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(54) Title: METHOD FOR MODULATING CAR-INDUCED IMMUNE CELLS ACTIVITY

(57) Abstract: The present invention relates to a method to modulate the level of activation of an engineered immune cell (such as a Chimeric Antigen Receptor T-cell) for immunotherapy. The present invention also relates to cells obtained by the present method, preferably comprising said modulable/tunable chimeric antigen receptors for use in therapeutic or prophylactic treatment.



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METHOD FOR MODULATING CAR-INDUCED IMMUNE CELLS ACTIVITY**Field of the description**

The present invention relates to a method to modulate the transduction signal of a CAR (chimeric antigen receptor) the level of this transduction signal determining the level of activation of an engineered immune cell, such as a Chimeric Antigen Receptor T-cell used in immunotherapy. In particular, the inventors have developed a molecular switch system and new CAR architectures allowing a tunable activation of said cells upon administration of a soluble compound that induces co-localization of inhibitory and activating signaling domains, especially via chemical induced dimerization (CID). Consequently, the activation of an engineered immune cell triggered by a Chimeric Antigen Receptor (CAR), can be monitored or shunted via inhibitory signaling domain(s) on demand. The invention opens the way to a prospect of a tunable and safer adoptive immunotherapy.

Background of the invention

Adoptive immunotherapy, which involves the transfer of autologous antigen-specific T-cells generated *ex vivo*, is a promising strategy to treat cancer. The T-cells used for adoptive immunotherapy can be generated either by expansion of antigen-specific T cells or redirection of T-cells through genetic engineering (Park, Rosenberg et al. 2011). Transfer of viral antigen specific T-cells is a well-established procedure used for the treatment of transplant associated viral infections and rare viral-related malignancies. Similarly, isolation and transfer of tumor specific T-cells has been shown to be successful in treating melanoma. Novel specificities in T-cells have been successfully generated through the genetic transfer of transgenic T cell receptors or chimeric antigen receptors (CARs). CARs are synthetic receptors consisting of a targeting moiety that is associated with one or more signaling domains in a single fusion molecule. CARs have successfully allowed T-cells to be redirected against antigens expressed at the surface of tumor cells from various malignancies including lymphomas and solid tumors (Jena, Dotti et al. 2010).

The first generation of CAR-modified T cell showed success in pre-clinical trials and has entered phase I clinical trials. Clinical trials have commenced in ovarian cancer, neuroblastoma and various types of leukemia and lymphoma (<https://clinicaltrials.gov/>). The clinical trials showed little evidence of anti-tumor activity with insufficient activation, persistence and homing to cancer tissue.

Diverse studies have reported partial first-generation CARs in the absence of costimulation leads to anergy and failure of *in vivo* expansion.

To overcome these limitations, second and the third generation CAR-modification T cells were designed in order to enhance the activation signal, proliferation, production of cytokines and effector function of CAR-modified T cell in preclinical trials. Second-generation CARs were developed to incorporate the intracellular domains of one or more costimulatory molecules such as CD28, OX40, and 4-1BB within the endodomain, and these improved antigen-specific T-cell activation and expansion. Third-generation CARs include a combination of costimulatory endodomains. Both the second and the third generation CAR-modified T cell have entered clinical trials now. The first clinical trial, which has involved T-cells expressing a CAR combining an anti-CD19binding domain with a 4-1BB costimulatory domain and CD3zeta as an activating signaling domain has led some patients to a complete remission, which has been ongoing 10 months after treatment. The CAR-modified T cells were found to expand 3-logs in these patients, infiltrating and lysing cancer tissue. Interestingly, a fraction of these cells displayed a memory phenotype of T cell for preventive tumor relapses. Although these CAR-modified T cell produced significant therapeutic effect, their activity led to life-threatening tumor lysis 3 weeks after the first infusion of CAR-modified T cell.

Recently adverse events were reported which stress the requirement of special precautions while using second and third generation of CAR-modified T cells. One patient died 5 days after cyclophosphamide chemotherapy followed by infusion of CAR-modified T cells recognizing the antigen ERBB2 (HER-2/neu) (Morgan et al. 2010). The toxicity leads to a clinically significant release of pro-inflammatory cytokines, pulmonary toxicity, multi-organ failure and eventual death of the patient. This and other adverse events highlight the need for caution when employing CAR-modified T cells, as unlike antibodies against tumor-associated antigens, these cells are not cleared from the body within a short amount of time.

There are many on-going researches to develop a safer CAR-based immunotherapy. Several studies reports diverse systems which aim to improve the efficacy and safety of T immunotherapy. T-cell mediated immunity in healthy persons includes multiple sequential steps regulated by a balance between co-stimulatory and inhibitory signals that fine-tune the immunity response. The inhibitory signals referred to as immune checkpoints (such as CTLA-4 or PD-1) are crucial for the maintenance of self-tolerance and also to limit immune-mediated collateral tissue damage (Dolan et al, 2014).

Recently, inhibitory chimeric antigen receptors (iCARs) were designed having as objective to put the brakes on T cell function upon encountering off-target cells. The iCAR is made up of an antigen-specific single-chain variable fragment (scFv) fused to a T cell inhibitory signaling domain. Cells expressing a tumor-associated antigen but not a normal-tissue antigen would induce T cell activation, cytotoxicity and cytokine signaling to kill the on-target cells. In a study (Federov et al. 2013), CTLA-4- or PD-1-based iCARs were shown to selectively limit cytokine secretion, cytotoxicity, and proliferation induced through the endogenous T cell receptor or an activating chimeric receptor. Therefore, to function, the iCAR technology relies on a preliminary selection of 2 antigens: one tumor associated antigen and one normal-tissue antigen. Moreover, the inhibitory effect of PD-1 or CTLA-4 is operating only on off-target cells.

Another system is described in Budde et al. (2013) in which a CD20 Chimeric Antigen Receptor is combined with an inducible caspase 9 (iC9) suicide switch. In the application US 2014/0286987, the latter gene is made functional in the presence of the prodrug AP1903 (tacrolimus) by binding to the mutated FK506-binding protein (FKBP1). A clinical trial is ongoing sponsored by the company Bellicum in which the above capsase technology (CaspaCID™) is engineered into GD2 targeted third generation CAR T cells. Viral transduction transfers DNA from a vector into the target cell and the vector-derived DNA directs expression of chemical induction dimerization (CID) and accessory proteins. In presence of the AP1903 drug, there will be a dimerization of the CID proteins, thus turning on the signal cascade. In the event of a serious of life-threatening toxicity caused by the administered T cells, AP1903 will be infused to trigger rapid destruction and elimination of the CaspaCID™-enabled cells. One important characteristic is that this expression is restricted to the cytoplasm of the cell. Moreover, according to the Bellicum's system, there is no possibility to modulate the activity of the T-cells, since the expression of CaspaCID™ in contact with the drug leads to the death of the T-cells. A similar apoptosis-inducing system based on a multimerizing agent is described in the application WO 2014/152177.

There is a need of a CAR-based immunotherapy technology which is able to inhibit or modulate, by addition of a soluble compound, the activation of chimeric antigen receptor (CAR) immune cells without killing them; which is flexible as the effect of the soluble compound can be either intracellular or extracellular, and which is independent of on/off target cells selection.

The present invention here provides such immunotherapy by which activation can be specifically inhibited/modulated in case of their cytotoxicity (i.e. when needed) by administration of a particular soluble compound.

Summary of the invention

5 In one aspect, the present invention provides methods for modulating the level of activation of a Chimeric Antigen Receptor-engineered immune cell, such as a CAR-T cell by administration of a soluble compound.

 The latter, which may be, in a preferred aspect, a small molecule (such as rapalogs), or a bispecific antibody, triggers a co-localization of at least one binding domain, and consequently
10 enhances a modulation of CAR-engineered immune cell via the action of inhibitory signaling domain(s).

 According to one aspect of the invention, an inhibitory membrane protein (IMP) comprising a binding (or dimerization) domain is co-expressed with a CAR into an immune cell. The CAR and the IMP are made both reactive to a soluble compound, especially through a second binding domain
15 comprised within the CAR, thereby allowing the co-localization, by dimerization or ligand recognition, of the inhibitory signaling domain borne by the IMP and of the signal transducing domain borne by the CAR, having the effect of turning down the CAR activation. The inhibitory signaling domain is preferably the programmed death-1 (PD-1), which attenuates T-cell receptor (TCR)-mediated activation of IL-2 production and T-cell proliferation. In Sheppard et al. (2004), it is shown that PD-1
20 modulation of T-cell function involves inhibition of TCR-mediated phosphorylation through ZAP70 and association with CD3zeta.

 The invention provides with several conformations that fall within the scope of the invention - for instance, depending of the type of soluble compound used, either the binding (or dimerization) domains can be extracellular or intracellular (Figures 1 and 2). On another hand, the Chimeric Antigen
25 Receptor (CAR) expressed in the immune cell can be either a multi-chain CAR or a single-chain CAR. The invention also provides a switch system independent from the selected CAR architecture, which does not necessarily requires inclusion of a second binding or dimerization domain into the CAR. According to this later aspect, the first and second binding (or dimerizing) domains are part of at least two heterologous inhibition membrane proteins (IMPs) expressed at the surface of the immune cells,
30 allowing the dimerization and the activation of an inhibitory signaling domain acting as a (indirect) molecular switch inhibiting CAR induced activation. An example of such switch involves the IL-10

pathway as shown in Figure 3. The dimerization inducer such as rapamycin allows the co-localization of the two dimerization domains. Once dimerized, IL-10R inhibits synthesis of pro-inflammatory cytokines such as IFN- γ , IL-2, IL-3, TNF α and GM-CSF. It appears that this inhibition is mediated by a cascade of reactions involving several intermediates, such as receptor-associated Janus kinase 1 (Jak1) and tyrosine kinase 2 (Tyk2) kinases, leading to tyrosine phosphorylation of STAT proteins as described in Finbloom et al. (1995).

Also, the present invention encompasses the isolated cells or cell lines obtainable by the method of the invention, more particularly isolated immune cells comprising or expressing any of the proteins, polypeptides, allelic variants, altered or deleted genes or vectors described herein. According to previous developments carried out by the applicants and described in WO 2013176915, the immune cells of the present invention or cell lines can be further engineered for allogeneous implantation into patients, for instance by disrupting T-cell receptors.

Following from the above, a further aspect of the invention concerns methods for treating or preventing conditions, such as cancer, where CAR induced immune cells are useful for targeting pathological cells in a patient, and where there is a need to keep the immune cell proliferation under control using a soluble compound.

Brief description of the figures and tables

Figure 1: Schematic representation of an extracellular based chemical induced dimerization (CID) strategy using PD-1 as inhibitory signaling domain, when both binding domains of the inhibitory membrane protein (IMP) complex and the multi-chain Chimeric Antigen Receptor (CAR) are localized extracellularly.

The system is composed of 2 parts: a first one comprises a polypeptide called inhibitory membrane protein (IMP) and the second one corresponds to a Chimeric Antigen Receptor (CAR). The IMP is a transmembrane protein with an extracellular moiety which is a dimerization domain capable to bind to a chemical inducer dimerization (CID) agent, and with an intracellular moiety which contains an inhibitory signaling domain (PD1 here).

The CAR represented in the drawing is a multichain CAR (mcCAR here) having 3 chains (α , β and γ) derived from Fc Receptor as described in WO 2014039523. The α chain bears a scFv binding domain recognizing a surface marker ligand, the β chain bears a co-stimulatory domain (41-BB here)

and the γ chain bears a intracellular transduction signaling domain (CD3 ζ here). Figure 1A shows dimerization domains borne on the extracellular part of the γ chain; Figure 1B shows a dimerization domain borne on the extracellular part of the α chain.

When the immune cell expressing the IMP molecule and the mcCAR is not in contact with a CID agent, the mcCAR can function in a normal way, i.e. *in fine* destroy the target cells which are recognized by the scFv specific moiety. In case of an inappropriate or excessive action of the mcCAR, CID agent (rapamycin here) may be administered to the patient in order to trigger the modutable inhibition switch such as explained thereafter.

In both configurations (Figure 1A and Figure 1B), the presence of rapamycin allows a co-localization of the 2 dimerization domains (one on IMP molecule and the other on α - or γ - chain of mcCAR), i.e. these 2 dimerization domains come closer each other. By this action, the inhibitory signaling domain PD1 colocalizes with the transduction signaling domain CD3 ζ of the mcCAR. A dephosphorylation of the latter enhances a reactions cascade starting from CD3 ζ and ultimately leads to an inhibition of the mcCAR.

Figure 2: Schematic representation of an intracellular based chemical induced dimerization (CID) strategy using PD-1 as inhibitory signaling domain, when both binding domains of the inhibitory membrane protein (IMP) complex and the multi-chain Chimeric Antigen Receptor (CAR) are localized intracellularly.

The system is composed of 2 parts such as presented in Figure 1, Figure 2A and Figure 2B corresponding to the cases when the dimerization domains are borne on the α chain and on the γ chain of mcCAR respectively. A difference with Figure 1 is that the dimerization domains of the IMP protein and mcCAR are located intracellularly. The functioning process is the same than that of Figure 1, excepted that the rapamycin needs to traverse the membrane of the immune cell to be able to bind to the binding domains.

Figure 3: Schematic representation of an extracellular based chemical induced dimerization (CID) strategy using IL-10R as inhibitory signaling domain, when both binding domains of the inhibitory membrane protein (IMP) P complex are localized extracellularly. The system presented here is a different of those presented in Figure 1 and 2 in the sense that the dimerization domain are

borne on the IMP complex and not on the mcCAR. It is based on an IMP complex and a Chimeric Antigen Receptor (here a mcCAR). The IMP complex is composed of 2 independent proteins, each one transmembrane, having extracellularly a dimerization domain, and intracellularly one monomer of the IL-10R inhibitory signaling domain (monomer IL-10R α and monomer IL-10R β). The mcCAR is the same that the one presented in Figure 1 and 2.

Figure 4: Schematic representation of an extracellular based chemical induced dimerization (CID) strategy using PD-1 as inhibitory signaling domain in the IMP molecule, and a single-chain CAR; when both binding domains in the IMP molecule and scCAR are localized extracellularly. In the absence of small molecule, the scCAR can function when it meets the tumoral cell surface antigen. In the presence of the small molecule, there is a dimerization of the CID binding domains, allowing a “co-localization” of the 2 polypeptides chains, and then the PD-1 can play its inhibitory role on the scCAR. The latter stops to function.

Figure 5: Schematic representation Schematic representation of an intracellular based chemical induced dimerization (CID) strategy using PD-1 as inhibitory signaling domain in the IMP molecule, and a single-chain CAR; when both binding domains in the IMP molecule and scCAR are localized intracellularly. This is the same principle than that of the extracellular one depicted in Figure 4, excepted that the small molecule must cross the membrane to be able to dimerize the 2 intracellular CID binding domains.

When needed, i.e. in case of an inappropriate or excessive effect of the CAR, the rapamycin is administered to the patient. The rapamycin allows the dimerization of the 2 dimerization domains borne on the IMP complex. This enhances the colocalization of the 2 monomers of IL-10R, and consequently its inhibitory activity on the CAR via a reaction cascade involving interferon IFN- γ and JAK-STAT signaling pathway. Therefore, the functional IL-10R dimer can indirectly monitor or shunt the activation of an immune cell by the Chimeric Antigen Receptor (CAR).

The following tables show the sequences for all components which are encompassed in the construction of the IMP complex and of the Chimeric Antigen Receptor (CAR).

Table 1: Exemplary sequences of modulable/tunable multi-chain CAR based on PD-1 inhibitory signaling domain presented in Figure 1
Extracellular CID strategy-, when the CID protein is located on the gamma chain.

Component	Functional domains	Description	SEQ ID #	Raw amino acid sequence
<i>Multi-chain CAR</i>				
Alpha-chain	Signal sequence	FceR1α-SP	SEQ ID NO.1	MAPAMESPTLLCVALLFFAPDGVLA
	scFv	CD123-scFv	SEQ ID NO.2	MAPAMESPTLLCVALLFFAPDGVLAQIQVQSGPELKKPGETVKISKASGYIFTNYGMNWWKQAPGK SFKWMGWINTYTGESTYSADFKGRFAFSLTASTAYLHINDLKNETATYFCARSGGYDPMYWGQ GTSVTYSSGGGGGGGGSDIVLTQSPASLAVSLGQRATISCRASEVDNYGNTFMHWYQQK PGQPKLLIYRASNLSEGPARGSGSRTDFTLTINPVEADDVATYYCQSQSNEDEPPTFGAGTKLELKR S
		KIα43-3-scFv	SEQ ID NO.3	MAPAMESPTLLCVALLFFAPDGVLAELVKGSGGLVQPGGSLSCAASGFTFTDYMSWVRQPPG KALEWLALIRSKADGYTTEYSASVKGRTFLSRDSSQILYQMNALRPEDSATYFCARDAAYSYVSPEG AMDYWGQGTSTVTSYSSGGGGGGGGGGGMDYKDIVMTQSHKFMSTVSGDRVNITCKASQN VDSAWAWYQQKPGQSPKALISASRYSGVPDRFTGRSGTDTLTISVQAEDLAVYCCQYVSTPW TFGGGKLEIKRSDP
		5T4WT19-scFv	SEQ ID NO.4	MAPAMESPTLLCVALLFFAPDGVLAELVQLQSGPDLVKPGASVKISKASGYFTGYMHWVKQSHG KSLEWIGRINPNNGVTLNQKFKDKAITVDKSTTAYMELSLTSEDSAVYCARSTMITNVMYD GQVTSVTYSSGGGGGGGGGGGGSSIVMTQTPTLLVSAGDRVTITCKASQSVNDVAVYQQKPG QSPTLLISYTSRYAGVPDRFIGSGYGTDTFTISTLQAEADVFCQQDYNSPPTFGGKLEIKRSDP
		VH-4G7-scFv	SEQ ID NO.5	MAPAMESPTLLCVALLFFAPDGVLAELVQLQSGPELKPASVKMSCKASGYFTTSYMHVWKQKP GQGLEWIGYINPYNDGTYNEKFKGKATLTSDKSSSTAYMELSLTSEDSAVYCARGTYYGSRVFDY WGQGTTLTVSSGGGGGGGGGGGGSDIVMTQAAPSPVTPGESVSISCRSKLLNSNGNTLYWF LQRPQGSPQLLIYRMSNLASGVPDFSGSGGTAFTRISRVEAEDVGVIYCMQHLEVPFTFGAGTKL ELKRSDP
	Hinge	CD8a	SEQ ID NO.6	TTTPAPRPPTPTAPTIA SQPLSLRPEACRPAAGGAVHTRGLDFACD
		IgG1	SEQ ID NO.7	EPKSPDKTHTCPPCAPPVAGPSVFLFPKPKDTLMIARTPEVTCWVDVSHEDPEVKFNWVWDGVEV HNAKTKPREQYNSTYRVSVTLVHQQDWLNGKEYCKVSNKALPAPIEKTIKAKGQPREPQVYTLPP SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGKKD
		EpoR_D2	SEQ ID NO.8	APVGLVARLADESGHVVLRWLPPETPTMTSHIRVEVDVSAGNGAGSVQRVEILEGRTECVLSNLRGR RYTFVAVRARMAPESFGGFWSAWSEPVSLTPSD

Transmembrane + intracellular domain - with hinge-	Alpha-TI-A	SEQ ID NO.9	IFIPLLVILFAVDLTGLFISTQQQVTFLLKIKRTRKGRLLNPHPKPNPKNNR
	Alpha-TI-B	SEQ ID NO.10	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFFIPLLVLFAVDLTGLFISTQQQVT FLLIKIRTRKGRLLNPHPKPNPKNNR
	CD19 alpha chain	SEQ ID NO.11	MAPAMESPTLLCVALLFFAPDGVLAEVQLQQSGPELIKPGASVKMSCKASGYTFTSYVMHVVKKQP GQGLEWIGYINPYNDGTYNEKFKGKATLTSKSSSTAYMELSSLTSEDSAVYCARGTYYGSRVFDY WGQGTTLTVSSGGGGGGGGGGSDIVMTQAAPSIPTPGESVSISCRSSKLLNSNGNTLYWVF LQRPQGSPQLLIYRMSNLASGVPDFRSGSGGTAFTRISRVEAEDVGYYCMQHLEYPFTFGAGTKL ELKRADTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFFIPLLVLFAVDLTGLFIST QQQVTFLLKIKRTRKGRLLNPHPKPNPKNNR
Beta-chain	beta-41BB chain	SEQ ID NO.12	MDTESNRRANLALPQEPSSVPAFEVLEISQEVSSGRLLKSASSPPLHTWLTVLKKEQFELGVTFQILTAM ICLCFGTVVCSVDISHIEGDIFSSFAGYFPFWGAFFISGMLSIISERNATYLVRGSLGANTASSIAGGT GITLIINLLKSLAYIHHSQCQFFETKCFMASFSTEIVMMMLFLTILGLGSAVSLTICGAGEELKGNKVPEKR GRKKLLYIFKQPFMRPVQTTQEEDGCSCRPEEEGGCEL
Gamma-chain	Signal sequence	SEQ ID NO.13	MAIPAVVLLLLLVEQAAAG
	CID_Protein	SEQ ID NO.14	SGGVQVETISPGDGRTPFKRGQTCVVHYTGMILEDGKKFDSSDRDNKPKFMLGKQEVIRGWEEGVA QMSVGQRAKLITISPDYAYGATGHPGIIPPHATLVFDVELLLEGSGAP
		SEQ ID NO.15	SGGRVAILWHEMWWHEGLEEASRLYFGERNVKGMFVLEPLHAMMERGPQTLKETSFNQAYGRDLIM EAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRIGSGAP
	Hinge	SEQ ID NO.6	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD
		SEQ ID NO.7	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWVVDGVEV HNAKTPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTIKAKGQPREPQVYTLPP SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGKKD
	EpoR_D2	SEQ ID NO.8	APVGLVARLADESGHVVLRLWLPPTPMTSHIRVEVDVSAGNGAGSVQRVEILEGRTECVLSNLRGRT

	Transmembrane intracellular domain -with hinge-	+	Gamma-TI-A	SEQ ID NO.16	RYTFAVRARMAEPFSGGFWSAWSEPVSLTPSD IGEPQLCYILDAILFLYGIVLTLYCRLKIQRKAATSYEKSRYKFSRSADAPAYQQGQNQLYNELNLGRRE EYDVLDKRRGRDPENMGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGDGLYQGLSTA TKDTYDALHMQALPPRE LGEPLCYILDAILFLYGIVLTLYCRLKIQRKAATSYEKSRYKFSRSADAPAYQQGQNQLYNELNLGRR EEYDVLDKRRGRDPENMGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGDGLYQGLST ATKDTYDALHMQALPPRE
	Transmembrane+ intracellular domain -without hinge-		Gamma-TI-B	SEQ ID NO.17	
<i>IMP complex</i>					
Sequence signal			VH-4G7-ss	SEQ ID NO.18	MALPVTALLPLALLHAARPG
Dimerization part	CID_Protein		FKBP	SEQ ID NO.14	SGGVQVETISPGDGRTPKRGQTGVVHYTGMELEDGKGFDSRRDNKPKFMLGKQEVIRGWEEGVA QMSVGQRAKLTISPDYAYGATGHPGPHATLVFDVLLKLEGGAP
			FRB	SEQ ID NO.15	SGGRVAILWHEMWHEGLEEASRLYFGERNVKGMEFVLEPLHAMMERGPQTLKETSFNQAVGRDLM EAQEWCRKYMKSGNVKDLTQAWDLVYHVFRRIGSGAP
Hinge			CD8a	SEQ ID NO.6	TTTPAPRPPTPAPTIASQPSLSRPEACRPAAGGAVHTRGLDFACD
			IgG1	SEQ ID NO.7	EPKSPDKTHTCPCPAPPVAGPSVLEFPKPKDTLMIARTPEVTCWVDVSHEDPEVKFNWVVDGVEV HNAKTPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTSKAKGQPREPQVYTLPP SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLSPGKKD
Trans membrane domain			EpoR_D2	SEQ ID NO.8	APVGLVARLADESGHVLRWLPPPTMTSHIRYEVVDVSAGNGAGSVQRVEILEGRTECVLSNLRGT RYTFAVRARMAEPFSGGFWSAWSEPVSLTPSD
			CD8a	SEQ ID NO.19	IYIWAFLAGTCGVLLLSLVITLYCR
Inhibitory signaling domain			4-1BB	SEQ ID NO.20	IISFFLALTSTALLFLFLFLTLRFVSVKRRG
			DAP10	SEQ ID NO.21	ILLAGLVAADAVASLLIVGAVFLCARR
			CD28	SEQ ID NO.22	IFWVLVVGGLVACYSLLVTVAFIHFWVRKRR
			PD1	SEQ ID NO.23	SRAARGTIGARRTGQPLKEDPSAVPVFVSDYGDLDQWREKTPPEPPVPCVPEQTEYATIVFPSGMGTS SPARRGSADGPRSAQPLRPEDGHCSWPLE

Table 2: Exemplary sequences of modulable/tunable multi-chain CAR based on PD-1 inhibitory signaling domain presented in Figure 1.

Component	Functional domains	Description	SEQ ID #	Raw amino acid sequence
Multi-chain CAR				
Alpha-chain	Signal sequence	FcεR1α-SP	SEQ ID NO.1	MAPAMESPTLLCVALLFFAPDGVLA
	scFv	CD123-scFv	SEQ ID NO.2	MAPAMESPTLLCVALLFFAPDGVLAQIQLVQSGLPELKPKGETVKISKASGYIFTNYGMNWWVKQAPGK SFKWMGWINTYTGESTYSADFKGRFAFSLETSASTAVLHINDLKNETATYFCARSGGYDPMDYWGQ GTSVTVSSGGGGGGGGSDIVLTQSPASLAVSLGQRATISCRASESDNYGNITFMHWYQQK PGQPPKLLIYRASNLSEGI PARFSGSGSRDTFTLTINPEADDVATYVCQSQSNEDPPTFGAGTKLEIKRS DPG
		Klo43-3-scFv	SEQ ID NO.3	MAPAMESPTLLCVALLFFAPDGVLAEVKLIVESGGGLVQPGGSLSLSCAASGFTFTDYMSWVVRQPPG KALEWLALIRSKADGYTTEYSASVKGRFTLSRDDSQSILYLMNALRPEDSATYFCARDAAYSYSPGEG AMDYWGQGTSTVTVSSGGGGGGGGGSMADYKDIVMTQSHKFMSTSVGDRVNITCKASQN VDSAVAWYQQKPGQSPKALIYSASYRYSYGVDPDRFTGRSGSGDTFTLTISVQAEADLAVYVCQQYYSTPW TFGGGKLEIKRSDPG
		5T4WT19-scFv	SEQ ID NO.4	MAPAMESPTLLCVALLFFAPDGVLAEVQLQQSGPDLVKPGASVKISCKASGYFTGYMHMWVKQSHG KSLEWIGRINPNNGVTLYNQKFCKDAILTVDKSSTAYMELRSLTSEDSAVYCARSTMITNVMYMDYW GQVTSVTVSSGGGGGGGGGSSIVMTQTPTFLVYSGDRVITITCKASQSVSNDVAVYQQKPG QSPRTLISYTSRYAGVDPDRFIGSGYGTDTFTISTLQAEADLAVFCQQDYNPPTFGGGTKLEIKRSDPG
		VH-4G7-scFv	SEQ ID NO.5	MAPAMESPTLLCVALLFFAPDGVLAEVQLQQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKP GGLEWIGYINPVNDGTIKYNEKFKGKATLTSKSSSTAYMELSLTSEDSAVYVCARGTYYGSRVFDY WGQGTTLTVSSGGGGGGGGGGSDIVMTQAAAPSIPTPGESVSI SCRSSKLLNSNGNTLYLVWF LQRPQSPQLLIYRMSNLASGVDPDRFSGSGGTFTLTISRVEAEDVGVVYCMQHLEVPFTFGAGTKL ELKRSDPG
		CID protein	FKBP	SEQ ID NO.14
	FRB		SEQ ID NO.15	SGGRVAILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLM EAQEWCRKYMKSGNVKDLTQAWDLVYHVFRRIGSGAP
	CD8α		SEQ ID NO.6	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD
		IgG1	SEQ ID NO.7	EPKSPDKTHTCPPCPAPPVAGPSVFLPPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVSVLTIVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVTLPP

	Hinge			SRDELTKNQVSLTCLVKGYFSPDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGKKD
		EpoR_D2	SEQ ID NO.8	APVGLVARLADESGHVLRWLPPEPTMTSHIRYEVVDVSAGNGAGSVQRVEILEGRTECVLSNLRGRTRYTFARARMMAEPSFGGFWSAWSEPVSLTPSD
	Transmembrane intracellular domain -with hinge-	Gamma-TI-A	SEQ ID NO.9	IGEPQLCYILDAILFLYGVLTLLYCRLLKIQVRKAAITSYEKSRVKFSRSADAPAYQQGQNQLYNELNLRREYDVLDKRRGRDPENMGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRRGKGDHGLYQGLSTATKDTYDALHMQALPPRE
	Transmembrane intracellular -without hinge-	Gamma-TI-B	SEQ ID NO.10	LGEPQLCYILDAILFLYGVLTLLYCRLLKIQVRKAAITSYEKSRVKFSRSADAPAYQQGQNQLYNELNLRREYDVLDKRRGRDPENMGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRRGKGDHGLYQGLSTATKDTYDALHMQALPPRE
Beta-chain	beta-41BB chain		SEQ ID NO.12	MDTESNRRANLALPQEPSSVPAFEVLEISPOEVSSGRLLKSSAPPLHTWLTVLKKEQEFGLVQTQILTAMICLCFGTVVCSVLDISHIEGDFSSFKAGYPFWGAIFFSISGMLSIISERRNATYLVIRGSLGANTASSIAGGTGITILINLKSLAYIHHSQCQKFFETKCFMASFSTEIVMMMLFLTILGLGSASVSLTICGAGEELKGNKVPEKRRKRLKLYIFKQPFMRPVQTTQEEDGSCSRFPPEEEGGCEL
	Signal sequence	Gamma-ss	SEQ ID NO.13	MAIPAVVLLLLLLVEQAAAG
Gamma-chain			SEQ ID NO.14	SGGVQVETISPGDGRTPKRGQTCVVHYTGMIEDGKFKDSSDRDNKPKFMLGKQEVIRGWEEGVQMSVGGQRAKLITISPDYAYGATGHPGIIPPHATLVFDVELLKLEGGAP
	CID_Protein	FKBP	SEQ ID NO.15	SGGRVAILWHHEMWHEGLEEASRLYFGERNVKGMEFVLEPLHAMMERGPQTLKTSFNQAYGRDLIMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRIIGSGAP
		CD8a	SEQ ID NO.6	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD
		IgG1	SEQ ID NO.7	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIAARTPEVTCVWVDVSHEDPEVKFNWVVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGYFSPDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGKKD
	Hinge		SEQ ID NO.8	APVGLVARLADESGHVLRWLPPEPTMTSHIRYEVVDVSAGNGAGSVQRVEILEGRTECVLSNLRGRTRYTFARARMMAEPSFGGFWSAWSEPVSLTPSD
	Transmembrane intracellular domain -with hinge-	Gamma-TI-A	SEQ ID NO.16	IGEPQLCYILDAILFLYGVLTLLYCRLLKIQVRKAAITSYEKSRVKFSRSADAPAYQQGQNQLYNELNLRREYDVLDKRRGRDPENMGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRRGKGDHGLYQGLSTATKDTYDALHMQALPPRE
	Transmembrane intracellular -without hinge-	Gamma-TI-B	SEQ ID NO.17	LGEPQLCYILDAILFLYGVLTLLYCRLLKIQVRKAAITSYEKSRVKFSRSADAPAYQQGQNQLYNELNLRREYDVLDKRRGRDPENMGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRRGKGDHGLYQGLSTATKDTYDALHMQALPPRE

	CD19 alpha chain	SEQ ID NO. 11	IMP complex		MAPAMESPTLLCVALLFPADGVLAEVQLQQSGPELIKPGASVKMSCKASGYTFTSYVMHWWKQKP GGGLEWIGYINPYNDGTYKNEKFKGKATLTSKSSSTAYMELSSLTSEDAVYCARGTYYGSRVFDY WGQGTTLTVSSGGGGGGGGSDIVMTQAAPSPVTPGESVSISSCRSKSLNSNGNTLYVWF LQRPQGSPQLLIYRMNSNLASGVDPDRFSGSGGTAFTRISRVEAEDVGYYCMQHLEVPFTFGAGTKL ELKRADTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFFIPLLVLFAVDTLGLFIST QQQVTFLLKIKRTRKGRLLNPHPKPNPKNN
Sequence signal	VH-4G7-ss	SEQ ID NO. 18	MALPVTALLPLALLHAARPG		
Dimerization part	FKBP	SEQ ID NO. 14	SGGVQVETISPGDGRTPFKRGQTCVVHYTGMILEDGKKFDSSRDNRNPKPFKMLGKQEVIRGWEEGVA QMSVGQRAKLITISPDYAYGATGHPGIIPPHATLVFDVELLKLEGGAP		
	FRB	SEQ ID NO. 15	SGGRVAILWHMWWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKTSFNQAYGRDLM EAQEWCRKYMKSGNVKDLTQAWDLYYHYVFRRIGSGAP		
Hinge	CD8a	SEQ ID NO. 6	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD		
	IgG1	SEQ ID NO. 7	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPDTLMIARTPEVTCVWVDVSHEDPEVKFNWVVDGVEV HNAKTPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTKISAKGQPREPQVYTLPP SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLSPGKKD		
	EpoR_D2	SEQ ID NO. 8	APVGLVARLADESGHVVLRLWLPPTPMTSHIRYEVVDVSAGNGAGSVQRVEILEGRTECVLSNLRGT RYTFAVRARMAEPSFGGFSWSEPVSLTSPD		
Transmembrane domain	CD8a	SEQ ID NO. 19	IYIWAPLAGTCGVLLSLVITLYCR		
	4-1BB	SEQ ID NO. 20	IISFFLALTSTALLFLFLFLTLRFSWKRGR		
	DAP10	SEQ ID NO. 21	ILLAGLVAADAVASLLIVGAVFLCARR		
	CD28	SEQ ID NO. 22	IFWVLVVGGLACYSLLVTVAFIHFWVRKRR		
Inhibitory signaling domain	PD1	SEQ ID NO. 23	SRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPPEPPVPCVPEQTEYATIVFPSGMGTS SPARRGSADGPRSAQPLRPEDGHCSWPLE		

Table 3: Exemplary sequences of modulable/tunable multi-chain CAR based on PD-1 inhibitory signaling domain presented in Figure 1.

Intracellular CID strategy-, when the CID protein is located on the alpha chain.

Several IMP molecules are possible depending of the positioning of the CID protein (dimerization part) and of the PD1 protein.

