenced by a diverse set of cytokines, chemokines, receptors, and intracellular signaling molecules. Differentiation of HSCs is regulated, in part, by growth factors and cytokines including colony-stimulating factors (CSFs) and interleukins (ILs) that activate intracellular signaling pathways. The factors depicted below are known to influence HSC multipotency, proliferation, and lineage commitment. HSCs and their differentiated progeny can be identified by the expression of specific cell surface lineage markers such as cluster of differentiation (CD) proteins and cytokine receptors into hematopoietic stem cells.

Gene therapy using HSCs has enormous potential to treat diseases of the hematopoietic system including immune diseases. In this approach, HSCs are collected from a patient, gene-modified ex-vivo using integrating retroviral vectors, and then infused into a patient. To date retroviral vectors have been the only effective gene delivery system for HSC gene therapy. Gene delivery to HSCs using integrating vectors thereby allowing for efficient delivery to HSC-derived mature hematopoietic cells. However, the gene-modified cells that are infused into a patient are a polyclonal population, where the different cells have vector proviruses integrated at different chromosomal locations, which can result into many adverse mutations, which may be amplified due to some proliferative/survival advantage of these mutations (Powers and Trobridge (2013) "Identification of Hematopoietic Stem Cell Engraftment Genes in Gene Therapy Studies" *J Stem Cell Res Ther* S3:004. doi:10.4172/2157-7633.S3-00).

HSCs are commonly harvested from the peripheral blood after mobilization (patients receive recombinant human granulocyte-colony stimulating factor (G-CSF)). The patient's peripheral blood is collected and enriched for HSCs using the CD34+ marker. HSCs are then cultured ex vivo and exposed to viral vectors. The ex vivo culture period varies from 1 to 4 days. Prior to the infusion of gene-modified HSCs, patients may be treated with chemotherapy agents or irradiation to help enhance the engraftment efficiency. Gene-modified HSCs are re-infused into the patient intravenously. The cells migrate into the bone marrow before finally residing in the sinusoids and perivascular tissue. Both homing and hematopoiesis are integral aspects of engraftment. Cells that have reached the stem cell niche through homing will begin producing mature myeloid and lymphoid cells from each blood lineage. Hematopoiesis continues through the action of long-term HSCs, which are capable of self-renewal for life-long generation of the patient's mature blood cells, in particular the production of common lymphoid progenitor cells, such as T cells and NK cells, which are key immune cells for eliminating infected and malignant cells.

The present invention provides with performing gene targeted insertion in HSCs to introduce exogenous coding sequences under the control of endogenous promoters, especially endogenous promoters of genes that are specifically activated into cells of a particular hematopoietic lineage or at particular differentiation stage, preferably at a late stage of differentiation. The HSCs can be transduced with a polynucleotide vector (donor template), such as an AAV vector, during an ex-vivo treatment as referred to in the previous paragraph, whereas a sequence specific nuclease reagent is expressed as to promote the insertion of the coding sequences at the selected locus. The resulting engineered HSCs can be then engrafted into a patient in need thereof for a long term *in-vivo* production of engineered immune cells that will comprise said exogenous coding sequences. Depending on the activity of the selected endogenous promoter, the coding sequences will be selectively expressed in certain lineages or in response to the local environment of the immune cells in-vivo, thereby providing adoptive immunotherapy.

According to one preferred aspect of the invention, the exogenous coding sequences are placed under the control of promoters of a gene, which transcriptional activity is specifically induced in common lymphoid progenitor cells, such as CD34, CD43, Flt-3/Flk-2, IL-7 R alpha/CD127 and Neprilysin/CD10.

More preferably, the exogenous coding sequences are placed under the control of promoters of a gene, which transcriptional activity is specifically induced in NK cells, such as CD161, CD229/SLAMF3, CD96, DNAM-1/CD226, Fc gamma RII/CD32, Fc gamma RII/RIII (CD32/CD16), Fc gamma RIII (CD16), IL-2 R beta, Integrin alpha 2/CD49b,

KIR/CD158, NCAM-1/CD56, NKG2A/CD159a, NKG2C/CD159c, NKG2D/CD314, NKp30/NCR3, NKp44/NCR2, NKp46/NCR1, NKp80/KLRF1, Siglec-7/CD328 and TIGIT, or induced in T-cells, such as CCR7, CD2, CD3, CD4, CD8, CD28, CD45, CD96, CD229/SLAMF3, DNAM-1/CD226, CD25/IL-2 R alpha, L-Selectin/CD62L and TIGIT.

The invention comprises as a preferred aspect the introduction of an exogenous sequence encoding a CAR, or a component thereof, into HSCs, preferably under the transcriptional control of a promoter of a gene that is not expressed in HSC, more preferably a gene that is only expressed in the hematopoietic cells produced by said HSC, and even more preferably of a gene that is only expressed in T-cells or NK cells.

Conditional CAR expression in HSCs to overpass the thymus barrier

A particular aspect of the present invention concerns the *in-vivo* production by the above engineered HSCs of hematopoietic immune cells, such as T-cells or NK-cells, expressing exogenous coding sequences, in particular a CAR or a component thereof.

One major bar of the production of hematopoietic CAR positive cells by engineered HSCs, for instance, is the rejection of the CAR positive cells by the immune system itself, especially by the thymus.

The blood–thymus barrier regulates exchange of substances between the circulatory system and thymus, providing a sequestered environment for immature T cells to develop. The barrier also prevents the immature T cells from contacting foreign antigens (since contact with antigens at this stage will cause the T cells to die by apoptosis).

One solution provided by the present invention is to place the sequences encoding the CAR components in the HSCs under the transcriptional control of promoters which are not significantly transcribed into the hematopoietic cells when they pass through the thymus barrier. One example of a gene that offers a conditional expression of the CAR into the hematopoietic cells with reduced or no significant transcriptional activity in the thymus is LCK (Uniprot: P06239).

According to a preferred aspect of the invention the exogenous sequence encoding a CAR, or a component thereof, is introduced into the HSC under the transcriptional control of a gene that is described as being specifically expressed in T-cells or NK cells, preferably in these types of cells only.

The invention thereby provides with a method of producing HSCs comprising an exogenous coding sequences to be expressed exclusively in selected hematopoietic lineage(s), said coding sequences encoding preferably at least one component of a CAR or of an antigen in order to stimulate the immune system.

More broadly, the invention provides with a method of engineering HSCs by gene targeted insertion of an exogenous coding sequences to be selectively expressed in the hematopoietic cells produced by said HSCs. As a preferred embodiment, said hematopoietic cells produced by said engineered HSCs express said exogenous coding sequences in response to selected environmental factors or in-vivo stimuli to improve their therapeutic potential.

Combining targeted sequence insertion(s) in immune cells with the inactivation of endogenous genomic sequences

One particular focus of the present invention is to perform gene inactivation in primary immune cells at a locus, by integrating exogenous coding sequence at said locus, the expression of which improves the therapeutic potential of said engineered cells. Examples of relevant exogenous coding sequences that can be inserted according to the invention have been presented above in connection with their positive effects on the therapeutic potential of the cells. Here below are presented the endogenous gene that are preferably targeted by gene targeted insertion and the advantages associated with their inactivation.

According to a preferred aspect of the invention, the insertion of the coding sequence has the effect of reducing or preventing the expression of genes involved into self and non-self recognition to reduce host versus graft disease (GVHD) reaction or immune rejection upon introduction of the allogeneic cells into a recipient patient. For instance, one of the sequence-specific reagents used in the method can reduce or prevent the expression of TCR in primary T-cells, such as the genes encoding TCR-alpha or TCR-beta.

As another preferred aspect, one gene editing step is to reduce or prevent the expression of the ß2m protein and/or another protein involved in its regulation such as C2TA (Uniprot P33076) or in MHC recognition, such as HLA proteins. This permits the engineered immune cells to be less alloreactive when infused into patients.

By “allogeneic therapeutic use” is meant that the cells originate from a donor in view of being infused into patients having a different haplotype. Indeed, the present invention provides with an efficient method for obtaining primary cells, which can be gene edited in various gene loci involved into host-graft interaction and recognition.

Other loci may also be edited in view of improving the activity, the persistence of the therapeutic activity of the engineered primary cells as detailed here after:

Inactivation of checkpoint receptors and immune cells inhibitory pathways:

According to a preferred aspect of the invention, the inserted exogenous coding sequence has the effect of reducing or preventing the expression of a protein involved in immune cells inhibitory pathways, in particular those referred to in the literature as "immune checkpoint" (Pardoll, D.M. (2012) The blockade of immune checkpoints in cancer immunotherapy, *Nature Reviews Cancer,* 12:252-264). In the sense of the present invention, "immune cells inhibitory pathways" means any gene expression in immune cells that leads to a reduction of the cytotoxic activity of the lymphocytes towards malignant or infected cells. This can be for instance a gene involved into the expression of FOXP3, which is known to drive the activity of Tregs upon T cells (moderating T-cell activity).

"Immune checkpoints" are molecules in the immune system that either turn up a signal (co-stimulatory molecules) or turn down a signal of activation of an immune cell. As per the present invention, immune checkpoints more particularly designate surface proteins involved in the ligand–receptor interactions between T cells and antigen-presenting cells (APCs) that regulate the T cell response to antigen (which is mediated by peptide–major histocompatibility complex (MHC) molecule complexes that are recognized by the T cell receptor (TCR)). These interactions can occur at the initiation of T cell responses in lymph nodes (where the major APCs are dendritic cells) or in peripheral tissues or tumours (where effector responses are regulated). One important family of membrane-bound ligands that bind both co-stimulatory and inhibitory receptors is the B7 family. All of the B7 family members and their known ligands belong to the immunoglobulin superfamily. Many of the receptors for more recently identified B7 family members have not yet been identified. Tumour necrosis factor (TNF) family members that bind to cognate TNF receptor family molecules represent a second family of regulatory ligand–receptor pairs. These receptors predominantly deliver co-stimulatory signals when engaged by their cognate ligands. Another major category of signals that regulate the activation of T cells comes from soluble cytokines in the microenvironment. In other cases, activated T cells upregulate ligands, such as CD40L, that engage cognate receptors on APCs. A2aR, adenosine A2a receptor; B7RP1, B7-related protein 1; BTLA, B and T lymphocyte attenuator; GAL9, galectin 9; HVEM, herpesvirus entry mediator; ICOS, inducible T cell co-stimulator; IL, interleukin; KIR, killer cell immunoglobulin-like receptor; LAG3, lymphocyte activation gene 3; PD1, programmed cell death protein 1; PDL, PD1 ligand; TGFβ, transforming growth factor-β; TIM3, T cell membrane protein 3.

Examples of further endogenous genes, which expression could be reduced or suppressed to turn-up activation in the engineered immune cells according the present invention are listed in Table 3.

For instance, the inserted exogenous coding sequence(s) can have the effect of reducing or preventing the expression, by the engineered immune cell of at least one protein selected from PD1 (Uniprot Q15116), CTLA4 (Uniprot P16410), PPP2CA (Uniprot P67775), PPP2CB (Uniprot P62714), PTPN6 (Uniprot P29350), PTPN22 (Uniprot Q9Y2R2), LAG3 (Uniprot P18627), HAVCR2 (Uniprot Q8TDQ0), BTLA (Uniprot Q7Z6A9), CD160 (Uniprot O95971), TIGIT (Uniprot Q495A1), CD96 (Uniprot P40200), CRTAM (Uniprot O95727), LAIR1 (Uniprot Q6GTX8), SIGLEC7 (Uniprot Q9Y286), SIGLEC9 (Uniprot Q9Y336), CD244 (Uniprot Q9BZW8), TNFRSF10B (Uniprot O14763), TNFRSF10A (Uniprot O00220), CASP8 (Uniprot Q14790), CASP10 (Uniprot Q92851), CASP3 (Uniprot P42574), CASP6 (Uniprot P55212), CASP7 (Uniprot P55210), FADD (Uniprot Q13158), FAS (Uniprot P25445), TGFBRII (Uniprot P37173), TGFRBRI (Uniprot Q15582), SMAD2 (Uniprot Q15796), SMAD3 (Uniprot P84022), SMAD4 (Uniprot Q13485), SMAD10 (Uniprot B7ZSB5), SKI (Uniprot P12755), SKIL (Uniprot P12757), TGIF1 (Uniprot Q15583), IL10RA (Uniprot Q13651), IL10RB (Uniprot Q08334), HMOX2 (Uniprot P30519), IL6R (Uniprot P08887), IL6ST (Uniprot P40189), EIF2AK4 (Uniprot Q9P2K8), CSK (Uniprot P41240), PAG1 (Uniprot Q9NWQ8), SIT1 (Uniprot Q9Y3P8), FOXP3 (Uniprot Q9BZS1), PRDM1 (Uniprot Q60636), BATF (Uniprot Q16520), GUCY1A2 (Uniprot P33402), GUCY1A3 (Uniprot Q02108), GUCY1B2 (Uniprot Q8BXH3) and GUCY1B3 (Uniprot Q02153). The gene editing introduced in the genes encoding the above proteins is preferably combined with an inactivation of TCR in CAR T cells.

Preference is given to inactivation of PD1 and/or CTLA4, in combination with the expression of non-endogenous immunosuppressive polypeptide, such as a PD-L1 ligand and/or CTLA-4 Ig (see also peptides of Table 1 and 2).

Table 3: List of genes involved into immune cells inhibitory pathways

Pathway		Genes that can be inactivated In the pathway
Co-inhibitory receptors	CTLA4 (CD152)	CTLA4, PPP2CA, PPP2CB, PTPN6, PTPN22
	PDCD1 (PD-1, CD279)	PDCD1
	CD223 (lag3)	LAG3
	HAVCR2 (tim3)	HAVCR2
	BTLA(cd272)	BTLA
	CD160(by55)	CD160
	IgSF family	TIGIT
		CD96
		CRTAM
	LAIR1(cd305)	LAIR1
	SIGLECs	SIGLEC7

		SIGLEC9
	CD244(2b4)	CD244
Death receptors	TRAIL	TNFRSF10B, TNFRSF10A, CASP8, CASP10, CASP3, CASP6, CASP7
	FAS	FADD, FAS
Cytokine signalling	TGF-beta signaling	TGFBRII, TGFBRI, SMAD2, SMAD3, SMAD4, SMAD10, SKI, SKIL, TGIF1
	IL10 signalling	IL10RA, IL10RB, HMOX2
	IL6 signalling	IL6R, IL6ST
Prevention of TCR signalling		CSK, PAG1
		SIT1
Induced Treg	induced Treg	FOXP3
Transcription factors controlling exhaustion	transcription factors controlling exhaustion	PRDM1
		BATF
Hypoxia mediated tolerance	iNOS induced guanylated cyclase	GUCY1A2, GUCY1A3, GUCY1B2, GUCY1B3

Inhibiting suppressive cytokines/metabolites

According to another aspect of the invention, the inserted exogenous coding sequence has the effect of reducing or preventing the expression of genes encoding or positively regulating suppressive cytokines or metabolites or receptors thereof, in particular TGFbeta (Uniprot:P01137), TGFbR (Uniprot:P37173), IL10 (Uniprot:P22301), IL10R (Uniprot: Q13651 and/or Q08334), A2aR (Uniprot: P29274), GCN2 (Uniprot: P15442) and PRDM1 (Uniprot: O75626).

Preference is given to engineered immune cells in which a sequence encoding IL-2, IL-12 or IL-15 replaces the sequence of at least one of the above endogenous genes.

Inducing resistance to chemotherapy drugs

According to another aspect of the present method, the inserted exogenous coding sequence has the effect of reducing or preventing the expression of a gene responsible for the sensitivity of the immune cells to compounds used in standard of care treatments for cancer or infection, such as drugs purine nucleotide analogs (PNA) or 6-Mercaptopurine (6MP) and 6 thio-guanine (6TG) commonly used in chemotherapy. Reducing or inactivating the genes involved into the mode of action of such compounds (referred to as “drug sensitizing genes”) improves the resistance of the immune cells to same.

Examples of drug sensitizing gene are those encoding DCK (Uniprot P27707) with respect to the activity of PNA, such a clorofarabine et fludarabine, HPRT (Uniprot P00492)

with respect to the activity of purine antimetabolites such as 6MP and 6TG, and GGH (Uniprot Q92820) with respect to the activity of antifolate drugs, in particular methotrexate.

This enables the cells to be used after or in combination with conventional anti-cancer chemotherapies.

Resistance to immune-suppressive treatments

According to another aspect of the present invention, the inserted exogenous coding sequence has the effect of reducing or preventing the expression of receptors or proteins, which are drug targets, making said cells resistant to immune-depletion drug treatments. Such target can be glucocorticoids receptors or antigens, to make the engineered immune cells resistant to glucocorticoids or immune depletion treatments using antibodies such as Alemtuzumab, which is used to deplete CD52 positive immune cells in many cancer treatments.

Also the method of the invention can comprise gene targeted insertion in endogenous gene(s) encoding or regulating the expression of CD52 (Uniprot P31358) and/or GR (Glucocorticoids receptor also referred to as NR3C1 - Uniprot P04150).

Improving CAR positive immune cells activity and survival

According to another aspect of the present invention, the inserted exogenous coding sequence can have the effect of reducing or preventing the expression of a surface antigen, such as BCMA, CS1 and CD38, wherein such antigen is one targeted by a CAR expressed by said immune cells.

This embodiment can solve the problem of CAR targeting antigens that are present at the surface of infected or malignant cells, but also to some extent expressed by the immune cell itself.

According to a preferred embodiment the exogenous sequence encoding the CAR or one of its constituents is integrated into the gene encoding the antigen targeted by said CAR to avoid self-destruction of the immune cells.

<u>Engineered immune cells and populations of immune cells</u>

The present invention is also drawn to the variety of engineered immune cells obtainable according to one of the method described previously under isolated form or as part of populations of cells.

According to a preferred aspect of the invention the engineered cells are primary immune cells, such as NK cells or T-cells, which are generally part of populations of cells

that may involve different types of cells. In general, population deriving from patients or donors isolated by leukapheresis from PBMC (peripheral blood mononuclear cells).

According to a preferred aspect of the invention, more than 50% of the immune cells comprised in said population are TCR negative T-cells. According to a more preferred aspect of the invention, more than 50% of the immune cells comprised in said population are CAR positive T-cells.

The present invention encompasses immune cells comprising any combinations of the different exogenous coding sequences and gene inactivation, which have been respectively and independently described above. Among these combinations are particularly preferred those combining the expression of a CAR under the transcriptional control of an endogenous promoter that is steadily active during immune cell activation and preferably independently from said activation, and the expression of an exogenous sequence encoding a cytokine, such as IL-2, IL-12 or IL-15, under the transcriptional control of a promoter that is up- regulated during the immune cell activation.

Another preferred combination is the insertion of an exogenous sequence encoding a CAR or one of its constituents under the transcription control of the hypoxia-inducible factor 1 gene promoter (Uniprot: Q16665).

The invention is also drawn to a pharmaceutical composition comprising an engineered primary immune cell or immune cell population as previously described for the treatment of infection or cancer, and to a method for treating a patient in need thereof, wherein said method comprises:

- preparing a population of engineered primary immune cells according to the method of the invention as previously described;
- optionally, purifying or sorting said engineered primary immune cells;
- activating said population of engineered primary immune cells upon or after infusion of said cells into said patient.

Activation and expansion of T cells

Whether prior to or after genetic modification, the immune cells according to the present invention can be activated or expanded, even if they can activate or proliferate independently of antigen binding mechanisms. T-cells, in particular, can be activated and expanded using methods as described, for example, in U.S. Patents 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005. T cells can be expanded *in vitro* or *in vivo*. T cells are generally expanded by contact with an agent that stimulates a CD3 TCR

complex and a co-stimulatory molecule on the surface of the T cells to create an activation signal for the T-cell. For example, chemicals such as calcium ionophore A23187, phorbol 12-myristate 13-acetate (PMA), or mitogenic lectins like phytohemagglutinin (PHA) can be used to create an activation signal for the T-cell.

As non-limiting examples, T cell populations may be stimulated *in vitro* such as by contact with an anti-CD3 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody immobilized on a surface, or by contact with a protein kinase C activator (e.g., bryostatin) in conjunction with a calcium ionophore. For co-stimulation of an accessory molecule on the surface of the T cells, a ligand that binds the accessory molecule is used. For example, a population of T cells can be contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. Conditions appropriate for T cell culture include an appropriate media (e.g., Minimal Essential Media or RPMI Media 1640 or, X-vivo 5, (Lonza)) that may contain factors necessary for proliferation and viability, including serum (e.g., fetal bovine or human serum), interleukin-2 (IL-2), insulin, IFN-g , 1L-4, 1L-7, GM-CSF, -10, - 2, 1L-15, TGFp, and TNF- or any other additives for the growth of cells known to the skilled artisan. Other additives for the growth of cells include, but are not limited to, surfactant, plasmanate, and reducing agents such as N-acetyl-cysteine and 2-mercaptoethanoi. Media can include RPMI 1640, A1M-V, DMEM, MEM, a-MEM, F-12, X-Vivo 1, and X-Vivo 20, Optimizer, with added amino acids, sodium pyruvate, and vitamins, either serum-free or supplemented with an appropriate amount of serum (or plasma) or a defined set of hormones, and/or an amount of cytokine(s) sufficient for the growth and expansion of T cells. Antibiotics, e.g., penicillin and streptomycin, are included only in experimental cultures, not in cultures of cells that are to be infused into a subject. The target cells are maintained under conditions necessary to support growth, for example, an appropriate temperature (e.g., 37° C) and atmosphere (e.g., air plus 5% C02). T cells that have been exposed to varied stimulation times may exhibit different characteristics

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

Therapeutic compositions and applications

The method of the present invention described above allows producing engineered primary immune cells within a limited time frame of about 15 to 30 days, preferably between 15 and 20 days, and most preferably between 18 and 20 days so that they keep their full immune therapeutic potential, especially with respect to their cytotoxic activity.

These cells form a population of cells, which preferably originate from a single donor or patient. These populations of cells can be expanded under closed culture recipients to comply with highest manufacturing practices requirements and can be frozen prior to infusion into a patient, thereby providing “off the shelf” or “ready to use” therapeutic compositions.

As per the present invention, a significant number of cells originating from the same Leukapheresis can be obtained, which is critical to obtain sufficient doses for treating a patient. Although variations between populations of cells originating from various donors may be observed, the number of immune cells procured by a leukapheresis is generally about from 10^8 to 10^{10} cells of PBMC. PBMC comprises several types of cells: granulocytes, monocytes and lymphocytes, among which from 30 to 60 % of T-cells, which generally represents between 10^8 to 10^9 of primary T-cells from one donor. The method of the present invention generally ends up with a population of engineered cells that reaches generally more than about 10^8 T-cells , more generally more than about 10^9 T-cells, even more generally more than about 10^{10} T-cells, and usually more than 10^{11} T-cells.

The invention is thus more particularly drawn to a therapeutically effective population of primary immune cells, wherein at least 30 %, preferably 50 %, more preferably 80 % of the cells in said population have been modified according to any one the methods described herein. Said therapeutically effective population of primary immune cells, as per the present invention, comprises immune cells that have integrated at least one exogenous genetic sequence under the transcriptional control of an endogenous promoter from at least one of the genes listed in Table 6.

Such compositions or populations of cells can therefore be used as medicaments; especially for treating cancer, particularly for the treatment of lymphoma, but also for solid tumors such as melanomas, neuroblastomas, gliomas or carcinomas such as lung, breast, colon, prostate or ovary tumors in a patient in need thereof.

The invention is more particularly drawn to populations of primary TCR negative T-cells originating from a single donor, wherein at least 20 %, preferably 30 %, more preferably 50 % of the cells in said population have been modified using sequence-specific reagents in at least two, preferably three different loci.

In another aspect, the present invention relies on methods for treating patients in need thereof, said method comprising at least one of the following steps:

(a) Determining specific antigen markers present at the surface of patients tumors biopsies;

(b) providing a population of engineered primary immune cells engineered by one of the methods of the present invention previously described expressing a CAR directed against said specific antigen markers;

(c) Administrating said engineered population of engineered primary immune cells to said patient,

Generally, said populations of cells mainly comprises CD4 and CD8 positive immune cells, such as T-cells, which can undergo robust *in vivo* T cell expansion and can persist for an extended amount of time *in-vitro* and *in-vivo*.

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

In another embodiment, said isolated cell according to the invention or cell line derived from said isolated cell can be used for the treatment of liquid tumors, and preferably of T-cell acute lymphoblastic leukemia.

Adult tumors/cancers and pediatric tumors/cancers are also included.

The treatment with the engineered immune cells according to the invention may be in combination with one or more therapies against cancer selected from the group of antibodies therapy, chemotherapy, cytokines therapy, dendritic cell therapy, gene therapy, hormone therapy, laser light therapy and radiation therapy.

According to a preferred embodiment of the invention, said treatment can be administrated into patients undergoing an immunosuppressive treatment. Indeed, the present invention preferably relies on cells or population of cells, which have been made resistant to at least one immunosuppressive agent due to the inactivation of a gene encoding a receptor for such immunosuppressive agent. In this aspect, the immunosuppressive treatment should help the selection and expansion of the T-cells according to the invention within the patient.

The administration of the cells or population of cells according to the present invention may be carried out in any convenient manner, including by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. The compositions described herein may be administered to a patient subcutaneously, intradermally,

intratumorally, intranodally, intramedullary, intramuscularly, by intravenous or intralymphatic injection, or intraperitoneally. In one embodiment, the cell compositions of the present invention are preferably administered by intravenous injection.

The administration of the cells or population of cells can consist of the administration of 10^4-10^9 cells per kg body weight, preferably 10^5 to 10^6 cells/kg body weight including all integer values of cell numbers within those ranges. The present invention thus can provide more than 10, generally more than 50, more generally more than 100 and usually more than 1000 doses comprising between 10^6 to 10^8 gene edited cells originating from a single donor's or patient's sampling.

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

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

In certain embodiments of the present invention, cells are administered to a patient in conjunction with (e.g., before, simultaneously or following) any number of relevant treatment modalities, including but not limited to treatment with agents such as antiviral therapy, cidofovir and interleukin-2, Cytarabine (also known as ARA-C) or natalizumab treatment for MS patients or efalizumab treatment for psoriasis patients or other treatments for PML patients. In further embodiments, the T cells of the invention may be used in combination with chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies or other antibody therapies, cytoxin, fludaribine, cyclosporin, FK506, rapamycin, mycoplienolic acid, steroids, FR901228, cytokines, and irradiation. These drugs inhibit either the calcium dependent phosphatase calcineurin (cyclosporine and FK506) or inhibit the p70S6 kinase that is important for growth factor induced signaling (rapamycin) (Henderson, Naya et al.

1991; Liu, Albers et al. 1992; Bierer, Hollander et al. 1993). In a further embodiment, the cell compositions of the present invention are administered to a patient in conjunction with (e.g., before, simultaneously or following) bone marrow transplantation, T cell ablative therapy using either chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, or antibodies such as OKT3 or CAMPATH, In another embodiment, the cell compositions of the present invention are administered following B-cell ablative therapy such as agents that react with CD20, e.g., Rituxan. For example, in one embodiment, subjects may undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain embodiments, following the transplant, subjects receive an infusion of the expanded immune cells of the present invention. In an additional embodiment, expanded cells are administered before or following surgery.

When CARs are expressed in the immune cells or populations of immune cells according to the present invention, the preferred CARs are those targeting at least one antigen selected from CD22, CD38, CD123, CS1, HSP70, ROR1, GD3, and CLL1.

The engineered immune cells according to the present invention endowed with a CAR or a modified TCR targeting CD22 are preferably used for treating leukemia, such as acute lymphoblastic leukemia (ALL), those with a CAR or a modified TCR targeting CD38 are preferably used for treating leukemia such as T-cell acute lymphoblastic leukemia (T-ALL) or multiple myeloma (MM), those with a CAR or a modified TCR targeting CD123 are preferably used for treating leukemia, such as acute myeloid leukemia (AML), and blastic plasmacytoid dendritic cells neoplasm (BPDCN), those with a CAR or a modified TCR targeting CS1 are preferably used for treating multiple myeloma (MM).

The present invention also encompasses means for detecting the engineered cells of the present invention comprising the desired genetic insertions, especially by carrying out steps of using PCR methods for detecting insertions of exogenous coding sequences at the endogenous loci referred to in the present specification, especially at the PD1, CD25, CD69 and TCR loci, by using probes or primers hybridizing any sequences represented by SEQ ID NO:36 to 40.

Immunological assays may also be performed for detecting the expression by the engineered cells of CARs, GP130, and to check absence or reduction of the expression of TCR, PD1, IL-6 or IL-8 in the cells where such genes have been knocked-out or their expression reduced.

Other definitions

- Amino acid residues in a polypeptide sequence are designated herein according to the one-letter code, in which, for example, Q means Gln or Glutamine residue, R means Arg or Arginine residue and D means Asp or Aspartic acid residue.

- Amino acid substitution means the replacement of one amino acid residue with another, for instance the replacement of an Arginine residue with a Glutamine residue in a peptide sequence is an amino acid substitution.

- Nucleotides are designated as follows: one-letter code is used for designating the base of a nucleoside: a is adenine, t is thymine, c is cytosine, and g is guanine. For the degenerated nucleotides, r represents g or a (purine nucleotides), k represents g or t, s represents g or c, w represents a or t, m represents a or c, y represents t or c (pyrimidine nucleotides), d represents g, a or t, v represents g, a or c, b represents g, t or c, h represents a, t or c, and n represents g, a, t or c.

- "As used herein, "nucleic acid" or "polynucleotides" refers to nucleotides and/or polynucleotides, such as deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), oligonucleotides, fragments generated by the polymerase chain reaction (PCR), and fragments generated by any of ligation, scission, endonuclease action, and exonuclease action. Nucleic acid molecules can be composed of monomers that are naturally-occurring nucleotides (such as DNA and RNA), or analogs of naturally-occurring nucleotides (e.g., enantiomeric forms of naturally-occurring nucleotides), or a combination of both. Modified nucleotides can have alterations in sugar moieties and/or in pyrimidine or purine base moieties. Sugar modifications include, for example, replacement of one or more hydroxyl groups with halogens, alkyl groups, amines, and azido groups, or sugars can be functionalized as ethers or esters. Moreover, the entire sugar moiety can be replaced with sterically and electronically similar structures, such as aza-sugars and carbocyclic sugar analogs. Examples of modifications in a base moiety include alkylated purines and pyrimidines, acylated purines or pyrimidines, or other well-known heterocyclic substitutes. Nucleic acid monomers can be linked by phosphodiester bonds or analogs of such linkages. Nucleic acids can be either single stranded or double stranded.

- The term "endonuclease" refers to any wild-type or variant enzyme capable of catalyzing the hydrolysis (cleavage) of bonds between nucleic acids within a DNA or RNA molecule, preferably a DNA molecule. Endonucleases do not cleave the DNA or RNA molecule irrespective of its sequence, but recognize and cleave the DNA or RNA molecule at specific polynucleotide sequences, further referred to as "target sequences" or "target sites". Endonucleases can be classified as rare-cutting endonucleases when having typically a polynucleotide recognition site greater than 10 base pairs (bp) in length,

more preferably of 14-55 bp. Rare-cutting endonucleases significantly increase homologous recombination by inducing DNA double-strand breaks (DSBs) at a defined locus thereby allowing gene repair or gene insertion therapies (Pingoud, A. and G. H. Silva (2007). Precision genome surgery. *Nat. Biotechnol.* 25(7): 743-4.).

- By “DNA target”, “DNA target sequence”, “target DNA sequence”, “nucleic acid target sequence”, “target sequence” , or “processing site” is intended a polynucleotide sequence that can be targeted and processed by a rare-cutting endonuclease according to the present invention. These terms refer to a specific DNA location, preferably a genomic location in a cell, but also a portion of genetic material that can exist independently to the main body of genetic material such as plasmids, episomes, virus, transposons or in organelles such as mitochondria as non-limiting example. As non-limiting examples of RNA guided target sequences, are those genome sequences that can hybridize the guide RNA which directs the RNA guided endonuclease to a desired locus.

- By “mutation” is intended the substitution, deletion, insertion of up to one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, twenty, twenty five, thirty, fourty, fifty, or more nucleotides/amino acids in a polynucleotide (cDNA, gene) or a polypeptide sequence. The mutation can affect the coding sequence of a gene or its regulatory sequence. It may also affect the structure of the genomic sequence or the structure/stability of the encoded mRNA.

- By “vector” is meant a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. A “vector” in the present invention includes, but is not limited to, a viral vector, a plasmid, a RNA vector or a linear or circular DNA or RNA molecule which may consists of a chromosomal, non chromosomal, semi-synthetic or synthetic nucleic acids. Preferred vectors are those capable of autonomous replication (episomal vector) and/or expression of nucleic acids to which they are linked (expression vectors). Large numbers of suitable vectors are known to those of skill in the art and commercially available. Viral vectors include retrovirus, adenovirus, parvovirus (e. g. adenoassociated viruses (AAV), coronavirus, negative strand RNA viruses such as orthomyxovirus (e. g., influenza virus), rhabdovirus (e. g., rabies and vesicular stomatitis virus), paramyxovirus (e. g. measles and Sendai), positive strand RNA viruses such as picornavirus and alphavirus, and double-stranded DNA viruses including adenovirus, herpesvirus (e. g., Herpes Simplex virus types 1 and 2, Epstein-Barr virus, cytomegalovirus), and poxvirus (e. g., vaccinia, fowlpox and canarypox). Other viruses include Norwalk virus, togavirus, flavivirus, reoviruses, papovavirus, hepadnavirus, and hepatitis

virus, for example. Examples of retroviruses include: avian leukosis-sarcoma, mammalian C-type, B-type viruses, D type viruses, HTLV-BLV group, lentivirus, spumavirus (Coffin, J. M., Retroviridae: The viruses and their replication, In Fundamental Virology, Third Edition, B. N. Fields, et al., Eds., Lippincott-Raven Publishers, Philadelphia, 1996).

- As used herein, the term “locus” is the specific physical location of a DNA sequence (e.g. of a gene) into a genome. The term “locus” can refer to the specific physical location of a rare-cutting endonuclease target sequence on a chromosome or on an infection agent’s genome sequence. Such a locus can comprise a target sequence that is recognized and/or cleaved by a sequence-specific endonuclease according to the invention. It is understood that the locus of interest of the present invention can not only qualify a nucleic acid sequence that exists in the main body of genetic material (i.e. in a chromosome) of a cell but also a portion of genetic material that can exist independently to said main body of genetic material such as plasmids, episomes, virus, transposons or in organelles such as mitochondria as non-limiting examples.

- The term “cleavage” refers to the breakage of the covalent backbone of a polynucleotide. Cleavage can be initiated by a variety of methods including, but not limited to, enzymatic or chemical hydrolysis of a phosphodiester bond. Both single-stranded cleavage and double-stranded cleavage are possible, and double-stranded cleavage can occur as a result of two distinct single-stranded cleavage events. Double stranded DNA, RNA, or DNA/RNA hybrid cleavage can result in the production of either blunt ends or staggered ends.

-"identity" refers to sequence identity between two nucleic acid molecules or polypeptides. Identity can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base, then the molecules are identical at that position. A degree of similarity or identity between nucleic acid or amino acid sequences is a function of the number of identical or matching nucleotides at positions shared by the nucleic acid sequences. Various alignment algorithms and/or programs may be used to calculate the identity between two sequences, including FASTA, or BLAST which are available as a part of the GCG sequence analysis package (University of Wisconsin, Madison, Wis.), and can be used with, e.g., default setting. For example, polypeptides having at least 70%, 85%, 90%, 95%, 98% or 99% identity to specific polypeptides described herein and preferably exhibiting substantially the same functions, as well as polynucleotide encoding such polypeptides, are contemplated.

- The term "subject" or “patient” as used herein includes all members of the animal kingdom including non-human primates and humans.

- The above written description of the invention provides a manner and process of making and using it such that any person skilled in this art is enabled to make and use the same, this enablement being provided in particular for the subject matter of the appended claims, which make up a part of the original description.

Where a numerical limit or range is stated herein, the endpoints are included. Also, all values and subranges within a numerical limit or range are specifically included as if explicitly written out.

Having generally described this invention, a further understanding can be obtained by reference to certain specific examples, which are provided herein for purposes of illustration only, and are not intended to limit the scope of the claimed invention.

EXAMPLES

Example 1: AAV driven homologous recombination in human primary T-cells at various loci under control of endogenous promoters with knock-out of the endogenous gene.

Introduction

Sequence specific endonuclease reagents, such as TALEN® (Cellectis, 8 rue de la Croix Jarry, 75013 PARIS) enable the site-specific induction of double-stranded breaks (DSBs) in the genome at desired loci. Repair of DSBs by cellular enzymes occurs mainly through two pathways: non-homologous end joining (NHEJ) and homology directed repair (HDR). HDR uses a homologous piece of DNA (template DNA) to repair the DSB by recombination and can be used to introduce any genetic sequence comprised in the template DNA. As shown therein, said template DNA can be delivered by recombinant adeno-associated virus (rAAV) along with an engineered nuclease such as TALEN® to introduce a site-specific DSB.

Design of the integration matrices

1.1. Insertion of an apoptosis CAR in an upregulated locus with knock-out of the endogenous PD1 gene coding sequence

The location of the TALEN target site has been designed to be located in the targeted endogenous PDCD1 gene (Programmed cell death protein 1 referred to as PD1 – Uniprot # Q15116). The sequence encompassing 1000bp upstream and downstream the TALEN targets is given in SEQ ID NO.1 and SEQ ID NO.2. Target sequences of the TALEN (SEQ ID: SEQ ID NO.3 and NO.4) is given in SEQ ID NO.5. The integration matrix is designed to be composed of a sequence (300 bp) homologous to the endogenous gene upstream of the TALEN site (SEQ ID NO.1), followed by a 2A regulatory element (SEQ ID NO.6), followed by a sequence encoding an apoptosis inducing CAR without the start codon (SEQ ID NO.7), followed by a STOP codon (TAG), followed by a polyadenylation sequence (SEQ ID NO.8), followed by a sequence (1000bp) homologous to the endogenous gene downstream of the TALEN site (SEQ ID NO.2)). The insertion matrix is subsequently cloned into a promoterless rAAV vector and used to produce AAV6.

1.2 Insertion of an interleukin in an upregulated locus with knock-out of the endogenous gene

The location of the TALEN target site is designed to be located in the targeted endogenous PDCD1 gene (Programmed cell death protein 1, PD1). The sequence encompassing 1000bp upstream and downstream the TALEN targets is given in SEQ ID NO.1 and SEQ ID NO.2. Target sequences of the TALEN (SEQ ID: SEQ ID NO.3 and NO.4) is given in SEQ ID NO.5. The integration matrix is designed to be composed of a sequence (300 bp) homologous to the endogenous gene upstream of the TALEN site (SEQ ID NO.1), followed by a 2A regulatory element (SEQ ID NO.6), followed by a sequence encoding an engineered single-chained human IL-12 p35 (SEQ ID NO.9) and p40 (SEQ ID NO.10) subunit fusion protein, followed by a STOP codon (TAG), followed by a polyadenylation sequence (SEQ ID NO.8), followed by a sequence (1000bp) homologous to the endogenous gene downstream of the TALEN site (SEQ ID NO.2). The insertion matrix is subsequently cloned into a promoterless rAAV vector and used to produce AAV6.

1.3 Insertion of an apoptosis CAR in a weakly expressed locus without knocking out the endogenous gene – N-terminal insertion

The location of the TALEN target site is designed to be located as close as possible to the start codon of the targeted endogenous LCK gene (LCK, LCK proto-oncogene, Src family tyrosine kinase [Homo sapiens (human)]). The sequence encompassing 1000bp upstream and downstream the start codon is given in SEQ ID NO.11 and NO.12. The integration matrix is designed to be composed of a sequence (1000bp) homologous to the endogenous gene upstream of the start codon, followed by a sequence encoding an apoptosis inducing CAR containig a start codon (SEQ ID NO.13), followed by a 2A regulatory element (SEQ ID NO.8), followed by a sequence (1000bp) homologous to the endogenous gene downstream of the start codon (SEQ ID NO.12). The insertion matrix is subsequently cloned into a promoterless rAAV vector and used to produce AAV6.

1.4 Insertion of an apoptosis CAR in a weakly expressed locus without knocking out the endogenous gene – C-terminal insertion

The location of the TALEN target site is designed to be located as close as possible to the stop codon of the targeted endogenous LCK gene (LCK, LCK proto-oncogene, Src family tyrosine kinase [Homo sapiens (human)]). The sequence encompassing 1000bp upstream and downstream the stop codon is given in SEQ ID NO.14 and NO.15. The integration matrix is designed to be composed of a sequence (1000bp) homologous to the endogenous gene upstream of the stop codon, followed by a 2A regulatory element (SEQ ID NO.8), followed by a sequence encoding an apoptosis inducing CAR without the start codon (SEQ ID NO.7), followed by a STOP codon (TAG), followed by a sequence (1000bp) homologous to the endogenous gene downstream of the stop codon (SEQ ID NO.15). The insertion matrix is subsequently cloned into a promoterless rAAV vector and used to produce AAV6.

Expression of the sequence-specific nuclease reagents in the transduced cells

TALEN® mRNA is synthesized using the mMessage mMachine T7 Ultra kit (Thermo Fisher Scientific, Grand Island, NY) as each TALEN is cloned downstream of a T7 promoter, purified using RNeasy columns (Qiagen, Valencia, CA) and eluted in "cytoporation medium T" (Harvard Apparatus, Holliston, MA). Human T-cells are collected and activated from whole peripheral blood provided by ALLCELLS (Alameda, CA) in X-Vivo-15 medium (Lonza, Basel, Switzerland) supplemented with 20 ng/ml human IL-2 (Miltenyi Biotech, San Diego, CA), 5% human AB serum (Gemini Bio-Products, West San Francisco, CA) and Dynabeads Human T-activator CD3/CD28 at a 1:1 bead:cell ratio (Thermo Fisher Scientific, Grand Island, NY). Beads are removed after 3 days and 5 x 10^6 cells are electroporated with 10 µg mRNA of each of the two adequate TALEN® using Cytopulse (BTX Harvard Apparatus, Holliston, MA) by applying two 0.1 mS pulses at 3,000 V/cm followed by four 0.2 mS pulses at 325 V/cm in 0.4 cm gap cuvettes in a final volume of 200 µl of "cytoporation medium T" (BTX Harvard Apparatus, Holliston, Massachusetts). Cells are immediately diluted in X-Vivo-15 media with 20 ng/mL IL-2 and incubated at 37°C with 5% CO_2. After two hours, cells are incubated with AAV6 particles at 3 x 10^5 viral genomes (vg) per cell (37^0C, 16 hours). Cells are passaged and maintained in X-Vivo-15 medium supplemented with 5% human AB serum and 20 ng/mL IL-2 until examined by flow cytometry for expression of the respective inserted gene sequences.

Table 4: Sequences referred to in example 1

Sequence name	Ref. sequences	Polynucleotide or polypeptide sequences
PD1 left homology	SEQ ID NO.1	CCAAGCCCTGACCCTGGCAGGCATATGTTTCAGGAGGTCCTTGTCTTGGGA GCCCAGGGTCGGGGGCCCCGTGTCTGTCCACATCCGAGTCAATGGCCCAT CTCGTCTCTGAAGCATCTTTGCTGTGAGCTCTAGTCCCCACTGTCTTGCTGG AAAATGTGGAGGCCCCACTGCCCACTGCCCAGGGCAGCAATGCCCATACC ACGTGGTCCCAGCTCCGAGCTTGTCCTGAAAAGGGGGCAAAGACTGGACC CTGAGCCTGCCAAGGGGCCACACTCCTCCCAGGGCTGGGGTCTCCATGGG CAGCCCCCCACCCACCCAGACCAGTTACACTCCCCTGTGCCAGAGCAGTGC AGACAGGACCAGGCCAGGATGCCCAAGGGTCAGGGGCTGGGGATGGGT AGCCCCCAAACAGCCCTTTCTGGGGGAACTGGCCTCAACGGGGAAGGGG GTGAAGGCTCTTAGTAGGAAATCAGGGAGACCCAAGTCAGAGCCAGGTG CTGTGCAGAAGCTGCAGCCTCACGTAGAAGGAAGAGGCTCTGCAGTGGA GGCCAGTGCCCATCCCCGGGTGGCAGAGGCCCCAGCAGAGACTTCTCAAT GACATTCCAGCTGGGGTGGCCCTTCCAGAGCCCTTGCTGCCCGAGGGATG TGAGCAGGTGGCCGGGGAGGCTTTGTGGGGCCACCCAGCCCCTTCCTCAC CTCTCTCCATCTCTCAGACTCCCCAGACAGGCCCTGGAACCCCCCCACCTTC TCCCCAGCCCTGCTCGTGGTGACCGAAGGGGACAACGCCACCTTCACCTGC AGCTTCTCCAACACATCGGAGAGCTTCGTGCTAAACTGGTACCGCATGAGC CCCAGCAACCAGACGGACAAGCTGGCCGCCTTCCCCGAGGACCGCAGCCA GCCCGGCCAGGACTGCCGCTTCCGTGTCACACAACTGCCCAACGGGCGTG ACTTCCACATGAGCGTGGTCAGGGCCCGGCGCAATGACAGCGGCACC
PD1 right homology	SEQ ID NO.2	GCCTGCGGGCAGAGCTCAGGGTGACAGGTGCGGCCTCGGAGGCCCCGGG GCAGGGGTGAGCTGAGCCGGTCCTGGGGTGGGTGTCCCCTCCTGCACAG GATCAGGAGCTCCAGGGTCGTAGGGCAGGGACCCCCCAGCTCCAGTCCAG GGCTCTGTCCTGCACCTGGGGAATGGTGACCGGCATCTCTGTCCTCTAGCT CTGGAAGCACCCCAGCCCCTCTAGTCTGCCCTCACCCCTGACCCTGACCCTC CACCCTGACCCCGTCCTAACCCCTGACCTTTGTGCCCTTCCAGAGAGAAGG GCAGAAGTGCCCACAGCCCACCCCAGCCCCTCACCCAGGCCAGCCGGCCA GTTCCAAACCCTGGTGGTTGGTGTCGTGGGCGGCCTGCTGGGCAGCCTGG TGCTGCTAGTCTGGGTCCTGGCCGTCATCTGCTCCCGGGCCGCACGAGGTA ACGTCATCCCAGCCCCTCGGCCTGCCCTGCCCTAACCCTGCTGGCGGCCCT CACTCCCGCCTCCCCTTCCTCCACCCTTCCCTCACCCCACCCCACCTCCCCCC ATCTCCCCGCCAGGCTAAGTCCCTGATGAAGGCCCCTGGACTAAGACCCCC CACCTAGGAGCACGGCTCAGGGTCGGCCTGGTGACCCCAAGTGTGTTTCT CTGCAGGGACAATAGGAGCCAGGCGCACCGGCCAGCCCCTGGTGAGTCTC ACTCTTTTCCTGCATGATCCACTGTGCCTTCCTTCCTGGGTGGGCAGAGGT GGAAGGACAGGCTGGGACCACACGGCCTGCAGGACTCACATTCTATTATA GCCAGGACCCCACCTCCCCAGCCCCCAGGCAGCAACCTCAATCCCTAAAGC CATGATCTGGGGCCCCAGCCCACCTGCGGTCTCCGGGGGTGCCCGGCCCA TGTGTGTGCCTGCCTGCGGTCTCCAGGGGTGCCTGGCCCACGCGTGTGCC CGCCTGCGGTCTCTGGGGGTGCCCGGCCCACATATGTGCC
PD1_T3C-L2	SEQ ID NO.3	ATGGGCGATCCTAAAAAGAAACGTAAGGTCATCGATATCGCCGATCTACG CACGCTCGGCTACAGCCAGCAGCAACAGGAGAAGATCAAACCGAAGGTTC GTTCGACAGTGGCGCAGCACCACGAGGCACTGGTCGGCCACGGGTTTACA CACGCGCACATCGTTGCGTTAAGCCAACACCCGGCAGCGTTAGGGACCGT CGCTGTCAAGTATCAGGACATGATCGCAGCGTTGCCAGAGGCGACACACG AAGCGATCGTTGGCGTCGGCAAACAGTGGTCCGGCGCACGCGCTCTGGA GGCCTTGCTCACGGTGGCGGGAGAGTTGAGAGGTCCACCGTTACAGTTGG

		ACACAGGCCAACTTCTCAAGATTGCAAAACGTGGCGGCGTGACCGCAGTG GAGGCAGTGCATGCATGGCGCAATGCACTGACGGGTGCCCCGCTCAACTT GACCCCCGAGCAAGTGGTGGCTATCGCTTCCAAGCTGGGGGGAAAGCAG GCCCTGGAGACCGTCCAGGCCCTTCTCCCAGTGCTTTGCCAGGCTCACGGA CTGACCCCTGAACAGGTGGTGGCAATTGCCTCACACGACGGGGGCAAGCA GGCACTGGAGACTGTCCAGCGGCTGCTGCCTGTCCTCTGCCAGGCCCACG GACTCACTCCTGAGCAGGTCGTGGCCATTGCCAGCCACGATGGGGGCAAA CAGGCTCTGGAGACCGTGCAGCGCCTCCTCCCAGTGCTGTGCCAGGCTCAT GGGCTGACCCCACAGCAGGTCGTCGCCATTGCCAGTAACGGCGGGGGGA AGCAGGCCCTCGAAACAGTGCAGAGGCTGCTGCCCGTCTTGTGCCAAGCA CACGGCCTGACACCCGAGCAGGTGGTGGCCATCGCCTCTCATGACGGCGG CAAGCAGGCCCTTGAGACAGTGCAGAGACTGTTGCCCGTGTTGTGTCAGG CCCACGGGTTGACACCCCAGCAGGTGGTCGCCATCGCCAGCAATGGCGGG GGAAAGCAGGCCCTTGAGACCGTGCAGCGGTTGCTTCCAGTGTTGTGCCA GGCACACGGACTGACCCCTCAACAGGTGGTCGCAATCGCCAGCTACAAGG GCGGAAAGCAGGCTCTGGAGACAGTGCAGCGCCTCCTGCCCGTGCTGTGT CAGGCTCACGGACTGACACCACAGCAGGTGGTCGCCATCGCCAGTAACGG GGGCGGCAAGCAGGCTTTGGAGACCGTCCAGAGACTCCTCCCCGTCCTTT GCCAGGCCCACGGGTTGACACCTCAGCAGGTCGTCGCCATTGCCTCCAAC AACGGGGGCAAGCAGGCCCTCGAAACTGTGCAGAGGCTGCTGCCTGTGCT GTGCCAGGCTCATGGGCTGACACCCCAGCAGGTGGTGGCCATTGCCTCTA ACAACGGCGGCAAACAGGCACTGGAGACCGTGCAAAGGCTGCTGCCCGT CCTCTGCCAAGCCCACGGGCTCACTCCACAGCAGGTCGTGGCCATCGCCTC AAACAATGGCGGGAAGCAGGCCCTGGAGACTGTGCAAAGGCTGCTCCCT GTGCTCTGCCAGGCACACGGACTGACCCCTCAGCAGGTGGTGGCAATCGC TTCCAACAACGGGGGAAAGCAGGCCCTCGAAACCGTGCAGCGCCTCCTCC CAGTGCTGTGCCAGGCACATGGCCTCACACCCGAGCAAGTGGTGGCTATC GCCAGCCACGACGGAGGGAAGCAGGCTCTGGAGACCGTGCAGAGGCTGC TGCCTGTCCTGTGCCAGGCCCACGGGCTTACTCCAGAGCAGGTCGTCGCCA TCGCCAGTCATGATGGGGGGAAGCAGGCCCTTGAGACAGTCCAGCGGCT GCTGCCAGTCCTTTGCCAGGCTCACGGCTTGACTCCCGAGCAGGTCGTGGC CATTGCCTCAAACATTGGGGGCAAACAGGCCCTGGAGACAGTGCAGGCCC TGCTGCCCGTGTTGTGTCAGGCCCACGGCTTGACACCCCAGCAGGTGGTC GCCATTGCCTCTAATGGCGGCGGGAGACCCGCCTTGGAGAGCATTGTTGC CCAGTTATCTCGCCCTGATCCGGCGTTGGCCGCGTTGACCAACGACCACCT CGTCGCCTTGGCCTGCCTCGGCGGGCGTCCTGCGCTGGATGCAGTGAAAA AGGGATTGGGGGATCCTATCAGCCGTTCCCAGCTGGTGAAGTCCGAGCTG GAGGAGAAGAAATCCGAGTTGAGGCACAAGCTGAAGTACGTGCCCCACG AGTACATCGAGCTGATCGAGATCGCCCGGAACAGCACCCAGGACCGTATC CTGGAGATGAAGGTGATGGAGTTCTTCATGAAGGTGTACGGCTACAGGG GCAAGCACCTGGGCGGCTCCAGGAAGCCCGACGGCGCCATCTACACCGTG GGCTCCCCCATCGACTACGGCGTGATCGTGGACACCAAGGCCTACTCCGG CGGCTACAACCTGCCCATCGGCCAGGCCGACGAAATGCAGAGGTACGTGG AGGAGAACCAGACCAGGAACAAGCACATCAACCCCAACGAGTGGTGGAA GGTGTACCCCTCCAGCGTGACCGAGTTCAAGTTCCTGTTCGTGTCCGGCCA CTTCAAGGGCAACTACAAGGCCCAGCTGACCAGGCTGAACCACATCACCA ACTGCAACGGCGCCGTGCTGTCCGTGGAGGAGCTCCTGATCGGCGGCGA GATGATCAAGGCCGGCACCCTGACCCTGGAGGAGGTGAGGAGGAAGTTC

		AACAACGGCGAGATCAACTTCGCGGCCGACTGATAA
PD1T3R	SEQ ID NO.4	ATGGGCGATCCTAAAAAGAAACGTAAGGTCATCGATATCGCCGATCTACG CACGCTCGGCTACAGCCAGCAGCAACAGGAGAAGATCAAACCGAAGGTTC GTTCGACAGTGGCGCAGCACCACGAGGCACTGGTCGGCCACGGGTTTACA CACGCGCACATCGTTGCGTTAAGCCAACACCCGGCAGCGTTAGGGACCGT CGCTGTCAAGTATCAGGACATGATCGCAGCGTTGCCAGAGGCGACACACG AAGCGATCGTTGGCGTCGGCAAACAGTGGTCCGGCGCACGCGCTCTGGA GGCCTTGCTCACGGTGGCGGGAGAGTTGAGAGGTCCACCGTTACAGTTGG ACACAGGCCAACTTCTCAAGATTGCAAAACGTGGCGGCGTGACCGCAGTG GAGGCAGTGCATGCATGGCGCAATGCACTGACGGGTGCCCCGCTCAACTT GACCCCCGAGCAAGTCGTCGCAATCGCCAGCCATGATGGAGGGAAGCAA GCCCTCGAAACCGTGCAGCGGTTGCTTCCTGTGCTCTGCCAGGCCCACGGC CTTACCCCTCAGCAGGTGGTGGCCATCGCAAGTAACGGAGGAGGAAAGCA AGCCTTGGAGACAGTGCAGCGCCTGTTGCCCGTGCTGTGCCAGGCACACG GCCTCACACCAGAGCAGGTCGTGGCCATTGCCTCCCATGACGGGGGGAAA CAGGCTCTGGAGACCGTCCAGAGGCTGCTGCCCGTCCTCTGTCAAGCTCAC GGCCTGACTCCCCAACAAGTGGTCGCCATCGCCTCTAATGGCGGCGGGAA GCAGGCACTGGAAACAGTGCAGAGACTGCTCCCTGTGCTTTGCCAAGCTC ATGGGTTGACCCCCCAACAGGTCGTCGCTATTGCCTCAAACGGGGGGGGC AAGCAGGCCCTTGAGACTGTGCAGAGGCTGTTGCCAGTGCTGTGTCAGGC TCACGGGCTCACTCCACAACAGGTGGTCGCAATTGCCAGCAACGGCGGCG GAAAGCAAGCTCTTGAAACCGTGCAACGCCTCCTGCCCGTGCTCTGTCAGG CTCATGGCCTGACACCACAACAAGTCGTGGCCATCGCCAGTAATAATGGC GGGAAACAGGCTCTTGAGACCGTCCAGAGGCTGCTCCCAGTGCTCTGCCA GGCACACGGGCTGACCCCCGAGCAGGTGGTGGCTATCGCCAGCAATATTG GGGGCAAGCAGGCCCTGGAAACAGTCCAGGCCCTGCTGCCAGTGCTTTGC CAGGCTCACGGGCTCACTCCCCAGCAGGTCGTGGCAATCGCCTCCAACGG CGGAGGGAAGCAGGCTCTGGAGACCGTGCAGAGACTGCTGCCCGTCTTGT GCCAGGCCCACGGACTCACACCTGAACAGGTCGTCGCCATTGCCTCTCACG ATGGGGGCAAACAAGCCCTGGAGACAGTGCAGCGGCTGTTGCCTGTGTTG TGCCAAGCCCACGGCTTGACTCCTCAACAAGTGGTCGCCATCGCCTCAAAT GGCGGCGGAAAACAAGCTCTGGAGACAGTGCAGAGGTTGCTGCCCGTCC TCTGCCAAGCCCACGGCCTGACTCCCCAACAGGTCGTCGCCATTGCCAGCA ACAACGGAGGAAAGCAGGCTCTCGAAACTGTGCAGCGGCTGCTTCCTGTG CTGTGTCAGGCTCATGGGCTGACCCCCGAGCAAGTGGTGGCTATTGCCTCT AATGGAGGCAAGCAAGCCCTTGAGACAGTCCAGAGGCTGTTGCCAGTGCT GTGCCAGGCCCACGGGCTCACACCCCAGCAGGTGGTCGCCATCGCCAGTA ACAACGGGGGCAAACAGGCATTGGAAACCGTCCAGCGCCTGCTTCCAGTG CTCTGCCAGGCACACGGACTGACACCCGAACAGGTGGTGGCCATTGCATC CCATGATGGGGGCAAGCAGGCCCTGGAGACCGTGCAGAGACTCCTGCCA GTGTTGTGCCAAGCTCACGGCCTCACCCCTCAGCAAGTCGTGGCCATCGCC TCAAACGGGGGGGGCCGGCCTGCACTGGAGAGCATTGTTGCCCAGTTATC TCGCCCTGATCCGGCGTTGGCCGCGTTGACCAACGACCACCTCGTCGCCTT GGCCTGCCTCGGCGGGCGTCCTGCGCTGGATGCAGTGAAAAAGGGATTG GGGGATCCTATCAGCCGTTCCCAGCTGGTGAAGTCCGAGCTGGAGGAGAA GAAATCCGAGTTGAGGCACAAGCTGAAGTACGTGCCCCACGAGTACATCG AGCTGATCGAGATCGCCCGGAACAGCACCCAGGACCGTATCCTGGAGATG AAGGTGATGGAGTTCTTCATGAAGGTGTACGGCTACAGGGGCAAGCACCT

		GGGCGGCTCCAGGAAGCCCGACGGCGCCATCTACACCGTGGGCTCCCCCA TCGACTACGGCGTGATCGTGGACACCAAGGCCTACTCCGGCGGCTACAAC CTGCCCATCGGCCAGGCCGACGAAATGCAGAGGTACGTGGAGGAGAACC AGACCAGGAACAAGCACATCAACCCCAACGAGTGGTGGAAGGTGTACCCC TCCAGCGTGACCGAGTTCAAGTTCCTGTTCGTGTCCGGCCACTTCAAGGGC AACTACAAGGCCCAGCTGACCAGGCTGAACCACATCACCAACTGCAACGG CGCCGTGCTGTCCGTGGAGGAGCTCCTGATCGGCGGCGAGATGATCAAG GCCGGCACCCTGACCCTGGAGGAGGTGAGGAGGAAGTTCAACAACGGCG AGATCAACTTCGCGGCCGACTGATAA
PD1-T3	SEQ ID NO.5	TACCTCTGTGGGGCCATCTCCCTGGCCCCCAAGGCGCAGATCAAAGAGA
2A-element	SEQ ID NO.6	TCCGGTGAGGGCAGAGGAAGTCTTCTAACATGCGGTGACGTGGAGGAGA ATCCGGGCCCC
apoptosis CAR (without start codon)	SEQ ID NO.7	GCTTTGCCTGTCACTGCCTTGCTGCTTCCACTTGCTCTGTTGTTGCACGCCG CAAGACCCGAGGTCAAGCTCCAGGAAAGCGGACCAGGGCTGGTGGCCCC TAGTCAGTCATTGAGCGTCACTTGCACCGTCAGCGGCGTGTCTCTGCCCGA TTACGGCGTGAGCTGGATCAGACAGCCCCCAAGGAAGGGACTGGAGTGG CTGGGCGTCATCTGGGGGAGCGAGACTACCTACTACAACAGCGCCCTGAA GAGCAGGCTGACCATCATTAAGGACAACTCCAAGTCCCAGGTCTTTCTGAA AATGAACAGCCTGCAGACTGATGACACTGCCATCTACTACTGCGCCAAGCA TTACTACTACGGGGGCAGCTACGCTATGGACTACTGGGGGCAGGGGACCT CTGTCACAGTGTCAAGTGGCGGAGGAGGCAGTGGCGGAGGGGGAAGTG GGGGCGGCGGCAGCGACATCCAGATGACCCAGACAACATCCAGCCTCTCC GCCTCTCTGGGCGACAGAGTGACAATCAGCTGCCGGGCCAGTCAGGACAT CAGCAAGTATCTCAATTGGTACCAGCAGAAACCAGACGGGACAGTGAAAT TGCTGATCTACCACACATCCAGGCTGCACTCAGGAGTCCCCAGCAGGTTTT CCGGCTCCGGCTCCGGGACAGATTACAGTCTGACCATTTCCAACCTGGAGC AGGAGGATATTGCCACATACTTTTGCCAGCAAGGCAACACTCTGCCCTATA CCTTCGGCGGAGGCACAAAACTGGAGATTACTCGGTCGGATCCCGAGCCC AAATCTCCTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTCCCGTG GCCGGCCCGTCAGTGTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCGCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA GGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTG TGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAG TACAAGTGCAAGGTGTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAAC CATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGC CCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTG GTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGG GCAACCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACG GCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGC AGGGGAACGTGTTCTCATGCTCCGTGATGCATGAGGCCCTGCACAATCACT ATACCCAGAAATCTCTGAGTCTGAGCCCAGGCAAGAAGGATATTTTGGGG TGGCTTTGCCTTCTTCTTTTGCCAATTCCACTAATTGTTTGGGTGAAGAGAA AGGAAGTACAGAAAACATGCAGAAAGCACAGAAAGGAAAACCAAGGTTC TCATGAATCTCCAACCTTAAATCCTGAAACAGTGGCAATAAATTTATCTGAT GTTGACTTGAGTAAATATATCACCACTATTGCTGGAGTCATGACACTAAGT

		CAAGTTAAAGGCTTTGTTCGAAAGAATGGTGTCAATGAAGCCAAAATAGA TGAGATCAAGAATGACAATGTCCAAGACACAGCAGAACAGAAAGTTCAAC TGCTTCGTAATTGGCATCAACTTCATGGAAAGAAAGAAGCGTATGACACAT TGATTGCAGATCTCAAAAAAGCCAATCTTTGTACTCTTGCAGAGAAAATTC AGACTATCATCCTCAAGGACATTACTAGTGACTCAGAAAATTCAAACTTCA GAAATGAAATCCAGAGCTTGGTCGAA
BGH polyA	SEQ ID NO.8	TCTAGAGGGCCCGTTTAAACCCGCTGATCAGCCTCGACTGTGCCTTCTAGT TGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAG GTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATT GTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAG CAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGATGCGGT GGGCTCTATGACTAGTGGCGAATTC
Interleukin-12 subunit alpha	SEQ ID NO.9	MCPARSLLLVATLVLLDHLSLARNLPVATPDPGMFPCLHHSQNLLRAVSNML QKARQTLEFYPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNG SCLASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNML AVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYL NAS
Interleukin-12 subunit beta	SEQ ID NO.10	MCHQQLVISWFSLVFLASPLVAIWELKKDVYVVELDWYPDAPGEMVVLTCDT PEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLLHK KEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKSSR GSSDPQGVTCGAATLSAERVRGDNKEYEYSVECQEDSACPAAEESLPIEVMV DAVHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPH SYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWS EWASVPCS
Lck left homology	SEQ ID NO.11	GGGATAGGGGGTGCCTCTGTGTGTGTGTGTGAGAGTGTGTGTGTGTAGG GTGTGTATATGTATAGGGTGTGTGTGAGTGTGTGTGTGTGAGAGAGTGTG TGTGTGGCAGAATAGACTGCGGAGGTGGATTTCATCTTGATATGAAAGGT CTGGAATGCATGGTACATTAAACTTTGAGGACAGCGCTTTCCAAGCACTCT GAGGAGCAGCCCTAGAGAAGGAGGAGCTGCAGGGACTCCGGGGGCTTCA AAGTGAGGGCCCCACTCTGCTTCAGGCAAAACAGGCACACATTTATCACTT TATCTATGGAGTTCTGCTTGATTTCATCAGACAAAAAATTTCCACTGCTAAA ACAGGCAAATAAACAAAAAAAAAGTTATGGCCAACAGAGTCACTGGAGG GTTTTCTGCTGGGGAGAAGCAAGCCCGTGTTTGAAGGAACCCTGTGAGAT GACTGTGGGCTGTGTGAGGGGAACAGCGGGGGCTTGATGGTGGACTTCG GGAGCAGAAGCCTCTTTCTCAGCCTCCTCAGCTAGACAGGGGAATTATAAT AGGAGGTGTGGCGTGCACACCTCTCCAGTAGGGGAGGGTCTGATAAGTC AGGTCTCTCCCAGGCTTGGGAAAGTGTGTGTCATCTCTAGGAGGTGGTCCT CCCAACACAGGGTACTGGCAGAGGGAGAGGGAGGGGGCAGAGGCAGGA AGTGGGTAACTAGACTAACAAAGGTGCCTGTGGCGGTTTGCCCATCCCAG GTGGGAGGGTGGGGCTAGGGCTCAGGGGCCGTGTGTGAATTTACTTGTA GCCTGAGGGCTCAGAGGGAGCACCGGTTTGGAGCTGGGACCCCCTATTTT AGCTTTTCTGTGGCTGGTGAATGGGGATCCCAGGATCTCACAATCTCAGGT ACTTTTGGAACTTTCCAGGGCAAGGCCCCATTATATCTGATGTTGGGGGAG CAGATCTTGGGGGAGCCCCTTCAGCCCCCTCTTCCATTCCCTCAGGGACC
lck right homology	SEQ ID NO.12	GGCTGTGGCTGCAGCTCACACCCGGAAGATGACTGGATGGAAAACATCGA TGTGTGTGAGAACTGCCATTATCCCATAGTCCCACTGGATGGCAAGGGCA CGGTAAGAGGCGAGACAGGGGCCTTGGTGAGGGAGTTGGGTAGAGAAT GCAACCCAGGAGAAAGAAATGACCAGCACTACAGGCCCTTGAAAGAATA GAGTGGCCCTCTCCCCTGAAATACAGAAAGGAAAAGAGGCCCAGAGAGG GGAAGGGAATCTCCTAAGATCACACAGAAAGTAGTTGGTAAACTCAGGGA

		TAACATCTAACCAGGCTGGAGAGGCTGAGAGCAGAGCAGGGGGGAAGG GGGCCAGGGTCTGACCCAATCTTCTGCTTTCTGACCCCACCCTCATCCCCCA CTCCACAGCTGCTCATCCGAAATGGCTCTGAGGTGCGGGACCCACTGGTTA CCTACGAAGGCTCCAATCCGCCGGCTTCCCCACTGCAAGGTGACCCCAGGC AGCAGGGCCTGAAAGACAAGGCCTGCGGATCCCTGGCTGTTGGCTTCCAC CTCTCCCCCACCTACTTTCTCCCCGGTCTTGCCTTCCTTGTCCCCCACCCTGT AACTCCAGGCTTCCTGCCGATCCCAGCTCGGTTCTCCCTGATGCCCCTTGTC TTTACAGACAACCTGGTTATCGCTCTGCACAGCTATGAGCCCTCTCACGAC GGAGATCTGGGCTTTGAGAAGGGGGAACAGCTCCGCATCCTGGAGCAGT GAGTCCCTCTCCACCTTGCTCTGGCGGAGTCCGTGAGGGAGCGGCGATCT CCGCGACCCGCAGCCCTCCTGCGGCCCTTGACCAGCTCGGGGTGGCCGCC CTTGGGACAAAATTCGAGGCTCAGTATTGCTGAGCCAGGGTTGGGGGAG GCTGGCTTAAGGGGTGGAGGGGTCTTTGAGGGAGGGTCTCAGGTCGACG GCTGAGCGAGCCACACTGACCCACCTCCGTGGCGCAGGAGCGGCGAGTG
apoptosis CAR (with start codon)	SEQ ID NO.13	ATGGCTTTGCCTGTCACTGCCTTGCTGCTTCCACTTGCTCTGTTGTTGCACG CCGCAAGACCCGAGGTCAAGCTCCAGGAAAGCGGACCAGGGCTGGTGGC CCCTAGTCAGTCATTGAGCGTCACTTGCACCGTCAGCGGCGTGTCTCTGCC CGATTACGGCGTGAGCTGGATCAGACAGCCCCCAAGGAAGGGACTGGAG TGGCTGGGCGTCATCTGGGGGAGCGAGACTACCTACTACAACAGCGCCCT GAAGAGCAGGCTGACCATCATTAAGGACAACTCCAAGTCCCAGGTCTTTCT GAAAATGAACAGCCTGCAGACTGATGACACTGCCATCTACTACTGCGCCAA GCATTACTACTACGGGGGCAGCTACGCTATGGACTACTGGGGGCAGGGG ACCTCTGTCACAGTGTCAAGTGGCGGAGGAGGCAGTGGCGGAGGGGGAA GTGGGGGCGGCGGCAGCGACATCCAGATGACCCAGACAACATCCAGCCTC TCCGCCTCTCTGGGCGACAGAGTGACAATCAGCTGCCGGGCCAGTCAGGA CATCAGCAAGTATCTCAATTGGTACCAGCAGAAACCAGACGGGACAGTGA AATTGCTGATCTACCACACATCCAGGCTGCACTCAGGAGTCCCCAGCAGGT TTTCCGGCTCCGGCTCCGGGACAGATTACAGTCTGACCATTTCCAACCTGG AGCAGGAGGATATTGCCACATACTTTTGCCAGCAAGGCAACACTCTGCCCT ATACCTTCGGCGGAGGCACAAAACTGGAGATTACTCGGTCGGATCCCGAG CCCAAATCTCCTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTCCC GTGGCCGGCCCGTCAGTGTTCCTCTTCCCCCCAAAACCCAAGGACACCCTC ATGATCGCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCA CGAGGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTG CATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACC GTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAG GAGTACAAGTGCAAGGTGTCCAACAAAGCCCTCCCAGCCCCCATCGAGAA AACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCC TGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGC CTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA TGGGCAACCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGC AGCAGGGGAACGTGTTCTCATGCTCCGTGATGCATGAGGCCCTGCACAAT CACTATACCCAGAAATCTCTGAGTCTGAGCCCAGGCAAGAAGGATATTTTG GGGTGGCTTTGCCTTCTTCTTTTGCCAATTCCACTAATTGTTTGGGTGAAGA GAAAGGAAGTACAGAAAACATGCAGAAAGCACAGAAAGGAAAACCAAGG TTCTCATGAATCTCCAACCTTAAATCCTGAAACAGTGGCAATAAATTTATCT GATGTTGACTTGAGTAAATATATCACCACTATTGCTGGAGTCATGACACTA

		AGTCAAGTTAAAGGCTTTGTTCGAAAGAATGGTGTCAATGAAGCCAAAAT AGATGAGATCAAGAATGACAATGTCCAAGACACAGCAGAACAGAAAGTTC AACTGCTTCGTAATTGGCATCAACTTCATGGAAAGAAAGAAGCGTATGAC ACATTGATTGCAGATCTCAAAAAAGCCAATCTTTGTACTCTTGCAGAGAAA ATTCAGACTATCATCCTCAAGGACATTACTAGTGACTCAGAAAATTCAAAC TTCAGAAATGAAATCCAGAGCTTGGTCGAA
Lck left homology	SEQ ID NO.14	CTCATAACAATTCTATGAGGTAGGAACAGTTATTTACTCTATTTTCCAAATA AGGAAACTGGGCTCGCCCAAGGTTCCACAACTAACATGTGTGTATTATTGA GCATTTAATTTACACCAGGGAAGCAGGTTGTGGTGGTGTGCACCTGTTGTC CAGCTATTTAGGAGGCTGAGGTGAAAGGATCACTTGAACGGAGGAGTTCA AATTTGCAATGTGCTATGATTGTGCCTGTGAACAGCTGCTGCACTCCAGCC TGGGCAACATAGTGAGATCCCTTATCTAAAACATTTTTTTTAAGTAAATAAT CAGGTGGGCACGGTGGCTCACGCCTGTAATCCAGCACTTTGGGAGGCTGA GGCGGGCGGATCACCTGAGGTCAGGAGTTCAAGACCAGCCTGACCAACAT GGAGAAACCCGTCTCTACTAAAAATACAAAATTAGCTTGGCGTGGTGGTG CATGCCTGTAATCCCAGCTACTCGAGAAGCTGAGGCAGGAGAATTGTTTG AACCTGGGAGGTGGAGGTTGCGGTGAGCCGAGATCGCACCATTGCACTCC AGCCTGGGCAACAAGAGTGAAATTGCATCTCAAAAAAAAAGAAAAGGAA ATAATCTATACCAGGCACTCCAAGTGGTGTGACTGATATTCAACAAGTACC TCTAGTGTGACCTTACCATTGATGAAGACCAAGATTCTTTTGGATTGGTGC TCACACTGTGCCAGTTAAATATTCCGAACATTACCCTTGCCTGTGGGCTTCC AGTGCCTGACCTTGATGTCCTTTCACCCATCAACCCGTAGGGATGACCAAC CCGGAGGTGATTCAGAACCTGGAGCGAGGCTACCGCATGGTGCGCCCTGA CAACTGTCCAGAGGAGCTGTACCAACTCATGAGGCTGTGCTGGAAGGAGC GCCCAGAGGACCGGCCCACCTTTGACTACCTGCGCAGTGTGCTGGAGGAC TTCTTCACGGCCACAGAGGGCCAGTACCAGCCTCAGCCT
lck right homology	SEQ ID NO.15	GAGGCCTTGAGAGGCCCTGGGGTTCTCCCCCTTTCTCTCCAGCCTGACTTG GGGAGATGGAGTTCTTGTGCCATAGTCACATGGCCTATGCACATATGGAC TCTGCACATGAATCCCACCCACATGTGACACATATGCACCTTGTGTCTGTAC ACGTGTCCTGTAGTTGCGTGGACTCTGCACATGTCTTGTACATGTGTAGCC TGTGCATGTATGTCTTGGACACTGTACAAGGTACCCCTTTCTGGCTCTCCCA TTTCCTGAGACCACAGAGAGAGGGGAGAAGCCTGGGATTGACAGAAGCT TCTGCCCACCTACTTTTCTTTCCTCAGATCATCCAGAAGTTCCTCAAGGGCC AGGACTTTATCTAATACCTCTGTGTGCTCCTCCTTGGTGCCTGGCCTGGCAC ACATCAGGAGTTCAATAAATGTCTGTTGATGACTGTTGTACATCTCTTTGCT GTCCACTCTTTGTGGGTGGGCAGTGGGGGTTAAGAAAATGGTAATTAGGT CACCCTGAGTTGGGGTGAAAGATGGGATGAGTGGATGTCTGGAGGCTCT GCAGACCCCTTCAAATGGGACAGTGCTCCTCACCCCTCCCCAAAGGATTCA GGGTGACTCCTACCTGGAATCCCTTAGGGAATGGGTGCGTCAAAGGACCT TCCTCCCCATTATAAAAGGGCAACAGCATTTTTTACTGATTCAAGGGCTATA TTTGACCTCAGATTTTGTTTTTTTAAGGCTAGTCAAATGAAGCGGCGGGAA TGGAGGAGGAACAAATAAATCTGTAACTATCCTCAGATTTTTTTTTTTTTT GAGACTGGGTCTCACTTTTTCATCCAGGCTGGAGTGCAGTCGCATGATCAC GGCTCACTGTAGCCTCAACCTCTCCAGCTCAAATGCTCCTCCTGTCTCAGCC TCCCGAGTACCTGGGACTACTTTCTTGAGGCCAGGAATTCAAGAACAGAG TAAGATCCTGGTCTCCAAAAAAAGTTTTAAA

Example 2: TALEN®-mediated double targeted integration of IL-15 and CAR encoding matrices in T-cells

Materials

X-vivo-15 was obtained for Lonza (cat#BE04-418Q), IL-2 from Miltenyi Biotech (cat#130-097-748), human serum AB from Seralab (cat#GEM-100-318), human T activator CD3/CD28 from Life Technology (cat#11132D), QBEND10-APC from R&D Systems (cat#FAB7227A), vioblue-labeled anti-CD3, PE-labeled anti-LNGFR, APC-labeled anti-CD25 and PE-labeled anti-PD1 from Miltenyi (cat# 130-094-363, 130-112-790, 130-109-021 and 130-104-892 respectively) 48 wells treated plates (CytoOne, cat#CC7682-7548), human IL-15 Quantikine ELISA kit from R&D systems (cat#S1500), ONE-Glo from Promega (cat#E6110). AAV6 batches containing the different matrices were obtained from Virovek, PBMC cells were obtained from Allcells, (cat#PB004F) and Raji-Luciferase cells were obtained after Firefly Luciferase-encoding lentiviral particles transduction of Raji cells from ATCC (cat#CCL-86).

Methods

2.1-Transfection-transduction

The double targeted integration at TRAC and PD1 or CD25 loci were performed as follows. PBMC cells were first thawed, washed, resuspended and cultivated in X-vivo-15 complete media (X-vivo-15, 5% AB serum, 20 ng/mL IL-2). One day later, cells were activated by Dynabeads human T activator CD3/CD28 (25 uL of beads/$1E^6$ CD3 positive cells) and cultivated at a density of $1E^6$ cells/mL for 3 days in X-vivo complete media at 37°C in the presence of 5% CO_2. Cells were then split in fresh complete media and transduced/transfected the next day according to the following procedure. On the day of transduction-transfection, cells were first de-beaded by magnetic separation (EasySep), washed twice in Cytoporation buffer T (BTX Harvard Apparatus, Holliston, Massachusetts) and resuspended at a final concentration of $28E^6$ cells/mL in the same solution. Cellular suspension was mixed with 5 µg mRNA encoding TRAC TALEN® arms (SEQ ID NO:16 and 17) in the presence or in the absence of 15 µg of mRNA encoding arms of either CD25 or PD1 TALEN® (SEQ ID NO:18 and 19 and SEQ ID NO:20 and 21 respectively) in a final volume of 200 µl. TALEN® is a standard format of TALE-nucleases resulting from a fusion of TALE with Fok-1 Transfection was performed using Pulse Agile technology, by applying two 0.1 mS pulses at 3,000 V/cm followed by four 0.2 mS pulses at 325 V/cm in 0.4 cm gap cuvettes and in a final volume of 200 µl of Cytoporation buffer T (BTX Harvard

Apparatus, Holliston, Massachusetts). Electroporated cells were then immediately transferred to a 12-well plate containing 1 mL of prewarm X-vivo-15 serum-free media and incubated for 37°C for 15 min. Cells were then concentrated to $8E^6$ cells/mL in 250 µL of the same media in the presence of AAV6 particles (MOI=$3E^5$ vg/cells) comprising the donor matrices in 48 wells regular treated plates. After 2 hours of culture at 30°C, 250 µL of Xvivo-15 media supplemented by 10% AB serum and 40 ng/ml IL-2 was added to the cell suspension and the mix was incubated 24 hours in the same culture conditions. One day later, cells were seeded at $1E^6$ cells/mL in complete X-vivo-15 media and cultivated at 37°C in the presence of 5% CO_2.

2.2-Activation-dependent expression of ΔLNGFR and secretion of IL15

Engineered T-cells were recovered from the transfection-transduction process described earlier and seeded at $1E^6$ cells/mL alone or in the presence of Raji cells (E:T=1:1) or Dynabeads (12.5 uL/$1E^6$ cells) in 100 µL final volume of complete X-vivo-15 media. Cells were cultivated for 48 hours before being recovered, labeled and analyzed by flow cytometry. Cells were labeled with two independent sets of antibodies. The first sets of antibodies, aiming at detecting the presence of ΔLNGFR, CAR and CD3 cells, consisted in QBEND10-APC (diluted 1/10), vioblue-labeled anti CD3 (diluted 1/25) and PE-labeled anti-ΔLNGFR (diluted 1/25). The second sets of antibodies, aiming at detecting expression of endogenous CD25 and PD1, consisted in APC-labeled anti-CD25 (diluted 1/25) and vioblue-labeled anti PD1 (diluted 1/25).

The same experimental set up was used to study IL-15 secretion in the media. Cells mixture were kept in co-culture for 2, 4, 7 and 10 days before collecting and analyzing supernatant using an IL-15 specific ELISA kit.

2.3-Serial killing assay

To assess the antitumor activity of engineered CAR T-cells, a serial killing assay was performed. The principle of this assay is to challenge CAR T-cell antitumor activity everyday by a daily addition of a constant amount of tumor cells. Tumor cell proliferation, control and relapse could be monitored via luminescence read out thanks to a Luciferase marker stably integrated in Tumor cell lines.

Typically, CAR T-cells are mixed to a suspension of $2.5x10^5$ Raji-luc tumor cells at variable E:T ratio (E:T=5:1 or 1:1) in a total volume of 1 mL of Xvivo 5% AB, 20 ng/uL IL-2. The mixture is incubated 24 hours before determining the luminescence of 25 uL of cell suspension using ONE-Glo reagent. Cells mixture are then spun down, the old media is discarded and substituted with 1 mL of fresh complete X-vivo-15 media containing $2.5x10^5$

Raji-Luc cells and the resulting cell mixture is incubated for 24 hours. This protocol is repeated 4 days.

Experiments and results

This example describes methods to improve the therapeutic outcome of CAR T-cell therapies by integrating an IL-15/soluble IL-15 receptor alpha heterodimer (IL15/sIL15rα) expression cassette under the control of the endogenous T-cell promoters regulating PD1 and CD25 genes. Because both genes are known to be upregulated upon tumor engagement by CAR T-cells, they could be hijacked to re-express IL- IL15/sIL15rα only in vicinity of a tumor. This method aims to reduce the potential side effects of IL15/sIL15rα systemic secretion while maintaining its capacity to reduced activation induced T-cell death (AICD), promote T-cell survival, enhance T-cell antitumor activity and to reverse T-cell anergy.

The method developed to integrate IL15/sIL15rα at PD1 and CD25 loci consisted in generating a double-strand break at both loci using TALEN in the presence of a DNA repair matrix vectorized by AAV6. This matrix consists of two homology arms embedding IL15/sIL15rα coding regions separated by a 2A cis acting elements and regulatory elements (stop codon and polyA sequences). Depending on the locus targeted and its involvement in T-cell activity, the targeted endogenous gene could be inactivated or not via specific matrix design. When CD25 gene was considered as targeted locus, the insertion matrix was designed to knock-in (KI) IL15/sIL15rα without inactivating CD25 because the protein product of this gene is regarded as essential for T-cell function. By constrast, because PD1 is involved in T-cell inhibition/exhaustion of T-cells, the insertion matrix was designed to prevent its expression while enabling the expression and secretion of IL15/sIL15rα.

To illustrate this approach and demonstrate the feasibility of double targeted insertion in primary T-cells, three different matrices were designed (figure 2A, 2B and 2C). The first one named CARm represented by SEQ ID NO:36 was designed to insert an anti-CD22 CAR cDNA at the TRAC locus in the presence of TRAC TALEN® (SEQ ID NO:16 and 17). The second one, IL-15_CD25m (SEQ ID NO:37) was designed to integrate IL15, sIL15rα and the surface marker named ΔLNGFR cDNAs separated by 2A cis-acting elements just before the stop codon of CD25 endogenous coding sequence using CD25 TALEN® (SEQ ID NO:18 and 19). The third one, IL-15_PD1m (SEQ ID NO:38), contained the same expression cassette and was designed to integrate in the middle of the PD1

open reading frame using PD1 TALEN® (SEQ ID NO:20 and 21). The three matrices contained an additional 2A cis-acting element located upstream expression cassettes to enable co-expression of IL15/sIL15rα and CAR with the endogenous gene targeted.

We first assessed the efficiency of double targeted insertion in T-cells by transducing them with one of the AAV6 encoding IL15/sIL15rα matrices (SEQ ID NO:41; pCLS30519) along with the one encoding the CAR and subsequently transfected the corresponding TALEN®. AAV6-assisted vectorization of matrices in the presence of mRNA encoding TRAC TALEN® (SEQ ID NO:22 and 23) and PD1 TALEN® (SEQ ID NO:24 and 25) or CD25 TALEN® (SEQ ID NO:26 and 27) enabled expression of the anti CD22 CAR in up to 46% of engineered T-cells (figure 3).

To determine the extent of IL15m integration at CD25 and PD1 locus, engineered T-cells were activated with either antiCD3/CD28 coated beads or with CD22 expressing Raji tumor cells. 2 days post activation, cells were recovered and analyzed by FACS using LNGFR expression as IL15/sIL15rα secretion surrogate (figure 4 and 5). Our results showed that antiCD3/CD28 coated beads induced expression of ΔLNGFR by T-cells containing IL-15m_CD25 or IL-15m_PD1, independently of the presence of the anti CD22 CAR (figure 4A-B). Tumor cells however, only induced expression of ΔLNGFR by T-cell treated by both CARm and IL-15m. This indicated that expression of ΔLNGFR could be specifically induced through tumor cell engagement by the CAR (figures 5 and 6).

As expected the endogenous CD25 gene was still expressed in activated treated T-cells (figures 7 and 8) while PD1 expression was strongly impaired (figure 12).

To verify that expression of ΔLNGFR correlated with secretion of IL15 in the media, T-cells expressing the anti-CD22 CAR and ΔLNGFR were incubated in the presence of CD22 expressing Raji tumor cells (E:T ratio = 1:1) for a total of 10 days. Supernatant were recovered at day 2, 4, 7 and 10 and the presence of IL15 was quantified by ELISA assay. Our results showed that IL15 was secreted in the media only by T-cells that were co-treated by both CARm and IL15m matrices along with their corresponding TALEN® (figure 13). T-cell treated with either one of these matrices were unable to secrete any significant level of IL15 with respect to resting T-cells. Interestingly, IL-15 secretion level was found transitory, with a maximum peak centered at day 4 (Figure 14).

To assess whether the level of secreted IL-15 (SEQ ID NO:59) could impact CAR T-cell activity, CAR T-cell were co-cultured in the presence of tumor cells at E:T ratio of 5:1 for 4 days. Their antitumor activity was challenged everyday by pelleting and

resuspended them in a culture media lacking IL-2 and containing fresh tumor cells. Antitumor activity of CAR T-cell was monitored everyday by measuring the luminescence of the remaining Raji tumor cells expressing luciferase. Our results showed that CAR T-cells co-expressing IL-15 had a higher antitumor activity than those lacking IL15 at all time points considered (figure 15).

Thus, together our results showed that we have developed a method allowing simultaneous targeted insertions of CAR and IL15 cDNA at TRAC and CD25 or PD1 loci. This double targeted insertion led to robust expression of an antiCD22 CAR and to the secretion of IL15 in the media. Levels of secreted IL15 were sufficient to enhance the activity of CAR T-cells.

Table 5: Sequences referred to in example 2.

SEQ ID NO#	Sequence Name	Polypeptide sequence	RVD sequence
16	TALEN right TRAC	MGDPKKKRKVIDYPYDVPDYAIDIADLRTLGYSQQQQEKIKPKVRSTVA QHHEALVGHGFTHAHIVALSQHPAALGTVAVKYQDMIAALPEATHEAIV GVGKQWSGARALEALLTVAGELRGPPLQLDTGQLLKIAKRGGVTAVEA VHAWRNALTGAPLNLTPQQVVAIASNGGGKQALETVQRLLPVLCQAHG LTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNGG GKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVL CQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIA SHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQAL LPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQ VVAIASNIGGKQALETVQALLPVLCQAHGLTPQQVVAIASNNGGKQALE TVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQALLPVLCQAHGL TPQQVVAIASNGGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGK QALETVQALLPVLCQAHGLTPQQVVAIASNGGGKQALETVQRLLPVLC QAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIAS NGGGRPALESIVAQLSRPDPALAALTNDHLVALACLGGRPALDAVKKGL GDPISRSQLVKSELEEKKSELRHKLKYVPHEYIELIEIARNSTQDRILEMK VMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIVDTKAYSGGY NLPIGQADEMQRYVEENQTRNKHINPNEWWKVYPSSVTEFKFLFVSGH FKGNYKAQLTRLNHITNCNGAVLSVEELLIGGEMIKAGTLTLEEVRRKFN NGEINFAAD	NG-NN-NG-HD-HD-HD-NI-HD-NI-NN-NI-NG-NI-NG-HD-NG#
17	TALEN Left TRAC	MGDPKKKRKVIDKETAAAKFERQHMDSIDIADLRTLGYSQQQQEKIKPK VRSTVAQHHEALVGHGFTHAHIVALSQHPAALGTVAVKYQDMIAALPEA THEAIVGVGKQWSGARALEALLTVAGELRGPPLQLDTGQLLKIAKRGGV TAVEAVHAWRNALTGAPLNLTPEQVVAIASHDGGKQALETVQRLLPVL CQAHGLTPQQVVAIASNGGGKQALETVQRLLPVLCQAHGLTPEQVVAI ASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQA LLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPE QVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNGGGKQA LETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQA HGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASN GGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQALLP VLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVV AIASNIGGKQALETVQALLPVLCQAHGLTPEQVVAIASHDGGKQALETV QRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLT PQQVVAIASNGGGRPALESIVAQLSRPDPALAALTNDHLVALACLGGRP	HD-NG-HD-NI-NN-HD-NG-NN-NN-NG-NI-HD-NI-HD-NN-NG#

		ALDAVKKGLGDPISRSQLVKSELEEKKSELRHKLKYVPHEYIELIEIARNS TQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIVD TKAYSGGYNLPIGQADEMQRYVEENQTRNKHINPNEWWKVYPSSVTE FKFLFVSGHFKGNYKAQLTRLNHITNCNGAVLSVEELLIGGEMIKAGTLT LEEVRRKFNNGEINFAAD	
18	TALEN right CD25	MGDPKKKRKVIDYPYDVPDYAIDIADLRTLGYSQQQQEKIKPKVRSTVA QHHEALVGHGFTHAHIVALSQHPAALGTVAVKYQDMIAALPEATHEAIV GVGKQWSGARALEALLTVAGELRGPPLQLDTGQLLKIAKRGGVTAVEA VHAWRNALTGAPLNLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHG LTPQQVVAIASNGGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNGG GKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVL CQAHGLTPQQVVAIASNGGGKQALETVQRLLPVLCQAHGLTPQQVVAI ASNGGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNGGGKQALETVQ RLLPVLCQAHGLTPQQVVAIASNGGGKQALETVQRLLPVLCQAHGLTP QQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQ ALETVQRLLPVLCQAHGLTPQQVVAIASNGGGKQALETVQRLLPVLCQ AHGLTPQQVVAIASNGGGKQALETVQRLLPVLCQAHGLTPQQVVAIAS NGGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNGGGKQALETVQRL LPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQ VVAIASNGGGRPALESIVAQLSRPDPSGSGSGGDPISRSQLVKSELEEK KSELRHKLKYVPHEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHL GGSRKPDGAIYTVGSPIDYGVIVDTKAYSGGYNLPIGQADEMQRYVEEN QTRNKHINPNEWWKVYPSSVTEFKFLFVSGHFKGNYKAQLTRLNHITN CNGAVLSVEELLIGGEMIKAGTLTLEEVRRKFNNGEINFAAD	NN-NG-NG-HD-NG-NG-NG-NG-NN-NN-NG-NG-NG-NG-HD-NG#
19	TALEN left CD25	MGDPKKKRKVIDYPYDVPDYAIDIADLRTLGYSQQQQEKIKPKVRSTVA QHHEALVGHGFTHAHIVALSQHPAALGTVAVKYQDMIAALPEATHEAIV GVGKQWSGARALEALLTVAGELRGPPLQLDTGQLLKIAKRGGVTAVEA VHAWRNALTGAPLNLTPEQVVAIASNIGGKQALETVQALLPVLCQAHGL TPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGK QALETVQALLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLC QAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIAS NIGGKQALETVQALLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLL PVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQV VAIASNIGGKQALETVQALLPVLCQAHGLTPEQVVAIASNIGGKQALETV QALLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLT PEQVVAIASNIGGKQALETVQALLPVLCQAHGLTPQQVVAIASNNGGKQ ALETVQRLLPVLCQAHGLTPQQVVAIASNGGGKQALETVQRLLPVLCQ AHGLTPEQVVAIASNIGGKQALETVQALLPVLCQAHGLTPQQVVAIASN GGGRPALESIVAQLSRPDPSGSGSGGDPISRSQLVKSELEEKKSELRH KLKYVPHEYIELIEIARNSTQDRILEMKVMEFFMKVYGYRGKHLGGSRK PDGAIYTVGSPIDYGVIVDTKAYSGGYNLPIGQADEMQRYVEENQTRNK HINPNEWWKVYPSSVTEFKFLFVSGHFKGNYKAQLTRLNHITNCNGAV LSVEELLIGGEMIKAGTLTLEEVRRKFNNGEINFAAD	NI-HD-NI-NN-NN-NI-NN-NN-NI-NI-NN-NI-NN-NG-NI-NG#
20	TALEN right PD1	MGDPKKKRKVIDYPYDVPDYAIDIADLRTLGYSQQQQEKIKPKVRSTVA QHHEALVGHGFTHAHIVALSQHPAALGTVAVKYQDMIAALPEATHEAIV GVGKQWSGARALEALLTVAGELRGPPLQLDTGQLLKIAKRGGVTAVEA VHAWRNALTGAPLNLTPEQVVAIASKLGGKQALETVQALLPVLCQAHGL TPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGG KQALETVQRLLPVLCQAHGLTPQQVVAIASNGGGKQALETVQRLLPVL CQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAI ASNGGGKQALETVQRLLPVLCQAHGLTPQQVVAIASYKGGKQALETVQ RLLPVLCQAHGLTPQQVVAIASNGGGKQALETVQRLLPVLCQAHGLTP QQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQ ALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQA HGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHD GGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLP VLCQAHGLTPEQVVAIASNIGGKQALETVQALLPVLCQAHGLTPQQVVA IASNGGGRPALESIVAQLSRPDPALAALTNDHLVALACLGGRPALDAVK KGLGDPISRSQLVKSELEEKKSELRHKLKYVPHEYIELIEIARNSTQDRIL EMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIVDTKAYS GGYNLPIGQADEMQRYVEENQTRNKHINPNEWWKVYPSSVTEFKFLFV SGHFKGNYKAQLTRLNHITNCNGAVLSVEELLIGGEMIKAGTLTLEEVRR KFNNGEINFAAD	KL-HD-HD-NG-HD-NG-YK-NG-NN-NN-NN-NN-HD-HD-NI-NG#

21	TALEN Left PD1	MGDPKKKRKVIDKETAAAKFERQHMDSIDIADLRTLGYSQQQQEKIKPK VRSTVAQHHEALVGHGFTHAHIVALSQHPAALGTVAVKYQDMIAALPEA THEAIVGVGKQWSGARALEALLTVAGELRGPPLQLDTGQLLKIAKRGGV TAVEAVHAWRNALTGAPLNLTPEQVVAIASHDGGKQALETVQRLLPVL CQAHGLTPQQVVAIASNGGGKQALETVQRLLPVLCQAHGLTPEQVVAI ASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNGGGKQALETVQ RLLPVLCQAHGLTPQQVVAIASNGGGKQALETVQRLLPVLCQAHGLTP QQVVAIASNGGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQ ALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQALLPVLCQA HGLTPQQVVAIASNGGGKQALETVQRLLPVLCQAHGLTPEQVVAIASH DGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNGGGKQALETVQRLL PVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQV VAIASNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETV QRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLT PQQVVAIASNGGGRPALESIVAQLSRPDPALAALTNDHLVALACLGGRP ALDAVKKGLGDPISRSQLVKSELEEKKSELRHKLKYVPHEYIELIEIARNS TQDRILEMKVMEFFMKVYGYRGKHLGGSRKPDGAIYTVGSPIDYGVIVD TKAYSGGYNLPIGQADEMQRYVEENQTRNKHINPNEWWKVYPSSVTE FKFLFVSGHFKGNYKAQLTRLNHITNCNGAVLSVEELLIGGEMIKAGTLT LEEVRRKFNNGEINFAAD	HD-NG-HD-NG-NG-NG-NN-NI-NG-HD-NG-NN-N-NN-HD-NG#

Table 5 (continued): Sequences referred to in example 2.