Component	Functional domains	Description	SEQ ID #	Raw amino acid sequence
<i>Multi-chain CAR</i>				
Alpha-chain	Signal sequence	FcεR1α-SP	SEQ ID NO.1	MAPAMESPTLLCVALLFFAPDGVLA
	svFc	CD123-scFv	SEQ ID NO.2	MAPAMESPTLLCVALLFFAPDGVLAQILVQSGPELKPGETVKISCKASGYIFTNYGMNWWKQAPGK SFKWMGWINTYTGESTYSADFKGRFAFLETSASTAYLHINDLKNEATATYFCARSGGYDPMYWGQ GTSVTVSSGGGGGGGGGGSDIVLTQSPASLAVSLGQRATISCRASEVDNYGNTFMHWYQQK PGQPKLLIYRASNLSEGIPIRFGSGSRDFTLTINPVEADDVATYYCQSNEDPPTFGAGTKLEIKRS DP
		KIα43-3-scFv	SEQ ID NO.3	MAPAMESPTLLCVALLFFAPDGVLAELVKGESGGGLVQPGGSLSCAASGFTFTDYMSWVRQPPG KALEWLALIRSKADGYTTEYSASVKGRTLSRDDSQSILYLQMNALRPEDSATYYCARDAAAYSYSPG AMDYWGQGTSTVTVSSGGGGGGGGGGSDIVMTQTPTLLVSAGDRVTITCKASQSVNDVAWYQQKPG VDSAAWYQQKPGQSPKALISASRYSGVPDRFTGRSGTDTLTLTSSVQAEDLAVYCCQQYVSTPW TFGGGKLEIKRSDP
		5T4WT19-scFv	SEQ ID NO.4	MAPAMESPTLLCVALLFFAPDGVLAELVQLQQSGPDLVKPGASVKISCKASGSYFTGYMHWVKQSHG KSLEWIGRINPNNGVTLYNQKFKDKAITVDKSTTAYMELSLTSEDSAVYCARSTMITNVMYVMDYV GQVTSVTVSSGGGGGGGGGGSDIVMTQTPTLLVSAGDRVTITCKASQSVNDVAWYQQKPG QSPDLLISYTSRYAGVPDRFIGSGYGTDTFTLTSLQAEDLAVYCCQQDYNSPPTFGGGTKLEIKRSDP
		VH-4G7-scFv	SEQ ID NO.5	MAPAMESPTLLCVALLFFAPDGVLAELVQLQQSGPELKPGASVKMCKASGYTFTSYVMHWVKQKP QGGLWIGYINPYNDGTYNEKFKGKATLTSKSSSTAYMELSLTSEDSAVYCARGTYYGSRVFDY WGQGTTLTVSSGGGGGGGGGGSDIVMTQAAPSPVTPGESVISCRSKSLNSNGNTLYWF LQRPQGSPQLLIYRMSNLASGVDRFSGSGGTAFTRISRVEAEDVGYYCMQHLEYPFTFGAGTKL ELKRS DP
		CD8a	SEQ ID NO.6	TTTPAPRPPTPTAPTIASQPSLRPEACRPAAGGAVHTRGLDFACD

Hinge	IgG1	SEQ ID NO.7	EPKSPDKTHTCPPCPAPPVAGPSVFLPPKPKDTLMIAARTPEVTCVWVDVSHEDPEVKFNWVVDGVEV HNAKTPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMIHEALHNHYTQKSLSLSPGKKD
	EpoR_D2	SEQ ID NO.8	APVGLVARLADESGHVLRWLPPETPTMTSHIRVEVDVSAGNGAGSVQRVEILEGRTECVLSNLRGRT RYTFARARMAEPSFGGFWSAWSEPVSLLTPSD
	Alpha-TI-A	SEQ ID NO.9	IFIPLLVILFAVDTGLFISTQQQVFTLLKIKRTRKGRFLLNPHPKPNPKNNR
Transmembrane + intracellular domain - with hinge-	Alpha-TI-B	SEQ ID NO.10	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAAGAVHTRGLDFACDFFIPLLVILFAVDTGLFISTQQQV FLLKIKRTRKGRFLLNPHPKPNPKNNR
			Without linker
	FKBP_pos4-ter- alpha	SEQ ID NO.24	SGGVQVETISPGDGRTPFKRGQTCVVHYTGMILEDGKFDSSDRDNKPKFMLGKQEVIRGWEEGVA QMSVGGQRAKLTISPDYAYGATGHPGIIPPHATLVFDVELLKEE
	FRB_pos4-ter- alpha	SEQ ID NO.25	SGGRVAILWHEMWHHEGLEEASRLYFGERNVKGMEVLEPLHAMMERGPQTLKETSFNQAYGRDLIM EAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRIE
Dimerization part			With linker
	CD28	SEQ ID NO.26	SRLLSHYMNMTPRRPGPTRKHYPVAPPRDFAAYRSGSGSGSGS
	4-1BB	SEQ ID NO.27	GRKKLLYIFKQPFMRPVQTTQEEDGCSRCRFPPEEEGGCELGSGSGSGS
	OX40	SEQ ID NO.28	ALYLLRRDQRLPPDAHKKPPGGGSRFTPIQEEQADAHSTLAKIGSGSGSGS
	DAP10	SEQ ID NO.29	PRRSPAQEDGKVYINMPGRGSGSGSGS
	CD18	SEQ ID NO.30	KALIHLSDLREYRFEKEKLKQWNNNDNPLFKSATTTVMNPKFAESGSGSGSGS
	CD28	SEQ ID NO.31	RSKRSLLSHYMNMTPRRPGPTRKHYPVAPPRDFAAYRSGSGSGSGS

[illegible]

Beta-chain	beta-41BB chain		SEQ ID NO.12	MDTESNRRANLALPQEPSSVPAFEVLEISPOEVSSGRLLKSASSPPLHTWLTVLKKEQFGLVQTILTAM ICLCFGTVVCSVLDISHIEGDIFSSFKAGYPFWGAIFFSISGMLSIISERRNATYLVIRGSLGANTASSIAGGT GITLIINLKSLAYIHSCQKFFETKCFMASFSTEIVMMMLFLTILGLGSVSLTICGAGEELKGNKVPEKR GRKKLLYIFKQPFMRPVQTTQEEDGSCSRPEEEGGCEL
Gamma-chain	gamma-CD3z chain		SEQ ID NO.49	MIPAVVLLLLLVEQAAALGEPQLCVILDAILFLYGIVLTLLYCRKIQVRKAATSYEKSRRVKFSRSADAPAY QQGQNQLYNELNIGRREYDVLDKRRGRDPENMGKPRRKNPQEGLYNELQDKMAEAYSEIGMKG ERRRGKHDGLYQGLSTATKDTYDALHMQALPPR
<i>IMP complex (IMP molecule #1)</i>				
Sequence signal			SEQ ID NO.18	MALPVTALLPLALLHAAARP GSD
Transmembrane domain		VH-4G7-ss		
		CD8a	SEQ ID NO.19	IYIWAPLAGTCGVLLLSLIVITLYCR
		4-1BB	SEQ ID NO.20	IISFFLALTSTALLFLFLTLRFSVVKRGR
		DAP10	SEQ ID NO.21	ILLAGLVAADAVASLLIVGAVFLCARR
Dimerization part	CID_Protein	CD28	SEQ ID NO.22	IFWVLVVVGGVACYSLLVTVAFIIFWVRSKRR
		FKBP_pos3-IMP	SEQ ID NO.24	SGGVQVETISPGDGRTPFKRGQTCTVHYTGMLEDGKKFDSRRDNKPKFMLGKQEVIRGWEEGVA QMSVGGQRAKLTISPDYAYGATGHPHPIPHATLVDFVELLKLEGGSS
		FRB_pos3-IMP	SEQ ID NO.25	SGGRVAILWHMWMHEGLEEASRLYFGERNVKGMEFVLEPLHAMMERGPQTLKTSFNQAYGRDLM EAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRIGSGSS
		PD1	SEQ ID NO.23	SRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPPEPPVPCVPEQTEYATVFPSPGMGTS SPARRGSADGPRSAQPLRPEDGHCSWPLE
Inhibitory signaling domain				
<i>IMP complex (IMP molecule #2)</i>				
Sequence signal			SEQ ID NO.18	MALPVTALLPLALLHAAARP GSD
Transmembrane domain		VH-4G7-ss		
		CD8a	SEQ ID NO.26	IYIWAPLAGTCGVLLLSLIVITLYCR
		4-1BB	SEQ ID NO.27	IISFFLALTSTALLFLFLTLRFSVVKRGR
		DAP10	SEQ ID NO.28	ILLAGLVAADAVASLLIVGAVFLCARR
		CD28	SEQ ID NO.29	IFWVLVVVGGVACYSLLVTVAFIIFWVRSKRR
		CD28 N	SEQ ID NO.26	SRLHSDYMNMTPRRPGTRKHVQPYAPPRDFAAYRSGSGSGSGS
		4-1BB	SEQ ID NO.27	GRKKLLYIFKQPFMRPVQTTQEEDGSCSRPEEEGGCELGSGSGSGS
		OX40	SEQ ID NO.28	ALYLLRRDQRLPPDAHKPPGGGSRFTPIQEEQADAHSTLAKIGSGSGSGS

[illegible]

[illegible]

	CD229	SEQ ID NO.45	LYSVLSQGYEKLDTPLRARQQPTPTSDSSDNLTEEDDRPEVHKPISGRYEVFDQVTQEGAGHD PAPEGQADYDPVTPVYTESVVGENTMYAQVFNQKTPV/SQKESSATYCSIRKPQVPPPPQQN DLEIPESPTYENFTGSGSGSGS
	LTBR	SEQ ID NO.46	KAHPYFDLVQPLLPISGDVSPVSTGLPAAVLEAGVPQQQSPDLTLTREPQLEPGEQSQVAHGTNGIH VTGSGMTITGNIYNGPVLGGPPGDLPATPEPPYPIEEGDPGPPGLSTPHQEDGKAWHLAETE HCGATPSNGSGSGSGS
Dimerization part	FKBP_pos4-ter-IMP	SEQ ID NO.54	SGGVQVETISPGDGRTPFKRGQTCVVHYTGMILEDGKKFDSRDNRNPKFKFMLGKQEVIRGWEEGVA QMSVGQRAKLTISPDYAVGATGHPGIIPPHATLVFDVELLKEE
	FRB_pos4-ter-IMP MTOR_HUMAN	SEQ ID NO.55	SGGRVAILWHMWMHEGLEEASRLYFGERNVKGMEVLEPLHAMMERGPQTLKETSFNQAYGRDLIM EAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRIE
IMP complex (IMP molecule #4)			
Sequence signal	VH-4G7-ss	SEQ ID NO.18	MALPVTALLPLALLHAARPGSD
Transmembrane domain	CD8a	SEQ ID NO.19	IYIWAPLAGTCGVLLLSLVITLYCR
	4-1BB	SEQ ID NO.20	IISFFALSTALLFLFLTLRFSVVKRGR
	DAP10	SEQ ID NO.21	ILLAGLVAADAVASLLIVGAVFLCARR
	CD28 CD28_HUMAN	SEQ ID NO.22	IFWVLVVVGGLACYSLLVTVAFIIFWVRSKRR
	CD28	SEQ ID NO.26	SRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSGSGSGSGS
	4-1BB	SEQ ID NO.27	GRKLLYIFKQPFMRPVQTTQEEEDGSCRFEEEEEGGCELGSGSGSGS
	OX40	SEQ ID NO.28	ALYLLRRDQRLPPDAHKPPGGGSRFTPIQEEQADAHSTLAKIGSGSGSGS
	DAP10	SEQ ID NO.29	PRRSPAQEDGKVYINMPGRGGSGSGSGS
	CD18	SEQ ID NO.30	KALIHLSDLREYRFEKEKLSQWNNDNPLFKSATTVMNPKFAESGSGSGSGS
	CD28	SEQ ID NO.31	RSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSGSGSGSGS
	CD275	SEQ ID NO.32	RDRCLQHSYAGAWAVSPETELTGHVSGSGSGS
	HVEM	SEQ ID NO.33	CVKRRKPRGDVVKVSVQKRQEAEGEATVIEALQAPPDVTVAVEETIPSTGRSPNHGSGSGSGS
	LIGHT	SEQ ID NO.34	MEESVVRPSVFVVDGQTDIPFTRLGRSHRRQSCSVARGSGSGSGS
	CD40L	SEQ ID NO.35	MIETYNQTSRPSAATGLPSMKGSGSGSGS
	GITR	SEQ ID NO.36	QLGLHIWQLRSQCMWPRETQLLLVPPSTEDARSCQFPEEERGERSAEEKGRGLDWVSGSGSGSGS
	TIM1	SEQ ID NO.37	KKYFFKKEVQQLSVSFSLQIKALQNAVEKEVQAEDNIYIENSLYATDGSFGSGSGS
	SLAMF	SEQ ID NO.38	QLRRRGKTNHYQTTVEKSLTYAQVKPGPLQKLDSPAQDPCTTIYVAATEPVESVQETNSITV

Linker				YASVTLPESGSGSGS	KRKKQSRNRNDEELETRAHRVATEERGRKPHQIPASTPQNPAATSQHPHPPPPGHRSQAPSHRPPPPGH RVQHQPQKRPPAPSGTQVHQKQGPPLPRPRVQPKPHGAAENSLSPSSNGSGSGS
	CD2		SEQ ID NO.39		KKRHMASYSMCDPSTRDPPGRPEVPVEVLIGSGSGS
	TLT-2		SEQ ID NO.40		HLWRRQWRPRRFSALEQGHPPQAQSKIEELEQEPEPEPEPEPEPEPEQLGSGSGS
	LAG3		SEQ ID NO.41		YFLGRLLVPRGRGAAEAATRKQITETESPVQELQQRSDVSDINTQRPYKSGSGSGS
	DAP12		SEQ ID NO.42		RLFKRRQGRIFEGSCLNTFTKNPYAASKTIYIMASRNTQPAESRIYDEILQSKVLPSKEEPVNTVYS EVQFADKMGKASTQDSKPPGTSSVEIVIGSGSGS
	CD84		SEQ ID NO.43		EFLTIVEDVKDLKTRRNHEQEQTTPGGGGSTIYMIQSSAPTSQEPAYTLYSLIQPSRKSGRKRNHSP SFNSTIYEVIGKSQPKAQNPARLSRKELENFVYSGSGSGS
	CD244		SEQ ID NO.44		LYSVLSQGYEKLDTPLRARQQPTPTSDSSDSNLTTEDDRPEVHKPISGRYEVFDQVTQEGAGHD PAPEGQADYDPVTPYVTEVESVVGENTMYAQVFNQLQKTPVSQKESSATIYCSIRKPQVPPPPQN DLEIPESPTYENFTGSGSGS
	CD229		SEQ ID NO.45		KAHPYFDLVQPLLPISGDVSPVSTGLPAAPVLEAGVPQQQSPDLTREPQLEPGEQSQVAHGTNGIH VTGGSMTITGNIYNGPVLGGPPGPDLPATPEPPYPIEEDGPPGLSTPHQEDGKAWHLAETE HCGATPSNGSGSGS
	LTBR		SEQ ID NO.46		SRAARGTIGARRTGQPLKEDPSAVPVFSVDYGLDFQWREKTPPEPPVPCVPEQTEYATIVFPSGMGTS SPARRGSADGPRSAQPLRPEDGHCSWPLGSGS
	PD1_pos4		SEQ ID NO.56		GVQVETISPGDGRTPFKRGQTCVVHYTGMLEDGKKFDDSRDRNKPFKFMLGKQEVIRGWEEGVAQ MSVGQRAKLTISPDIYAYGATGHPGIIPPHATLVFDVELLLEE
Inhibitory signaling domain					GRVAILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEA QEWCRKYMKSGNVKDLTQAWDLYYHVFRRIE
Dimerization part					
CID_Protein					

Table 4: Exemplary sequences of modulable/tunable multi-chain CAR based on IL-10R inhibitory signaling domain presented in Figure 3

Component	Functional domains	Description	SEQ ID #	Raw amino acid sequence
<i>Multi-chain CAR</i>				
Alpha-chain	Signal sequence	Fc α R1 α -SP	SEQ ID NO.1	MAPAMESPTLLCVALLFFAPDGVLA
		CD123-scFv	SEQ ID NO.2	MAPAMESPTLLCVALLFFAPDGVLAQIQLVQSGPELKPGETVKISKASGYIFTNYGMNWWKQAPGKSKFWMGWINTYTGESTYSADFKGRFAFLETSASTAYLHINDLKNEDTATYFCARSGGYDPM DYWGQGTSTVTVSSGGGGGGGGSDIVLTQSPASLAVSLGQRATISCRASEVDNYGNTFMH WYQQKPGQPPKLLIYRASNLSEGPARGSGSRDFTLTINPVEADDVATYYCQQSNEDPPTFGAGT KLELKRSDP
		KI α 43-3-scFv	SEQ ID NO.3	MAPAMESPTLLCVALLFFAPDGVLAEVKLVSGLVQPGGSLSCAASGFTFTDYYMSWVRQPP GKALEWLALIRSKADGYTTEYSASVKGRTLSRDDSSQILYLMNALRPEDSATYYCARDAAVYSSP EGAMDYWGQGTSTVTVSSGGGGGGGGGGGSMADYKDIVMTQSHKFMSTSVGDRVNITCKA SQNVDSAVAWYQQKPGQSPKALIYSARYSGVDPDRFTGRSGTDTLTITSSVQAEALAVYCCQQY STPWTFGGGTKLEKRSDP
		5T4WT19-scFv	SEQ ID NO.4	MAPAMESPTLLCVALLFFAPDGVLAEVQLQQSGPDLVPGASVKISCKASGYFTGYMHVWKQSH GKSLWIGRINPNNGVTLYNQKFKDKAILTVDKSSTTAYMELRSLTSEDSAVVYCARSTMITNYVM DYWGQVTSTVSSGGGGGGGGGGSSIVMTQTPTFLVLSAGDRVTITCKASQSVSNDVAWYQQ KPGQSPSTLLISYTSRYAGVPDRFIGSGYGTDTFTITSLQAEALAVYFCQQDYNSPPTFGGGTKLEKR SDP
		VH-4G7-scFv	SEQ ID NO.5	MAPAMESPTLLCVALLFFAPDGVLAEVQLQQSGPELKPASVKMSCKASGYFTTSVMHWKQK PGQGLEWIGYINPYNDGTYNEKFKGKATLTSKSSSTAYMELSLTSEDSAVVYCARGTYYGSRVF DYWGQGTTLTVSSGGGGGGGGGGSDIVMTQAAPSPVTPGESVSISSRSSKLLNSNGNTYL YWFLQRPQSPQLLIYRMSNLASGVDPDRFSGSGGTFTLRISRVEAEDVGVVYCMQHLEYPFTFGA GTKLELKRSDP
	Hinge	CD8a	SEQ ID NO.6	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD
		IgG1	SEQ ID NO.7	EPKSPDKTHTCPPCAPPVAGPSVFLFPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIKAKGQPREPQVY TLPSSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFCSVMHEALHNHYTQKSLSLSPGKKD

	EpoR_D2	SEQ ID NO.8	APVGLVARLADSGHVLRWLPPETPMTSHIRYEVDSAGNGAGSVQRVEILEGRTECVLSNLRG RTRYTFAVRARMAEPSEFGGFWSAWSEPVSLLTPSD
	Transmembrane + intracellular domain - with hinge-	SEQ ID NO.9	IFIPLLVLFAVDTGLFISTQQQVTFLLKIKRTRKGFRLLNPHPKPNPKNNR
	Transmembrane + intracellular domain - without hinge-	SEQ ID NO.10	TTTPAPRPPTAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFFIPLLVLFAVDTGLFISTQQQVTF LLKIKRTRKGFRLLNPHPKPNPKNNR
Gamma-chain	CD19 alpha chain	SEQ ID NO.11	MAPAMESPTLLCVALLFFAPDGVLAEVQLQQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQK PGQGLEWIGYINPYNDGTKYNEKFKGKATILTSKSSSTAYMELSLTSEDSAVYVCARGTYYGSRVF DYWGQGTTLTVSSGGGGGGGGGGSDIVMTQAAPSPVTPGESVSISSCRSSKSLNSNGNTYL YWFQRPQSQPLLIRMSNLASGVDPDRFSGSGGTFTLRISRVEAEDGVVYCMQHLEYPTTFGA GTKLELKRADTTTPAPRPPTAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFFIPLLVLFAVDT GLFISTQQQVTFLLKIKRTRKGFRLLNPHPKPNPKNNR
		SEQ ID NO.49	MIPAVLLLLLVEQAAALGEPQLCYILDAILFLYGVILTLTYCRLLKIQVRKAITSYEKSRVKFSRSADAPA YQQGNQLYNELNLRREEYDVLDKRRGRDPEMGKPRRKNPQEGLYNELQDKMAEAYSEIGM KGERRRGKGDGLYQGLSTATKDTYDALHMQALPPR
		SEQ ID NO.12	MDTESNRRANLALPQEPSSVPAFEVLEISPQEVSSGRLLKSASSPPLHTWTLVLKKEQEFGLVQTILTA MICLCFGTVVCSVDISHIEGDIFFSFKAGYPFWGAIFISGMLSIISERRNATYLVIRGSLGANTASSIA GGTGITILIINLKSLAYIIHSCQKFFETKCFMASFTEIVVMMFLITILGLSAVSLTICGAGEELKGNK VPEKGRKKLLYIFKQPFMRPVQTTQEEEDGCSCRFPEEEGGCEL
IL-10A- and IL-10B based IMP molecules			
Signal sequence	VH-4G7-ss	SEQ ID NO.18	MALPVTALLPLALLHAARPG
Dimerization part	FKBP	SEQ ID NO.14	SGGVQVETISPGDGRTPKRGQTCVWHYTGMLDGGKFDSSDRDNKPKFMILGKQEVIRGWEEGV AQMSVGQRAKLITSPDYAYGATGHPGIIPPHATLVDFVELLKLEGGAP
	FRB	SEQ ID NO.15	SGGRVAILWHEMWHHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDL MEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRIRGGAP

Hinge	CD8a	SEQ ID NO.6	TTTPAPRPPTPTAPTASQPLSLRPEACRPAAGGAVHTRGLDFACD
	IgG1	SEQ ID NO.7	EPKSPDKTHITCPPCAPPVAGPSVFLPPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNNYKTPPVLDSDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGKKD
	EpoR_D2	SEQ ID NO.8	APVGLVARLADESGHVLRWLPPPETPMTSHIRYEVDVSAGNGAGSVQRVEILEGRTECVLSNLRG RTRYTFVARMARMAEPSFGGFWSAWSEPVSLLTPSD
	IL10R1_HUMAN	SEQ ID NO.59	IVIIFFAFVLLSGALAYCLALQLVRRRKKLPVLLFKKPSPFIFISQRPSPETQDTIHPLDEEAFLKVSPEL KNLDLHGSTDSGFGSTKPSLQTEEPQFLPDHPQADRTLGNREPPVLGDCSSGSSNSTDSGICLQE PSLSPSTGPTWEQQVGSNSRGQDDSGIDLQNSEGRAGDTQGGGALGHHSPPEVPGEEDPAAV AFQGYLRQTRCAEEKATKTGCLEESPLTDGLGPKFGRCLVDEAGLHPPALAKGYLKQDPLEMTLASS GAPTQQWNQPTTEEWSLLALSSCDLGISDWSFAHDLAPLGCVAAPGGLLGSFNSDLVTLPLISSLQS SE
	IL10R2_HUMAN	SEQ ID NO.60	IWMVAVILMASFMVCLALLGCFALLWCVYKTKYAFSPRNSLPQHILKEFLGHPHHNTLLFFSFPLS DENDVFDKLSVIAEDSESGKQNPGDSCSLGTPPGQGPQSE
Transmembrane domain + inhibitory signaling domain	IR-10RA inhibitory domain		
	IR-10B inhibitory domain		

Detailed description of the invention

The ability to control functional responses in adoptive T cell therapy is a key issue. In such therapeutic strategies, T cells are engineered by expressing surface-exposed chimeric antigen receptor (CAR) that achieves high tumor specific target cell recognition. However, to control and minimize potential toxic effects, design of modifiable switch systems is highly desirable.

The inventors developed methods of engineering such immune cells based on the design of a chimeric multi-protein complex which is able to inactivate the Chimeric Antigen Receptor (CAR) through the addition of a soluble compound, such as rapalogs.

In particular, the present invention provides a method for modulating the level of activation of an engineered immune cell, said method comprising the following steps of:

(a) transfecting an immune cell with at least a first polynucleotide encoding a Chimeric Antigen Receptor (CAR), which can be activated in-vivo and/or in vitro by an external ligand; said CAR comprising a first binding domain and ;

(b) further transfecting said immune cell with at least a second polynucleotide encoding an engineered inhibitory membrane protein (IMP) complex, comprising at least one intracellular inhibitory signaling domain and one second binding domain,

such that said immune cell co-expresses, said CAR, and said inhibitory membrane protein (IMP) complex, and;

(c) contacting said engineered immune cell with said external ligand, so that a signal is transduced by the CAR, and then;

(d) reducing the level of said signal transduction of said CAR by adding a soluble compound that binds the binding domain of said IMP and the binding domain of the CAR molecule to co-localize said IMP and said CAR,

thereby modulating the level of activation of the engineered immune cell.

By “modulating” the level of activation, it is intended that an inhibition response is obtained on the CAR-engineered immune cells by the administration of a soluble compound, and preferably not a destructive response in contrast to other systems from the prior art. This is particularly useful to

adjust the CAR induced activation to patient's needs and more critically, when a severe case of adverse event occurs in a patient.

According to a preferred embodiment, said signal of transduction of the CAR is an activation of the immune cell and said immune cell is activated.

5 According to another preferred embodiment, the co-localization of the IMP and CAR molecules has the effect of switching off the CAR signal transduction.

One interesting feature of the system of the invention is its flexibility based on the co-localization of proteins i.e no-covalent binding. Thus, after a short while following the discontinuation of administration of the soluble compound (such as a rapalog), one can expect the soluble compound
10 will not bind anymore the binding domains, the "switch off" will cease to be operational, and the CAR engineered immune cells will be able to retrieve their potential.

According to a preferred embodiment, first and second binding domains are CID binding domains.

In the present invention, it is also contemplated the possibility to perform a « fine tuning »
15 of a CAR transduction signal: a dose of soluble can be adjusted; depending of the severity of the adverse event following an inadequate/excessive activity of the CAR engineered immune cells administrated to the patient.

The signal transduced by a CAR in an engineered immune cell may be an activation signal or an inactivation signal on the engineered immune cell, depending of the nature of the signal. This
20 depends on the transduction signaling domain included in the CAR (activating or inhibiting signaling domain, which is expressed by the immune cell. When the immune cell expresses a "positive CAR" which usually comprise an activation domain comprising ITAM component(s), with the effect of activating said cell (i.e. its immune function) upon recognition of a tumoral surface specific-antigen, then the IMP will act as a brake on the cell activation, and further as a "switch-off" system,.
25 Conversely, in the event the transduction signal is generated by a "negative CAR" that comprises, for instance, an inhibitory signaling domain, such as immunoreceptor tyrosine-based inhibition motif (ITIM) , then the inhibition will be partially or totally lifted, acting as a "switch-on" system.

Inhibitory membrane protein (IMP) complex

According to another aspect, the present invention discloses an inhibitory dual CAR/IMP complex, comprising at least two transmembrane chimeric polypeptides:

- a first one encoding a Chimeric Antigen Receptor which comprises one dimerization
5 binding domain;

-the second one encoding an engineered inhibitory membrane protein (IMP) complex, said IMP complex comprising at least one intracellular inhibitory signaling domain and one dimerization binding domain.

According to a preferred embodiment, said inhibitory dual CAR/IMP complex comprises dimerization
10 binding domains which are located extracellularly.

According to an embodiment, the CAR which is part of said inhibitory dual CAR/IMP complex is a multi-chain CAR.

According to an embodiment, the CAR which is part of said inhibitory dual CAR/IMP complex is a single-chain CAR.

15 In one embodiment, the intra inhibitory domain which is part of the engineered inhibitory membrane protein (IMP) complex is the PD-1 protein (also called "Programmed cell death protein 1" or CD279).

According to a preferred embodiment, the dimerization binding domains are FKBP or FRB. According to a more preferred embodiment, said first and second binding domains have at least 80 % identity with SEQ ID NO 14 and SEQ ID NO 15.

20 According to the invention, the inhibitory membrane (IMP) complex corresponds to at least one transmembrane chimeric protein; the latter containing at least one intracellular inhibitory signaling domain and one binding domain.

In one embodiment, the IMP complex involves one transmembrane chimeric protein, comprising at least one inhibitory signaling domain and a first binding domain that can bind to a
25 second binding domain borne on the Chimeric Antigen Receptor (CAR) through the presence of a soluble compound (Figures 1 and 2).

These inhibitory signaling domains may belong to the "immune checkpoints" molecules effectively serve as "brakes" to down-modulate or inhibit an immune response.

Amongst these inhibitory signaling domains, some can be "functional" inhibitors because
30 they can interact by (reversible) post-translational modification, such as by dephosphorylation

mechanism (i.e. for PD-1), some can be “structural” inhibitors, such as antibodies (preferably an humanized intrabodies) which can physically block the protein.

According to the invention, these inhibitory signaling domains can be from, but are not limited to, Programmed Death 1 (PD-1, also known as PDCD1 or CD279, accession number: NM_005018), Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4, also known as CD152, GenBank accession number AF414120.1), LAG3 (also known as CD223, accession number: NM_002286.5), Tim3 (also known as HAVCR2, GenBank accession number: JX049979.1), BTLA (also known as CD272, accession number: NM_181780.3), BY55 (also known as CD160, GenBank accession number: CR541888.1), TIGIT (also known as VSTM3, accession number: NM_173799), LAIR1 (also known as CD305, GenBank accession number: CR542051.1, (Meyaard, Adema et al. 1997)), SIGLEC10 (GeneBank accession number: AY358337.1), 2B4 (also known as CD244, accession number: NM_001166664.1), PPP2CA, PPP2CB, PTPN6, PTPN22, CD96, CRTAM, SIGLEC7 (Nicoll, Ni et al. 1999), SIGLEC9 (Zhang, Nicoll et al. 2000; Ikehara, Ikehara et al. 2004), TNFRSF10B, TNFRSF10A, CASP8, CASP10, CASP3, CASP6, CASP7, FADD, FAS, TGFBR2, TGFBR1, SMAD2, SMAD3, SMAD4, SMAD10, SKI, SKIL, TGIF1, IL10RA, IL10RB, HMOX2, IL6R, IL6ST, EIF2AK4, CSK, PAG1, SIT1, FOXP3, PRDM1, BATF (Quigley, Pereyra et al. 2010), GUCY1A2, GUCY1A3, GUCY1B2, GUCY1B3, which proteins have been described as having ability to inhibit immune cells activation.

A particular preferred inhibitory signaling domain is from PD-1 and preferably comprises the amino acid sequence that has at least 80% sequence identity with SEQ ID NO.23.

Beside these immune checkpoints (such as PD-1), other inhibitors towards the immune response are encompassed within the invention: for instance, some cytokines.

According to an alternative embodiment, the IMP complex of the invention involves two transmembrane chimeric proteins, each comprising a binding domain that may be bound by a soluble compound (Figure 3).

In accordance with one preferred embodiment, inhibitory signaling domains are the interleukin IL-10R α and IL-10R β monomers, and preferably comprise the amino acid sequences that have at least 80% sequence identity with SEQ ID NO.59 and SEQ ID NO.60 respectively.

In general, IL-10R is composed of two subunits to be active: IL-10R α (Ref. Uniprot: Q13651; RefSeq: NP_001549); and IL-10R β (Ref.Uniprot: Q08334, RefSeq: NM_000628 for the human species).

According to Satoshi et al. 1999), the inhibitory action of IL-10 on immune cells -such as the CAR-

lymphocytes T of the invention- is obtained via the inhibition of expression of both interferon α - and interferon γ - induced genes.

Typically, IL10RA/IL10B polypeptides of the invention respectively comprise the amino acid sequence has at least 80% sequence identity with SEQ ID NO: 59 and SEQ ID NO: 60 respectively.

5 The inhibitory action of the IL-10R occurs after the dimerization of the IL10RA/IL10B polypeptides and leads to the inhibition of cytokines such as interferon IFN- γ , IL-2, IL-3 or TNF- α involving the JAK-STAT signaling pathway (Finbloom et al. 1995). Therefore, the functional IL-10R dimer can indirectly monitor or shunt the activation of an immune cell by the Chimeric Antigen Receptor (CAR).

10 In addition to IL-10R interleukin, other examples of switches can be used according to the system presented in Figure 3, as long as they are negative regulators on immune cells and they are multimeric. Amongst them, one can find TGF- β (transforming growth factor beta), VEGF (Vascular endothelial growth factor), or the apoptosis inducing-multimeric receptors such as TNFR (tumor necrosis factor receptor) or DR3 (Death-receptor-3).

15 In view of the preceding, one of the particularities of an IMP according to the invention comprising an inhibitory signaling domain such as IL-10R is that this inhibitory system does not require any component from the CAR to initiate its action. Consequently, it can be used in combination with any CAR regardless its specificity and architecture, to down regulate activated CAR T-cell, acting as a "universal" switch. Subsequently, the invention contemplates the combined use of a
20 CAR and a molecular switch as previously described whatever be the antigen targeted by the CAR.

The transmembrane part of the IMP complex is chosen amongst not only those used for the Chimeric Antigen Receptor (CAR) as presented in the following section "Chimeric Antigen Receptor" but also by many others which appear suitable for the skilled person in the construction of such multipart polypeptide.

25 The binding domain of the IMP complex according to the invention is a protein which can bind to a soluble compound which, via the signaling domain, mediates a modulation on the activation of the CAR. Preferably, the system of the invention is composed of two binding domains which can co-localized or dimerized by the intervention of soluble compound.

The binding domain of the present invention is preferably a dimerization domain.

According to one or the other above embodiments, either these two binding domains are borne on two different IMPs, or one binding domain is part of one IMP and the other on the CAR, depending of the type and action of the inhibitory signaling domain used.

5 According to a preferred embodiment, both binding domains interact with the same soluble compound.

By “co-localization” or “dimerization” (also called “chemically induced dimerization” or CID) of the two binding domains is meant that the two proteins come close together to make is a macromolecular complex, non-covalently bound, in the presence of a certain small molecule, enzyme or other dimerizing agent. This CID system allows the manipulation of signaling pathways in the case
10 of the present invention.

According to one embodiment, the binding or dimerization domains are extracellular. This configuration is favored/more favorable when the small molecule acting as dimerizing agent is not immunogenic and/ or cannot come easily across the membrane of the immune cell. The first and second binding or dimerization domains can be borne respectively on the IMP protein and on the
15 CAR structure (Figure 1), or both on two separate 2 polypeptides from the IMP complex (Figure 3) depending of the inhibiting signaling domain used (by instance, IL10R versus PD-1). In the first situation, where one binding domain is present on the CAR structure, the action of the inhibitory signaling domain will be directly on the CAR, in contrast to the second situation, where the IMP complex has an inhibitory function on the immune cell activation that is deemed independent from
20 the activation by the CAR.

According to the alternative embodiment, the binding or dimerization domains are intracellular. This conformation applies when one binding or dimerization domain is part of one IMP (having an inhibitory signaling domain) and a second one is part of the CAR (Figure 2). This chemical induction dimerization (CID) strategy will be preferred, for instance, when potential immunogenic
25 small molecules are used.

The localization of the binding/dimerization domain on the alpha chain may be advantageous for a structural or conformational reason.

Still within the scope of the invention, dimerization domains are the preferred binding domains, therefore one binding domain binds to another domain, when they are put in presence of a
30 dimerizing agent.

Amongst binding domains which may be contemplated, one can find number of couples such as FKBP/FKBP with the dimerizing agent FK1012 (Spencer et al, 1993); FKBP/CAN with the dimerizing agent FK506 (Ho et al, 1996); FKBP/CyP-Fas with the dimerizing agent FKCsA (Belshaw et al, 1996); FKBP/FRB with the dimerizing agent rapamycin (Rivera et al, 1996); GyrB/GyrB with the dimerizing agent coumermycin (Farrar et al, 1996); GAI/GID1 with the dimerizing agent gibberellin (Miyamoto et al, 2012). In the last publication, the system has been shown functioning not only in higher plant but in mammalian cells.

According to a preferred embodiment, the binding domains are FKBP/FRB, and the dimerizing agent is a rapalog, and according to a more preferred embodiment, the rapalog is rapamycin.

In accordance with particular embodiments, the binding domains FKBP/FRB are polypeptides comprising the amino acid sequence that has at least 80% sequence identity with SEQ ID NO:14 and SEQ ID NO: 15 respectively.

According to one embodiment, the present invention relates to a retroviral vector comprising the polynucleotide as described previously.

Soluble compounds

By « soluble compound » is meant compounds that will be soluble in the serum of a patient, so that it will not precipitate and will act on the various engineered immune cells present in patient's blood circulation. A soluble compound according to the invention is preferably a small molecules", but may also be bi-specific antibodies. A "small molecule", as used herein, is a low molecular weight (<2000 daltons) organic compound. Non-limiting examples of small molecules which find application in the present invention include the macrolide rapamycin and its analogs, also known as "rapalogs", such as AP21967, Deforolimus (AP23573), everolimus (RAD001), and temsirolimus (CCI-779). Other non-limiting examples of small molecules which find application in the present invention include tacrolimus (FK506), FK506 derivatives, such as FK1012, FK506 analogs, such as AP1903. Yet other non-limiting examples of small molecules which find application in the present invention include coumermycin, gibberellin, HaXs, AP1510, AP20187 and AP21967. These "small molecules" can rapidly diffuse across cell membranes so that they can reach intracellular sites of action and to bind to a specific protein; they act as an effector, modifying the activity of function of the protein. Libraries of

such compounds can be found, for instance, in http://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&term=Small+Molecule+Libraries.

Amongst preferred small molecules, the ones which are particularly suited to the invention are the agents able to dimerize binding domains, called also dimerizing agents, such as rapalogs.

5 Rapalogs correspond to rapamycin analogs, including rapamycin (sirolimus), CCI779 (temsirolimus) and RAD001 (everolimus). Rapamycin is a macrocyclic antibiotic produced by the bacterium *Streptomyces hygroscopicus* found in the soil of Easter Island. Rapamycin was discovered as a potent antifungal agent, but it also exhibited what was at first considered to be an undesirable immunosuppressive effect, which subsequently led to its development as a clinically useful drug.

10 Amongst the “soluble compounds” envisioned by the invention, one may also contemplate the use of antibodies, and more particularly bispecific and monoclonal antibodies. Like the small molecules and dimerizing agents, bispecific monoclonal antibodies are designed in such a way that their epitopes can bind simultaneously both binding domains borne on IMP complex and/or the CAR structure. Their bindings generally allow co-localization of the inhibitory signaling domains of the IMP complex

15 and/or the CAR, and consequently a modulated action on the CAR.

As few examples, preferred bispecific monoclonal antibodies can be directed to an epitope of the FRB protein and one of the FKBP protein; or to two different epitopes of the FKBP protein; or to an epitope on the KBP protein and one on the CAN protein; or to an epitope on the FKBP protein and one on the CyP-Fas protein; or to two different epitopes of the GyrB protein; or to one epitope

20 on the GAI and one of the GID1 protein. Methods for obtaining bi-specific monoclonal antibodies are well known in the art (Springer T.A, 1985).

Chimeric Antigen Receptors

The present invention aims to produce engineered immune cells in which the level of

25 activation can be modulated through the IMP/CAR system. In order to allow this modulation, the present invention provides with specific design for the production of Chimeric Antigen Receptors (CAR) which are more prompt to interact with the IMP complex, either directly (Figures 1-2) or indirectly (Figure 3).

In general, CAR consists of an extracellular single chain antibody (scFv) fused to the

30 intracellular signaling domain of the T-cell antigen receptor complex zeta chain (scFv:ζ) and have the ability, when expressed in T-cells, to redirect antigen recognition based on the monoclonal antibody's

specificity as described elsewhere (WO2010025177A, WO 2012079000A WO2013126712A, EP2126054A) Several examples of CAR which may be used in the present invention is a CAR directing against CD123 (clones #43 and # 32716 from Cellectis), CS1 and TPBG (5T4) and can comprise as non-limiting example the amino acid sequences : SEQ ID NO:2, SEQ ID NO.3, SEQ ID NO.4 and SEQ ID NO.5.

Recent advances in the immunophenotyping of AML cells have revealed several AML associated cell surface antigens that may act as targets for future therapies. The interleukin 3 receptor alpha chain (IL-3R α ; CD123 – NCBI reference: NP_001254642) has been identified as a potential immunotherapeutic target since it is over-expressed on AML tumor cells compared to normal hematopoietic stem cells. Additionally, two phase I trials for CD123-specific therapeutics have been completed with both drugs displaying good safety profiles (ClinicalTrials.gov ID: NCT00401739 and NCT00397579).

One candidate antigen of immunotherapies for solid tumors, including the colorectal, ovarian and gastric and also for non-solid tumors such as childhood acute lymphoblastic leukemia (ALL) is the trophoblast glycoprotein, also known as TPBG or 5T4 (UniProt: Q13641). 5T4 is often referred to as an oncofetal antigen due to its expression in foetal trophoblast (where it was first discovered) or trophoblast glycoprotein (TPBG). 5T4 protein is an N-glycosylated transmembrane 72 kDa glycoprotein containing seven leucine-rich repeat regions (Hole et al, 1988). The 5T4 antigen was found to be expressed in number of carcinoma including gastric (Starzynska et al. 1995), ovarian and carcinoma (Wrigley et al. 1995). Also, 5T4 oncofetal antigen is expressed in high risk of relapse childhood pre-B acute lymphoblastic leukemia (Castro et al. 2012). It has very limited expression in normal tissue but is widespread in malignant tumors throughout their development (Carsberg et al. 1995).

CS1 (Gene ref: CS1 UNQ576/PRO1138, Uniprot ref: Q9NQ25) is a cell surface glycoprotein belonging to the CD2 subset of the immunoglobulin superfamily (IgSF) and is highly expressed by multiple myeloma cells, but minimally expressed by normal cells (Chu et al. 2013). The new Chimeric Antigen Receptor architectures according to the invention include an additional binding domain, distinct from that antigen recognition domain directed against a component present on the target cell, and that will be reactive with the same soluble component that acts on the IMP protein.

Single chain CAR according to the invention is basically a conventional single chain generation CAR which contains in supplement a binding (or dimerization) domain to the soluble molecule.

Depending of the CID strategy used, the binding (or dimerization) domain may be located extracellularly or intracellularly.

Both 2nd generation CAR (no combination of co-stimulatory molecules) and 3rd generation CARs (combination of co-stimulatory molecules) are contemplated in the scope of the present invention.

In one configuration of the present invention where the binding (or dimerization) domain is extracellular, a CAR according to the invention can contain one or several of the following components:

(a) a signal sequence and one of the 2 antigen-specific targeting regions (either the heavy chain or the light chain of scFV);

(b) optionally a linker;

(c) a binding (or dimerizing) domain

(d) the remaining antigen-specific targeting region (either the heavy chain or the light chain of scFV);

(e) optionally a hinge (or interspacer);

(f) a transmembrane domain;

(g) an intracellular domain containing at least one co-stimulatory molecule.

From the above structure, the position of the binding (or dimerization) domain relative to that the other extracellular components may change.

The invention may also involve a multi chain CAR as previously described by the applicant in WO 2014039523A or in PCT/EP2014/059662.

Both multichain Chimeric Antigen Receptor (mcCAR) and single chain Chimeric Antigen Receptor (scCAR) configurations are encompassed in the scope of the invention. Multi chain CAR structure according to the invention can be adapted from previous multi chain CAR, by introducing a binding (or dimerization) domain, which is sensitive to a soluble compound.

Depending of the CID strategy used, the binding domain may be located extracellularly or intracellularly as shown in Figures 1-2.

In the situation where the multi chain CAR is derived from a Fc receptor as described in WO 2014039523A, the binding (or dimerization) domain may be positioned either on the alpha chain (FCεRα), beta chain FCεRβ) or gamma chain (FCεRγ).

According to a particular embodiment, the engineered immune cells are transfected by a multi-chain based chimeric antigen receptor (CAR) wherein one of the dimerization domains is part of the α-chain.

Such mcCAR can comprise one or a subset of the following components:

- an alpha chain (FCεRα) containing :

- (a) a signal sequence and an antigen-specific targeting region;
- (b) a binding (or dimerization) domain;
- (c) an extracellular spacer domain (hinge);
- (d) a transmembrane domain;

- a beta chain (FCεRβ) containing:

- (a) a signal sequence;
- (b) an extracellular spacer domain (hinge);
- (c) a transmembrane domain;
- (d) a co-stimulatory ligand;

- a gamma chain (FCεRγ) containing :

- (a) a signal sequence;
- (b) an extracellular spacer domain (hinge);
- (c) a transmembrane domain;
- (d) a signal transducing domain.

According to a another particular embodiment, the engineered immune cells are transfected by a multi-chain based chimeric antigen receptor (mcCAR) wherein one of the dimerization domains is part of the γ-chain; such mcCAR can comprise one or a subset of the following components:

- an alpha chain (FCεRα) containing:

- (a) a signal sequence and an antigen-specific targeting region;

- (b) an extracellular spacer domain (hinge);
- (c) a transmembrane domain;
- (d) optionally, one or more intracellular domain;

- a beta chain (FC ϵ R β) containing:

- 5 (a) a signal sequence;
- (b) an extracellular spacer domain (hinge);
- (c) a transmembrane domain;
- (d) a co-stimulatory ligand;

- a gamma chain (FC ϵ R γ) containing at least:

- 10 (a) a signal sequence;
- (b) a binding (or dimerization) domain;
- (c) an extracellular spacer domain (hinge);
- (d) a transmembrane domain;
- (e) a signal transducing domain.

15

The term “extracellular ligand-binding domain” as used herein is defined as an oligo- or polypeptide that is capable of binding a ligand. Preferably, the domain will be capable of interacting with a cell surface molecule.

Said extracellular ligand-binding domain is a single chain antibody fragment (scFv) comprising the light (V_L) and the heavy (V_H) variable fragment of a target antigen specific monoclonal antibody specific to a particular target antigen joined by a flexible linker.. Binding domain specific to a specific antigen other than scFv can also be used for predefined targeting of lymphocytes, such as camelid or shark (VNAR) single-domain antibody fragments or receptor ligands like a vascular endothelial growth factor polypeptide, an integrin-binding peptide, heregulin or an IL-13 mutein, antibody binding domains, antibody hypervariable loops or CDRs as non-limiting examples.

Said first transmembrane polypeptide may further comprise a stalk region between said extracellular ligand-binding domain and said transmembrane domain. The term “stalk region” used herein generally means any oligo- or polypeptide that functions to link the transmembrane domain to the extracellular ligand-binding domain. In particular, stalk region are used to provide more flexibility and accessibility for the extracellular ligand-binding domain. A stalk region may comprise up to 300 amino acids, preferably 10 to 100 amino acids and most preferably 25 to 50 amino acids. Stalk region

may be derived from all or part of naturally occurring molecules, such as from all or part of the extracellular region of CD8, CD4 or CD28, or from all or part of an antibody constant region. Alternatively the stalk region may be a synthetic sequence that corresponds to a naturally occurring stalk sequence, or may be an entirely synthetic stalk sequence. In a preferred embodiment said stalk region is a part of human CD8 alpha chain (e.g. NP_001139345.1).

Thus, the expression of multi-chain CAR in immune cells results in modified cells that selectively and eliminate defined targets, including but not limited to malignant cells carrying a respective tumor-associated surface antigen or virus infected cells carrying a virus-specific surface antigen, or target cells carrying a lineage-specific or tissue-specific surface antigen.

A multi-chain CAR according to the invention can comprise several extracellular ligand-binding domains, to simultaneously bind different elements in target thereby augmenting immune cell activation and function. The extracellular ligand-binding domains may be placed in tandem on the same transmembrane polypeptide, and optionally can be separated by a linker. In another embodiment, said different extracellular ligand-binding domains can be placed on different transmembrane polypeptides composing the multi-chain CAR. The present invention may relate to a population of multi-chain CARs comprising each one different extracellular ligand binding domains.

Also, the invention may encompass engineered immune cells which express at the surface of said cell a population of multi-chain CAR each one comprising different extracellular ligand binding domains. The present invention may relate to engineered immune cell in which are introduced polynucleotides encoding polypeptides composing a population of multi-chain CAR each one comprising different extracellular ligand binding domains. By population of multi-chain CARs, it is meant at least two, three, four, five, six or more multi-chain CARs each one comprising different extracellular ligand binding domains. The different extracellular ligand binding domains according to the present invention may simultaneously bind different elements in target thereby augmenting immune cell activation and function.

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

Examples of signal transducing domain for use in multi-chain CAR can be the cytoplasmic sequences of the Fc receptor or T cell receptor and co-receptors that act in concert to initiate signal transduction following antigen receptor engagement, as well as any derivate or variant of these sequences and any synthetic sequence that as the same functional capability. Signal transduction domain comprises two distinct classes of cytoplasmic signaling sequence, those that initiate antigen-dependent primary activation, and those that act in an antigen-independent manner to provide a secondary or co-stimulatory signal. Primary cytoplasmic signaling sequence can comprise signaling motifs which are known as immunoreceptor tyrosine-based activation motifs of ITAMs. ITAMs are well defined signaling motifs found in the intracytoplasmic tail of a variety of receptors that serve as binding sites for syk/zap70 class tyrosine kinases. Examples of ITAM used in the invention can include as non limiting examples those derived from TCRzeta, FcRgamma, FcRbeta, FcRepsilon, CD3gamma, CD3delta, CD3epsilon, CD5, CD22, CD79a, CD79b and CD66d. In a preferred embodiment, the signaling transducing domain of the multi-chain CAR can comprise the CD3zeta signaling domain, or the intracytoplasmic domain of the FcεRI beta or gamma chains.

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

“Co-stimulatory ligand” refers to a molecule on an antigen presenting cell that specifically binds a cognate co-stimulatory molecule on a T-cell, thereby providing a signal which, in addition to the primary signal provided by, for instance, binding of a TCR/CD3 complex with an MHC molecule loaded with peptide, mediates a T cell response, including, but not limited to, proliferation activation, differentiation and the like. A co-stimulatory ligand can include but is not limited to CD7, B7-1 (CD80), B7-2 (CD86), PD-L1, PD-L2, 4-1BBL, OX40L, inducible costimulatory ligand (ICOS-L), intercellular adhesion molecule (ICAM, CD30L, CD40, CD70, CD83, HLA-G, MICA, M1CB, HVEM, lymphotoxin beta receptor, 3/TR6, ILT3, ILT4, an agonist or antibody that binds Toll ligand receptor and a ligand that specifically binds with B7-H3. A co-stimulatory ligand also encompasses, inter alia, an antibody that specifically binds with a co-stimulatory molecule present on a T cell, such as but not limited to, CD27, CD28, 4-1BB, OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LTGHT, NKG2C, B7-H3, a ligand that specifically binds with CD83.

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

CD27, CD28, CD8, 4-1BB (CD137), OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3 and a ligand that specifically binds with CD83 and the like.

Said signal transducing domain may be a TNFR-associated Factor 2 (TRAF2) binding motifs, intracytoplasmic tail of costimulatory TNFR member family. Cytoplasmic tail of costimulatory TNFR family member contains TRAF2 binding motifs consisting of the major conserved motif (P/S/A)X(Q/E)E or the minor motif (PXQXXD), wherein X is any amino acid. TRAF proteins are recruited to the intracellular tails of many TNFRs in response to receptor trimerization.

The signal transduction domain of the multi-chain CAR of the present invention may comprise a part of co-stimulatory signal molecule which is 4-1BB (GenBank: AAA53133.).

The distinguishing features of appropriate transmembrane polypeptides comprise the ability to be expressed at the surface of an immune cell, in particular lymphocyte cells or Natural killer (NK) cells, and to interact together for directing cellular response of immune cell against a predefined target cell. The different transmembrane polypeptides of the multi-chain CAR of the present invention comprising an extracellular ligand-binding domain and/or a signal transducing domain interact together to take part in signal transduction following the binding with a target ligand and induce an immune response. The transmembrane domain can be derived either from a natural or from a synthetic source. The transmembrane domain can be derived from any membrane-bound or transmembrane protein. As non-limiting examples, the transmembrane polypeptide can be a subunit of the T cell receptor such as α , β , γ or ζ , polypeptide constituting CD3 complex, IL2 receptor p55 (α chain), p75 (β chain) or γ chain, subunit chain of Fc receptors, in particular Fc γ receptor III or CD proteins. Alternatively the transmembrane domain can be synthetic and can comprise predominantly hydrophobic residues such as leucine and valine.

The multi-chain CAR may comprise a transmembrane polypeptide derived from a Fc ϵ RI chain, such as a Fc ϵ RI α chain, in which the extracellular domain is replaced by an extracellular ligand-binding domain.

Said multi-chain CAR may comprise a part of Fc ϵ RI alpha chain and a part of Fc ϵ RI beta chain or variant thereof such that said Fc ϵ RI chains spontaneously dimerize together to form a dimeric Chimeric Antigen Receptor. The multi-chain Chimeric Antigen may comprise a part of Fc ϵ RI alpha chain and a part of a Fc ϵ RI gamma chain or variant thereof such that said Fc ϵ RI chains spontaneously trimerize together to form a trimeric Chimeric Antigen Receptor. Another alternative is a multi-chain Chimeric Antigen Receptor which may comprise a part of Fc ϵ RI alpha chain, a part of

FcεRI beta chain and a part of FcεRI gamma chain or variants thereof such that said FcεRI chains spontaneously tetramerize together to form a tetrameric Chimeric Antigen Receptor.

Polynucleotides, vectors:

5 The present invention also relates to polynucleotides, vectors encoding the above described modulable/tunable IMP complex and CAR polypeptide structures according to the invention. The present invention provides polynucleotides, including DNA and RNA molecules that encode the transmembrane polypeptides disclosed herein that can be included in the multi-chain or mono-chain CAR. In particular, the invention relates to a polynucleotide comprising a nucleic acid sequence
10 encoding at least one transmembrane polypeptide composing the multi-chain/mono-chain CAR as described above. More particularly the invention relates to a polynucleotide comprising two or more nucleic acid sequences encoding transmembrane polypeptides composing the multi-chain/mono-chain CAR as described above.

The polynucleotide may consist in an expression cassette or expression vector (e.g. a plasmid for
15 introduction into a bacterial host cell, or a viral vector such as a baculovirus vector for transfection of an insect host cell, or a plasmid or viral vector such as a lentivirus for transfection of a mammalian host cell).

According to one embodiment, the transfection realized during the method of the invention for producing an engineered immune is performed using of a lentiviral or a retroviral vector for a stable
20 integration of the CAR and/or IMP into the immune cells genome

According to another embodiment, said transfection is performed by the use of CAR/IMP encoding polycistronic mRNA for a transitory expression.

The different nucleic acid sequences can be included in one polynucleotide or vector which comprises a nucleic acid sequence encoding ribosomal skip sequence such as a sequence encoding a
25 2A peptide. 2A peptides, which were identified in the Aphthovirus subgroup of picornaviruses, causes a ribosomal "skip" from one codon to the next without the formation of a peptide bond between the two amino acids encoded by the codons (see Donnelly et al., J. of General Virology 82: 1013-1025 (2001); Donnelly et al., J. of Gen. Virology 78: 13-21 (1997); Doronina et al., Mol. And. Cell. Biology 28(13): 4227-4239 (2008); Atkins et al., RNA 13: 803-810 (2007)). By "codon" is meant three
30 nucleotides on an mRNA (or on the sense strand of a DNA molecule) that are translated by a ribosome into one amino acid residue. Thus, two polypeptides can be synthesized from a single, contiguous open reading frame within an mRNA when the polypeptides are separated by a 2A

oligopeptide sequence that is in frame. Such ribosomal skip mechanisms are well known in the art and are known to be used by several vectors for the expression of several proteins encoded by a single messenger RNA.

To direct, transmembrane polypeptide such as FcεR into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in polynucleotide sequence or vector sequence. The secretory signal sequence may be that of FcεR, or may be derived from another secreted protein (e.g., t-PA) or synthesized *de novo*. The secretory signal sequence is operably linked to the transmembrane nucleic acid sequence, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized polypeptide into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the nucleic acid sequence encoding the polypeptide of interest, although certain secretory signal sequences may be positioned elsewhere in the nucleic acid sequence of interest (see, e.g., Welch et al., U.S. Patent No. 5,037,743; Holland et al., U.S. Patent No. 5,143,830). In a preferred embodiment the signal peptide comprises the residues 1 to 25 of the FcεRI alpha chain (NP_001992.1).

Those skilled in the art will recognize that, in view of the degeneracy of the genetic code, considerable sequence variation is possible among these polynucleotide molecules. Preferably, the nucleic acid sequences of the present invention are codon-optimized for expression in mammalian cells, preferably for expression in human cells. Codon-optimization refers to the exchange in a sequence of interest of codons that are generally rare in highly expressed genes of a given species by codons that are generally frequent in highly expressed genes of such species, such codons encoding the amino acids as the codons that are being exchanged.

Engineered immune cells

The present invention also relates to an isolated immune cell which is a Chimeric Antigen Receptor (CAR) having at least an engineered (IMP) inhibitory membrane protein.

The immune cell to be used in accordance of the present invention may, for instance, be a T-cell, a cytotoxic T cell, a regulatory T cell or a NK cell.

According to a particular embodiment, the immune cell is a T-cell.

Said engineered immune cells may be infused into a patient upon the step of IMP complex transfection and before the step of incubation with the external ligand (such as a surface antigen).

According to certain embodiment, the present invention provides a modifiable/tunable CAR immune cell which is also engineered to be allogeneic. This non-autologous characteristic is particularly useful for the development of a standardized therapy in which allogeneic therapeutic cells could be pre-manufactured and available for immediate administration to patients.

5 Such methods comprise the step of inactivating at least one gene encoding a T-Cell Receptor (TCR) component, in particular TCR α , TCR β genes.

 The step of inactivation of, for instance the TCR component may be performed at any time during the manufacturing of the modifiable/tunable CAR-engineered immune cell of the invention. However, it is preferable to perform it before the transfection steps in order to not interact too much
10 on the growth/expansion of the cells.

 Is also encompassed in the scope of the present invention, the possibility to engineer further the immune cells (i.e T-cells) to make them resistant to chemotherapy drugs, such as purine nucleotide analogs (clofarabine, fludarabine...).

 One way particularly suitable according to the invention to realize these gene inactivations
15 is the use of exonucleases such as TALE nucleases. This can be performed such as described elsewhere (WO2012138927 and prior art cited in the next section "DEFINITIONS").

Methods of engineering immune cells

 The present invention also relates to a method for producing an modifiable/tunable CAR-
20 engineered immune cell comprising two steps of transfection, the first one being of at least a first polynucleotide encoding a Chimeric Antigen Receptor (CAR); and the second one of a second polynucleotide having the inhibitory membrane protein (IMP) complex, and finally a step of selection of immune cells having co-expressed the said polynucleotides.

 In another embodiment, the present invention relates to a method of producing engineered
25 immune cells for immunotherapy comprising introducing into said cells the different polypeptides composing said CAR/IMP and expanding said cells. In a preferred embodiment, said polynucleotides are included in lentiviral vectors in view of being stably expressed in the cells. Such lentivirus vectors may comprise a marker gene such as GFP and/or firefly luciferase.

 In still another embodiment, said transfection step a) in the method of producing
30 engineered immune cells is performed by insertion of the CAR and IMP polynucleotides via recombination process, preferably homologous. This embodiment has the advantage to a more

specific integration, and less ectopic insertions. In a preferred embodiment, such site-specific insertion is made by expressing an exogenous specific-endonuclease and the addition of at least one polynucleotide template encoding said CAR/IMP peptides. As an example, the site-specific insertion may be done in the TCR gene, which allows reducing or disabling TCR (T cell receptor) function, with the effect of rendering the immune cells, in particular T-cells less alloreactive. This later aspect is particular sought to reduce the risk of GVHD in a context of immunotherapy where the immune cells are allogeneic.

Specific nucleases usually create double-stranded break (DSBs) at desired locations in the genome, and harness the cell's endogenous mechanisms to repair the induced break by natural processes of homologous recombination (HR) and non-homologous end-joining (NHEJ). Engineered nucleases such as zinc finger nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), engineered homing endonucleases and RNA or DNA guided endonucleases, such as CRISPR/Cas, Cpf1 or Argonaute systems, are particularly appropriate to carry out gene insertion or inactivation according to the present invention.

Among other references, TALEN and Cas9 systems are respectively described in WO 2013/176915 and WO 2014/191128. The Zinc-finger nucleases (ZFNs) have been initially described in Kim, YG; Cha, J.; Chandrasegaran, S. (1996). "Hybrid restriction enzymes: zinc finger fusions to Fok I cleavage domain". Proc Natl Acad Sci USA 93 (3): 1156–60.

Delivery methods

The different methods described above involve expressing a protein of interest such as IMP complex, Chimeric Antigen Receptor (CAR) into a cell. Polypeptides may be expressed in the cell as a result of the introduction of polynucleotides encoding said polypeptides into the cell. Alternatively, said polypeptides could be produced outside the cell and then introduced thereto. Methods for introducing a polynucleotide construct into cells are known in the art and include as non limiting examples stable transformation methods wherein the polynucleotide construct is integrated into the genome of the cell, transient transformation methods wherein the polynucleotide construct is not integrated into the genome of the cell and virus mediated methods. Said polynucleotides may be introduced into a cell by for example, recombinant viral vectors (e.g. retroviruses, adenoviruses), liposome and the like. For example, transient transformation methods include for example microinjection, electroporation or particle bombardment. Said polynucleotides may be included in

vectors, more particularly plasmids or virus, in view of being expressed in cells. Said plasmid vector can comprise a selection marker which provides for identification and/or selection of cells which received said vector. Different transgenes can be included in one vector. Said vector can comprise a nucleic acid sequence encoding ribosomal skip sequence such as a sequence encoding a 2A peptide.

2A peptides, which were identified in the Aphthovirus subgroup of picornaviruses, causes a ribosomal "skip" from one codon to the next without the formation of a peptide bond between the two amino acids encoded by the codons (see Donnelly et al., J. of General Virology 82: 1013-1025 (2001); Donnelly et al., J. of Gen. Virology 78: 13-21 (1997); Doronina et al., Mol. And. Cell. Biology 28(13): 4227-4239 (2008); Atkins et al., RNA 13: 803-810 (2007)). By "codon" is meant three nucleotides on an mRNA (or on the sense strand of a DNA molecule) that are translated by a ribosome into one amino acid residue. Thus, two polypeptides can be synthesized from a single, contiguous open reading frame within an mRNA when the polypeptides are separated by a 2A oligopeptide sequence that is in frame. Such ribosomal skip mechanisms are well known in the art and are known to be used by several vectors for the expression of several proteins encoded by a single messenger RNA.

Polynucleotides encoding polypeptides according to the present invention can be mRNA which is introduced directly into the cells, for example by electroporation. The inventors determined the optimal condition for mRNA electroporation in T-cell. The inventor used the cytoPulse technology which allows, by the use of pulsed electric fields, to transiently permeabilize living cells for delivery of material into the cells. The technology, based on the use of PulseAgile (BTX Havard Apparatus, 84 October Hill Road, Holliston, MA 01746, USA) electroporation waveforms grants the precise control of pulse duration, intensity as well as the interval between pulses (U.S. patent 6,010,613 and International PCT application WO2004083379). All these parameters can be modified in order to reach the best conditions for high transfection efficiency with minimal mortality. Basically, the first high electric field pulses allow pore formation, while subsequent lower electric field pulses allow to move the polynucleotide into the cell.

Activation and expansion of T-cells

Whether prior to or after genetic modification of the T-cells, the T-cells can be activated and expanded generally using methods as described, for example, in U.S. Patents 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005. T-cells can be expanded *in vitro* or *in vivo*. Generally, the T cells of the invention are 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. To stimulate proliferation of either CD4+ T-cells or CD8+ T-cells, an anti-CD3 antibody and an anti-CD28 antibody. For example, the agents providing each signal may be in solution or coupled to a surface. As those of ordinary skill in the art can readily appreciate, the ratio of particles to cells may depend on particle size relative to the target cell.

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- γ , 1L-4, 1L-7, GM-CSF, -10, -2, 1L-15, TGF β , IL-21 and TNF- or any other additives for the growth of cells known to the skilled artisan. Other additives for the growth of cells include, but are not limited to, surfactant, plasmanate, and reducing agents such as N-acetyl-cysteine and 2-mercaptoethanol. Media can include RPMI 1640, A1M-V, DMEM, MEM, α -MEM, F-12, X-Vivo 1, and X-Vivo 20, Optimizer, with added amino acids, sodium pyruvate, and vitamins, either serum-free or supplemented with an appropriate amount of serum (or plasma) or a defined set of hormones, and/or an amount of cytokine(s) sufficient for the growth and expansion of T-cells. Antibiotics, e.g., penicillin and streptomycin, are included only in experimental cultures, not in cultures of cells that are to be infused into a subject. The target cells are maintained under conditions necessary to support growth; for example, an appropriate temperature (e.g., 37° C) and atmosphere (e.g., air plus 5% CO₂). T cells that have been exposed to varied stimulation times may exhibit different characteristics.

Therapeutic applications

In another embodiment, isolated immune cells obtained as previously described can be used in adoptive cell immunotherapy.

According to an alternative embodiment, said immune cells are recovered from the patient himself. According to one embodiment, said immune cells are recovered from donors.

According to another embodiment, said immune cells are rendered allogeneic in order to prepare batch of cells which can be administered to a panel of patients and not only the donor himself. This feature, which represents a real advantage in economic terms, is compulsory to drop the risk of graft rejection.

To achieve this goal, the immune cells such as T-cells undergo a knock-out (KO) in the T-cell receptor (TCR) gene that is responsible for recognizing antigens bound to major histocompatibility complex (MHC) molecules. By inactivating the TCR gene, the latter cannot engage with antigenic peptide and MHC (peptide/MHC), and therefore there is not activation of the T lymphocyte

According to an embodiment, the inactivation of the TCR gene by knock-out (KO) is performed by endonucleases, preferably by TALE-nucleases.

In particular, said T-cells according to the present invention can be used for treating cancer , infections or auto-immune disease in a patient in need thereof.

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) providing an isolated T-cell obtainable by any one of the methods previously described;

(b) Administrating said cells to said patient.

Said T-cells of the invention can undergo robust *in vivo* expansion and can persist for an extended amount of time.

Said treatment can be ameliorating, curative or prophylactic. This may be done under standard protocols and reproduced as many times as needed. The resulting modified T-cells may be administrated to the patient or to one or several patients depending of its availability as an “off the shelf” therapeutic product.

Cells that can be used with the disclosed methods are described in the previous section. Said treatment can be used to treat patients diagnosed with cancer, viral infection and autoimmune disorders. Cancers that may be treated include tumors that are not vascularized, or not yet substantially vascularized, as well as vascularized tumors. The cancers may comprise nonsolid tumors

(such as hematological tumors, for example, leukemias and lymphomas) or may comprise solid tumors. Types of cancers to be treated with the allogeneic T-cell resistant to drugs of the invention include, but are not limited to, carcinoma, blastoma, and sarcoma, and certain leukemia or lymphoid malignancies, benign and malignant tumors, and malignancies e.g., sarcomas, carcinomas, and melanomas. Adult tumors/cancers and pediatric tumors/cancers are also included. In an embodiment of the present invention, childhood acute lymphoblastic leukemia (ALL) and amyotrophic myeloma leukemia (AML) diseases are typically treated by allogeneic drug resistant T-cells according to the invention. This can be achieved by using drug resistant KO TRAC CD19⁺ CAR T-cells and drug resistant KO TRAC CD123⁺ T-cells respectively. "TRAC" refers to "T cell receptor α constant"» and corresponds to TCR α subunit constant gene.

It can be a treatment 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.

Said treatment may be administrated into patients undergoing an immunosuppressive treatment, such as cells or population of cells, which have been made resistant to at least one drug agent due to either expression of a drug resistance gene or the inactivation of a drug sensitizing gene. In this aspect, the drug 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, intracranially, 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 10^3 - 10^{10} cells per kg body weight, preferably 10^5 to 10^6 cells/kg body weight including all integer values of cell numbers within those ranges. The cells or population of cells can be 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 administered will be dependent upon the age, health and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired.

Said effective amount of cells or pharmaceutical composition may be preferably administered parenterally. Said administration can be an intravenous administration. Said administration can be directly done by injection within a tumor.

Cells may be administered to a patient in conjunction with (e.g., before, simultaneously or following) any number of relevant treatment modalities, including but not limited to treatment with agents such as antiviral therapy, cidofovir and interleukin-2, Cytarabine (also known as ARA-C) or natalizimab treatment for MS patients or efalizumab treatment for psoriasis patients or other treatments for PML patients. The T-cells of the invention may be used in combination with chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies or other antibody therapies, cytoxin, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, cytokines, and irradiation. These drugs inhibit either the calcium dependent phosphatase calcineurin (cyclosporine and FK506) or inhibit the p70S6 kinase that is important for growth factor induced signaling (rapamycin) (Liu et al., Cell 66:807-815, 1991; Henderson et al., Immun. 73:316-321, 1991; Bierer et al., Crit. Opin. Immun. 5:763-773, 1993). The cell compositions of the present invention may be 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. The cell compositions of the present invention may be administered following B-cell ablative therapy such as agents that react with CD20, e.g., Rituxan. For example, subjects may undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. Following the transplant, subjects may receive an infusion of the expanded immune cells of the present invention. Expanded cells may be administered before or following surgery.

Pharmaceutical composition

The isolated T-cells of the present invention may be administered either alone, or as a pharmaceutical composition in combination with diluents and/or with other components. Briefly, pharmaceutical compositions of the present invention may comprise T-cells as described herein, in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (e.g. aluminum hydroxide); and preservatives. Compositions of the present invention are preferably formulated for intravenous administration. Pharmaceutical compositions of the present invention may be administered in a manner appropriate to the disease to be treated (or prevented). The quantity and frequency of administration will be determined by such factors as the condition of the patient, and the type and severity of the patient's disease, although appropriate dosages may be determined by clinical trials

Kit and vector

The present invention encompasses a kit or a vector for engineering immune cells with modutable level of activation, which comprises:

-a first polynucleotide encoding a Chimeric Antigen Receptor (CAR); and

- a second polynucleotide encoding an engineered inhibitory membrane protein (IMP)

complex as described above in the "Inhibitory membrane complex" paragraph.

DEFINITIONS

In the description above, a number of terms are used extensively. The following definitions are provided to facilitate understanding of the present embodiments.

- 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.

- 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 “nucleic acid molecule” 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. Nucleic acids can be either single stranded or double stranded.

- By “gene” is meant the basic unit of heredity, consisting of a segment of DNA arranged in a linear manner along a chromosome, which codes for a specific protein or segment of protein, small RNA and the like. A gene typically includes a promoter, a 5' untranslated region, one or more coding sequences (exons), optionally introns, a 3' untranslated region. The gene may further comprise a terminator, enhancers and/or silencers.

- By “genome” it is meant the entire genetic material contained in a cell such as nuclear genome, chloroplastic genome, mitochondrial genome.

- By “mutation” is intended the substitution, deletion, insertion of one or more nucleotides/amino acids in a polynucleotide (cDNA, gene) or a polypeptide sequence. Said 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.

“TALE-nuclease” refers to engineered proteins resulting from the fusion of a DNA binding domain typically derived from Transcription Activator like Effector proteins (TALE), with an endonuclease catalytic domain. Such catalytic domain is preferably a nuclease domain and more preferably a domain having endonuclease activity, like for instance I-TevI, ColE7, NucA and Fok-I. In a particular embodiment, said nuclease is a monomeric TALE-Nuclease . A monomeric Nuclease is a nuclease that does not require dimerization for specific recognition and cleavage, such as the fusions of engineered DNA binding domain with the catalytic domain of I-TevI described in WO2012138927. In another particular embodiment, said rare-cutting endonuclease is a dimeric TALE-nuclease, preferably comprising a DNA binding domain fused to FokI. TALE-nuclease have been already described and used to stimulate gene targeting and gene modifications (Boch, Scholze et al. 2009;

Moscou and Bogdanove 2009; Christian, Cermak et al. 2010). Such engineered TALE-nucleases are commercially available under the trade name TALENTM (Collectis, 8 rue de la Croix Jarry, 75013 Paris, France).

- The term "cleavage" refers to the breakage of the covalent backbone of a polynucleotide.

5 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.

10 - By "chimeric antigen receptor "(CAR) it is meant a chimeric receptor which comprises an extracellular ligand-binding domain, a transmembrane domain and a signaling transducing domain.

- The term "extracellular ligand-binding domain" as used herein is defined as an oligo- or polypeptide that is capable of binding a ligand. Preferably, the domain will be capable of interacting with a cell surface molecule. For example, the extracellular ligand-binding domain may be chosen to
15 recognize a ligand that acts as a cell surface marker on target cells associated with a particular disease state.

In a preferred embodiment, said extracellular ligand-binding domain comprises a single chain antibody fragment (scFv) comprising the light (V_L) and the heavy (V_H) variable fragment of a target antigen specific monoclonal antibody joined by a flexible linker. In a preferred embodiment,
20 said scFV is derived from a CD123, 5T4 or CS1 antibody.

The signal transducing domain or intracellular signaling domain of the CAR according to the present invention is responsible for intracellular signaling following the binding of extracellular ligand binding domain to the target resulting in the activation of the immune cell and immune response. Preferred examples of signal transducing domain for use in a CAR can be the cytoplasmic sequences
25 of the T-cell receptor and co-receptors that act in concert to initiate signal transduction following antigen receptor engagement. Signal transduction domain comprises two distinct classes of cytoplasmic signaling sequence, those that initiate antigen-dependent primary activation, and those that act in an antigen-independent manner to provide a secondary or co-stimulatory signal. Primary cytoplasmic signaling sequence can comprise signaling motifs which are known as immunoreceptor
30 tyrosine-based activation motifs of ITAMs. In particular embodiment the signal transduction domain of the CAR of the present invention comprises a co-stimulatory signal molecule. A co-stimulatory

molecule is a cell surface molecule other than an antigen receptor or their ligands that is required for an efficient immune response. Co-stimulatory molecules include, but are not limited to an MHC class I molecule, BTLA and Toll ligand receptor. Examples of costimulatory molecules include CD27, CD28, CD8, 4-1BB (CD137), OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3 and a ligand that specifically binds with CD83 and the like.

The CAR according to the present invention is expressed on the surface membrane of the cell. Thus, the CAR can comprise a transmembrane domain. The distinguishing features of appropriate transmembrane domains comprise the ability to be expressed at the surface of a cell, preferably in the present invention an immune cell, in particular lymphocyte cells or Natural killer (NK) cells, and to interact together for directing cellular response of immune cell against a predefined target cell. The transmembrane domain can further comprise a stalk region between said extracellular ligand-binding domain and said transmembrane domain. The term "stalk region" used herein generally means any oligo- or polypeptide that functions to link the transmembrane domain to the extracellular ligand-binding domain. In particular, stalk region are used to provide more flexibility and accessibility for the extracellular ligand-binding domain. A stalk region may comprise up to 300 amino acids, preferably 10 to 100 amino acids and most preferably 25 to 50 amino acids. Stalk region may be derived from all or part of naturally occurring molecules, such as from all or part of the extracellular region of CD8, CD4 or CD28, or from all or part of an antibody constant region. Alternatively the stalk region may be a synthetic sequence that corresponds to a naturally occurring stalk sequence, or may be an entirely synthetic stalk sequence.

Downregulation or mutation of target antigens is commonly observed in cancer cells, creating antigen-loss escape variants. Thus, to offset tumor escape and render immune cells more specific to target, the CD19 specific CAR can comprise another extracellular ligand-binding domains, to simultaneously bind different elements in target thereby augmenting immune cell activation and function. Examples of CD19 specific CAR are ScFv FMC63 (Kochenderfer JN, Wilson WH, Janik JE, et al. *Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. Blood* 2010;116(20):4099-410) or ScFv 4G7 CAR (described in the application filed under the number PCT/EP2014/059662). In one embodiment, the extracellular ligand-binding domains can be placed in tandem on the same transmembrane polypeptide, and optionally can be separated by a linker. In another embodiment, said different extracellular ligand-binding domains can be placed on different transmembrane polypeptides composing the CAR. In another embodiment, the present invention relates to a population of CARs comprising each one different extracellular ligand binding domains. In a particular, the present invention relates to a

method of engineering immune cells comprising providing an immune cell and expressing at the surface of said cell a population of CAR each one comprising different extracellular ligand binding domains. In another particular embodiment, the present invention relates to a method of engineering an immune cell comprising providing an immune cell and introducing into said cell polynucleotides encoding polypeptides composing a population of CAR each one comprising different extracellular ligand binding domains. By population of CARs, it is meant at least two, three, four, five, six or more CARs each one comprising different extracellular ligand binding domains. The different extracellular ligand binding domains according to the present invention can preferably simultaneously bind different elements in target thereby augmenting immune cell activation and function. The present invention also relates to an isolated immune cell which comprises a population of CARs each one comprising different extracellular ligand binding domains.

- The terms "vector" refer to 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.

- By "delivery vector" is intended any delivery vector which can be used in the present invention to put into cell contact (i.e. "contacting") or deliver inside cells or subcellular compartments (i.e. "introducing") agents/chemicals and molecules (proteins or nucleic acids) needed in the present invention. It includes, but is not limited to liposomal delivery vectors, viral delivery vectors, drug delivery vectors, chemical carriers, polymeric carriers, lipoplexes, polyplexes, dendrimers, microbubbles (ultrasound contrast agents), nanoparticles, emulsions or other appropriate transfer vectors.

- Viral vectors include retrovirus, adenovirus, parvovirus (e. g. adenoassociated viruses), 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).

5 - By “lentiviral vector” is meant HIV-Based lentiviral vectors that are very promising for gene delivery because of their relatively large packaging capacity, reduced immunogenicity and their ability to stably transduce with high efficiency a large range of different cell types. Lentiviral vectors are usually generated following transient transfection of three (packaging, envelope and transfer) or more plasmids into producer cells. Like HIV, lentiviral vectors enter the target cell through the
10 interaction of viral surface glycoproteins with receptors on the cell surface. On entry, the viral RNA undergoes reverse transcription, which is mediated by the viral reverse transcriptase complex. The product of reverse transcription is a double-stranded linear viral DNA, which is the substrate for viral integration in the DNA of infected cells. By “integrative lentiviral vectors (or LV)”, is meant such vectors as non limiting example, that are able to integrate the genome of a target cell. At the
15 opposite by “non-integrative lentiviral vectors (or NILV)” is meant efficient gene delivery vectors that do not integrate the genome of a target cell through the action of the virus integrase.

- By cell or cells is intended any eukaryotic living cells, primary cells and cell lines derived from these organisms for *in vitro* cultures.

- By “primary cell” or “primary cells” are intended cells taken directly from living tissue (i.e.
20 biopsy material) and established for growth in vitro, that have undergone very few population doublings and are therefore more representative of the main functional components and characteristics of tissues from which they are derived from, in comparison to continuous tumorigenic or artificially immortalized cell lines. As non limiting examples cell lines can be selected from the group consisting of CHO-K1 cells; HEK293 cells; Caco2 cells; U2-OS cells; NIH 3T3 cells; NSO cells; SP2
25 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.

- Because some variability may arise from the genomic data from which these polypeptides derive, and also to take into account the possibility to substitute some of the amino acids present in these polypeptides without significant loss of activity (functional variants), the invention
30 encompasses polypeptides variants of the above polypeptides that share at least 70%, preferably at least 80 %, more preferably at least 90 % and even more preferably at least 95 % identity with the sequences provided in this patent application.

The present invention is thus drawn to polypeptides comprising a polypeptide sequence that has at least 70%, preferably at least 80%, more preferably at least 90 %, 95 % 97 % or 99 % sequence identity with amino acid sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 60.

5 -"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
10 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
15 substantially the same functions, as well as polynucleotide encoding such polypeptides, are contemplated.

In addition to a general method for engineering T-cells resistant to purine nucleotide analogs (PNA) drugs , in particular clofarabine and fludarabine, by endonuclease inactivation of dck gene(s).

20 GENERAL METHODS

Primary cells

Peripheral blood mononuclear cells are isolated by density gradient centrifugation from buffy coats from healthy volunteer donors (Etablissement Français du Sang). T lymphocytes are then
25 purified using the EasySep human T cell enrichment kit (Stemcell Technologies), and activated with Dynabeads Human T-Activator CD3/CD28 (Life Technologies) in X-vivo 15 medium (Lonza) supplemented with 20 ng/ml IL-2 (Miltenyi) and 5% human AB serum (Seralab).

Cell lines

30 The CD123-positive cell lines such as KG1a or MOLM13 and CD123-negative cell line such as RPMI-8226 for multiple myeloma (MM) are obtained from the American Type Culture

Collection. Typically, the cells are cultured in RPMI 1640 supplemented with 10-20% heat-inactivated FCS, 2mmol/L L-glutamine and 100 units/ml penicillin, and 100µg/mL streptomycin.

Synthesis of IMP/CAR encoding mRNAs

5 All individual chains of the CAR architecture were amplified by PCR to introduce a T7 promoter and a stop codon sequence prior to mRNA synthesis. mRNA encoding the proteins of interest were in vitro transcribed from the PCR product and polyadenylated using the mMessage mMachine T7 Ultra kit (Life technologies) following the manufacturer's instructions. RNAs were purified with RNeasy columns (Qiagen), eluted in cytoporation medium T and quantified by
10 measuring absorbance at 260 nm using a Nanodrop ND-1000 spectrophotometer. Quality of the RNA was verified on a denaturing formaldehyde/MOPS agarose gel.

Transiently expression in T cells

The switch system of the present invention constituted of a CAR and a second
15 polynucleotide encoding an engineered inhibitory membrane protein (IMP) complex are expressed in human T cells after electroporation of polycistronic mRNA. T cells were electroporated with capped and polyadenylated polycistronic mRNA that were produced using the mMESSAGE mMACHINE kit and linearized plasmids as template. The plasmids used as template contained the T7 RNA polymerase promoter followed by a polycistronic DNA sequence encoding the different CAR/IMP
20 variants.

The electroporation of the polycistronic mRNAs into the human T cells is proceeded using the CytolVT-S device (Celectis), according to the following protocol: 5×10^6 T cells preactivated several days (3-5) with anti CD3/CD28 coated beads and IL2 are resuspended in cytoporation buffer T, and electroporated with 45µg of mRNA. Twenty-four hours after electroporation, human T cells
25 engineered using polycistronic mRNAs encoding the multi-chain CARs are labeled with a fixable viability dye eFluor-780 and a PE-conjugated goat anti mouse IgG F(ab')₂ fragment specific, and analysed by flow cytometry.

The live T cells engineered using polycistronic mRNAs express the multi-chain CARs on their surface.