SEQ ID NO#	Sequence Name	Polynucleotide sequence
22	TALEN TRAC pCLS11370	ATGGGCGATCCTAAAAAGAAACGTAAGGTCATCGATTACCCATACGATGTTCCAGATTACGCTAT CGATATCGCCGATCTACGCACGCTCGGCTACAGCCAGCAGCAACAGGAGAAGATCAAACCGAA GGTTCGTTCGACAGTGGCGCAGCACCACGAGGCACTGGTCGGCCACGGGTTTACACACGCGC ACATCGTTGCGTTAAGCCAACACCCGGCAGCGTTAGGGACCGTCGCTGTCAAGTATCAGGACA TGATCGCAGCGTTGCCAGAGGCGACACACGAAGCGATCGTTGGCGTCGGCAAACAGTGGTCC GGCGCACGCGCTCTGGAGGCCTTGCTCACGGTGGCGGGAGAGTTGAGAGGTCCACCGTTACA GTTGGACACAGGCCAACTTCTCAAGATTGCAAAACGTGGCGGCGTGACCGCAGTGGAGGCAGT GCATGCATGGCGCAATGCACTGACGGGTGCCCCGCTCAACTTGACCCCCCAGCAGGTGGTGG CCATCGCCAGCAATGGCGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTG CTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATAATGGTGG CAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGA CCCCCCAGCAGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCAGGCGCTGGAGACGGT CCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCA TCGCCAGCCACGATGGCGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTG TGCCAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCGCCAGCCACGATGGCGGCAA GCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCC CGGAGCAGGTGGTGGCCATCGCCAGCCACGATGGCGGCAAGCAGGCGCTGGAGACGGTCCA GCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCG CCAGCAATATTGGTGGCAAGCAGGCGCTGGAGACGGTGCAGGCGCTGTTGCCGGTGCTGTGC CAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCGCCAGCCACGATGGCGGCAAGCA GGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCG GAGCAGGTGGTGGCCATCGCCAGCAATATTGGTGGCAAGCAGGCGCTGGAGACGGTGCAGGC GCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCA GCAATAATGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAG GCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCGCCAGCAATATTGGTGGCAAGCAGGC GCTGGAGACGGTGCAGGCGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGC AGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCT GTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCGCCAGCA ATATTGGTGGCAAGCAGGCGCTGGAGACGGTGCAGGCGCTGTTGCCGGTGCTGTGCCAGGCC CACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCAGGCGCT GGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGCAG GTGGTGGCCATCGCCAGCCACGATGGCGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTT GCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCTCAGCAGGTGGTGGCCATCGCCAGCAATG GCGGCGGCAGGCCGGCGCTGGAGAGCATTGTTGCCCAGTTATCTCGCCCTGATCCGGCGTTG GCCGCGTTGACCAACGACCACCTCGTCGCCTTGGCCTGCCTCGGCGGGCGTCCTGCGCTGGA TGCAGTGAAAAAGGGATTGGGGGATCCTATCAGCCGTTCCCAGCTGGTGAAGTCCGAGCTGGA GGAGAAGAAATCCGAGTTGAGGCACAAGCTGAAGTACGTGCCCCACGAGTACATCGAGCTGAT

		CGAGATCGCCCGGAACAGCACCCAGGACCGTATCCTGGAGATGAAGGTGATGGAGTTCTTCAT GAAGGTGTACGGCTACAGGGGCAAGCACCTGGGCGGCTCCAGGAAGCCCGACGGCGCCATCT ACACCGTGGGCTCCCCCATCGACTACGGCGTGATCGTGGACACCAAGGCCTACTCCGGCGGC TACAACCTGCCCATCGGCCAGGCCGACGAAATGCAGAGGTACGTGGAGGAGAACCAGACCAG GAACAAGCACATCAACCCCAACGAGTGGTGGAAGGTGTACCCCTCCAGCGTGACCGAGTTCAA GTTCCTGTTCGTGTCCGGCCACTTCAAGGGCAACTACAAGGCCCAGCTGACCAGGCTGAACCA CATCACCAACTGCAACGGCGCCGTGCTGTCCGTGGAGGAGCTCCTGATCGGCGGCGAGATGA TCAAGGCCGGCACCCTGACCCTGGAGGAGGTGAGGAGGAAGTTCAACAACGGCGAGATCAAC TTCGCGGCCGACTGATAA
23	TALEN TRAC pCLS11369	ATGGGCGATCCTAAAAAGAAACGTAAGGTCATCGATAAGGAGACCGCCGCTGCCAAGTTCGAG AGACAGCACATGGACAGCATCGATATCGCCGATCTACGCACGCTCGGCTACAGCCAGCAGCAA CAGGAGAAGATCAAACCGAAGGTTCGTTCGACAGTGGCGCAGCACCACGAGGCACTGGTCGG CCACGGGTTTACACACGCGCACATCGTTGCGTTAAGCCAACACCCGGCAGCGTTAGGGACCGT CGCTGTCAAGTATCAGGACATGATCGCAGCGTTGCCAGAGGCGACACACGAAGCGATCGTTGG CGTCGGCAAACAGTGGTCCGGCGCACGCGCTCTGGAGGCCTTGCTCACGGTGGCGGGAGAGT TGAGAGGTCCACCGTTACAGTTGGACACAGGCCAACTTCTCAAGATTGCAAAACGTGGCGGCG TGACCGCAGTGGAGGCAGTGCATGCATGGCGCAATGCACTGACGGGTGCCCCGCTCAACTTG ACCCCGGAGCAGGTGGTGGCCATCGCCAGCCACGATGGCGGCAAGCAGGCGCTGGAGACGG TCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCC ATCGCCAGCAATGGCGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCT GTGCCAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCGCCAGCCACGATGGCGGC AAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGAC CCCGGAGCAGGTGGTGGCCATCGCCAGCAATATTGGTGGCAAGCAGGCGCTGGAGACGGTGC AGGCGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATC GCCAGCAATAATGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTG CCAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCGCCAGCCACGATGGCGGCAAG CAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCC CCAGCAGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCAGGCGCTGGAGACGGTCCAG CGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGC CAGCAATAATGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCC AGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATAATGGTGGCAAGCAG GCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCA GCAGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGG CTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCGCCAG CAATATTGGTGGCAAGCAGGCGCTGGAGACGGTGCAGGCGCTGTTGCCGGTGCTGTGCCAGG CCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCGCCAGCCACGATGGCGGCAAGCAGGC GCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGC AGGTGGTGGCCATCGCCAGCAATATTGGTGGCAAGCAGGCGCTGGAGACGGTGCAGGCGCTG TTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCGCCAGCCA CGATGGCGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCC CACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATAATGGTGGCAAGCAGGCGCT GGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCTCAGCAGG TGGTGGCCATCGCCAGCAATGGCGGCGGCAGGCCGGCGCTGGAGAGCATTGTTGCCCAGTTA TCTCGCCCTGATCCGGCGTTGGCCGCGTTGACCAACGACCACCTCGTCGCCTTGGCCTGCCTC GGCGGGCGTCCTGCGCTGGATGCAGTGAAAAAGGGATTGGGGGATCCTATCAGCCGTTCCCA GCTGGTGAAGTCCGAGCTGGAGGAGAAGAAATCCGAGTTGAGGCACAAGCTGAAGTACGTGCC CCACGAGTACATCGAGCTGATCGAGATCGCCCGGAACAGCACCCAGGACCGTATCCTGGAGAT GAAGGTGATGGAGTTCTTCATGAAGGTGTACGGCTACAGGGGCAAGCACCTGGGCGGCTCCA GGAAGCCCGACGGCGCCATCTACACCGTGGGCTCCCCCATCGACTACGGCGTGATCGTGGAC ACCAAGGCCTACTCCGGCGGCTACAACCTGCCCATCGGCCAGGCCGACGAAATGCAGAGGTA CGTGGAGGAGAACCAGACCAGGAACAAGCACATCAACCCCAACGAGTGGTGGAAGGTGTACC CCTCCAGCGTGACCGAGTTCAAGTTCCTGTTCGTGTCCGGCCACTTCAAGGGCAACTACAAGG CCCAGCTGACCAGGCTGAACCACATCACCAACTGCAACGGCGCCGTGCTGTCCGTGGAGGAG CTCCTGATCGGCGGCGAGATGATCAAGGCCGGCACCCTGACCCTGGAGGAGGTGAGGAGGAA GTTCAACAACGGCGAGATCAACTTCGCGGCCGACTGATAA
24	TALEN CD25 pCLS30480	ATGGGCGATCCTAAAAAGAAACGTAAGGTCATCGATTACCCATACGATGTTCCAGATTACGCTAT CGATATCGCCGATCTACGCACGCTCGGCTACAGCCAGCAGCAACAGGAGAAGATCAAACCGAA GGTTCGTTCGACAGTGGCGCAGCACCACGAGGCACTGGTCGGCCACGGGTTTACACACGCGC ACATCGTTGCGTTAAGCCAACACCCGGCAGCGTTAGGGACCGTCGCTGTCAAGTATCAGGACA TGATCGCAGCGTTGCCAGAGGCGACACACGAAGCGATCGTTGGCGTCGGCAAACAGTGGTCC GGCGCACGCGCTCTGGAGGCCTTGCTCACGGTGGCGGGAGAGTTGAGAGGTCCACCGTTACA GTTGGACACAGGCCAACTTCTCAAGATTGCAAAACGTGGCGGCGTGACCGCAGTGGAGGCAGT GCATGCATGGCGCAATGCACTGACGGGTGCCCCGCTCAACTTGACCCCCCAGCAGGTGGTGG CCATCGCCAGCAATAATGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTG CTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATGGCGGTGG CAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGA CCCCCCAGCAGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCAGGCGCTGGAGACGGT CCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCA TCGCCAGCCACGATGGCGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTG TGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAA GCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCC CCCAGCAGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCAGGCGCTGGAGACGGTCCA

		GCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCG CCAGCAATGGCGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGC CAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCA GGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCC AGCAGGTGGTGGCCATCGCCAGCAATAATGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGG CTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAG CAATAATGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGG CCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCAGGCG CTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGCA GGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTG TTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAA TGGCGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCC CACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCAGGCGCT GGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGCAG GTGGTGGCCATCGCCAGCCACGATGGCGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTT GCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCTCAGCAGGTGGTGGCCATCGCCAGCAATG GCGGCGGCAGGCCGGCGCTGGAGAGCATTGTTGCCCAGTTATCTCGCCCTGATCCGAGTGGC AGCGGAAGTGGCGGGGATCCTATCAGCCGTTCCCAGCTGGTGAAGTCCGAGCTGGAGGAGAA GAAATCCGAGTTGAGGCACAAGCTGAAGTACGTGCCCCACGAGTACATCGAGCTGATCGAGAT CGCCCGGAACAGCACCCAGGACCGTATCCTGGAGATGAAGGTGATGGAGTTCTTCATGAAGGT GTACGGCTACAGGGGCAAGCACCTGGGCGGCTCCAGGAAGCCCGACGGCGCCATCTACACCG TGGGCTCCCCCATCGACTACGGCGTGATCGTGGACACCAAGGCCTACTCCGGCGGCTACAACC TGCCCATCGGCCAGGCCGACGAAATGCAGAGGTACGTGGAGGAGAACCAGACCAGGAACAAG CACATCAACCCCAACGAGTGGTGGAAGGTGTACCCCTCCAGCGTGACCGAGTTCAAGTTCCTG TTCGTGTCCGGCCACTTCAAGGGCAACTACAAGGCCCAGCTGACCAGGCTGAACCACATCACC AACTGCAACGGCGCCGTGCTGTCCGTGGAGGAGCTCCTGATCGGCGGCGAGATGATCAAGGC CGGCACCCTGACCCTGGAGGAGGTGAGGAGGAAGTTCAACAACGGCGAGATCAACTTCGCGG CCGACTGATAA
25	TALEN CD25 pCLS30479	ATGGGCGATCCTAAAAAGAAACGTAAGGTCATCGATTACCCATACGATGTTCCAGATTACGCTAT CGATATCGCCGATCTACGCACGCTCGGCTACAGCCAGCAGCAACAGGAGAAGATCAAACCGAA GGTTCGTTCGACAGTGGCGCAGCACCACGAGGCACTGGTCGGCCACGGGTTTACACACGCGC ACATCGTTGCGTTAAGCCAACACCCGGCAGCGTTAGGGACCGTCGCTGTCAAGTATCAGGACA TGATCGCAGCGTTGCCAGAGGCGACACACGAAGCGATCGTTGGCGTCGGCAAACAGTGGTCC GGCGCACGCGCTCTGGAGGCCTTGCTCACGGTGGCGGGAGAGTTGAGAGGTCCACCGTTACA GTTGGACACAGGCCAACTTCTCAAGATTGCAAAACGTGGCGGCGTGACCGCAGTGGAGGCAGT GCATGCATGGCGCAATGCACTGACGGGTGCCCCGCTCAACTTGACCCCGGAGCAGGTGGTGG CCATCGCCAGCAATATTGGTGGCAAGCAGGCGCTGGAGACGGTGCAGGCGCTGTTGCCGGTG CTGTGCCAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCGCCAGCCACGATGGCGG CAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGA CCCCGGAGCAGGTGGTGGCCATCGCCAGCAATATTGGTGGCAAGCAGGCGCTGGAGACGGTG CAGGCGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCAT CGCCAGCAATAATGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGT GCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATAATGGTGGCAAG CAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCC GGAGCAGGTGGTGGCCATCGCCAGCAATATTGGTGGCAAGCAGGCGCTGGAGACGGTGCAGG CGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCC AGCAATAATGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCA GGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATAATGGTGGCAAGCAGG CGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAG CAGGTGGTGGCCATCGCCAGCAATATTGGTGGCAAGCAGGCGCTGGAGACGGTGCAGGCGCT GTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGCAGGTGGTGGCCATCGCCAGCA ATATTGGTGGCAAGCAGGCGCTGGAGACGGTGCAGGCGCTGTTGCCGGTGCTGTGCCAGGCC CACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATAATGGTGGCAAGCAGGCGCT GGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGCAG GTGGTGGCCATCGCCAGCAATATTGGTGGCAAGCAGGCGCTGGAGACGGTGCAGGCGCTGTT GCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATA ATGGTGGCAAGCAGGCGCTGGAGACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCAC GGCTTGACCCCCCAGCAGGTGGTGGCCATCGCCAGCAATGGCGGTGGCAAGCAGGCGCTGGA GACGGTCCAGCGGCTGTTGCCGGTGCTGTGCCAGGCCCACGGCTTGACCCCGGAGCAGGTGG TGGCCATCGCCAGCAATATTGGTGGCAAGCAGGCGCTGGAGACGGTGCAGGCGCTGTTGCCG GTGCTGTGCCAGGCCCACGGCTTGACCCCTCAGCAGGTGGTGGCCATCGCCAGCAATGGCGG CGGCAGGCCGGCGCTGGAGAGCATTGTTGCCCAGTTATCTCGCCCTGATCCGAGTGGCAGCG GAAGTGGCGGGGATCCTATCAGCCGTTCCCAGCTGGTGAAGTCCGAGCTGGAGGAGAAGAAAT CCGAGTTGAGGCACAAGCTGAAGTACGTGCCCCACGAGTACATCGAGCTGATCGAGATCGCCC GGAACAGCACCCAGGACCGTATCCTGGAGATGAAGGTGATGGAGTTCTTCATGAAGGTGTACG GCTACAGGGGCAAGCACCTGGGCGGCTCCAGGAAGCCCGACGGCGCCATCTACACCGTGGGC TCCCCCATCGACTACGGCGTGATCGTGGACACCAAGGCCTACTCCGGCGGCTACAACCTGCCC ATCGGCCAGGCCGACGAAATGCAGAGGTACGTGGAGGAGAACCAGACCAGGAACAAGCACAT CAACCCCAACGAGTGGTGGAAGGTGTACCCCTCCAGCGTGACCGAGTTCAAGTTCCTGTTCGT GTCCGGCCACTTCAAGGGCAACTACAAGGCCCAGCTGACCAGGCTGAACCACATCACCAACTG CAACGGCGCCGTGCTGTCCGTGGAGGAGCTCCTGATCGGCGGCGAGATGATCAAGGCCGGCA CCCTGACCCTGGAGGAGGTGAGGAGGAAGTTCAACAACGGCGAGATCAACTTCGCGGCCGAC TGATAA

26	TALEN PD1 pCLS28959	ATGGGCGATCCTAAAAAGAAACGTAAGGTCATCGATTACCCATACGATGTTCCAGATTACGCTAT CGATATCGCCGATCTACGCACGCTCGGCTACAGCCAGCAGCAACAGGAGAAGATCAAACCGAA GGTTCGTTCGACAGTGGCGCAGCACCACGAGGCACTGGTCGGCCACGGGTTTACACACGCGC ACATCGTTGCGTTAAGCCAACACCCGGCAGCGTTAGGGACCGTCGCTGTCAAGTATCAGGACA TGATCGCAGCGTTGCCAGAGGCGACACACGAAGCGATCGTTGGCGTCGGCAAACAGTGGTCC GGCGCACGCGCTCTGGAGGCCTTGCTCACGGTGGCGGGAGAGTTGAGAGGTCCACCGTTACA GTTGGACACAGGCCAACTTCTCAAGATTGCAAAACGTGGCGGCGTGACCGCAGTGGAGGCAGT GCATGCATGGCGCAATGCACTGACGGGTGCCCCGCTCAACTTGACCCCCGAGCAAGTGGTGG CTATCGCTTCCAAGCTGGGGGGAAAGCAGGCCCTGGAGACCGTCCAGGCCCTTCTCCCAGTG CTTTGCCAGGCTCACGGACTGACCCCTGAACAGGTGGTGGCAATTGCCTCACACGACGGGGG CAAGCAGGCACTGGAGACTGTCCAGCGGCTGCTGCCTGTCCTCTGCCAGGCCCACGGACTCA CTCCTGAGCAGGTCGTGGCCATTGCCAGCCACGATGGGGGCAAACAGGCTCTGGAGACCGTG CAGCGCCTCCTCCCAGTGCTGTGCCAGGCTCATGGGCTGACCCCACAGCAGGTCGTCGCCATT GCCAGTAACGGCGGGGGGAAGCAGGCCCTCGAAACAGTGCAGAGGCTGCTGCCCGTCTTGTG CCAAGCACACGGCCTGACACCCGAGCAGGTGGTGGCCATCGCCTCTCATGACGGCGGCAAGC AGGCCCTTGAGACAGTGCAGAGACTGTTGCCCGTGTTGTGTCAGGCCCACGGGTTGACACCCC AGCAGGTGGTCGCCATCGCCAGCAATGGCGGGGGAAAGCAGGCCCTTGAGACCGTGCAGCGG TTGCTTCCAGTGTTGTGCCAGGCACACGGACTGACCCCTCAACAGGTGGTCGCAATCGCCAGC TACAAGGGCGGAAAGCAGGCTCTGGAGACAGTGCAGCGCCTCCTGCCCGTGCTGTGTCAGGC TCACGGACTGACACCACAGCAGGTGGTCGCCATCGCCAGTAACGGGGGCGGCAAGCAGGCTT TGGAGACCGTCCAGAGACTCCTCCCCGTCCTTTGCCAGGCCCACGGGTTGACACCTCAGCAGG TCGTCGCCATTGCCTCCAACAACGGGGGCAAGCAGGCCCTCGAAACTGTGCAGAGGCTGCTG CCTGTGCTGTGCCAGGCTCATGGGCTGACACCCCAGCAGGTGGTGGCCATTGCCTCTAACAAC GGCGGCAAACAGGCACTGGAGACCGTGCAAAGGCTGCTGCCCGTCCTCTGCCAAGCCCACGG GCTCACTCCACAGCAGGTCGTGGCCATCGCCTCAAACAATGGCGGGAAGCAGGCCCTGGAGA CTGTGCAAAGGCTGCTCCCTGTGCTCTGCCAGGCACACGGACTGACCCCTCAGCAGGTGGTG GCAATCGCTTCCAACAACGGGGGAAAGCAGGCCCTCGAAACCGTGCAGCGCCTCCTCCCAGT GCTGTGCCAGGCACATGGCCTCACACCCGAGCAAGTGGTGGCTATCGCCAGCCACGACGGAG GGAAGCAGGCTCTGGAGACCGTGCAGAGGCTGCTGCCTGTCCTGTGCCAGGCCCACGGGCTT ACTCCAGAGCAGGTCGTCGCCATCGCCAGTCATGATGGGGGGAAGCAGGCCCTTGAGACAGT CCAGCGGCTGCTGCCAGTCCTTTGCCAGGCTCACGGCTTGACTCCCGAGCAGGTCGTGGCCAT TGCCTCAAACATTGGGGGCAAACAGGCCCTGGAGACAGTGCAGGCCCTGCTGCCCGTGTTGTG TCAGGCCCACGGCTTGACACCCCAGCAGGTGGTCGCCATTGCCTCTAATGGCGGCGGGAGAC CCGCCTTGGAGAGCATTGTTGCCCAGTTATCTCGCCCTGATCCGGCGTTGGCCGCGTTGACCA ACGACCACCTCGTCGCCTTGGCCTGCCTCGGCGGGCGTCCTGCGCTGGATGCAGTGAAAAAG GGATTGGGGGATCCTATCAGCCGTTCCCAGCTGGTGAAGTCCGAGCTGGAGGAGAAGAAATCC GAGTTGAGGCACAAGCTGAAGTACGTGCCCCACGAGTACATCGAGCTGATCGAGATCGCCCGG AACAGCACCCAGGACCGTATCCTGGAGATGAAGGTGATGGAGTTCTTCATGAAGGTGTACGGC TACAGGGGCAAGCACCTGGGCGGCTCCAGGAAGCCCGACGGCGCCATCTACACCGTGGGCTC CCCCATCGACTACGGCGTGATCGTGGACACCAAGGCCTACTCCGGCGGCTACAACCTGCCCAT CGGCCAGGCCGACGAAATGCAGAGGTACGTGGAGGAGAACCAGACCAGGAACAAGCACATCA ACCCCAACGAGTGGTGGAAGGTGTACCCCTCCAGCGTGACCGAGTTCAAGTTCCTGTTCGTGT CCGGCCACTTCAAGGGCAACTACAAGGCCCAGCTGACCAGGCTGAACCACATCACCAACTGCA ACGGCGCCGTGCTGTCCGTGGAGGAGCTCCTGATCGGCGGCGAGATGATCAAGGCCGGCACC CTGACCCTGGAGGAGGTGAGGAGGAAGTTCAACAACGGCGAGATCAACTTCGCGGCCGACTG ATAA
27	TALEN PD1 pCLS18792	ATGGGCGATCCTAAAAAGAAACGTAAGGTCATCGATAAGGAGACCGCCGCTGCCAAGTTCGAG AGACAGCACATGGACAGCATCGATATCGCCGATCTACGCACGCTCGGCTACAGCCAGCAGCAA CAGGAGAAGATCAAACCGAAGGTTCGTTCGACAGTGGCGCAGCACCACGAGGCACTGGTCGG CCACGGGTTTACACACGCGCACATCGTTGCGTTAAGCCAACACCCGGCAGCGTTAGGGACCGT CGCTGTCAAGTATCAGGACATGATCGCAGCGTTGCCAGAGGCGACACACGAAGCGATCGTTGG CGTCGGCAAACAGTGGTCCGGCGCACGCGCTCTGGAGGCCTTGCTCACGGTGGCGGGAGAGT TGAGAGGTCCACCGTTACAGTTGGACACAGGCCAACTTCTCAAGATTGCAAAACGTGGCGGCG TGACCGCAGTGGAGGCAGTGCATGCATGGCGCAATGCACTGACGGGTGCCCCGCTCAACTTG ACCCCCGAGCAAGTCGTCGCAATCGCCAGCCATGATGGAGGGAAGCAAGCCCTCGAAACCGT GCAGCGGTTGCTTCCTGTGCTCTGCCAGGCCCACGGCCTTACCCCTCAGCAGGTGGTGGCCAT CGCAAGTAACGGAGGAGGAAAGCAAGCCTTGGAGACAGTGCAGCGCCTGTTGCCCGTGCTGT GCCAGGCACACGGCCTCACACCAGAGCAGGTCGTGGCCATTGCCTCCCATGACGGGGGGAAA CAGGCTCTGGAGACCGTCCAGAGGCTGCTGCCCGTCCTCTGTCAAGCTCACGGCCTGACTCCC CAACAAGTGGTCGCCATCGCCTCTAATGGCGGCGGGAAGCAGGCACTGGAAACAGTGCAGAG ACTGCTCCCTGTGCTTTGCCAAGCTCATGGGTTGACCCCCCAACAGGTCGTCGCTATTGCCTCA AACGGGGGGGGCAAGCAGGCCCTTGAGACTGTGCAGAGGCTGTTGCCAGTGCTGTGTCAGGC TCACGGGCTCACTCCACAACAGGTGGTCGCAATTGCCAGCAACGGCGGCGGAAAGCAAGCTCT TGAAACCGTGCAACGCCTCCTGCCCGTGCTCTGTCAGGCTCATGGCCTGACACCACAACAAGT CGTGGCCATCGCCAGTAATAATGGCGGGAAACAGGCTCTTGAGACCGTCCAGAGGCTGCTCCC AGTGCTCTGCCAGGCACACGGGCTGACCCCCGAGCAGGTGGTGGCTATCGCCAGCAATATTG GGGGCAAGCAGGCCCTGGAAACAGTCCAGGCCCTGCTGCCAGTGCTTTGCCAGGCTCACGGG CTCACTCCCCAGCAGGTCGTGGCAATCGCCTCCAACGGCGGAGGGAAGCAGGCTCTGGAGAC CGTGCAGAGACTGCTGCCCGTCTTGTGCCAGGCCCACGGACTCACACCTGAACAGGTCGTCGC CATTGCCTCTCACGATGGGGGCAAACAAGCCCTGGAGACAGTGCAGCGGCTGTTGCCTGTGTT GTGCCAAGCCCACGGCTTGACTCCTCAACAAGTGGTCGCCATCGCCTCAAATGGCGGCGGAAA ACAAGCTCTGGAGACAGTGCAGAGGTTGCTGCCCGTCCTCTGCCAAGCCCACGGCCTGACTCC

		CCAACAGGTCGTCGCCATTGCCAGCAACAACGGAGGAAAGCAGGCTCTCGAAACTGTGCAGCG GCTGCTTCCTGTGCTGTGTCAGGCTCATGGGCTGACCCCCGAGCAAGTGGTGGCTATTGCCTC TAATGGAGGCAAGCAAGCCCTTGAGACAGTCCAGAGGCTGTTGCCAGTGCTGTGCCAGGCCCA CGGGCTCACACCCCAGCAGGTGGTCGCCATCGCCAGTAACAACGGGGGCAAACAGGCATTGG AAACCGTCCAGCGCCTGCTTCCAGTGCTCTGCCAGGCACACGGACTGACACCCGAACAGGTGG TGGCCATTGCATCCCATGATGGGGGCAAGCAGGCCCTGGAGACCGTGCAGAGACTCCTGCCA GTGTTGTGCCAAGCTCACGGCCTCACCCCTCAGCAAGTCGTGGCCATCGCCTCAAACGGGGG GGGCCGGCCTGCACTGGAGAGCATTGTTGCCCAGTTATCTCGCCCTGATCCGGCGTTGGCCG CGTTGACCAACGACCACCTCGTCGCCTTGGCCTGCCTCGGCGGGCGTCCTGCGCTGGATGCA GTGAAAAAGGGATTGGGGGATCCTATCAGCCGTTCCCAGCTGGTGAAGTCCGAGCTGGAGGAG AAGAAATCCGAGTTGAGGCACAAGCTGAAGTACGTGCCCCACGAGTACATCGAGCTGATCGAG ATCGCCCGGAACAGCACCCAGGACCGTATCCTGGAGATGAAGGTGATGGAGTTCTTCATGAAG GTGTACGGCTACAGGGGCAAGCACCTGGGCGGCTCCAGGAAGCCCGACGGCGCCATCTACAC CGTGGGCTCCCCCATCGACTACGGCGTGATCGTGGACACCAAGGCCTACTCCGGCGGCTACA ACCTGCCCATCGGCCAGGCCGACGAAATGCAGAGGTACGTGGAGGAGAACCAGACCAGGAAC AAGCACATCAACCCCAACGAGTGGTGGAAGGTGTACCCCTCCAGCGTGACCGAGTTCAAGTTC CTGTTCGTGTCCGGCCACTTCAAGGGCAACTACAAGGCCCAGCTGACCAGGCTGAACCACATC ACCAACTGCAACGGCGCCGTGCTGTCCGTGGAGGAGCTCCTGATCGGCGGCGAGATGATCAA GGCCGGCACCCTGACCCTGGAGGAGGTGAGGAGGAAGTTCAACAACGGCGAGATCAACTTCG CGGCCGACTGATAA
28	TALEN target TRAC	TTGTCCCACAGATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGA
29	TALEN target CD25	TACAGGAGGAAGAGTAGAAGAACAATCTAGAAAACCAAAAGAACA
30	TALEN target PD1	TACCTCTGTGGGGCCATCTCCCTGGCCCCCAAGGCGCAGATCAAAGAGA
31	Matrice TRAC locus_CubiCAR CD22 pCLS30056	TTGCTGGGCCTTTTTCCCATGCCTGCCTTTACTCTGCCAGAGTTATATTGCTGGGGTTTTGAAGA AGATCCTATTAAATAAAAGAATAAGCAGTATTATTAAGTAGCCCTGCATTTCAGGTTTCCTTGAGT GGCAGGCCAGGCCTGGCCGTGAACGTTCACTGAAATCATGGCCTCTTGGCCAAGATTGATAGC TTGTGCCTGTCCCTGAGTCCCAGTCCATCACGAGCAGCTGGTTTCTAAGATGCTATTTCCCGTA TAAAGCATGAGACCGTGACTTGCCAGCCCCACAGAGCCCCGCCCTTGTCCATCACTGGCATCT GGACTCCAGCCTGGGTTGGGGCAAAGAGGGAAATGAGATCATGTCCTAACCCTGATCCTCTTG TCCCACAGATATCCAGTACCCCTACGACGTGCCCGACTACGCCTCCGGTGAGGGCAGAGGAAG TCTTCTAACATGCGGTGACGTGGAGGAGAATCCGGGCCCCGGATCCGCTCTGCCCGTCACCGC TCTGCTGCTGCCACTGGCACTGCTGCTGCACGCTGCTAGGCCCGGAGGGGGAGGCAGCTGCC CCTACAGCAACCCCAGCCTGTGCAGCGGAGGCGGCGGCAGCGGCGGAGGGGGTAGCCAGGT GCAGCTGCAGCAGAGCGGCCCTGGCCTGGTGAAGCCAAGCCAGACACTGTCCCTGACCTGCG CCATCAGCGGCGATTCCGTGAGCTCCAACTCCGCCGCCTGGAATTGGATCAGGCAGTCCCCTT CTCGGGGCCTGGAGTGGCTGGGAAGGACATACTATCGGTCTAAGTGGTACAACGATTATGCCG TGTCTGTGAAGAGCAGAATCACAATCAACCCTGACACCTCCAAGAATCAGTTCTCTCTGCAGCT GAATAGCGTGACACCAGAGGACACCGCCGTGTACTATTGCGCCAGGGAGGTGACCGGCGACC TGGAGGATGCCTTTGACATCTGGGGCCAGGGCACAATGGTGACCGTGAGCTCCGGAGGCGGC GGATCTGGCGGAGGAGGAAGTGGGGGCGGCGGGAGTGATATCCAGATGACACAGTCCCCATC CTCTCTGAGCGCCTCCGTGGGCGACAGAGTGACAATCACCTGTAGGGCCTCCCAGACCATCTG GTCTTACCTGAACTGGTATCAGCAGAGGCCCGGCAAGGCCCCTAATCTGCTGATCTACGCAGC AAGCTCCCTGCAGAGCGGAGTGCCATCCAGATTCTCTGGCAGGGGCTCCGGCACAGACTTCAC CCTGACCATCTCTAGCCTGCAGGCCGAGGACTTCGCCACCTACTATTGCCAGCAGTCTTATAGC ATCCCCCAGACATTTGGCCAGGGCACCAAGCTGGAGATCAAGTCGGATCCCGGAAGCGGAGG GGGAGGCAGCTGCCCCTACAGCAACCCCAGCCTGTGCAGCGGAGGCGGCGGCAGCGAGCTG CCCACCCAGGGCACCTTCTCCAACGTGTCCACCAACGTGAGCCCAGCCAAGCCCACCACCACC GCCTGTCCTTATTCCAATCCTTCCCTGTGTGCTCCCACCACAACCCCCGCTCCAAGGCCCCCTA CCCCCGCACCAACTATTGCCTCCCAGCCACTCTCACTGCGGCCTGAGGCCTGTCGGCCCGCTG CTGGAGGCGCAGTGCATACAAGGGGCCTCGATTTCGCCTGCGATATTTACATCTGGGCACCCC TCGCCGGCACCTGCGGGGTGCTTCTCCTCTCCCTGGTGATTACCCTGTATTGCAGACGGGGCC GGAAGAAGCTCCTCTACATTTTTAAGCAGCCTTTCATGCGGCCAGTGCAGACAACCCAAGAGGA GGATGGGTGTTCCTGCAGATTCCCTGAGGAAGAGGAAGGCGGGTGCGAGCTGAGAGTGAAGT TCTCCAGGAGCGCAGATGCCCCCGCCTATCAACAGGGCCAGAACCAGCTCTACAACGAGCTTA ACCTCGGGAGGCGCGAAGAATACGACGTGTTGGATAAGAGAAGGGGGCGGGACCCCGAGATG GGAGGAAAGCCCCGGAGGAAGAACCCTCAGGAGGGCCTGTACAACGAGCTGCAGAAGGATAA GATGGCCGAGGCCTACTCAGAGATCGGGATGAAGGGGGAGCGGCGCCGCGGGAAGGGGCAC GATGGGCTCTACCAGGGGCTGAGCACAGCCACAAAGGACACATACGACGCCTTGCACATGCAG GCCCTTCCACCCCGGGAATAGTCTAGAGGGCCCGTTTAAACCCGCTGATCAGCCTCGACTGTG CCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTG CCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCAT TCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAG GCATGCTGGGGATGCGGTGGGCTCTATGACTAGTGGCGAATTCCCGTGTACCAGCTGAGAGAC TCTAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAACAAATGTGTCACA AAGTAAGGATTCTGATGTGTATATCACAGACAAAACTGTGCTAGACATGAGGTCTATGGACTTCA AGAGCAACAGTGCTGTGGCCTGGAGCAACAAATCTGACTTTGCATGTGCAAACGCCTTCAACAA

		CAGCATTATTCCAGAAGACACCTTCTTCCCCAGCCCAGGTAAGGGCAGCTTTGGTGCCTTCGCA GGCTGTTTCCTTGCTTCAGGAATGGCCAGGTTCTGCCCAGAGCTCTGGTCAATGATGTCTAAAA CTCCTCTGATTGGTGGTCTCGGCCTTATCCATTGCCACCAAAACCCTCTTTTTACTAA
32	Matrice CD25 locus_IL15_2A_sIL15Ra pCLS30519	GTTTATTATTCCTGTTCCACAGCTATTGTCTGCCATATAAAAACTTAGGCCAGGCACAGTGGCTC ACACCTGTAATCCCAGCACTTTGGAAGGCCGAGGCAGGCAGATCACAAGGTCAGGAGTTCGAG ACCAGCCTGGCCAACATAGCAAAACCCCATCTCTACTAAAAATACAAAAATTAGCCAGGCATGG TGGCGTGTGCACTGGTTTAGAGTGAGGACCACATTTTTTTGGTGCCGTGTTACACATATGACCG TGACTTTGTTACACCACTACAGGAGGAAGAGTAGAAGAACAATCGGTTCTGGCGTGAAACAGAC TTTGAATTTTGACCTTCTCAAGTTGGCGGGAGACGTGGAGTCCAACCCAGGGCCCGGTACCGG GTCCGCCACCATGGACTGGACCTGGATTCTGTTCCTCGTGGCTGCTGCTACAAGAGTGCACAG CGGCATTCATGTCTTCATTTTGGGCTGTTTCAGTGCAGGGCTTCCTAAAACAGAAGCCAACTGG GTGAATGTAATAAGTGATTTGAAAAAAATTGAAGATCTTATTCAATCTATGCATATTGATGCTACT TTATATACGGAAAGTGATGTTCACCCCAGTTGCAAAGTAACAGCAATGAAGTGCTTTCTCTTGGA GTTACAAGTTATTTCACTTGAGTCCGGAGATGCAAGTATTCATGATACAGTAGAAAATCTGATCA TCCTAGCAAACAACAGTTTGTCTTCTAATGGGAATGTAACAGAATCTGGATGCAAAGAATGTGAG GAACTGGAGGAAAAAAATATTAAAGAATTTTTGCAGAGTTTTGTACATATTGTCCAAATGTTCATC AACACTTCTGGAAGCGGAGCTACTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGAGGAG AACCCTGGACCTGGGACCGGCTCTGCAACCATGGATTGGACGTGGATCCTGTTTCTCGTGGCA GCTGCCACAAGAGTTCACAGTATCACGTGCCCTCCCCCCATGTCCGTGGAACACGCAGACATC TGGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTACATTTGTAACTCTGGTTTCAAGCGTA AAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGAATGTCGCCCACTGG ACAACCCCCAGTCTCAAATGCATTAGAGACCCTGCCCTGGTTCACCAAAGGCCAGCGCCACCC TCCACAGTAACGACGGCAGGGGTGACCCCACAGCCAGAGAGCCTCTCCCCTTCTGGAAAAGAG CCCGCAGCTTCATCTCCCAGCTCAAACAACACAGCGGCCACAACAGCAGCTATTGTCCCGGGC TCCCAGCTGATGCCTTCAAAATCACCTTCCACAGGAACCACAGAGATAAGCAGTCATGAGTCCT CCCACGGCACCCCCTCTCAGACAACAGCCAAGAACTGGGAACTCACAGCATCCGCCTCCCACC AGCCGCCAGGTGTGTATCCACAGGGCCACAGCGACACCACTGAGGGCAGAGGCAGCCTGCTG ACCTGCGGCGACGTCGAGGAGAACCCCGGGCCCATGGGGGCAGGTGCCACCGGCCGCGCCA TGGACGGGCCGCGCCTGCTGCTGTTGCTGCTTCTGGGGGTGTCCCTTGGAGGTGCCAAGGAG GCATGCCCCACAGGCCTGTACACACACAGCGGTGAGTGCTGCAAAGCCTGCAACCTGGGCGA GGGTGTGGCCCAGCCTTGTGGAGCCAACCAGACCGTGTGTGAGCCCTGCCTGGACAGCGTGA CGTTCTCCGACGTGGTGAGCGCGACCGAGCCGTGCAAGCCGTGCACCGAGTGCGTGGGGCTC CAGAGCATGTCGGCGCCGTGCGTGGAGGCCGATGACGCCGTGTGCCGCTGCGCCTACGGCTA CTACCAGGATGAGACGACTGGGCGCTGCGAGGCGTGCCGCGTGTGCGAGGCGGGCTCGGGC CTCGTGTTCTCCTGCCAGGACAAGCAGAACACCGTGTGCGAGGAGTGCCCCGACGGCACGTAT TCCGACGAGGCCAACCACGTGGACCCGTGCCTGCCCTGCACCGTGTGCGAGGACACCGAGCG CCAGCTCCGCGAGTGCACACGCTGGGCCGACGCCGAGTGCGAGGAGATCCCTGGCCGTTGGA TTACACGGTCCACACCCCCAGAGGGCTCGGACAGCACAGCCCCCAGCACCCAGGAGCCTGAG GCACCTCCAGAACAAGACCTCATAGCCAGCACGGTGGCAGGTGTGGTGACCACAGTGATGGG CAGCTCCCAGCCCGTGGTGACCCGAGGCACCACCGACAACCTCATCCCTGTCTATTGCTCCAT CCTGGCTGCTGTGGTTGTGGGTCTTGTGGCCTACATAGCCTTCAAGAGGTGAAAAACCAAAAGA ACAAGAATTTCTTGGTAAGAAGCCGGGAACAGACAACAGAAGTCATGAAGCCCAAGTGAAATCA AAGGTGCTAAATGGTCGCCCAGGAGACATCCGTTGTGCTTGCCTGCGTTTTGGAAGCTCTGAA GTCACATCACAGGACACGGGGCAGTGGCAACCTTGTCTCTATGCCAGCTCAGTCCCATCAGAG AGCGAGCGCTACCCACTTCTAAATAGCAATTTCGCCGTTGAAGAGGAAGGGCAAAACCACTAGA ACTCTCCATCTTATTTTCATGTATATGTGTTCAT
33	Matrice PD1 locus_IL15_2A_sIL15Ra pCLS30513	GACTCCCCAGACAGGCCCTGGAACCCCCCCACCTTCTCCCCAGCCCTGCTCGTGGTGACCGAA GGGGACAACGCCACCTTCACCTGCAGCTTCTCCAACACATCGGAGAGCTTCGTGCTAAACTGG TACCGCATGAGCCCCAGCAACCAGACGGACAAGCTGGCCGCCTTCCCCGAGGACCGCAGCCA GCCCGGCCAGGACTGCCGCTTCCGTGTCACACAACTGCCCAACGGGCGTGACTTCCACATGAG CGTGGTCAGGGCCCGGCGCAATGACAGCGGCACCTACCTCTGTGGGGCCGGTTCTGGCGTGA AACAGACTTTGAATTTTGACCTTCTCAAGTTGGCGGGAGACGTGGAGTCCAACCCAGGGCCCG GTACCGGGTCCGCCACCATGGACTGGACCTGGATTCTGTTCCTCGTGGCTGCTGCTACAAGAG TGCACAGCGGCATTCATGTCTTCATTTTGGGCTGTTTCAGTGCAGGGCTTCCTAAAACAGAAGC CAACTGGGTGAATGTAATAAGTGATTTGAAAAAAATTGAAGATCTTATTCAATCTATGCATATTGA TGCTACTTTATATACGGAAAGTGATGTTCACCCCAGTTGCAAAGTAACAGCAATGAAGTGCTTTC TCTTGGAGTTACAAGTTATTTCACTTGAGTCCGGAGATGCAAGTATTCATGATACAGTAGAAAAT CTGATCATCCTAGCAAACAACAGTTTGTCTTCTAATGGGAATGTAACAGAATCTGGATGCAAAGA ATGTGAGGAACTGGAGGAAAAAAATATTAAAGAATTTTTGCAGAGTTTTGTACATATTGTCCAAAT GTTCATCAACACTTCTGGAAGCGGAGCTACTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGT GGAGGAGAACCCTGGACCTGGGACCGGCTCTGCAACCATGGATTGGACGTGGATCCTGTTTCT CGTGGCAGCTGCCACAAGAGTTCACAGTATCACGTGCCCTCCCCCCATGTCCGTGGAACACGC AGACATCTGGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTACATTTGTAACTCTGGTTTC AAGCGTAAAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGAATGTCGC CCACTGGACAACCCCCAGTCTCAAATGCATTAGAGACCCTGCCCTGGTTCACCAAAGGCCAGC GCCACCCTCCACAGTAACGACGGCAGGGGTGACCCCACAGCCAGAGAGCCTCTCCCCTTCTG GAAAAGAGCCCGCAGCTTCATCTCCCAGCTCAAACAACACAGCGGCCACAACAGCAGCTATTG TCCCGGGCTCCCAGCTGATGCCTTCAAAATCACCTTCCACAGGAACCACAGAGATAAGCAGTCA TGAGTCCTCCCACGGCACCCCCTCTCAGACAACAGCCAAGAACTGGGAACTCACAGCATCCGC CTCCCACCAGCCGCCAGGTGTGTATCCACAGGGCCACAGCGACACCACTGAGGGCAGAGGCA GCCTGCTGACCTGCGGCGACGTCGAGGAGAACCCCGGGCCCATGGGGGCAGGTGCCACCGG CCGCGCCATGGACGGGCCGCGCCTGCTGCTGTTGCTGCTTCTGGGGGTGTCCCTTGGAGGTG

		CCAAGGAGGCATGCCCCACAGGCCTGTACACACACAGCGGTGAGTGCTGCAAAGCCTGCAAC CTGGGCGAGGGTGTGGCCCAGCCTTGTGGAGCCAACCAGACCGTGTGTGAGCCCTGCCTGGA CAGCGTGACGTTCTCCGACGTGGTGAGCGCGACCGAGCCGTGCAAGCCGTGCACCGAGTGCG TGGGGCTCCAGAGCATGTCGGCGCCGTGCGTGGAGGCCGATGACGCCGTGTGCCGCTGCGC CTACGGCTACTACCAGGATGAGACGACTGGGCGCTGCGAGGCGTGCCGCGTGTGCGAGGCGG GCTCGGGCCTCGTGTTCTCCTGCCAGGACAAGCAGAACACCGTGTGCGAGGAGTGCCCCGAC GGCACGTATTCCGACGAGGCCAACCACGTGGACCCGTGCCTGCCCTGCACCGTGTGCGAGGA CACCGAGCGCCAGCTCCGCGAGTGCACACGCTGGGCCGACGCCGAGTGCGAGGAGATCCCT GGCCGTTGGATTACACGGTCCACACCCCCAGAGGGCTCGGACAGCACAGCCCCCAGCACCCA GGAGCCTGAGGCACCTCCAGAACAAGACCTCATAGCCAGCACGGTGGCAGGTGTGGTGACCA CAGTGATGGGCAGCTCCCAGCCCGTGGTGACCCGAGGCACCACCGACAACCTCATCCCTGTCT ATTGCTCCATCCTGGCTGCTGTGGTTGTGGGTCTTGTGGCCTACATAGCCTTCAAGAGGTGATC TAGAGGGCCCGTTTAAACCCGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTT GTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAAT AAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGG GCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCT CTATGACTAGTGGCGAATTCGGCGCAGATCAAAGAGAGCCTGCGGGCAGAGCTCAGGGTGACA GGTGCGGCCTCGGAGGCCCCGGGGCAGGGGTGAGCTGAGCCGGTCCTGGGGTGGGTGTCCC CTCCTGCACAGGATCAGGAGCTCCAGGGTCGTAGGGCAGGGACCCCCCAGCTCCAGTCCAGG GCTCTGTCCTGCACCTGGGGAATGGTGACCGGCATCTCTGTCCTCTAGCTCTGGAAGCACCCC AGCCCCTCTAGTCTGCCCTCACCCCTGACCCTGACCCTCCACCCTGACCCCGTCCTAACCCCT GACCTTTG
34	Matrice CD25 locus_IL12a_ 2A_IL12b pCLS30520	GTTTATTATTCCTGTTCCACAGCTATTGTCTGCCATATAAAAACTTAGGCCAGGCACAGTGGCTC ACACCTGTAATCCCAGCACTTTGGAAGGCCGAGGCAGGCAGATCACAAGGTCAGGAGTTCGAG ACCAGCCTGGCCAACATAGCAAAACCCCATCTCTACTAAAAATACAAAAATTAGCCAGGCATGG TGGCGTGTGCACTGGTTTAGAGTGAGGACCACATTTTTTTGGTGCCGTGTTACACATATGACCG TGACTTTGTTACACCACTACAGGAGGAAGAGTAGAAGAACAATCGGTTCTGGCGTGAAACAGAC TTTGAATTTTGACCTTCTCAAGTTGGCGGGAGACGTGGAGTCCAACCCAGGGCCCATGTGGCC CCCTGGGTCAGCCTCCCAGCCACCGCCCTCACCTGCCGCGGCCACAGGTCTGCATCCAGCGG CTCGCCCTGTGTCCCTGCAGTGCCGGCTCAGCATGTGTCCAGCGCGCAGCCTCCTCCTTGTGG CTACCCTGGTCCTCCTGGACCACCTCAGTTTGGCCAGAAACCTCCCCGTGGCCACTCCAGACC CAGGAATGTTCCCATGCCTTCACCACTCCCAAAACCTGCTGAGGGCCGTCAGCAACATGCTCCA GAAGGCCAGACAAACTCTAGAATTTTACCCTTGCACTTCTGAAGAGATTGATCATGAAGATATCA CAAAAGATAAAACCAGCACAGTGGAGGCCTGTTTACCATTGGAATTAACCAAGAATGAGAGTTG CCTAAATTCCAGAGAGACCTCTTTCATAACTAATGGGAGTTGCCTGGCCTCCAGAAAGACCTCT TTTATGATGGCCCTGTGCCTTAGTAGTATTTATGAAGACTTGAAGATGTACCAGGTGGAGTTCAA GACCATGAATGCAAAGCTTCTGATGGATCCTAAGAGGCAGATCTTTCTAGATCAAAACATGCTG GCAGTTATTGATGAGCTGATGCAGGCCCTGAATTTCAACAGTGAGACTGTGCCACAAAAATCCT CCCTTGAAGAACCGGATTTTTATAAAACTAAAATCAAGCTCTGCATACTTCTTCATGCTTTCAGAA TTCGGGCAGTGACTATTGATAGAGTGATGAGCTATCTGAATGCTTCCGGAAGCGGAGCTACTAA CTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGAGGAGAACCCTGGACCTATGTGTCACCAGCA GTTGGTCATCTCTTGGTTTTCCCTGGTTTTTCTGGCATCTCCCCTCGTGGCCATATGGGAACTGA AGAAAGATGTTTATGTCGTAGAATTGGATTGGTATCCGGATGCCCCTGGAGAAATGGTGGTCCT CACCTGTGACACCCCTGAAGAAGATGGTATCACCTGGACCTTGGACCAGAGCAGTGAGGTCTT AGGCTCTGGCAAAACCCTGACCATCCAAGTCAAAGAGTTTGGAGATGCTGGCCAGTACACCTGT CACAAAGGAGGCGAGGTTCTAAGCCATTCGCTCCTGCTGCTTCACAAAAAGGAAGATGGAATTT GGTCCACTGATATTTTAAAGGACCAGAAAGAACCCAAAAATAAGACCTTTCTAAGATGCGAGGC CAAGAATTATTCTGGACGTTTCACCTGCTGGTGGCTGACGACAATCAGTACTGATTTGACATTCA GTGTCAAAAGCAGCAGAGGCTCTTCTGACCCCCAAGGGGTGACGTGCGGAGCTGCTACACTCT CTGCAGAGAGAGTCAGAGGGGACAACAAGGAGTATGAGTACTCAGTGGAGTGCCAGGAGGAC AGTGCCTGCCCAGCTGCTGAGGAGAGTCTGCCCATTGAGGTCATGGTGGATGCCGTTCACAAG CTCAAGTATGAAAACTACACCAGCAGCTTCTTCATCAGGGACATCATCAAACCTGACCCACCCA AGAACTTGCAGCTGAAGCCATTAAAGAATTCTCGGCAGGTGGAGGTCAGCTGGGAGTACCCTG ACACCTGGAGTACTCCACATTCCTACTTCTCCCTGACATTCTGCGTTCAGGTCCAGGGCAAGAG CAAGAGAGAAAAGAAAGATAGAGTCTTCACGGACAAGACCTCAGCCACGGTCATCTGCCGCAA AAATGCCAGCATTAGCGTGCGGGCCCAGGACCGCTACTATAGCTCATCTTGGAGCGAATGGGC ATCTGTGCCCTGCAGTGAGGGCAGAGGCAGCCTGCTGACCTGCGGCGACGTCGAGGAGAACC CCGGGCCCATGGGGGCAGGTGCCACCGGCCGCGCCATGGACGGGCCGCGCCTGCTGCTGTT GCTGCTTCTGGGGGTGTCCCTTGGAGGTGCCAAGGAGGCATGCCCCACAGGCCTGTACACAC ACAGCGGTGAGTGCTGCAAAGCCTGCAACCTGGGCGAGGGTGTGGCCCAGCCTTGTGGAGCC AACCAGACCGTGTGTGAGCCCTGCCTGGACAGCGTGACGTTCTCCGACGTGGTGAGCGCGAC CGAGCCGTGCAAGCCGTGCACCGAGTGCGTGGGGCTCCAGAGCATGTCGGCGCCGTGCGTG GAGGCCGATGACGCCGTGTGCCGCTGCGCCTACGGCTACTACCAGGATGAGACGACTGGGCG CTGCGAGGCGTGCCGCGTGTGCGAGGCGGGCTCGGGCCTCGTGTTCTCCTGCCAGGACAAGC AGAACACCGTGTGCGAGGAGTGCCCCGACGGCACGTATTCCGACGAGGCCAACCACGTGGAC CCGTGCCTGCCCTGCACCGTGTGCGAGGACACCGAGCGCCAGCTCCGCGAGTGCACACGCTG GGCCGACGCCGAGTGCGAGGAGATCCCTGGCCGTTGGATTACACGGTCCACACCCCCAGAGG GCTCGGACAGCACAGCCCCCAGCACCCAGGAGCCTGAGGCACCTCCAGAACAAGACCTCATA GCCAGCACGGTGGCAGGTGTGGTGACCACAGTGATGGGCAGCTCCCAGCCCGTGGTGACCCG AGGCACCACCGACAACCTCATCCCTGTCTATTGCTCCATCCTGGCTGCTGTGGTTGTGGGTCTT GTGGCCTACATAGCCTTCAAGAGGTGAAAAACCAAAAGAACAAGAATTTCTTGGTAAGAAGCCG GGAACAGACAACAGAAGTCATGAAGCCCAAGTGAAATCAAAGGTGCTAAATGGTCGCCCAGGA GACATCCGTTGTGCTTGCCTGCGTTTTGGAAGCTCTGAAGTCACATCACAGGACACGGGGCAG TGGCAACCTTGTCTCTATGCCAGCTCAGTCCCATCAGAGAGCGAGCGCTACCCACTTCTAAATA