30

Lenviral expression in T cells

In vitro screening of CAR-specific IMP/CAR

The polycistronic genes encoding a CAR and a second polynucleotide encoding an engineered inhibitory membrane protein (IMP) complex are vectorized in human T cells using lentiviral vectors as reported previously. Firstly the cell surface expression profile is assessed over time of the 2 above polynucleotide-encoded peptides in transduced T cells. For that purpose, the anti-CD123 scFv /Fc fusion protein may be used. Typically, it is observed that both peptides are highly expressed on the cell surface 3 days post transduction and remained relatively highly expressed over a 2 weeks period. The capacity of both peptides is then assessed to mediate antigen-dependent T cells activation. To address this issue, activity assays is performed using a CD123 - positive cell line (as KG1 or MOLM13), and a CD123-negative cell line (RPMI-8226). It is generally observed that both peptides are able to activate T cells in the presence of CD123-positive cell line but not in the presence of CD123-negative cell line as shown with the results of the degranulation assay, the cytotoxicity assay and the IFN γ secretion assay.

EXAMPLES

Example 1. Assembly of IMPs (switch-off receptors) and engineered multi chain CARs (mcCARs)

Assembly of constructs are done using Golden Gate assembly strategies according to published protocols [such as Engler C, Kandzia R, Marillonnet S; (2008) "*A one pot, one step, precision cloning method with high throughput capability*", PLoS One. 3(11)]. Switch-off receptors and engineered CARs are thus cloned in separated shuttle cloning plasmid. Non exhaustive examples for assembled constructs are given in the following Table 5; all of the systems presented here are "switch OFF".

Sequences of modules to assemble IMPs (switch-off receptors) are obtained from the SEQ ID NO. 61-64 (extracellular CID binding domain) or 83-98 (intracellular CID binding domain) and from engineered mcCAR with SEQ ID NO.65-76 (extracellular CID binding domain) or 99-106 (intracellular CID binding domain). Their configuration is depicted in the Figures 2A and 2B.

Table 5: Switch OFF receptors and engineered CARs

Component	Architecture: Signal sequence Interacting partner Hinge transmembrane intracellular	SEQ ID NO.	Amino acid sequence
EXTRA CELLULAR CID BINDING DOMAINS			
IMP complex (switch OFF receptor)	CD8a- ss FKBP	61	MALPVTALLPLALLHAAARPGSGGVQVETISPGDGRTPFKRGQTCVVHYTGMLEDGKKFDSSRDNRNKPFFKMLGKQEVIRG WEEGVAQMSVGQRAKLTTISPDYAYGATGHPGIIIPPHATLVFDVELLKLKLEGGAPTTTPAPRPPTPAPTIASQLSLPEACR PAAAGGAVHTRGLDFACDIYIWAFLAGTCGVLLLSLVITLYCRSRAARGTIGARRTGQPLKEDPSAVFVSVDYGEILDFFQWRE KTPEPPVPCVPEQTEYATIVFPSSMGTSPPARRGSADGPRSAQPLRPEDGHCSWPLE
	CD8a		
	CD8a PD1		
IMP complex (switch OFF receptor)	CD8a- ss FRB IgG1 4-1BB PD1	62	MALPVTALLPLALLHAAARPGSGGRVAILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSTNQAY GRDLMEAEQWCRKYMKSGNVKDLTQAWDLYYHVFRIRGSGAPEKSPDKTHTCPPCPAPPVAGPSVFLFPKPKDILMTART PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHREALHNNHYTEQKSLSPGKDKDIIISFFFLATSTALLLFFLTLRFVSVKRGSRRAARGTIGARRTGQPLKEDPS AVPVFSDYGEILDFFQWREKTPPEPPVPCVPEQTEYATIVFPSSMGTSPPARRGSADGPRSAQPLRPEDGHCSWPLE
	CD8a		
	CD8a- ss FKBP EpoR_ D2 DAP1	63	MALPVTALLPLALLHAAARPGSGGVQVETISPGDGRTPFKRGQTCVVHYTGMLEDGKKFDSSRDNRNKPFFKMLGKQEVIRG WEEGVAQMSVGQRAKLTTISPDYAYGATGHPGIIIPPHATLVFDVELLKLKLEGGAPAPVGLVARLADESGHVVLRLWLPPEPTM TSHIRYEVDSAGNGAGSVQVVEILEGRTECVLSNLRGRTRYFAVAPMAEPSPFGGFWSAWSEPVSLTTPSDILLAGLVAA DAVASLLIVGAVFLCARRSRAARGTIGARRTGQPLKEDPSAVFVSVDYGEILDFFQWREKTPPEPPVPCVPEQTEYATIVFPSSG MGTSSPARRGSADGPRSAQPLRPEDGHCSWPLE

CID binding domain on γ chain of multi chain CAR	0 PD1				MALPVTALLLLPLALLLHAARPGSGGRVAILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAY GRDLMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRIIGSGAPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGL DFACDIFWLVVVGVLACYSLLVTVAFIIFWVRSKRRSRAARGTIGARRTGQPLKEDPSAVPVFSVDYIGELDFQWREKTP PPVPCVPEQTEYATTVFPSSMGTSPPARRGSADGPRSAQPLRPEDGHCSWPLE
	CD8a-ss FRB CD8a CD28 PD1	64			MAIPAVVLLLLLLVEQAAAAGSGGVQVETISPGDGRTPFKRGQTCVVHYTGMLEDGKKFDSRDRNKPFFKFMGLKQEVIRGWE EGVAQMSVGQRAKLTISPDIYAGATGHPGIIIPPHATLVFDVLELLKLEGSGAPTTTPAPRPPTPAPTIASQPLSLRPEACRPA AGGAVHTRGLDFACDIDGEPQLCYILDAILFLYGIIVTLTYCRLLKIQVRKAAITSYEKSRVKFSRSADAPAYQQGQNLNEL NLGRREEYDVLDKRRGRDPGEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRE
	Gamma-ss FKBP CD8a Gamma-CD3z	65			MAIPAVVLLLLLLVEQAAAAGSGGRVAILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGR DLMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRIIGSGAPEKSPDKTHTCPPCPAPPVAGPSVFLFPKPKDTILMIARTPE VTCTVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYCKVKVSNKALPAPTEKTIISKAK GQPREPQVYITLPPSRDELTKNQVSLTCLVKGYFPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCVMHEALHNHYTQKSLSLSPGKKDIGEPQLCYILDAILFLYGIIVTLTYCRLLKIQVRKAAITSYEKSRVKFSRSADAPA YQQGQNQLYNELNLRREEYDVLDKRRGRDPGEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGHDGLYQGLS TATKDTYDALHMQALPPRE
	Gamma-ss FKBP EpoR_D2 Gamma-CD3z	67			MAIPAVVLLLLLLVEQAAAAGSGGVQVETISPGDGRTPFKRGQTCVVHYTGMLEDGKKFDSRDRNKPFFKFMGLKQEVIRGWE EGVAQMSVGQRAKLTISPDIYAGATGHPGIIIPPHATLVFDVLELLKLEGSGAPAPVGLVARLADESGHVVLRLWLPPEPMTS HIRYEVDSAGNGAGSVQVVEIIEGRTECVLSNLRGRTRYTFVAVRARNAPESFGGFWSAWSEPVSLTSPDIDGEPQLCYILD AIFLYGIIVTLTYCRLLKIQVRKAAITSYEKSRVKFSRSADAPAYQQGQNLNELNLRREEYDVLDKRRGRDPGEMGGKPR RKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRE
	Gamma-ss	68			MAIPAVVLLLLLLVEQAAAAGSGGRVAILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGR DLMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRIIGSGAPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF

	FRB CD8a Gamma- CD3z		ACDIGEPQLCYILDAILFLYIGIVLTLLYCRKIQVRKAAITSYEKSrvKFSRSADAPAYQQGQNLNGLRREEYDILD KRRGRDPEMGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKHDGLYQGLSTATKDTYDALHMQALPPRE
	Gamma- ss FKBP -	69	MAIPAVVLLLLLVEQAAAAGSGGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKFSSRDRNKPFFKMLGKQEVIRGWE EGVAQMSVGQRAKLTISPDIAYGATGHPGIIPPHATLVFDVLLKLEGSAPLGEPLCYILDAILFLYIGIVLTLLYCRKIKI QVRKAAITSYEKSrvKFSRSADAPAYQQGQNLNGLRREEYDILDKRRGRDPEMGKPRRKNPQEGLYNELQDKMAE AYSEIGMKGERRRGKHDGLYQGLSTATKDTYDALHMQALPPRE
	Gamma- ss FRB -	70	MAIPAVVLLLLLVEQAAAAGSGGRVAILWHHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGR DLMEAQEWCKYMKSGNVKDLTQAWDLYYHVFRRIGSGAPLGEPLCYILDAILFLYIGIVLTLLYCRKIKIQVRKAAITSYEK SRVKFSRSADAPAYQQGQNLNGLRREEYDILDKRRGRDPEMGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERR RGKHDGLYQGLSTATKDTYDALHMQALPPRE
	Gamma- CD3z		MAPAMESPTLLCVALLFFAPDGVLAEVQLQQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAAPSIPTPGESVSISSRSKSLNSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGSVDPDRFSGSGSGTAFTLRISRVEA EDVGYYCMQHLEYPTTFGAGTKLELKRSDPGSGGVQVETISPGDGRTPPKRGQTCVVHYTGMLEDGKKFSSRDRNKPFFK MLGKQEVIRGWEQVAGMSVGQRAKLTISPDIAYGATGHPGIIPPHATLVFDVLLKLEGSAPAPVGLVARLADESGHVVL RWLPPPETPMTSHIRYEVDSAGNGAGSVQRVEILEGRTECVLSNLRGRTRYTFVAVRAPMAEPSTFGGFWSAWSEPVSLTTPS DIFIPLLVILFAVDTGFLFISTQQQVTFLLKIKRTRKGRLLNPHKPNKNNNE
CID binding domain on α chain of multi chain CAR	VH-4G7- scFv FKBP EpoR_D2 Alpha	71	MAPAMESPTLLCVALLFFAPDGVLAEVQLQQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAAPSIPTPGESVSISSRSKSLNSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGSVDPDRFSGSGSGTAFTLRISRVEA EDVGYYCMQHLEYPTTFGAGTKLELKRSDPGSGGVQVETISPGDGRTPPKRGQTCVVHYTGMLEDGKKFSSRDRNKPFFK MLGKQEVIRGWEQVAGMSVGQRAKLTISPDIAYGATGHPGIIPPHATLVFDVLLKLEGSAPAPVGLVARLADESGHVVL RWLPPPETPMTSHIRYEVDSAGNGAGSVQRVEILEGRTECVLSNLRGRTRYTFVAVRAPMAEPSTFGGFWSAWSEPVSLTTPS DIFIPLLVILFAVDTGFLFISTQQQVTFLLKIKRTRKGRLLNPHKPNKNNNE
	VH-4G7- scFv FRB EpoR_D2 Alpha	72	MAPAMESPTLLCVALLFFAPDGVLAEVQLQQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAAPSIPTPGESVSISSRSKSLNSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGSVDPDRFSGSGSGTAFTLRISRVEA EDVGYYCMQHLEYPTTFGAGTKLELKRSDPGSGGRVAILWHHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQT LKETSFNQAYGRDLMEAEQEWCKYMKSGNVKDLTQAWDLYYHVFRRIGSGAPAPVGLVARLADESGHVVLRLWLPPEPTMTS

CID binding domain on α chain of multi chain CAR	VH-4G7-scFvFKBP IgG1 Alpha	73	HIRYEVDSAGNGAGSVQRVEILEGRTECVLSNLRGRTRYTFAVRARMAEPSEFGGFWSAWSEFVSLLTSPSDFIFLPLVVILF AVDTGLFISTQOQVTFLLKIKRTRKGRLLNPHKPNPKNNE MAPAMESPTLLCVALLFFAPDGVLAEVQLQSQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAPSIPVTPGESVSISCRSSKSLNLSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGVDPDRFSGSGSGTAFTLRISRYEA EDVGYYCMQHLEYPTFTFGAGTKLELKRSDPGSGGVQVETISPGDGRFTFPKRGQTCVVHYTGMLEDGKKFSSRDRNKPFFK MLGKQEVIRGWEEGVAQMSVGQRAKLTISPDIAYGATGHPGIIIPPHATLVFDVELLLKLEGSAGEPKSPDKTHTCPPCPAPP VAGPSVFLFPKPKDTLMTARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKKDIFIPLLVVLFAVDTGLFISTQOQVTFLLKI KRTRKGRLLNPHKPNPKNNE MAPAMESPTLLCVALLFFAPDGVLAEVQLQSQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAPSIPVTPGESVSISCRSSKSLNLSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGVDPDRFSGSGSGTAFTLRISRYEA EDVGYYCMQHLEYPTFTFGAGTKLELKRSDPGSGGRVALIWMHMHGEEASRLYFGERNVKGMFEVLEPLHAMMERGPQT LKETSFNQAYGRDLMEAEWCWKYMKSGNVKDLTQAWDLYYHVFRIRIGSGAGEPKSPDKTHTCPPCPAPPVAGPSVFLFPFK PKDTLMTARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKAL PAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGGSFFLYSKL TVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKKDIFIPLLVVLFAVDTGLFISTQOQVTFLLKIKRTRKGRLLNP HPKPNPKNNE MAPAMESPTLLCVALLFFAPDGVLAEVQLQSQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAPSIPVTPGESVSISCRSSKSLNLSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGVDPDRFSGSGSGTAFTLRISRYEA EDVGYYCMQHLEYPTFTFGAGTKLELKRSDPGSGGVQVETISPGDGRFTFPKRGQTCVVHYTGMLEDGKKFSSRDRNKPFFK MLGKQEVIRGWEEGVAQMSVGQRAKLTISPDIAYGATGHPGIIIPPHATLVFDVELLLKLEGSAGTPTTTPAPRPPTPAPTIASQ
	VH-4G7-scFvFKBP IgG1 Alpha	74	HIRYEVDSAGNGAGSVQRVEILEGRTECVLSNLRGRTRYTFAVRARMAEPSEFGGFWSAWSEFVSLLTSPSDFIFLPLVVILF AVDTGLFISTQOQVTFLLKIKRTRKGRLLNPHKPNPKNNE MAPAMESPTLLCVALLFFAPDGVLAEVQLQSQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAPSIPVTPGESVSISCRSSKSLNLSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGVDPDRFSGSGSGTAFTLRISRYEA EDVGYYCMQHLEYPTFTFGAGTKLELKRSDPGSGGVQVETISPGDGRFTFPKRGQTCVVHYTGMLEDGKKFSSRDRNKPFFK MLGKQEVIRGWEEGVAQMSVGQRAKLTISPDIAYGATGHPGIIIPPHATLVFDVELLLKLEGSAGEPKSPDKTHTCPPCPAPP VAGPSVFLFPKPKDTLMTARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKKDIFIPLLVVLFAVDTGLFISTQOQVTFLLKI KRTRKGRLLNPHKPNPKNNE MAPAMESPTLLCVALLFFAPDGVLAEVQLQSQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAPSIPVTPGESVSISCRSSKSLNLSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGVDPDRFSGSGSGTAFTLRISRYEA EDVGYYCMQHLEYPTFTFGAGTKLELKRSDPGSGGRVALIWMHMHGEEASRLYFGERNVKGMFEVLEPLHAMMERGPQT LKETSFNQAYGRDLMEAEWCWKYMKSGNVKDLTQAWDLYYHVFRIRIGSGAGEPKSPDKTHTCPPCPAPPVAGPSVFLFPFK PKDTLMTARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKAL PAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGGSFFLYSKL TVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKKDIFIPLLVVLFAVDTGLFISTQOQVTFLLKIKRTRKGRLLNP HPKPNPKNNE MAPAMESPTLLCVALLFFAPDGVLAEVQLQSQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAPSIPVTPGESVSISCRSSKSLNLSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGVDPDRFSGSGSGTAFTLRISRYEA EDVGYYCMQHLEYPTFTFGAGTKLELKRSDPGSGGVQVETISPGDGRFTFPKRGQTCVVHYTGMLEDGKKFSSRDRNKPFFK MLGKQEVIRGWEEGVAQMSVGQRAKLTISPDIAYGATGHPGIIIPPHATLVFDVELLLKLEGSAGTPTTTPAPRPPTPAPTIASQ
	VH-4G7-scFvFKBP CD8a Alpha	75	HIRYEVDSAGNGAGSVQRVEILEGRTECVLSNLRGRTRYTFAVRARMAEPSEFGGFWSAWSEFVSLLTSPSDFIFLPLVVILF AVDTGLFISTQOQVTFLLKIKRTRKGRLLNPHKPNPKNNE MAPAMESPTLLCVALLFFAPDGVLAEVQLQSQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAPSIPVTPGESVSISCRSSKSLNLSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGVDPDRFSGSGSGTAFTLRISRYEA EDVGYYCMQHLEYPTFTFGAGTKLELKRSDPGSGGVQVETISPGDGRFTFPKRGQTCVVHYTGMLEDGKKFSSRDRNKPFFK MLGKQEVIRGWEEGVAQMSVGQRAKLTISPDIAYGATGHPGIIIPPHATLVFDVELLLKLEGSAGEPKSPDKTHTCPPCPAPP VAGPSVFLFPKPKDTLMTARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKKDIFIPLLVVLFAVDTGLFISTQOQVTFLLKI KRTRKGRLLNPHKPNPKNNE MAPAMESPTLLCVALLFFAPDGVLAEVQLQSQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAPSIPVTPGESVSISCRSSKSLNLSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGVDPDRFSGSGSGTAFTLRISRYEA EDVGYYCMQHLEYPTFTFGAGTKLELKRSDPGSGGRVALIWMHMHGEEASRLYFGERNVKGMFEVLEPLHAMMERGPQT LKETSFNQAYGRDLMEAEWCWKYMKSGNVKDLTQAWDLYYHVFRIRIGSGAGEPKSPDKTHTCPPCPAPPVAGPSVFLFPFK PKDTLMTARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKAL PAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGGSFFLYSKL TVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKKDIFIPLLVVLFAVDTGLFISTQOQVTFLLKIKRTRKGRLLNP HPKPNPKNNE MAPAMESPTLLCVALLFFAPDGVLAEVQLQSQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDG TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGSDIV MTQAAPSIPVTPGESVSISCRSSKSLNLSNGNTYLYWFLQRPQGSPQLLIYRMSNLAGVDPDRFSGSGSGTAFTLRISRYEA EDVGYYCMQHLEYPTFTFGAGTKLELKRSDPGSGGVQVETISPGDGRFTFPKRGQTCVVHYTGMLEDGKKFSSRDRNKPFFK MLGKQEVIRGWEEGVAQMSVGQRAKLTISPDIAYGATGHPGIIIPPHATLVFDVELLLKLEGSAGTPTTTPAPRPPTPAPTIASQ

CID binding domain on α chain of single chain CAR	VH-4G7-scFv FRB CD8a Alpha	76	PLSLRPEACRPAAGGAVHTRGLDFACDFFIPLLVVILFAVDTGLFI STQQVTFLLKIKRTRKGRLLNPHPKPNPKNNE MAPAMESPTLLCVALLFFAPDGVLAFAVQLQQSGPELKKPGASVKMSCKASGYFTTSYVMHWVKQKPGQGLEWIGYINPNYNDG TKYNEKFKGKATLTSKSSSTAYMELSSLTSEDSAVYVCARGTYYYGSRVFDYWGQGTTLTVSSGGGGGGGGGGGGSDIV MTQAAPSIPVTPGESVSISCRSSKSLNLSNGNTYLYWFLQRPQSPQLLIYRMSNLASGVDPDRFSGSGGTAFTLRI SRVEA EDVGYYICMQLHEYPFTFGAGTKLELKRSDPGSGGRVAILWHEMWHGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQT LKETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRI GSGAPTTTPAPRPPTPAPTIASQPLSLRPEACRPA AGGAVHTRGLDFACDFFIPLLVVILFAVDTGLFI STQQVTFLLKIKRTRKGRLLNPHPKPNPKNNE
	sc_scFV_C D12 FKBP CD8a CD8a 4-1BB- CD3z	77	MALPV'TALLPLALLHAARPQIQLVQSGPELKKPGETVKISCKASGYIFTN'YGMNWVKQAPGKSFKWMGWINTYTGEESTYS ADFKGRFAFSLETSASTAYLHINDLKNEDTATYFCARSGGYDPMDYWGQGTSVTVSSGGGGGGGGGGGGSDIVLTQSPAS LAVSLGQRATISCRASESVDNYGNTFMHWYQQKPGQPPKLLIYRASNL ESGIPARFSGSGSRITDFTLTINPVEADDDVATYYC QQSNEDPPTFGAGTKLELKRSDPGSGGVQVETISPGDGRTPFKRGQTCVVHYTGMLEDGKKFDSRRDRNKPFKFMGLKQEV I RGWEEGVAQMSVGQRAKLTISPDIYAGATGHPGIIPPHATLVFDVELLKLKLESGAPTTTPAPRPPTPAPTIASQPLSLRPEA CRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCRRGRKKLLYIFKQPFMRPVQTTQEEEDGSCSRFPPEEEEGG CELVRKFSRSADAPAYQQGNQLYNEINLGRREYDVLDKRRGRDPEMGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGE RRRGKGHDGLYQGLSTATKDTYDALHMQALPPRE
	sc_scFV_C D12 FRB CD8a CD8a 4-1BB- CD3z	78	MALPV'TALLPLALLHAARPQIQLVQSGPELKKPGETVKISCKASGYIFTN'YGMNWVKQAPGKSFKWMGWINTYTGEESTYS ADFKGRFAFSLETSASTAYLHINDLKNEDTATYFCARSGGYDPMDYWGQGTSVTVSSGGGGGGGGGGGGSDIVLTQSPAS LAVSLGQRATISCRASESVDNYGNTFMHWYQQKPGQPPKLLIYRASNL ESGIPARFSGSGSRITDFTLTINPVEADDDVATYYC QQSNEDPPTFGAGTKLELKRSDPGSGGRVAILWHEMWHGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQ AYGRDLMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRI GSGAPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACDIYIWAPLAGTCGVLLLSLVITLYCRRGRKKLLYIFKQPFMRPVQTTQEEEDGSCSRFPPEEEEGGCELVRKFSRSAD APAYQQGNQLYNEINLGRREYDVLDKRRGRDPEMGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRRGKGHDGLYQ GLSTATKDTYDALHMQALPPRE
CID binding domain on α chain of single chain CAR	sc_scFV_C D12 FKBP	79	MALPV'TALLPLALLHAARPQIQLVQSGPELKKPGETVKISCKASGYIFTN'YGMNWVKQAPGKSFKWMGWINTYTGEESTYS ADFKGRFAFSLETSASTAYLHINDLKNEDTATYFCARSGGYDPMDYWGQGTSVTVSSGGGGGGGGGGGGSDIVLTQSPAS

CID binding domain on α chain of single chain CAR	IgG1 CD8a 4-1BB- CD3z		LAVSLGQRATISCRASESDNYGNTFMHWYQQKPGQPPKLLIYRASNLSEGI PARFSGSGSRTDFTLTINPVEADDDVATYYC QQSNEDPPTFGAGTKLELKRSDPGSGGVQVETISPGDGRTPFKRGQTCVVHYTGMLEDGKKFDSRRDRNKPFKFMGLGKQEV RGWEEGVAQMSVGQRAKLTISPDIYAGATGHPGIIIPPHATLVDFVELLKLEGS GAPEKSPDKTHTCPPCPAPPVAGPSVFL FPPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV NKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFLL YSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGKKDIYIWAFLAGTCGVL LLSLVITLYCRRGRKKLLYIFKQPF MRPVQTTQEEEDGSCRFPEEEEGGCELVRVKFSRSADAPAYQQGNQLYNE LNLGRREYDVLDRRGRDPEMGKPRRKNPQ EGLYNELQDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRE
	sc_scFV_C D12 FRB IgG1 CD8a 4-1BB- CD3z	80	MALPVTALLPLALLLHAARPQIQLVQSGPELKKPGETVKISCKASGYIFTNYGMNWVKQAPGKSFKWMGWINTYTGESTYS ADFKGRFAFSLETSASTAYLHINDLKNEDTATYFCARSGGYDPMYWGQGTSVTVSSGGGGSGGGGGSDIVLTQSPAS LAVSLGQRATISCRASESDNYGNTFMHWYQQKPGQPPKLLIYRASNLSEGI PARFSGSGSRTDFTLTINPVEADDDVATYYC QQSNEDPPTFGAGTKLELKRSDPGSGGRVAILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSTNQ AYGRDLMEAEQWCRKYMKSGNVKDLTQANDLYYHVFRRIGSGAPEKSPDKTHTCPPCPAPPVAGPSVFLPFPKPKDTLMLIA RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT SKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFLLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGKKDIYIWAFLAGTCGVL LLSLVITLYCRRGRKKLLYIFKQPFMRPVQTTQEEEDG CSCRFPEEEEGGCELVRVKFSRSADAPAYQQGNQLYNE LNLGRREYDVLDRRGRDPEMGKPRRKNPQEGLYNELQDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRE
	sc_scFV_C D12 FKBP EpoR_D2 CD8a 4-1BB- CD3z	81	MALPVTALLPLALLLHAARPQIQLVQSGPELKKPGETVKISCKASGYIFTNYGMNWVKQAPGKSFKWMGWINTYTGESTYS ADFKGRFAFSLETSASTAYLHINDLKNEDTATYFCARSGGYDPMYWGQGTSVTVSSGGGGSGGGGGSDIVLTQSPAS LAVSLGQRATISCRASESDNYGNTFMHWYQQKPGQPPKLLIYRASNLSEGI PARFSGSGSRTDFTLTINPVEADDDVATYYC QQSNEDPPTFGAGTKLELKRSDPGSGGVQVETISPGDGRTPFKRGQTCVVHYTGMLEDGKKFDSRRDRNKPFKFMGLGKQEV RGWEEGVAQMSVGQRAKLTISPDIYAGATGHPGIIIPPHATLVDFVELLKLEGS GAPEKSPDKTHTCPPCPAPPVAGPSVFL PMTSHIRYEVDSAGNGAGSVQVREIILEGRTECVLSNLGRTRYTFVAVARMAE PSFGGFWSAWSEPVSLTTPSDIYIWAFL AGTCGVLLLSLVITLYCRRGRKKLLYIFKQPFMRPVQTTQEEEDGSCRFPEEEEGGCELVRVKFSRSADAPAYQQGNQLYNE

			INLGRREEYDVLKRRGRDPGEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGHDLGYQGLSTATKDTYDALH MQALPPRE
	sc_scFV_C D12 FRB EpoR_D2 CD8a 4-1BB- CD3z	82	MALPVTALLPLALLHAARPQIQLVQSGPELKKPGETVKISCKASGIIFTNYGMNWKQAPGSKFKWGWINTYTGESTYS ADFKGRFAFSLETSASTAYLHINDLKNEDTATYFCARSGGYDPMYWGQTSVTSSGGGGSGGGGSDIVLTQSPAS LAVSLGORATISCRASESVNDYGNFTFMHWYQOKPGQPPKLLIYRASNLSEGI PARFSGSGSRITDFTLTINPVEADDDVATYYC QQSNEDPPTFGAGTKLELKRSDPGSGGRVAILWHENMHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQ AYGRDLMEAQEWCRKYMKSNGNVKDLTQAWDLYYHVFRRIIGSGAPAPVGLVARLADESHVVLRWLPPPETMTSHIRYEDV SAGNGAGSVQRVEILEGRTECVLSNLRGRTRYTFVAPRMAEPSPFGGFWSAWSEPVSLLTSPSDIYIWAFLAGTCGVLLLSLV ITLYCRRGRKKLLYIFKQPFMRPVQTTQEEEDGCSRCRFPPEEEGGCELLVKFERSADAPAYQQGQNQLYNEINLGRREEYDVL DKRRGRDPGEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGHDLGYQGLSTATKDTYDALHMQALPPRE
INTRA CELLULAR CID BINDING DOMAINS			
IMP complex (switch OFF receptor)	VH- 4G7-ss CD8a FKBP PD1	83	MALPVTALLPLALLHAARPGSDIYIWAFLAGTCGVLLLSLVITLYCRSGGVQVETISPGDGRTFPKRGQTCVVHYTGMLE DGKKFDSRRDRNKPFFKFMKGQEVIRGWEEGVAQMSVGQRAKLTTISPDYAYGATGHPGIIPPHATLVDFVELLKLEGGSSSS RAARGTIGARRTGQPLKEDPSAVPVFVSVDYGELDFQWREKTPPEPPVPCVPEQTEYATIVFPSSMGMTSSPARRGSADGPRSAQ PLRPEDGHCSWPLE
	VH- 4G7-ss CD8a FRB PD1	84	MALPVTALLPLALLHAARPGSDIYIWAFLAGTCGVLLLSLVITLYCRSGGRVAILWHENMHEGLEEASRLYFGERNVKGM FEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAQEWCRKYMKSNGNVKDLTQAWDLYYHVFRRIIGSGSSSRAARGTIGARRT GQPLKEDPSAVPVFVSVDYGELDFQWREKTPPEPPVPCVPEQTEYATIVFPSSMGMTSSPARRGSADGPRSAQPLRPEDGHCSWP LE
	VH- 4G7-ss CD8a OX40 FKBP PD1	85	MALPVTALLPLALLHAARPGSDIYIWAFLAGTCGVLLLSLVITLYCRALYLLRRDQRLPPDAHKKPPGGGSRFTPIQEEQA DAHSTLAKIGSGSGSGSGGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKFDSRRDRNKPFFKFMKGQEVIRGWEEGV AQMSVGQRAKLTTISPDYAYGATGHPGIIPPHATLVDFVELLKLEGGSGSRAARGTIGARRTGQPLKEDPSAVPVFVSVDYGE LDFQWREKTPPEPPVPCVPEQTEYATIVFPSSMGMTSSPARRGSADGPRSAQPLRPEDGHCSWPLE
	VH- 4G7-ss	86	MALPVTALLPLALLHAARPGSDIYIWAFLAGTCGVLLLSLVITLYCRPRRSPAQEDGKVYINMPGRGGSGSGSGSGGVQ

IMP complex (switch OFF receptor)	CD8a DAP10 FKBP PD1		VETISPGDGRTPFKRGQTCVVHYTGMLEDGKKFDSRRDNKPKFKFMLGKQEVIRGWEEGVAQMSVGQRAKLTTISPDYAYGAT GHPGIIPPHATLVFDVELLKLEGGSGSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPPEPPVPCVPEQTE YATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPLE
	VH- 4G7-ss CD8a HVEM FKBP PD1	87	MALPVTALLPLALLHHAARPGSDIYIWAPLAGTCGVLLLSLVITLYCRVCVKRRKPRGDVVKVIVSVQRRKQEAEGEATVIE ALQAPPDVTTVAVEETIPSTTGRSPNHGSGSGSGSGGVQVETISPGDGRTPFKRGQTCVVHYTGMLEDGKKFDSRRDNKPK FKFMLGKQEVIRGWEEGVAQMSVGQRAKLTTISPDYAYGATGHPGIIPPHATLVFDVELLKLEGGSGSRAARGTIGARRTGQ PLKEDPSAVPVFSVDYGELDFQWREKTPPEPPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPLE
	VH- 4G7-ss CD8a OX40 FRB PD1	88	MALPVTALLPLALLHHAARPGSDIYIWAPLAGTCGVLLLSLVITLYCRALYLLRRDQRLPPDAHKKPPGGGSRFTPIQEEQA DAHSTLAKIGSGSGSGSGGRVAILWHEMWHHEGLEEASRLYFGERNVKGMFEVILEPLHAMMERGPQTLKETSFNQAYGRDLM EAQEWCRKYMKSGNVKDLTQAWDLXYHVFRIRIGSGSGSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPPEP PVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPLE
	VH- 4G7-ss CD8a DAP10 FRB PD1	89	MALPVTALLPLALLHHAARPGSDIYIWAPLAGTCGVLLLSLVITLYCRPRRSPAQEDGKVYINMPGRGSGSGSGSGGRV AILWHEMWHHEGLEEASRLYFGERNVKGMFEVILEPLHAMMERGPQTLKETSFNQAYGRDLM EAQEWCRKYMKSGNVKDLTQAW DLXYHVFRIRIGSGSGSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPPEPPVPCVPEQTEYATIVFPSGMGT SSPARRGSADGPRSAQPLRPEDGHCSWPLE
	VH- 4G7-ss CD8a HVEM FRB PD1	90	MALPVTALLPLALLHHAARPGSDIYIWAPLAGTCGVLLLSLVITLYCRVCVKRRKPRGDVVKVIVSVQRRKQEAEGEATVIE ALQAPPDVTTVAVEETIPSTTGRSPNHGSGSGSGSGGRVAILWHEMWHHEGLEEASRLYFGERNVKGMFEVILEPLHAMMERG PQTLKETSFNQAYGRDLM EAQEWCRKYMKSGNVKDLTQAWDLXYHVFRIRIGSGSGSRAARGTIGARRTGQPLKEDPSAVPVF SVDYGELDFQWREKTPPEPPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPLE
	VH- 4G7-ss CD8a PD1	91	MALPVTALLPLALLHHAARPGSDIYIWAPLAGTCGVLLLSLVITLYCRSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGE LDFQWREKTPPEPPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPLGSGSGSGGVQVETISPGDG RTFPKRGQTCVVHYTGMLEDGKKFDSRRDNKPKFKFMLGKQEVIRGWEEGVAQMSVGQRAKLTTISPDYAYGATGHPGIIPPH

IMP complex (switch OFF receptor)	FKBP		ATLVDFVELLKLEE
	VH- 4G7-ss CD8a PD1 FRB	92	MALPVTALLPLALLHAAARPGSDIYIWAPLAGTCGVLLLSLVITLTYCRSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGE LDFQWREKTPPEPPVPCVPEQTEYATIVFPSSMGTSAPARRGSADGPRSAQPLRPEDGHCSWPLGSGSSGGRRVAILWHENMWH EGLEEAASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAEQEWCRKYNKMSGNVKDLTQAWDLYYHVFRFR IE
	VH- 4G7-ss CD8a OX40 PD1 FKBP _r	93	MALPVTALLPLALLHAAARPGSDIYIWAPLAGTCGVLLLSLVITLTYCRALYLLRRDQRLPPDAHKKPPGGGSTRPTIQEEQA DAHSTLAKIGSGSGSSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGEIDFQWREKTPPEPPVPCVPEQTEYATIVFPSSGM GTSSPARRGSADGPRSAQPLRPEDGHCSWPLGSGSGGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKFDDSSRDNRNKKPF KFMKGQEVIRGWEEGVAQMSVGQRAKLTTISPDYAYGATGHPGIIPPHATLVDFVELLKLEE
	VH- 4G7-ss CD8a DAP10 PD1 FKBP	94	MALPVTALLPLALLHAAARPGSDIYIWAPLAGTCGVLLLSLVITLTYCRPRRSPAQEDGKVYINMPGRGGSGSGSSRAAR GTIGARRTGQPLKEDPSAVPVFSVDYGEIDFQWREKTPPEPPVPCVPEQTEYATIVFPSSMGTSAPARRGSADGPRSAQPLRP EDGHCSWPLGSGSGGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKFDDSSRDNRNKKPFKFMKGQEVIRGWEEGVAQMSV GQRAKLTTISPDYAYGATGHPGIIPPHATLVDFVELLKLEE
	VH- 4G7-ss CD8a HVEM PD1 FKBP	95	MALPVTALLPLALLHAAARPGSDIYIWAPLAGTCGVLLLSLVITLTYCRVCVKKRPRGDVVKVIVSVQKRKQEAEGEATVIE ALQAPPDVTTVAVEETIPSTFTGRSPNHGSGSGSSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGEIDFQWREKTPPEPPV PCVPEQTEYATIVFPSSMGTSAPARRGSADGPRSAQPLRPEDGHCSWPLGSGSGGVQVETISPGDGRTFPKRGQTCVVHYTG MLEDGKKFDDSSRDNRNKKPFKFMKGQEVIRGWEEGVAQMSVGQRAKLTTISPDYAYGATGHPGIIPPHATLVDFVELLKLEE
	VH- 4G7-ss CD8a OX40 PD1 FRB	96	MALPVTALLPLALLHAAARPGSDIYIWAPLAGTCGVLLLSLVITLTYCRALYLLRRDQRLPPDAHKKPPGGGSTRPTIQEEQA DAHSTLAKIGSGSGSSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGEIDFQWREKTPPEPPVPCVPEQTEYATIVFPSSGM GTSSPARRGSADGPRSAQPLRPEDGHCSWPLGSGSGGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKFDDSSRDNRNKKPF QTLKETSFNQAYGRDLMEAEQEWCRKYNKMSGNVKDLTQAWDLYYHVFRRIE
	VH-	97	MALPVTALLPLALLHAAARPGSDIYIWAPLAGTCGVLLLSLVITLTYCRPRRSPAQEDGKVYINMPGRGGSGSGSSRAAR

CID binding domain on single-chain CAR	4G7-ss CD8a DAP10 PD1 FRB		GTIGARRTGQPLKEDPSAVPVFSVDYGEILDQWREKTPPEPPVPCVPEQTEYATIVFPSSGMGTSSPARRGSADGPRSAQPLRP EDGHCWPLGSGGGRVAIILWHEMWHHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAEW CRKYMKSGNVKDLTQAWDLYYHVFRRIE
	VH- 4G7-ss CD8a HVEM PD1 FRB	98	MALPVTALLPLALLHAAARPGSDIYIWAPLAGTCGVLLLSLVITLTCRCVKRKRPRGDVVKVIIVSVQRKRQEAEGEATVIE ALQAPPDVTTVAVEETIPSTGRSPNHGSGSGSRAARGTTIGARRTGQPLKEDPSAVPVFSVDYGEILDQWREKTPPEPPV PCVPEQTEYATIVFPSSGMGTSSPARRGSADGPRSAQPLRPEDGHCWPLGSGGGRVAIILWHEMWHHEGLEEASRLYFGERNV KGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAEWCRKYMKSGNVKDLTQAWDLYYHVFRRIE
	CD123- scFv CD8a FKBP	99	MAPAMESPTLLCVALLFFAPDGVLAQIQLVQSGPELKKPGETVKISCKASGYIFTNNGMNWVKQAPGKSFKWMGWINTYTGE STYSADFKGRFAFSLETSASTAYILHINDLKNEDTATYFCARSGGYDPMDYWGQGTSVTVSSGGGGSGGGGGSDIVLTQ SPASLAVSLGQRATISCRASESVNDYGNTFMHWYQQKPGQPPKLLIYRASNLSESGIPARFSGSGSRTDFTLTINPVEADDDVA TYCQQQSNEDPPTFGAGTKLELKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFFIPLLVVIL FAVDTGLFIQTQQQVTFLLKIKRTRKGRLLNPHPKPNKNNRSGGVQVETISPGDGRTPFKRGQTCVVHYTGMLEDDGKKFD SSDRNKPFFKFMKGQEVIRGWEEGVAQMSVGQRAKLTI SPDYAYGATGHPGIIIPPHATLVDFVELLLEE
CID binding domain on single-chain CAR	CD123- scFv CD8a FRB	100	MAPAMESPTLLCVALLFFAPDGVLAQIQLVQSGPELKKPGETVKISCKASGYIFTNNGMNWVKQAPGKSFKWMGWINTYTGE STYSADFKGRFAFSLETSASTAYILHINDLKNEDTATYFCARSGGYDPMDYWGQGTSVTVSSGGGGSGGGGGSDIVLTQ SPASLAVSLGQRATISCRASESVNDYGNTFMHWYQQKPGQPPKLLIYRASNLSESGIPARFSGSGSRTDFTLTINPVEADDDVA TYCQQQSNEDPPTFGAGTKLELKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFFIPLLVVIL FAVDTGLFIQTQQQVTFLLKIKRTRKGRLLNPHPKPNKNNRSGGRVAIILWHEMWHHEGLEEASRLYFGERNVKGMFEVLEP LHAMMERGPQTLKETSFNQAYGRDLMEAEWCRKYMKSGNVKDLTQAWDLYYHVFRRIE
	CD123- scFv CD8a OX40 FKBP	101	MAPAMESPTLLCVALLFFAPDGVLAQIQLVQSGPELKKPGETVKISCKASGYIFTNNGMNWVKQAPGKSFKWMGWINTYTGE STYSADFKGRFAFSLETSASTAYILHINDLKNEDTATYFCARSGGYDPMDYWGQGTSVTVSSGGGGSGGGGGSDIVLTQ SPASLAVSLGQRATISCRASESVNDYGNTFMHWYQQKPGQPPKLLIYRASNLSESGIPARFSGSGSRTDFTLTINPVEADDDVA TYCQQQSNEDPPTFGAGTKLELKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFFIPLLVVIL

CID binding domain on single-chain CAR			FAVDTGLFI STQQQVTFLLKIKRTRKGFRLNPHPKPNKNNRALYLLRRDQRLPPDAHKPPGGGSRFTPIQEEQADAHSTLAKIGSGSGSGGGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKFDDSSRDNRNPKPKFMLGKQEVIRGWEEGVAQMSVGQRAKLTI SPDYAYGATGHPGII PPHTATLVDFVELLKLEE
	CD123- scFv CD8a DAP10 FKBP	102	MAPAMESPTLLCVALLFFAPDGVLAQIQLVQSGPELKKPGETVKISCKASGYIFTNNGMNVKQAPGKSKFWMGWINTYTGE STYSADFKGRFAFSLETSASTAYLHINDLKNEATYFCARSGGYDPMYWGQTSVTSSGGGSGGGSGGGSDIVLTQ SPASLAVSLGQRATISCRASEVDNYGNTFMHWYQQKPGQPPKLLIYRASNLKESGIPARFSGSGSRDTFTLTINPVEADDDVA TYCQQQSNEDPPTFGAGTKLELKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGAVHTRGLDFACDFFIPLLVVIL FAVDTGLFI STQQQVTFLLKIKRTRKGFRLNPHPKPNKNNRPRRSPAQEDGKVYINMPGRGGSGSGSGGGVQVETISPDGRTFPKRGQTCVVHYTGMLEDGKKFDDSSRDNRNPKPKFMLGKQEVIRGWEEGVAQMSVGQRAKLTI SPDYAYGATGHPGII PPHTATLVDFVELLKLEE
	CD123- scFv CD8a HVEM FKBP	103	MAPAMESPTLLCVALLFFAPDGVLAQIQLVQSGPELKKPGETVKISCKASGYIFTNNGMNVKQAPGKSKFWMGWINTYTGE STYSADFKGRFAFSLETSASTAYLHINDLKNEATYFCARSGGYDPMYWGQTSVTSSGGGSGGGSGGGSDIVLTQ SPASLAVSLGQRATISCRASEVDNYGNTFMHWYQQKPGQPPKLLIYRASNLKESGIPARFSGSGSRDTFTLTINPVEADDDVA TYCQQQSNEDPPTFGAGTKLELKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGAVHTRGLDFACDFFIPLLVVIL FAVDTGLFI STQQQVTFLLKIKRTRKGFRLNPHPKPNKNNRCVKKRPRGDVVKVIVSVQRRKQEAEGEATVIEALQAPP DVTTVAVEETIPSTGRSPNHGSGSGSGSGGGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKFDDSSRDNRNPKPKFMLG KQEVIRGWEEGVAQMSVGQRAKLTI SPDYAYGATGHPGII PPHTATLVDFVELLKLEE
	CD123- scFv CD8a OX40 FRB	104	MAPAMESPTLLCVALLFFAPDGVLAQIQLVQSGPELKKPGETVKISCKASGYIFTNNGMNVKQAPGKSKFWMGWINTYTGE STYSADFKGRFAFSLETSASTAYLHINDLKNEATYFCARSGGYDPMYWGQTSVTSSGGGSGGGSGGGSDIVLTQ SPASLAVSLGQRATISCRASEVDNYGNTFMHWYQQKPGQPPKLLIYRASNLKESGIPARFSGSGSRDTFTLTINPVEADDDVA TYCQQQSNEDPPTFGAGTKLELKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGAVHTRGLDFACDFFIPLLVVIL FAVDTGLFI STQQQVTFLLKIKRTRKGFRLNPHPKPNKNNRALYLLRRDQRLPPDAHKPPGGGSRFTPIQEEQADAHSTL AKIGSGSGSGSGGRVALIWHMMWHEGLEEASRLYFGERNVKGMEFVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAEWC RKYMKSGNVKDLTQAWDLYYHVFRRIE
	CD123-	105	MAPAMESPTLLCVALLFFAPDGVLAQIQLVQSGPELKKPGETVKISCKASGYIFTNNGMNVKQAPGKSKFWMGWINTYTGE

	scFv CD8a DAP10 FRB		STYSADFKGRFAFSLETSASTAYLHINDLKNEDTATYFCARSGGYDPMDYWGQTSVTVS SGGGGSGGGSGGGSDIVLTQ SPASLAVSLGQRATISCRASESVNDYGNTFHWYQQKPGQPPKLLIYRASNLSESGIPARFSGSGRTDFTLTINPVEADDDVA TYCQQQSNEDPPTFGAGTKLELKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFFIPLLVVIL FAVDTGLFI STQQQVTFLLKIKRTRKGRLLNPHPKPNKNNRPRRSPAQEDGKVIYINMPGRGGSGSGSGGGRVAI L WHE MWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQITLKETSFNQAYGRDLMEAEQWCRKYNKSGNVKDLTQAWNDLYYHV FRRIE
	CD123- scFv CD8a HVEM FRB	106	MAPAMESPTLLCVALLFFAPDGVLAQIQLVQSGPELKKPGETVKISCKASGYIFTNYGMNWVKQAPGKSFKMGWINTYTGE STYSADFKGRFAFSLETSASTAYLHINDLKNEDTATYFCARSGGYDPMDYWGQTSVTVS SGGGGSGGGSGGGSDIVLTQ SPASLAVSLGQRATISCRASESVNDYGNTFHWYQQKPGQPPKLLIYRASNLSESGIPARFSGSGRTDFTLTINPVEADDDVA TYCQQQSNEDPPTFGAGTKLELKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFFIPLLVVIL FAVDTGLFI STQQQVTFLLKIKRTRKGRLLNPHPKPNKNNRPRRSPAQEDGKVIYINMPGRGGSGSGSGGGRVAI L WHE MWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQITLKETSFNQAYGRDLMEAEQWCRKYNKSGNVKDLTQAWNDLYYHV FRRIE
CID binding domain on single-chain CAR	klo43_scFV CD8a CD8a 41BB-CD3z FKBP	107	MALPVTALLPLALLHAARPEVKLVESGGGLVQPGGSLSLSCAASGFTTDDYMSWVRQPPGKALEWLALIRSKADGYTTE YSASVKGRFTLSRDDSQSILYLQMNALRPEDSATYICARDAAYYSYSPGAMDYWGQTSVTVS SGGGGSGGGSGGGGSGM ADYKDIVMTQSHKFMSTSVGDRVNITCKASQNVDSAVAWYQQKPGQSPKALLYSASVRYSGVPDRFTTGRSGTDFLTITSSV QAEDLAVYYCQYYSTPWTFFGGGKLEIKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIW APLAGTCGVLLLSLVITLYCRRGRKLLYIFKQPFMRPVQTTQEEEDGCSGCRFPEEEGGCELLRVKFSRSADAPAYQQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKHDGLYQGLSTATKDTYD ALHMQALPPRSSGGVQVETISPGDGRTPFKRGQTCVVHYTGMLEDGKFKFDSRDRNKPFFKFMGLKQEVIRGWEEGVAQMSVG QRAKLTI SPDYAYGATGHPGIIIPPHATLVFDVELLKLEE
	klo43_s cFV CD8a CD8a 41BB-	108	MALPVTALLPLALLHAARPEVKLVESGGGLVQPGGSLSLSCAASGFTTDDYMSWVRQPPGKALEWLALIRSKADGYTTE YSASVKGRFTLSRDDSQSILYLQMNALRPEDSATYICARDAAYYSYSPGAMDYWGQTSVTVS SGGGGSGGGSGGGGSGM ADYKDIVMTQSHKFMSTSVGDRVNITCKASQNVDSAVAWYQQKPGQSPKALLYSASVRYSGVPDRFTTGRSGTDFLTITSSV QAEDLAVYYCQYYSTPWTFFGGGKLEIKRSDPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIW

CID binding domain on single-chain CAR	CD3z FRB		APLAGTCGVLLLSLVITILYCRGRKKLLYIFKQPFMRPVQTTQEEEDGSCSRFPPEEEGGCELLVKFQRSADAPAYQQGQNQL YNELNLGRREEYDVLDKRRGRDPENGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRKGHDGLYQGLSTATKDTYD ALHMQALPPRSSGGRVAILWHENWHEGLEEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAEQEW RKYMKSGNVKDLTQAWDLYYHVFRRIE
	klo43_s cFV CD8a CD8a 41BB FKBP CD3z	109	MALPVTALLPLALLHHAARPEVKLVESGGGLVQPGGSLSLSCAASGFTFTDYMSWVRQPPGKALEWLALIRSKADGYTTE YSAVKGRFTLSRDDSQSILYLQMNALRPEDSATYYCARDAAYYSYSPGAMDYWGQGTSVTVSSGGGGGGGGGGGSM ADYKDIVMTQSHKFMSTSVGDRVNIITCKASQNVDSAVAWYQQKPGQSPKALIYSAASYRYSYGVDPDRFTGRSGTDFTLTSSV QAEDLAVYYCQYYSTPWTFFGGGKLEIKRSDPTTTPAPRPPTPAPTIIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYW APLAGTCGVLLLSLVITILYCRGRKKLLYIFKQPFMRPVQTTQEEEDGSCSRFPPEEEGGCELLGSGSGSGSGGVQVETISPGD GRTFPKRGQTCVVHYTGMLEDGKKFDSSDRDNKPKFKFMLGKQEVIRGWEEGVAQMSVGQRAKLITISPDYAYGATGHPIIPP HATLVFDVELLKLEGGSGRVKFSRSADAPAYQQGQNQLYNEINLGRREEYDVLDKRRGRDPENGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRKGHDGLYQGLSTATKDTYDALHMQALPPRE
	klo43_s cFV CD8a CD8a 41BB FRB CD3z	110	MALPVTALLPLALLHHAARPEVKLVESGGGLVQPGGSLSLSCAASGFTFTDYMSWVRQPPGKALEWLALIRSKADGYTTE YSAVKGRFTLSRDDSQSILYLQMNALRPEDSATYYCARDAAYYSYSPGAMDYWGQGTSVTVSSGGGGGGGGGGGSM ADYKDIVMTQSHKFMSTSVGDRVNIITCKASQNVDSAVAWYQQKPGQSPKALIYSAASYRYSYGVDPDRFTGRSGTDFTLTSSV QAEDLAVYYCQYYSTPWTFFGGGKLEIKRSDPTTTPAPRPPTPAPTIIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYW APLAGTCGVLLLSLVITILYCRGRKKLLYIFKQPFMRPVQTTQEEEDGSCSRFPPEEEGGCELLGSGSGSGSGGVAILWHENW HEGLEEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAEQEWCRKYNMKSNGNVKDLTQAWDLYYHFR RIGSGSGRVKFSRSADAPAYQQGQNQLYNEINLGRREEYDVLDKRRGRDPENGGKPRRKNPQEGLYNELQKDKMAEAYSEIG MKGERRRKGHDGLYQGLSTATKDTYDALHMQALPPRE
	klo43_s cFV CD8a CD8a FKBP 41BB- CD3z	111	MALPVTALLPLALLHHAARPEVKLVESGGGLVQPGGSLSLSCAASGFTFTDYMSWVRQPPGKALEWLALIRSKADGYTTE YSAVKGRFTLSRDDSQSILYLQMNALRPEDSATYYCARDAAYYSYSPGAMDYWGQGTSVTVSSGGGGGGGGGGGSM ADYKDIVMTQSHKFMSTSVGDRVNIITCKASQNVDSAVAWYQQKPGQSPKALIYSAASYRYSYGVDPDRFTGRSGTDFTLTSSV QAEDLAVYYCQYYSTPWTFFGGGKLEIKRSDPTTTPAPRPPTPAPTIIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYW APLAGTCGVLLLSLVITILYCRSGGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKFDSSDRDNKPKFKFMLGKQEVIRGW

			EEGVAQMSVGQRAKLTISPDIAYGATGHPGIIPPHATLVFDVELLKLEGGSSRGRKKLLYIFKQPTMRPVQTTQEEEDGCSC RFPEEEEGGCEL RVKFSRSADAPAYQQGNQNLNGLGRREEYDVLDKRRGRDPENGGKPRRKNPQEGLYNELQKDKMAFA YSEIGMKGERRRGKHDGLYQGLSTATKDTYDALHMQALPPRE
	klo43_s cFV CD8a CD8a FRB 41BB- CD3z	112	MALPVTALLPLALLHHAARPEVKLVESGGGLVQPGGSLSLSCAASGFTFTDYMSWVRQPPGKALEWLALIRSKADGYTTE YSASVKGRFTLSRDDSQSILYLQMNALRPEDSATYYICARDAAYSYSPGAMDYWGQTSVTVSSGGGGSGGGSGGSM ADYKDIVMTQSHKFMSTSVGDRVNI TCKASQNVDSAVAWYQQKPGQSPKALITYSASYRYSVGPDRFTGRGSGTDFTLTISSV QAEDLAVYYCQQYYSTPWTFTGGGTTKLEIKRSDPTTTTAPRPPPTTAPPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIW APLAGTCGVLLLSLVITLYCRSGGRVAIIWHENWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSTFNQAYG RDLMEAEQEWCRKYNMKSNGVKDLTQAWDLYYHVFRIRIGSGSSRGRKKLLYIFKQPTMRPVQTTQEEEDGCCRFPEEEEGGCEL RVKFSRSADAPAYQQGNQNLNGLGRREEYDVLDKRRGRDPENGGKPRRKNPQEGLYNELQKDKMAFAYSEIGMKGERRR GKHDGLYQGLSTATKDTYDALHMQALPPRE

Switch-off receptors and engineered CARs, including additional adequate chains of the mcCAR (beta and gamma or alpha), are further subcloned in a lentiviral production plasmid, possibly upstream a 2A cis-acting hydrolase element (GSG-P2A and GSG-T2A ribosomal skip peptides) followed by a reporter marker (e.g. fluorescent proteins), or membranar protein (such as RQR8) either separately or together separated by 2A cis-acting hydrolase elements. Standard molecular biology technics such as PCR, enzymatic restriction digestion and ligation are applied to create all constructions.

Example 2. Lentiviral delivery of switch-off receptors and engineered mcCARs in primary

T-cells

Viral vectors are either produced according to standard protocols or by an external contractor. Primary T-cells are transduced simultaneously or sequentially using switch-off receptor and engineered mcCAR lentiviral particles. The transduced T-cells are purified for positive engineered mcCAR and switch-off receptor expression using bulk FACS sorting or magnetic separation. The whole bulk engineered mcCAR / switch-off receptor positive population is then assessed for engineered mcCAR driven activation (degranulation/cytotoxicity), proliferation, and cytokine release using a model cell line expressing the engineered CAR target antigens in absence of small molecule (Rapamycin, rapalogs or synthetic rapalogs). The same experiment is then reproduced in presence of the small molecule to assess the inhibition properties of the system.

Example 3. Assembly of switch-off receptors and engineered scCARs (single chain CARs)

Sequences of modules to assemble IMPs (switch-off receptors) are obtained from the SEQ ID NO. 61-64 (extracellular CID binding domain) or 83-98 (intracellular CID binding domain) and from engineered scCAR with SEQ ID NO.77-82 (extracellular CID binding domain) or 107-112 (intracellular CID binding domain) such as depicted in the above Table 5. Their configuration is depicted in the Figures 4 (extracellular CID binding domain) and Figure 5 (intracellular CID binding domain).

Assembly of constructs are done using Golden Gate assembly strategies according to published protocols. Switch-off receptors and engineered CARs are thus cloned in separated shuttle cloning plasmid. Switch-off receptors and engineered scCARs are further subcloned in a lentiviral production plasmid, possibly upstream a 2A cis-acting hydrolase element followed by a reporter

marker (e.g. fluorescent proteins) either separately or together separated by 2A cis-acting hydrolase elements. Standard molecular biology technics such as PCR, enzymatic restriction digestion and ligation are applied to create all constructions.

5 **Example 4. Lentiviral delivery of switch-off receptors and engineered scCARs in primary T-cells**

Viral vectors were either produced according to standard protocols or by an external contractor. Primary T-cells are transduced simultaneously or sequentially using switch-off receptor and engineered scCAR lentiviral particles. The transduced T-cells are purified for positive engineered
 10 scCAR and switch-off receptor expression using bulk FACS sorting or magnetic separation. The whole bulk engineered scCAR / switch-off receptor positive population is then assessed for engineered scCAR driven activation (degranulation/cytotoxicity), proliferation, and cytokine release using a model cell line expressing the engineered CAR target antigens in absence of small molecule (Rapamycin, rapalogs or synthetic rapalogs). The same experiment is then reproduced in presence of
 15 the small molecule to assess the inhibition properties of the system.

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CLAIMS

1. Method for modulating the level of activation of an engineered immune cell, said method comprising the following steps of:
 - (a) transfecting an immune cell with at least a first polynucleotide encoding a Chimeric Antigen Receptor (CAR) , which can be activated in-vivo and/or in vitro by an external ligand; said CAR comprising a first binding domain and ;
 - (b) further transfecting said immune cell with at least a second polynucleotide encoding an engineered inhibitory membrane protein (IMP) complex, comprising at least one intracellular inhibitory signaling domain and one second binding domain, such that said immune cell co-expresses, said CAR, and said inhibitory membrane protein (IMP) complex, and;
 - (c) contacting said engineered immune cell with said external ligand, so that a signal is transduced by the CAR, and then;
 - (d) reducing the level of said signal transduction of said CAR by adding a soluble compound that binds the binding domain of said IMP and the binding domain of the CAR molecule to co-localize said IMP and said CAR, thereby modulating the level of activation of the engineered immune cell.
2. Method for modulating the level of activation according to claim 1, wherein said signal of transduction of the CAR is an activation of the immune cell and said immune cell is activated.
3. Method for modulating the level of activation according to claim 1 or claim 2, wherein the co-localization of the IMP and CAR has the effect of switching off the CAR signal transduction.
4. Method for modulating the level of activation of an engineered immune cell according to any one of claim 1 to 3, wherein said IMP complex comprises at least two transmembrane polypeptides, each comprising a binding domain that is bound by said soluble compound.

5. Method for modulating the level of activation of an engineered immune cell according to any one of claim 1 to 4, wherein first and second binding domains are CID binding domains.

6. Method according to any one of claim 1 to 5, wherein the step d) of reduction of the level of activation is performed by co-localization of two inhibitory signaling domains IL10RA and IL10B born on two different polypeptides of the inhibitory membrane protein (IMP) complex.

7. Method for modulating the level of activation of an engineered immune cell according to one of claim 1 to 5, wherein the step d) of reduction of the level of activation is performed by co-localization of the IMP and the CAR structures through said soluble compound.

8. Method for modulating the level of activation of an engineered immune cell according to one of claim 1-5 or claim 7, wherein the CAR comprises a second binding domain, so that the same soluble compound can bind together the CAR and the IMP

9. Method for modulating the level of activation of an engineered immune cell according to anyone of claim 1-8, wherein said method further comprises the step of infusing the immune cell into a patient upon step b).

10. Method for modulating the level of activation of an engineered immune cell according to anyone of claim 1-9, wherein said immune cell is a T-cell.

11. Method for modulating the level of activation of an engineered immune cell according to anyone of claim 1-10, wherein said CAR is a single chain CAR.

12. Method for modulating the level of activation of an engineered immune cell according to anyone of claim 1-10, wherein said CAR is a multi-chain CAR.

13. Method for modulating the level of activation of an engineered immune cell according to anyone of claim 1-12, wherein said binding domain(s) is (are) extracellular.

14. Method for modulating the level of activation of an engineered immune cell according to anyone of claim 1-12, wherein both said binding domain(s) is (are) intracellular.

15. Method for modulating the level of activation of an engineered immune cell according to anyone of claim 1-5 or claim 7-14, wherein said inhibitory signaling domain is from PD1.

16. Method for modulating the level of activation of an engineered immune cell according to anyone of claim 1-15, wherein said soluble compound is a small molecule

17. Method for modulating the level of activation of an engineered immune cell according to claim 16, wherein said soluble compound is a rapalog.

18. Method for modulating the level of activation of an engineered immune cell according to anyone of claim 17, wherein said small molecule is the rapamycin.

19. Method for modulating the level of activation of an engineered immune cell according to anyone of claim 1-18, wherein said first and second binding domain have at least 80% identity with SEQ ID NO 14 and SEQ ID NO 15.

20. Method for modulating the level of activation of an engineered immune cell according to anyone of claim 1-19, wherein said soluble compound a bi-specific antibody.

21. Method for producing an engineered immune cell, which level of activation by a CAR is controlled by an inhibitory membrane protein (IMP) complex, said method comprising the step of:

(a) transfecting an immune cell with at least a first polynucleotide encoding a Chimeric Antigen Receptor (CAR); and

(b) transfecting said immune cell with at least a second polynucleotide encoding engineered inhibitory membrane protein (IMP) complex, said IMP complex comprising at least one inhibitory signaling domain and one binding domain to be contacted with a soluble compound that translocates the inhibitory domain

(c) selecting the immune cells where the first and second polypeptides are co-expressed into their membrane.

22. Method for producing an engineered immune cell according to claim 21, wherein the transfection is performed by the use of a retroviral vector.

23. Method for producing an engineered immune cell according to claim 21, wherein the transfection is performed by the use of polycistronic CAR/IMP-encoding mRNA.

24. Method for producing an engineered immune cell according to anyone of claim 21-23, comprising further a step of producing allogeneic immune cells by inactivation of at least one gene encoding a T-cell receptor (TCR) component.

25. Method for producing an engineered immune cell according to claim 24, wherein the step of allogeneic immune cells production is performed by the use of TALE nuclease.

26. Inhibitory dual CAR/IMP complex, comprising at least two transmembrane chimeric polypeptides:

- a first one encoding a Chimeric Antigen Receptor which comprises one dimerization binding domain;
- the second one encoding an engineered inhibitory membrane protein (IMP) complex, said IMP complex comprising at least one intracellular inhibitory signaling domain and one dimerization binding domain.

27. Inhibitory dual CAR/IMP complex according to claim 26, wherein both dimerization binding domains are located extracellularly.

28. Inhibitory dual CAR/IMP complex according to anyone of claim 26 or claim 27, wherein the CAR is a multi-chain CAR.

29. Inhibitory dual CAR/IMP complex according to claim 26 or claim 27, wherein the CAR is a single-chain CAR.

30. Inhibitory dual CAR/IMP complex according to anyone of claim 26 to 29, wherein the inhibitory domain is PD-1.

31. Inhibitory dual CAR/IMP complex according to anyone of claim 26 to 30, wherein the dimerization domain is FKBP or FRB.

32. Inhibitory dual CAR/IMP complex according to anyone of claim 31, wherein said first and second binding domains have at least 80 % identity with SEQ ID NO 14 and SEQ ID NO 15.

33. An inhibitory membrane protein (IMP) complex, comprising at least two transmembrane chimeric polypeptides, each of them comprising at least, an inhibitory domain and a binding domain, both binding domains interacting with a soluble compound, so that the respective inhibitory domains co-localize upon addition of said soluble compound.

34. An inhibitory membrane protein (IMP) complex according to claim 33 wherein the inhibitory domains are IL-10R α /IL-10R β , TGF- β , VEGF, TNFR or DR3.

35. An inhibitory membrane protein (IMP) complex according to claim 33 or claim 34, wherein the dimerization domain is FKBP or FRB.

36. An inhibitory membrane protein (IMP) complex according to claim 35, wherein said first and second binding domains have at least 80 % identity with SEQ ID NO 14 and SEQ ID NO 15.

37. A polynucleotide encoding an inhibitory membrane complex according to anyone of claims 33-36.

38. A retroviral vector comprising the polynucleotide according to anyone of claims 33-37.
39. An engineered immune cell comprising an inhibitory membrane complex according to claim 33-36 or transfected with a polynucleotide according to claim 37 or with the retroviral vector according to claim 38.
40. An engineered immune cell according to claim 39, wherein it further expresses a Chimeric Antigen Receptor (CAR).
41. An engineered immune cell that expresses a CAR on its surface along with an inhibitory membrane protein (IMP), wherein said CAR and inhibitory transmembrane polypeptides each comprises a binding domain, both binding domains interacting with the same soluble compound.
42. An engineered immune cell according to claim 41, wherein said inhibitory domain of the IMP chimeric polypeptide is chosen amongst PD-1, CTLA-4, LAG3, Tim3, BTLA, BY55, TIGIT, LAIR1, SIGLEC10, 2B4, PPP2CA, PPP2CB, PTPN6, PTPN22, CD96, CRTAM, SIGLEC7, SIGLEC9, TNFRSF10B, TNFRSF10A, CASP8, CASP10, CASP3, CASP6, CASP7, FADD, FAS, TGFBRII, TGFBRI, SMAD2, SMAD3, SMAD4, SMAD10, SKI, SKIL, TGIF1, IL10RA, IL10RB, HMOX2, IL6R, IL6ST, EIF2AK4, CSK, PAG1, SIT1, FOXP3, PRDM1, BATF, GUCY1A2, GUCY1A3, GUCY1B2, GUCY1B3,.
43. An engineered immune cell according to claim 41 or claim 42, wherein both binding domains are extracellular.
44. An engineered immune cell according to claim 41 or claim 42, wherein both binding domains are intracellular.
45. An engineered immune cell according to anyone of claims 39-44, wherein the chimeric antigen receptor (CAR) is a multichain CAR (mcCAR).
46. An engineered immune cell according to claim 45, wherein the multichain chimeric antigen receptor (mcCAR) comprises at least an alpha chain (FC ϵ R α), a beta chain (FC ϵ R β) and a gamma chain (FC ϵ R γ).
47. An engineered immune cell according to claim 46, wherein the binding domain is part of the alpha chain (FC ϵ R α).
48. An engineered immune cell according to claim 46 or claim 47, wherein the multi-chain based chimeric antigen receptor (CAR) comprises:
- an alpha chain (FC ϵ R α) containing at least:

- (a) a signal sequence and an antigen-specific targeting region;
- (b) a binding domain;
- (c) an extracellular spacer domain (hinge);
- (d) a transmembrane domain;

- a beta chain (FC ϵ R β) contains at least:

- (a) a signal sequence;
- (b) an extracellular spacer domain (hinge);
- (c) a transmembrane domain;
- (d) a co-stimulatory ligand;

- a gamma chain (FC ϵ R γ) contains at least:

- (a) a signal sequence;
- (b) an extracellular spacer domain (hinge);
- (c) a transmembrane domain;
- (d) a signal transducing domain.

49. A method for treating a patient in need thereof comprising:

- (a) providing a immune cell according to any one of the claims 39 to 48.
- (b) administering said immune cell to said patient,
- (c) administering a chemical inducer of dimerization (CID) to modulate the activation of said immune cell in the patient.

50. The method for treating a patient of claim 49, wherein said chemical inducer of dimerization (CID) is rapamycin.

51. The method for treating a patient of claim 50, wherein said immune cells are recovered from donors.

52. The method for treating a patient of anyone of claim 48, wherein said immune cell is recovered from the patient himself.

53. A kit or vector for engineering immune cells with modutable level of activation, which comprises:

- a first polynucleotide encoding a Chimeric Antigen Receptor (CAR); and;
- a second polynucleotide encoding an engineered inhibitory membrane protein (IMP) complex according to anyone of claims 27-32.

Figure 1A

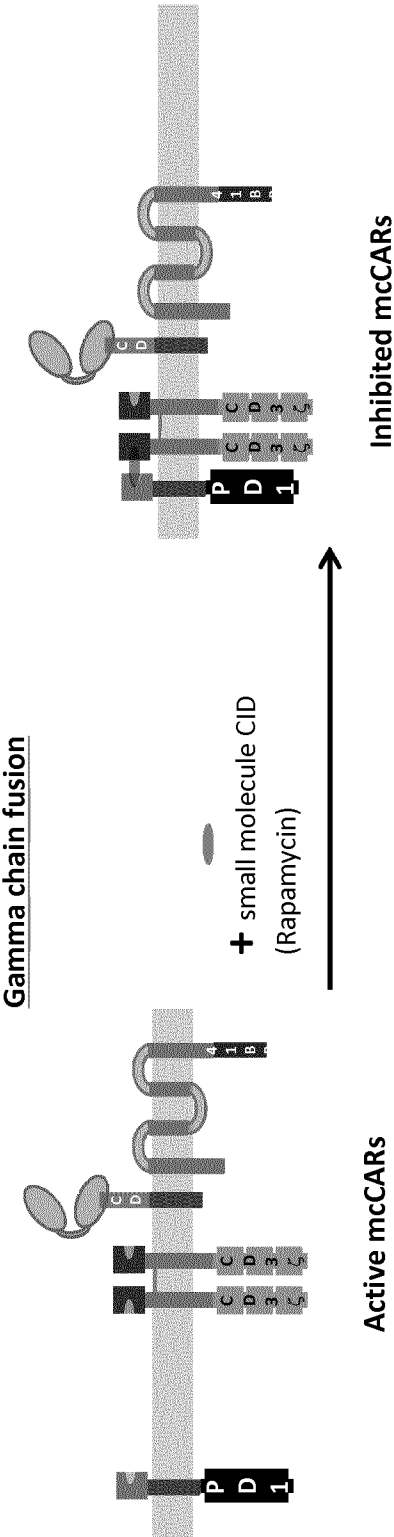


Figure 1B

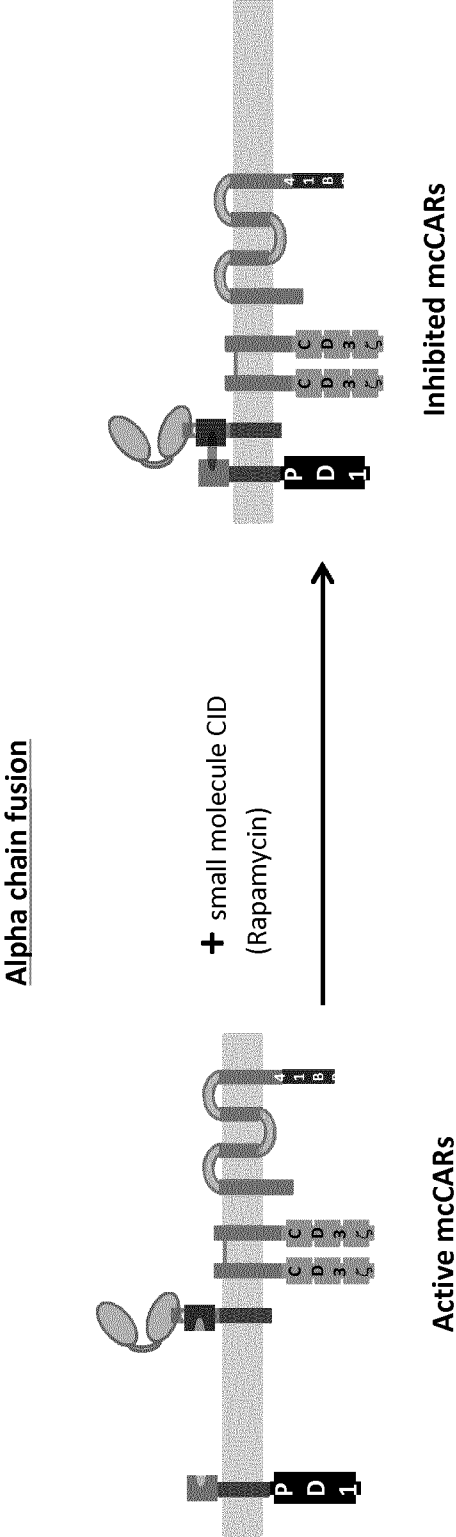


Figure 2A

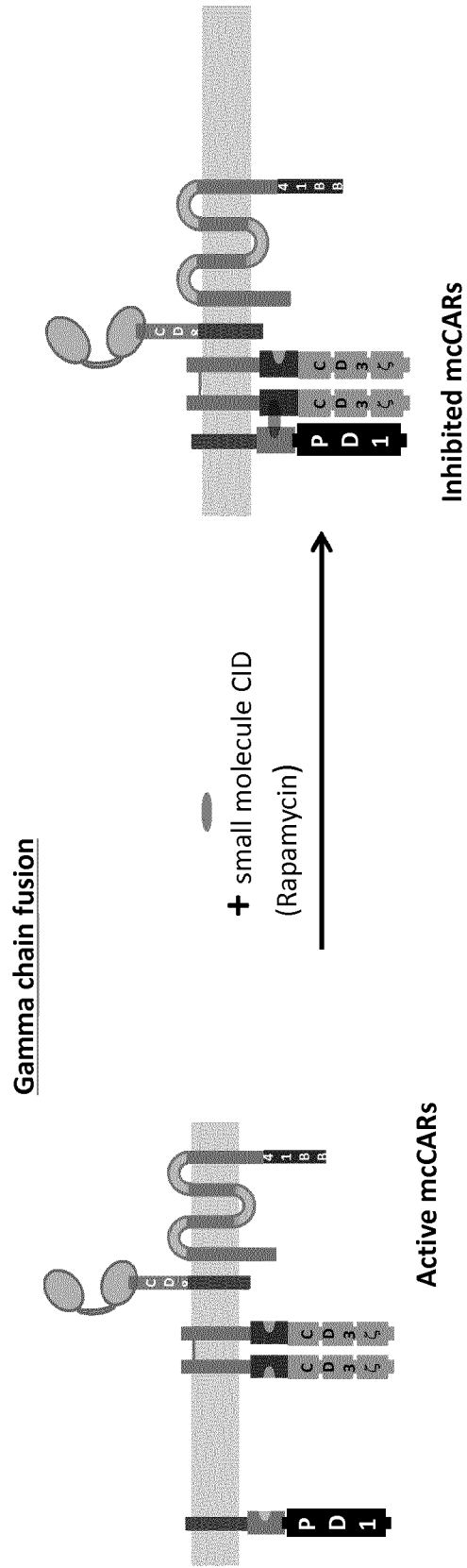


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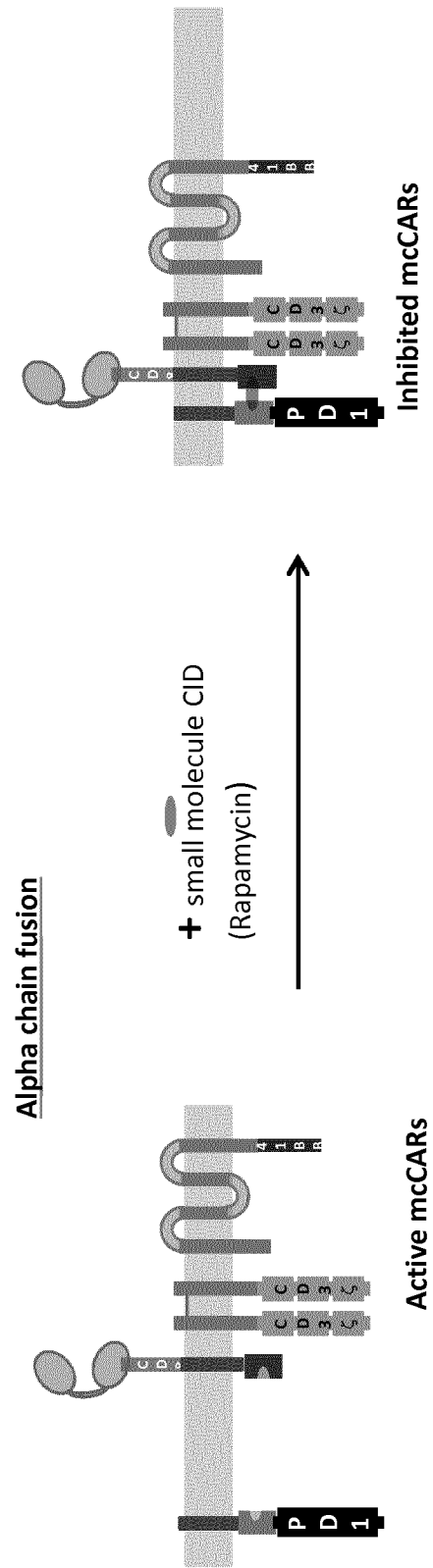