		GCAATTTCGCCGTTGAAGAGGAAGGGCAAAACCACTAGAACTCTCCATCTTATTTTCATGTATAT GTGTTCAT
35	Matrice PD1 locus_IL12a_ 2A_IL12b pCLS30511	GACTCCCCAGACAGGCCCTGGAACCCCCCCACCTTCTCCCCAGCCCTGCTCGTGGTGACCGAA GGGGACAACGCCACCTTCACCTGCAGCTTCTCCAACACATCGGAGAGCTTCGTGCTAAACTGG TACCGCATGAGCCCCAGCAACCAGACGGACAAGCTGGCCGCCTTCCCCGAGGACCGCAGCCA GCCCGGCCAGGACTGCCGCTTCCGTGTCACACAACTGCCCAACGGGCGTGACTTCCACATGAG CGTGGTCAGGGCCCGGCGCAATGACAGCGGCACCTACCTCTGTGGGGCCGGTTCTGGCGTGA AACAGACTTTGAATTTTGACCTTCTCAAGTTGGCGGGAGACGTGGAGTCCAACCCAGGGCCCAT GTGGCCCCCTGGGTCAGCCTCCCAGCCACCGCCCTCACCTGCCGCGGCCACAGGTCTGCATC CAGCGGCTCGCCCTGTGTCCCTGCAGTGCCGGCTCAGCATGTGTCCAGCGCGCAGCCTCCTC CTTGTGGCTACCCTGGTCCTCCTGGACCACCTCAGTTTGGCCAGAAACCTCCCCGTGGCCACT CCAGACCCAGGAATGTTCCCATGCCTTCACCACTCCCAAAACCTGCTGAGGGCCGTCAGCAAC ATGCTCCAGAAGGCCAGACAAACTCTAGAATTTTACCCTTGCACTTCTGAAGAGATTGATCATGA AGATATCACAAAAGATAAAACCAGCACAGTGGAGGCCTGTTTACCATTGGAATTAACCAAGAAT GAGAGTTGCCTAAATTCCAGAGAGACCTCTTTCATAACTAATGGGAGTTGCCTGGCCTCCAGAA AGACCTCTTTTATGATGGCCCTGTGCCTTAGTAGTATTTATGAAGACTTGAAGATGTACCAGGTG GAGTTCAAGACCATGAATGCAAAGCTTCTGATGGATCCTAAGAGGCAGATCTTTCTAGATCAAAA CATGCTGGCAGTTATTGATGAGCTGATGCAGGCCCTGAATTTCAACAGTGAGACTGTGCCACAA AAATCCTCCCTTGAAGAACCGGATTTTTATAAAACTAAAATCAAGCTCTGCATACTTCTTCATGCT TTCAGAATTCGGGCAGTGACTATTGATAGAGTGATGAGCTATCTGAATGCTTCCGGAAGCGGAG CTACTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGAGGAGAACCCTGGACCTATGTGTC ACCAGCAGTTGGTCATCTCTTGGTTTTCCCTGGTTTTTCTGGCATCTCCCCTCGTGGCCATATGG GAACTGAAGAAAGATGTTTATGTCGTAGAATTGGATTGGTATCCGGATGCCCCTGGAGAAATGG TGGTCCTCACCTGTGACACCCCTGAAGAAGATGGTATCACCTGGACCTTGGACCAGAGCAGTG AGGTCTTAGGCTCTGGCAAAACCCTGACCATCCAAGTCAAAGAGTTTGGAGATGCTGGCCAGTA CACCTGTCACAAAGGAGGCGAGGTTCTAAGCCATTCGCTCCTGCTGCTTCACAAAAAGGAAGAT GGAATTTGGTCCACTGATATTTTAAAGGACCAGAAAGAACCCAAAAATAAGACCTTTCTAAGATG CGAGGCCAAGAATTATTCTGGACGTTTCACCTGCTGGTGGCTGACGACAATCAGTACTGATTTG ACATTCAGTGTCAAAAGCAGCAGAGGCTCTTCTGACCCCCAAGGGGTGACGTGCGGAGCTGCT ACACTCTCTGCAGAGAGAGTCAGAGGGGACAACAAGGAGTATGAGTACTCAGTGGAGTGCCAG GAGGACAGTGCCTGCCCAGCTGCTGAGGAGAGTCTGCCCATTGAGGTCATGGTGGATGCCGTT CACAAGCTCAAGTATGAAAACTACACCAGCAGCTTCTTCATCAGGGACATCATCAAACCTGACC CACCCAAGAACTTGCAGCTGAAGCCATTAAAGAATTCTCGGCAGGTGGAGGTCAGCTGGGAGT ACCCTGACACCTGGAGTACTCCACATTCCTACTTCTCCCTGACATTCTGCGTTCAGGTCCAGGG CAAGAGCAAGAGAGAAAAGAAAGATAGAGTCTTCACGGACAAGACCTCAGCCACGGTCATCTG CCGCAAAAATGCCAGCATTAGCGTGCGGGCCCAGGACCGCTACTATAGCTCATCTTGGAGCGA ATGGGCATCTGTGCCCTGCAGTGAGGGCAGAGGCAGCCTGCTGACCTGCGGCGACGTCGAGG AGAACCCCGGGCCCATGGGGGCAGGTGCCACCGGCCGCGCCATGGACGGGCCGCGCCTGCT GCTGTTGCTGCTTCTGGGGGTGTCCCTTGGAGGTGCCAAGGAGGCATGCCCCACAGGCCTGTA CACACACAGCGGTGAGTGCTGCAAAGCCTGCAACCTGGGCGAGGGTGTGGCCCAGCCTTGTG GAGCCAACCAGACCGTGTGTGAGCCCTGCCTGGACAGCGTGACGTTCTCCGACGTGGTGAGC GCGACCGAGCCGTGCAAGCCGTGCACCGAGTGCGTGGGGCTCCAGAGCATGTCGGCGCCGT GCGTGGAGGCCGATGACGCCGTGTGCCGCTGCGCCTACGGCTACTACCAGGATGAGACGACT GGGCGCTGCGAGGCGTGCCGCGTGTGCGAGGCGGGCTCGGGCCTCGTGTTCTCCTGCCAGG ACAAGCAGAACACCGTGTGCGAGGAGTGCCCCGACGGCACGTATTCCGACGAGGCCAACCAC GTGGACCCGTGCCTGCCCTGCACCGTGTGCGAGGACACCGAGCGCCAGCTCCGCGAGTGCAC ACGCTGGGCCGACGCCGAGTGCGAGGAGATCCCTGGCCGTTGGATTACACGGTCCACACCCC CAGAGGGCTCGGACAGCACAGCCCCCAGCACCCAGGAGCCTGAGGCACCTCCAGAACAAGAC CTCATAGCCAGCACGGTGGCAGGTGTGGTGACCACAGTGATGGGCAGCTCCCAGCCCGTGGT GACCCGAGGCACCACCGACAACCTCATCCCTGTCTATTGCTCCATCCTGGCTGCTGTGGTTGT GGGTCTTGTGGCCTACATAGCCTTCAAGAGGTGATCTAGAGGGCCCGTTTAAACCCGCTGATCA GCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGA CCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCT GAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGG AAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCTATGACTAGTGGCGAATTCGGCGCAG ATCAAAGAGAGCCTGCGGGCAGAGCTCAGGGTGACAGGTGCGGCCTCGGAGGCCCCGGGGC AGGGGTGAGCTGAGCCGGTCCTGGGGTGGGTGTCCCCTCCTGCACAGGATCAGGAGCTCCAG GGTCGTAGGGCAGGGACCCCCCAGCTCCAGTCCAGGGCTCTGTCCTGCACCTGGGGAATGGT GACCGGCATCTCTGTCCTCTAGCTCTGGAAGCACCCCAGCCCCTCTAGTCTGCCCTCACCCCT GACCCTGACCCTCCACCCTGACCCCGTCCTAACCCCTGACCTTTG
36	Inserted matrice TRAC locus_CubiCA R CD22 (60 nucleotides upstream and downstream)	ATGAGATCATGTCCTAACCCTGATCCTCTTGTCCCACAGATATCCAGAACCCTGACCCTGTTGCT GGGCCTTTTTCCCATGCCTGCCTTTACTCTGCCAGAGTTATATTGCTGGGGTTTTGAAGAAGATC CTATTAAATAAAAGAATAAGCAGTATTATTAAGTAGCCCTGCATTTCAGGTTTCCTTGAGTGGCA GGCCAGGCCTGGCCGTGAACGTTCACTGAAATCATGGCCTCTTGGCCAAGATTGATAGCTTGT GCCTGTCCCTGAGTCCCAGTCCATCACGAGCAGCTGGTTTCTAAGATGCTATTTCCCGTATAAA GCATGAGACCGTGACTTGCCAGCCCCACAGAGCCCCGCCCTTGTCCATCACTGGCATCTGGAC TCCAGCCTGGGTTGGGGCAAAGAGGGAAATGAGATCATGTCCTAACCCTGATCCTCTTGTCCCA CAGATATCCAGTACCCCTACGACGTGCCCGACTACGCCTCCGGTGAGGGCAGAGGAAGTCTTC TAACATGCGGTGACGTGGAGGAGAATCCGGGCCCCGGATCCGCTCTGCCCGTCACCGCTCTG CTGCTGCCACTGGCACTGCTGCTGCACGCTGCTAGGCCCGGAGGGGGAGGCAGCTGCCCCTA CAGCAACCCCAGCCTGTGCAGCGGAGGCGGCGGCAGCGGCGGAGGGGGTAGCCAGGTGCAG CTGCAGCAGAGCGGCCCTGGCCTGGTGAAGCCAAGCCAGACACTGTCCCTGACCTGCGCCAT

		CAGCGGCGATTCCGTGAGCTCCAACTCCGCCGCCTGGAATTGGATCAGGCAGTCCCCTTCTCG GGGCCTGGAGTGGCTGGGAAGGACATACTATCGGTCTAAGTGGTACAACGATTATGCCGTGTC TGTGAAGAGCAGAATCACAATCAACCCTGACACCTCCAAGAATCAGTTCTCTCTGCAGCTGAAT AGCGTGACACCAGAGGACACCGCCGTGTACTATTGCGCCAGGGAGGTGACCGGCGACCTGGA GGATGCCTTTGACATCTGGGGCCAGGGCACAATGGTGACCGTGAGCTCCGGAGGCGGCGGAT CTGGCGGAGGAGGAAGTGGGGGCGGCGGGAGTGATATCCAGATGACACAGTCCCCATCCTCT CTGAGCGCCTCCGTGGGCGACAGAGTGACAATCACCTGTAGGGCCTCCCAGACCATCTGGTCT TACCTGAACTGGTATCAGCAGAGGCCCGGCAAGGCCCCTAATCTGCTGATCTACGCAGCAAGC TCCCTGCAGAGCGGAGTGCCATCCAGATTCTCTGGCAGGGGCTCCGGCACAGACTTCACCCTG ACCATCTCTAGCCTGCAGGCCGAGGACTTCGCCACCTACTATTGCCAGCAGTCTTATAGCATCC CCCAGACATTTGGCCAGGGCACCAAGCTGGAGATCAAGTCGGATCCCGGAAGCGGAGGGGGA GGCAGCTGCCCCTACAGCAACCCCAGCCTGTGCAGCGGAGGCGGCGGCAGCGAGCTGCCCA CCCAGGGCACCTTCTCCAACGTGTCCACCAACGTGAGCCCAGCCAAGCCCACCACCACCGCCT GTCCTTATTCCAATCCTTCCCTGTGTGCTCCCACCACAACCCCCGCTCCAAGGCCCCCTACCCC CGCACCAACTATTGCCTCCCAGCCACTCTCACTGCGGCCTGAGGCCTGTCGGCCCGCTGCTGG AGGCGCAGTGCATACAAGGGGCCTCGATTTCGCCTGCGATATTTACATCTGGGCACCCCTCGC CGGCACCTGCGGGGTGCTTCTCCTCTCCCTGGTGATTACCCTGTATTGCAGACGGGGCCGGAA GAAGCTCCTCTACATTTTTAAGCAGCCTTTCATGCGGCCAGTGCAGACAACCCAAGAGGAGGAT GGGTGTTCCTGCAGATTCCCTGAGGAAGAGGAAGGCGGGTGCGAGCTGAGAGTGAAGTTCTC CAGGAGCGCAGATGCCCCCGCCTATCAACAGGGCCAGAACCAGCTCTACAACGAGCTTAACCT CGGGAGGCGCGAAGAATACGACGTGTTGGATAAGAGAAGGGGGCGGGACCCCGAGATGGGA GGAAAGCCCCGGAGGAAGAACCCTCAGGAGGGCCTGTACAACGAGCTGCAGAAGGATAAGAT GGCCGAGGCCTACTCAGAGATCGGGATGAAGGGGGAGCGGCGCCGCGGGAAGGGGCACGAT GGGCTCTACCAGGGGCTGAGCACAGCCACAAAGGACACATACGACGCCTTGCACATGCAGGC CCTTCCACCCCGGGAATAGTCTAGAGGGCCCGTTTAAACCCGCTGATCAGCCTCGACTGTGCC TTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCC ACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTC TATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGC ATGCTGGGGATGCGGTGGGCTCTATGACTAGTGGCGAATTCCCGTGTACCAGCTGAGAGACTC TAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAACAAATGTGTCACAAA GTAAGGATTCTGATGTGTATATCACAGACAAAACTGTGCTAGACATGAGGTCTATGGACTTCAAG AGCAACAGTGCTGTGGCCTGGAGCAACAAATCTGACTTTGCATGTGCAAACGCCTTCAACAACA GCATTATTCCAGAAGACACCTTCTTCCCCAGCCCAGGTAAGGGCAGCTTTGGTGCCTTCGCAG GCTGTTTCCTTGCTTCAGGAATGGCCAGGTTCTGCCCAGAGCTCTGGTCAATGATGTCTAAAAC TCCTCTGATTGGTGGTCTCGGCCTTATCCATTGCCACCAAAACCCTCTTTTTACTAAGAAACAGT GAGCCTTGTTCTGGCAGTCCAGAGAATGACACGGGAAAAAAGCAGATGAAGA
37	Inserted matrice CD25 locus_IL15_2A_sIL15Ra (60 nucleotides upstream and downstream)	AGTGCTGGCTAGAAACCAAGTGCTTTACTGCATGCACATCATTTAGCACAGTTAGTTGCTGTTTA TTATTCCTGTTCCACAGCTATTGTCTGCCATATAAAAACTTAGGCCAGGCACAGTGGCTCACACC TGTAATCCCAGCACTTTGGAAGGCCGAGGCAGGCAGATCACAAGGTCAGGAGTTCGAGACCAG CCTGGCCAACATAGCAAAACCCCATCTCTACTAAAAATACAAAAATTAGCCAGGCATGGTGGCG TGTGCACTGGTTTAGAGTGAGGACCACATTTTTTTGGTGCCGTGTTACACATATGACCGTGACTT TGTTACACCACTACAGGAGGAAGAGTAGAAGAACAATCGGTTCTGGCGTGAAACAGACTTTGAA TTTTGACCTTCTCAAGTTGGCGGGAGACGTGGAGTCCAACCCAGGGCCCGGTACCGGGTCCGC CACCATGGACTGGACCTGGATTCTGTTCCTCGTGGCTGCTGCTACAAGAGTGCACAGCGGCAT TCATGTCTTCATTTTGGGCTGTTTCAGTGCAGGGCTTCCTAAAACAGAAGCCAACTGGGTGAAT GTAATAAGTGATTTGAAAAAAATTGAAGATCTTATTCAATCTATGCATATTGATGCTACTTTATATA CGGAAAGTGATGTTCACCCCAGTTGCAAAGTAACAGCAATGAAGTGCTTTCTCTTGGAGTTACA AGTTATTTCACTTGAGTCCGGAGATGCAAGTATTCATGATACAGTAGAAAATCTGATCATCCTAG CAAACAACAGTTTGTCTTCTAATGGGAATGTAACAGAATCTGGATGCAAAGAATGTGAGGAACT GGAGGAAAAAAATATTAAAGAATTTTTGCAGAGTTTTGTACATATTGTCCAAATGTTCATCAACAC TTCTGGAAGCGGAGCTACTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGAGGAGAACCC TGGACCTGGGACCGGCTCTGCAACCATGGATTGGACGTGGATCCTGTTTCTCGTGGCAGCTGC CACAAGAGTTCACAGTATCACGTGCCCTCCCCCCATGTCCGTGGAACACGCAGACATCTGGGT CAAGAGCTACAGCTTGTACTCCAGGGAGCGGTACATTTGTAACTCTGGTTTCAAGCGTAAAGCC GGCACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGAATGTCGCCCACTGGACAAC CCCCAGTCTCAAATGCATTAGAGACCCTGCCCTGGTTCACCAAAGGCCAGCGCCACCCTCCAC AGTAACGACGGCAGGGGTGACCCCACAGCCAGAGAGCCTCTCCCCTTCTGGAAAAGAGCCCG CAGCTTCATCTCCCAGCTCAAACAACACAGCGGCCACAACAGCAGCTATTGTCCCGGGCTCCC AGCTGATGCCTTCAAAATCACCTTCCACAGGAACCACAGAGATAAGCAGTCATGAGTCCTCCCA CGGCACCCCCTCTCAGACAACAGCCAAGAACTGGGAACTCACAGCATCCGCCTCCCACCAGCC GCCAGGTGTGTATCCACAGGGCCACAGCGACACCACTGAGGGCAGAGGCAGCCTGCTGACCT GCGGCGACGTCGAGGAGAACCCCGGGCCCATGGGGGCAGGTGCCACCGGCCGCGCCATGGA CGGGCCGCGCCTGCTGCTGTTGCTGCTTCTGGGGGTGTCCCTTGGAGGTGCCAAGGAGGCAT GCCCCACAGGCCTGTACACACACAGCGGTGAGTGCTGCAAAGCCTGCAACCTGGGCGAGGGT GTGGCCCAGCCTTGTGGAGCCAACCAGACCGTGTGTGAGCCCTGCCTGGACAGCGTGACGTT CTCCGACGTGGTGAGCGCGACCGAGCCGTGCAAGCCGTGCACCGAGTGCGTGGGGCTCCAGA GCATGTCGGCGCCGTGCGTGGAGGCCGATGACGCCGTGTGCCGCTGCGCCTACGGCTACTAC CAGGATGAGACGACTGGGCGCTGCGAGGCGTGCCGCGTGTGCGAGGCGGGCTCGGGCCTCG TGTTCTCCTGCCAGGACAAGCAGAACACCGTGTGCGAGGAGTGCCCCGACGGCACGTATTCCG ACGAGGCCAACCACGTGGACCCGTGCCTGCCCTGCACCGTGTGCGAGGACACCGAGCGCCAG CTCCGCGAGTGCACACGCTGGGCCGACGCCGAGTGCGAGGAGATCCCTGGCCGTTGGATTAC ACGGTCCACACCCCCAGAGGGCTCGGACAGCACAGCCCCCAGCACCCAGGAGCCTGAGGCAC CTCCAGAACAAGACCTCATAGCCAGCACGGTGGCAGGTGTGGTGACCACAGTGATGGGCAGCT CCCAGCCCGTGGTGACCCGAGGCACCACCGACAACCTCATCCCTGTCTATTGCTCCATCCTGG

		CTGCTGTGGTTGTGGGTCTTGTGGCCTACATAGCCTTCAAGAGGTGAAAAACCAAAAGAACAAG AATTTCTTGGTAAGAAGCCGGGAACAGACAACAGAAGTCATGAAGCCCAAGTGAAATCAAAGGT GCTAAATGGTCGCCCAGGAGACATCCGTTGTGCTTGCCTGCGTTTTGGAAGCTCTGAAGTCACA TCACAGGACACGGGGCAGTGGCAACCTTGTCTCTATGCCAGCTCAGTCCCATCAGAGAGCGAG CGCTACCCACTTCTAAATAGCAATTTCGCCGTTGAAGAGGAAGGGCAAAACCACTAGAACTCTC CATCTTATTTTCATGTATATGTGTTCATTAAAGCATGAATGGTATGGAACTCTCTCCACCCTATAT GTAGTATAAAGAAAAGTAGGTT
38	Inserted matrice PD1 locus_IL15_2A_sIL15Ra (60 nucleotides upstream and downstream)	GGTGGCCGGGGAGGCTTTGTGGGGCCACCCAGCCCCTTCCTCACCTCTCTCCATCTCTCAGAC TCCCCAGACAGGCCCTGGAACCCCCCCACCTTCTCCCCAGCCCTGCTCGTGGTGACCGAAGG GGACAACGCCACCTTCACCTGCAGCTTCTCCAACACATCGGAGAGCTTCGTGCTAAACTGGTAC CGCATGAGCCCCAGCAACCAGACGGACAAGCTGGCCGCCTTCCCCGAGGACCGCAGCCAGCC CGGCCAGGACTGCCGCTTCCGTGTCACACAACTGCCCAACGGGCGTGACTTCCACATGAGCGT GGTCAGGGCCCGGCGCAATGACAGCGGCACCTACCTCTGTGGGGCCGGTTCTGGCGTGAAAC AGACTTTGAATTTTGACCTTCTCAAGTTGGCGGGAGACGTGGAGTCCAACCCAGGGCCCGGTA CCGGGTCCGCCACCATGGACTGGACCTGGATTCTGTTCCTCGTGGCTGCTGCTACAAGAGTGC ACAGCGGCATTCATGTCTTCATTTTGGGCTGTTTCAGTGCAGGGCTTCCTAAAACAGAAGCCAA CTGGGTGAATGTAATAAGTGATTTGAAAAAAATTGAAGATCTTATTCAATCTATGCATATTGATGC TACTTTATATACGGAAAGTGATGTTCACCCCAGTTGCAAAGTAACAGCAATGAAGTGCTTTCTCT TGGAGTTACAAGTTATTTCACTTGAGTCCGGAGATGCAAGTATTCATGATACAGTAGAAAATCTG ATCATCCTAGCAAACAACAGTTTGTCTTCTAATGGGAATGTAACAGAATCTGGATGCAAAGAATG TGAGGAACTGGAGGAAAAAAATATTAAAGAATTTTTGCAGAGTTTTGTACATATTGTCCAAATGTT CATCAACACTTCTGGAAGCGGAGCTACTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGA GGAGAACCCTGGACCTGGGACCGGCTCTGCAACCATGGATTGGACGTGGATCCTGTTTCTCGT GGCAGCTGCCACAAGAGTTCACAGTATCACGTGCCCTCCCCCCATGTCCGTGGAACACGCAGA CATCTGGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTACATTTGTAACTCTGGTTTCAAG CGTAAAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGAATGTCGCCCA CTGGACAACCCCCAGTCTCAAATGCATTAGAGACCCTGCCCTGGTTCACCAAAGGCCAGCGCC ACCCTCCACAGTAACGACGGCAGGGGTGACCCCACAGCCAGAGAGCCTCTCCCCTTCTGGAAA AGAGCCCGCAGCTTCATCTCCCAGCTCAAACAACACAGCGGCCACAACAGCAGCTATTGTCCC GGGCTCCCAGCTGATGCCTTCAAAATCACCTTCCACAGGAACCACAGAGATAAGCAGTCATGAG TCCTCCCACGGCACCCCCTCTCAGACAACAGCCAAGAACTGGGAACTCACAGCATCCGCCTCC CACCAGCCGCCAGGTGTGTATCCACAGGGCCACAGCGACACCACTGAGGGCAGAGGCAGCCT GCTGACCTGCGGCGACGTCGAGGAGAACCCCGGGCCCATGGGGGCAGGTGCCACCGGCCGC GCCATGGACGGGCCGCGCCTGCTGCTGTTGCTGCTTCTGGGGGTGTCCCTTGGAGGTGCCAA GGAGGCATGCCCCACAGGCCTGTACACACACAGCGGTGAGTGCTGCAAAGCCTGCAACCTGG GCGAGGGTGTGGCCCAGCCTTGTGGAGCCAACCAGACCGTGTGTGAGCCCTGCCTGGACAGC GTGACGTTCTCCGACGTGGTGAGCGCGACCGAGCCGTGCAAGCCGTGCACCGAGTGCGTGGG GCTCCAGAGCATGTCGGCGCCGTGCGTGGAGGCCGATGACGCCGTGTGCCGCTGCGCCTACG GCTACTACCAGGATGAGACGACTGGGCGCTGCGAGGCGTGCCGCGTGTGCGAGGCGGGCTC GGGCCTCGTGTTCTCCTGCCAGGACAAGCAGAACACCGTGTGCGAGGAGTGCCCCGACGGCA CGTATTCCGACGAGGCCAACCACGTGGACCCGTGCCTGCCCTGCACCGTGTGCGAGGACACC GAGCGCCAGCTCCGCGAGTGCACACGCTGGGCCGACGCCGAGTGCGAGGAGATCCCTGGCC GTTGGATTACACGGTCCACACCCCCAGAGGGCTCGGACAGCACAGCCCCCAGCACCCAGGAG CCTGAGGCACCTCCAGAACAAGACCTCATAGCCAGCACGGTGGCAGGTGTGGTGACCACAGTG ATGGGCAGCTCCCAGCCCGTGGTGACCCGAGGCACCACCGACAACCTCATCCCTGTCTATTGC TCCATCCTGGCTGCTGTGGTTGTGGGTCTTGTGGCCTACATAGCCTTCAAGAGGTGATCTAGAG GGCCCGTTTAAACCCGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTG CCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAAT GAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAG GACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCTAT GACTAGTGGCGAATTCGGCGCAGATCAAAGAGAGCCTGCGGGCAGAGCTCAGGGTGACAGGT GCGGCCTCGGAGGCCCCGGGGCAGGGGTGAGCTGAGCCGGTCCTGGGGTGGGTGTCCCCTC CTGCACAGGATCAGGAGCTCCAGGGTCGTAGGGCAGGGACCCCCCAGCTCCAGTCCAGGGCT CTGTCCTGCACCTGGGGAATGGTGACCGGCATCTCTGTCCTCTAGCTCTGGAAGCACCCCAGC CCCTCTAGTCTGCCCTCACCCCTGACCCTGACCCTCCACCCTGACCCCGTCCTAACCCCTGAC CTTTGTGCCCTTCCAGAGAGAAGGGCAGAAGTGCCCACAGCCCACCCCAGCCCCTCACCCAGG CC
39	Inserted matrice CD25 locus_IL12a_2A_IL12b (60 nucleotides upstream and downstream)	AGTGCTGGCTAGAAACCAAGTGCTTTACTGCATGCACATCATTTAGCACAGTTAGTTGCTGTTTA TTATTCCTGTTCCACAGCTATTGTCTGCCATATAAAAACTTAGGCCAGGCACAGTGGCTCACACC TGTAATCCCAGCACTTTGGAAGGCCGAGGCAGGCAGATCACAAGGTCAGGAGTTCGAGACCAG CCTGGCCAACATAGCAAAACCCCATCTCTACTAAAAATACAAAAATTAGCCAGGCATGGTGGCG TGTGCACTGGTTTAGAGTGAGGACCACATTTTTTTGGTGCCGTGTTACACATATGACCGTGACTT TGTTACACCACTACAGGAGGAAGAGTAGAAGAACAATCGGTTCTGGCGTGAAACAGACTTTGAA TTTTGACCTTCTCAAGTTGGCGGGAGACGTGGAGTCCAACCCAGGGCCCATGTGGCCCCCTGG GTCAGCCTCCCAGCCACCGCCCTCACCTGCCGCGGCCACAGGTCTGCATCCAGCGGCTCGCC CTGTGTCCCTGCAGTGCCGGCTCAGCATGTGTCCAGCGCGCAGCCTCCTCCTTGTGGCTACCC TGGTCCTCCTGGACCACCTCAGTTTGGCCAGAAACCTCCCCGTGGCCACTCCAGACCCAGGAA TGTTCCCATGCCTTCACCACTCCCAAAACCTGCTGAGGGCCGTCAGCAACATGCTCCAGAAGG CCAGACAAACTCTAGAATTTTACCCTTGCACTTCTGAAGAGATTGATCATGAAGATATCACAAAA GATAAAACCAGCACAGTGGAGGCCTGTTTACCATTGGAATTAACCAAGAATGAGAGTTGCCTAA ATTCCAGAGAGACCTCTTTCATAACTAATGGGAGTTGCCTGGCCTCCAGAAAGACCTCTTTTATG ATGGCCCTGTGCCTTAGTAGTATTTATGAAGACTTGAAGATGTACCAGGTGGAGTTCAAGACCA

		TGAATGCAAAGCTTCTGATGGATCCTAAGAGGCAGATCTTTCTAGATCAAAACATGCTGGCAGTT ATTGATGAGCTGATGCAGGCCCTGAATTTCAACAGTGAGACTGTGCCACAAAAATCCTCCCTTG AAGAACCGGATTTTTATAAAACTAAAATCAAGCTCTGCATACTTCTTCATGCTTTCAGAATTCGGG CAGTGACTATTGATAGAGTGATGAGCTATCTGAATGCTTCCGGAAGCGGAGCTACTAACTTCAG CCTGCTGAAGCAGGCTGGAGACGTGGAGGAGAACCCTGGACCTATGTGTCACCAGCAGTTGGT CATCTCTTGGTTTTCCCTGGTTTTTCTGGCATCTCCCCTCGTGGCCATATGGGAACTGAAGAAA GATGTTTATGTCGTAGAATTGGATTGGTATCCGGATGCCCCTGGAGAAATGGTGGTCCTCACCT GTGACACCCCTGAAGAAGATGGTATCACCTGGACCTTGGACCAGAGCAGTGAGGTCTTAGGCT CTGGCAAAACCCTGACCATCCAAGTCAAAGAGTTTGGAGATGCTGGCCAGTACACCTGTCACAA AGGAGGCGAGGTTCTAAGCCATTCGCTCCTGCTGCTTCACAAAAAGGAAGATGGAATTTGGTCC ACTGATATTTTAAAGGACCAGAAAGAACCCAAAAATAAGACCTTTCTAAGATGCGAGGCCAAGAA TTATTCTGGACGTTTCACCTGCTGGTGGCTGACGACAATCAGTACTGATTTGACATTCAGTGTCA AAAGCAGCAGAGGCTCTTCTGACCCCCAAGGGGTGACGTGCGGAGCTGCTACACTCTCTGCAG AGAGAGTCAGAGGGGACAACAAGGAGTATGAGTACTCAGTGGAGTGCCAGGAGGACAGTGCC TGCCCAGCTGCTGAGGAGAGTCTGCCCATTGAGGTCATGGTGGATGCCGTTCACAAGCTCAAG TATGAAAACTACACCAGCAGCTTCTTCATCAGGGACATCATCAAACCTGACCCACCCAAGAACTT GCAGCTGAAGCCATTAAAGAATTCTCGGCAGGTGGAGGTCAGCTGGGAGTACCCTGACACCTG GAGTACTCCACATTCCTACTTCTCCCTGACATTCTGCGTTCAGGTCCAGGGCAAGAGCAAGAGA GAAAAGAAAGATAGAGTCTTCACGGACAAGACCTCAGCCACGGTCATCTGCCGCAAAAATGCCA GCATTAGCGTGCGGGCCCAGGACCGCTACTATAGCTCATCTTGGAGCGAATGGGCATCTGTGC CCTGCAGTGAGGGCAGAGGCAGCCTGCTGACCTGCGGCGACGTCGAGGAGAACCCCGGGCC CATGGGGGCAGGTGCCACCGGCCGCGCCATGGACGGGCCGCGCCTGCTGCTGTTGCTGCTTC TGGGGGTGTCCCTTGGAGGTGCCAAGGAGGCATGCCCCACAGGCCTGTACACACACAGCGGT GAGTGCTGCAAAGCCTGCAACCTGGGCGAGGGTGTGGCCCAGCCTTGTGGAGCCAACCAGAC CGTGTGTGAGCCCTGCCTGGACAGCGTGACGTTCTCCGACGTGGTGAGCGCGACCGAGCCGT GCAAGCCGTGCACCGAGTGCGTGGGGCTCCAGAGCATGTCGGCGCCGTGCGTGGAGGCCGA TGACGCCGTGTGCCGCTGCGCCTACGGCTACTACCAGGATGAGACGACTGGGCGCTGCGAGG CGTGCCGCGTGTGCGAGGCGGGCTCGGGCCTCGTGTTCTCCTGCCAGGACAAGCAGAACACC GTGTGCGAGGAGTGCCCCGACGGCACGTATTCCGACGAGGCCAACCACGTGGACCCGTGCCT GCCCTGCACCGTGTGCGAGGACACCGAGCGCCAGCTCCGCGAGTGCACACGCTGGGCCGAC GCCGAGTGCGAGGAGATCCCTGGCCGTTGGATTACACGGTCCACACCCCCAGAGGGCTCGGA CAGCACAGCCCCCAGCACCCAGGAGCCTGAGGCACCTCCAGAACAAGACCTCATAGCCAGCA CGGTGGCAGGTGTGGTGACCACAGTGATGGGCAGCTCCCAGCCCGTGGTGACCCGAGGCACC ACCGACAACCTCATCCCTGTCTATTGCTCCATCCTGGCTGCTGTGGTTGTGGGTCTTGTGGCCT ACATAGCCTTCAAGAGGTGAAAAACCAAAAGAACAAGAATTTCTTGGTAAGAAGCCGGGAACAG ACAACAGAAGTCATGAAGCCCAAGTGAAATCAAAGGTGCTAAATGGTCGCCCAGGAGACATCC GTTGTGCTTGCCTGCGTTTTGGAAGCTCTGAAGTCACATCACAGGACACGGGGCAGTGGCAAC CTTGTCTCTATGCCAGCTCAGTCCCATCAGAGAGCGAGCGCTACCCACTTCTAAATAGCAATTT CGCCGTTGAAGAGGAAGGGCAAAACCACTAGAACTCTCCATCTTATTTTCATGTATATGTGTTCA TGAATGGTATGGAACTCTCTCCACCCTATATGTAGTATAAAGAAAAGTAGGTT
40	Inserted matrice PD1 locus_IL12a_ 2A_IL12b (60 nucleotides upstream and downstream)	GGTGGCCGGGGAGGCTTTGTGGGGCCACCCAGCCCCTTCCTCACCTCTCTCCATCTCTCAGAC TCCCCAGACAGGCCCTGGAACCCCCCCACCTTCTCCCCAGCCCTGCTCGTGGTGACCGAAGG GGACAACGCCACCTTCACCTGCAGCTTCTCCAACACATCGGAGAGCTTCGTGCTAAACTGGTAC CGCATGAGCCCCAGCAACCAGACGGACAAGCTGGCCGCCTTCCCCGAGGACCGCAGCCAGCC CGGCCAGGACTGCCGCTTCCGTGTCACACAACTGCCCAACGGGCGTGACTTCCACATGAGCGT GGTCAGGGCCCGGCGCAATGACAGCGGCACCTACCTCTGTGGGGCCGGTTCTGGCGTGAAAC AGACTTTGAATTTTGACCTTCTCAAGTTGGCGGGAGACGTGGAGTCCAACCCAGGGCCCATGT GGCCCCCTGGGTCAGCCTCCCAGCCACCGCCCTCACCTGCCGCGGCCACAGGTCTGCATCCA GCGGCTCGCCCTGTGTCCCTGCAGTGCCGGCTCAGCATGTGTCCAGCGCGCAGCCTCCTCCTT GTGGCTACCCTGGTCCTCCTGGACCACCTCAGTTTGGCCAGAAACCTCCCCGTGGCCACTCCA GACCCAGGAATGTTCCCATGCCTTCACCACTCCCAAAACCTGCTGAGGGCCGTCAGCAACATG CTCCAGAAGGCCAGACAAACTCTAGAATTTTACCCTTGCACTTCTGAAGAGATTGATCATGAAGA TATCACAAAAGATAAAACCAGCACAGTGGAGGCCTGTTTACCATTGGAATTAACCAAGAATGAG AGTTGCCTAAATTCCAGAGAGACCTCTTTCATAACTAATGGGAGTTGCCTGGCCTCCAGAAAGA CCTCTTTTATGATGGCCCTGTGCCTTAGTAGTATTTATGAAGACTTGAAGATGTACCAGGTGGAG TTCAAGACCATGAATGCAAAGCTTCTGATGGATCCTAAGAGGCAGATCTTTCTAGATCAAAACAT GCTGGCAGTTATTGATGAGCTGATGCAGGCCCTGAATTTCAACAGTGAGACTGTGCCACAAAAA TCCTCCCTTGAAGAACCGGATTTTTATAAAACTAAAATCAAGCTCTGCATACTTCTTCATGCTTTC AGAATTCGGGCAGTGACTATTGATAGAGTGATGAGCTATCTGAATGCTTCCGGAAGCGGAGCTA CTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGAGGAGAACCCTGGACCTATGTGTCACC AGCAGTTGGTCATCTCTTGGTTTTCCCTGGTTTTTCTGGCATCTCCCCTCGTGGCCATATGGGAA CTGAAGAAAGATGTTTATGTCGTAGAATTGGATTGGTATCCGGATGCCCCTGGAGAAATGGTGG TCCTCACCTGTGACACCCCTGAAGAAGATGGTATCACCTGGACCTTGGACCAGAGCAGTGAGG TCTTAGGCTCTGGCAAAACCCTGACCATCCAAGTCAAAGAGTTTGGAGATGCTGGCCAGTACAC CTGTCACAAAGGAGGCGAGGTTCTAAGCCATTCGCTCCTGCTGCTTCACAAAAAGGAAGATGGA ATTTGGTCCACTGATATTTTAAAGGACCAGAAAGAACCCAAAAATAAGACCTTTCTAAGATGCGA GGCCAAGAATTATTCTGGACGTTTCACCTGCTGGTGGCTGACGACAATCAGTACTGATTTGACA TTCAGTGTCAAAAGCAGCAGAGGCTCTTCTGACCCCCAAGGGGTGACGTGCGGAGCTGCTACA CTCTCTGCAGAGAGAGTCAGAGGGGACAACAAGGAGTATGAGTACTCAGTGGAGTGCCAGGAG GACAGTGCCTGCCCAGCTGCTGAGGAGAGTCTGCCCATTGAGGTCATGGTGGATGCCGTTCAC AAGCTCAAGTATGAAAACTACACCAGCAGCTTCTTCATCAGGGACATCATCAAACCTGACCCAC CCAAGAACTTGCAGCTGAAGCCATTAAAGAATTCTCGGCAGGTGGAGGTCAGCTGGGAGTACC CTGACACCTGGAGTACTCCACATTCCTACTTCTCCCTGACATTCTGCGTTCAGGTCCAGGGCAA GAGCAAGAGAGAAAAGAAAGATAGAGTCTTCACGGACAAGACCTCAGCCACGGTCATCTGCCG

		CAAAAATGCCAGCATTAGCGTGCGGGCCCAGGACCGCTACTATAGCTCATCTTGGAGCGAATG GGCATCTGTGCCCTGCAGTGAGGGCAGAGGCAGCCTGCTGACCTGCGGCGACGTCGAGGAGA ACCCCGGGCCCATGGGGGCAGGTGCCACCGGCCGCGCCATGGACGGGCCGCGCCTGCTGCT GTTGCTGCTTCTGGGGGTGTCCCTTGGAGGTGCCAAGGAGGCATGCCCCACAGGCCTGTACAC ACACAGCGGTGAGTGCTGCAAAGCCTGCAACCTGGGCGAGGGTGTGGCCCAGCCTTGTGGAG CCAACCAGACCGTGTGTGAGCCCTGCCTGGACAGCGTGACGTTCTCCGACGTGGTGAGCGCG ACCGAGCCGTGCAAGCCGTGCACCGAGTGCGTGGGGCTCCAGAGCATGTCGGCGCCGTGCGT GGAGGCCGATGACGCCGTGTGCCGCTGCGCCTACGGCTACTACCAGGATGAGACGACTGGGC GCTGCGAGGCGTGCCGCGTGTGCGAGGCGGGCTCGGGCCTCGTGTTCTCCTGCCAGGACAAG CAGAACACCGTGTGCGAGGAGTGCCCCGACGGCACGTATTCCGACGAGGCCAACCACGTGGA CCCGTGCCTGCCCTGCACCGTGTGCGAGGACACCGAGCGCCAGCTCCGCGAGTGCACACGCT GGGCCGACGCCGAGTGCGAGGAGATCCCTGGCCGTTGGATTACACGGTCCACACCCCCAGAG GGCTCGGACAGCACAGCCCCCAGCACCCAGGAGCCTGAGGCACCTCCAGAACAAGACCTCAT AGCCAGCACGGTGGCAGGTGTGGTGACCACAGTGATGGGCAGCTCCCAGCCCGTGGTGACCC GAGGCACCACCGACAACCTCATCCCTGTCTATTGCTCCATCCTGGCTGCTGTGGTTGTGGGTCT TGTGGCCTACATAGCCTTCAAGAGGTGATCTAGAGGGCCCGTTTAAACCCGCTGATCAGCCTC GACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTG GAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTA GGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGAC AATAGCAGGCATGCTGGGGATGCGGTGGGCTCTATGACTAGTGGCGAATTCGGCGCAGATCAA AGAGAGCCTGCGGGCAGAGCTCAGGGTGACAGGTGCGGCCTCGGAGGCCCCGGGGCAGGGG TGAGCTGAGCCGGTCCTGGGGTGGGTGTCCCCTCCTGCACAGGATCAGGAGCTCCAGGGTCG TAGGGCAGGGACCCCCCAGCTCCAGTCCAGGGCTCTGTCCTGCACCTGGGGAATGGTGACCG GCATCTCTGTCCTCTAGCTCTGGAAGCACCCCAGCCCCTCTAGTCTGCCCTCACCCCTGACCCT GACCCTCCACCCTGACCCCGTCCTAACCCCTGACCTTTGTGCCCTTCCAGAGAGAAGGGCAGA AGTGCCCACAGCCCACCCCAGCCCCTCACCCAGGCC
41	upstream TRAC locus polynucleotide sequence	ATGAGATCATGTCCTAACCCTGATCCTCTTGTCCCACAGATATCCAGAACCCTGACC CTG
42	downstream TRAC locus polynucleotide sequence	GAAACAGTGAGCCTTGTTCTGGCAGTCCAGAGAATGACACGGGAAAAAAGCAGATG AAGA
43	upstream CD25 locus polynucleotide sequence	AGTGCTGGCTAGAAACCAAGTGCTTTACTGCATGCACATCATTTAGCACAGTTAGTT GCT
44	downstream CD25 locus polynucleotide sequence	GAATGGTATGGAACTCTCTCCACCCTATATGTAGTATAAAGAAAAGTAGGTT
45	upstream PD1 locus polynucleotide sequence	GGTGGCCGGGGAGGCTTTGTGGGGCCACCCAGCCCCTTCCTCACCTCTCTCCATCT CTCA
46	downstream PD1 locus polynucleotide sequence	TGCCCTTCCAGAGAGAAGGGCAGAAGTGCCCACAGCCCACCCCAGCCCCTCACCC AGGCC
47	IL-12a polynucleotide	ATGTGGCCCCCTGGGTCAGCCTCCCAGCCACCGCCCTCACCTGCCGCGGCCACAG GTCTGCATCCAGCGGCTCGCCCTGTGTCCCTGCAGTGCCGGCTCAGCATGTGTCCA GCGCGCAGCCTCCTCCTTGTGGCTACCCTGGTCCTCCTGGACCACCTCAGTTTGGC CAGAAACCTCCCCGTGGCCACTCCAGACCCAGGAATGTTCCCATGCCTTCACCACT CCCAAAACCTGCTGAGGGCCGTCAGCAACATGCTCCAGAAGGCCAGACAAACTCTA GAATTTTACCCTTGCACTTCTGAAGAGATTGATCATGAAGATATCACAAAAGATAAAA CCAGCACAGTGGAGGCCTGTTTACCATTGGAATTAACCAAGAATGAGAGTTGCCTAA ATTCCAGAGAGACCTCTTTCATAACTAATGGGAGTTGCCTGGCCTCCAGAAAGACCT CTTTTATGATGGCCCTGTGCCTTAGTAGTATTTATGAAGACTTGAAGATGTACCAGGT GGAGTTCAAGACCATGAATGCAAAGCTTCTGATGGATCCTAAGAGGCAGATCTTTCT AGATCAAAACATGCTGGCAGTTATTGATGAGCTGATGCAGGCCCTGAATTTCAACAG

		TGAGACTGTGCCACAAAAATCCTCCCTTGAAGAACCGGATTTTTATAAAACTAAAATC AAGCTCTGCATACTTCTTCATGCTTTCAGAATTCGGGCAGTGACTATTGATAGAGTGA TGAGCTATCTGAATGCTTCC
48	IL12b polynucleotide	ATGTGTCACCAGCAGTTGGTCATCTCTTGGTTTTCCCTGGTTTTTCTGGCATCTCCCC TCGTGGCCATATGGGAACTGAAGAAAGATGTTTATGTCGTAGAATTGGATTGGTATC CGGATGCCCCTGGAGAAATGGTGGTCCTCACCTGTGACACCCCTGAAGAAGATGGT ATCACCTGGACCTTGGACCAGAGCAGTGAGGTCTTAGGCTCTGGCAAAACCCTGAC CATCCAAGTCAAAGAGTTTGGAGATGCTGGCCAGTACACCTGTCACAAAGGAGGCG AGGTTCTAAGCCATTCGCTCCTGCTGCTTCACAAAAAGGAAGATGGAATTTGGTCCA CTGATATTTTAAAGGACCAGAAAGAACCCAAAAATAAGACCTTTCTAAGATGCGAGG CCAAGAATTATTCTGGACGTTTCACCTGCTGGTGGCTGACGACAATCAGTACTGATT TGACATTCAGTGTCAAAAGCAGCAGAGGCTCTTCTGACCCCCAAGGGGTGACGTGC GGAGCTGCTACACTCTCTGCAGAGAGAGTCAGAGGGGACAACAAGGAGTATGAGTA CTCAGTGGAGTGCCAGGAGGACAGTGCCTGCCCAGCTGCTGAGGAGAGTCTGCCC ATTGAGGTCATGGTGGATGCCGTTCACAAGCTCAAGTATGAAAACTACACCAGCAGC TTCTTCATCAGGGACATCATCAAACCTGACCCACCCAAGAACTTGCAGCTGAAGCCA TTAAAGAATTCTCGGCAGGTGGAGGTCAGCTGGGAGTACCCTGACACCTGGAGTAC TCCACATTCCTACTTCTCCCTGACATTCTGCGTTCAGGTCCAGGGCAAGAGCAAGAG AGAAAAGAAAGATAGAGTCTTCACGGACAAGACCTCAGCCACGGTCATCTGCCGCA AAAATGCCAGCATTAGCGTGCGGGCCCAGGACCGCTACTATAGCTCATCTTGGAGC GAATGGGCATCTGTGCCCTGCAGT
49	IL15 polynucleotide	GGCATTCATGTCTTCATTTTGGGCTGTTTCAGTGCAGGGCTTCCTAAAACAGAAGCC AACTGGGTGAATGTAATAAGTGATTTGAAAAAAATTGAAGATCTTATTCAATCTATGC ATATTGATGCTACTTTATATACGGAAAGTGATGTTCACCCCAGTTGCAAAGTAACAGC AATGAAGTGCTTTCTCTTGGAGTTACAAGTTATTTCACTTGAGTCCGGAGATGCAAGT ATTCATGATACAGTAGAAAATCTGATCATCCTAGCAAACAACAGTTTGTCTTCTAATG GGAATGTAACAGAATCTGGATGCAAAGAATGTGAGGAACTGGAGGAAAAAAATATTA AAGAATTTTTGCAGAGTTTTGTACATATTGTCCAAATGTTCATCAACACTTCT
50	sIL15ra polynucleotide	ATCACGTGCCCTCCCCCCATGTCCGTGGAACACGCAGACATCTGGGTCAAGAGCTA CAGCTTGTACTCCAGGGAGCGGTACATTTGTAACTCTGGTTTCAAGCGTAAAGCCGG CACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGAATGTCGCCCACTGGA CAACCCCCAGTCTCAAATGCATTAGAGACCCTGCCCTGGTTCACCAAAGGCCAGCG CCACCCTCCACAGTAACGACGGCAGGGGTGACCCCACAGCCAGAGAGCCTCTCCC CTTCTGGAAAAGAGCCCGCAGCTTCATCTCCCAGCTCAAACAACACAGCGGCCACA ACAGCAGCTATTGTCCCGGGCTCCCAGCTGATGCCTTCAAAATCACCTTCCACAGGA ACCACAGAGATAAGCAGTCATGAGTCCTCCCACGGCACCCCCTCTCAGACAACAGC CAAGAACTGGGAACTCACAGCATCCGCCTCCCACCAGCCGCCAGGTGTGTATCCAC AGGGCCACAGCGACACCACT
51	soluble GP130 polynucleotide	ATGCTGACACTGCAGACTTGGCTGGTGCAGGCACTGTTTATTTTTCTGACTACTGAA TCAACTGGCGAACTGCTGGACCCTTGTGGCTACATCAGCCCTGAGTCCCCAGTGGT GCAGCTGCACAGCAACTTCACCGCCGTGTGCGTGCTGAAGGAGAAGTGTATGGACT ACTTTCACGTGAACGCCAATTATATCGTGTGGAAAACCAACCACTTCACAATCCCCAA GGAGCAGTACACCATCATCAATAGGACAGCCAGCTCCGTGACCTTTACAGACATCG CCTCCCTGAACATCCAGCTGACCTGCAATATCCTGACATTCGGCCAGCTGGAGCAG AACGTGTATGGCATCACCATCATCTCTGGCCTGCCCCCTGAGAAGCCTAAGAACCTG AGCTGCATCGTGAATGAGGGCAAGAAGATGCGGTGTGAGTGGGACGGCGGCAGAG AGACACACCTGGAGACAAACTTCACCCTGAAGTCCGAGTGGGCCACACACAAGTTT GCCGACTGCAAGGCCAAGCGCGATACCCCAACATCCTGTACCGTGGATTACTCTAC AGTGTATTTTGTGAACATCGAAGTGTGGGTGGAGGCCGAGAATGCCCTGGGCAAGG TGACCTCCGACCACATCAACTTCGATCCCGTGTACAAGGTGAAGCCTAACCCACCCC ACAATCTGAGCGTGATCAATTCCGAGGAGCTGTCTAGCATCCTGAAGCTGACCTGGA CAAACCCATCTATCAAGAGCGTGATCATCCTGAAGTACAATATCCAGTATCGGACCA AGGACGCCTCCACATGGAGCCAGATCCCTCCAGAGGATACCGCCAGCACAAGATCC TCTTTCACCGTGCAGGACCTGAAGCCCTTCACAGAGTACGTGTTTCGGATCAGATGT ATGAAGGAGGACGGCAAGGGCTACTGGAGCGATTGGTCCGAGGAGGCCAGCGGCA TCACCTATGAGGACAGGCCTTCTAAGGCCCCCAGCTTCTGGTACAAGATCGATCCAT CCCACACCCAGGGCTATCGCACAGTGCAGCTGGTGTGGAAAACCCTGCCCCCTTTC GAGGCCAACGGCAAGATCCTGGACTACGAGGTGACCCTGACACGGTGGAAGTCCC ACCTGCAGAACTATACCGTGAATGCCACCAAGCTGACAGTGAACCTGACAAATGATC GGTACCTGGCCACCCTGACAGTGAGAAACCTGGTGGGCAAGTCTGACGCCGCCGT GCTGACCATCCCTGCCTGCGATTTCCAGGCCACACACCCAGTGATGGACCTGAAGG CCTTTCCCAAGGATAATATGCTGTGGGTGGAGTGGACCACACCTAGAGAGTCCGTG