Figure 3

IL10R based chimera

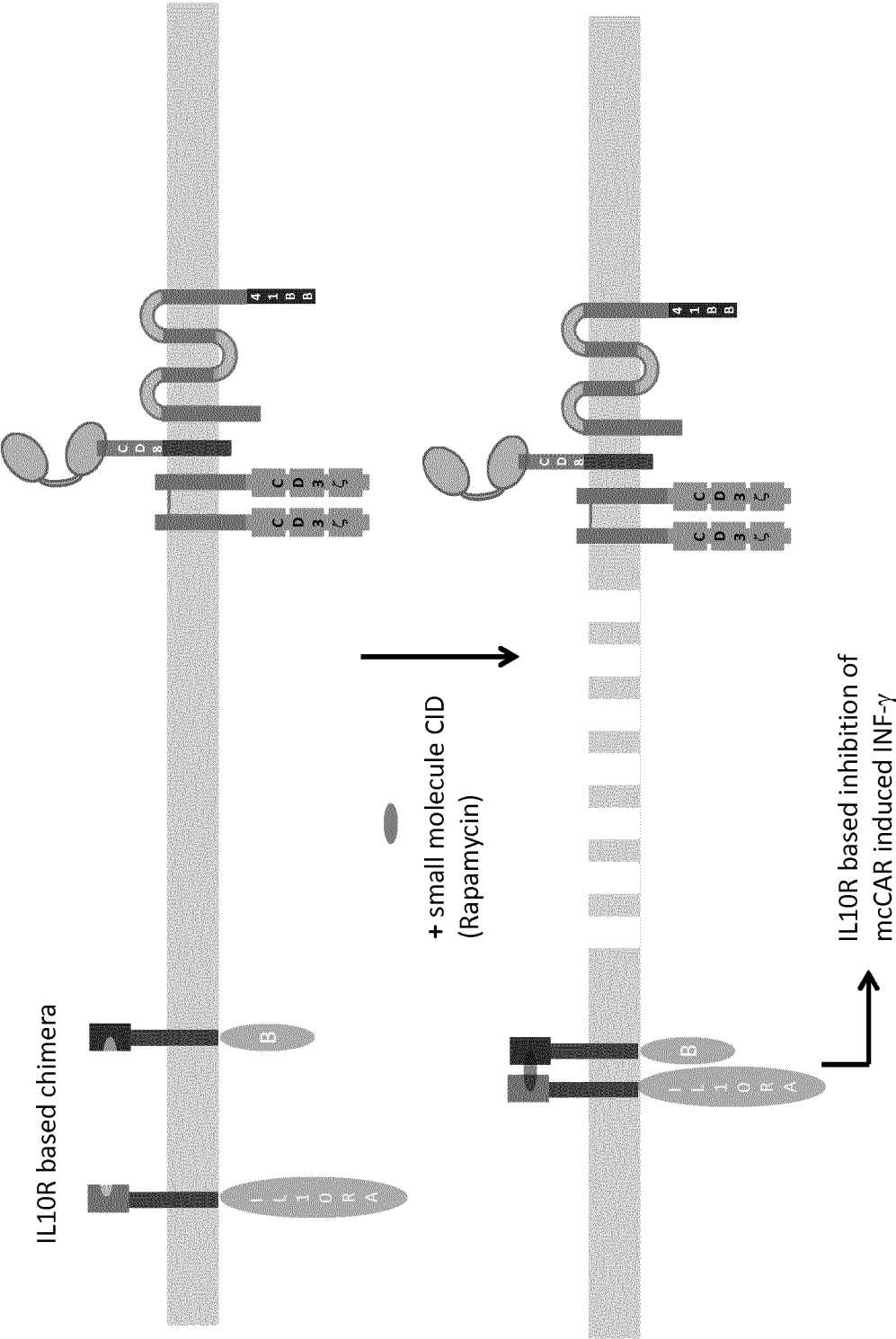


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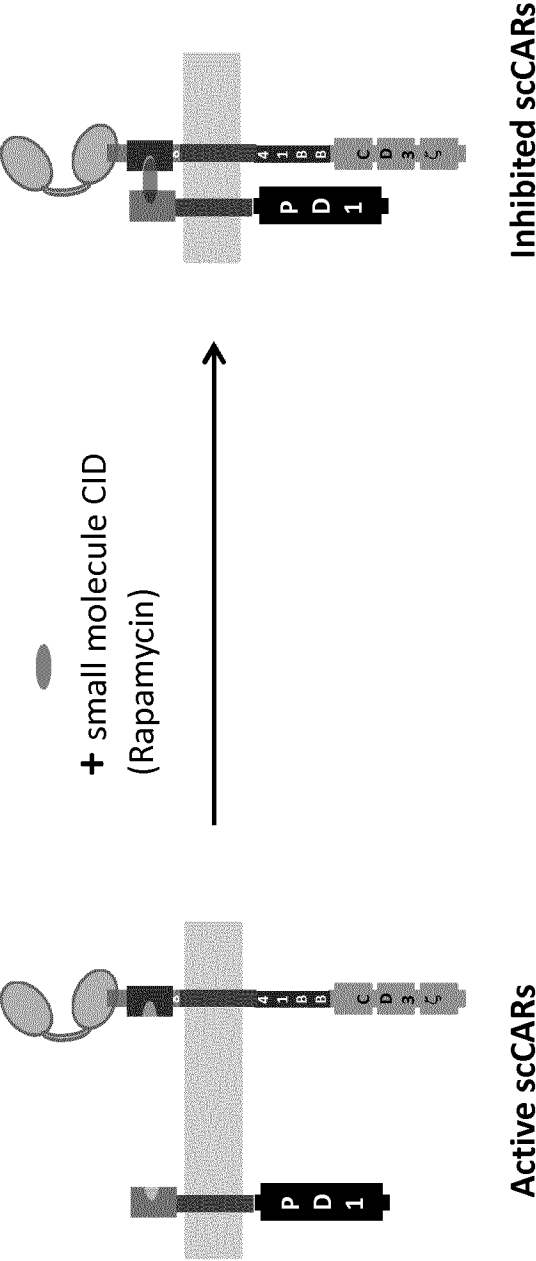
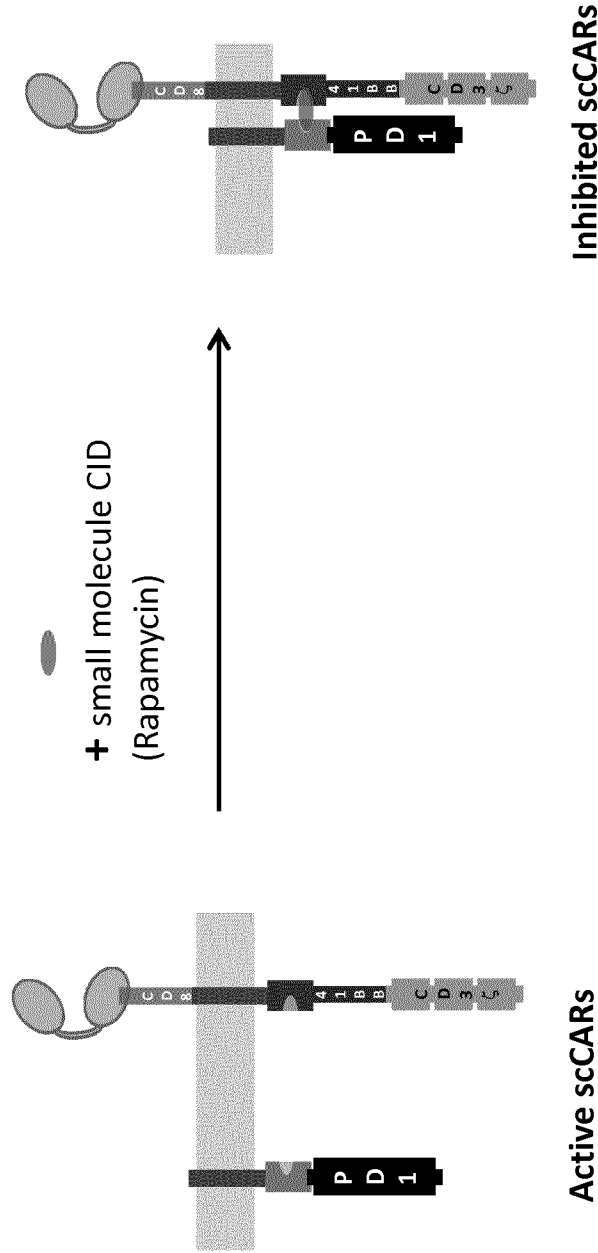


Figure 5



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Arg Gly Arg Thr Arg Tyr Thr Phe Ala Val Arg Ala Arg Met Ala Glu
65 70 75 80

Pro Ser Phe Gly Gly Phe Trp Ser Ala Trp Ser Glu Pro Val Ser Leu
85 90 95

Leu Thr Pro Ser Asp
100

<210> 9

<211> 53

<212> PRT

<213> artificial sequence

<220>

<223> Alpha-TI-A TM domain

<400> 9

Ile Phe Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly
1 5 10 15

Leu Phe Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys
20 25 30

Arg Thr Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn
35 40 45

Pro Lys Asn Asn Arg
50

<210> 10

<211> 98

<212> PRT

<213> artificial sequence

<220>

<223> Alpha-TI-B TM domain

<400> 10

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

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

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

Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly Leu Phe Ile
50 55 60

Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys Arg Thr Arg
65 70 75 80

eo1f-seq1

Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn Pro Lys Asn
85 90 95

Asn Arg

<210> 11

<211> 373

<212> PRT

<213> artificial sequence

<220>

<223> CD19 alpha chain

<400> 11

Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Glu Val Gln Leu Gln Gln Ser
20 25 30

Gly Pro Glu Leu Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln
50 55 60

Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn
65 70 75 80

Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
85 90 95

Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr
100 105 110

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr
115 120 125

Gly Ser Arg Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
130 135 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro
165 170 175

Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn
180 185 190

Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln

eo1f-seq1

195

200

205

Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val
210 215 220

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg
225 230 235 240

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
245 250 255

His Leu Glu Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
260 265 270

Lys Arg Ala Asp Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
275 280 285

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
290 295 300

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305 310 315 320

Asp Phe Phe Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr
325 330 335

Gly Leu Phe Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile
340 345 350

Lys Arg Thr Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro
355 360 365

Asn Pro Lys Asn Asn
370

<210> 12

<211> 257

<212> PRT

<213> artificial sequence

<220>

<223> beta-41BB chain

<400> 12

Met Asp Thr Glu Ser Asn Arg Arg Ala Asn Leu Ala Leu Pro Gln Glu
1 5 10 15

Pro Ser Ser Val Pro Ala Phe Glu Val Leu Glu Ile Ser Pro Gln Glu
20 25 30

Val Ser Ser Gly Arg Leu Leu Lys Ser Ala Ser Ser Pro Pro Leu His
35 40 45

eo1f-seq1

Thr Trp Leu Thr Val Leu Lys Lys Glu Gln Glu Phe Leu Gly Val Thr
50 55 60

Gln Ile Leu Thr Ala Met Ile Cys Leu Cys Phe Gly Thr Val Val Cys
65 70 75 80

Ser Val Leu Asp Ile Ser His Ile Glu Gly Asp Ile Phe Ser Ser Phe
85 90 95

Lys Ala Gly Tyr Pro Phe Trp Gly Ala Ile Phe Phe Ser Ile Ser Gly
100 105 110

Met Leu Ser Ile Ile Ser Glu Arg Arg Asn Ala Thr Tyr Leu Val Arg
115 120 125

Gly Ser Leu Gly Ala Asn Thr Ala Ser Ser Ile Ala Gly Gly Thr Gly
130 135 140

Ile Thr Ile Leu Ile Ile Asn Leu Lys Lys Ser Leu Ala Tyr Ile His
145 150 155 160

Ile His Ser Cys Gln Lys Phe Phe Glu Thr Lys Cys Phe Met Ala Ser
165 170 175

Phe Ser Thr Glu Ile Val Val Met Met Leu Phe Leu Thr Ile Leu Gly
180 185 190

Leu Gly Ser Ala Val Ser Leu Thr Ile Cys Gly Ala Gly Glu Glu Leu
195 200 205

Lys Gly Asn Lys Val Pro Glu Lys Arg Gly Arg Lys Lys Leu Leu Tyr
210 215 220

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
225 230 235 240

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
245 250 255

Leu

<210> 13

<211> 20

<212> PRT

<213> artificial sequence

<220>

<223> Sequence signal Gamma

<400> 13

Met Ala Ile Pro Ala Val Val Leu Leu Leu Leu Leu Val Glu Gln

eo1f-seq1
10

1 5 15

Ala Ala Ala Gly
20

<210> 14

<211> 114

<212> PRT

<213> homo sapiens

<220>

<223> FKBP

<400> 14

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

Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu
20 25 30

Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe
35 40 45

Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly
50 55 60

Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro
65 70 75 80

Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His
85 90 95

Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Gly Ser Gly
100 105 110

Ala Pro

<210> 15

<211> 102

<212> PRT

<213> homo sapiens

<220>

<223> FRB

<400> 15

Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly
1 5 10 15

Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly
20 25 30

Met Phe Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro

eo1f-seq1

35

40

45

Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu
50 55 60

Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val
65 70 75 80

Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg
85 90 95

Ile Gly Ser Gly Ala Pro
100

<210> 16

<211> 156

<212> PRT

<213> artificial sequence

<220>

<223> Gamma-TI-A

<400> 16

Ile Gly Glu Pro Gln Leu Cys Tyr Ile Leu Asp Ala Ile Leu Phe Leu
1 5 10 15

Tyr Gly Ile Val Leu Thr Leu Leu Tyr Cys Arg Leu Lys Ile Gln Val
20 25 30

Arg Lys Ala Ala Ile Thr Ser Tyr Glu Lys Ser Arg Val Lys Phe Ser
35 40 45

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
50 55 60

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
65 70 75 80

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
85 90 95

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
100 105 110

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
115 120 125

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
130 135 140

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Glu
145 150 155

eo1f-seq1

<210> 17

<211> 156

<212> PRT

<213> artificial sequence

<220>

<223> Gamma-TI-B

<400> 17

Leu Gly Glu Pro Gln Leu Cys Tyr Ile Leu Asp Ala Ile Leu Phe Leu
1 5 10 15

Tyr Gly Ile Val Leu Thr Leu Leu Tyr Cys Arg Leu Lys Ile Gln Val
20 25 30

Arg Lys Ala Ala Ile Thr Ser Tyr Glu Lys Ser Arg Val Lys Phe Ser
35 40 45

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
50 55 60

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
65 70 75 80

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
85 90 95

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
100 105 110

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
115 120 125

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
130 135 140

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Glu
145 150 155

<210> 18

<211> 22

<212> PRT

<213> artificial sequence

<220>

<223> VH-4G7-ss

<400> 18

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

His Ala Ala Arg Pro Gly
20

eo1f-seq1

<210> 19

<211> 25

<212> PRT

<213> homo sapiens

<220>

<223> CD8a TM

<400> 19

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

Ser Leu Val Ile Thr Leu Tyr Cys Arg
20 25

<210> 20

<211> 31

<212> PRT

<213> homo sapiens

<220>

<223> 4-1BB TM

<400> 20

Ile Ile Ser Phe Phe Leu Ala Leu Thr Ser Thr Ala Leu Leu Phe Leu
1 5 10 15

Leu Phe Phe Leu Thr Leu Arg Phe Ser Val Val Lys Arg Gly Arg
20 25 30

<210> 21

<211> 27

<212> PRT

<213> homo sapiens

<220>

<223> DAP10 TM

<400> 21

Ile Leu Leu Ala Gly Leu Val Ala Ala Asp Ala Val Ala Ser Leu Leu
1 5 10 15

Ile Val Gly Ala Val Phe Leu Cys Ala Arg Arg
20 25

<210> 22

<211> 33

<212> PRT

<213> homo sapiens

<220>

<223> CD28 TM

<400> 22

Ile Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
1 5 10 15

eo1f-seq1

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg
20 25 30

Arg

<210> 23

<211> 97

<212> PRT

<213> homo sapiens

<220>

<223> PD1 inhibitory signaling domain

<400> 23

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
1 5 10 15

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
20 25 30

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
35 40 45

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
50 55 60

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
65 70 75 80

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
85 90 95

Glu

<210> 24

<211> 110

<212> PRT

<213> homo sapiens

<220>

<223> FKBP_pos3_IMP

<400> 24

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

Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu
20 25 30

Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe
35 40 45

eo1f-seq1

Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly
50 55 60

Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro
65 70 75 80

Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His
85 90 95

Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Glu
100 105 110

<210> 25

<211> 98

<212> PRT

<213> homo sapiens

<220>

<223> FRB_pos3_IMP

<400> 25

Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly
1 5 10 15

Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly
20 25 30

Met Phe Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro
35 40 45

Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu
50 55 60

Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val
65 70 75 80

Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg
85 90 95

Ile Glu

<210> 26

<211> 45

<212> PRT

<213> homo sapiens

<220>

<223> CD28 linker

<400> 26

Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
1 5 10 15

eo1f-seq1

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
 20 25 30

Ala Ala Tyr Arg Ser Gly Ser Gly Ser Gly Ser Gly Ser
 35 40 45

<210> 27

<211> 48

<212> PRT

<213> homo sapiens

<220>

<223> 4-1BB linker

<400> 27

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

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

Glu Glu Glu Gly Gly Cys Glu Leu Gly Ser Gly Ser Gly Ser Gly Ser
 35 40 45

<210> 28

<211> 50

<212> PRT

<213> homo sapiens

<220>

<223> OX40 linker

<400> 28

Ala Leu Tyr Leu Leu Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His
 1 5 10 15

Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln
 20 25 30

Ala Asp Ala His Ser Thr Leu Ala Lys Ile Gly Ser Gly Ser Gly Ser
 35 40 45

Gly Ser
 50

<210> 29

<211> 28

<212> PRT

<213> homo sapiens

<220>

eo1f-seq1

<223> DAP10 linker

<400> 29

Pro Arg Arg Ser Pro Ala Gln Glu Asp Gly Lys Val Tyr Ile Asn Met
1 5 10 15

Pro Gly Arg Gly Gly Ser Gly Ser Gly Ser Gly Ser
20 25

<210> 30

<211> 54

<212> PRT

<213> homo sapiens

<220>

<223> CD18 linker

<400> 30

Lys Ala Leu Ile His Leu Ser Asp Leu Arg Glu Tyr Arg Arg Phe Glu
1 5 10 15

Lys Glu Lys Leu Lys Ser Gln Trp Asn Asn Asp Asn Pro Leu Phe Lys
20 25 30

Ser Ala Thr Thr Thr Val Met Asn Pro Lys Phe Ala Glu Ser Gly Ser
35 40 45

Gly Ser Gly Ser Gly Ser
50

<210> 31

<211> 49

<212> PRT

<213> homo sapiens

<220>

<223> CD28 linker

<400> 31

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
1 5 10 15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
20 25 30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Gly Ser Gly Ser Gly Ser Gly
35 40 45

Ser

<210> 32

<211> 33

<212> PRT

<213> homo sapiens

eo1f-seq1

<220>

<223> CD275 linker

<400> 32

Arg Asp Arg Cys Leu Gln His Ser Tyr Ala Gly Ala Trp Ala Val Ser
1 5 10 15

Pro Glu Thr Glu Leu Thr Gly His Val Gly Ser Gly Ser Gly Ser Gly
20 25 30

Ser

<210> 33

<211> 68

<212> PRT

<213> homo sapiens

<220>

<223> HVEM linker

<400> 33

Cys Val Lys Arg Arg Lys Pro Arg Gly Asp Val Val Lys Val Ile Val
1 5 10 15

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

Glu Ala Leu Gln Ala Pro Pro Asp Val Thr Thr Val Ala Val Glu Glu
35 40 45

Thr Ile Pro Ser Phe Thr Gly Arg Ser Pro Asn His Gly Ser Gly Ser
50 55 60

Gly Ser Gly Ser
65

<210> 34

<211> 45

<212> PRT

<213> homo sapiens

<220>

<223> LIGHT linker

<400> 34

Met Glu Glu Ser Val Val Arg Pro Ser Val Phe Val Val Asp Gly Gln
1 5 10 15

Thr Asp Ile Pro Phe Thr Arg Leu Gly Arg Ser His Arg Arg Gln Ser
20 25 30

Cys Ser Val Ala Arg Gly Ser Gly Ser Gly Ser Gly Ser
35 40 45

eo1f-seq1

<210> 35

<211> 30

<212> PRT

<213> homo sapiens

<220>

<223> CD40L linker

<400> 35

Met Ile Glu Thr Tyr Asn Gln Thr Ser Pro Arg Ser Ala Ala Thr Gly
1 5 10 15

Leu Pro Ile Ser Met Lys Gly Ser Gly Ser Gly Ser Gly Ser
20 25 30

<210> 36

<211> 66

<212> PRT

<213> homo sapiens

<220>

<223> GITR linker

<400> 36

Gln Leu Gly Leu His Ile Trp Gln Leu Arg Ser Gln Cys Met Trp Pro
1 5 10 15

Arg Glu Thr Gln Leu Leu Leu Glu Val Pro Pro Ser Thr Glu Asp Ala
20 25 30

Arg Ser Cys Gln Phe Pro Glu Glu Glu Arg Gly Glu Arg Ser Ala Glu
35 40 45

Glu Lys Gly Arg Leu Gly Asp Leu Trp Val Gly Ser Gly Ser Gly Ser
50 55 60

Gly Ser
65

<210> 37

<211> 56

<212> PRT

<213> homo sapiens

<220>

<223> TIM1 linker

<400> 37

Lys Lys Tyr Phe Phe Lys Lys Glu Val Gln Gln Leu Ser Val Ser Phe
1 5 10 15

Ser Ser Leu Gln Ile Lys Ala Leu Gln Asn Ala Val Glu Lys Glu Val
20 25 30

Gln Ala Glu Asp Asn Ile Tyr Ile Glu Asn Ser Leu Tyr Ala Thr Asp
Page 21

eo1f-seq1

35

40

45

Gly Ser Gly Ser Gly Ser Gly Ser
50 55

<210> 38

<211> 85

<212> PRT

<213> homo sapiens

<220>

<223> SLAM linker

<400> 38

Gln Leu Arg Arg Arg Gly Lys Thr Asn His Tyr Gln Thr Thr Val Glu
1 5 10 15

Lys Lys Ser Leu Thr Ile Tyr Ala Gln Val Gln Lys Pro Gly Pro Leu
20 25 30

Gln Lys Lys Leu Asp Ser Phe Pro Ala Gln Asp Pro Cys Thr Thr Ile
35 40 45

Tyr Val Ala Ala Thr Glu Pro Val Pro Glu Ser Val Gln Glu Thr Asn
50 55 60

Ser Ile Thr Val Tyr Ala Ser Val Thr Leu Pro Glu Ser Gly Ser Gly
65 70 75 80

Ser Gly Ser Gly Ser
85

<210> 39

<211> 124

<212> PRT

<213> homo sapiens

<220>

<223> CD2 linker

<400> 39

Lys Arg Lys Lys Gln Arg Ser Arg Arg Asn Asp Glu Glu Leu Glu Thr
1 5 10 15

Arg Ala His Arg Val Ala Thr Glu Glu Arg Gly Arg Lys Pro His Gln
20 25 30

Ile Pro Ala Ser Thr Pro Gln Asn Pro Ala Thr Ser Gln His Pro Pro
35 40 45

Pro Pro Pro Gly His Arg Ser Gln Ala Pro Ser His Arg Pro Pro Pro
50 55 60

Pro Gly His Arg Val Gln His Gln Pro Gln Lys Arg Pro Pro Ala Pro

65 70 75 80

self-seq1

Ser Gly Thr Gln Val₈₅ His Gln Gln Lys Gly₉₀ Pro Pro Leu Pro Arg₉₅ Pro

Arg Val Gln Pro₁₀₀ Lys Pro Pro His Gly₁₀₅ Ala Ala Glu Asn Ser₁₁₀ Leu Ser

Pro Ser Ser₁₁₅ Asn Gly Ser Gly Ser₁₂₀ Gly Ser Gly Ser

eo1f-seq1

<220>

<223> DAP12 linker

<400> 42

Tyr Phe Leu Gly Arg Leu Val Pro Arg Gly Arg Gly Ala Ala Glu Ala
1 5 10 15

Ala Thr Arg Lys Gln Arg Ile Thr Glu Thr Glu Ser Pro Tyr Gln Glu
20 25 30

Leu Gln Gly Gln Arg Ser Asp Val Tyr Ser Asp Leu Asn Thr Gln Arg
35 40 45

Pro Tyr Tyr Lys Gly Ser Gly Ser Gly Ser Gly Ser
50 55 60

<210> 43

<211> 107

<212> PRT

<213> homo sapiens

<220>

<223> CD84 linker

<400> 43

Arg Leu Phe Lys Arg Arg Gln Gly Arg Ile Phe Pro Glu Gly Ser Cys
1 5 10 15

Leu Asn Thr Phe Thr Lys Asn Pro Tyr Ala Ala Ser Lys Lys Thr Ile
20 25 30

Tyr Thr Tyr Ile Met Ala Ser Arg Asn Thr Gln Pro Ala Glu Ser Arg
35 40 45

Ile Tyr Asp Glu Ile Leu Gln Ser Lys Val Leu Pro Ser Lys Glu Glu
50 55 60

Pro Val Asn Thr Val Tyr Ser Glu Val Gln Phe Ala Asp Lys Met Gly
65 70 75 80

Lys Ala Ser Thr Gln Asp Ser Lys Pro Pro Gly Thr Ser Ser Tyr Glu
85 90 95

Ile Val Ile Gly Ser Gly Ser Gly Ser Gly Ser
100 105

<210> 44

<211> 113

<212> PRT

<213> homo sapiens

<220>

<223> CD244 linker

eo1f-seq1

<400> 44

Glu Phe Leu Thr Ile Tyr Glu Asp Val Lys Asp Leu Lys Thr Arg Arg
1 5 10 15

Asn His Glu Gln Glu Gln Thr Phe Pro Gly Gly Gly Ser Thr Ile Tyr
20 25 30

Ser Met Ile Gln Ser Gln Ser Ser Ala Pro Thr Ser Gln Glu Pro Ala
35 40 45

Tyr Thr Leu Tyr Ser Leu Ile Gln Pro Ser Arg Lys Ser Gly Ser Arg
50 55 60

Lys Arg Asn His Ser Pro Ser Phe Asn Ser Thr Ile Tyr Glu Val Ile
65 70 75 80

Gly Lys Ser Gln Pro Lys Ala Gln Asn Pro Ala Arg Leu Ser Arg Lys
85 90 95

Glu Leu Glu Asn Phe Asp Val Tyr Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser

<210> 45

<211> 157

<212> PRT

<213> homo sapiens

<220>

<223> CD229 linker

<400> 45

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

Arg Pro Ala Arg Gln Gln Pro Thr Pro Thr Ser Asp Ser Ser Ser Asp
20 25 30

Ser Asn Leu Thr Thr Glu Glu Asp Glu Asp Arg Pro Glu Val His Lys
35 40 45

Pro Ile Ser Gly Arg Tyr Glu Val Phe Asp Gln Val Thr Gln Glu Gly
50 55 60

Ala Gly His Asp Pro Ala Pro Glu Gly Gln Ala Asp Tyr Asp Pro Val
65 70 75 80

Thr Pro Tyr Val Thr Glu Val Glu Ser Val Val Gly Glu Asn Thr Met
85 90 95

Tyr Ala Gln Val Phe Asn Leu Gln Gly Lys Thr Pro Val Ser Gln Lys

eo1f-seq1

100

105

110

Glu Glu Ser Ser Ala Thr Ile Tyr Cys Ser Ile Arg Lys Pro Gln Val
115 120 125

Val Pro Pro Pro Gln Gln Asn Asp Leu Glu Ile Pro Glu Ser Pro Thr
130 135 140

Tyr Glu Asn Phe Thr Gly Ser Gly Ser Gly Ser Gly Ser
145 150 155

<210> 46

<211> 151

<212> PRT

<213> homo sapiens

<220>

<223> LTBR linker

<400> 46

Lys Ala His Pro Tyr Phe Pro Asp Leu Val Gln Pro Leu Leu Pro Ile
1 5 10 15

Ser Gly Asp Val Ser Pro Val Ser Thr Gly Leu Pro Ala Ala Pro Val
20 25 30

Leu Glu Ala Gly Val Pro Gln Gln Gln Ser Pro Leu Asp Leu Thr Arg
35 40 45

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

Asn Gly Ile His Val Thr Gly Gly Ser Met Thr Ile Thr Gly Asn Ile
65 70 75 80

Tyr Ile Tyr Asn Gly Pro Val Leu Gly Gly Pro Pro Gly Pro Gly Asp
85 90 95

Leu Pro Ala Thr Pro Glu Pro Pro Tyr Pro Ile Pro Glu Glu Gly Asp
100 105 110

Pro Gly Pro Pro Gly Leu Ser Thr Pro His Gln Glu Asp Gly Lys Ala
115 120 125

Trp His Leu Ala Glu Thr Glu His Cys Gly Ala Thr Pro Ser Asn Gly
130 135 140

Ser Gly Ser Gly Ser Gly Ser
145 150

<210> 47

<211> 110

eo1f-seq1

<212> PRT
<213> homo sapiens

<220>
<223> FKBP_pos5-ter-alpha

<400> 47
Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr
1 5 10 15

Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu
20 25 30

Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe
35 40 45

Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly
50 55 60

Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro
65 70 75 80

Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His
85 90 95

Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Glu
100 105 110

<210> 48

<211> 98
<212> PRT
<213> homo sapiens

<220>
<223> FRB_pos5-ter-alpha

<400> 48
Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly
1 5 10 15

Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly
20 25 30

Met Phe Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro
35 40 45

Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu
50 55 60

Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val
65 70 75 80

Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg
85 90 95

eo1f-seq1

Ile Glu

<210> 49

<211> 173

<212> PRT

<213> artificial sequence

<220>

<223> gamma-CD3z chain

<400> 49

Met Ile Pro Ala Val Val Leu Leu Leu Leu Leu Val Glu Gln Ala
1 5 10 15

Ala Ala Leu Gly Glu Pro Gln Leu Cys Tyr Ile Leu Asp Ala Ile Leu
20 25 30

Phe Leu Tyr Gly Ile Val Leu Thr Leu Leu Tyr Cys Arg Leu Lys Ile
35 40 45

Gln Val Arg Lys Ala Ala Ile Thr Ser Tyr Glu Lys Ser Arg Val Lys
50 55 60

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
65 70 75 80

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
85 90 95

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
100 105 110

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
115 120 125

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
130 135 140

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
145 150 155 160

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
165 170

<210> 50

<211> 101

<212> PRT

<213> homo sapiens

<220>

<223> PD1_pos3

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<400> 50
 Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
 1 5 10 15
 Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
 20 25 30
 Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
 35 40 45
 Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
 50 55 60
 Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
 65 70 75 80
 Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
 85 90 95
 Gly Ser Gly Ser Ser
 100

<210> 51

<211> 114

<212> PRT

<213> homo sapiens

<220>

<223> FKBP_pos4-IMP

<400> 51

Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr
 1 5 10 15
 Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu
 20 25 30
 Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe
 35 40 45
 Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly
 50 55 60
 Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro
 65 70 75 80
 Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His
 85 90 95
 Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Gly Ser Gly
 100 105 110
 Ser Gly

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<210> 52

<211> 102

<212> PRT

<213> homo sapiens

<220>

<223> FRB_pos4-IMP

<400> 52

Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly
1 5 10 15

Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly
20 25 30

Met Phe Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro
35 40 45

Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu
50 55 60

Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val
65 70 75 80

Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg
85 90 95

Ile Gly Ser Gly Ser Gly
100

<210> 53

<211> 97

<212> PRT

<213> homo sapiens

<220>

<223> PD1_pos5-ter

<400> 53

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
1 5 10 15

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
20 25 30

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
35 40 45

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
50 55 60

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
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75

65 70 80
Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
 85 90 95

Glu

<210> 54

<211> 110

<212> PRT

<213> homo sapiens

<220>

<223> FKBP_pos4-ter-IMP

<400> 54

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

Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu
 20 25 30

Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe
 35 40 45

Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly
 50 55 60

Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro
65 70 75 80

Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His
 85 90 95

Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Glu
 100 105 110

<210> 55

<211> 98

<212> PRT

<213> homo sapiens

<220>

<223> FRB_pos4-ter-IMP

<400> 55

Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly
1 5 10 15

Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly
 20 25 30

Met Phe Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro

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35

40

45

Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu
50 55 60

Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val
65 70 75 80

Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg
85 90 95

Ile Glu

<210> 56

<211> 101

<212> PRT

<213> homo sapiens

<220>

<223> PD1_pos4

<400> 56

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
1 5 10 15

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
20 25 30

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
35 40 45

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
50 55 60

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
65 70 75 80

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
85 90 95

Gly Ser Gly Ser Gly
100

<210> 57

<211> 108

<212> PRT

<213> homo sapiens

<220>

<223> FKBP_pos5-ter-IMP

<400> 57

Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro

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1 5 10 15

Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp
20 25 30

Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe
35 40 45

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

Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr
65 70 75 80

Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr
85 90 95

Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Glu
100 105

<210> 58

<211> 96

<212> PRT

<213> homo sapiens

<220>

<223> FRB_pos5-ter-IMP

<400> 58

Gly Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu
1 5 10 15

Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe
20 25 30

Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr
35 40 45

Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu
50 55 60

Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp
65 70 75 80

Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Glu
85 90 95

<210> 59

<211> 344

eo1f-seq1

<212> PRT
<213> homo sapiens

<220>
<223> IR-10RA inhibitory domain

<400> 59
Ile Val Ile Ile Phe Phe Ala Phe Val Leu Leu Leu Ser Gly Ala Leu
1 5 10 15

Ala Tyr Cys Leu Ala Leu Gln Leu Tyr Val Arg Arg Arg Lys Lys Leu
20 25 30

Pro Ser Val Leu Leu Phe Lys Lys Pro Ser Pro Phe Ile Phe Ile Ser
35 40 45

Gln Arg Pro Ser Pro Glu Thr Gln Asp Thr Ile His Pro Leu Asp Glu
50 55 60

Glu Ala Phe Leu Lys Val Ser Pro Glu Leu Lys Asn Leu Asp Leu His
65 70 75 80

Gly Ser Thr Asp Ser Gly Phe Gly Ser Thr Lys Pro Ser Leu Gln Thr
85 90 95

Glu Glu Pro Gln Phe Leu Leu Pro Asp Pro His Pro Gln Ala Asp Arg
100 105 110

Thr Leu Gly Asn Arg Glu Pro Pro Val Leu Gly Asp Ser Cys Ser Ser
115 120 125

Gly Ser Ser Asn Ser Thr Asp Ser Gly Ile Cys Leu Gln Glu Pro Ser
130 135 140

Leu Ser Pro Ser Thr Gly Pro Thr Trp Glu Gln Gln Val Gly Ser Asn
145 150 155 160

Ser Arg Gly Gln Asp Asp Ser Gly Ile Asp Leu Val Gln Asn Ser Glu
165 170 175

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

Pro Pro Glu Pro Glu Val Pro Gly Glu Glu Asp Pro Ala Ala Val Ala
195 200 205

Phe Gln Gly Tyr Leu Arg Gln Thr Arg Cys Ala Glu Glu Lys Ala Thr
210 215 220

Lys Thr Gly Cys Leu Glu Glu Glu Ser Pro Leu Thr Asp Gly Leu Gly
225 230 235 240

Pro Lys Phe Gly Arg Cys Leu Val Asp Glu Ala Gly Leu His Pro Pro
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eo1f-seq1
250

245

255

Ala Leu Ala Lys Gly Tyr Leu Lys Gln Asp Pro Leu Glu Met Thr Leu
260 265 270

Ala Ser Ser Gly Ala Pro Thr Gly Gln Trp Asn Gln Pro Thr Glu Glu
275 280 285

Trp Ser Leu Leu Ala Leu Ser Ser Cys Ser Asp Leu Gly Ile Ser Asp
290 295 300

Trp Ser Phe Ala His Asp Leu Ala Pro Leu Gly Cys Val Ala Ala Pro
305 310 315 320

Gly Gly Leu Leu Gly Ser Phe Asn Ser Asp Leu Val Thr Leu Pro Leu
325 330 335

Ile Ser Ser Leu Gln Ser Ser Glu
340

<210> 60

<211> 107

<212> PRT

<213> homo sapiens

<220>

<223> IR-10B inhibitory domain

<400> 60

Ile Trp Met Val Ala Val Ile Leu Met Ala Ser Val Phe Met Val Cys
1 5 10 15

Leu Ala Leu Leu Gly Cys Phe Ala Leu Leu Trp Cys Val Tyr Lys Lys
20 25 30

Thr Lys Tyr Ala Phe Ser Pro Arg Asn Ser Leu Pro Gln His Leu Lys
35 40 45

Glu Phe Leu Gly His Pro His His Asn Thr Leu Leu Phe Phe Ser Phe
50 55 60

Pro Leu Ser Asp Glu Asn Asp Val Phe Asp Lys Leu Ser Val Ile Ala
65 70 75 80

Glu Asp Ser Glu Ser Gly Lys Gln Asn Pro Gly Asp Ser Cys Ser Leu
85 90 95

Gly Thr Pro Pro Gly Gln Gly Pro Gln Ser Glu
100 105

<210> 61

<211> 303

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<212> PRT
<213> artificial sequence

<220>
<223> IMP-exCID-n°1

<400> 61
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gly Ser Gly Gly Val Gln Val Glu Thr Ile Ser
20 25 30

Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val
35 40 45

His Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg
50 55 60

Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile
65 70 75 80

Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala
85 90 95

Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro
100 105 110

Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu
115 120 125

Lys Leu Glu Gly Ser Gly Ala Pro Thr Thr Thr Pro Ala Pro Arg Pro
130 135 140

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
145 150 155 160

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
165 170 175

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
180 185 190

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Arg
195 200 205

Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro Leu Lys
210 215 220

Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly Glu Leu
225 230 235 240

Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro Cys Val

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245

250

255

Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly Met Gly
260 265 270

Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg Ser Ala
275 280 285

Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu Glu
290 295 300

<210> 62

<211> 485

<212> PRT

<213> artificial sequence

<220>

<223> IMP-exCID-n°2

<400> 62

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

His Ala Ala Arg Pro Gly Ser Gly Gly Arg Val Ala Ile Leu Trp His
20 25 30

Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly
35 40 45

Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala
50 55 60

Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln
65 70 75 80

Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr
85 90 95

Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr
100 105 110

Tyr His Val Phe Arg Arg Ile Gly Ser Gly Ala Pro Glu Pro Lys Ser
115 120 125

Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala
130 135 140

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
145 150 155 160

Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
165 170 175

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Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 180 185 190
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 195 200 205
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 210 215 220
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
 225 230 235 240
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 245 250 255
 Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
 260 265 270
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 275 280 285
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 290 295 300
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 305 310 315 320
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 325 330 335
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 340 345 350
 Pro Gly Lys Lys Asp Ile Ile Ser Phe Phe Leu Ala Leu Thr Ser Thr
 355 360 365
 Ala Leu Leu Phe Leu Leu Phe Phe Leu Thr Leu Arg Phe Ser Val Val
 370 375 380
 Lys Arg Gly Arg Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg
 385 390 395 400
 Thr Gly Gln Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser
 405 410 415
 Val Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu
 420 425 430
 Pro Pro Val Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val
 435 440 445

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Phe Pro Ser Gly Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala
450 455 460

Asp Gly Pro Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys
465 470 475 480

Ser Trp Pro Leu Glu
485

<210> 63

<211> 361

<212> PRT

<213> artificial sequence

<220>

<223> IMP-exCID-n°3

<400> 63

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

His Ala Ala Arg Pro Gly Ser Gly Gly Val Gln Val Glu Thr Ile Ser
20 25 30

Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val
35 40 45

His Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg
50 55 60

Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile
65 70 75 80

Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala
85 90 95

Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro
100 105 110

Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu
115 120 125

Lys Leu Glu Gly Ser Gly Ala Pro Ala Pro Val Gly Leu Val Ala Arg
130 135 140

Leu Ala Asp Glu Ser Gly His Val Val Leu Arg Trp Leu Pro Pro Pro
145 150 155 160

Glu Thr Pro Met Thr Ser His Ile Arg Tyr Glu Val Asp Val Ser Ala
165 170 175

Gly Asn Gly Ala Gly Ser Val Gln Arg Val Glu Ile Leu Glu Gly Arg

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180 185 190

Thr Glu Cys Val Leu Ser Asn Leu Arg Gly Arg Thr Arg Tyr Thr Phe
195 200 205

Ala Val Arg Ala Arg Met Ala Glu Pro Ser Phe Gly Gly Phe Trp Ser
210 215 220

Ala Trp Ser Glu Pro Val Ser Leu Leu Thr Pro Ser Asp Ile Leu Leu
225 230 235

Ala Gly Leu Val Ala Ala Asp Ala Val Ala Ser Leu Leu Ile Val Gly
245 250 255

Ala Val Phe Leu Cys Ala Arg Arg Ser Arg Ala Ala Arg Gly Thr Ile
260 265 270

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

Pro Val Phe Ser Val Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu
290 295 300

Lys Thr Pro Glu Pro Pro Val Pro Cys Val Pro Glu Gln Thr Glu Tyr
305 310 315 320

Ala Thr Ile Val Phe Pro Ser Gly Met Gly Thr Ser Ser Pro Ala Arg
325 330 335

Arg Gly Ser Ala Asp Gly Pro Arg Ser Ala Gln Pro Leu Arg Pro Glu
340 345 350

Asp Gly His Cys Ser Trp Pro Leu Glu
355 360

<210> 64
<211> 299
<212> PRT
<213> artificial sequence

<220>
<223> IMP-exCID-n°4

<400> 64
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gly Ser Gly Gly Arg Val Ala Ile Leu Trp His
20 25 30

Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly
35 40 45

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Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala
 50 55 60
 Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln
 65 70 75 80
 Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr
 85 90 95
 Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr
 100 105 110
 Tyr His Val Phe Arg Arg Ile Gly Ser Gly Ala Pro Thr Thr Thr Pro
 115 120 125
 Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
 130 135 140
 Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
 145 150 155 160
 Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Phe Trp Val Leu Val Val
 165 170 175
 Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe
 180 185 190
 Ile Ile Phe Trp Val Arg Ser Lys Arg Arg Ser Arg Ala Ala Arg Gly
 195 200 205
 Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro Leu Lys Glu Asp Pro Ser
 210 215 220
 Ala Val Pro Val Phe Ser Val Asp Tyr Gly Glu Leu Asp Phe Gln Trp
 225 230 235 240
 Arg Glu Lys Thr Pro Glu Pro Pro Val Pro Cys Val Pro Glu Gln Thr
 245 250 255
 Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly Met Gly Thr Ser Ser Pro
 260 265 270
 Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg Ser Ala Gln Pro Leu Arg
 275 280 285
 Pro Glu Asp Gly His Cys Ser Trp Pro Leu Glu
 290 295