		AAGAAGTACATCCTGGAGTGGTGCGTGCTGTCTGACAAGGCCCCATGTATCACCGA CTGGCAGCAGGAGGATGGCACCGTGCACAGGACATATCTGCGCGGCAACCTGGCC GAGTCTAAGTGTTACCTGATCACCGTGACACCCGTGTATGCAGACGGACCAGGCTC TCCTGAGAGCATCAAGGCCTACCTGAAGCAGGCACCACCAAGCAAGGGACCAACCG TGCGGACAAAGAAGGTCGGCAAGAATGAGGCCGTGCTGGAGTGGGACCAGCTGCC TGTGGATGTGCAGAACGGCTTCATCAGGAATTACACCATCTTTTATCGCACAATCATC GGCAACGAGACAGCCGTGAATGTGGACAGCTCCCACACCGAGTATACACTGTCTAG CCTGACCTCCGATACACTGTACATGGTGAGGATGGCCGCCTATACAGACGAGGGCG GCAAGGATGGCCCCGAGTTT
52	IgE signal sequence	GGTACCGGGTCCGCCACCATGGACTGGACCTGGATTCTGTTCCTCGTGGCTGCTGC TACAAGAGTGCACAGC
53	F2A	GGTTCTGGCGTGAAACAGACTTTGAATTTTGACCTTCTCAAGTTGGCGGGAGACGTG GAGTCCAACCCAGGGCCC
54	P2A	GGAAGCGGAGCTACTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGAGGAGA ACCCTGGACCT
55	T2A	GAGGGCAGAGGCAGCCTGCTGACCTGCGGCGACGTCGAGGAGAACCCCGGGCCC
56	LNGFR	ATGGGGGCAGGTGCCACCGGCCGCGCCATGGACGGGCCGCGCCTGCTGCTGTTG CTGCTTCTGGGGGTGTCCCTTGGAGGTGCCAAGGAGGCATGCCCCACAGGCCTGT ACACACACAGCGGTGAGTGCTGCAAAGCCTGCAACCTGGGCGAGGGTGTGGCCCA GCCTTGTGGAGCCAACCAGACCGTGTGTGAGCCCTGCCTGGACAGCGTGACGTTCT CCGACGTGGTGAGCGCGACCGAGCCGTGCAAGCCGTGCACCGAGTGCGTGGGGC TCCAGAGCATGTCGGCGCCGTGCGTGGAGGCCGATGACGCCGTGTGCCGCTGCGC CTACGGCTACTACCAGGATGAGACGACTGGGCGCTGCGAGGCGTGCCGCGTGTGC GAGGCGGGCTCGGGCCTCGTGTTCTCCTGCCAGGACAAGCAGAACACCGTGTGCG AGGAGTGCCCCGACGGCACGTATTCCGACGAGGCCAACCACGTGGACCCGTGCCT GCCCTGCACCGTGTGCGAGGACACCGAGCGCCAGCTCCGCGAGTGCACACGCTGG GCCGACGCCGAGTGCGAGGAGATCCCTGGCCGTTGGATTACACGGTCCACACCCC CAGAGGGCTCGGACAGCACAGCCCCCAGCACCCAGGAGCCTGAGGCACCTCCAGA ACAAGACCTCATAGCCAGCACGGTGGCAGGTGTGGTGACCACAGTGATGGGCAGCT CCCAGCCCGTGGTGACCCGAGGCACCACCGACAACCTCATCCCTGTCTATTGCTCC ATCCTGGCTGCTGTGGTTGTGGGTCTTGTGGCCTACATAGCCTTCAAGAGGTGA
SEQ ID NO#	**Sequence Name**	**Polypeptide sequence**
57	IL-12a polypeptide	MWPPGSASQPPPSPAAATGLHPAARPVSLQCRLSMCPARSLLLVATLVLLDHLSLARNL PVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKDKTSTVEA CLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAK LLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRA VTIDRVMSYLNAS
58	IL12b polypeptide	MCHQQLVISWFSLVFLASPLVAIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAE RVRGDNKEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPP KNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSA TVICRKNASISVRAQDRYYSSSWSEWASVPCS
59	IL15 polypeptide	GIHVFILGCFSAGLPKTEANWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKC FLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV HIVQMFINTS
60	sIL15ra polypeptide	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPS LKCIRDPALVHQRPAPPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGS QLMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASHQPPGVYPQGHSDTT
61	soluble gp130	MLTLQTWLVQALFIFLTTESTGELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHV NANYIVWKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGITIISGL

		PPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSC TVDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYKVKPNPPHNLSVINSEELSSILKLT WTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKE DGKGYWSDWSEEASGITYEDRPSKAPSFWYKIDPSHTQGYRTVQLVWKTLPPFEANGK ILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTIPACDFQA THPVMDLKAFPKDNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQEDGTVHRTY LRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVRTKKVGKNEAVLEWD QLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSDTLYMVRMAAYTDEGG KDGPEF
62	soluble gp130 fused to a Fc	MLTLQTWLVQALFIFLTTESTGELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHV NANYIVWKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGITIISGL PPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSC TVDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYKVKPNPPHNLSVINSEELSSILKLT WTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKE DGKGYWSDWSEEASGITYEDRPSKAPSFWYKIDPSHTQGYRTVQLVWKTLPPFEANGK ILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTIPACDFQA THPVMDLKAFPKDNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQEDGTVHRTY LRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVRTKKVGKNEAVLEWD QLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSDTLYMVRMAAYTDEGG KDGPEFRSCDKTHTCPPCPAPEAEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
SEQ ID NO#	**Sequence Name**	**Polynucleotide sequence**
63	Matrice TRAC locus_CubiCAR CD22 pCLS30056 full sequence	GTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACA TTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAA AAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGC ATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAA GATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGAT CCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTG CTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCG CATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTT ACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAAC ACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTT TTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGA ATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACA ACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAA TAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCG GCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGTTCTCGCGGTAT CATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGA CGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCC TCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGA TTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCAT GACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAA GATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACA AAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTT TTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTTCTTCTAGTG TAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCT CTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGG GTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGG GGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCT ACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGG TATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGG GAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTC GATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCG GCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGGTCTTTCCTGCGT TATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTC GCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAGAGCG CCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGCTGGC ACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAGT

		TAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGT GTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATGACCATGATTACG CCAAGCGCGTCAATTAACCCTCACTAAAGGGAACAAAAGCTGTTAATTAATTGCTGG GCCTTTTTCCCATGCCTGCCTTTACTCTGCCAGAGTTATATTGCTGGGGTTTTGAAGA AGATCCTATTAAATAAAAGAATAAGCAGTATTATTAAGTAGCCCTGCATTTCAGGTTT CCTTGAGTGGCAGGCCAGGCCTGGCCGTGAACGTTCACTGAAATCATGGCCTCTTG GCCAAGATTGATAGCTTGTGCCTGTCCCTGAGTCCCAGTCCATCACGAGCAGCTGG TTTCTAAGATGCTATTTCCCGTATAAAGCATGAGACCGTGACTTGCCAGCCCCACAG AGCCCCGCCCTTGTCCATCACTGGCATCTGGACTCCAGCCTGGGTTGGGGCAAAGA GGGAAATGAGATCATGTCCTAACCCTGATCCTCTTGTCCCACAGATATCCAGTACCC CTACGACGTGCCCGACTACGCCTCCGGTGAGGGCAGAGGAAGTCTTCTAACATGCG GTGACGTGGAGGAGAATCCGGGCCCCGGATCCGCTCTGCCCGTCACCGCTCTGCT GCTGCCACTGGCACTGCTGCTGCACGCTGCTAGGCCCGGAGGGGGAGGCAGCTGC CCCTACAGCAACCCCAGCCTGTGCAGCGGAGGCGGCGGCAGCGGCGGAGGGGGT AGCCAGGTGCAGCTGCAGCAGAGCGGCCCTGGCCTGGTGAAGCCAAGCCAGACAC TGTCCCTGACCTGCGCCATCAGCGGCGATTCCGTGAGCTCCAACTCCGCCGCCTGG AATTGGATCAGGCAGTCCCCTTCTCGGGGCCTGGAGTGGCTGGGAAGGACATACTA TCGGTCTAAGTGGTACAACGATTATGCCGTGTCTGTGAAGAGCAGAATCACAATCAA CCCTGACACCTCCAAGAATCAGTTCTCTCTGCAGCTGAATAGCGTGACACCAGAGGA CACCGCCGTGTACTATTGCGCCAGGGAGGTGACCGGCGACCTGGAGGATGCCTTT GACATCTGGGGCCAGGGCACAATGGTGACCGTGAGCTCCGGAGGCGGCGGATCTG GCGGAGGAGGAAGTGGGGGCGGCGGGAGTGATATCCAGATGACACAGTCCCCATC CTCTCTGAGCGCCTCCGTGGGCGACAGAGTGACAATCACCTGTAGGGCCTCCCAGA CCATCTGGTCTTACCTGAACTGGTATCAGCAGAGGCCCGGCAAGGCCCCTAATCTG CTGATCTACGCAGCAAGCTCCCTGCAGAGCGGAGTGCCATCCAGATTCTCTGGCAG GGGCTCCGGCACAGACTTCACCCTGACCATCTCTAGCCTGCAGGCCGAGGACTTCG CCACCTACTATTGCCAGCAGTCTTATAGCATCCCCCAGACATTTGGCCAGGGCACCA AGCTGGAGATCAAGTCGGATCCCGGAAGCGGAGGGGGAGGCAGCTGCCCCTACAG CAACCCCAGCCTGTGCAGCGGAGGCGGCGGCAGCGAGCTGCCCACCCAGGGCAC CTTCTCCAACGTGTCCACCAACGTGAGCCCAGCCAAGCCCACCACCACCGCCTGTC CTTATTCCAATCCTTCCCTGTGTGCTCCCACCACAACCCCCGCTCCAAGGCCCCCTA CCCCCGCACCAACTATTGCCTCCCAGCCACTCTCACTGCGGCCTGAGGCCTGTCGG CCCGCTGCTGGAGGCGCAGTGCATACAAGGGGCCTCGATTTCGCCTGCGATATTTA CATCTGGGCACCCCTCGCCGGCACCTGCGGGGTGCTTCTCCTCTCCCTGGTGATTA CCCTGTATTGCAGACGGGGCCGGAAGAAGCTCCTCTACATTTTTAAGCAGCCTTTCA TGCGGCCAGTGCAGACAACCCAAGAGGAGGATGGGTGTTCCTGCAGATTCCCTGAG GAAGAGGAAGGCGGGTGCGAGCTGAGAGTGAAGTTCTCCAGGAGCGCAGATGCCC CCGCCTATCAACAGGGCCAGAACCAGCTCTACAACGAGCTTAACCTCGGGAGGCGC GAAGAATACGACGTGTTGGATAAGAGAAGGGGGCGGGACCCCGAGATGGGAGGAA AGCCCCGGAGGAAGAACCCTCAGGAGGGCCTGTACAACGAGCTGCAGAAGGATAA GATGGCCGAGGCCTACTCAGAGATCGGGATGAAGGGGGAGCGGCGCCGCGGGAA GGGGCACGATGGGCTCTACCAGGGGCTGAGCACAGCCACAAAGGACACATACGAC GCCTTGCACATGCAGGCCCTTCCACCCCGGGAATAGTCTAGAGGGCCCGTTTAAAC CCGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTC CCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAA TGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGT GGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGAT GCGGTGGGCTCTATGACTAGTGGCGAATTCCCGTGTACCAGCTGAGAGACTCTAAA TCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAACAAATGTGTCAC AAAGTAAGGATTCTGATGTGTATATCACAGACAAAACTGTGCTAGACATGAGGTCTAT GGACTTCAAGAGCAACAGTGCTGTGGCCTGGAGCAACAAATCTGACTTTGCATGTG CAAACGCCTTCAACAACAGCATTATTCCAGAAGACACCTTCTTCCCCAGCCCAGGTA AGGGCAGCTTTGGTGCCTTCGCAGGCTGTTTCCTTGCTTCAGGAATGGCCAGGTTC TGCCCAGAGCTCTGGTCAATGATGTCTAAAACTCCTCTGATTGGTGGTCTCGGCCTT ATCCATTGCCACCAAAACCCTCTTTTTACTAAGCGATCGCTCCGGTGCCCGTCAGTG GGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAAT TGAACGGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGT ACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTC GCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAACACAGCTGAAGCTTCG AGGGGCTCGCATCTCTCCTTCACGCGCCCGCCGCCCTACCTGAGGCCGCCATCCA CGCCGGTTGAGTCGCGTTCTGCCGCCTCCCGCCTGTGGTGCCTCCTGAACTGCGTC CGCCGTCTAGGTAAGTTTAAAGCTCAGGTCGAGACCGGGCCTTTGTCCGGCGCTCC CTTGGAGCCTACCTAGACTCAGCCGGCTCTCCACGCTTTGCCTGACCCTGCTTGCT CAACTCTACGTCTTTGTTTCGTTTTCTGTTCTGCGCCGTTACAGATCCAAGCTGTGAC CGGCGCCTACCTGAGATCACCGGCGCCACCATGGCTTCTTACCCTGGACACCAGCA TGCTTCTGCCTTTGACCAGGCTGCCAGATCCAGGGGCCACTCCAACAGGAGAACTG CCCTAAGACCCAGAAGACAGCAGGAAGCCACTGAGGTGAGGCCTGAGCAGAAGAT

		GCCAACCCTGCTGAGGGTGTACATTGATGGACCTCATGGCATGGGCAAGACCACCA CCACTCAACTGCTGGTGGCACTGGGCTCCAGGGATGACATTGTGTATGTGCCTGAG CCAATGACCTACTGGAGAGTGCTAGGAGCCTCTGAGACCATTGCCAACATCTACACC ACCCAGCACAGGCTGGACCAGGGAGAAATCTCTGCTGGAGATGCTGCTGTGGTGAT GACCTCTGCCCAGATCACAATGGGAATGCCCTATGCTGTGACTGATGCTGTTCTGGC TCCTCACATTGGAGGAGAGGCTGGCTCTTCTCATGCCCCTCCACCTGCCCTGACCC TGATCTTTGACAGACACCCCATTGCAGCCCTGCTGTGCTACCCAGCAGCAAGGTAC CTCATGGGCTCCATGACCCCACAGGCTGTGCTGGCTTTTGTGGCCCTGATCCCTCC AACCCTCCCTGGCACCAACATTGTTCTGGGAGCACTGCCTGAAGACAGACACATTGA CAGGCTGGCAAAGAGGCAGAGACCTGGAGAGAGACTGGACCTGGCCATGCTGGCT GCAATCAGAAGGGTGTATGGACTGCTGGCAAACACTGTGAGATACCTCCAGTGTGG AGGCTCTTGGAGAGAGGACTGGGGACAGCTCTCTGGAACAGCAGTGCCCCCTCAA GGAGCTGAGCCCCAGTCCAATGCTGGTCCAAGACCCCACATTGGGGACACCCTGTT CACCCTGTTCAGAGCCCCTGAGCTGCTGGCTCCCAATGGAGACCTGTACAATGTGT TTGCCTGGGCTCTGGATGTTCTAGCCAAGAGGCTGAGGTCCATGCATGTGTTCATCC TGGACTATGACCAGTCCCCTGCTGGATGCAGAGATGCTCTGCTGCAACTAACCTCTG GCATGGTGCAGACCCATGTGACCACCCCTGGCAGCATCCCCACCATCTGTGACCTA GCCAGAACCTTTGCCAGGGAGATGGGAGAGGCCAACTAAGGCGCGCCACTCGAGC GCTAGCTGGCCAGACATGATAAGATACATTGATGAGTTTGGACAAACCACAACTAGA ATGCAGTGAAAAAAATGCTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAAC CATTATAAGCTGCAATAAACAAGTTAACAACAACAATTGCATTCATTTTATGTTTCAGG TTCAGGGGGAGGTGTGGGAGGTTTTTTAAAGCAAGTAAAACCTCTACAAATGTGGTA TGGAAGGCGCGCCCAATTCGCCCTATAGTGAGTCGTATTACGTCGCGCTCACTGGC CGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCCAACTTAATCGCCT TGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGAAA CGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGGGAGCGCCCTGTAGCGG CGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCC AGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCC GGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCT TTACGGCACCTCGACCCCAAAAAACTTGATTAGGGTGATGGTTGGCCTGTAGTGGG CCATAGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATA GTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGTCTATTCTTTTGA TTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAA AAATTTAACGCGAATTTTAACAAAATATTAACGCTTACAATTTAG
64	Matrice CD25 locus_IL15_2A_sIL15Ra pCLS30519 full sequence	GTTTATTATTCCTGTTCCACAGCTATTGTCTGCCATATAAAAACTTAGGCCAGGCACA GTGGCTCACACCTGTAATCCCAGCACTTTGGAAGGCCGAGGCAGGCAGATCACAAG GTCAGGAGTTCGAGACCAGCCTGGCCAACATAGCAAAACCCCATCTCTACTAAAAAT ACAAAAATTAGCCAGGCATGGTGGCGTGTGCACTGGTTTAGAGTGAGGACCACATTT TTTTGGTGCCGTGTTACACATATGACCGTGACTTTGTTACACCACTACAGGAGGAAG AGTAGAAGAACAATCGGTTCTGGCGTGAAACAGACTTTGAATTTTGACCTTCTCAAGT TGGCGGGAGACGTGGAGTCCAACCCAGGGCCCGGTACCGGGTCCGCCACCATGGA CTGGACCTGGATTCTGTTCCTCGTGGCTGCTGCTACAAGAGTGCACAGCGGCATTC ATGTCTTCATTTTGGGCTGTTTCAGTGCAGGGCTTCCTAAAACAGAAGCCAACTGGG TGAATGTAATAAGTGATTTGAAAAAAATTGAAGATCTTATTCAATCTATGCATATTGAT GCTACTTTATATACGGAAAGTGATGTTCACCCCAGTTGCAAAGTAACAGCAATGAAG TGCTTTCTCTTGGAGTTACAAGTTATTTCACTTGAGTCCGGAGATGCAAGTATTCATG ATACAGTAGAAAATCTGATCATCCTAGCAAACAACAGTTTGTCTTCTAATGGGAATGT AACAGAATCTGGATGCAAAGAATGTGAGGAACTGGAGGAAAAAAATATTAAAGAATT TTTGCAGAGTTTTGTACATATTGTCCAAATGTTCATCAACACTTCTGGAAGCGGAGCT ACTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGAGGAGAACCCTGGACCTGG GACCGGCTCTGCAACCATGGATTGGACGTGGATCCTGTTTCTCGTGGCAGCTGCCA CAAGAGTTCACAGTATCACGTGCCCTCCCCCCATGTCCGTGGAACACGCAGACATC TGGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTACATTTGTAACTCTGGTTTC AAGCGTAAAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGA ATGTCGCCCACTGGACAACCCCCAGTCTCAAATGCATTAGAGACCCTGCCCTGGTTC ACCAAAGGCCAGCGCCACCCTCCACAGTAACGACGGCAGGGGTGACCCCACAGCC AGAGAGCCTCTCCCCTTCTGGAAAAGAGCCCGCAGCTTCATCTCCCAGCTCAAACAA CACAGCGGCCACAACAGCAGCTATTGTCCCGGGCTCCCAGCTGATGCCTTCAAAAT CACCTTCCACAGGAACCACAGAGATAAGCAGTCATGAGTCCTCCCACGGCACCCCC TCTCAGACAACAGCCAAGAACTGGGAACTCACAGCATCCGCCTCCCACCAGCCGCC AGGTGTGTATCCACAGGGCCACAGCGACACCACTGAGGGCAGAGGCAGCCTGCTG ACCTGCGGCGACGTCGAGGAGAACCCCGGGCCCATGGGGGCAGGTGCCACCGGC CGCGCCATGGACGGGCCGCGCCTGCTGCTGTTGCTGCTTCTGGGGGTGTCCCTTG GAGGTGCCAAGGAGGCATGCCCCACAGGCCTGTACACACACAGCGGTGAGTGCTG CAAAGCCTGCAACCTGGGCGAGGGTGTGGCCCAGCCTTGTGGAGCCAACCAGACC

		GTGTGTGAGCCCTGCCTGGACAGCGTGACGTTCTCCGACGTGGTGAGCGCGACCG AGCCGTGCAAGCCGTGCACCGAGTGCGTGGGGCTCCAGAGCATGTCGGCGCCGTG CGTGGAGGCCGATGACGCCGTGTGCCGCTGCGCCTACGGCTACTACCAGGATGAG ACGACTGGGCGCTGCGAGGCGTGCCGCGTGTGCGAGGCGGGCTCGGGCCTCGTG TTCTCCTGCCAGGACAAGCAGAACACCGTGTGCGAGGAGTGCCCCGACGGCACGT ATTCCGACGAGGCCAACCACGTGGACCCGTGCCTGCCCTGCACCGTGTGCGAGGA CACCGAGCGCCAGCTCCGCGAGTGCACACGCTGGGCCGACGCCGAGTGCGAGGA GATCCCTGGCCGTTGGATTACACGGTCCACACCCCCAGAGGGCTCGGACAGCACA GCCCCCAGCACCCAGGAGCCTGAGGCACCTCCAGAACAAGACCTCATAGCCAGCA CGGTGGCAGGTGTGGTGACCACAGTGATGGGCAGCTCCCAGCCCGTGGTGACCCG AGGCACCACCGACAACCTCATCCCTGTCTATTGCTCCATCCTGGCTGCTGTGGTTGT GGGTCTTGTGGCCTACATAGCCTTCAAGAGGTGAAAAACCAAAAGAACAAGAATTTC TTGGTAAGAAGCCGGGAACAGACAACAGAAGTCATGAAGCCCAAGTGAAATCAAAG GTGCTAAATGGTCGCCCAGGAGACATCCGTTGTGCTTGCCTGCGTTTTGGAAGCTCT GAAGTCACATCACAGGACACGGGGCAGTGGCAACCTTGTCTCTATGCCAGCTCAGT CCCATCAGAGAGCGAGCGCTACCCACTTCTAAATAGCAATTTCGCCGTTGAAGAGGA AGGGCAAAACCACTAGAACTCTCCATCTTATTTTCATGTATATGTGTTCATGCGATCG CTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTG GGGGGAGGGGTCGGCAATTGAACGGGTGCCTAGAGAAGGTGGCGCGGGGTAAACT GGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCG TATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGA ACACAGCTGAAGCTTCGAGGGGCTCGCATCTCTCCTTCACGCGCCCGCCGCCCTAC CTGAGGCCGCCATCCACGCCGGTTGAGTCGCGTTCTGCCGCCTCCCGCCTGTGGT GCCTCCTGAACTGCGTCCGCCGTCTAGGTAAGTTTAAAGCTCAGGTCGAGACCGGG CCTTTGTCCGGCGCTCCCTTGGAGCCTACCTAGACTCAGCCGGCTCTCCACGCTTT GCCTGACCCTGCTTGCTCAACTCTACGTCTTTGTTTCGTTTTCTGTTCTGCGCCGTTA CAGATCCAAGCTGTGACCGGCGCCTACCTGAGATCACCGGCGCCACCATGGCTTCT TACCCTGGACACCAGCATGCTTCTGCCTTTGACCAGGCTGCCAGATCCAGGGGCCA CTCCAACAGGAGAACTGCCCTAAGACCCAGAAGACAGCAGGAAGCCACTGAGGTGA GGCCTGAGCAGAAGATGCCAACCCTGCTGAGGGTGTACATTGATGGACCTCATGGC ATGGGCAAGACCACCACCACTCAACTGCTGGTGGCACTGGGCTCCAGGGATGACAT TGTGTATGTGCCTGAGCCAATGACCTACTGGAGAGTGCTAGGAGCCTCTGAGACCA TTGCCAACATCTACACCACCCAGCACAGGCTGGACCAGGGAGAAATCTCTGCTGGA GATGCTGCTGTGGTGATGACCTCTGCCCAGATCACAATGGGAATGCCCTATGCTGT GACTGATGCTGTTCTGGCTCCTCACATTGGAGGAGAGGCTGGCTCTTCTCATGCCC CTCCACCTGCCCTGACCCTGATCTTTGACAGACACCCCATTGCAGCCCTGCTGTGCT ACCCAGCAGCAAGGTACCTCATGGGCTCCATGACCCCACAGGCTGTGCTGGCTTTT GTGGCCCTGATCCCTCCAACCCTCCCTGGCACCAACATTGTTCTGGGAGCACTGCC TGAAGACAGACACATTGACAGGCTGGCAAAGAGGCAGAGACCTGGAGAGAGACTG GACCTGGCCATGCTGGCTGCAATCAGAAGGGTGTATGGACTGCTGGCAAACACTGT GAGATACCTCCAGTGTGGAGGCTCTTGGAGAGAGGACTGGGGACAGCTCTCTGGAA CAGCAGTGCCCCCTCAAGGAGCTGAGCCCCAGTCCAATGCTGGTCCAAGACCCCAC ATTGGGGACACCCTGTTCACCCTGTTCAGAGCCCCTGAGCTGCTGGCTCCCAATGG AGACCTGTACAATGTGTTTGCCTGGGCTCTGGATGTTCTAGCCAAGAGGCTGAGGT CCATGCATGTGTTCATCCTGGACTATGACCAGTCCCCTGCTGGATGCAGAGATGCTC TGCTGCAACTAACCTCTGGCATGGTGCAGACCCATGTGACCACCCCTGGCAGCATC CCCACCATCTGTGACCTAGCCAGAACCTTTGCCAGGGAGATGGGAGAGGCCAACTA AGGCGCGCCACTCGAGCGCTAGCTGGCCAGACATGATAAGATACATTGATGAGTTT GGACAAACCACAACTAGAATGCAGTGAAAAAAATGCTTTATTTGTGAAATTTGTGATG CTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAAGTTAACAACAACAATTGC ATTCATTTTATGTTTCAGGTTCAGGGGGAGGTGTGGGAGGTTTTTTAAAGCAAGTAAA ACCTCTACAAATGTGGTATGGAAGGCGCGCCCAATTCGCCCTATAGTGAGTCGTATT ACGTCGCGCTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGT TACCCAACTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGA AGAGGCCCGCACCGAAACGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATG GGAGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCG TGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCT TTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAG GGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTAGGGTGATG GTTGGCCTGTAGTGGGCCATAGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGA GTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATC TCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAA TGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGCTTACAATTT AGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATA CATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATT GAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGC GGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGC

		TGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTA AGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGT TCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTC GCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGC ATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTG ATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACC GCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAG CTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGC AACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACA ATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCC TTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGTTCTCGC GGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTAC ACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGG TGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAG ATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAAT CTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTA GAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGC AAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAA CTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTTCTTCT AGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCT CGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTAC CGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACG GGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATA CCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGAC AGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAG GGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGC GTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAAC GCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGGTCTTTCCT GCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACC GCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAG AGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGC TGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATGT GAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCGGCTCGTAT GTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATGACCATGA TTACGCCAAGCGCGTCAATTAACCCTCACTAAAGGGAACAAAAGCTGTTAATTAA
65	Matrice PD1 locus_IL15_2A_sIL15Ra pCLS30513 full sequence	GACTCCCCAGACAGGCCCTGGAACCCCCCCACCTTCTCCCCAGCCCTGCTCGTGGT GACCGAAGGGGACAACGCCACCTTCACCTGCAGCTTCTCCAACACATCGGAGAGCT TCGTGCTAAACTGGTACCGCATGAGCCCCAGCAACCAGACGGACAAGCTGGCCGCC TTCCCCGAGGACCGCAGCCAGCCCGGCCAGGACTGCCGCTTCCGTGTCACACAAC TGCCCAACGGGCGTGACTTCCACATGAGCGTGGTCAGGGCCCGGCGCAATGACAG CGGCACCTACCTCTGTGGGGCCGGTTCTGGCGTGAAACAGACTTTGAATTTTGACCT TCTCAAGTTGGCGGGAGACGTGGAGTCCAACCCAGGGCCCGGTACCGGGTCCGCC ACCATGGACTGGACCTGGATTCTGTTCCTCGTGGCTGCTGCTACAAGAGTGCACAG CGGCATTCATGTCTTCATTTTGGGCTGTTTCAGTGCAGGGCTTCCTAAAACAGAAGC CAACTGGGTGAATGTAATAAGTGATTTGAAAAAAATTGAAGATCTTATTCAATCTATG CATATTGATGCTACTTTATATACGGAAAGTGATGTTCACCCCAGTTGCAAAGTAACAG CAATGAAGTGCTTTCTCTTGGAGTTACAAGTTATTTCACTTGAGTCCGGAGATGCAAG TATTCATGATACAGTAGAAAATCTGATCATCCTAGCAAACAACAGTTTGTCTTCTAAT GGGAATGTAACAGAATCTGGATGCAAAGAATGTGAGGAACTGGAGGAAAAAAATATT AAAGAATTTTTGCAGAGTTTTGTACATATTGTCCAAATGTTCATCAACACTTCTGGAA GCGGAGCTACTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGAGGAGAACCCT GGACCTGGGACCGGCTCTGCAACCATGGATTGGACGTGGATCCTGTTTCTCGTGGC AGCTGCCACAAGAGTTCACAGTATCACGTGCCCTCCCCCCATGTCCGTGGAACACG CAGACATCTGGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTACATTTGTAACT CTGGTTTCAAGCGTAAAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTTGAACAAG GCCACGAATGTCGCCCACTGGACAACCCCCAGTCTCAAATGCATTAGAGACCCTGC CCTGGTTCACCAAAGGCCAGCGCCACCCTCCACAGTAACGACGGCAGGGGTGACC CCACAGCCAGAGAGCCTCTCCCCTTCTGGAAAAGAGCCCGCAGCTTCATCTCCCAG CTCAAACAACACAGCGGCCACAACAGCAGCTATTGTCCCGGGCTCCCAGCTGATGC CTTCAAAATCACCTTCCACAGGAACCACAGAGATAAGCAGTCATGAGTCCTCCCACG GCACCCCCTCTCAGACAACAGCCAAGAACTGGGAACTCACAGCATCCGCCTCCCAC CAGCCGCCAGGTGTGTATCCACAGGGCCACAGCGACACCACTGAGGGCAGAGGCA GCCTGCTGACCTGCGGCGACGTCGAGGAGAACCCCGGGCCCATGGGGGCAGGTG CCACCGGCCGCGCCATGGACGGGCCGCGCCTGCTGCTGTTGCTGCTTCTGGGGGT GTCCCTTGGAGGTGCCAAGGAGGCATGCCCCACAGGCCTGTACACACACAGCGGT

		GAGTGCTGCAAAGCCTGCAACCTGGGCGAGGGTGTGGCCCAGCCTTGTGGAGCCA ACCAGACCGTGTGTGAGCCCTGCCTGGACAGCGTGACGTTCTCCGACGTGGTGAG CGCGACCGAGCCGTGCAAGCCGTGCACCGAGTGCGTGGGGCTCCAGAGCATGTCG GCGCCGTGCGTGGAGGCCGATGACGCCGTGTGCCGCTGCGCCTACGGCTACTACC AGGATGAGACGACTGGGCGCTGCGAGGCGTGCCGCGTGTGCGAGGCGGGCTCGG GCCTCGTGTTCTCCTGCCAGGACAAGCAGAACACCGTGTGCGAGGAGTGCCCCGA CGGCACGTATTCCGACGAGGCCAACCACGTGGACCCGTGCCTGCCCTGCACCGTG TGCGAGGACACCGAGCGCCAGCTCCGCGAGTGCACACGCTGGGCCGACGCCGAGT GCGAGGAGATCCCTGGCCGTTGGATTACACGGTCCACACCCCCAGAGGGCTCGGA CAGCACAGCCCCCAGCACCCAGGAGCCTGAGGCACCTCCAGAACAAGACCTCATAG CCAGCACGGTGGCAGGTGTGGTGACCACAGTGATGGGCAGCTCCCAGCCCGTGGT GACCCGAGGCACCACCGACAACCTCATCCCTGTCTATTGCTCCATCCTGGCTGCTG TGGTTGTGGGTCTTGTGGCCTACATAGCCTTCAAGAGGTGATCTAGAGGGCCCGTTT AAACCCGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCC CCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAAT AAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTG GGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGG GGATGCGGTGGGCTCTATGACTAGTGGCGAATTCGGCGCAGATCAAAGAGAGCCTG CGGGCAGAGCTCAGGGTGACAGGTGCGGCCTCGGAGGCCCCGGGGCAGGGGTGA GCTGAGCCGGTCCTGGGGTGGGTGTCCCCTCCTGCACAGGATCAGGAGCTCCAGG GTCGTAGGGCAGGGACCCCCCAGCTCCAGTCCAGGGCTCTGTCCTGCACCTGGGG AATGGTGACCGGCATCTCTGTCCTCTAGCTCTGGAAGCACCCCAGCCCCTCTAGTCT GCCCTCACCCCTGACCCTGACCCTCCACCCTGACCCCGTCCTAACCCCTGACCTTT GGCGATCGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCG AGAAGTTGGGGGGAGGGGTCGGCAATTGAACGGGTGCCTAGAGAAGGTGGCGCGG GGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGG GAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTG CCGCCAGAACACAGCTGAAGCTTCGAGGGGCTCGCATCTCTCCTTCACGCGCCCGC CGCCCTACCTGAGGCCGCCATCCACGCCGGTTGAGTCGCGTTCTGCCGCCTCCCG CCTGTGGTGCCTCCTGAACTGCGTCCGCCGTCTAGGTAAGTTTAAAGCTCAGGTCG AGACCGGGCCTTTGTCCGGCGCTCCCTTGGAGCCTACCTAGACTCAGCCGGCTCTC CACGCTTTGCCTGACCCTGCTTGCTCAACTCTACGTCTTTGTTTCGTTTTCTGTTCTG CGCCGTTACAGATCCAAGCTGTGACCGGCGCCTACCTGAGATCACCGGCGCCACCA TGGCTTCTTACCCTGGACACCAGCATGCTTCTGCCTTTGACCAGGCTGCCAGATCCA GGGGCCACTCCAACAGGAGAACTGCCCTAAGACCCAGAAGACAGCAGGAAGCCAC TGAGGTGAGGCCTGAGCAGAAGATGCCAACCCTGCTGAGGGTGTACATTGATGGAC CTCATGGCATGGGCAAGACCACCACCACTCAACTGCTGGTGGCACTGGGCTCCAGG GATGACATTGTGTATGTGCCTGAGCCAATGACCTACTGGAGAGTGCTAGGAGCCTCT GAGACCATTGCCAACATCTACACCACCCAGCACAGGCTGGACCAGGGAGAAATCTC TGCTGGAGATGCTGCTGTGGTGATGACCTCTGCCCAGATCACAATGGGAATGCCCT ATGCTGTGACTGATGCTGTTCTGGCTCCTCACATTGGAGGAGAGGCTGGCTCTTCTC ATGCCCCTCCACCTGCCCTGACCCTGATCTTTGACAGACACCCCATTGCAGCCCTG CTGTGCTACCCAGCAGCAAGGTACCTCATGGGCTCCATGACCCCACAGGCTGTGCT GGCTTTTGTGGCCCTGATCCCTCCAACCCTCCCTGGCACCAACATTGTTCTGGGAG CACTGCCTGAAGACAGACACATTGACAGGCTGGCAAAGAGGCAGAGACCTGGAGAG AGACTGGACCTGGCCATGCTGGCTGCAATCAGAAGGGTGTATGGACTGCTGGCAAA CACTGTGAGATACCTCCAGTGTGGAGGCTCTTGGAGAGAGGACTGGGGACAGCTCT CTGGAACAGCAGTGCCCCCTCAAGGAGCTGAGCCCCAGTCCAATGCTGGTCCAAGA CCCCACATTGGGGACACCCTGTTCACCCTGTTCAGAGCCCCTGAGCTGCTGGCTCC CAATGGAGACCTGTACAATGTGTTTGCCTGGGCTCTGGATGTTCTAGCCAAGAGGCT GAGGTCCATGCATGTGTTCATCCTGGACTATGACCAGTCCCCTGCTGGATGCAGAG ATGCTCTGCTGCAACTAACCTCTGGCATGGTGCAGACCCATGTGACCACCCCTGGC AGCATCCCCACCATCTGTGACCTAGCCAGAACCTTTGCCAGGGAGATGGGAGAGGC CAACTAAGGCGCGCCACTCGAGCGCTAGCTGGCCAGACATGATAAGATACATTGAT GAGTTTGGACAAACCACAACTAGAATGCAGTGAAAAAAATGCTTTATTTGTGAAATTT GTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAAGTTAACAACAAC AATTGCATTCATTTTATGTTTCAGGTTCAGGGGGAGGTGTGGGAGGTTTTTTAAAGCA AGTAAAACCTCTACAAATGTGGTATGGAAGGCGCGCCCAATTCGCCCTATAGTGAGT CGTATTACGTCGCGCTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCT GGCGTTACCCAACTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAAT AGCGAAGAGGCCCGCACCGAAACGCCCTTCCCAACAGTTGCGCAGCCTGAATGGC GAATGGGAGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCG CAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCC CTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCC CTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTAGG GTGATGGTTGGCCTGTAGTGGGCCATAGCCCTGATAGACGGTTTTTCGCCCTTTGAC GTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAAC

		CCTATCTCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGT TAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGCTT ACAATTTAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTT CTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAA TAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCT TTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAA AGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACA GCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTT TTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAAC TCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAG AAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCA TGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAG CTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAA CCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGC AATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCG GCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCT CGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGT TCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGT TATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTG AGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATAT ACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTT TTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGA CCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGC TGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAG CTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACT GTTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCT ACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCG TGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGG CTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAA CTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAA GGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGA GCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTG ACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACG CCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGG TCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGC TGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAA GCGGAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAA TGCAGCTGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAA TTAATGTGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCGGC TCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATGA CCATGATTACGCCAAGCGCGTCAATTAACCCTCACTAAAGGGAACAAAAGCTGTTAA TTAA
66	Matrice CD25 locus_IL12a_ 2A_IL12b pCLS30520 full sequence	GTTTATTATTCCTGTTCCACAGCTATTGTCTGCCATATAAAAACTTAGGCCAGGCACA GTGGCTCACACCTGTAATCCCAGCACTTTGGAAGGCCGAGGCAGGCAGATCACAAG GTCAGGAGTTCGAGACCAGCCTGGCCAACATAGCAAAACCCCATCTCTACTAAAAAT ACAAAAATTAGCCAGGCATGGTGGCGTGTGCACTGGTTTAGAGTGAGGACCACATTT TTTTGGTGCCGTGTTACACATATGACCGTGACTTTGTTACACCACTACAGGAGGAAG AGTAGAAGAACAATCGGTTCTGGCGTGAAACAGACTTTGAATTTTGACCTTCTCAAGT TGGCGGGAGACGTGGAGTCCAACCCAGGGCCCATGTGGCCCCCTGGGTCAGCCTC CCAGCCACCGCCCTCACCTGCCGCGGCCACAGGTCTGCATCCAGCGGCTCGCCCT GTGTCCCTGCAGTGCCGGCTCAGCATGTGTCCAGCGCGCAGCCTCCTCCTTGTGGC TACCCTGGTCCTCCTGGACCACCTCAGTTTGGCCAGAAACCTCCCCGTGGCCACTC CAGACCCAGGAATGTTCCCATGCCTTCACCACTCCCAAAACCTGCTGAGGGCCGTC AGCAACATGCTCCAGAAGGCCAGACAAACTCTAGAATTTTACCCTTGCACTTCTGAA GAGATTGATCATGAAGATATCACAAAAGATAAAACCAGCACAGTGGAGGCCTGTTTA CCATTGGAATTAACCAAGAATGAGAGTTGCCTAAATTCCAGAGAGACCTCTTTCATAA CTAATGGGAGTTGCCTGGCCTCCAGAAAGACCTCTTTTATGATGGCCCTGTGCCTTA GTAGTATTTATGAAGACTTGAAGATGTACCAGGTGGAGTTCAAGACCATGAATGCAA AGCTTCTGATGGATCCTAAGAGGCAGATCTTTCTAGATCAAAACATGCTGGCAGTTA TTGATGAGCTGATGCAGGCCCTGAATTTCAACAGTGAGACTGTGCCACAAAAATCCT CCCTTGAAGAACCGGATTTTTATAAAACTAAAATCAAGCTCTGCATACTTCTTCATGC TTTCAGAATTCGGGCAGTGACTATTGATAGAGTGATGAGCTATCTGAATGCTTCCGG AAGCGGAGCTACTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGAGGAGAACC CTGGACCTATGTGTCACCAGCAGTTGGTCATCTCTTGGTTTTCCCTGGTTTTTCTGG CATCTCCCCTCGTGGCCATATGGGAACTGAAGAAAGATGTTTATGTCGTAGAATTGG

		ATTGGTATCCGGATGCCCCTGGAGAAATGGTGGTCCTCACCTGTGACACCCCTGAA GAAGATGGTATCACCTGGACCTTGGACCAGAGCAGTGAGGTCTTAGGCTCTGGCAA AACCCTGACCATCCAAGTCAAAGAGTTTGGAGATGCTGGCCAGTACACCTGTCACAA AGGAGGCGAGGTTCTAAGCCATTCGCTCCTGCTGCTTCACAAAAAGGAAGATGGAA TTTGGTCCACTGATATTTTAAAGGACCAGAAAGAACCCAAAAATAAGACCTTTCTAAG ATGCGAGGCCAAGAATTATTCTGGACGTTTCACCTGCTGGTGGCTGACGACAATCAG TACTGATTTGACATTCAGTGTCAAAAGCAGCAGAGGCTCTTCTGACCCCCAAGGGGT GACGTGCGGAGCTGCTACACTCTCTGCAGAGAGAGTCAGAGGGGACAACAAGGAG TATGAGTACTCAGTGGAGTGCCAGGAGGACAGTGCCTGCCCAGCTGCTGAGGAGA GTCTGCCCATTGAGGTCATGGTGGATGCCGTTCACAAGCTCAAGTATGAAAACTACA CCAGCAGCTTCTTCATCAGGGACATCATCAAACCTGACCCACCCAAGAACTTGCAGC TGAAGCCATTAAAGAATTCTCGGCAGGTGGAGGTCAGCTGGGAGTACCCTGACACC TGGAGTACTCCACATTCCTACTTCTCCCTGACATTCTGCGTTCAGGTCCAGGGCAAG AGCAAGAGAGAAAAGAAAGATAGAGTCTTCACGGACAAGACCTCAGCCACGGTCAT CTGCCGCAAAAATGCCAGCATTAGCGTGCGGGCCCAGGACCGCTACTATAGCTCAT CTTGGAGCGAATGGGCATCTGTGCCCTGCAGTGAGGGCAGAGGCAGCCTGCTGAC CTGCGGCGACGTCGAGGAGAACCCCGGGCCCATGGGGGCAGGTGCCACCGGCCG CGCCATGGACGGGCCGCGCCTGCTGCTGTTGCTGCTTCTGGGGGTGTCCCTTGGA GGTGCCAAGGAGGCATGCCCCACAGGCCTGTACACACACAGCGGTGAGTGCTGCA AAGCCTGCAACCTGGGCGAGGGTGTGGCCCAGCCTTGTGGAGCCAACCAGACCGT GTGTGAGCCCTGCCTGGACAGCGTGACGTTCTCCGACGTGGTGAGCGCGACCGAG CCGTGCAAGCCGTGCACCGAGTGCGTGGGGCTCCAGAGCATGTCGGCGCCGTGCG TGGAGGCCGATGACGCCGTGTGCCGCTGCGCCTACGGCTACTACCAGGATGAGAC GACTGGGCGCTGCGAGGCGTGCCGCGTGTGCGAGGCGGGCTCGGGCCTCGTGTT CTCCTGCCAGGACAAGCAGAACACCGTGTGCGAGGAGTGCCCCGACGGCACGTAT TCCGACGAGGCCAACCACGTGGACCCGTGCCTGCCCTGCACCGTGTGCGAGGACA CCGAGCGCCAGCTCCGCGAGTGCACACGCTGGGCCGACGCCGAGTGCGAGGAGA TCCCTGGCCGTTGGATTACACGGTCCACACCCCCAGAGGGCTCGGACAGCACAGC CCCCAGCACCCAGGAGCCTGAGGCACCTCCAGAACAAGACCTCATAGCCAGCACG GTGGCAGGTGTGGTGACCACAGTGATGGGCAGCTCCCAGCCCGTGGTGACCCGAG GCACCACCGACAACCTCATCCCTGTCTATTGCTCCATCCTGGCTGCTGTGGTTGTGG GTCTTGTGGCCTACATAGCCTTCAAGAGGTGAAAAACCAAAAGAACAAGAATTTCTT GGTAAGAAGCCGGGAACAGACAACAGAAGTCATGAAGCCCAAGTGAAATCAAAGGT GCTAAATGGTCGCCCAGGAGACATCCGTTGTGCTTGCCTGCGTTTTGGAAGCTCTG AAGTCACATCACAGGACACGGGGCAGTGGCAACCTTGTCTCTATGCCAGCTCAGTC CCATCAGAGAGCGAGCGCTACCCACTTCTAAATAGCAATTTCGCCGTTGAAGAGGAA GGGCAAAACCACTAGAACTCTCCATCTTATTTTCATGTATATGTGTTCATGCGATCGC TCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGG GGGGAGGGGTCGGCAATTGAACGGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTG GGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGT ATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAA CACAGCTGAAGCTTCGAGGGGCTCGCATCTCTCCTTCACGCGCCCGCCGCCCTACC TGAGGCCGCCATCCACGCCGGTTGAGTCGCGTTCTGCCGCCTCCCGCCTGTGGTG CCTCCTGAACTGCGTCCGCCGTCTAGGTAAGTTTAAAGCTCAGGTCGAGACCGGGC CTTTGTCCGGCGCTCCCTTGGAGCCTACCTAGACTCAGCCGGCTCTCCACGCTTTG CCTGACCCTGCTTGCTCAACTCTACGTCTTTGTTTCGTTTTCTGTTCTGCGCCGTTAC AGATCCAAGCTGTGACCGGCGCCTACCTGAGATCACCGGCGCCACCATGGCTTCTT ACCCTGGACACCAGCATGCTTCTGCCTTTGACCAGGCTGCCAGATCCAGGGGCCAC TCCAACAGGAGAACTGCCCTAAGACCCAGAAGACAGCAGGAAGCCACTGAGGTGAG GCCTGAGCAGAAGATGCCAACCCTGCTGAGGGTGTACATTGATGGACCTCATGGCA TGGGCAAGACCACCACCACTCAACTGCTGGTGGCACTGGGCTCCAGGGATGACATT GTGTATGTGCCTGAGCCAATGACCTACTGGAGAGTGCTAGGAGCCTCTGAGACCAT TGCCAACATCTACACCACCCAGCACAGGCTGGACCAGGGAGAAATCTCTGCTGGAG ATGCTGCTGTGGTGATGACCTCTGCCCAGATCACAATGGGAATGCCCTATGCTGTGA CTGATGCTGTTCTGGCTCCTCACATTGGAGGAGAGGCTGGCTCTTCTCATGCCCCTC CACCTGCCCTGACCCTGATCTTTGACAGACACCCCATTGCAGCCCTGCTGTGCTACC CAGCAGCAAGGTACCTCATGGGCTCCATGACCCCACAGGCTGTGCTGGCTTTTGTG GCCCTGATCCCTCCAACCCTCCCTGGCACCAACATTGTTCTGGGAGCACTGCCTGA AGACAGACACATTGACAGGCTGGCAAAGAGGCAGAGACCTGGAGAGAGACTGGAC CTGGCCATGCTGGCTGCAATCAGAAGGGTGTATGGACTGCTGGCAAACACTGTGAG ATACCTCCAGTGTGGAGGCTCTTGGAGAGAGGACTGGGGACAGCTCTCTGGAACAG CAGTGCCCCCTCAAGGAGCTGAGCCCCAGTCCAATGCTGGTCCAAGACCCCACATT GGGGACACCCTGTTCACCCTGTTCAGAGCCCCTGAGCTGCTGGCTCCCAATGGAGA CCTGTACAATGTGTTTGCCTGGGCTCTGGATGTTCTAGCCAAGAGGCTGAGGTCCAT GCATGTGTTCATCCTGGACTATGACCAGTCCCCTGCTGGATGCAGAGATGCTCTGCT GCAACTAACCTCTGGCATGGTGCAGACCCATGTGACCACCCCTGGCAGCATCCCCA CCATCTGTGACCTAGCCAGAACCTTTGCCAGGGAGATGGGAGAGGCCAACTAAGGC

		GCGCCACTCGAGCGCTAGCTGGCCAGACATGATAAGATACATTGATGAGTTTGGAC AAACCACAACTAGAATGCAGTGAAAAAAATGCTTTATTTGTGAAATTTGTGATGCTAT TGCTTTATTTGTAACCATTATAAGCTGCAATAAACAAGTTAACAACAACAATTGCATTC ATTTTATGTTTCAGGTTCAGGGGGAGGTGTGGGAGGTTTTTTAAAGCAAGTAAAACC TCTACAAATGTGGTATGGAAGGCGCGCCCAATTCGCCCTATAGTGAGTCGTATTACG TCGCGCTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTAC CCAACTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGA GGCCCGCACCGAAACGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGGGA GCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGA CCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTC TCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGG TTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTAGGGTGATGGT TGGCCTGTAGTGGGCCATAGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGT CCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTC GGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAAT GAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGCTTACAATTTA GGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATAC ATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGA AAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGG CATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGA AGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGA TCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCT GCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCC GCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCT TACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAA CACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTT TTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGA ATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACA ACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAA TAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCG GCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGTTCTCGCGGTAT CATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGA CGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCC TCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGA TTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCAT GACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAA GATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACA AAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTT TTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTTCTTCTAGTG TAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCT CTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGG GTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGG GGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCT ACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGG TATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGG GAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTC GATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCG GCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGGTCTTTCCTGCGT TATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTC GCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAGAGCG CCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGCTGGC ACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAGT TAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGT GTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATGACCATGATTACG CCAAGCGCGTCAATTAACCCTCACTAAAGGGAACAAAAGCTGTTAATTAA
67	Matrice PD1 locus_IL12a_ 2A_IL12b pCLS30511 full sequence	TCGCGCGTTTCGGTGATGACGGTGAAAACCTCTGACACATGCAGCTCCCGGAGACG GTCACAGCTTGTCTGTAAGCGGATGCCGGGAGCAGACAAGCCCGTCAGGGCGCGT CAGCGGGTGTTGGCGGGTGTCGGGGCTGGCTTAACTATGCGGCATCAGAGCAGAT TGTACTGAGAGTGCACCATATGCGGTGTGAAATACCGCACAGATGCGTAAGGAGAA AATACCGCATCAGGCGCCATTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGGCGA TCGGTGCGGGCCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTGCAA GGCGATTAAGTTGGGTAACGCCAGGGTTTTCCCAGTCACGACGTTGTAAAACGACG GCCAGTGAATTCGAGCTCGGTACCTCGCGAATGCATCTAGATGACTCCCCAGACAG GCCCTGGAACCCCCCCACCTTCTCCCCAGCCCTGCTCGTGGTGACCGAAGGGGAC AACGCCACCTTCACCTGCAGCTTCTCCAACACATCGGAGAGCTTCGTGCTAAACTGG

		TACCGCATGAGCCCCAGCAACCAGACGGACAAGCTGGCCGCCTTCCCCGAGGACC GCAGCCAGCCCGGCCAGGACTGCCGCTTCCGTGTCACACAACTGCCCAACGGGCG TGACTTCCACATGAGCGTGGTCAGGGCCCGGCGCAATGACAGCGGCACCTACCTCT GTGGGGCCGGTTCTGGCGTGAAACAGACTTTGAATTTTGACCTTCTCAAGTTGGCG GGAGACGTGGAGTCCAACCCAGGGCCCATGTGGCCCCCTGGGTCAGCCTCCCAGC CACCGCCCTCACCTGCCGCGGCCACAGGTCTGCATCCAGCGGCTCGCCCTGTGTC CCTGCAGTGCCGGCTCAGCATGTGTCCAGCGCGCAGCCTCCTCCTTGTGGCTACCC TGGTCCTCCTGGACCACCTCAGTTTGGCCAGAAACCTCCCCGTGGCCACTCCAGAC CCAGGAATGTTCCCATGCCTTCACCACTCCCAAAACCTGCTGAGGGCCGTCAGCAA CATGCTCCAGAAGGCCAGACAAACTCTAGAATTTTACCCTTGCACTTCTGAAGAGAT TGATCATGAAGATATCACAAAAGATAAAACCAGCACAGTGGAGGCCTGTTTACCATT GGAATTAACCAAGAATGAGAGTTGCCTAAATTCCAGAGAGACCTCTTTCATAACTAAT GGGAGTTGCCTGGCCTCCAGAAAGACCTCTTTTATGATGGCCCTGTGCCTTAGTAGT ATTTATGAAGACTTGAAGATGTACCAGGTGGAGTTCAAGACCATGAATGCAAAGCTT CTGATGGATCCTAAGAGGCAGATCTTTCTAGATCAAAACATGCTGGCAGTTATTGAT GAGCTGATGCAGGCCCTGAATTTCAACAGTGAGACTGTGCCACAAAAATCCTCCCTT GAAGAACCGGATTTTTATAAAACTAAAATCAAGCTCTGCATACTTCTTCATGCTTTCA GAATTCGGGCAGTGACTATTGATAGAGTGATGAGCTATCTGAATGCTTCCGGAAGCG GAGCTACTAACTTCAGCCTGCTGAAGCAGGCTGGAGACGTGGAGGAGAACCCTGGA CCTATGTGTCACCAGCAGTTGGTCATCTCTTGGTTTTCCCTGGTTTTTCTGGCATCTC CCCTCGTGGCCATATGGGAACTGAAGAAAGATGTTTATGTCGTAGAATTGGATTGGT ATCCGGATGCCCCTGGAGAAATGGTGGTCCTCACCTGTGACACCCCTGAAGAAGAT GGTATCACCTGGACCTTGGACCAGAGCAGTGAGGTCTTAGGCTCTGGCAAAACCCT GACCATCCAAGTCAAAGAGTTTGGAGATGCTGGCCAGTACACCTGTCACAAAGGAG GCGAGGTTCTAAGCCATTCGCTCCTGCTGCTTCACAAAAAGGAAGATGGAATTTGGT CCACTGATATTTTAAAGGACCAGAAAGAACCCAAAAATAAGACCTTTCTAAGATGCGA GGCCAAGAATTATTCTGGACGTTTCACCTGCTGGTGGCTGACGACAATCAGTACTGA TTTGACATTCAGTGTCAAAAGCAGCAGAGGCTCTTCTGACCCCCAAGGGGTGACGT GCGGAGCTGCTACACTCTCTGCAGAGAGAGTCAGAGGGGACAACAAGGAGTATGAG TACTCAGTGGAGTGCCAGGAGGACAGTGCCTGCCCAGCTGCTGAGGAGAGTCTGC CCATTGAGGTCATGGTGGATGCCGTTCACAAGCTCAAGTATGAAAACTACACCAGCA GCTTCTTCATCAGGGACATCATCAAACCTGACCCACCCAAGAACTTGCAGCTGAAGC CATTAAAGAATTCTCGGCAGGTGGAGGTCAGCTGGGAGTACCCTGACACCTGGAGT ACTCCACATTCCTACTTCTCCCTGACATTCTGCGTTCAGGTCCAGGGCAAGAGCAAG AGAGAAAAGAAAGATAGAGTCTTCACGGACAAGACCTCAGCCACGGTCATCTGCCG CAAAAATGCCAGCATTAGCGTGCGGGCCCAGGACCGCTACTATAGCTCATCTTGGA GCGAATGGGCATCTGTGCCCTGCAGTGAGGGCAGAGGCAGCCTGCTGACCTGCGG CGACGTCGAGGAGAACCCCGGGCCCATGGGGGCAGGTGCCACCGGCCGCGCCAT GGACGGGCCGCGCCTGCTGCTGTTGCTGCTTCTGGGGGTGTCCCTTGGAGGTGCC AAGGAGGCATGCCCCACAGGCCTGTACACACACAGCGGTGAGTGCTGCAAAGCCT GCAACCTGGGCGAGGGTGTGGCCCAGCCTTGTGGAGCCAACCAGACCGTGTGTGA GCCCTGCCTGGACAGCGTGACGTTCTCCGACGTGGTGAGCGCGACCGAGCCGTGC AAGCCGTGCACCGAGTGCGTGGGGCTCCAGAGCATGTCGGCGCCGTGCGTGGAGG CCGATGACGCCGTGTGCCGCTGCGCCTACGGCTACTACCAGGATGAGACGACTGG GCGCTGCGAGGCGTGCCGCGTGTGCGAGGCGGGCTCGGGCCTCGTGTTCTCCTGC CAGGACAAGCAGAACACCGTGTGCGAGGAGTGCCCCGACGGCACGTATTCCGACG AGGCCAACCACGTGGACCCGTGCCTGCCCTGCACCGTGTGCGAGGACACCGAGCG CCAGCTCCGCGAGTGCACACGCTGGGCCGACGCCGAGTGCGAGGAGATCCCTGGC CGTTGGATTACACGGTCCACACCCCCAGAGGGCTCGGACAGCACAGCCCCCAGCA CCCAGGAGCCTGAGGCACCTCCAGAACAAGACCTCATAGCCAGCACGGTGGCAGG TGTGGTGACCACAGTGATGGGCAGCTCCCAGCCCGTGGTGACCCGAGGCACCACC GACAACCTCATCCCTGTCTATTGCTCCATCCTGGCTGCTGTGGTTGTGGGTCTTGTG GCCTACATAGCCTTCAAGAGGTGATCTAGAGGGCCCGTTTAAACCCGCTGATCAGC CTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTC CTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGC ATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACA GCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCTC TATGACTAGTGGCGAATTCGGCGCAGATCAAAGAGAGCCTGCGGGCAGAGCTCAGG GTGACAGGTGCGGCCTCGGAGGCCCCGGGGCAGGGGTGAGCTGAGCCGGTCCTG GGGTGGGTGTCCCCTCCTGCACAGGATCAGGAGCTCCAGGGTCGTAGGGCAGGGA CCCCCCAGCTCCAGTCCAGGGCTCTGTCCTGCACCTGGGGAATGGTGACCGGCAT CTCTGTCCTCTAGCTCTGGAAGCACCCCAGCCCCTCTAGTCTGCCCTCACCCCTGA CCCTGACCCTCCACCCTGACCCCGTCCTAACCCCTGACCTTTGATCGGATCCCGGG CCCGTCGACTGCAGAGGCCTGCATGCAAGCTTGGCGTAATCATGGTCATAGCTGTT TCCTGTGTGAAATTGTTATCCGCTCACAATTCCACACAACATACGAGCCGGAAGCAT AAAGTGTAAAGCCTGGGGTGCCTAATGAGTGAGCTAACTCACATTAATTGCGTTGCG CTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTGCCAGCTGCATTAATGAATCG

		GCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCCGCTTCCTCGCT CACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTATCAGCTCACTCAA AGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATGTGA GCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTT CCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGAGGT GGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTC GTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCT TCGGGAAGCGTGGCGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTA GGTCGTTCGCTCCAAGCTGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCT GCGCCTTATCCGGTAACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGC CACTGGCAGCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCT ACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGAACAGTATTTGGT ATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCC GGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGATTACG CGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCT CAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATC TTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGA GTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGAT CTGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGATA CGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCACGCTC ACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGCGCAGAA GTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCCGGGAAGCTA GAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGGCA TCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGAT CAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTC CTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAG CACTGCATAATTCTCTTACTGTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGA GTACTCAACCAAGTCATTCTGAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCC GGCGTCAATACGGGATAATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCAT TGGAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAG TTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGC GTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGC GACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATC AGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAAT AGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACCTGACGTCTAAGAAACCATTAT TATCATGACATTAACCTATAAAAATAGGCGTATCACGAGGCCCTTTCGTC

Table 6: Preferred human endogenous gene loci responsive to T-cell activation

symbol	description	inductionRatio12hr	T.8Nve.Sp.OT1	T.8Eff.Sp.OT1. 12hr.LisOva	T.8Eff.Sp.OT1. 48hr.LisOva	T.8Eff.Sp.OT1. d6.LisOva
Il3	interleukin 21	16,4	12,8	208,9	18,4	13,6
Il2	interleukin 3	97,0	16,0	1554,4	17,7	18,1
Ccl4	isopentenyl-diphosphate delta isomerase 2	2,1	16,8	35,6	17,6	19,7
Il21	granzyme C	9,2	17,4	160,5	20,4	24,9
Gp49a	chemokine (C-C motif) receptor 8	5,9	18,5	108,4	31,5	20,9
Cxcl10	interleukin 2	58,4	21,1	1229,6	32,7	17,9
Nr4a3	interleukin 1 receptor, type I	2,6	21,2	54,6	35,5	21,7
Lilrb4	tumor necrosis factor (ligand) superfamily, member 4	4,1	21,8	88,8	29,3	20,0
Cd200	neuronal calcium sensor 1	4,5	24,1	109,6	46,3	23,2
Cdkn1a	CDK5 and Abl enzyme substrate 1	3,1	26,2	80,9	49,1	32,8
Gzmc	transmembrane and tetratricopeptide repeat containing 2	2,0	26,8	53,9	26,2	29,4
Nr4a2	LON peptidase N-terminal domain and ring finger 1	3,2	28,4	90,4	50,4	28,3
Cish	glycoprotein 49 A	15,0	31,6	472,4	30,6	212,5
Nr4a1	polo-like kinase 2	3,6	31,7	114,3	39,0	32,5
Tnf	lipase, endothelial	2,1	32,4	66,7	35,9	33,3
Ccr8	cyclin-dependent kinase inhibitor 1A (P21)	9,7	34,6	335,4	54,4	71,0
Lad1	grainyhead-like 1 (Drosophila)	2,1	35,1	73,4	52,0	44,1
Slamf1	cellular retinoic acid binding protein II	5,3	35,4	187,2	43,3	36,3
Crabp2	adenylate kinase 4	2,2	35,9	80,4	58,5	39,8
Furin	microtubule-associated protein 1B	2,1	36,2	77,7	36,4	38,4
Gadd45g	acyl-CoA synthetase long-chain family member 6	2,0	37,2	76,0	45,2	41,3

Bcl2l1	zinc finger E-box binding homeobox 2	2,1	38,6	80,7	44,9	455,4
Ncs1	CD200 antigen	9,8	41,2	404,3	70,4	36,8
Ciart	carboxypeptidase D	3,1	41,6	127,7	71,4	71,6
Ahr	thioredoxin reductase 3	3,6	43,4	157,8	61,7	28,8
Spry1	myosin IE	2,3	43,6	100,2	61,3	77,0
Tnfsf4	RNA binding protein with multiple splicing 2	2,1	43,6	91,5	49,8	36,5
Myo10	mitogen-activated protein kinase kinase 3, opposite strand	2,9	44,8	127,9	66,4	43,1
Dusp5	PERP, TP53 apoptosis effector	2,8	44,9	127,2	78,4	72,4
Myc	myosin X	4,1	45,5	184,9	81,6	57,5
Psrc1	immediate early response 3	2,7	45,6	121,6	63,9	66,2
St6galnac4	folliculin interacting protein 2	2,6	47,5	124,2	87,4	96,6
Nfkbid	leukocyte immunoglobulin-like receptor, subfamily B, member 4	9,9	48,9	483,3	64,5	179,1
Bst2	circadian associated repressor of transcription	4,5	50,6	225,5	100,3	33,8
Txnrd3	RAR-related orphan receptor gamma	2,1	51,7	106,7	47,5	52,8
Plk2	proline/serine-rich coiled-coil 1	3,9	52,9	205,9	92,3	79,6
Gfi1	cysteine rich protein 2	2,4	54,2	127,7	90,3	182,9
Pim1	cAMP responsive element modulator	2,0	55,7	112,6	54,4	57,3
Pvt1	chemokine (C-C motif) ligand 4	20,2	55,8	1125,8	103,1	89,0
Nfkbib	nuclear receptor subfamily 4, group A, member 2	7,8	58,5	457,6	78,7	72,0
Gnl2	transglutaminase 2, C polypeptide	2,3	58,7	132,1	69,8	64,7
Cd69	synapse defective 1, Rho GTPase, homolog 2 (C, elegans)	2,1	62,5	132,7	111,3	31,0
Dgat2	sprouty homolog 1 (Drosophila)	4,2	63,8	268,5	76,8	61,4
Atf3	activating transcription factor 3	3,2	65,8	210,3	88,3	75,8
Tnfrsf21	pogo transposable element with KRAB domain	2,9	68,6	196,9	91,1	293,2
Lonrf1	tumor necrosis factor receptor superfamily,	3,2	70,6	224,5	126,5	72,9

	member 21					
Cables1	cytokine inducible SH2-containing protein	7,5	74,3	558,7	82,5	133,9
Cpd	lymphotoxin A	2,6	74,6	197,2	93,4	58,6
Qtrtd1	FBJ osteosarcoma oncogene	3,0	74,9	224,1	89,0	61,1
Polr3d	signaling lymphocytic activation molecule family member 1	5,4	75,6	412,0	108,4	190,4
Kcnq5	syndecan 3	2,4	76,0	180,0	77,2	85,3
Fos	mitochondrial ribosomal protein L47	2,1	77,2	161,7	152,0	72,3
Slc19a2	ladinin	5,5	77,3	423,2	152,5	70,4
Hif1a	E2F transcription factor 5	2,5	77,7	198,0	92,0	65,2
Il15ra	ISG15 ubiquitin-like modifier	2,8	77,9	221,0	88,9	45,1
Nfkb1	aryl-hydrocarbon receptor	4,2	78,7	333,2	145,7	91,4
Phlda3	diacylglycerol O-acyltransferase 2	3,2	81,0	259,2	150,0	84,4
Mtrr	FBJ osteosarcoma oncogene B	2,0	81,3	163,7	139,3	98,5
Pogk	pleckstrin homology-like domain, family A, member 3	2,9	84,8	244,5	126,9	83,8
Map2k3os	potassium voltage-gated channel, subfamily Q, member 5	3,0	86,3	261,0	118,1	63,4
Egr2	tumor necrosis factor receptor superfamily, member 10b	2,5	88,6	219,0	106,1	51,0
Isg15	Mir17 host gene 1 (non-protein coding)	2,1	90,4	190,1	120,0	51,2
Perp	glucose-fructose oxidoreductase domain containing 1	2,2	92,9	208,5	168,7	237,4
Ipo4	plexin A1	2,1	94,8	200,7	118,0	90,3
Mphosph10	heat shock factor 2	2,4	96,8	233,2	191,0	104,8
Plk3	carbohydrate sulfotransferase 11	2,4	96,8	235,1	180,8	385,7
Ifitm3	growth arrest and DNA-damage-inducible 45 gamma	4,8	104,6	504,8	109,3	95,0
Polr1b	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	2,1	107,0	227,3	192,8	75,8
Usp18	interferon induced transmembrane protein 3	2,8	109,2	302,6	43,9	106,4

Top1mt	DENN/MADD domain containing 5A	2,6	109,5	279,9	102,0	517,4
Dkc1	plasminogen activator, urokinase receptor	2,1	112,4	234,8	55,7	57,3
Polr1c	solute carrier family 19 (thiamine transporter), member 2	3,0	115,4	343,1	221,7	138,4
Cdk6	ubiquitin domain containing 2	2,2	117,4	255,7	198,9	122,2
Ier3	nuclear receptor subfamily 4, group A, member 3	11,8	118,0	1394,1	114,2	69,6
Lta	zinc finger protein 52	2,5	118,8	295,6	160,9	167,4
Ptprs	SH3 domain containing ring finger 1	2,4	119,3	280,9	116,5	156,5
Fnip2	dihydrouridine synthase 2	2,1	122,7	260,3	237,7	202,8
Asna1	cyclin-dependent kinase 5, regulatory subunit 1 (p35)	2,1	122,7	259,3	168,4	124,0
Mybbp1a	processing of precursor 7, ribonuclease P family, (S, cerevisiae)	2,1	125,9	264,9	235,7	150,6
Il1r1	growth factor independent 1	3,5	126,8	437,7	212,0	156,6
Dennd5a	interleukin 15 receptor, alpha chain	2,9	130,9	380,1	144,3	167,8
E2f5	BCL2-like 1	4,7	133,7	627,4	257,4	231,2
Rcl1	protein tyrosine phosphatase, receptor type, S	2,6	136,6	358,8	157,5	125,0
Fosl2	plasmacytoma variant translocation 1	3,4	136,7	465,5	179,8	140,7
Atad3a	fos-like antigen 2	2,5	137,0	347,5	107,2	177,8
Bax	BCL2-associated X protein	2,5	138,0	347,3	260,1	150,2
Phf6	solute carrier family 4, sodium bicarbonate cotransporter, member 7	2,3	140,3	328,2	258,7	397,5
Zfp52	tumor necrosis factor receptor superfamily, member 4	2,2	141,7	311,1	161,7	111,6
Crtam	chemokine (C-X-C motif) ligand 10	12,7	141,7	1798,3	242,1	59,4
Nop14	polo-like kinase 3	2,8	144,8	406,3	200,1	119,9
Rel	CD3E antigen, epsilon polypeptide associated protein	2,2	158,7	350,2	260,9	111,4
Gramd1b	tumor necrosis factor (ligand) superfamily,	2,1	162,4	342,1	242,1	169,7

	member 11					
Ifi27l2a	polymerase (RNA) III (DNA directed) polypeptide D	3,0	166,3	503,7	296,1	121,6
Tnfrsf10b	early growth response 2	2,8	173,5	494,0	136,3	68,2
Rpl7l1	DnaJ (Hsp40) homolog, subfamily C, member 2	2,1	173,6	369,4	346,2	254,3
Eif1a	DNA topoisomerase 1, mitochondrial	2,7	182,2	498,2	338,6	114,4
Nfkb2	tripartite motif-containing 30D	2,3	182,6	423,4	65,8	90,6
Heatr1	DnaJ (Hsp40) homolog, subfamily C, member 21	2,0	190,1	389,4	285,5	228,2
Utp20	SAM domain, SH3 domain and nuclear localization signals, 1	2,2	191,5	422,1	222,8	304,1
Chst11	solute carrier family 5 (inositol transporters), member 3	2,1	191,6	400,2	210,0	123,4
Ddx21	mitochondrial ribosomal protein L15	2,1	191,6	396,3	329,8	137,7
Hsf2	dual specificity phosphatase 5	4,0	203,5	818,1	307,5	560,7
Bccip	apoptosis enhancing nuclease	2,3	211,1	478,5	288,2	137,9
Tagap	ets variant 6	2,3	218,3	508,1	220,5	297,3
Sdc3	DIM1 dimethyladenosine transferase 1-like (S, cerevisiae)	2,2	218,4	486,0	356,0	129,7
Sytl3	2'-5' oligoadenylate synthetase-like 1	2,1	229,0	473,3	130,7	124,3
Gtpbp4	UTP18, small subunit (SSU) processome component, homolog (yeast)	2,1	232,0	494,3	384,9	189,5
Crip2	BRCA2 and CDKN1A interacting protein	2,4	234,6	563,3	437,5	269,8
Sh3rf1	synaptotagmin-like 3	2,4	242,4	572,9	316,7	700,7
Nsfl1c	5-methyltetrahydrofolate-homocysteine methyltransferase reductase	2,9	245,7	706,5	334,6	150,6
Gtf2f1	URB2 ribosome biogenesis 2 homolog (S, cerevisiae)	2,0	245,7	500,2	489,8	184,6
Slc4a7	ubiquitin-conjugating enzyme E2C binding protein	2,1	251,2	530,5	288,2	85,2
Etv6	lysine (K)-specific demethylase 2B	2,2	251,8	547,1	332,7	262,1

Trim30d	queuine tRNA-ribosyltransferase domain containing 1	3,0	260,3	788,7	358,0	75,5
Ddx27	ubiquitin specific peptidase 31	2,0	265,2	533,2	277,1	176,2
Pwp2	eukaryotic translation initiation factor 2-alpha kinase 2	2,0	267,7	540,5	260,8	244,8
Chchd2	ATPase family, AAA domain containing 3A	2,5	268,8	679,7	523,1	147,1
Myo1e	adhesion molecule, interacts with CXADR antigen 1	2,3	269,5	610,9	272,9	182,8
Eif5b	SUMO/sentrin specific peptidase 3	2,0	272,5	548,7	544,5	298,4
Stat5a	ESF1, nucleolar pre-rRNA processing protein, homolog (S, cerevisiae)	2,2	276,3	610,4	482,2	266,5
Cops6	deoxynucleotidyltransferase, terminal, interacting protein 2	2,1	282,9	600,4	359,9	326,1
D19Bwg1357e	TGFB-induced factor homeobox 1	2,1	300,5	618,9	217,5	210,6
Aatf	eukaryotic translation initiation factor 1A	2,5	300,8	738,7	597,7	262,8
Aen	interferon-stimulated protein	2,1	305,7	651,2	144,3	138,4
Amica1	pleiomorphic adenoma gene-like 2	2,1	311,5	651,9	376,2	405,9
Wdr43	PWP2 periodic tryptophan protein homolog (yeast)	2,3	321,8	743,3	586,5	189,3
Cct4	furin (paired basic amino acid cleaving enzyme)	5,2	329,7	1728,3	271,7	421,5
Nifk	tumor necrosis factor	6,6	330,7	2188,4	489,9	213,3
Tgm2	apoptosis antagonizing transcription factor	2,3	331,4	754,8	523,1	221,5
Ero1l	interferon, alpha-inducible protein 27 like 2A	2,5	334,0	828,1	296,0	221,4
Gfod1	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 4	3,9	338,4	1311,3	636,0	298,2
Ak4	methyltransferase like 1	2,2	339,4	744,7	662,8	94,5
Sdad1	notchless homolog 1 (Drosophila)	2,0	339,4	690,3	610,3	158,1
Dimt1	mitochondrial ribosomal protein L3	2,1	340,0	725,5	651,4	359,8
Esf1	UBX domain protein 2A	2,1	343,8	732,9	532,1	428,5

Cd3eap	guanine nucleotide binding protein-like 2 (nucleolar)	3,2	347,6	1124,7	647,4	227,5
Samsn1	programmed cell death 11	2,0	353,9	711,8	435,9	287,4
Tnfrsf4	cyclin-dependent kinase 8	2,0	364,0	731,1	702,5	346,2
Mettl1	eukaryotic translation initiation factor 5B	2,3	365,1	838,2	544,5	355,5
Cd274	RNA terminal phosphate cyclase-like 1	2,5	373,3	948,8	746,4	155,8
Ubtd2	NSFL1 (p97) cofactor (p47)	2,3	374,1	876,1	725,9	369,7
Icos	nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, delta	3,9	378,5	1465,1	389,9	224,0
Kdm2b	M-phase phosphoprotein 10 (U3 small nucleolar ribonucleoprotein)	2,8	379,8	1069,3	738,4	290,8
Larp4	GRAM domain containing 1B	2,5	382,7	949,6	363,4	659,2
Eif3d	ERO1-like (S, cerevisiae)	2,2	387,7	872,3	773,0	520,9
Tnfaip3	nuclear receptor subfamily 4, group A, member 1	6,8	387,8	2639,0	343,7	220,7
Map1b	surfeit gene 2	2,1	399,8	852,2	696,3	204,0
Cdv3	N(alpha)-acetyltransferase 25, NatB auxiliary subunit	2,1	405,7	847,3	669,5	194,1
Plac8	yrdC domain containing (E,coli)	2,0	406,7	830,8	635,3	267,0
Mrpl3	La ribonucleoprotein domain family, member 4	2,2	408,8	887,9	586,6	358,3
Surf2	SDA1 domain containing 1	2,2	419,8	939,9	631,4	284,7
Ubxn2a	importin 4	2,8	420,3	1183,6	777,8	173,5
Utp18	inducible T cell co-stimulator	2,2	423,9	920,9	818,8	796,9
Isg20	solute carrier family 7 (cationic amino acid transporter, y+ system), member 1	2,1	439,4	934,4	842,6	344,6
Dnajc2	arsA arsenite transporter, ATP-binding, homolog 1 (bacterial)	2,6	446,6	1165,0	717,9	963,9
Jak2	polymerase (RNA) I polypeptide C	2,7	447,8	1208,4	854,0	295,9
Slc7a1	spermatogenesis associated 5	2,0	450,8	920,2	516,0	361,6
Syde2	ubiquitin specific peptidase 18	2,7	451,8	1240,5	296,0	250,7

Slc5a6	placenta-specific 8	2,1	452,4	967,3	888,6	590,8
Dnttip2	general transcription factor IIF, polypeptide 1	2,3	454,8	1063,9	890,0	680,8
Idi2	nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, beta	3,4	456,4	1535,5	679,1	502,7
Dus2	PHD finger protein 6	2,5	462,0	1159,5	775,8	510,4
Pitrm1	RRN3 RNA polymerase I transcription factor homolog (yeast)	2,1	462,2	948,4	913,2	388,9
Plxna1	cytotoxic and regulatory T cell molecule	2,5	473,7	1177,8	586,8	431,8
Cdk5r1	COP9 (constitutive photomorphogenic) homolog, subunit 6 (Arabidopsis thaliana)	2,3	483,6	1101,9	947,8	560,3
Ube2cbp	asparagine-linked glycosylation 3 (alpha-1,3-mannosyltransferase)	2,1	485,9	1006,3	758,7	339,4
Tnfsf11	tryptophanyl-tRNA synthetase	2,0	486,1	987,1	897,1	504,7
Pop7	hypoxia up-regulated 1	2,0	494,3	996,6	802,4	690,3
Psme3	family with sequence similarity 60, member A	2,0	500,8	1002,1	834,7	417,6
Mir17hg	bone marrow stromal cell antigen 2	3,8	502,5	1922,9	925,5	246,0
Tsr1	nuclear factor of kappa light polypeptide gene enhancer in B cells 2, p49/p100	2,4	503,2	1231,8	494,0	341,8
Rbpms2	UTP20, small subunit (SSU) processome component, homolog (yeast)	2,4	510,5	1240,2	696,4	245,8
Mrpl47	CD274 antigen	2,2	516,6	1128,7	246,9	220,2
Rab8b	proviral integration site 1	3,4	518,4	1766,4	676,9	970,0
Plagl2	signal transducer and activator of transcription 5A	2,3	530,0	1210,4	496,6	507,8
Grhl1	CD69 antigen	3,2	535,7	1725,8	289,5	153,9
Zeb2	pitrilysin metallepetidase 1	2,1	544,9	1153,8	968,4	349,3
sept-02	cyclin-dependent kinase 6	2,7	550,3	1476,5	1064,0	642,1
Slc5a3	DEAD (Asp-Glu-Ala-Asp) box polypeptide 27	2,3	556,2	1286,9	987,2	480,4
Naa25	polymerase (RNA) I polypeptide B	2,8	556,2	1536,0	1070,4	201,3
Plaur	tumor necrosis factor, alpha-induced protein 3	2,2	560,6	1212,2	255,5	446,0

Metap1	nodal modulator 1	2,1	563,0	1161,0	988,9	439,8
Alg3	NOP14 nucleolar protein	2,5	570,9	1418,9	925,3	398,0
Mrpl15	ribosomal protein L7-like 1	2,5	586,7	1448,7	1030,2	687,2
Oasl1	methionyl aminopeptidase 1	2,1	597,5	1244,1	1139,3	433,4
Rorc	hypoxia inducible factor 1, alpha subunit	3,0	624,2	1854,6	809,4	838,4
Nomo1	Janus kinase 2	2,1	624,5	1328,7	390,6	917,8
Tgif1	nuclear factor of kappa light polypeptide gene enhancer in B cells 1, p105	2,9	661,5	1913,3	713,9	720,5
Lipg	reticuloendotheliosis oncogene	2,5	678,9	1686,4	409,8	580,5
Rrn3	septin 2	2,1	687,3	1436,0	1354,1	1181,3
Dnajc21	nucleolar protein interacting with the FHA domain of MKI67	2,3	733,4	1658,2	1280,0	407,2
Yrdc	elongation factor Tu GTP binding domain containing 2	2,0	739,3	1483,5	1439,0	904,3
Acsl6	myelocytomatosis oncogene	4,0	761,0	3022,8	1064,0	211,5
Spata5	dyskeratosis congenita 1, dyskerin	2,7	778,2	2112,0	1549,5	484,2
Urb2	carnitine deficiency-associated gene expressed in ventricle 3	2,1	801,6	1718,2	1274,7	1010,3
Nle1	GTP binding protein 4	2,4	824,2	1942,6	1578,7	567,3
Wars	HEAT repeat containing 1	2,4	830,3	2020,6	1235,5	495,4
Crem	proteaseome (prosome, macropain) activator subunit 3 (PA28 gamma, Ki)	2,1	838,4	1763,5	1471,1	936,1
Larp1	La ribonucleoprotein domain family, member 1	2,0	861,7	1742,1	1250,9	854,3
Eif2ak2	DNA segment, Chr 19, Brigham & Women's Genetics 1357 expressed	2,3	868,6	1978,4	1218,0	653,4
Hyou1	eukaryotic translation initiation factor 3, subunit D	2,2	909,1	1971,6	1641,9	920,6
Senp3	TSR1 20S rRNA accumulation	2,1	913,9	1915,9	1474,6	477,2
Tmtc2	MYB binding protein (P160) 1a	2,6	1140,0	2962,9	2200,7	459,8
Fosb	T cell activation Rho GTPase activating	2,4	1176,7	2794,4	489,3	704,2

	protein						
Pdcd11	RAB8B, member RAS oncogene family	2,1	1189,5	2492,2	1671,3		2512,5
Usp31	DEAD (Asp-Glu-Ala-Asp) box polypeptide 21	2,4	1210,2	2928,0	2221,1		1098,2
Cdk8	chaperonin containing Tcp1, subunit 4 (delta)	2,3	1321,4	2989,7	2462,5		1294,8
Eftud2	coiled-coil-helix-coiled-coil-helix domain containing 2	2,3	1374,2	3171,2	2636,9		1008,9
Fam60a	WD repeat domain 43	2,3	1727,6	3912,6	2927,5		1014,9

Table 7: Selection of preferred endogenous genes that are constantly active during immune cell activation (dependent or independent from T-cell activation).

Symbol	Gene description
CD3G	CD3 gamma
Rn28s1	28S ribosomal RNA
Rn18s	18S ribosomal RNA
Rn7sk	RNA, 7SK, nuclear
Actg1	actin, gamma, cytoplasmic 1
B2m	beta-2 microglobulin
Rpl18a	ribosomal protein L18A
Pabpc1	poly(A) binding protein, cytoplasmic 1
Gapdh	glyceraldehyde-3-phosphate dehydrogenase
Rpl19	ribosomal protein L19
Rpl17	ribosomal protein L17
Rplp0	ribosomal protein, large, P0
Cfl1	cofilin 1, non-muscle
Pfn1	profilin 1

Table 8: Selection of genes that are transiently upregulated upon T-cell activation.

Symbol	Gene description
Il3	interleukin 3
Il2	interleukin 2
Ccl4	chemokine (C-C motif) ligand 4
Il21	interleukin 21
Gp49a	glycoprotein 49 A
Nr4a3	nuclear receptor subfamily 4, group A, member 3
Lilrb4	leukocyte immunoglobulin-like receptor, subfamily B, member 4
Cd200	CD200 antigen
Cdkn1a	cyclin-dependent kinase inhibitor 1A (P21)
Gzmc	granzyme C
Nr4a2	nuclear receptor subfamily 4, group A, member 2
Cish	cytokine inducible SH2-containing protein
Ccr8	chemokine (C-C motif) receptor 8
Lad1	ladinin
Crabp2	cellular retinoic acid binding protein II

Table 9: Selection of genes that are upregulated over more than 24 hours upon T-cell activation.

Symbol	Description
Gzmb	granzyme B
Tbx21	T-box 21
Pdcd1	programmed cell death 1
Plek	pleckstrin
Chek1	checkpoint kinase 1
Slamf7	SLAM family member 7
Zbtb32	zinc finger and BTB domain containing 32
Tigit	T cell immunoreceptor with Ig and ITIM domains
Lag3	lymphocyte-activation gene 3
Gzma	granzyme A
Wee1	WEE 1 homolog 1 (S. pombe)
Il12rb2	interleukin 12 receptor, beta 2
Ccr5	chemokine (C-C motif) receptor 5
Eea1	early endosome antigen 1
Dtl	denticleless homolog (Drosophila)

Table 10: Selection of genes that are down-regulated upon immune cell activation.

Symbol	Gene description
Spata6	spermatogenesis associated 6
Itga6	integrin alpha 6
Rcbtb2	regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 2
Cd1d1	CD1d1 antigen
St8sia4	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4
Itgae	integrin alpha E, epithelial-associated
Fam214a	family with sequence similarity 214, member A
Slc6a19	solute carrier family 6 (neurotransmitter transporter), member 19
Cd55	CD55 antigen
Xkrx	X Kell blood group precursor related X linked
Mturn	maturin, neural progenitor differentiation regulator homolog (Xenopus)
H2-Ob	histocompatibility 2, O region beta locus
Cnr2	cannabinoid receptor 2 (macrophage)
Itgae	integrin alpha E, epithelial-associated
Raver2	ribonucleoprotein, PTB-binding 2
Zbtb20	zinc finger and BTB domain containing 20
Arrb1	arrestin, beta 1
Abca1	ATP-binding cassette, sub-family A (ABC1), member 1
Tet1	tet methylcytosine dioxygenase 1
Slc16a5	solute carrier family 16 (monocarboxylic acid transporters), member 5
Trav14-1	T cell receptor alpha variable 14-1
Ampd3	adenosine monophosphate deaminase 3

Table 11:.Selection of human genes that are silent upon T-cell activation (safe harbor gene targeted integration loci).

Symbol	Gene description
Zfp640	zinc finger protein 640
LOC100038422	uncharacterized LOC100038422
Zfp600	zinc finger protein 600
Serpinb3a	serine (or cysteine) peptidase inhibitor, clade B (ovalbumin), member 3A
Tas2r106	taste receptor, type 2, member 106
Magea3	melanoma antigen, family A, 3
Omt2a	oocyte maturation, alpha
Cpxcr1	CPX chromosome region, candidate 1
Hsf3	heat shock transcription factor 3
Pbsn	Probasin
Sbp	spermine binding protein
Wfdc6b	WAP four-disulfide core domain 6B
Meiob	meiosis specific with OB domains
Dnm3os	dynamin 3, opposite strand
Skint11	selection and upkeep of intraepithelial T cells 11

Table 12: List of gene loci upregulated in tumor exhausted infiltrating lymphocytes (compiled from multiple tumors) useful for gene integration of exogenous coding sequences as per the present invention

Gene names	Uniprot ID (human)
CXCL13	O43927
TNFRSF1B	P20333
RGS2	P41220
TIGIT	Q495A1
CD27	P26842
TNFRSF9	Q12933
SLA	Q13239
INPP5F	Q01968
XCL2	Q9UBD3
HLA-DMA	P28067
FAM3C	Q92520
WARS	P23381
EIF3L	Q9Y262
KCNK5	O95279
TMBIM6	P55061
CD200	P41217
C3H7A	O60880
SH2D1A	O60880
ATP1B3	P54709
THADA	Q6YHU6
PARK7	Q99497
EGR2	P11161
FDFT1	P37268
CRTAM	O95727
IFI16	Q16666

Table 13: List of gene loci upregulated in hypoxic tumor conditions useful for gene integration of exogenous coding sequences as per the present invention

Gene names	Strategy	
CTLA-4	KO/KI	Target shown to be upregulated in T-cells upon hypoxia exposure and T cell exhaustion
LAG-3 (CD223)	KO/KI	
PD1	KO/KI	
4-1BB (CD137)	KI	
GITR	KI	
OX40	KI	
IL10	KO/KI	
ABCB1	KI	HIF target
ABCG2	KI	
ADM	KI	
ADRA1B	KI	
AK3	KI	
ALDOA	KI	
BHLHB2	KI	
BHLHB3	KI	
BNIP3	KI	
BNIP3L	KI	
CA9	KI	
CCNG2	KI	
CD99	KI	
CDKN1A	KI	
CITED2	KI	
COL5A1	KI	
CP	KI	

CTGF	KI	
CTSD	KI	
CXCL12	KI	
CXCR4	KI	
CYP2S1	KI	
DDIT4	KI	
DEC1	KI	
EDN1	KI	
EGLN1	KI	
EGLN3	KI	
ENG	KI	
ENO1	KI	
EPO	KI	
ETS1	KI	
FECH	KI	
FN1	KI	
FURIN	KI	
GAPDH	KI	
GPI	KI	
GPX3	KI	
HK1	KI	
HK2	KI	
HMOX1	KI	
HSP90B1	KI	
ID2	KI	
IGF2	KI	
IGFBP1	KI	
IGFBP2	KI	
IGFBP3	KI	

ITGB2	KI	
KRT14	KI	
KRT18	KI	
KRT19	KI	
LDHA	KI	
LEP	KI	
LOX	KI	
LRP1	KI	
MCL1	KI	
MET	KI	
MMP14	KI	
MMP2	KI	
MXI1	KI	
NOS2A	KI	
NOS3	KI	
NPM1	KI	
NR4A1	KI	
NT5E	KI	
PDGFA	KI	
PDK1	KI	
PFKFB3	KI	
PFKL	KI	
PGK1	KI	
PH-4	KI	
PKM2	KI	
PLAUR	KI	
PMAIP1	KI	
PPP5C	KI	
PROK1	KI	

SERPINE1	KI	
SLC2A1	KI	
TERT	KI	
TF	KI	
TFF3	KI	
TFRC	KI	
TGFA	KI	
TGFB3	KI	
TGM2	KI	
TPI1	KI	
VEGFA	KI	
VIM	KI	
TMEM45A	KI	
AKAP12	KI	
SEC24A	KI	
ANKRD37	KI	
RSBN1	KI	
GOPC	KI	
SAMD12	KI	
CRKL	KI	
EDEM3	KI	
TRIM9	KI	
GOSR2	KI	
MIF	KI	
ASPH	KI	
WDR33	KI	
DHX40	KI	
KLF10	KI	
R3HDM1	KI	

RARA	KI	
LOC162073	KI	
PGRMC2	KI	
ZWILCH	KI	
TPCN1	KI	
WSB1	KI	
SPAG4	KI	
GYS1	KI	
RRP9	KI	
SLC25A28	KI	
NTRK2	KI	
NARF	KI	
ASCC1	KI	
UFM1	KI	
TXNIP	KI	
MGAT2	KI	
VDAC1	KI	
SEC61G	KI	
SRP19	KI	
JMJD2C	KI	
SNRPD1	KI	
RASSF4	KI	

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CLAIMS

1. Method for preparing engineered immune cells for cell immunotherapy, said method comprising:
   - providing a population of primary immune cells;
   - introducing into a proportion of said primary immune cells:
   i) at least one nucleic acid comprising an exogenous nucleotide or polynucleotide sequence to be integrated at a selected endogenous locus to encode at least one molecule improving the therapeutic potential of said immune cells population;
   ii) at least one sequence-specific reagent that specifically targets said selected endogenous locus,

wherein said exogenous nucleotide or polynucleotide sequence is inserted by targeted gene integration into said endogenous locus, so that said exogenous nucleotide or polynucleotide sequence forms an exogenous coding sequence under transcriptional control of an endogenous promoter present at said locus,
wherein the transcriptional activity of said endogenous promoter is upregulated upon immune cell activation.

2. The method according to claim 1, wherein said sequence specific reagent is a specific endonuclease reagent.

3. The method according to claim 1 or 2, wherein said targeted gene integration is operated by homologous recombination or NHEJ into said immune cells.

4. The method according to any one of claims 1 to 3, wherein said molecule encoded by said exogenous coding sequence is a RNA transcript, such as a RNAi, or a polypeptide, such as a functional protein.

5. The method according to any one of claims 1 to 4, wherein said molecule improving the therapeutic potential activity of said population of primary immune cells, confers resistance of the immune cells to a drug, increases persistence of the immune cells (*in-vivo* or *in-vitro*) or its safety.

6. The method according to claim 5, wherein said molecule enhancing the persistence of the primary immune cells is selected from a cytokine receptor, a protein conferring resistance to a drug or a secreted antibody directed against inhibitory peptides or

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proteins, such as an anti-IDO1, anti-IL10, anti-PD1, anti-PDL1, anti-IL6 or anti-PGE2 antibody.

7. The method according to any one of claims 1 to 5, wherein said exogenous sequence encodes a chemokine or a cytokine, such as IL-2, IL-12 and IL-15.

8. The method according to any one of claims 1 to 5, wherein said exogenous sequence enhancing the therapeutic activity of the T-cell encodes a secreted inhibitor of Tumor Associated Macrophages (TAM), such as a CCR2/CCL2 neutralization agent.

9. The method according to any one of claims 1 to 5, wherein said exogenous sequence enhancing the safety of the primary immune cell encodes a component of a chimeric antigen receptor (CAR).

10. The method according to claim 9, wherein said CAR is an inhibitory CAR that contributes to an improved specificity of the immune cell against a given cell type.

11. The method according to any one of claims 1 to 5, wherein said exogenous sequence enhancing the safety of the primary immune cell encodes cytochrome(s) P450, CYP2D6-1, CYP2D6-2, CYP2C9, CYP3A4, CYP2C19 or CYP1A2, conferring hypersensitivity of said immune cells to a drug, such as cyclophosphamide and/or isophosphamide.

12. The method according to any one of claims 1 to 11, wherein said endogenous promoter is induced in T-cells and is selected among CCR7, CD2, CD3, CD4, CD8, CD28, CD45, CD96, CD229/SLAMF3, DNAM-1/CD226, CD25/IL-2 R alpha, L-Selectin/CD62L and TIGIT.

13. The method according to any one of claims 1 to 11, wherein said endogenous promoter is induced in NK cells and is selected among CD161, CD229/SLAMF3, CD96, DNAM-1/CD226, Fc gamma RII/CD32, Fc gamma RII/RIII (CD32/CD16), Fc gamma RIII (CD16), IL-2 R beta, Integrin alpha 2/CD49b, KIR/CD158, NCAM-1/CD56, NKG2A/CD159a, NKG2C/CD159c, NKG2D/CD314, NKp30/NCR3, NKp44/NCR2, NKp46/NCR1, NKp80/KLRF1, Siglec-7/CD328 and TIGIT.

14. The method according to any one of claims 1 to 11, wherein said transcriptional activity of said endogenous promoter is transient upon immune cell activation.

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15. The method according to any one of claims 1 to 11, wherein said promoter is up-regulated over less than 12 hours upon immune cell activation and is selected from *Spata6, Itga6, Rcbtb2, Cd1d1, St8sia4, Itgae* and *Fam214a*.

16. The method according to any one of claims 1 to 11, wherein said promoter is up-regulated over less than 24 hours upon immune cell activation and is selected from *IL3, IL2, Ccl4, IL21, Gp49a, Nr4a3, Lilrb4, Cd200, Cdkn1a, Gzmc, Nr4a2, Cish, Ccr8, Lad1* and *Crabp2*.

17) The method according to any one of claims 1 to 11, wherein said gene is up-regulated over more than 24 hours upon immune cell activation andis selected from *Gzmb, Tbx21, Plek, Chek1, Slamf7, Zbtb32, Tigit, Lag3, Gzma, Wee1, IL12rb2, Eea1* and *Dtl*.

18) The method according to any one of claims 1 to 17, wherein a chimeric antigen receptor (CAR) or a modified TCR is being independently expressed in the transfected immune cells.

19) The method according to claim 18, wherein said endogenous promoter activity is dependent on said CAR expressed into the transfected immune cells.

20) The method according to any one of claims 1 to 19, wherein said specific endonuclease reagent is introduced by electroporation as a polypeptide or under a mRNA, which is translated into the cell.

21) The method according to any one of claims 1 to 20, wherein said exogenous nucleic acid comprising said coding sequence is included in a DNA vector, preferably a viral vector, such as an AAV vector.

22) The method according to claim 21, wherein the nucleic acid encoding said sequence-specific endonuclease reagent and said exogenous nucleic acid are both included into said DNA vector.

23) The method according to any one of claims 1 to 22, wherein the exogenous sequence that is introduced into the immune cell is preceded or followed by a sequence encoding

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a 2A peptide to enable the transcription of said exogenous coding sequence along with at least one part of the endogenous gene.

24) The method according to any one of claims 1 to 23, wherein the exogenous sequence is introduced with the effect of inactivating the expression of at least one endogenous genomic sequence initially present in said gene.

25) The method according to claim 24, wherein said endogenous genomic sequence that is being inactivated encodes suppressive cytokines, kinases or their receptors thereof, such as TGFb, TGFbR, IL-10, IL-10R, GCN2 or PRDM1.

26) The method according to claim 24, wherein said endogenous genomic sequence that is being inactivated encodes a protein acting as an immune checkpoint, such as PD1, PDL1, CTLA4, TIM3 or LAG3.

27) The method according to claim 24, wherein said endogenous genomic sequence that is being inactivated expresses an enzyme that activates a prodrug, such as DCK, HPRT or GGH.

28) The method according to any one of claims 1 to 27, wherein said immune cell is a primary T-cell or NK cell.

29) An engineered immune cell obtained by the method of any of claims 1 to 28.

30) An engineered immune cell, which comprises an exogenous coding sequence under transcriptional control of an endogenous gene promoter, wherein said endogenous gene promoter is responsive to the activation of said immune cell, preferably up-regulated, and wherein said engineered immune cell is a primary cell endowed with a chimeric antigen receptor.

31) The engineered immune cell according to any one claims 29 to 30, wherein said endogenous gene is selected from the following: Il3, Il2, Ccl4, Il21, Gp49a, Cxcl10, Nr4a3, Lilrb4, Cd200, Cdkn1a, Gzmc, Nr4a2, Cish, Nr4a1, Tnf ,Ccr8, Lad1, Slamf1, Crabp2, Furin, Gadd45g, Bcl2l1, Ncs1, Ciart, Ahr, Spry1 ,Tnfsf4, , Myo10, Dusp5, Myc, Psrc1, St6galnac4, Nfkbid, Bst2, Txnrd3, Plk2, Gfi1, Pim1, Pvt1, Nfkbib, Gnl2, Cd69, Dgat2, Atf3, Tnfrsf21, Lonrf1, Cables1, Cpd, Qtrtd1, Polr3d, Kcnq5, Fos, Slc19a2, Hif1a, Il15ra, Nfkb1, Phlda3, Mtrr, Pogk, Map2k3os, Egr2, Isg15, Perp, Ipo4, Mphosph10, Plk3, Ifitm3, Polr1b, Usp18, Top1mt, Dkc1, Polr1c, Cdk6, Ier3, Lta, Ptprs, Fnip2, Asna1, Mybbp1a, Il1r1, Dennd5a, E2f5, Rcl1, Fosl2, Atad3a, Bax ,Phf6 ,Zfp52, Crtam ,Nop14, Rel ,Gramd1b ,Ifi27l2a ,Tnfrsf10b, Rpl7l1, Eif1a, Nfkb2, Heatr1, Utp20, Chst11, Ddx21, Hsf2, Bccip, Tagap, Sdc3, Sytl3, Gtpbp4, Crip2, Sh3rf1, Nsfl1c, Gtf2f1,

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Slc4a7, Etv6, Trim30d, Ddx27, Pwp2, Chchd2, Myo1e, Eif5b, Stat5a, Cops6, D19Bwg1357e, Aatf, Aen, Amica1, Wdr43, Cct4, Nifk, Tgm2, Ero1l, Gfod1, Ak4, Sdad1, Dimt1, Esf1, Cd3eap, Samsn1, Tnfrsf4, Mettl1, Cd274, Ubtd2, Icos, Kdm2b, Larp4, Eif3d, Tnfaip3, Map1b, Cdv3, Plac8, Mrpl3, Surf2, Ubxn2a, Utp18, Isg20, Dnajc2, Jak2, Slc7a1, Syde2, Slc5a6, Dnttip2, Idi2, Dus2, Pitrm1, Plxna1, Cdk5r1, Ube2cbp, Tnfsf11, Pop7, Psme3, Mir17hg, Tsr1, Rbpms2, Mrpl47, Rab8b, Plagl2, Grhl1, Zeb2, Slc5a3, Naa25, Plaur, Metap1, Alg3, Mrpl15, Oasl1, Rorc, Nomo1, Tgif1, Lipg, Rrn3, Dnajc21, Yrdc, Acsl6, Spata5, Urb2, Nle1, Wars, Crem, Larp1, Eif2ak2, Hyou1, Senp3, Tmtc2, Fosb, Pdcd11, Usp31, Cdk8, Eftud2, and Fam60a.

32) The engineered immune cell according to any one of claims 29 to 31, wherein said immune cell is a primary T-cell or a NK-cell.

33) The engineered immune cell according to any one of claims 29 to 32, wherein said cell expresses a first exogenous sequence encoding a CAR at the TCR locus, thereby disrupting TCR expression, and expresses a second exogenous coding sequence under transcriptional activity of an endogenous locus selected from PD1, CD25, CD71 or CD69.

34) The engineered immune cell according to claim 33, wherein said transcriptional control of said endogenous gene promoter is responsive to the signal activation of said chimeric antigen receptor (CAR).

35) A therapeutically effective population of immune cells, comprising at least 30 %, preferably 50 %, more preferably 80 % of cells according to any one of claims 29 to 35.