<210> 65

<211> 335

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<212> PRT
<213> artificial sequence

<220>
<223> γ-mCCAR-exCID-n°1

<400> 65
Met Ala Ile Pro Ala Val Val Leu Leu Leu Leu Leu Val Glu Gln
1 5 10 15

Ala Ala Ala Gly Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly
20 25 30

Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr
35 40 45

Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg
50 55 60

Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly
65 70 75 80

Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu
85 90 95

Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile
100 105 110

Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu
115 120 125

Glu Gly Ser Gly Ala Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
130 135 140

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

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
165 170 175

Ala Cys Asp Ile Gly Glu Pro Gln Leu Cys Tyr Ile Leu Asp Ala Ile
180 185 190

Leu Phe Leu Tyr Gly Ile Val Leu Thr Leu Leu Tyr Cys Arg Leu Lys
195 200 205

Ile Gln Val Arg Lys Ala Ala Ile Thr Ser Tyr Glu Lys Ser Arg Val
210 215 220

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
225 230 235 240

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val

									eolf-seq1												
	245								250						255						
Leu	Asp	Lys	Arg 260	Arg	Gly	Arg	Asp	Pro 265	Glu	Met	Gly	Gly	Lys 270	Pro	Arg						
Arg	Lys	Asn 275	Pro	Gln	Glu	Gly	Leu 280	Tyr	Asn	Glu	Leu	Gln 285	Lys	Asp	Lys						
Met	Ala 290	Glu	Ala	Tyr	Ser	Glu 295	Ile	Gly	Met	Lys	Gly 300	Glu	Arg	Arg	Arg						
Gly 305	Lys	Gly	His	Asp	Gly 310	Leu	Tyr	Gln	Gly	Leu 315	Ser	Thr	Ala	Thr	Lys 320						
Asp	Thr	Tyr	Asp	Ala 325	Leu	His	Met	Gln	Ala 330	Leu	Pro	Pro	Arg	Glu 335							
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<212>	PRT																				
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<400>	66																				
Met 1	Ala	Ile	Pro	Ala 5	Val	Val	Leu	Leu	Leu 10	Leu	Leu	Leu	Val	Glu 15	Gln						
Ala	Ala	Ala	Gly 20	Ser	Gly	Gly	Arg	Val 25	Ala	Ile	Leu	Trp	His 30	Glu	Met						
Trp	His	Glu 35	Gly	Leu	Glu	Glu	Ala 40	Ser	Arg	Leu	Tyr	Phe 45	Gly	Glu	Arg						
Asn	Val 50	Lys	Gly	Met	Phe	Glu 55	Val	Leu	Glu	Pro	Leu 60	His	Ala	Met	Met						
Glu 65	Arg	Gly	Pro	Gln	Thr 70	Leu	Lys	Glu	Thr	Ser 75	Phe	Asn	Gln	Ala	Tyr 80						
Gly	Arg	Asp	Leu	Met 85	Glu	Ala	Gln	Glu	Trp 90	Cys	Arg	Lys	Tyr	Met 95	Lys						
Ser	Gly	Asn	Val 100	Lys	Asp	Leu	Thr	Gln 105	Ala	Trp	Asp	Leu	Tyr 110	Tyr	His						
Val	Phe	Arg 115	Arg	Ile	Gly	Ser	Gly 120	Ala	Pro	Glu	Pro	Lys 125	Ser	Pro	Asp						
Lys	Thr 130	His	Thr	Cys	Pro	Pro 135	Cys	Pro	Ala	Pro	Pro 140	Val	Ala	Gly	Pro						

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

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
165 170 175

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
180 185 190

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
195 200 205

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
210 215 220

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
225 230 235 240

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

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
260 265 270

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
275 280 285

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
290 295 300

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
305 310 315 320

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
325 330 335

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
340 345 350

Lys Lys Asp Ile Gly Glu Pro Gln Leu Cys Tyr Ile Leu Asp Ala Ile
355 360 365

Leu Phe Leu Tyr Gly Ile Val Leu Thr Leu Leu Tyr Cys Arg Leu Lys
370 375 380

Ile Gln Val Arg Lys Ala Ala Ile Thr Ser Tyr Glu Lys Ser Arg Val
385 390 395 400

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
405 410 415

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Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
420 425 430

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
435 440 445

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
450 455 460

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
465 470 475 480

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
485 490 495

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Glu
500 505 510

<210> 67

<211> 391

<212> PRT

<213> artificial sequence

<220>

<223> γ-mcCAR-exCID-n°3

<400> 67

Met Ala Ile Pro Ala Val Val Leu Leu Leu Leu Leu Val Glu Gln
1 5 10 15

Ala Ala Ala Gly Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly
20 25 30

Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr
35 40 45

Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg
50 55 60

Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly
65 70 75 80

Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu
85 90 95

Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile
100 105 110

Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu
115 120 125

Glu Gly Ser Gly Ala Pro Ala Pro Val Gly Leu Val Ala Arg Leu Ala

eo1f-seq1
140

130

135

Asp Glu Ser Gly His Val Val Leu Arg Trp Leu Pro Pro Pro Glu Thr
145 150 155 160

Pro Met Thr Ser His Ile Arg Tyr Glu Val Asp Val Ser Ala Gly Asn
165 170 175

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

Cys Val Leu Ser Asn Leu Arg Gly Arg Thr Arg Tyr Thr Phe Ala Val
195 200 205

Arg Ala Arg Met Ala Glu Pro Ser Phe Gly Gly Phe Trp Ser Ala Trp
210 215 220

Ser Glu Pro Val Ser Leu Leu Thr Pro Ser Asp Ile Gly Glu Pro Gln
225 230 235 240

Leu Cys Tyr Ile Leu Asp Ala Ile Leu Phe Leu Tyr Gly Ile Val Leu
245 250 255

Thr Leu Leu Tyr Cys Arg Leu Lys Ile Gln Val Arg Lys Ala Ala Ile
260 265 270

Thr Ser Tyr Glu Lys Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
275 280 285

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
290 295 300

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

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

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

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

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

Gln Ala Leu Pro Pro Arg Glu
385 390

<210> 68

eo1f-seq1

<211> 323
 <212> PRT
 <213> artificial sequence

<220>
 <223> γ-mcCAR-exCID-n°4

<400> 68
 Met Ala Ile Pro Ala Val Val Leu Leu Leu Leu Leu Val Glu Gln
 1 5 10 15
 Ala Ala Ala Gly Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu Met
 20 25 30
 Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg
 35 40 45
 Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala Met Met
 50 55 60
 Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr
 65 70 75 80
 Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys
 85 90 95
 Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His
 100 105 110
 Val Phe Arg Arg Ile Gly Ser Gly Ala Pro Thr Thr Thr Pro Ala Pro
 115 120 125
 Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
 130 135 140
 Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
 145 150 155 160
 Gly Leu Asp Phe Ala Cys Asp Ile Gly Glu Pro Gln Leu Cys Tyr Ile
 165 170 175
 Leu Asp Ala Ile Leu Phe Leu Tyr Gly Ile Val Leu Thr Leu Leu Tyr
 180 185 190
 Cys Arg Leu Lys Ile Gln Val Arg Lys Ala Ala Ile Thr Ser Tyr Glu
 195 200 205
 Lys Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
 210 215 220
 Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
 225 230 235 240

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Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
245 250 255

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
260 265 270

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
275 280 285

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
290 295 300

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
305 310 315 320

Pro Arg Glu

<210> 69

<211> 290

<212> PRT

<213> artificial sequence

<220>

<223> γ-mCCAR-exCID-n°5

<400> 69

Met Ala Ile Pro Ala Val Val Leu Leu Leu Leu Leu Val Glu Gln
1 5 10 15

Ala Ala Ala Gly Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly
20 25 30

Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr
35 40 45

Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg
50 55 60

Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly
65 70 75 80

Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu
85 90 95

Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile
100 105 110

Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu
115 120 125

Glu Gly Ser Gly Ala Pro Leu Gly Glu Pro Gln Leu Cys Tyr Ile Leu

eo1f-seq1
140

130

135

Asp Ala Ile Leu Phe Leu Tyr Gly Ile Val Leu Thr Leu Leu Tyr Cys
145 150 155 160

Arg Leu Lys Ile Gln Val Arg Lys Ala Ala Ile Thr Ser Tyr Glu Lys
165 170 175

Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
180 185 190

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
195 200 205

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
210 215 220

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
225 230 235 240

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
245 250 255

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
260 265 270

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
275 280 285

Arg Glu
290

<210> 70

<211> 278

<212> PRT

<213> artificial sequence

<220>

<223> γ-mCCAR-exCID-n°6

<400> 70

Met Ala Ile Pro Ala Val Val Leu Leu Leu Leu Leu Val Glu Gln
1 5 10 15

Ala Ala Ala Gly Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu Met
20 25 30

Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg
35 40 45

Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala Met Met
50 55 60

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Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr
65 70 75 80

Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys
85 90 95

Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His
100 105 110

Val Phe Arg Arg Ile Gly Ser Gly Ala Pro Leu Gly Glu Pro Gln Leu
115 120 125

Cys Tyr Ile Leu Asp Ala Ile Leu Phe Leu Tyr Gly Ile Val Leu Thr
130 135 140

Leu Leu Tyr Cys Arg Leu Lys Ile Gln Val Arg Lys Ala Ala Ile Thr
145 150 155 160

Ser Tyr Glu Lys Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
165 170 175

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
180 185 190

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
195 200 205

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
210 215 220

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
225 230 235 240

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
245 250 255

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
260 265 270

Ala Leu Pro Pro Arg Glu
275

<210> 71

<211> 546

<212> PRT

<213> artificial sequence

<220>

<223> alpha-mcCAR-exCID-n°1

<400> 71

Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
Page 50

10

1					5					10					15
Phe	Phe	Ala	Pro 20	Asp	Gly	Val	Leu	Ala 25	Glu	Val	Gln	Leu	Gln 30	Gln	Ser
Gly	Pro	Glu 35	Leu	Ile	Lys	Pro	Gly 40	Ala	Ser	Val	Lys	Met 45	Ser	Cys	Lys
Ala	Ser 50	Gly	Tyr	Thr	Phe	Thr 55	Ser	Tyr	Val	Met	His 60	Trp	Val	Lys	Gln
Lys 65	Pro	Gly	Gln	Gly	Leu 70	Glu	Trp	Ile	Gly	Tyr 75	Ile	Asn	Pro	Tyr	Asn 80
Asp	Gly	Thr	Lys	Tyr 85	Asn	Glu	Lys	Phe	Lys 90	Gly	Lys	Ala	Thr	Leu 95	Thr
Ser	Asp	Lys	Ser 100	Ser	Ser	Thr	Ala	Tyr 105	Met	Glu	Leu	Ser	Ser 110	Leu	Thr
Ser	Glu	Asp 115	Ser	Ala	Val	Tyr	Tyr 120	Cys	Ala	Arg	Gly	Thr 125	Tyr	Tyr	Tyr
Gly	Ser 130	Arg	Val	Phe	Asp	Tyr 135	Trp	Gly	Gln	Gly	Thr 140	Thr	Leu	Thr	Val
Ser 145	Ser	Gly	Gly	Gly	Gly 150	Ser	Gly	Gly	Gly	Gly 155	Ser	Gly	Gly	Gly	Gly 160
Ser	Asp	Ile	Val	Met 165	Thr	Gln	Ala	Ala	Pro 170	Ser	Ile	Pro	Val	Thr 175	Pro
Gly	Glu	Ser	Val 180	Ser	Ile	Ser	Cys	Arg 185	Ser	Ser	Lys	Ser	Leu 190	Leu	Asn
Ser	Asn	Gly 195	Asn	Thr	Tyr	Leu	Tyr 200	Trp	Phe	Leu	Gln	Arg 205	Pro	Gly	Gln
Ser	Pro 210	Gln	Leu	Leu	Ile	Tyr 215	Arg	Met	Ser	Asn	Leu 220	Ala	Ser	Gly	Val
Pro 225	Asp	Arg	Phe	Ser	Gly 230	Ser	Gly	Ser	Gly	Thr 235	Ala	Phe	Thr	Leu	Arg 240
Ile	Ser	Arg	Val	Glu 245	Ala	Glu	Asp	Val	Gly 250	Val	Tyr	Tyr	Cys	Met 255	Gln
His	Leu	Glu	Tyr 260	Pro	Phe	Thr	Phe	Gly 265	Ala	Gly	Thr	Lys	Leu 270	Glu	Leu
Lys	Arg	Ser	Asp	Pro	Gly	Ser	Gly	Gly	Val	Gln	Val	Glu	Thr	Ile	Ser

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275

280

285

Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val
 290 295 300

His Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg
 305 310 315 320

Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile
 325 330 335

Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala
 340 345 350

Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro
 355 360 365

Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu
 370 375 380

Lys Leu Glu Gly Ser Gly Ala Pro Ala Pro Val Gly Leu Val Ala Arg
 385 390 395 400

Leu Ala Asp Glu Ser Gly His Val Val Leu Arg Trp Leu Pro Pro Pro
 405 410 415

Glu Thr Pro Met Thr Ser His Ile Arg Tyr Glu Val Asp Val Ser Ala
 420 425 430

Gly Asn Gly Ala Gly Ser Val Gln Arg Val Glu Ile Leu Glu Gly Arg
 435 440 445

Thr Glu Cys Val Leu Ser Asn Leu Arg Gly Arg Thr Arg Tyr Thr Phe
 450 455 460

Ala Val Arg Ala Arg Met Ala Glu Pro Ser Phe Gly Gly Phe Trp Ser
 465 470 475 480

Ala Trp Ser Glu Pro Val Ser Leu Leu Thr Pro Ser Asp Ile Phe Ile
 485 490 495

Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly Leu Phe Ile
 500 505 510

Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys Arg Thr Arg
 515 520 525

Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn Pro Lys Asn
 530 535 540

Asn Glu

eo1f-seq1

545

<210> 72

<211> 534

<212> PRT

<213> artificial sequence

<220>

<223> alpha-mcCAR-exCID-n°2

<400> 72

Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Glu Val Gln Leu Gln Gln Ser
20 25 30

Gly Pro Glu Leu Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln
50 55 60

Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn
65 70 75 80

Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
85 90 95

Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr
100 105 110

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr
115 120 125

Gly Ser Arg Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
130 135 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro
165 170 175

Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn
180 185 190

Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln
195 200 205

Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val
210 215 220

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Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg
 225 230 235 240
 Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
 245 250 255
 His Leu Glu Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
 260 265 270
 Lys Arg Ser Asp Pro Gly Ser Gly Gly Arg Val Ala Ile Leu Trp His
 275 280 285
 Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly
 290 295 300
 Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala
 305 310 315 320
 Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln
 325 330 335
 Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr
 340 345 350
 Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr
 355 360 365
 Tyr His Val Phe Arg Arg Ile Gly Ser Gly Ala Pro Ala Pro Val Gly
 370 375 380
 Leu Val Ala Arg Leu Ala Asp Glu Ser Gly His Val Val Leu Arg Trp
 385 390 395 400
 Leu Pro Pro Pro Glu Thr Pro Met Thr Ser His Ile Arg Tyr Glu Val
 405 410 415
 Asp Val Ser Ala Gly Asn Gly Ala Gly Ser Val Gln Arg Val Glu Ile
 420 425 430
 Leu Glu Gly Arg Thr Glu Cys Val Leu Ser Asn Leu Arg Gly Arg Thr
 435 440 445
 Arg Tyr Thr Phe Ala Val Arg Ala Arg Met Ala Glu Pro Ser Phe Gly
 450 455 460
 Gly Phe Trp Ser Ala Trp Ser Glu Pro Val Ser Leu Leu Thr Pro Ser
 465 470 475 480
 Asp Ile Phe Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr
 485 490 495

eo1f-seq1

Gly Leu Phe Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile
500 505 510

Lys Arg Thr Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro
515 520 525

Asn Pro Lys Asn Asn Glu
530

<210> 73

<211> 678

<212> PRT

<213> artificial sequence

<220>

<223> alpha-mcCAR-exCID-n°3

<400> 73

Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Glu Val Gln Leu Gln Gln Ser
20 25 30

Gly Pro Glu Leu Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln
50 55 60

Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn
65 70 75 80

Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
85 90 95

Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr
100 105 110

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr
115 120 125

Gly Ser Arg Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
130 135 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro
165 170 175

Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn

eo1f-seq1

180

185

190

Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln
195 200 205

Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val
210 215 220

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg
225 230 235 240

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
245 250 255

His Leu Glu Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
260 265 270

Lys Arg Ser Asp Pro Gly Ser Gly Gly Val Gln Val Glu Thr Ile Ser
275 280 285

Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val
290 295 300

His Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg
305 310 315 320

Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile
325 330 335

Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala
340 345 350

Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro
355 360 365

Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu
370 375 380

Lys Leu Glu Gly Ser Gly Ala Pro Glu Pro Lys Ser Pro Asp Lys Thr
385 390 395 400

His Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
405 410 415

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr
420 425 430

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
435 440 445

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys

eolf-seql

450 455 460

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
465 470 475 480

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 485 490 495

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
 500 505 510

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

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 530 535 540

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
545 550 555 560

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 565 570 575

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 580 585 590

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 595 600 605

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Lys
610 615 620

Asp Ile Phe Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr
625 630 635 640

Gly Leu Phe Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile
 645 650 655

Lys Arg Thr Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro
 660 665 670

Asn Pro Lys Asn Asn Glu
675

<210> 74

<211> 666

<212> PRT

<213> artificial sequence

<220>

<223> alpha-mcCAR-exCID-n°4

eo1f-seq1

<400> 74

Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Glu Val Gln Leu Gln Gln Ser
20 25 30

Gly Pro Glu Leu Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln
50 55 60

Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn
65 70 75 80

Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
85 90 95

Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr
100 105 110

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr
115 120 125

Gly Ser Arg Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
130 135 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro
165 170 175

Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn
180 185 190

Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln
195 200 205

Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val
210 215 220

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg
225 230 235 240

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
245 250 255

His Leu Glu Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
260 265 270

eo1f-seq1

Lys Arg Ser Asp Pro Gly Ser Gly Gly Arg Val Ala Ile Leu Trp His
 275 280 285
 Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly
 290 295 300
 Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala
 305 310 315 320
 Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln
 325 330 335
 Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr
 340 345 350
 Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr
 355 360 365
 Tyr His Val Phe Arg Arg Ile Gly Ser Gly Ala Pro Glu Pro Lys Ser
 370 375 380
 Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala
 385 390 395 400
 Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 405 410 415
 Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 420 425 430
 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 435 440 445
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 450 455 460
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 465 470 475 480
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
 485 490 495
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 500 505 510
 Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
 515 520 525
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 530 535 540

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Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
545 550 555 560

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
565 570 575

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
580 585 590

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
595 600 605

Pro Gly Lys Lys Asp Ile Phe Ile Pro Leu Leu Val Val Ile Leu Phe
610 615 620

Ala Val Asp Thr Gly Leu Phe Ile Ser Thr Gln Gln Gln Val Thr Phe
625 630 635 640

Leu Leu Lys Ile Lys Arg Thr Arg Lys Gly Phe Arg Leu Leu Asn Pro
645 650 655

His Pro Lys Pro Asn Pro Lys Asn Asn Glu
660 665

<210> 75

<211> 490

<212> PRT

<213> artificial sequence

<220>

<223> alpha-mcCAR-exCID-n°5

<400> 75

Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Glu Val Gln Leu Gln Gln Ser
20 25 30

Gly Pro Glu Leu Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln
50 55 60

Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn
65 70 75 80

Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
85 90 95

Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr
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100

105

110

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr
115 120 125

Gly Ser Arg Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
130 135 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro
165 170 175

Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn
180 185 190

Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln
195 200 205

Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val
210 215 220

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg
225 230 235 240

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
245 250 255

His Leu Glu Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
260 265 270

Lys Arg Ser Asp Pro Gly Ser Gly Gly Val Gln Val Glu Thr Ile Ser
275 280 285

Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val
290 295 300

His Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg
305 310 315 320

Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile
325 330 335

Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala
340 345 350

Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro
355 360 365

Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu

eo1f-seq1 380

370

375

Lys Leu Glu Gly Ser Gly Ala Pro Thr Thr Thr Pro Ala Pro Arg Pro
385 390 395 400

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
405 410 415

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

Asp Phe Ala Cys Asp Phe Phe Ile Pro Leu Leu Val Val Ile Leu Phe
435 440 445

Ala Val Asp Thr Gly Leu Phe Ile Ser Thr Gln Gln Gln Val Thr Phe
450 455 460

Leu Leu Lys Ile Lys Arg Thr Arg Lys Gly Phe Arg Leu Leu Asn Pro
465 470 475 480

His Pro Lys Pro Asn Pro Lys Asn Asn Glu
485 490

<210> 76

<211> 478

<212> PRT

<213> artificial sequence

<220>

<223> alpha-mcCAR-exCID-n°6

<400> 76

Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Glu Val Gln Leu Gln Gln Ser
20 25 30

Gly Pro Glu Leu Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln
50 55 60

Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn
65 70 75 80

Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
85 90 95

Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr
100 105 110

eo1f-seq1

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr
115 120 125

Gly Ser Arg Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
130 135 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro
165 170 175

Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn
180 185 190

Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln
195 200 205

Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val
210 215 220

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg
225 230 235 240

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
245 250 255

His Leu Glu Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
260 265 270

Lys Arg Ser Asp Pro Gly Ser Gly Gly Arg Val Ala Ile Leu Trp His
275 280 285

Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly
290 295 300

Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala
305 310 315 320

Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln
325 330 335

Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr
340 345 350

Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr
355 360 365

Tyr His Val Phe Arg Arg Ile Gly Ser Gly Ala Pro Thr Thr Thr Pro
370 375 380

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Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
385 390 395 400

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
405 410 415

Thr Arg Gly Leu Asp Phe Ala Cys Asp Phe Phe Ile Pro Leu Leu Val
420 425 430

Val Ile Leu Phe Ala Val Asp Thr Gly Leu Phe Ile Ser Thr Gln Gln
435 440 445

Gln Val Thr Phe Leu Leu Lys Ile Lys Arg Thr Arg Lys Gly Phe Arg
450 455 460

Leu Leu Asn Pro His Pro Lys Pro Asn Pro Lys Asn Asn Glu
465 470 475

<210> 77

<211> 608

<212> PRT

<213> artificial sequence

<220>

<223> CD123-sccAR extra CID n°1

<400> 77

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

His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu
20 25 30

Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ile Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys
50 55 60

Ser Phe Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly Glu Ser Thr
65 70 75 80

Tyr Ser Ala Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser
85 90 95

Ala Ser Thr Ala Tyr Leu His Ile Asn Asp Leu Lys Asn Glu Asp Thr
100 105 110

Ala Thr Tyr Phe Cys Ala Arg Ser Gly Gly Tyr Asp Pro Met Asp Tyr
115 120 125

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser

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140

130

135

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln
145 150 155 160

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

Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Asn Thr Phe Met His
180 185 190

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg
195 200 205

Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly
210 215 220

Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu Ala Asp Asp
225 230 235 240

Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Glu Asp Pro Pro Thr Phe
245 250 255

Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro Gly Ser Gly
260 265 270

Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro
275 280 285

Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp
290 295 300

Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe
305 310 315 320

Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala
325 330 335

Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr
340 345 350

Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr
355 360 365

Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Gly Ser Gly Ala Pro
370 375 380

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
385 390 395 400

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly

eol f-seq1															
405						410						415			
Gly	Ala	Val	His 420	Thr	Arg	Gly	Leu	Asp 425	Phe	Ala	Cys	Asp	Ile 430	Tyr	Ile
Trp	Ala	Pro 435	Leu	Ala	Gly	Thr	Cys 440	Gly	Val	Leu	Leu	Leu 445	Ser	Leu	Val
Ile	Thr 450	Leu	Tyr	Cys	Arg	Arg 455	Gly	Arg	Lys	Lys	Leu 460	Leu	Tyr	Ile	Phe
Lys 465	Gln	Pro	Phe	Met	Arg 470	Pro	Val	Gln	Thr	Thr 475	Gln	Glu	Glu	Asp	Gly 480
Cys	Ser	Cys	Arg	Phe 485	Pro	Glu	Glu	Glu	Glu 490	Gly	Gly	Cys	Glu	Leu 495	Arg
Val	Lys	Phe	Ser 500	Arg	Ser	Ala	Asp	Ala 505	Pro	Ala	Tyr	Gln	Gln 510	Gly	Gln
Asn	Gln	Leu 515	Tyr	Asn	Glu	Leu	Asn 520	Leu	Gly	Arg	Arg	Glu 525	Glu	Tyr	Asp
Val	Leu 530	Asp	Lys	Arg	Arg	Gly 535	Arg	Asp	Pro	Glu	Met 540	Gly	Gly	Lys	Pro
Arg 545	Arg	Lys	Asn	Pro	Gln 550	Glu	Gly	Leu	Tyr	Asn 555	Glu	Leu	Gln	Lys	Asp 560
Lys	Met	Ala	Glu	Ala 565	Tyr	Ser	Glu	Ile	Gly 570	Met	Lys	Gly	Glu	Arg 575	Arg
Arg	Gly	Lys	Gly 580	His	Asp	Gly	Leu	Tyr 585	Gln	Gly	Leu	Ser	Thr 590	Ala	Thr
Lys	Asp	Thr 595	Tyr	Asp	Ala	Leu	His 600	Met	Gln	Ala	Leu	Pro 605	Pro	Arg	Glu

<210>	78
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<212>	PRT
<213>	artificial sequence

<211> 596

<211>	350
<212>	PRT

<213> artificial sequence

$\langle 220 \rangle$

<223> CD123-scCAR extra CID n°2

<400> 78

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

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His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu
20 25 30

Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ile Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys
50 55 60

Ser Phe Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly Glu Ser Thr
65 70 75 80

Tyr Ser Ala Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser
85 90 95

Ala Ser Thr Ala Tyr Leu His Ile Asn Asp Leu Lys Asn Glu Asp Thr
100 105 110

Ala Thr Tyr Phe Cys Ala Arg Ser Gly Gly Tyr Asp Pro Met Asp Tyr
115 120 125

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser
130 135 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln
145 150 155 160

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

Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Asn Thr Phe Met His
180 185 190

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg
195 200 205

Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly
210 215 220

Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu Ala Asp Asp
225 230 235 240

Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Glu Asp Pro Pro Thr Phe
245 250 255

Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro Gly Ser Gly
260 265 270

Gly Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu
275 280 285

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Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe
 290 295 300
 Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr
 305 310 315 320
 Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu
 325 330 335
 Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp
 340 345 350
 Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Gly
 355 360 365
 Ser Gly Ala Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
 370 375 380
 Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
 385 390 395 400
 Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
 405 410 415
 Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
 420 425 430
 Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Arg Gly Arg Lys Lys Leu
 435 440 445
 Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
 450 455 460
 Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Gly
 465 470 475 480
 Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
 485 490 495
 Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
 500 505 510
 Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
 515 520 525
 Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
 530 535 540
 Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
 545 550 555 560

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Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
565 570 575

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
580 585 590

Pro Pro Arg Glu
595

<210> 79

<211> 796

<212> PRT

<213> artificial sequence

<220>

<223> CD123-sccAR extra CID n°3

<400> 79

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

His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu
20 25 30

Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ile Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys
50 55 60

Ser Phe Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly Glu Ser Thr
65 70 75 80

Tyr Ser Ala Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser
85 90 95

Ala Ser Thr Ala Tyr Leu His Ile Asn Asp Leu Lys Asn Glu Asp Thr
100 105 110

Ala Thr Tyr Phe Cys Ala Arg Ser Gly Gly Tyr Asp Pro Met Asp Tyr
115 120 125

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser
130 135 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln
145 150 155 160

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

Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Asn Thr Phe Met His
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180		185		190
Trp	Tyr	Gln	Gln	Lys
		195		
			Pro	Gly
				200
			Pro	Pro
			Lys	Leu
				205
			Ile	Tyr
			Arg	
Ala	Ser	Asn	Leu	Glu
	210			
			Ser	Gly
				215
			Ile	Pro
			Ala	Arg
				220
			Ser	Gly
			Ser	Gly
Ser	Arg	Thr	Asp	Phe
225				
			Thr	230
			Leu	Thr
			Ile	Asn
				235
			Pro	Val
			Glu	Ala
			Asp	Asp
				240
Val	Ala	Thr	Tyr	Tyr
				245
			Cys	Gln
			Gln	Ser
				250
			Asn	Glu
			Asp	Pro
			Pro	Thr
				255
			Phe	
Gly	Ala	Gly	Thr	Lys
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			Leu	Glu
			Leu	Lys
				265
			Arg	Ser
			Asp	Pro
				270
			Ser	Gly
Gly	Val	Gln	Val	Glu
				275
			Thr	Ile
				280
			Ser	Pro
			Gly	Asp
			Gly	Arg
				285
			Thr	Phe
				Pro
Lys	Arg	Gly	Gln	Thr
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			Cys	Val
				295
			Val	His
			Tyr	Thr
				300
			Gly	Met
				Leu
			Glu	Asp
Gly	Lys	Lys	Phe	Asp
305				
			Ser	Ser
				310
			Arg	Asp
			Arg	Asn
				315
			Lys	Pro
			Phe	Lys
				320
Met	Leu	Gly	Lys	Gln
				325
			Glu	Val
			Ile	Arg
				330
			Trp	Glu
			Glu	Gly
				335
			Val	Ala
Gln	Met	Ser	Val	Gly
				340
			Gln	Arg
			Ala	Lys
				345
			Leu	Thr
			Ile	Ser
				350
			Asp	Tyr
Ala	Tyr	Gly	Ala	Thr
				355
			Thr	Gly
			His	Pro
				360
			Gly	Ile
			Ile	Pro
				365
			His	Ala
				Thr
Leu	Val	Phe	Asp	Val
				370
			Glu	Leu
				375
			Leu	Lys
			Leu	Glu
				380
			Ser	Gly
			Ala	Pro
Glu	Pro	Lys	Ser	Pro
385				
			Asp	Lys
				390
			Thr	His
				395
			Cys	Pro
			Pro	Cys
				400
Pro	Pro	Val	Ala	Gly
				405
			Ser	Val
				410
			Phe	Leu
				415
			Pro	Pro
			Lys	Pro
				420
Asp	Thr	Leu	Met	Ile
				425
			Ala	Arg
			Thr	Pro
				430
			Glu	Val
			Thr	Cys
				435
			Val	Val
				440
Asp	Val	Ser	His	Glu
				445
			Asp	Pro
				450
			Glu	Val
			Lys	Phe
				455
			Asn	Trp
				460
			Tyr	Val
				465
			Asp	
Gly	Val	Glu	Val	His
				470
			Asn	Ala
				475
			Lys	Thr
				480
			Lys	Pro
			Arg	Glu
				485
			Glu	Gln
				490
			Tyr	

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460

450

455

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
465 470 475 480

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
485 490 495

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
500 505 510

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
515 520 525

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
530 535 540

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
545 550 555 560

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
565 570 575

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
580 585 590

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
595 600 605

Leu Ser Leu Ser Pro Gly Lys Lys Asp Ile Tyr Ile Trp Ala Pro Leu
610 615 620

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
625 630 635 640

Cys Arg Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
645 650 655

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
660 665 670

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
675 680 685

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
690 695 700

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
705 710 715 720

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn

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730

725

735

Pro Gln Glu Gly₇₄₀ Leu Tyr Asn Glu₇₄₅ Leu Gln Lys Asp Lys Met₇₅₀ Ala Glu

Ala Tyr Ser₇₅₅ Glu Ile Gly Met₇₆₀ Lys Gly Glu Arg Arg₇₆₅ Arg Gly Lys Gly

His Asp₇₇₀ Gly Leu Tyr Gln Gly₇₇₅ Leu Ser Thr Ala Thr₇₈₀ Lys Asp Thr Tyr

Asp₇₈₅ Ala Leu His Met Gln₇₉₀ Ala Leu Pro Pro Arg₇₉₅ Glu

<210> 80

<211> 784

<212> PRT

<213> artificial sequence

<220>

<223> CD123-sccAR extra CID n°4

<400> 80

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His Ala Ala Arg₂₀ Pro Gln Ile Gln₂₅ Leu Val Gln Ser Gly₃₀ Pro Glu Leu

Lys Lys Pro₃₅ Gly Glu Thr Val₄₀ Lys Ile Ser Cys Lys₄₅ Ala Ser Gly Tyr

Ile Phe₅₀ Thr Asn Tyr Gly₅₅ Met Asn Trp Val Lys₆₀ Gln Ala Pro Gly Lys

Ser₆₅ Phe Lys Trp Met₇₀ Gly Trp Ile Asn Thr₇₅ Tyr Thr Gly Glu Ser₈₀ Thr

Tyr Ser Ala Asp₈₅ Phe Lys Gly Arg Phe₉₀ Ala Phe Ser Leu Glu Thr₉₅ Ser

Ala Ser Thr₁₀₀ Ala Tyr Leu His Ile₁₀₅ Asn Asp Leu Lys Asn₁₁₀ Glu Asp Thr

Ala Thr Tyr₁₁₅ Phe Cys Ala Arg₁₂₀ Ser Gly Gly Tyr Asp₁₂₅ Pro Met Asp Tyr

Trp Gly₁₃₀ Gln Gly Thr Ser Val₁₃₅ Thr Val Ser Ser₁₄₀ Gly Gly Gly Gly Ser

Gly₁₄₅ Gly Gly Gly Ser₁₅₀ Gly Gly Gly Gly Ser₁₅₅ Asp Ile Val Leu Thr₁₆₀ Gln

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Ser Pro Ala Ser Leu₁₆₅ Ala Val Ser Leu Gly₁₇₀ Gln Arg Ala Thr Ile₁₇₅ Ser

Cys Arg Ala Ser₁₈₀ Glu Ser Val Asp Asn₁₈₅ Tyr Gly Asn Thr Phe₁₉₀ Met His

Trp Tyr Gln₁₉₅ Gln Lys Pro Gly Gln₂₀₀ Pro Pro Lys Leu Leu₂₀₅ Ile Tyr Arg

Ala Ser₂₁₀ Asn Leu Glu Ser Gly₂₁₅ Ile Pro Ala Arg Phe₂₂₀ Ser Gly Ser Gly

Ser₂₂₅ Arg Thr Asp Phe Thr₂₃₀ Leu Thr Ile Asn Pro₂₃₅ Val Glu Ala Asp Asp₂₄₀

Val Ala Thr Tyr Tyr₂₄₅ Cys Gln Gln Ser Asn₂₅₀ Glu Asp Pro Pro Thr₂₅₅ Phe

Gly Ala Gly Thr₂₆₀ Lys Leu Glu Leu Lys₂₆₅ Arg Ser Asp Pro Gly₂₇₀ Ser Gly

Gly Arg Val₂₇₅ Ala Ile Leu Trp His₂₈₀ Glu Met Trp His Glu₂₈₅ Gly Leu Glu

Glu Ala₂₉₀ Ser Arg Leu Tyr Phe₂₉₅ Gly Glu Arg Asn Val₃₀₀ Lys Gly Met Phe

Glu₃₀₅ Val Leu Glu Pro Leu₃₁₀ His Ala Met Met Glu₃₁₅ Arg Gly Pro Gln Thr₃₂₀

Leu Lys Glu Thr Ser₃₂₅ Phe Asn Gln Ala Tyr₃₃₀ Gly Arg Asp Leu Met₃₃₅ Glu

Ala Gln Glu Trp₃₄₀ Cys Arg Lys Tyr Met₃₄₅ Lys Ser Gly Asn Val₃₅₀ Lys Asp

Leu Thr Gln₃₅₅ Ala Trp Asp Leu Tyr₃₆₀ Tyr His Val Phe Arg₃₆₅ Arg Ile Gly

Ser Gly₃₇₀ Ala Pro Glu Pro Lys₃₇₅ Ser Pro Asp Lys Thr₃₈₀ His Thr Cys Pro

Pro₃₈₅ Cys Pro Ala Pro Pro₃₉₀ Val Ala Gly Pro Ser₃₉₅ Val Phe Leu Phe Pro₄₀₀

Pro Lys Pro Lys Asp₄₀₅ Thr Leu Met Ile Ala₄₁₀ Arg Thr Pro Glu Val₄₁₅ Thr

Cys Val Val₄₂₀ Val Asp Val Ser His Glu₄₂₅ Asp Pro Glu Val Lys₄₃₀ Phe Asn

eo1f-seq1

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
435 440 445

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
450 455 460

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
465 470 475 480

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
485 490 495

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
500 505 510

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
515 520 525

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
530 535 540

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
545 550 555 560

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
565 570 575

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
580 585 590

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Lys Asp Ile Tyr Ile
595 600 605

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
610 615 620

Ile Thr Leu Tyr Cys Arg Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
625 630 635 640

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
645 650 655

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
660 665 670

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
675 680 685

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
690 695 700

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Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
705 710 715 720

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
725 730 735

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
740 745 750

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
755 760 765

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Glu
770 775 780

<210> 81

<211> 664

<212> PRT

<213> artificial sequence

<220>

<223> CD123-sccAR extra CID n°5

<400> 81

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His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu
20 25 30

Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ile Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys
50 55 60

Ser Phe Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly Glu Ser Thr
65 70 75 80

Tyr Ser Ala Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser
85 90 95

Ala Ser Thr Ala Tyr Leu His Ile Asn Asp Leu Lys Asn Glu Asp Thr
100 105 110

Ala Thr Tyr Phe Cys Ala Arg Ser Gly Gly Tyr Asp Pro Met Asp Tyr
115 120 125

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser

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140

130

135

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln
145 150 155 160

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

Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Asn Thr Phe Met His
180 185 190

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg
195 200 205

Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly
210 215 220

Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu Ala Asp Asp
225 230 235 240

Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Glu Asp Pro Pro Thr Phe
245 250 255

Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro Gly Ser Gly
260 265 270

Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro
275 280 285

Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp
290 295 300

Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe
305 310 315 320

Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala
325 330 335

Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr
340 345 350

Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr
355 360 365

Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Gly Ser Gly Ala Pro
370 375 380

Ala Pro Val Gly Leu Val Ala Arg Leu Ala Asp Glu Ser Gly His Val
385 390 395 400

Val Leu Arg Trp Leu Pro Pro Pro Glu Thr Pro Met Thr Ser His Ile

eo1f-seq1

405

410

415

Arg Tyr Glu Val Asp Val Ser Ala Gly Asn Gly Ala Gly Ser Val Gln
420 425 430

Arg Val Glu Ile Leu Glu Gly Arg Thr Glu Cys Val Leu Ser Asn Leu
435 440 445

Arg Gly Arg Thr Arg Tyr Thr Phe Ala Val Arg Ala Arg Met Ala Glu
450 455 460

Pro Ser Phe Gly Gly Phe Trp Ser Ala Trp Ser Glu Pro Val Ser Leu
465 470 475 480

Leu Thr Pro Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
485 490 495

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

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

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

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

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
565 570 575

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

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

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

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
625 630 635 640

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

Met Gln Ala Leu Pro Pro Arg Glu
660

<210> 82

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<211> 652
 <212> PRT
 <213> artificial sequence

<220>
 <223> CD123-sccAR extra CID n°6

<400> 82
 Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
 1 5 10 15

His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu
 20 25 30

Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
 35 40 45

Ile Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys
 50 55 60

Ser Phe Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly Glu Ser Thr
 65 70 75 80