36) The population of immune cells according to claim 35, wherein more than 50% of said immune cells are TCR negative T-cells.

37) The population of immune cells according to any one of claims 35 and 36, wherein more than 50% of said immune cells are CAR positive cells.

38) A pharmaceutical composition comprising an engineered immune cell according to any one of claims 29 to 34 or the immune cell population according to any one of claims 35 to 37.

39) Use of an engineered immune cell according to any one of claims 29 to 34 or immune cell population according to any one of claims 35 to 37 or the pharmaceutical

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composition according to claim 38 in the manufacture of a medicament for the treatment of cancer.

40) A method for the treatment of cancer comprising administering a therapeutically effective dose of an engineered immune cell according to any one of claims 29 to 34 or immune cell population according to any one of claims 35 to 37 or the pharmaceutical composition according to claim 38 to a patient in need thereof.

Cellectis

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON

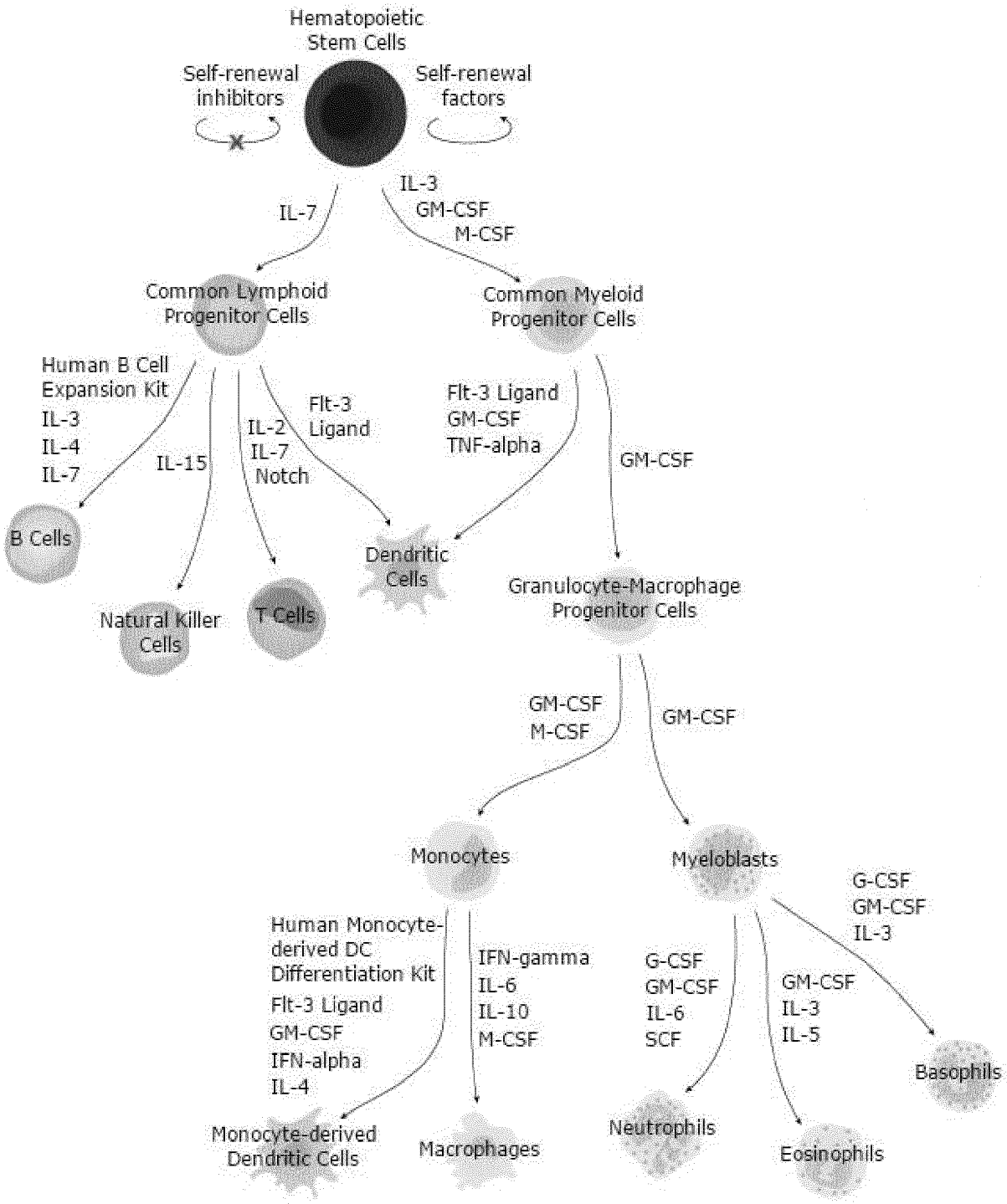

Hematopoietic Stem Cells
Self-renewal inhibitors
Self-renewal factors
IL-7
IL-3
GM-CSF
M-CSF
Common Lymphoid Progenitor Cells
Common Myeloid Progenitor Cells
Human B Cell Expansion Kit
IL-3
IL-4
IL-7
IL-15
IL-2
IL-7
Notch
Flt-3 Ligand
Flt-3 Ligand
GM-CSF
TNF-alpha
GM-CSF
B Cells
Natural Killer Cells
T Cells
Dendritic Cells
Granulocyte-Macrophage Progenitor Cells
GM-CSF
M-CSF
GM-CSF
Monocytes
Myeloblasts
Human Monocyte-derived DC Differentiation Kit
Flt-3 Ligand
GM-CSF
IFN-alpha
IL-4
IFN-gamma
IL-6
IL-10
M-CSF
G-CSF
GM-CSF
IL-6
SCF
GM-CSF
IL-3
IL-5
G-CSF
GM-CSF
IL-3
Basophils
Monocyte-derived Dendritic Cells
Macrophages
Neutrophils
Eosinophils

Figure 1

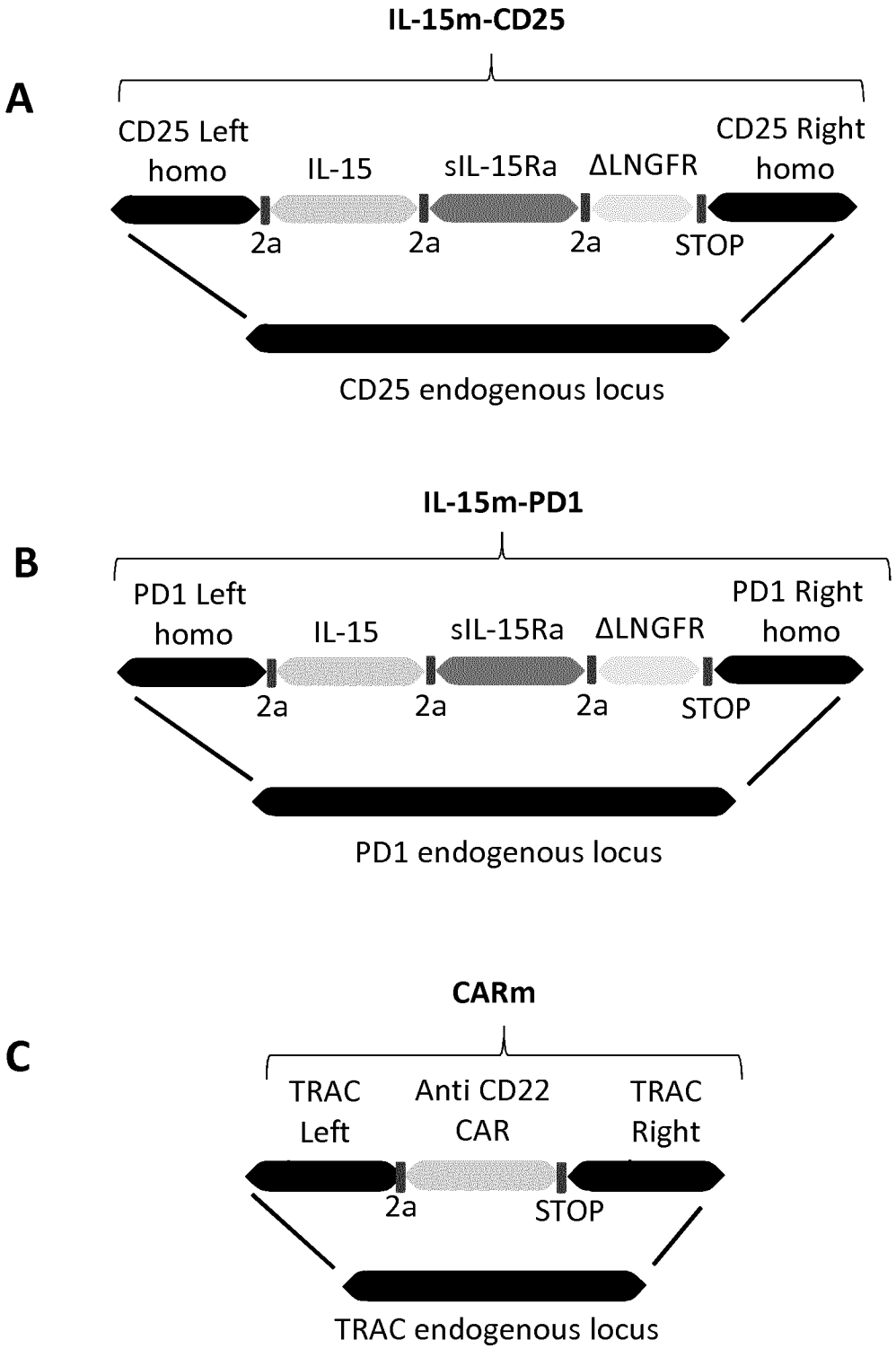

A
IL-15m-CD25
CD25 Left homo
IL-15
sIL-15Ra
ΔLNGFR
CD25 Right homo
2a
2a
2a
STOP
CD25 endogenous locus
B
IL-15m-PD1
PD1 Left homo
IL-15
sIL-15Ra
ΔLNGFR
PD1 Right homo
2a
2a
2a
STOP
PD1 endogenous locus
C
CARm
TRAC Left
Anti CD22 CAR
TRAC Right
2a
STOP
TRAC endogenous locus

Figure 2

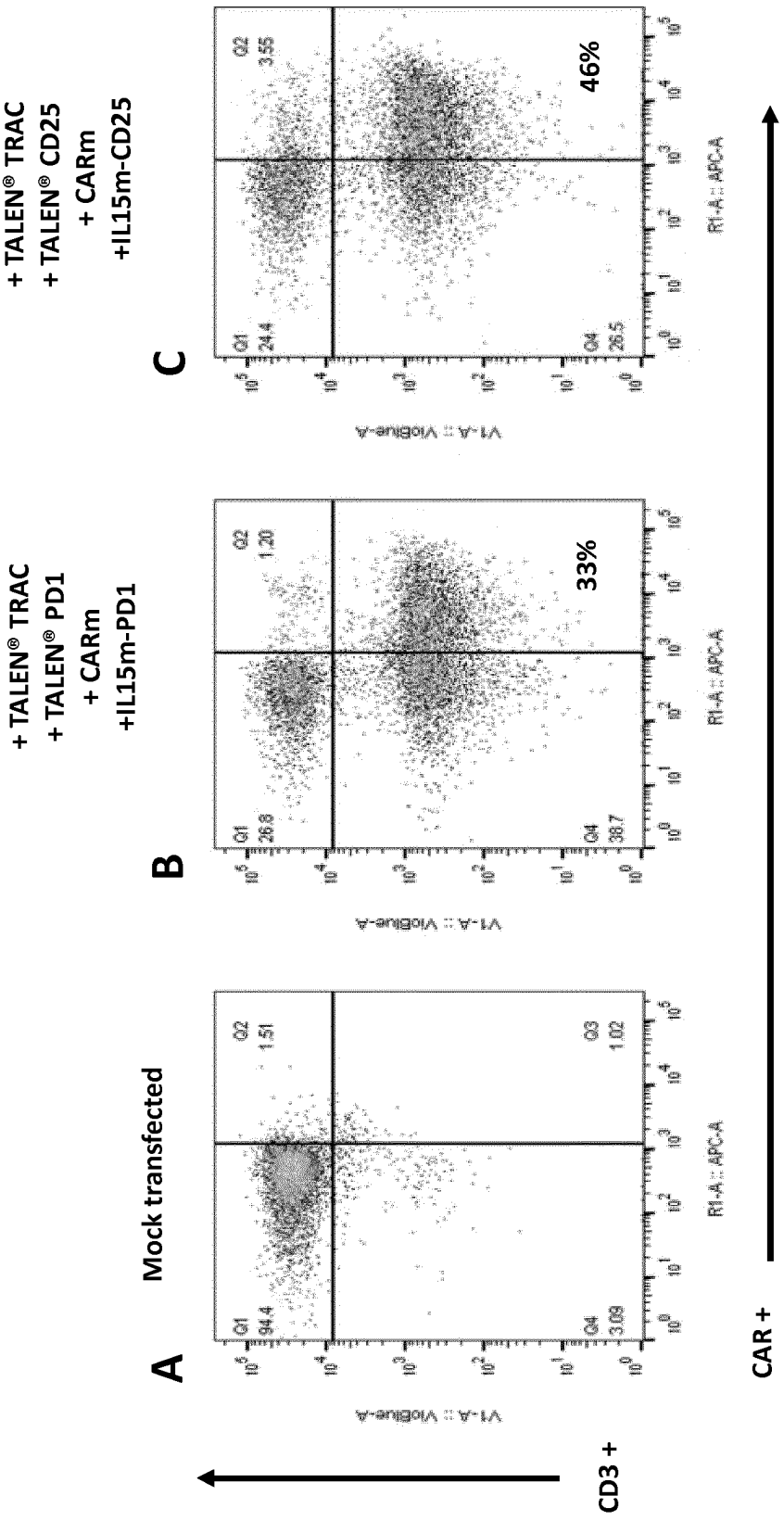

A
Mock transfected
B
+ TALEN® TRAC
+ TALEN® PD1
+ CARm
+IL15m-PD1
33%
C
+ TALEN® TRAC
+ TALEN® CD25
+ CARm
+IL15m-CD25
46%
CD3 +
CAR +
V1-A :: Violblue-A
R1-A :: APC-A

Figure 3

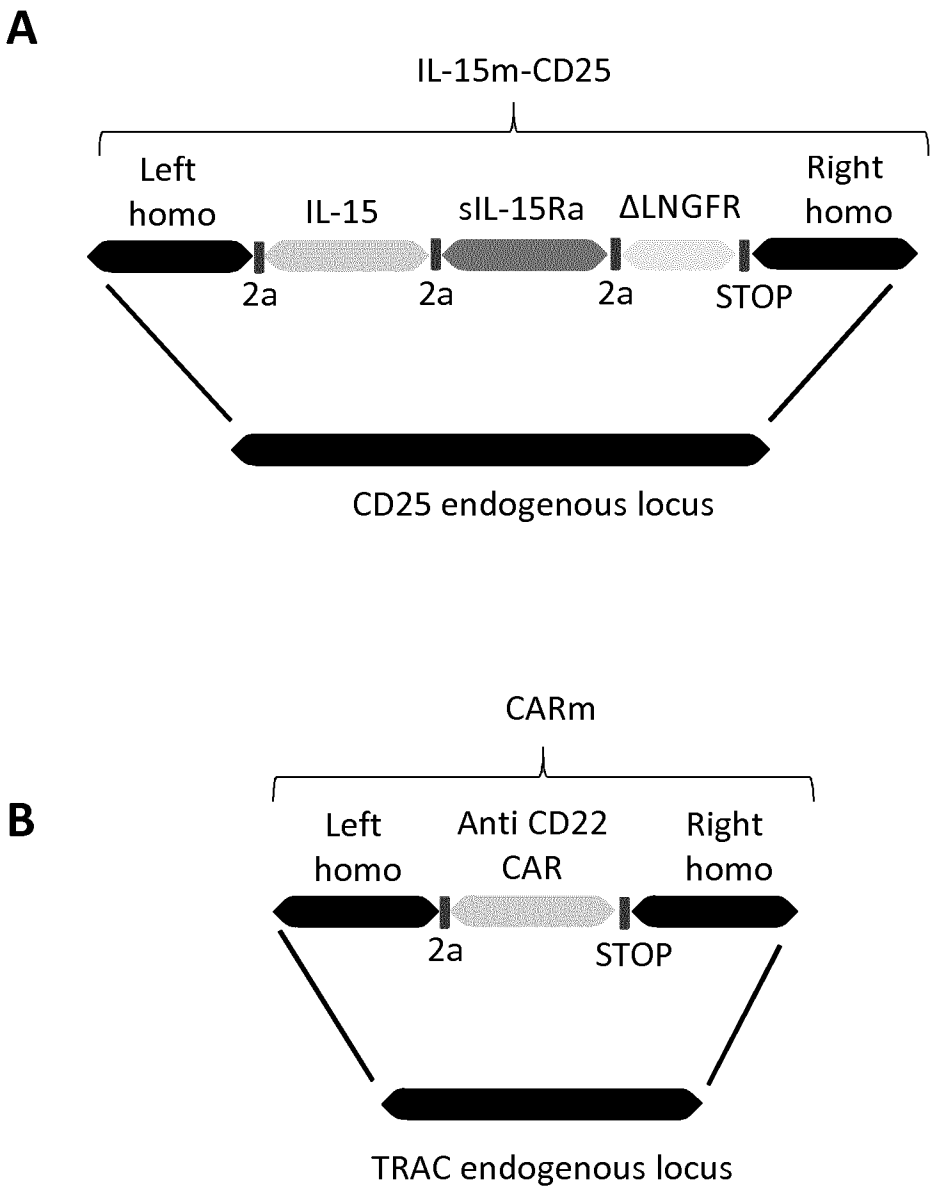

A
IL-15m-CD25
Left homo
IL-15
sIL-15Ra
ΔLNGFR
Right homo
2a
2a
2a
STOP
CD25 endogenous locus
B
CARm
Left homo
Anti CD22 CAR
Right homo
2a
STOP
TRAC endogenous locus

Figure 4

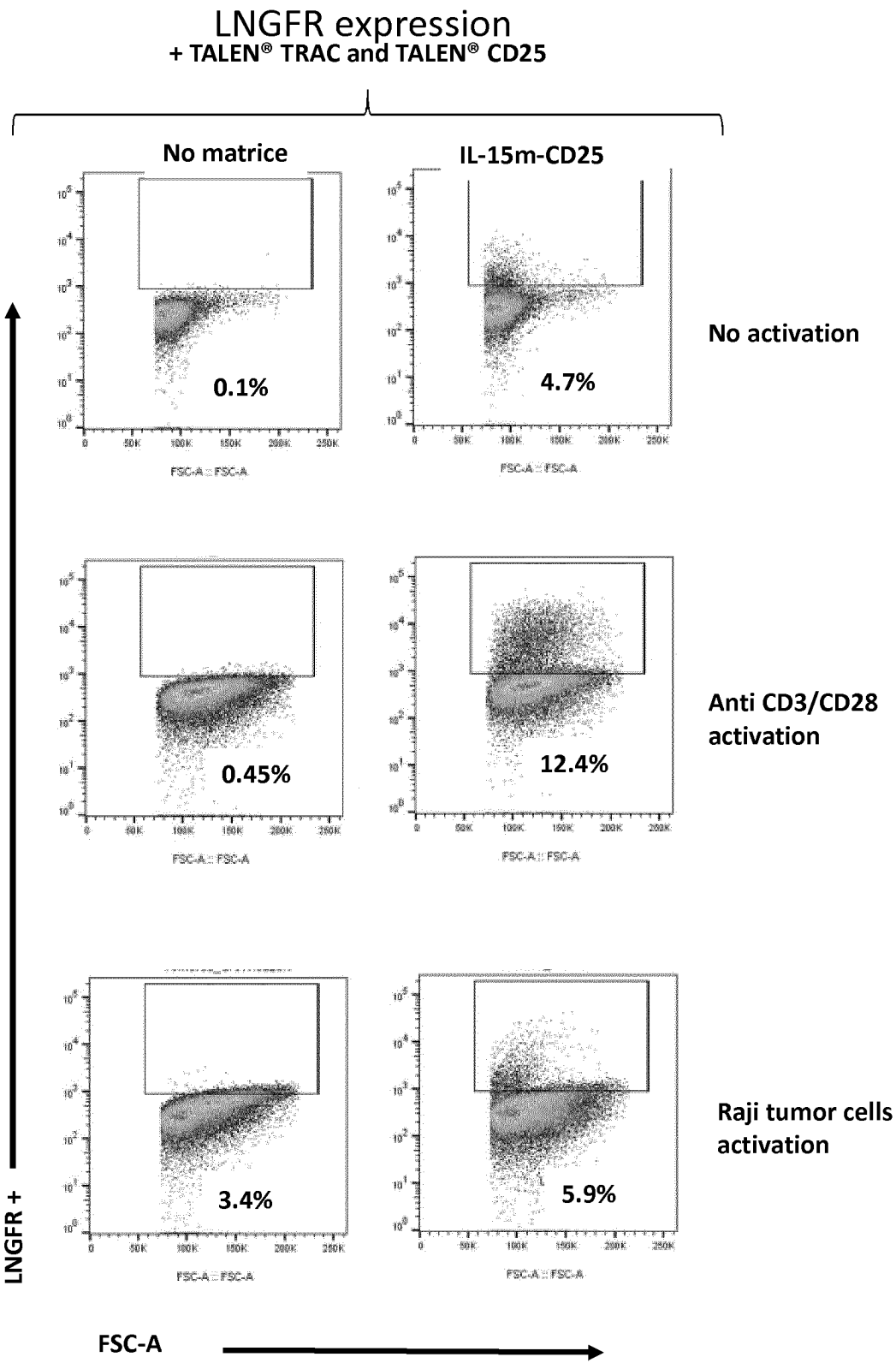

LNGFR expression
+ TALEN® TRAC and TALEN® CD25
No matrice
IL-15m-CD25
No activation
Anti CD3/CD28 activation
Raji tumor cells activation
0.1%
4.7%
0.45%
12.4%
3.4%
5.9%
FSC-A :: FSC-A
LNGFR +
FSC-A

Figure 5

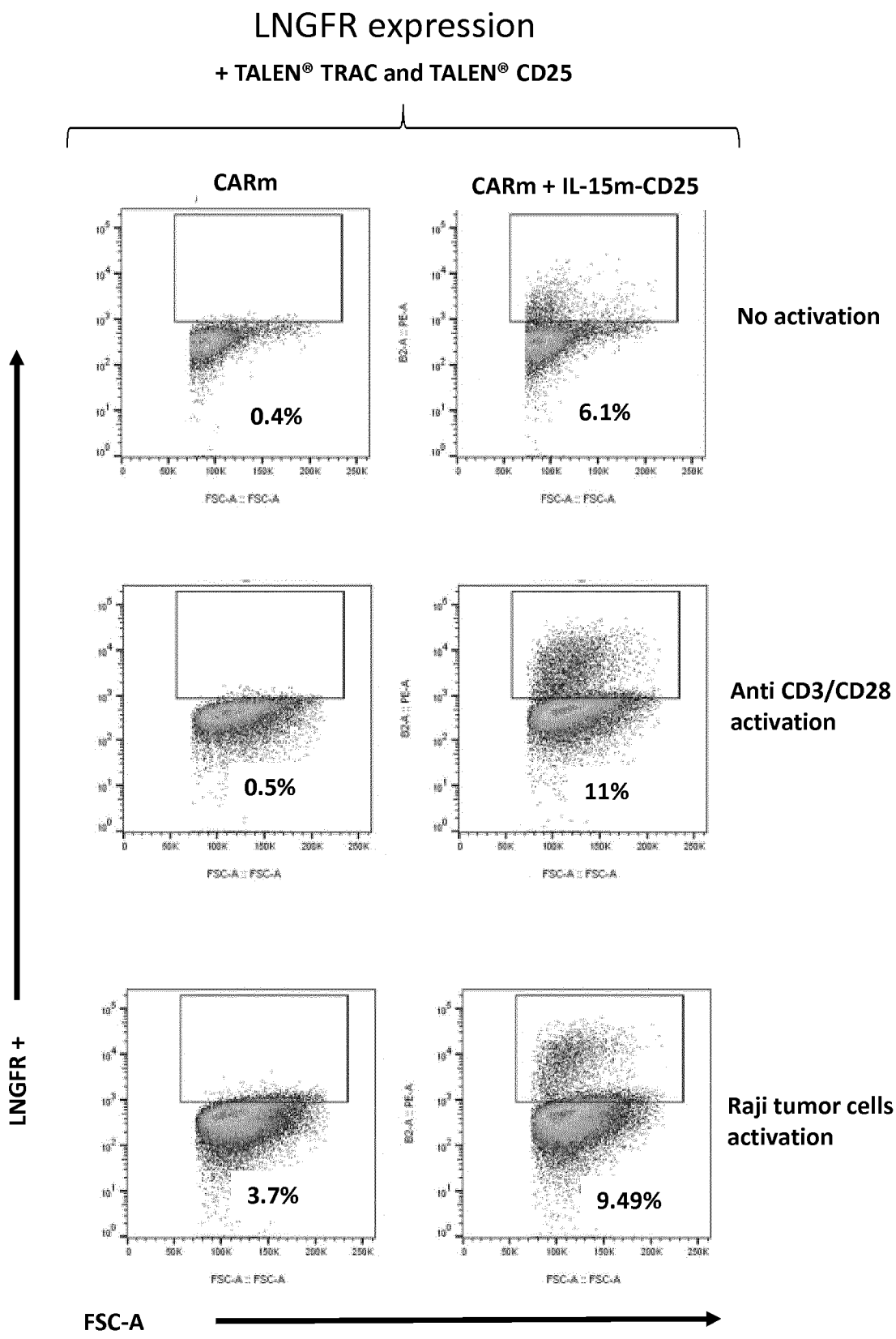

LNGFR expression
+ TALEN® TRAC and TALEN® CD25
CARm
CARm + IL-15m-CD25
No activation
Anti CD3/CD28 activation
Raji tumor cells activation
0.4%
6.1%
0.5%
11%
3.7%
9.49%
LNGFR +
FSC-A

Figure 6

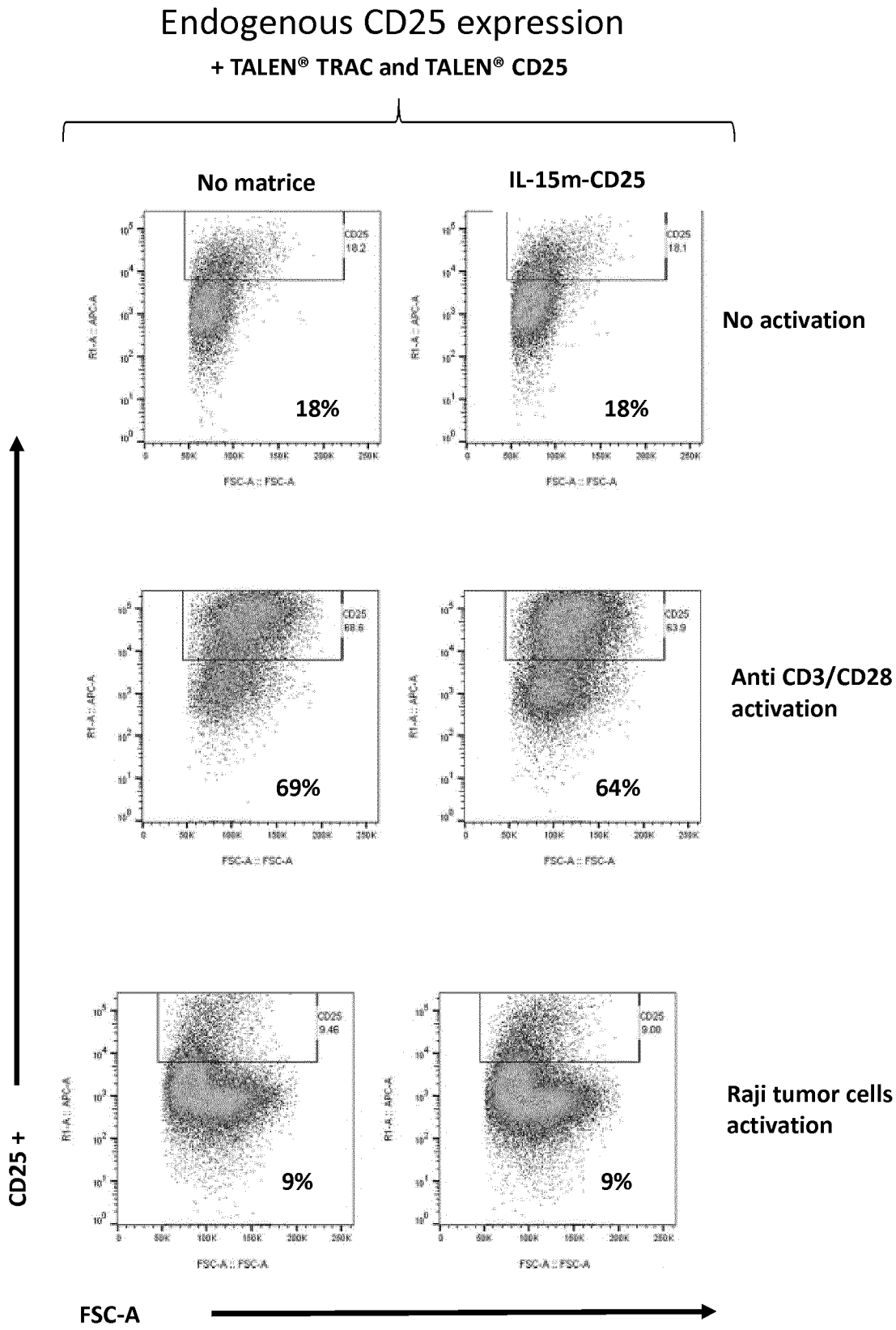

Endogenous CD25 expression
+ TALEN® TRAC and TALEN® CD25
No matrice
IL-15m-CD25
No activation
Anti CD3/CD28 activation
Raji tumor cells activation
18%
18%
69%
64%
9%
9%
CD25 +
FSC-A

Figure 7

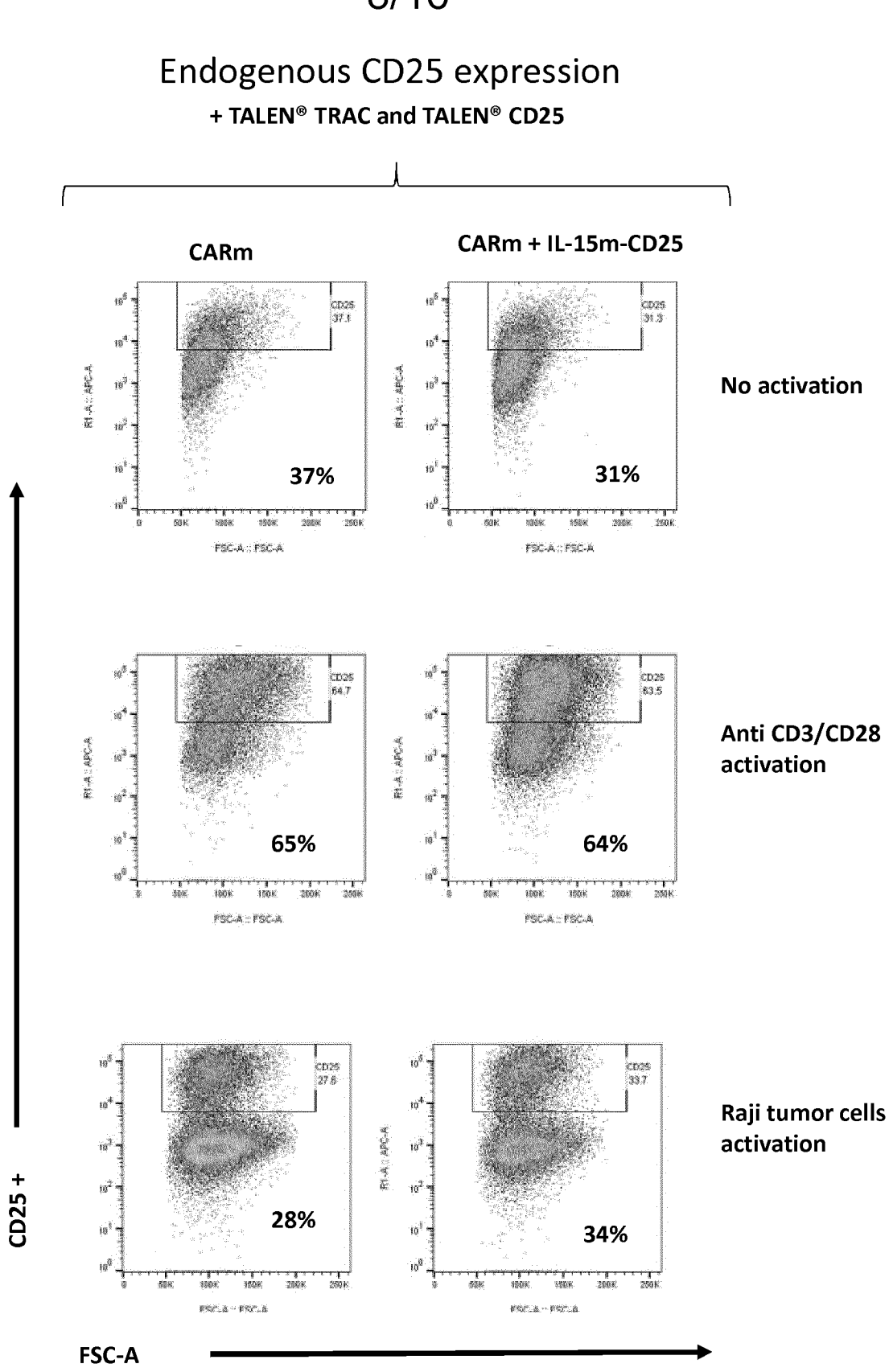

Endogenous CD25 expression
+ TALEN® TRAC and TALEN® CD25
CARm
CARm + IL-15m-CD25
No activation
Anti CD3/CD28 activation
Raji tumor cells activation
37%
31%
65%
64%
28%
34%
CD25 +
FSC-A

Figure 8

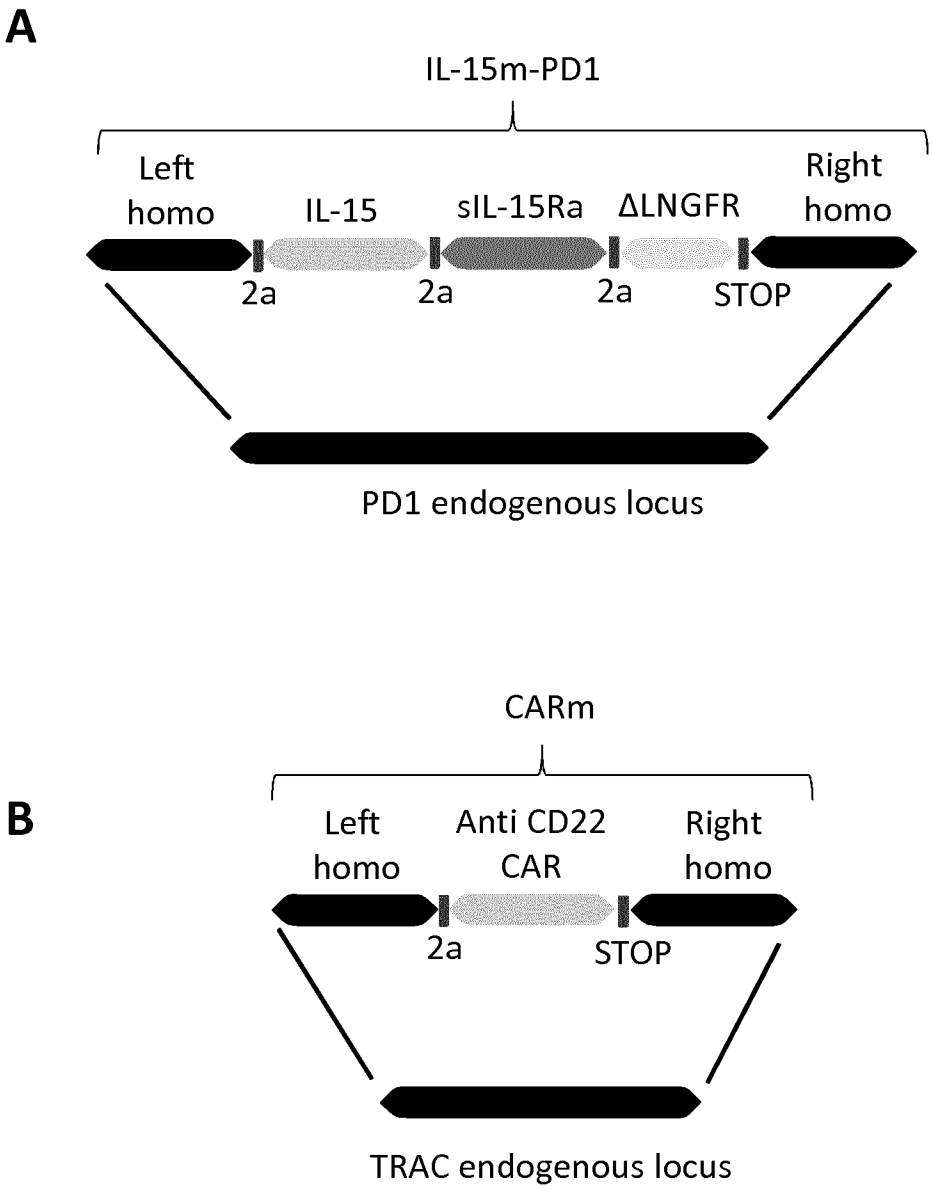

A
IL-15m-PD1
Left homo
IL-15
sIL-15Ra
ΔLNGFR
Right homo
2a
2a
2a
STOP
PD1 endogenous locus
B
CARm
Left homo
Anti CD22 CAR
Right homo
2a
STOP
TRAC endogenous locus

Figure 9

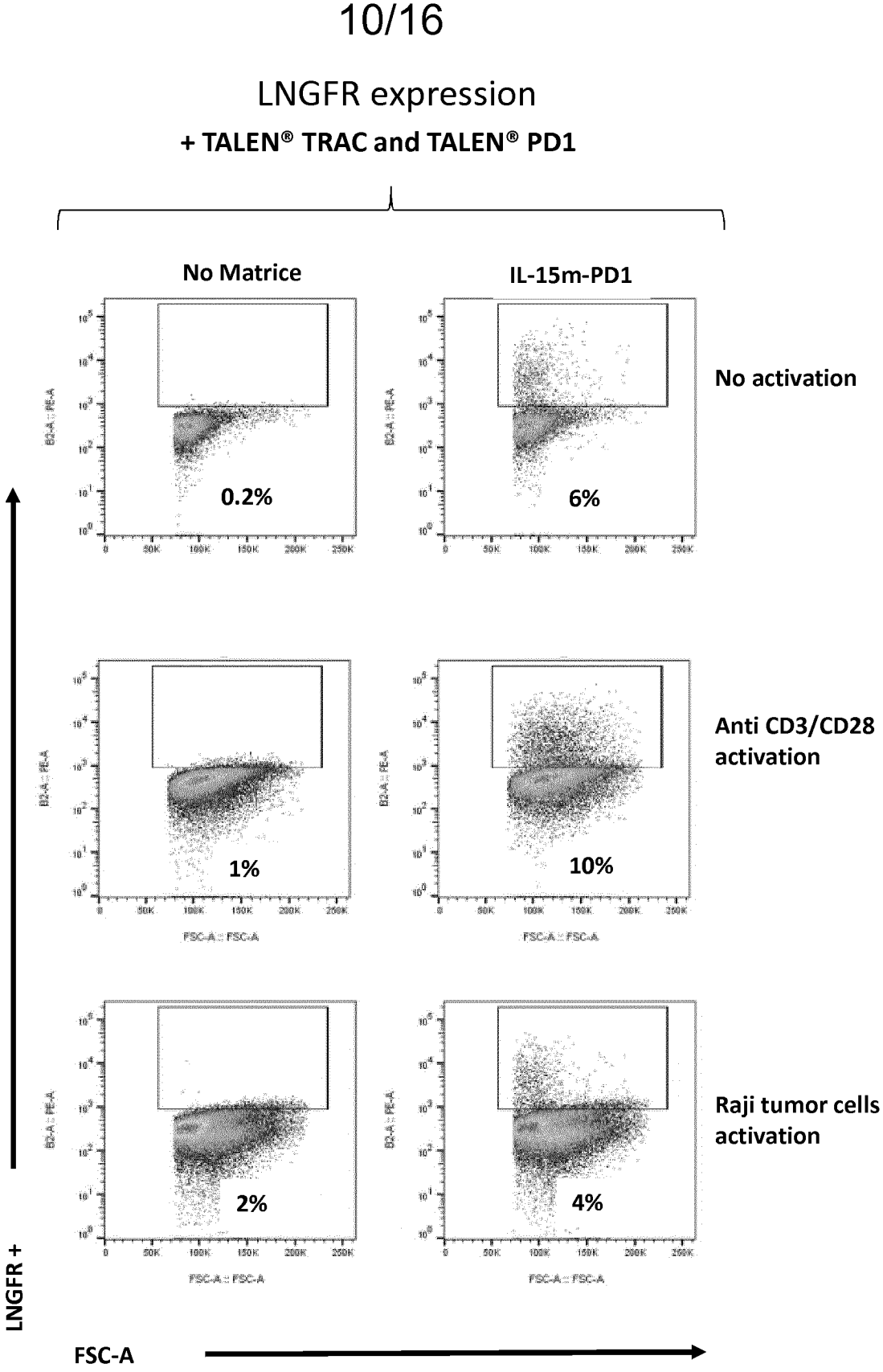

LNGFR expression
+ TALEN® TRAC and TALEN® PD1
No Matrice
IL-15m-PD1
No activation
Anti CD3/CD28 activation
Raji tumor cells activation
0.2%
6%
1%
10%
2%
4%
LNGFR +
FSC-A

Figure 10

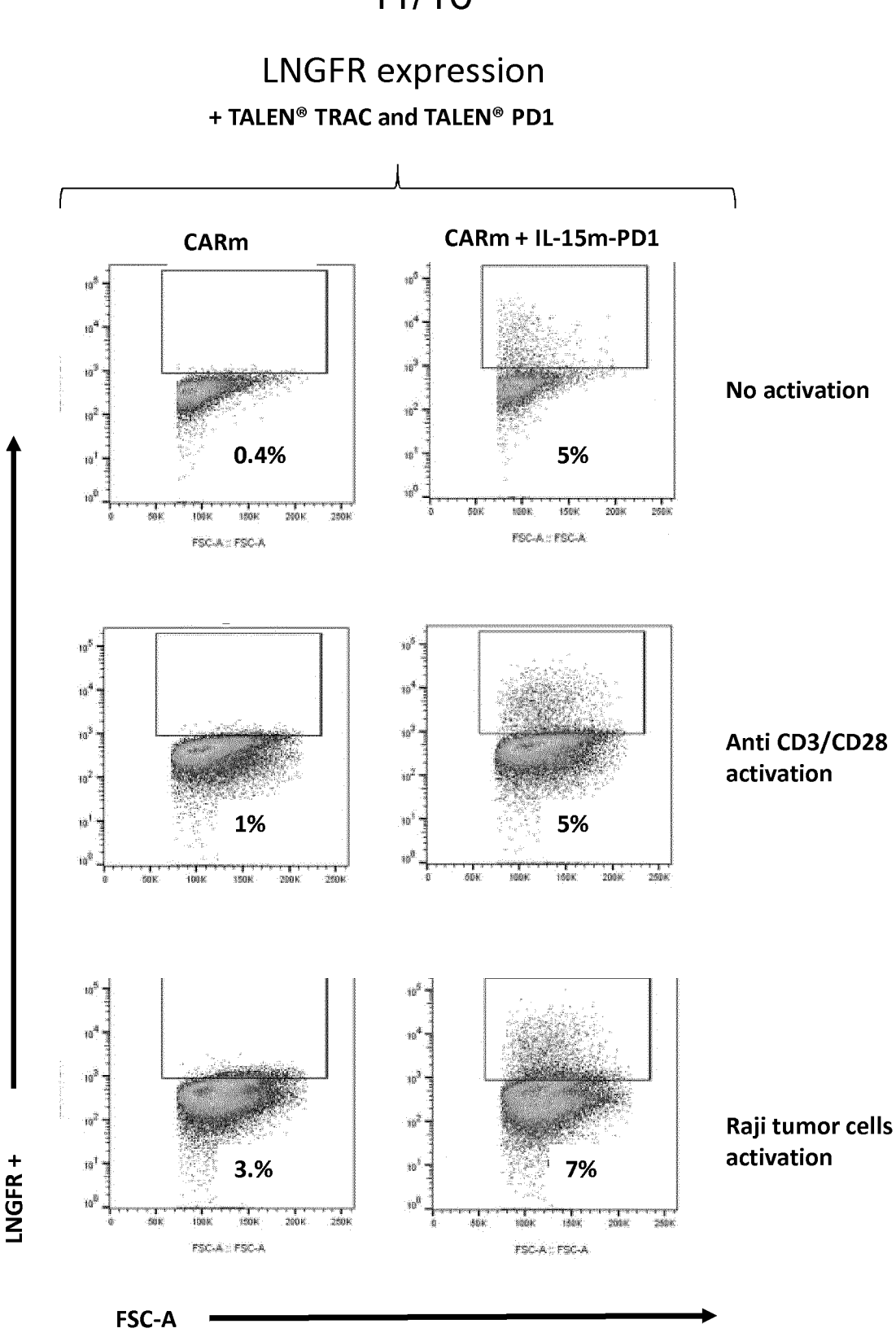

LNGFR expression
+ TALEN® TRAC and TALEN® PD1
CARm
CARm + IL-15m-PD1
No activation
Anti CD3/CD28 activation
Raji tumor cells activation
0.4%
5%
1%
5%
3.%
7%
LNGFR +
FSC-A

Figure 11

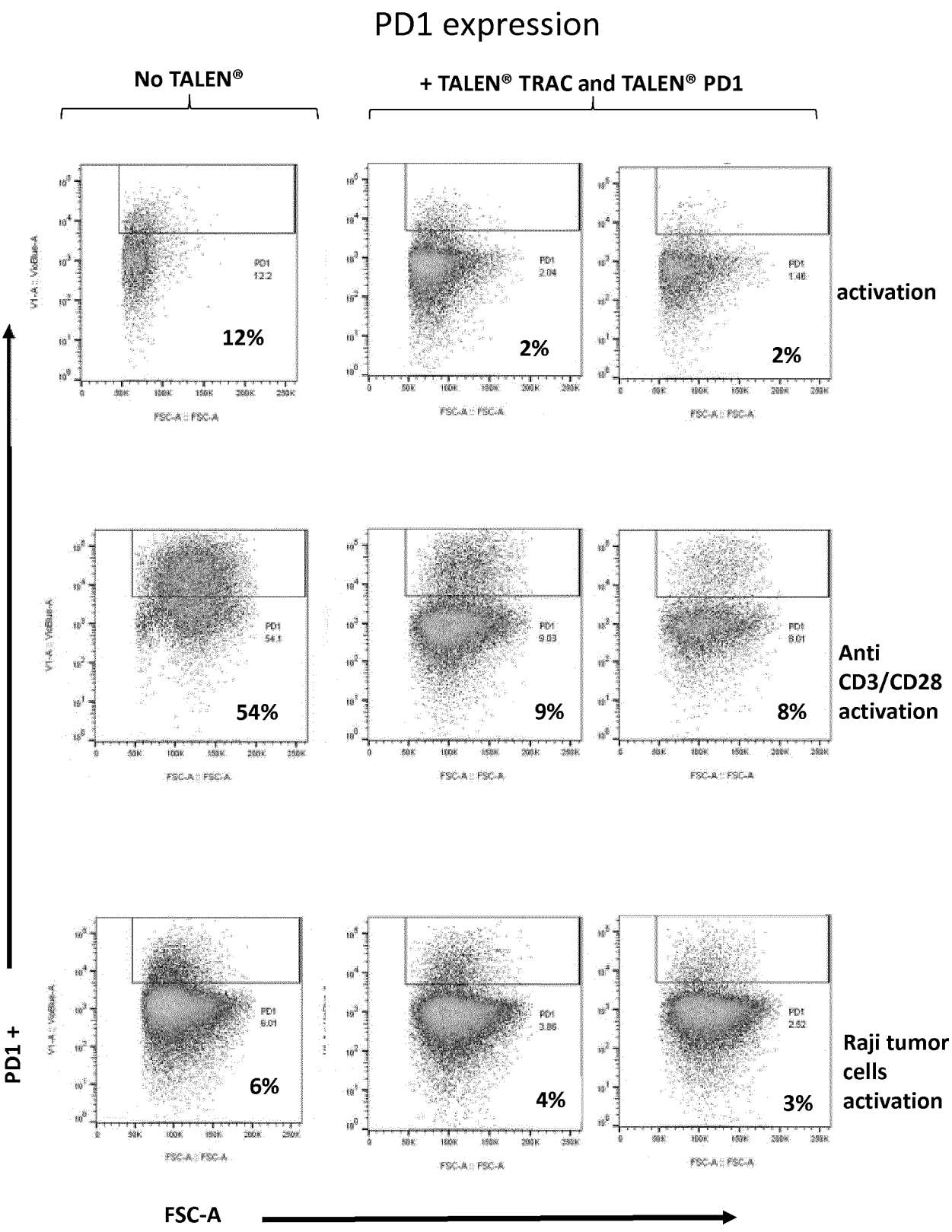

PD1 expression
No TALEN®
+ TALEN® TRAC and TALEN® PD1
activation
Anti CD3/CD28 activation
Raji tumor cells activation
PD1 +
FSC-A
12%
2%
2%
54%
9%
8%
6%
4%
3%

Figure 12

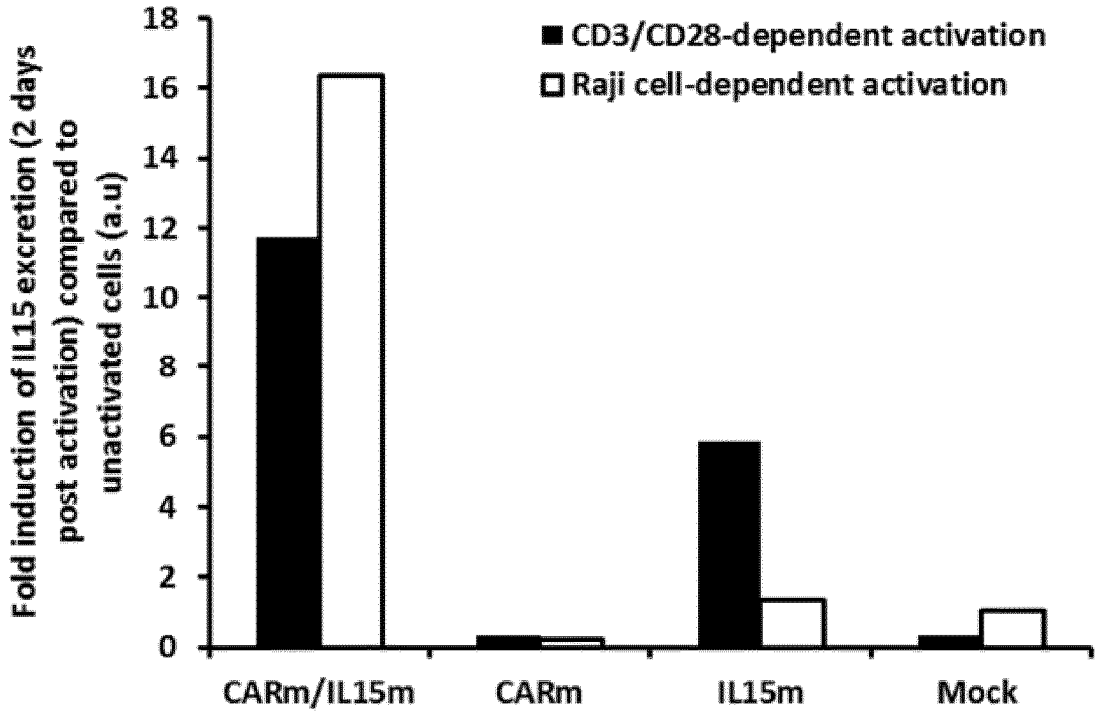

Fold induction of IL15 excretion (2 days post activation) compared to unactivated cells (a.u)
18
16
14
12
10
8
6
4
2
0
CD3/CD28-dependent activation
Raji cell-dependent activation
CARm/IL15m
CARm
IL15m
Mock

Figure 13

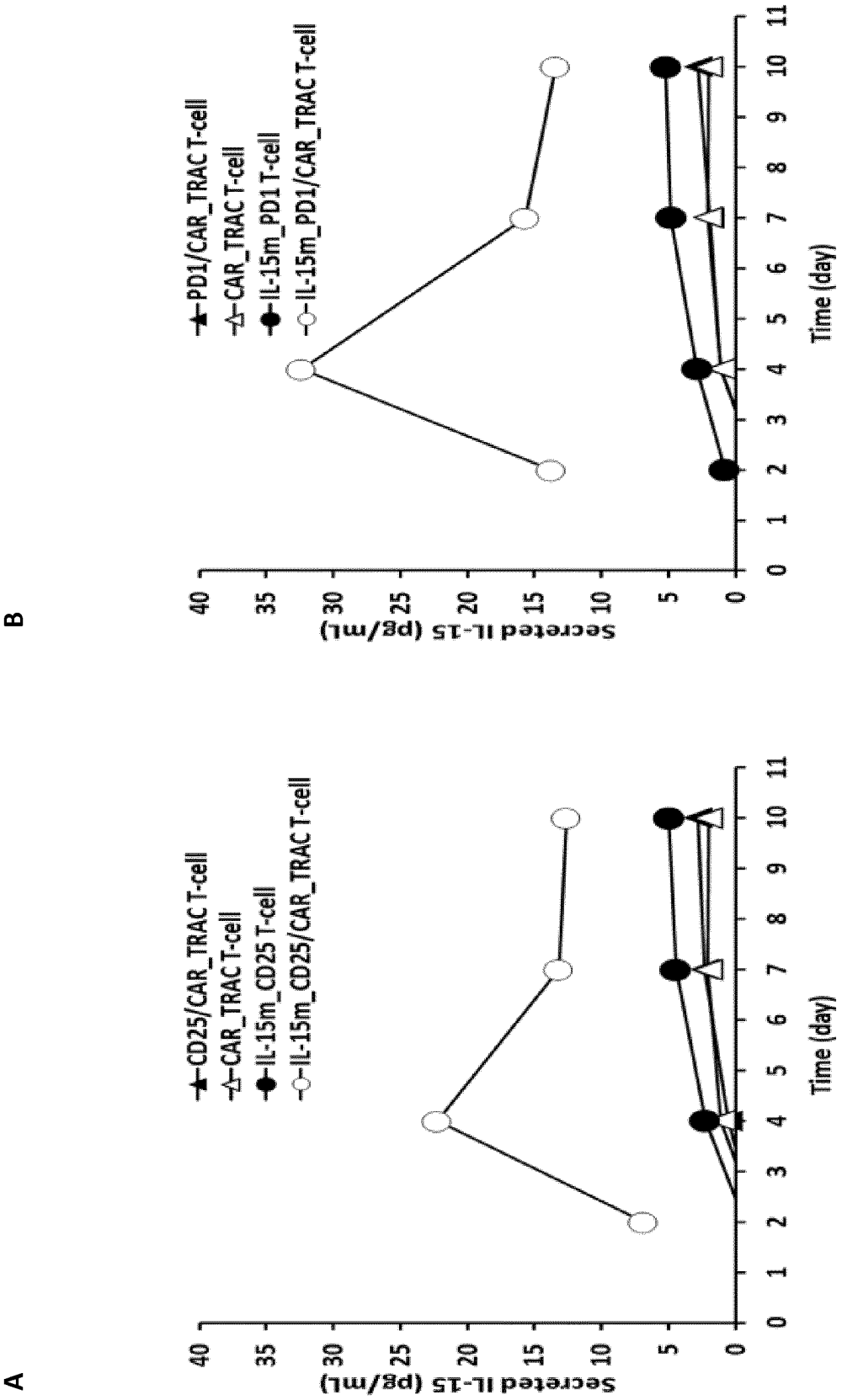
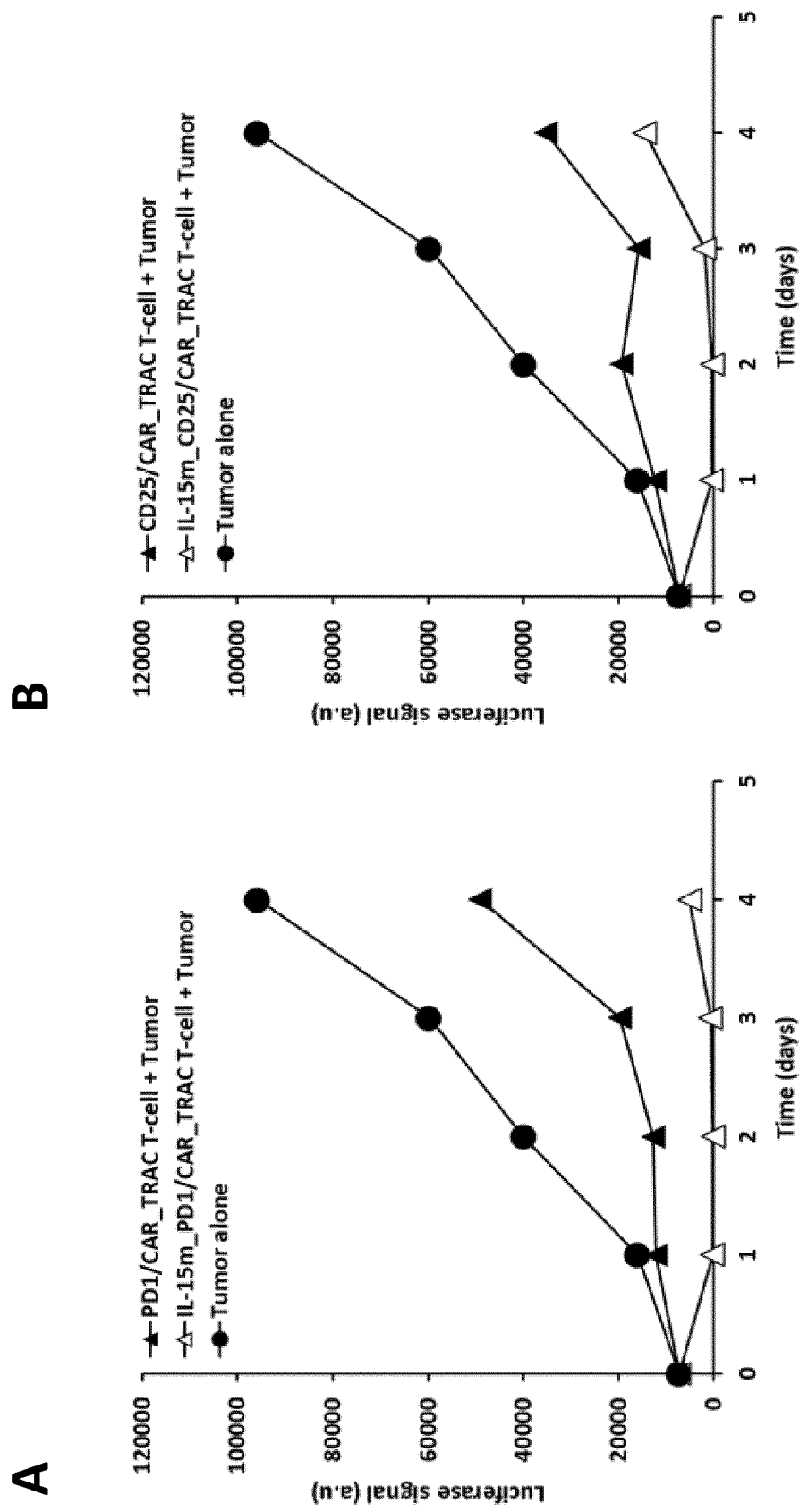

A
B
CD25/CAR_TRAC T-cell
CAR_TRAC T-cell
IL-15m_CD25 T-cell
IL-15m_CD25/CAR_TRAC T-cell
PD1/CAR_TRAC T-cell
CAR_TRAC T-cell
IL-15m_PD1 T-cell
IL-15m_PD1/CAR_TRAC T-cell
Secreted IL-15 (pg/mL)
Time (day)
0
5
10
15
20
25
30
35
40
0 1 2 3 4 5 6 7 8 9 10 11

Figure 14


A
B
PD1/CAR_TRAC T-cell + Tumor
IL-15m_PD1/CAR_TRAC T-cell + Tumor
Tumor alone
CD25/CAR_TRAC T-cell + Tumor
IL-15m_CD25/CAR_TRAC T-cell + Tumor
Tumor alone
Luciferase signal (a.u)
Time (days)
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80000
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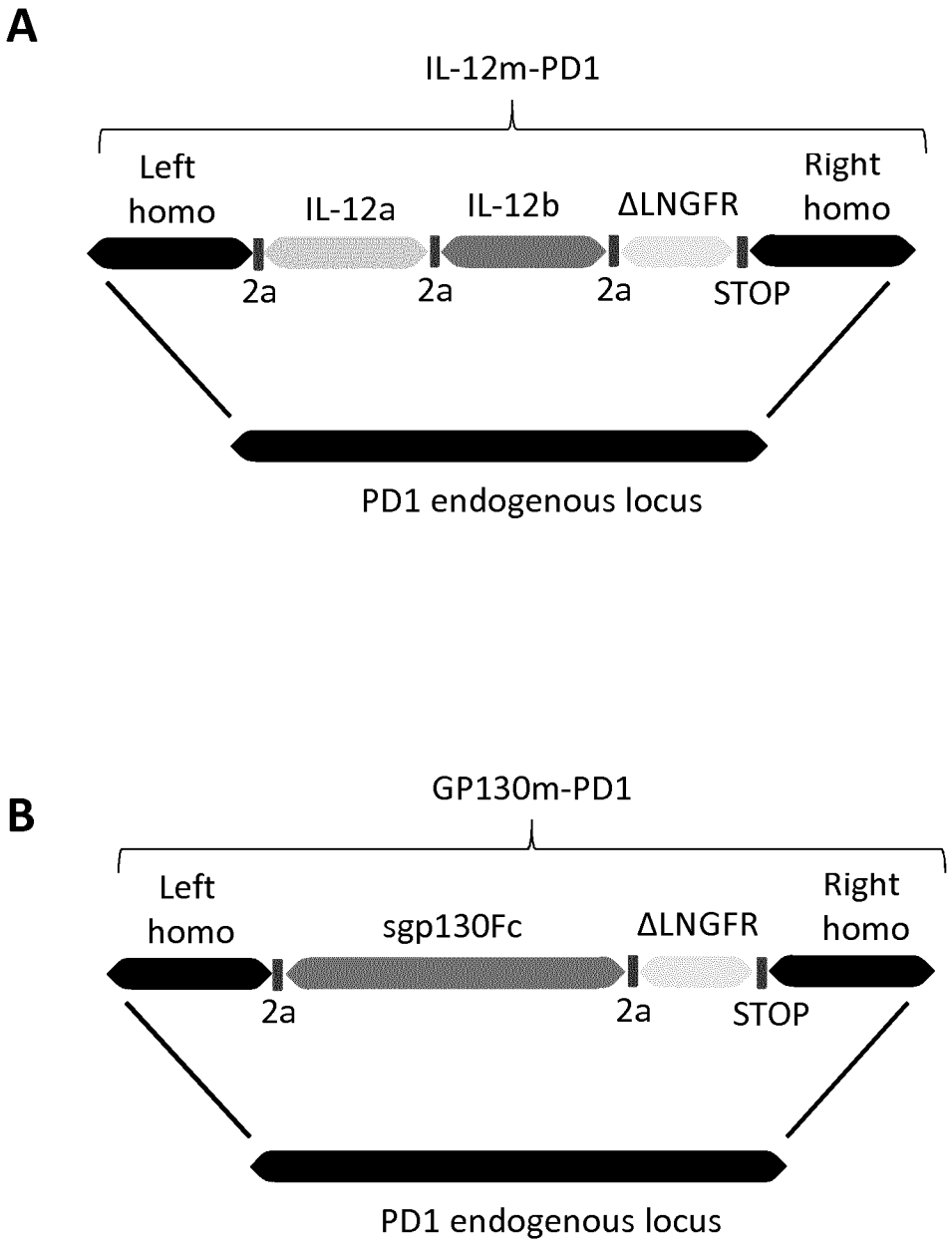
40000
20000
0
0
1
2
3
4
5

Figure 15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Left homo
IL-12a
IL-12b
ΔLNGFR
Right homo
2a
2a
2a
STOP
PD1 endogenous locus
B
GP130m-PD1
Left homo
sgp130Fc
ΔLNGFR
Right homo
2a
2a
STOP
PD1 endogenous locus

Figure 16

SEQUENCE LISTING

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<130> P81604915PCT00

<150> US62/410,187
<151> 2016-10-19

<150> PA201670840
<151> 2016-10-27

<160> 67

<170> PatentIn version 3.5

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<220>
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<220>
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```
Met Cys Pro Ala Arg Ser Leu Leu Leu Val Ala Thr Leu Val Leu Leu
1               5                  10                  15


Asp His Leu Ser Leu Ala Arg Asn Leu Pro Val Ala Thr Pro Asp Pro
            20                  25                  30


Gly Met Phe Pro Cys Leu His His Ser Gln Asn Leu Leu Arg Ala Val
        35                  40                  45


Ser Asn Met Leu Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr Pro Cys
    50                  55                  60


Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr Lys Asp Lys Thr Ser
65                  70                  75                  80


Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys Asn Glu Ser Cys
                85                  90                  95


Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn Gly Ser Cys Leu Ala
            100                 105                 110


Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys Leu Ser Ser Ile Tyr
        115                 120                 125


Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys Thr Met Asn Ala Lys
    130                 135                 140


Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu Asp Gln Asn Met Leu
145                 150                 155                 160


Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn Phe Asn Ser Glu Thr
                165                 170                 175
```

```
Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp Phe Tyr Lys Thr Lys
            180                 185                 190


Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg Ile Arg Ala Val Thr
        195                 200                 205


Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser
    210                 215


<210>  11

<211>  328
<212>  PRT
<213>  artificial sequence

<220>
<223>  Interleukin-12 subunit beta

<400>  11
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1               5                   10                  15


Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
            20                  25                  30


Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
        35                  40                  45


Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
    50                  55                  60


Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65                  70                  75                  80


Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
                85                  90                  95


Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
            100                 105                 110
```

```
Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
        115                 120                 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
    130                 135                 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145                 150                 155                 160

Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu Ser
                165                 170                 175

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
            180                 185                 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
        195                 200                 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
    210                 215                 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
225                 230                 235                 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
                245                 250                 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
            260                 265                 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
        275                 280                 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
    290                 295                 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305                 310                 315                 320
```

Glu Trp Ala Ser Val Pro Cys Ser
325

<210> 12

<211> 1000
<212> DNA
<213> artificial sequence

<220>
<223> lck right homology

<400> 12
ggctgtggct gcagctcaca cccggaagat gactggatgg aaaacatcga tgtgtgtgag 60
aactgccatt atcccatagt cccactggat ggcaagggca cggtaagagg cgagacaggg 120
gccttggtga gggagttggg tagagaatgc aacccaggag aaagaaatga ccagcactac 180
aggcccttga aagaatagag tggccctctc ccctgaaata cagaaaggaa aagaggccca 240
gagaggggaa gggaatctcc taagatcaca cagaaagtag ttggtaaact cagggataac 300
atctaaccag gctggagagg ctgagagcag agcaggggggg aaggggggcca gggtctgacc 360
caatcttctg ctttctgacc ccaccctcat cccccactcc acagctgctc atccgaaatg 420
gctctgaggt gcgggaccca ctggttacct acgaaggctc caatccgccg gcttccccac 480
tgcaaggtga ccccaggcag cagggcctga aagacaaggc ctgcggatcc ctggctgttg 540
gcttccacct ctccccccacc tactttctcc ccggtcttgc cttccttgtc ccccaccctg 600
taactccagg cttcctgccg atcccagctc ggttctccct gatgcccctt gtctttacag 660
acaacctggt tatcgctctg cacagctatg agccctctca cgacggagat ctgggctttg 720
agaaggggga acagctccgc atcctggagc agtgagtccc tctccacctt gctctggcgg 780
agtccgtgag ggagcggcga tctccgcgac ccgcagccct cctgcggccc ttgaccagct 840
cggggtggcc gcccttggga caaaattcga ggctcagtat tgctgagcca gggttggggg 900
aggctggctt aaggggtgga ggggtctttg agggagggtc tcaggtcgac ggctgagcga 960
gccacactga cccacctccg tggcgcagga gcggcgagtg 1000

<210> 13

<211> 1992
<212> DNA
<213> artificial sequence

<220>
<223> apoptosis CAR

<400> 13
atggctttgc ctgtcactgc cttgctgctt ccacttgctc tgttgttgca cgccgcaaga 60
cccgaggtca agctccagga aagcggacca gggctggtgg cccctagtca gtcattgagc 120
gtcacttgca ccgtcagcgg cgtgtctctg cccgattacg gcgtgagctg gatcagacag 180
cccccaagga agggactgga gtggctgggc gtcatctggg ggagcgagac tacctactac 240
aacagcgccc tgaagagcag gctgaccatc attaaggaca actccaagtc ccaggtcttt 300
ctgaaaatga acagcctgca gactgatgac actgccatct actactgcgc caagcattac 360
tactacgggg gcagctacgc tatggactac tgggggcagg ggacctctgt cacagtgtca 420
agtggcggag gaggcagtgg cggaggggga agtgggggcg gcggcagcga catccagatg 480
acccagacaa catccagcct ctccgcctct ctgggcgaca gagtgacaat cagctgccgg 540
gccagtcagg acatcagcaa gtatctcaat tggtaccagc agaaaccaga cgggacagtg 600

aaattgctga tctaccacac atccaggctg cactcaggag tccccagcag gttttccggc 660
tccggctccg ggacagatta cagtctgacc atttccaacc tggagcagga ggatattgcc 720
acatactttt gccagcaagg caacactctg ccctatacct tcggcggagg cacaaaactg 780
gagattactc ggtcggatcc cgagcccaaa tctcctgaca aaactcacac atgcccaccg 840
tgcccagcac ctcccgtggc cggcccgtca gtgttcctct tccccccaaa acccaaggac 900
accctcatga tcgcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgag 960
gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca 1020
aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg 1080
caccaggact ggctgaatgg caaggagtac aagtgcaagg tgtccaacaa agccctccca 1140
gcccccatcg agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac 1200
accctgcccc catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc 1260
aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca accggagaac 1320
aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag 1380
ctcaccgtgg acaagagcag gtggcagcag gggaacgtgt tctcatgctc cgtgatgcat 1440
gaggccctgc acaatcacta tacccagaaa tctctgagtc tgagcccagg caagaaggat 1500
attttggggt ggctttgcct tcttcttttg ccaattccac taattgtttg ggtgaagaga 1560
aaggaagtac agaaaacatg cagaaagcac agaaaggaaa accaaggttc tcatgaatct 1620
ccaaccttaa atcctgaaac agtggcaata aatttatctg atgttgactt gagtaaatat 1680
atcaccacta ttgctggagt catgacacta agtcaagtta aaggctttgt tcgaaagaat 1740
ggtgtcaatg aagccaaaat agatgagatc aagaatgaca atgtccaaga cacagcagaa 1800
cagaaagttc aactgcttcg taattggcat caacttcatg gaaagaaaga agcgtatgac 1860
acattgattg cagatctcaa aaaagccaat ctttgtactc ttgcagagaa aattcagact 1920
atcatcctca aggacattac tagtgactca gaaaattcaa acttcagaaa tgaaatccag 1980
agcttggtcg aa 1992

<210> 14

<211> 1000
<212> DNA
<213> artificial sequence

<220>
<223> Lck left homology

<400> 14
ctcataacaa ttctatgagg taggaacagt tatttactct attttccaaa taaggaaact 60
gggctcgccc aaggttccac aactaacatg tgtgtattat tgagcattta atttacacca 120
gggaagcagg ttgtggtggt gtgcacctgt tgtccagcta tttaggaggc tgaggtgaaa 180
ggatcacttg aacggaggag ttcaaatttg caatgtgcta tgattgtgcc tgtgaacagc 240
tgctgcactc cagcctgggc aacatagtga gatcccttat ctaaaacatt ttttttaagt 300
aaataatcag gtgggcacgg tggctcacgc ctgtaatcca gcactttggg aggctgaggc 360
gggcggatca cctgaggtca ggagttcaag accagcctga ccaacatgga gaaacccgtc 420
tctactaaaa atacaaaatt agcttggcgt ggtggtgcat gcctgtaatc ccagctactc 480
gagaagctga ggcaggagaa ttgtttgaac ctgggaggtg gaggttgcgg tgagccgaga 540
tcgcaccatt gcactccagc ctgggcaaca agagtgaaat tgcatctcaa aaaaaaagaa 600
aaggaaataa tctataccag gcactccaag tggtgtgact gatattcaac aagtacctct 660
agtgtgacct taccattgat gaagaccaag attcttttgg attggtgctc acactgtgcc 720
agttaaatat tccgaacatt acccttgcct gtgggcttcc agtgcctgac cttgatgtcc 780
tttcacccat caacccgtag ggatgaccaa cccggaggtg attcagaacc tggagcgagg 840
ctaccgcatg gtgcgccctg acaactgtcc agaggagctg taccaactca tgaggctgtg 900
ctggaaggag cgcccagagg accggcccac ctttgactac ctgcgcagtg tgctggagga 960

cttcttcacg gccacagagg gccagtacca gcctcagcct 1000

<210> 15

<211> 1000
<212> DNA
<213> artificial sequence

<220
<223> lck right homology

<400> 15
gaggccttga gaggccctgg ggttctcccc ctttctctcc agcctgactt ggggagatgg 60
agttcttgtg ccatagtcac atggcctatg cacatatgga ctctgcacat gaatcccacc 120
cacatgtgac acatatgcac cttgtgtctg tacacgtgtc ctgtagttgc gtggactctg 180
cacatgtctt gtacatgtgt agcctgtgca tgtatgtctt ggacactgta caaggtaccc 240
ctttctggct ctcccatttc ctgagaccac agagagaggg gagaagcctg ggattgacag 300
aagcttctgc ccacctactt ttctttcctc agatcatcca gaagttcctc aagggccagg 360
actttatcta atacctctgt gtgctcctcc ttggtgcctg gcctggcaca catcaggagt 420
tcaataaatg tctgttgatg actgttgtac atctctttgc tgtccactct ttgtgggtgg 480
gcagtggggg ttaagaaaat ggtaattagg tcaccctgag ttggggtgaa agatgggatg 540
agtggatgtc tggaggctct gcagacccct tcaaatggga cagtgctcct caccctccc 600
caaaggattc agggtgactc ctacctggaa tcccttaggg aatgggtgcg tcaaaggacc 660
ttcctcccca ttataaaagg gcaacagcat tttttactga ttcaagggct atatttgacc 720
tcagattttg ttttttaag gctagtcaaa tgaagcggcg ggaatggagg aggaacaaat 780
aaatctgtaa ctatcctcag attttttttt ttttttgaga ctgggtctca ctttttcatc 840
caggctggag tgcagtcgca tgatcacggc tcactgtagc ctcaacctct ccagctcaaa 900
tgctcctcct gtctcagcct cccgagtacc tgggactact ttcttgaggc caggaattca 960
agaacagagt aagatcctgg tctccaaaaa aagttttaaa 1000

<210> 16

<211> 936
<212> PRT
<213> artificial sequence

<220>
<223> TALEN TRAC

<400> 16
Met Gly Asp Pro Lys Lys Lys Arg Lys Val Ile Asp Tyr Pro Tyr Asp
1 5 10 15

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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


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


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


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


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


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


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


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


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


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


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


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


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

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

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

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

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

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

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

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

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

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

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

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

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

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

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


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


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


Gly Glu Ile Asn Phe Ala Ala Asp
    930                 935


<210>  17

<211>  942
<212>  PRT
<213>  artificial sequence

<220>
<223>  TALEN TRAC

<400>  17
Met Gly Asp Pro Lys Lys Lys Arg Lys Val Ile Asp Lys Glu Thr Ala
1               5                   10                  15


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


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


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


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


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

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

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

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

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

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

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

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

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

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

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

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

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

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

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


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


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


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


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


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


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


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


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


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


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


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


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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 18

<211> 913
<212> PRT
<213> artificial sequence

<220>
<223> TALEN CD25

<400> 18
Met Gly Asp Pro Lys Lys Lys Arg Lys Val Ile Asp Tyr Pro Tyr Asp
1 5 10 15

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Ser Gly Gly Asp Pro Ile Ser Arg Ser Gln Leu Val Lys Ser Glu
705                 710                 715                 720

Leu Glu Glu Lys Lys Ser Glu Leu Arg His Lys Leu Lys Tyr Val Pro
                725                 730                 735

His Glu Tyr Ile Glu Leu Ile Glu Ile Ala Arg Asn Ser Thr Gln Asp
            740                 745                 750

Arg Ile Leu Glu Met Lys Val Met Glu Phe Phe Met Lys Val Tyr Gly
        755                 760                 765

Tyr Arg Gly Lys His Leu Gly Gly Ser Arg Lys Pro Asp Gly Ala Ile
    770                 775                 780
```

```
Tyr Thr Val Gly Ser Pro Ile Asp Tyr Gly Val Ile Val Asp Thr Lys
785                 790                 795                 800


Ala Tyr Ser Gly Gly Tyr Asn Leu Pro Ile Gly Gln Ala Asp Glu Met
                805                 810                 815


Gln Arg Tyr Val Glu Glu Asn Gln Thr Arg Asn Lys His Ile Asn Pro
            820                 825                 830


Asn Glu Trp Trp Lys Val Tyr Pro Ser Ser Val Thr Glu Phe Lys Phe
        835                 840                 845


Leu Phe Val Ser Gly His Phe Lys Gly Asn Tyr Lys Ala Gln Leu Thr
    850                 855                 860


Arg Leu Asn His Ile Thr Asn Cys Asn Gly Ala Val Leu Ser Val Glu
865                 870                 875                 880


Glu Leu Leu Ile Gly Gly Glu Met Ile Lys Ala Gly Thr Leu Thr Leu
                885                 890                 895


Glu Glu Val Arg Arg Lys Phe Asn Asn Gly Glu Ile Asn Phe Ala Ala
            900                 905                 910


Asp
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<210> 19

<211> 913
<212> PRT
<213> artificial sequence

<220>
<223> TALEN CD25

<400> 19

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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


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


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


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


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


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


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


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


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


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


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


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


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

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


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


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


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


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


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


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


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


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


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


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


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


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

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

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

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

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

Gly Ser Gly Gly Asp Pro Ile Ser Arg Ser Gln Leu Val Lys Ser Glu
705                 710                 715                 720

Leu Glu Glu Lys Lys Ser Glu Leu Arg His Lys Leu Lys Tyr Val Pro
                725                 730                 735

His Glu Tyr Ile Glu Leu Ile Glu Ile Ala Arg Asn Ser Thr Gln Asp
            740                 745                 750

Arg Ile Leu Glu Met Lys Val Met Glu Phe Phe Met Lys Val Tyr Gly
        755                 760                 765

Tyr Arg Gly Lys His Leu Gly Gly Ser Arg Lys Pro Asp Gly Ala Ile
    770                 775                 780

Tyr Thr Val Gly Ser Pro Ile Asp Tyr Gly Val Ile Val Asp Thr Lys
785                 790                 795                 800

Ala Tyr Ser Gly Gly Tyr Asn Leu Pro Ile Gly Gln Ala Asp Glu Met
                805                 810                 815

Gln Arg Tyr Val Glu Glu Asn Gln Thr Arg Asn Lys His Ile Asn Pro
            820                 825                 830

Asn Glu Trp Trp Lys Val Tyr Pro Ser Ser Val Thr Glu Phe Lys Phe
        835                 840                 845
```

Leu Phe Val Ser Gly His Phe Lys Gly Asn Tyr Lys Ala Gln Leu Thr
850 855 860

Arg Leu Asn His Ile Thr Asn Cys Asn Gly Ala Val Leu Ser Val Glu
865 870 875 880

Glu Leu Leu Ile Gly Gly Glu Met Ile Lys Ala Gly Thr Leu Thr Leu
885 890 895

Glu Glu Val Arg Arg Lys Phe Asn Asn Gly Glu Ile Asn Phe Ala Ala
900 905 910

Asp

<210> 20

<211> 936
<212> PRT
<213> artificial sequence

<220>
<223> TALEN PD1

<400> 20
Met Gly Asp Pro Lys Lys Lys Arg Lys Val Ile Asp Tyr Pro Tyr Asp
1 5 10 15

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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


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


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


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


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


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


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


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


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


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


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


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


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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Glu Ile Asn Phe Ala Ala Asp
930 935

<210> 21

<211> 941
<212> PRT
<213> artificial sequence

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<223> TALEN PD1

<400> 21
Met Gly Asp Pro Lys Lys Lys Arg Lys Val Ile Asp Lys Glu Thr Ala
1 5 10 15

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

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

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

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

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

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

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

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

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


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


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


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


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


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


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


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


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


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


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


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


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

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

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

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

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

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

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

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

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

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

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

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

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

Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu
545                 550                 555                 560
```

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Arg Lys Phe Asn Asn Gly Glu Ile Asn Phe Ala Ala Asp
    930                 935                 940
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<212> DNA
<213> artificial sequence

<220>

<223> TALEN TRAC pCLS11370

<400> 22

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cat 3363

<210> 35

<211> 3639
<212> DNA
<213> artificial sequence

<220>
<223> Matrice PD1 locus_IL12a_2A_IL12b pCLS30511

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<210> 36

<211> 3017
<212> DNA
<213> artificial sequence

<220>
<223> Inserted matrice TRAC locus_CubiCAR CD22 (60 nucleotides upstream and downstream)

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gaagaagatc ctattaaata aaagaataag cagtattatt aagtagccct gcatttcagg 180
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tggtcaatga tgtctaaaac tcctctgatt ggtggtctcg gccttatcca ttgccaccaa 2940
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aaaaaagcag atgaaga 3017

<210> 37

<211> 2808
<212> DNA
<213> artificial sequence

<220>
<223> Inserted matrice CD25 locus_IL15_2A_sIL15Ra (60 nucleotides upstream and

downstream)

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ggctcacacc tgtaatccca gcactttgga aggccgaggc aggcagatca caaggtcagg 180
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<210> 38

<211> 3084
<212> DNA
<213> artificial sequence

<220>
<223> Inserted matrice PD1 locus_IL15_2A_sIL15Ra (60 nucleotides upstream and downstream)

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gaaggggaca acgccacctt cacctgcagc ttctccaaca catcggagag cttcgtgcta 180
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<210> 39

<211> 3475
<212> DNA
<213> artificial sequence

<220>
<223> Inserted matrice CD25 locus_IL12a_2A_IL12b (60 nucleotides upstream and downstream)

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gcggccacag gtctgcatcc agcggctcgc cctgtgtccc tgcagtgccg gctcagcatg 540
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tgaagcccaa gtgaaatcaa aggtgctaaa tggtcgccca ggagacatcc gttgtgcttg 3240
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<210> 40

<211> 3759
<212> DNA
<213> artificial sequence

<220>
<223> Inserted matrice PD1 locus_IL12a_2A_IL12b (60 nucleotides upstream and downstream)

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gaaggggaca acgccacctt cacctgcagc ttctccaaca catcggagag cttcgtgcta 180
aactggtacc gcatgagccc cagcaaccag acggacaagc tggccgcctt ccccgaggac 240
cgcagccagc ccggccagga ctgccgcttc cgtgtcacac aactgcccaa cgggcgtgac 300
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tccaacccag ggcccatgtg gccccctggg tcagcctccc agccaccgcc ctcacctgcc 480
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caaaacctgc tgagggccgt cagcaacatg ctccagaagg ccagacaaac tctagaattt    720
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<211> 60
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<213> artificial sequence

<220>
<223> upstream TRAC locus polynucleotide sequence

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<210> 42

<211> 60
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<220>
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<400> 42
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<210> 43

<211> 60
<212> DNA
<213> artificial sequence

<220>
<223> upstream CD25 locus polynucleotide sequence

<400> 43
agtgctggct agaaaccaag tgctttactg catgcacatc atttagcaca gttagttgct 60

<210> 44

<211> 52
<212> DNA
<213> artificial sequence

<220>
<223> downstream CD25 locus polynucleotide sequence

<400> 44
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<210> 45

<211> 60
<212> DNA
<213> artificial sequence

<220>
<223> upstream PD1 locus polynucleotide sequence

<400> 45
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<210> 46

<211> 60
<212> DNA
<213> artificial sequence

<220>
<223> downstream PD1 locus polynucleotide sequence

<400> 46
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<210> 47

<211> 759
<212> DNA
<213> artificial sequence

<220>
<223> IL-12a polynucleotide

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atgcaggccc tgaatttcaa cagtgagact gtgccacaaa aatcctccct tgaagaaccg 660
gatttttata aaactaaaat caagctctgc atacttcttc atgctttcag aattcgggca 720

gtgactattg atagagtgat gagctatctg aatgcttcc 759

<210> 48

<211> 984
<212> DNA
<213> artificial sequence

<220>
<223> IL12b polynucleotide

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<211> 399
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gaatctggat gcaaagaatg tgaggaactg gaggaaaaaa atattaaaga atttttgcag 360
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<210> 50

<211> 525
<212> DNA
<213> artificial sequence

<220>
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gcagacggac caggctctcc tgagagcatc aaggcctacc tgaagcaggc accaccaagc 1560
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atcatcggca acgagacagc cgtgaatgtg gacagctccc acaccgagta tacactgtct 1740
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aaggatggcc ccgagttt 1818

<210> 52

<211> 72
<212> DNA
<213> artificial sequence

<220>
<223> IgE signal sequence

<400> 52
ggtaccgggt ccgccaccat ggactggacc tggattctgt tcctcgtggc tgctgctaca 60
agagtgcaca gc 72

<210> 53

<211> 75
<212> DNA
<213> artificial sequence

<220>
<223> F2A

<400> 53
ggttctggcg tgaaacagac tttgaatttt gaccttctca agttggcggg agacgtggag 60
tccaacccag ggccc 75

<210> 54

<211> 66
<212> DNA
<213> artificial sequence

<220>
<223> P2A

<400> 54
ggaagcggag ctactaactt cagcctgctg aagcaggctg gagacgtgga ggagaaccct 60
ggacct 66

<210> 55

<211> 54
<212> DNA
<213> artificial sequence

<220>
<223> T2A

<400> 55
gagggcagag gcagcctgct gacctgcggc gacgtcgagg agaaccccgg gccc 54

<210> 56

<211> 825
<212> DNA
<213> artificial sequence

<220>
<223> LNGFR

<400> 56
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ggtgagtgct gcaaagcctg caacctgggc gagggtgtgg cccagccttg tggagccaac 180
cagaccgtgt gtgagccctg cctggacagc gtgacgttct ccgacgtggt gagcgcgacc 240
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cccccagagg gctcggacag cacagccccc agcacccagg agcctgaggc acctccagaa 660
caagacctca tagccagcac ggtggcaggt gtggtgacca cagtgatggg cagctcccag 720
cccgtggtga cccgaggcac caccgacaac ctcatccctg tctattgctc catcctggct 780
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<210> 57

<211> 253
<212> PRT
<213> artificial sequence

<220>
<223> IL-12a polypeptide

<400> 57
Met Trp Pro Pro Gly Ser Ala Ser Gln Pro Pro Pro Ser Pro Ala Ala
1 5 10 15

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

Leu Ser Met Cys Pro Ala Arg Ser Leu Leu Leu Val Ala Thr Leu Val
        35                  40                  45

Leu Leu Asp His Leu Ser Leu Ala Arg Asn Leu Pro Val Ala Thr Pro
    50                  55                  60

Asp Pro Gly Met Phe Pro Cys Leu His His Ser Gln Asn Leu Leu Arg
65                  70                  75                  80

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

Pro Cys Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr Lys Asp Lys
            100                 105                 110

Thr Ser Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys Asn Glu
        115                 120                 125

Ser Cys Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn Gly Ser Cys
    130                 135                 140

Leu Ala Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys Leu Ser Ser
145                 150                 155                 160

Ile Tyr Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys Thr Met Asn
                165                 170                 175

Ala Lys Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu Asp Gln Asn
            180                 185                 190

Met Leu Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn Phe Asn Ser
        195                 200                 205

Glu Thr Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp Phe Tyr Lys
    210                 215                 220
```

```
Thr Lys Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg Ile Arg Ala
225                 230                 235                 240


Val Thr Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser
                245                 250


<210>  58

<211>  328
<212>  PRT
<213>  artificial sequence

<220>
<223>  IL12b polypeptide

<400>  58
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1               5                   10                  15


Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
            20                  25                  30


Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
        35                  40                  45


Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
    50                  55                  60


Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65                  70                  75                  80


Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
                85                  90                  95


Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
            100                 105                 110


Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
        115                 120                 125
```

```
Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
    130                 135                 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145                 150                 155                 160

Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu Ser
                165                 170                 175

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
            180                 185                 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
        195                 200                 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
    210                 215                 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
225                 230                 235                 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
                245                 250                 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
            260                 265                 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
        275                 280                 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
    290                 295                 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305                 310                 315                 320

Glu Trp Ala Ser Val Pro Cys Ser
                325
```

245 250

<210> 59

<211> 133
<212> PRT
<213> artificial sequence

<220>
<223> IL15 polypeptide

<400> 59
Gly Ile His Val Phe Ile Leu Gly Cys Phe Ser Ala Gly Leu Pro Lys
1 5 10 15

Thr Glu Ala Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu
20 25 30

Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser
35 40 45

Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu
50 55 60

Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp
65 70 75 80

Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn
85 90 95

Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu
100 105 110

Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met
115 120 125

Phe Ile Asn Thr Ser
130

<210> 60

<211> 175
<212> PRT
<213> artificial sequence

<220>
<223> sIL15ra polypeptide

<400> 60

```
Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                  10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val
65                  70                  75                  80

Thr Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly
                85                  90                  95

Lys Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr
            100                 105                 110

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

Ser Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr
    130                 135                 140

Pro Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser
145                 150                 155                 160

His Gln Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr
                165                 170                 175
```

<210> 61

<211> 606
<212> PRT
<213> artificial sequence

<220>
<223> soluble gp130

<400> 61

```
Met Leu Thr Leu Gln Thr Trp Leu Val Gln Ala Leu Phe Ile Phe Leu
1               5                  10                  15


Thr Thr Glu Ser Thr Gly Glu Leu Leu Asp Pro Cys Gly Tyr Ile Ser
            20                  25                  30


Pro Glu Ser Pro Val Val Gln Leu His Ser Asn Phe Thr Ala Val Cys
        35                  40                  45


Val Leu Lys Glu Lys Cys Met Asp Tyr Phe His Val Asn Ala Asn Tyr
    50                  55                  60


Ile Val Trp Lys Thr Asn His Phe Thr Ile Pro Lys Glu Gln Tyr Thr
65                  70                  75                  80


Ile Ile Asn Arg Thr Ala Ser Ser Val Thr Phe Thr Asp Ile Ala Ser
                85                  90                  95


Leu Asn Ile Gln Leu Thr Cys Asn Ile Leu Thr Phe Gly Gln Leu Glu
            100                 105                 110


Gln Asn Val Tyr Gly Ile Thr Ile Ile Ser Gly Leu Pro Pro Glu Lys
        115                 120                 125


Pro Lys Asn Leu Ser Cys Ile Val Asn Glu Gly Lys Lys Met Arg Cys
    130                 135                 140


Glu Trp Asp Gly Gly Arg Glu Thr His Leu Glu Thr Asn Phe Thr Leu
145                 150                 155                 160


Lys Ser Glu Trp Ala Thr His Lys Phe Ala Asp Cys Lys Ala Lys Arg
                165                 170                 175
```

```
Asp Thr Pro Thr Ser Cys Thr Val Asp Tyr Ser Thr Val Tyr Phe Val
            180                 185                 190

Asn Ile Glu Val Trp Val Glu Ala Glu Asn Ala Leu Gly Lys Val Thr
        195                 200                 205

Ser Asp His Ile Asn Phe Asp Pro Val Tyr Lys Val Lys Pro Asn Pro
    210                 215                 220

Pro His Asn Leu Ser Val Ile Asn Ser Glu Glu Leu Ser Ser Ile Leu
225                 230                 235                 240

Lys Leu Thr Trp Thr Asn Pro Ser Ile Lys Ser Val Ile Ile Leu Lys
                245                 250                 255

Tyr Asn Ile Gln Tyr Arg Thr Lys Asp Ala Ser Thr Trp Ser Gln Ile
            260                 265                 270

Pro Pro Glu Asp Thr Ala Ser Thr Arg Ser Ser Phe Thr Val Gln Asp
        275                 280                 285

Leu Lys Pro Phe Thr Glu Tyr Val Phe Arg Ile Arg Cys Met Lys Glu
    290                 295                 300

Asp Gly Lys Gly Tyr Trp Ser Asp Trp Ser Glu Glu Ala Ser Gly Ile
305                 310                 315                 320

Thr Tyr Glu Asp Arg Pro Ser Lys Ala Pro Ser Phe Trp Tyr Lys Ile
                325                 330                 335

Asp Pro Ser His Thr Gln Gly Tyr Arg Thr Val Gln Leu Val Trp Lys
            340                 345                 350

Thr Leu Pro Pro Phe Glu Ala Asn Gly Lys Ile Leu Asp Tyr Glu Val
        355                 360                 365

Thr Leu Thr Arg Trp Lys Ser His Leu Gln Asn Tyr Thr Val Asn Ala
    370                 375                 380
```

```
Thr Lys Leu Thr Val Asn Leu Thr Asn Asp Arg Tyr Leu Ala Thr Leu
385                 390                 395                 400

Thr Val Arg Asn Leu Val Gly Lys Ser Asp Ala Ala Val Leu Thr Ile
                405                 410                 415

Pro Ala Cys Asp Phe Gln Ala Thr His Pro Val Met Asp Leu Lys Ala
            420                 425                 430

Phe Pro Lys Asp Asn Met Leu Trp Val Glu Trp Thr Thr Pro Arg Glu
        435                 440                 445

Ser Val Lys Lys Tyr Ile Leu Glu Trp Cys Val Leu Ser Asp Lys Ala
    450                 455                 460

Pro Cys Ile Thr Asp Trp Gln Gln Glu Asp Gly Thr Val His Arg Thr
465                 470                 475                 480

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

Thr Pro Val Tyr Ala Asp Gly Pro Gly Ser Pro Glu Ser Ile Lys Ala
            500                 505                 510

Tyr Leu Lys Gln Ala Pro Pro Ser Lys Gly Pro Thr Val Arg Thr Lys
        515                 520                 525

Lys Val Gly Lys Asn Glu Ala Val Leu Glu Trp Asp Gln Leu Pro Val
    530                 535                 540

Asp Val Gln Asn Gly Phe Ile Arg Asn Tyr Thr Ile Phe Tyr Arg Thr
545                 550                 555                 560

Ile Ile Gly Asn Glu Thr Ala Val Asn Val Asp Ser Ser His Thr Glu
                565                 570                 575

Tyr Thr Leu Ser Ser Leu Thr Ser Asp Thr Leu Tyr Met Val Arg Met
            580                 585                 590
```

Ala Ala Tyr Thr Asp Glu Gly Gly Lys Asp Gly Pro Glu Phe
595 600 605

<210> 62

<211> 836
<212> PRT
<213> artificial sequence

<220>
<223> soluble gp130 fused to a Fc

<400> 62
Met Leu Thr Leu Gln Thr Trp Leu Val Gln Ala Leu Phe Ile Phe Leu
1 5 10 15

Thr Thr Glu Ser Thr Gly Glu Leu Leu Asp Pro Cys Gly Tyr Ile Ser
20 25 30

Pro Glu Ser Pro Val Val Gln Leu His Ser Asn Phe Thr Ala Val Cys
35 40 45

Val Leu Lys Glu Lys Cys Met Asp Tyr Phe His Val Asn Ala Asn Tyr
50 55 60

Ile Val Trp Lys Thr Asn His Phe Thr Ile Pro Lys Glu Gln Tyr Thr
65 70 75 80

Ile Ile Asn Arg Thr Ala Ser Ser Val Thr Phe Thr Asp Ile Ala Ser
85 90 95

Leu Asn Ile Gln Leu Thr Cys Asn Ile Leu Thr Phe Gly Gln Leu Glu
100 105 110

Gln Asn Val Tyr Gly Ile Thr Ile Ile Ser Gly Leu Pro Pro Glu Lys
115 120 125

Pro Lys Asn Leu Ser Cys Ile Val Asn Glu Gly Lys Lys Met Arg Cys
130 135 140

```
Glu Trp Asp Gly Gly Arg Glu Thr His Leu Glu Thr Asn Phe Thr Leu
145                 150                 155                 160


Lys Ser Glu Trp Ala Thr His Lys Phe Ala Asp Cys Lys Ala Lys Arg
                165                 170                 175


Asp Thr Pro Thr Ser Cys Thr Val Asp Tyr Ser Thr Val Tyr Phe Val
            180                 185                 190


Asn Ile Glu Val Trp Val Glu Ala Glu Asn Ala Leu Gly Lys Val Thr
        195                 200                 205


Ser Asp His Ile Asn Phe Asp Pro Val Tyr Lys Val Lys Pro Asn Pro
    210                 215                 220


Pro His Asn Leu Ser Val Ile Asn Ser Glu Glu Leu Ser Ser Ile Leu
225                 230                 235                 240


Lys Leu Thr Trp Thr Asn Pro Ser Ile Lys Ser Val Ile Ile Leu Lys
                245                 250                 255


Tyr Asn Ile Gln Tyr Arg Thr Lys Asp Ala Ser Thr Trp Ser Gln Ile
            260                 265                 270


Pro Pro Glu Asp Thr Ala Ser Thr Arg Ser Ser Phe Thr Val Gln Asp
        275                 280                 285


Leu Lys Pro Phe Thr Glu Tyr Val Phe Arg Ile Arg Cys Met Lys Glu
    290                 295                 300


Asp Gly Lys Gly Tyr Trp Ser Asp Trp Ser Glu Glu Ala Ser Gly Ile
305                 310                 315                 320


Thr Tyr Glu Asp Arg Pro Ser Lys Ala Pro Ser Phe Trp Tyr Lys Ile
                325                 330                 335


Asp Pro Ser His Thr Gln Gly Tyr Arg Thr Val Gln Leu Val Trp Lys
            340                 345                 350
```

```
Thr Leu Pro Pro Phe Glu Ala Asn Gly Lys Ile Leu Asp Tyr Glu Val
        355                 360                 365

Thr Leu Thr Arg Trp Lys Ser His Leu Gln Asn Tyr Thr Val Asn Ala
    370                 375                 380

Thr Lys Leu Thr Val Asn Leu Thr Asn Asp Arg Tyr Leu Ala Thr Leu
385                 390                 395                 400

Thr Val Arg Asn Leu Val Gly Lys Ser Asp Ala Ala Val Leu Thr Ile
                405                 410                 415

Pro Ala Cys Asp Phe Gln Ala Thr His Pro Val Met Asp Leu Lys Ala
            420                 425                 430

Phe Pro Lys Asp Asn Met Leu Trp Val Glu Trp Thr Thr Pro Arg Glu
        435                 440                 445

Ser Val Lys Lys Tyr Ile Leu Glu Trp Cys Val Leu Ser Asp Lys Ala
    450                 455                 460

Pro Cys Ile Thr Asp Trp Gln Gln Glu Asp Gly Thr Val His Arg Thr
465                 470                 475                 480

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

Thr Pro Val Tyr Ala Asp Gly Pro Gly Ser Pro Glu Ser Ile Lys Ala
            500                 505                 510

Tyr Leu Lys Gln Ala Pro Pro Ser Lys Gly Pro Thr Val Arg Thr Lys
        515                 520                 525

Lys Val Gly Lys Asn Glu Ala Val Leu Glu Trp Asp Gln Leu Pro Val
    530                 535                 540

Asp Val Gln Asn Gly Phe Ile Arg Asn Tyr Thr Ile Phe Tyr Arg Thr
545                 550                 555                 560
```

```
Ile Ile Gly Asn Glu Thr Ala Val Asn Val Asp Ser Ser His Thr Glu
                565                 570                 575

Tyr Thr Leu Ser Ser Leu Thr Ser Asp Thr Leu Tyr Met Val Arg Met
            580                 585                 590

Ala Ala Tyr Thr Asp Glu Gly Gly Lys Asp Gly Pro Glu Phe Arg Ser
        595                 600                 605

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu
    610                 615                 620

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
625                 630                 635                 640

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
                645                 650                 655

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
            660                 665                 670

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
        675                 680                 685

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
    690                 695                 700

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
705                 710                 715                 720

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
                725                 730                 735

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
            740                 745                 750

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
        755                 760                 765
```

```
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
    770                 775                 780

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
785                 790                 795                 800

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
                805                 810                 815

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
            820                 825                 830

Ser Pro Gly Lys
        835
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<210> 63

<211> 7711
<212> DNA
<213> artificial sequence

<220>
<223> Matrice TRAC locus_CubiCAR CD22 pCLS30056 full sequence

<400> 63

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