Tyr Ser Ala Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser
 85 90 95

Ala Ser Thr Ala Tyr Leu His Ile Asn Asp Leu Lys Asn Glu Asp Thr
 100 105 110

Ala Thr Tyr Phe Cys Ala Arg Ser Gly Gly Tyr Asp Pro Met Asp Tyr
 115 120 125

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser
 130 135 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln
 145 150 155 160

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

Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Asn Thr Phe Met His
 180 185 190

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg
 195 200 205

Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly
 210 215 220

Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu Ala Asp Asp
 225 230 235 240

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Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Glu Asp Pro Pro Thr Phe
 245 250 255
 Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro Gly Ser Gly
 260 265 270
 Gly Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu
 275 280 285
 Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe
 290 295 300
 Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr
 305 310 315 320
 Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu
 325 330 335
 Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp
 340 345 350
 Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Gly
 355 360 365
 Ser Gly Ala Pro Ala Pro Val Gly Leu Val Ala Arg Leu Ala Asp Glu
 370 375 380
 Ser Gly His Val Val Leu Arg Trp Leu Pro Pro Pro Glu Thr Pro Met
 385 390 395 400
 Thr Ser His Ile Arg Tyr Glu Val Asp Val Ser Ala Gly Asn Gly Ala
 405 410 415
 Gly Ser Val Gln Arg Val Glu Ile Leu Glu Gly Arg Thr Glu Cys Val
 420 425 430
 Leu Ser Asn Leu Arg Gly Arg Thr Arg Tyr Thr Phe Ala Val Arg Ala
 435 440 445
 Arg Met Ala Glu Pro Ser Phe Gly Gly Phe Trp Ser Ala Trp Ser Glu
 450 455 460
 Pro Val Ser Leu Leu Thr Pro Ser Asp Ile Tyr Ile Trp Ala Pro Leu
 465 470 475 480
 Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
 485 490 495
 Cys Arg Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
 500 505 510

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Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
515 520 525

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
530 535 540

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
545 550 555 560

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
565 570 575

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
580 585 590

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
595 600 605

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
610 615 620

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
625 630 635 640

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Glu
645 650

<210> 83

<211> 260

<212> PRT

<213> artificial sequence

<220>

<223> IMP-intCID-n°1

<400> 83

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg
50 55 60

Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met
65 70 75 80

Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro

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90

85

95

Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu
100 105 110

Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser
115 120 125

Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro
130 135 140

His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Gly Ser
145 150 155 160

Gly Ser Ser Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr
165 170 175

Gly Gln Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val
180 185 190

Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro
195 200 205

Pro Val Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe
210 215 220

Pro Ser Gly Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp
225 230 235 240

Gly Pro Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser
245 250 255

Trp Pro Leu Glu
260

<210> 84

<211> 248

<212> PRT

<213> artificial sequence

<220>

<223> IMP-intCID-n°2

<400> 84

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

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Arg Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu
50 55 60

Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys
65 70 75 80

Gly Met Phe Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly
85 90 95

Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp
100 105 110

Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn
115 120 125

Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg
130 135 140

Arg Ile Gly Ser Gly Ser Ser Ser Arg Ala Ala Arg Gly Thr Ile Gly
145 150 155 160

Ala Arg Arg Thr Gly Gln Pro Leu Lys Glu Asp Pro Ser Ala Val Pro
165 170 175

Val Phe Ser Val Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys
180 185 190

Thr Pro Glu Pro Pro Val Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala
195 200 205

Thr Ile Val Phe Pro Ser Gly Met Gly Thr Ser Ser Pro Ala Arg Arg
210 215 220

Gly Ser Ala Asp Gly Pro Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp
225 230 235 240

Gly His Cys Ser Trp Pro Leu Glu
245

<210> 85

<211> 310

<212> PRT

<213> artificial sequence

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<223> IMP-intCID-n°3

<400> 85

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
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20

25

30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Ala Leu Tyr Leu Leu Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala
50 55 60

His Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu
65 70 75 80

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

Ser Gly Ser Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp
100 105 110

Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr
115 120 125

Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn
130 135 140

Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp
145 150 155 160

Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr
165 170 175

Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile
180 185 190

Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu
195 200 205

Gly Ser Gly Ser Gly Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg
210 215 220

Arg Thr Gly Gln Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe
225 230 235 240

Ser Val Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro
245 250 255

Glu Pro Pro Val Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile
260 265 270

Val Phe Pro Ser Gly Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser
275 280 285

Ala Asp Gly Pro Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His

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300

290

295

Cys Ser Trp Pro Leu Glu
305 310

<210> 86

<211> 288

<212> PRT

<213> artificial sequence

<220>

<223> IMP-intCID-n°4

<400> 86

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Pro Arg Arg Ser Pro Ala Gln Glu Asp Gly Lys Val Tyr Ile Asn
50 55 60

Met Pro Gly Arg Gly Gly Ser Gly Ser Gly Ser Gly Ser Ser Gly Gly
65 70 75 80

Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys
85 90 95

Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp Gly
100 105 110

Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met
115 120 125

Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln
130 135 140

Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala
145 150 155 160

Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu
165 170 175

Val Phe Asp Val Glu Leu Leu Lys Leu Glu Gly Ser Gly Ser Gly Ser
180 185 190

Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro Leu
195 200 205

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Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly Glu
210 215 220

Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro Cys
225 230 235 240

Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly Met
245 250 255

Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg Ser
260 265 270

Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu Glu
275 280 285

<210> 87

<211> 328

<212> PRT

<213> artificial sequence

<220>

<223> IMP-intCID-n°5

<400> 87

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Cys Val Lys Arg Arg Lys Pro Arg Gly Asp Val Val Lys Val Ile
50 55 60

Val Ser Val Gln Arg Lys Arg Gln Glu Ala Glu Gly Glu Ala Thr Val
65 70 75 80

Ile Glu Ala Leu Gln Ala Pro Pro Asp Val Thr Thr Val Ala Val Glu
85 90 95

Glu Thr Ile Pro Ser Phe Thr Gly Arg Ser Pro Asn His Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro
115 120 125

Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His

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140

130

135

Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp
145 150 155 160

Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg
165 170 175

Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys
180 185 190

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

Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys
210 215 220

Leu Glu Gly Ser Gly Ser Gly Ser Arg Ala Ala Arg Gly Thr Ile Gly
225 230 235 240

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

Val Phe Ser Val Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys
260 265 270

Thr Pro Glu Pro Pro Val Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala
275 280 285

Thr Ile Val Phe Pro Ser Gly Met Gly Thr Ser Ser Pro Ala Arg Arg
290 295 300

Gly Ser Ala Asp Gly Pro Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp
305 310 315 320

Gly His Cys Ser Trp Pro Leu Glu
325

<210> 88

<211> 298

<212> PRT

<213> artificial sequence

<220>

<223> IMP-intCID-n°6

<400> 88

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

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Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Ala Leu Tyr Leu Leu Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala
50 55 60

His Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu
65 70 75 80

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

Ser Gly Ser Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu Met Trp
100 105 110

His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn
115 120 125

Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala Met Met Glu
130 135 140

Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly
145 150 155 160

Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser
165 170 175

Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val
180 185 190

Phe Arg Arg Ile Gly Ser Gly Ser Gly Ser Arg Ala Ala Arg Gly Thr
195 200 205

Ile Gly Ala Arg Arg Thr Gly Gln Pro Leu Lys Glu Asp Pro Ser Ala
210 215 220

Val Pro Val Phe Ser Val Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg
225 230 235 240

Glu Lys Thr Pro Glu Pro Pro Val Pro Cys Val Pro Glu Gln Thr Glu
245 250 255

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

Arg Arg Gly Ser Ala Asp Gly Pro Arg Ser Ala Gln Pro Leu Arg Pro
275 280 285

Glu Asp Gly His Cys Ser Trp Pro Leu Glu
290 295

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<210> 89

<211> 276

<212> PRT

<213> artificial sequence

<220>

<223> IMP-intCID-n°7

<400> 89

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Pro Arg Arg Ser Pro Ala Gln Glu Asp Gly Lys Val Tyr Ile Asn
50 55 60

Met Pro Gly Arg Gly Gly Ser Gly Ser Gly Ser Gly Ser Ser Gly Gly
65 70 75 80

Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu Glu
85 90 95

Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu
100 105 110

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

Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala
130 135 140

Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu
145 150 155 160

Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Gly Ser
165 170 175

Gly Ser Gly Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr
180 185 190

Gly Gln Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val
195 200 205

Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro
210 215 220

Pro Val Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe
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Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met
180 185 190

Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr
195 200 205

His Val Phe Arg Arg Ile Gly Ser Gly Ser Gly Ser Arg Ala Ala Arg
210 215 220

Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro Leu Lys Glu Asp Pro
225 230 235 240

Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly Glu Leu Asp Phe Gln
245 250 255

Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro Cys Val Pro Glu Gln
260 265 270

Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly Met Gly Thr Ser Ser
275 280 285

Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg Ser Ala Gln Pro Leu
290 295 300

Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu Glu
305 310 315

<210> 91

<211> 260

<212> PRT

<213> artificial sequence

<220>

<223> IMP-intCID-n°9

<400> 91

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln
50 55 60

Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr
65 70 75 80

Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val

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90

85

95

Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser
100 105 110

Gly Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro
115 120 125

Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro
130 135 140

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

Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val
165 170 175

His Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg
180 185 190

Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile
195 200 205

Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala
210 215 220

Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro
225 230 235 240

Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu
245 250 255

Lys Leu Glu Glu
260

<210> 92

<211> 248

<212> PRT

<213> artificial sequence

<220>

<223> IMP-intCID-n°10

<400> 92

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

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Arg Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln
50 55 60

Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr
65 70 75 80

Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val
85 90 95

Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser
100 105 110

Gly Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro
115 120 125

Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro
130 135 140

Leu Gly Ser Gly Ser Ser Ser Gly Gly Arg Val Ala Ile Leu Trp His
145 150 155 160

Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly
165 170 175

Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala
180 185 190

Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln
195 200 205

Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr
210 215 220

Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr
225 230 235 240

Tyr His Val Phe Arg Arg Ile Glu
245

<210> 93

<211> 308

<212> PRT

<213> artificial sequence

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<223> IMP-intCID-n°11

<400> 93

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
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20

25

30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Ala Leu Tyr Leu Leu Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala
50 55 60

His Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu
65 70 75 80

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

Ser Gly Ser Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr
100 105 110

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

Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro
130 135 140

Pro Val Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe
145 150 155 160

Pro Ser Gly Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp
165 170 175

Gly Pro Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser
180 185 190

Trp Pro Leu Gly Ser Gly Ser Gly Gly Val Gln Val Glu Thr Ile Ser
195 200 205

Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val
210 215 220

His Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg
225 230 235 240

Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile
245 250 255

Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala
260 265 270

Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro
275 280 285

Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu

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300

290

295

Lys Leu Glu Glu
305

<210> 94

<211> 286

<212> PRT

<213> artificial sequence

<220>

<223> IMP-intCID-n°12

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Pro Arg Arg Ser Pro Ala Gln Glu Asp Gly Lys Val Tyr Ile Asn
50 55 60

Met Pro Gly Arg Gly Gly Ser Gly Ser Gly Ser Gly Ser Ser Arg Ala
65 70 75 80

Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro Leu Lys Glu
85 90 95

Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly Glu Leu Asp
100 105 110

Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro Cys Val Pro
115 120 125

Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly Met Gly Thr
130 135 140

Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg Ser Ala Gln
145 150 155 160

Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu Gly Ser Gly
165 170 175

Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr
180 185 190

Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu
195 200 205

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Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe
210 215 220

Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly
225 230 235 240

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

Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His
260 265 270

Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Glu
275 280 285

<210> 95

<211> 326

<212> PRT

<213> artificial sequence

<220>

<223> IMP-intCID-n°13

<400> 95

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Cys Val Lys Arg Arg Lys Pro Arg Gly Asp Val Val Lys Val Ile
50 55 60

Val Ser Val Gln Arg Lys Arg Gln Glu Ala Glu Gly Glu Ala Thr Val
65 70 75 80

Ile Glu Ala Leu Gln Ala Pro Pro Asp Val Thr Thr Val Ala Val Glu
85 90 95

Glu Thr Ile Pro Ser Phe Thr Gly Arg Ser Pro Asn His Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg
115 120 125

Arg Thr Gly Gln Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe
130 135 140

Ser Val Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro

eo1f-seq1

Arg Ala Leu Tyr Leu Leu Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala
50 55 60

His Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu
65 70 75 80

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

Ser Gly Ser Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr
100 105 110

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

Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro
130 135 140

Pro Val Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe
145 150 155 160

Pro Ser Gly Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp
165 170 175

Gly Pro Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser
180 185 190

Trp Pro Leu Gly Ser Gly Ser Gly Gly Arg Val Ala Ile Leu Trp His
195 200 205

Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly
210 215 220

Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala
225 230 235 240

Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln
245 250 255

Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr
260 265 270

Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr
275 280 285

Tyr His Val Phe Arg Arg Ile Glu
290 295

<210> 97

<211> 274

eo1f-seq1

<212> PRT
<213> artificial sequence

<220>
<223> IMP-intCID-n°15

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Pro Arg Arg Ser Pro Ala Gln Glu Asp Gly Lys Val Tyr Ile Asn
50 55 60

Met Pro Gly Arg Gly Gly Ser Gly Ser Gly Ser Gly Ser Ser Arg Ala
65 70 75 80

Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro Leu Lys Glu
85 90 95

Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly Glu Leu Asp
100 105 110

Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro Cys Val Pro
115 120 125

Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly Met Gly Thr
130 135 140

Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg Ser Ala Gln
145 150 155 160

Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu Gly Ser Gly
165 170 175

Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly
180 185 190

Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly
195 200 205

Met Phe Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro
210 215 220

Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu
225 230 235 240

Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val
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250

245

255

Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg
260 265 270

Ile Glu

<210> 98

<211> 314

<212> PRT

<213> artificial sequence

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<400> 98

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

His Ala Ala Arg Pro Gly Ser Asp Ile Tyr Ile Trp Ala Pro Leu Ala
20 25 30

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
35 40 45

Arg Cys Val Lys Arg Arg Lys Pro Arg Gly Asp Val Val Lys Val Ile
50 55 60

Val Ser Val Gln Arg Lys Arg Gln Glu Ala Glu Gly Glu Ala Thr Val
65 70 75 80

Ile Glu Ala Leu Gln Ala Pro Pro Asp Val Thr Thr Val Ala Val Glu
85 90 95

Glu Thr Ile Pro Ser Phe Thr Gly Arg Ser Pro Asn His Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg
115 120 125

Arg Thr Gly Gln Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe
130 135 140

Ser Val Asp Tyr Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro
145 150 155 160

Glu Pro Pro Val Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile
165 170 175

Val Phe Pro Ser Gly Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser
180 185 190

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Ala Asp Gly Pro Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His
195 200 205

Cys Ser Trp Pro Leu Gly Ser Gly Ser Gly Gly Arg Val Ala Ile Leu
210 215 220

Trp His Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr
225 230 235 240

Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu
245 250 255

His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe
260 265 270

Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg
275 280 285

Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp
290 295 300

Leu Tyr Tyr His Val Phe Arg Arg Ile Glu
305 310

<210> 99

<211> 481

<212> PRT

<213> artificial sequence

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Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Gln Ile Gln Leu Val Gln Ser
20 25 30

Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Ile Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln
50 55 60

Ala Pro Gly Lys Ser Phe Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr
65 70 75 80

Gly Glu Ser Thr Tyr Ser Ala Asp Phe Lys Gly Arg Phe Ala Phe Ser
85 90 95

Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu His Ile Asn Asp Leu Lys
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100

105

110

Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Ser Gly Gly Tyr Asp
115 120 125

Pro Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
145 150 155 160

Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg
165 170 175

Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Asn
180 185 190

Thr Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
195 200 205

Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe
210 215 220

Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val
225 230 235 240

Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Glu Asp
245 250 255

Pro Pro Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp
260 265 270

Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
275 280 285

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
290 295 300

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Phe Phe
305 310 315 320

Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly Leu Phe
325 330 335

Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys Arg Thr
340 345 350

Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn Pro Lys
355 360 365

Asn Asn Arg Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp

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370

375

Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr
385 390 395 400

Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn
405 410 415

Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp
420 425 430

Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr
435 440 445

Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile
450 455 460

Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu
465 470 475 480

Glu

<210> 100

<211> 469

<212> PRT

<213> artificial sequence

<220>

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Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Gln Ile Gln Leu Val Gln Ser
20 25 30

Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Ile Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln
50 55 60

Ala Pro Gly Lys Ser Phe Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr
65 70 75 80

Gly Glu Ser Thr Tyr Ser Ala Asp Phe Lys Gly Arg Phe Ala Phe Ser
85 90 95

Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu His Ile Asn Asp Leu Lys
100 105 110

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Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Ser Gly Gly Tyr Asp
115 120 125

Pro Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
145 150 155 160

Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg
165 170 175

Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Asn
180 185 190

Thr Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
195 200 205

Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe
210 215 220

Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val
225 230 235 240

Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Glu Asp
245 250 255

Pro Pro Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp
260 265 270

Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
275 280 285

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
290 295 300

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Phe Phe
305 310 315 320

Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly Leu Phe
325 330 335

Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys Arg Thr
340 345 350

Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn Pro Lys
355 360 365

Asn Asn Arg Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu Met Trp
370 375 380

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His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn
385 390 395 400

Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala Met Met Glu
405 410 415

Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly
420 425 430

Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser
435 440 445

Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val
450 455 460

Phe Arg Arg Ile Glu
465

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<212> PRT

<213> artificial sequence

<220>

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Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Gln Ile Gln Leu Val Gln Ser
20 25 30

Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Ile Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln
50 55 60

Ala Pro Gly Lys Ser Phe Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr
65 70 75 80

Gly Glu Ser Thr Tyr Ser Ala Asp Phe Lys Gly Arg Phe Ala Phe Ser
85 90 95

Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu His Ile Asn Asp Leu Lys
100 105 110

Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Ser Gly Gly Tyr Asp
115 120 125

Pro Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly

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140

130

135

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
145 150 155 160

Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg
165 170 175

Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Asn
180 185 190

Thr Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
195 200 205

Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe
210 215 220

Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val
225 230 235 240

Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Glu Asp
245 250 255

Pro Pro Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp
260 265 270

Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
275 280 285

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
290 295 300

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Phe Phe
305 310 315 320

Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly Leu Phe
325 330 335

Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys Arg Thr
340 345 350

Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn Pro Lys
355 360 365

Asn Asn Arg Ala Leu Tyr Leu Leu Arg Arg Asp Gln Arg Leu Pro Pro
370 375 380

Asp Ala His Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln
385 390 395 400

Glu Glu Gln Ala Asp Ala His Ser Thr Leu Ala Lys Ile Gly Ser Gly

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405

410

415

Ser Gly Ser Gly Ser Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro
420 425 430

Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His
435 440 445

Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp
450 455 460

Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg
465 470 475 480

Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys
485 490 495

Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly
500 505 510

Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys
515 520 525

Leu Glu Glu
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<210> 102

<211> 509

<212> PRT

<213> artificial sequence

<220>

<223> alpha-mcCAR-intCID-n°4

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Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Gln Ile Gln Leu Val Gln Ser
20 25 30

Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Ile Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln
50 55 60

Ala Pro Gly Lys Ser Phe Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr
65 70 75 80

Gly Glu Ser Thr Tyr Ser Ala Asp Phe Lys Gly Arg Phe Ala Phe Ser
85 90 95

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Leu Glu Thr Ser₁₀₀ Ala Ser Thr Ala Tyr₁₀₅ Leu His Ile Asn Asp₁₁₀ Leu Lys
 Asn Glu Asp₁₁₅ Thr Ala Thr Tyr Phe₁₂₀ Cys Ala Arg Ser Gly₁₂₅ Gly Tyr Asp
 Pro Met₁₃₀ Asp Tyr Trp Gly Gln₁₃₅ Gly Thr Ser Val Thr₁₄₀ Val Ser Ser Gly
 Gly₁₄₅ Gly Gly Ser Gly Gly₁₅₀ Gly Gly Ser Gly Gly₁₅₅ Gly Gly Ser Asp Ile₁₆₀
 Val Leu Thr Gln Ser₁₆₅ Pro Ala Ser Leu Ala₁₇₀ Val Ser Leu Gly Gln₁₇₅ Arg
 Ala Thr Ile Ser₁₈₀ Cys Arg Ala Ser Glu₁₈₅ Ser Val Asp Asn Tyr₁₉₀ Gly Asn
 Thr Phe Met₁₉₅ His Trp Tyr Gln Gln₂₀₀ Lys Pro Gly Gln Pro₂₀₅ Pro Lys Leu
 Leu Ile₂₁₀ Tyr Arg Ala Ser Asn₂₁₅ Leu Glu Ser Gly Ile₂₂₀ Pro Ala Arg Phe
 Ser₂₂₅ Gly Ser Gly Ser Arg₂₃₀ Thr Asp Phe Thr Leu₂₃₅ Thr Ile Asn Pro Val₂₄₀
 Glu Ala Asp Asp Val₂₄₅ Ala Thr Tyr Tyr Cys₂₅₀ Gln Gln Ser Asn Glu₂₅₅ Asp
 Pro Pro Thr Phe₂₆₀ Gly Ala Gly Thr Lys₂₆₅ Leu Glu Leu Lys Arg₂₇₀ Ser Asp
 Pro Thr Thr₂₇₅ Thr Pro Ala Pro Arg₂₈₀ Pro Pro Thr Pro Ala₂₈₅ Pro Thr Ile
 Ala Ser₂₉₀ Gln Pro Leu Ser Leu₂₉₅ Arg Pro Glu Ala Cys₃₀₀ Arg Pro Ala Ala
 Gly₃₀₅ Gly Ala Val His Thr₃₁₀ Arg Gly Leu Asp Phe₃₁₅ Ala Cys Asp Phe Phe₃₂₀
 Ile Pro Leu Leu Val₃₂₅ Val Ile Leu Phe Ala₃₃₀ Val Asp Thr Gly Leu₃₃₅ Phe
 Ile Ser Thr Gln₃₄₀ Gln Gln Val Thr Phe₃₄₅ Leu Leu Lys Ile Lys₃₅₀ Arg Thr
 Arg Lys Gly₃₅₅ Phe Arg Leu Leu Asn₃₆₀ Pro His Pro Lys Pro₃₆₅ Asn Pro Lys

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

Ile Asn Met Pro Gly Arg Gly Gly Ser Gly Ser Gly Ser Gly Ser Ser
385 390 395 400

Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe
405 410 415

Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu
420 425 430

Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys
435 440 445

Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val
450 455 460

Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp
465 470 475 480

Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala
485 490 495

Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Glu
500 505

<210> 103

<211> 549

<212> PRT

<213> artificial sequence

<220>

<223> alpha-mcCAR-intCID-n°5

<400> 103

Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Gln Ile Gln Leu Val Gln Ser
20 25 30

Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Ile Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln
50 55 60

Ala Pro Gly Lys Ser Phe Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr
65 70 75 80

Gly Glu Ser Thr Tyr Ser Ala Asp Phe Lys Gly Arg Phe Ala Phe Ser
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90

85

95

Leu Glu Thr Ser₁₀₀ Ala Ser Thr Ala Tyr₁₀₅ Leu His Ile Asn Asp₁₁₀ Leu Lys
 Asn Glu Asp₁₁₅ Thr Ala Thr Tyr Phe₁₂₀ Cys Ala Arg Ser Gly₁₂₅ Gly Tyr Asp
 Pro Met₁₃₀ Asp Tyr Trp Gly Gln₁₃₅ Gly Thr Ser Val Thr₁₄₀ Val Ser Ser Gly
 Gly₁₄₅ Gly Gly Ser Gly Gly₁₅₀ Gly Gly Ser Gly Gly₁₅₅ Gly Gly Ser Asp Ile₁₆₀
 Val Leu Thr Gln Ser₁₆₅ Pro Ala Ser Leu Ala₁₇₀ Val Ser Leu Gly Gln₁₇₅ Arg
 Ala Thr Ile Ser₁₈₀ Cys Arg Ala Ser Glu₁₈₅ Ser Val Asp Asn Tyr₁₉₀ Gly Asn
 Thr Phe Met₁₉₅ His Trp Tyr Gln Gln₂₀₀ Lys Pro Gly Gln Pro₂₀₅ Pro Lys Leu
 Leu Ile₂₁₀ Tyr Arg Ala Ser Asn₂₁₅ Leu Glu Ser Gly Ile₂₂₀ Pro Ala Arg Phe
 Ser₂₂₅ Gly Ser Gly Ser Arg₂₃₀ Thr Asp Phe Thr Leu₂₃₅ Thr Ile Asn Pro Val₂₄₀
 Glu Ala Asp Asp Val₂₄₅ Ala Thr Tyr Tyr Cys₂₅₀ Gln Gln Ser Asn Glu₂₅₅ Asp
 Pro Pro Thr Phe₂₆₀ Gly Ala Gly Thr Lys₂₆₅ Leu Glu Leu Lys Arg₂₇₀ Ser Asp
 Pro Thr Thr₂₇₅ Thr Pro Ala Pro Arg₂₈₀ Pro Pro Thr Pro Ala₂₈₅ Pro Thr Ile
 Ala Ser₂₉₀ Gln Pro Leu Ser Leu₂₉₅ Arg Pro Glu Ala Cys₃₀₀ Arg Pro Ala Ala
 Gly₃₀₅ Gly Ala Val His Thr₃₁₀ Arg Gly Leu Asp Phe₃₁₅ Ala Cys Asp Phe Phe₃₂₀
 Ile Pro Leu Leu Val₃₂₅ Val Ile Leu Phe Ala₃₃₀ Val Asp Thr Gly Leu₃₃₅ Phe
 Ile Ser Thr Gln₃₄₀ Gln Gln Val Thr Phe₃₄₅ Leu Leu Lys Ile Lys₃₅₀ Arg Thr
 Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn Pro Lys

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355 360 365

Asn Asn Arg Cys Val Lys Arg Arg Lys Pro Arg Gly Asp Val Val Lys
370 375 380

Val Ile Val Ser Val Gln Arg Lys Arg Gln Glu Ala Glu Gly Glu Ala
385 390 395 400

Thr Val Ile Glu Ala Leu Gln Ala Pro Pro Asp Val Thr Thr Val Ala
405 410 415

Val Glu Glu Thr Ile Pro Ser Phe Thr Gly Arg Ser Pro Asn His Gly
420 425 430

Ser Gly Ser Gly Ser Gly Ser Ser Gly Gly Val Gln Val Glu Thr Ile
435 440 445

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

Val His Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser
465 470 475 480

Arg Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val
485 490 495

Ile Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg
500 505 510

Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His
515 520 525

Pro Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu
530 535 540

Leu Lys Leu Glu Glu
545

<210> 104

<211> 519

<212> PRT

<213> artificial sequence

<220>

<223> alpha-mcCAR-intCID-n°6

<400> 104

Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Gln Ile Gln Leu Val Gln Ser
20 25 30

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Gly Pro Glu₃₅ Leu Lys Lys Pro Gly₄₀ Glu Thr Val Lys Ile₄₅ Ser Cys Lys

Ala Ser₅₀ Gly Tyr Ile Phe Thr₅₅ Asn Tyr Gly Met Asn₆₀ Trp Val Lys Gln

Ala₆₅ Pro Gly Lys Ser Phe₇₀ Lys Trp Met Gly Trp₇₅ Ile Asn Thr Tyr Thr₈₀

Gly Glu Ser Thr Tyr₈₅ Ser Ala Asp Phe Lys₉₀ Gly Arg Phe Ala Phe₉₅ Ser

Leu Glu Thr Ser₁₀₀ Ala Ser Thr Ala Tyr₁₀₅ Leu His Ile Asn Asp₁₁₀ Leu Lys

Asn Glu Asp₁₁₅ Thr Ala Thr Tyr Phe₁₂₀ Cys Ala Arg Ser Gly₁₂₅ Gly Tyr Asp

Pro Met₁₃₀ Asp Tyr Trp Gly Gln₁₃₅ Gly Thr Ser Val Thr₁₄₀ Val Ser Ser Gly

Gly₁₄₅ Gly Gly Ser Gly Gly₁₅₀ Gly Gly Ser Gly Gly₁₅₅ Gly Gly Ser Asp Ile₁₆₀

Val Leu Thr Gln Ser₁₆₅ Pro Ala Ser Leu Ala₁₇₀ Val Ser Leu Gly Gln₁₇₅ Arg

Ala Thr Ile Ser₁₈₀ Cys Arg Ala Ser Glu₁₈₅ Ser Val Asp Asn Tyr₁₉₀ Gly Asn

Thr Phe Met₁₉₅ His Trp Tyr Gln Gln₂₀₀ Lys Pro Gly Gln Pro₂₀₅ Pro Lys Leu

Leu Ile₂₁₀ Tyr Arg Ala Ser Asn₂₁₅ Leu Glu Ser Gly Ile₂₂₀ Pro Ala Arg Phe

Ser₂₂₅ Gly Ser Gly Ser Arg₂₃₀ Thr Asp Phe Thr Leu₂₃₅ Thr Ile Asn Pro Val₂₄₀

Glu Ala Asp Asp Val₂₄₅ Ala Thr Tyr Tyr Cys₂₅₀ Gln Gln Ser Asn Glu₂₅₅ Asp

Pro Pro Thr Phe₂₆₀ Gly Ala Gly Thr Lys₂₆₅ Leu Glu Leu Lys Arg₂₇₀ Ser Asp

Pro Thr Thr₂₇₅ Thr Pro Ala Pro Arg₂₈₀ Pro Pro Thr Pro Ala₂₈₅ Pro Thr Ile

Ala Ser₂₉₀ Gln Pro Leu Ser Leu₂₉₅ Arg Pro Glu Ala Cys₃₀₀ Arg Pro Ala Ala

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Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Phe Phe
305 310 315 320

Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly Leu Phe
325 330 335

Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys Arg Thr
340 345 350

Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn Pro Lys
355 360 365

Asn Asn Arg Ala Leu Tyr Leu Leu Arg Arg Asp Gln Arg Leu Pro Pro
370 375 380

Asp Ala His Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln
385 390 400

Glu Glu Gln Ala Asp Ala His Ser Thr Leu Ala Lys Ile Gly Ser Gly
405 410 415

Ser Gly Ser Gly Ser Ser Gly Gly Arg Val Ala Ile Leu Trp His Glu
420 425 430

Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu
435 440 445

Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His Ala Met
450 455 460

Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala
465 470 475 480

Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met
485 490 495

Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr
500 505 510

His Val Phe Arg Arg Ile Glu
515

<210> 105

<211> 497

<212> PRT

<213> artificial sequence

<220>

<223> alpha-mcCAR-intCID-n°7

<400> 105

Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
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10

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Phe	Phe	Ala	Pro	Asp	Gly	Val	Leu	Ala	Gln	Ile	Gln	Leu	Val	Gln	Ser
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Gly	Pro	Glu	Leu	Lys	Lys	Pro	Gly	Glu	Thr	Val	Lys	Ile	Ser	Cys	Lys
		35					40					45			
Ala	Ser	Gly	Tyr	Ile	Phe	Thr	Asn	Tyr	Gly	Met	Asn	Trp	Val	Lys	Gln
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Ala	Pro	Gly	Lys	Ser	Phe	Lys	Trp	Met	Gly	Trp	Ile	Asn	Thr	Tyr	Thr
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Gly	Glu	Ser	Thr	Tyr	Ser	Ala	Asp	Phe	Lys	Gly	Arg	Phe	Ala	Phe	Ser
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Leu	Glu	Thr	Ser	Ala	Ser	Thr	Ala	Tyr	Leu	His	Ile	Asn	Asp	Leu	Lys
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Asn	Glu	Asp	Thr	Ala	Thr	Tyr	Phe	Cys	Ala	Arg	Ser	Gly	Gly	Tyr	Asp
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Pro	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser	Gly
	130					135					140				
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile
145					150					155					160
Val	Leu	Thr	Gln	Ser	Pro	Ala	Ser	Leu	Ala	Val	Ser	Leu	Gly	Gln	Arg
				165					170					175	
Ala	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Glu	Ser	Val	Asp	Asn	Tyr	Gly	Asn
			180					185					190		
Thr	Phe	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu
		195					200					205			
Leu	Ile	Tyr	Arg	Ala	Ser	Asn	Leu	Glu	Ser	Gly	Ile	Pro	Ala	Arg	Phe
	210					215					220				
Ser	Gly	Ser	Gly	Ser	Arg	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asn	Pro	Val
225					230					235					240
Glu	Ala	Asp	Asp	Val	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Asn	Glu	Asp
				245					250					255	
Pro	Pro	Thr	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	Lys	Arg	Ser	Asp
			260					265					270		
Pro	Thr	Thr	Thr	Pro	Ala	Pro	Arg	Pro	Pro	Thr	Pro	Ala	Pro	Thr	Ile

eo1f-seq1

275

280

285

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
 290 295 300
 Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Phe Phe
 305 310 315 320
 Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly Leu Phe
 325 330 335
 Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys Arg Thr
 340 345 350
 Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn Pro Lys
 355 360 365
 Asn Asn Arg Pro Arg Arg Ser Pro Ala Gln Glu Asp Gly Lys Val Tyr
 370 375 380
 Ile Asn Met Pro Gly Arg Gly Gly Ser Gly Ser Gly Ser Gly Ser Ser
 385 390 395 400
 Gly Gly Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly Leu
 405 410 415
 Glu Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met
 420 425 430
 Phe Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro Gln
 435 440 445
 Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met
 450 455 460
 Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys
 465 470 475 480
 Asp Leu Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile
 485 490 495

Glu

<210> 106

<211> 537

<212> PRT

<213> artificial sequence

<220>

<223> alpha-mcCAR-intCID-n°8

eo1f-seq1

<400> 106
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20 25 30
Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys
35 40 45
Ala Ser Gly Tyr Ile Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln
50 55 60
Ala Pro Gly Lys Ser Phe Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr
65 70 75 80
Gly Glu Ser Thr Tyr Ser Ala Asp Phe Lys Gly Arg Phe Ala Phe Ser
85 90 95
Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu His Ile Asn Asp Leu Lys
100 105 110
Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Ser Gly Gly Tyr Asp
115 120 125
Pro Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly
130 135 140
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
145 150 155 160
Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg
165 170 175
Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Asn
180 185 190
Thr Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
195 200 205
Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe
210 215 220
Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val
225 230 235 240
Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Glu Asp
245 250 255
Pro Pro Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp
260 265 270

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Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
275 280 285

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
290 295 300

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Phe Phe
305 310 315 320

Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly Leu Phe
325 330 335

Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys Arg Thr
340 345 350

Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn Pro Lys
355 360 365

Asn Asn Arg Cys Val Lys Arg Arg Lys Pro Arg Gly Asp Val Val Lys
370 375 380

Val Ile Val Ser Val Gln Arg Lys Arg Gln Glu Ala Glu Gly Glu Ala
385 390 395 400

Thr Val Ile Glu Ala Leu Gln Ala Pro Pro Asp Val Thr Thr Val Ala
405 410 415

Val Glu Glu Thr Ile Pro Ser Phe Thr Gly Arg Ser Pro Asn His Gly
420 425 430

Ser Gly Ser Gly Ser Gly Ser Ser Gly Gly Arg Val Ala Ile Leu Trp
435 440 445

His Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe
450 455 460

Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His
465 470 475 480

Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn
485 490 495

Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys
500 505 510

Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu
515 520 525

Tyr Tyr His Val Phe Arg Arg Ile Glu
530 535

eo1f-seq1

<210> 107

<211> 613

<212> PRT

<213> artificial sequence

<220>

<223> CD123-sccAR-intraCID-n°1

<400> 107

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His Ala Ala Arg Pro Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Thr Asp Tyr Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys
50 55 60

Ala Leu Glu Trp Leu Ala Leu Ile Arg Ser Lys Ala Asp Gly Tyr Thr
65 70 75 80

Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Leu Ser Arg Asp
85 90 95

Asp Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn Ala Leu Arg Pro Glu
100 105 110

Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Asp Ala Ala Tyr Tyr Ser Tyr
115 120 125

Tyr Ser Pro Glu Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
130 135 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145 150 155 160

Gly Gly Ser Met Ala Asp Tyr Lys Asp Ile Val Met Thr Gln Ser His
165 170 175

Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Asn Ile Thr Cys Lys
180 185 190

Ala Ser Gln Asn Val Asp Ser Ala Val Ala Trp Tyr Gln Gln Lys Pro
195 200 205

Gly Gln Ser Pro Lys Ala Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser
210 215 220

Gly Val Pro Asp Arg Phe Thr Gly Arg Gly Ser Gly Thr Asp Phe Thr
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225		230		235		240									
Leu	Thr	Ile	Ser	Ser ₂₄₅	Val	Gln	Ala	Glu	Asp ₂₅₀	Leu	Ala	Val	Tyr	Tyr ₂₅₅	Cys
Gln	Gln	Tyr	Tyr ₂₆₀	Ser	Thr	Pro	Trp	Thr ₂₆₅	Phe	Gly	Gly	Gly	Thr ₂₇₀	Lys	Leu
Glu	Ile	Lys ₂₇₅	Arg	Ser	Asp	Pro	Thr ₂₈₀	Thr	Thr	Pro	Ala	Pro ₂₈₅	Arg	Pro	Pro
Thr	Pro ₂₉₀	Ala	Pro	Thr	Ile	Ala ₂₉₅	Ser	Gln	Pro	Leu	Ser ₃₀₀	Leu	Arg	Pro	Glu
Ala ₃₀₅	Cys	Arg	Pro	Ala	Ala ₃₁₀	Gly	Gly	Ala	Val	His ₃₁₅	Thr	Arg	Gly	Leu	Asp ₃₂₀
Phe	Ala	Cys	Asp	Ile ₃₂₅	Tyr	Ile	Trp	Ala	Pro ₃₃₀	Leu	Ala	Gly	Thr	Cys ₃₃₅	Gly
Val	Leu	Leu	Leu ₃₄₀	Ser	Leu	Val	Ile	Thr ₃₄₅	Leu	Tyr	Cys	Arg	Arg ₃₅₀	Gly	Arg
Lys	Lys	Leu ₃₅₅	Leu	Tyr	Ile	Phe	Lys ₃₆₀	Gln	Pro	Phe	Met	Arg ₃₆₅	Pro	Val	Gln
Thr	Thr ₃₇₀	Gln	Glu	Glu	Asp	Gly ₃₇₅	Cys	Ser	Cys	Arg	Phe ₃₈₀	Pro	Glu	Glu	Glu
Glu ₃₈₅	Gly	Gly	Cys	Glu	Leu ₃₉₀	Arg	Val	Lys	Phe	Ser ₃₉₅	Arg	Ser	Ala	Asp	Ala ₄₀₀
Pro	Ala	Tyr	Gln	Gln ₄₀₅	Gly	Gln	Asn	Gln	Leu ₄₁₀	Tyr	Asn	Glu	Leu	Asn ₄₁₅	Leu
Gly	Arg	Arg	Glu ₄₂₀	Glu	Tyr	Asp	Val	Leu ₄₂₅	Asp	Lys	Arg	Arg	Gly ₄₃₀	Arg	Asp
Pro	Glu	Met ₄₃₅	Gly	Gly	Lys	Pro	Arg ₄₄₀	Arg	Lys	Asn	Pro	Gln ₄₄₅	Glu	Gly	Leu
Tyr	Asn ₄₅₀	Glu	Leu	Gln	Lys	Asp ₄₅₅	Lys	Met	Ala	Glu	Ala ₄₆₀	Tyr	Ser	Glu	Ile
Gly ₄₆₅	Met	Lys	Gly	Glu	Arg ₄₇₀	Arg	Arg	Gly	Lys	Gly ₄₇₅	His	Asp	Gly	Leu	Tyr ₄₈₀
Gln	Gly	Leu	Ser	Thr ₄₈₅	Ala	Thr	Lys	Asp	Thr ₄₉₀	Tyr	Asp	Ala	Leu	His ₄₉₅	Met
Gln	Ala	Leu	Pro	Pro	Arg	Ser	Ser	Gly	Gly	Val	Gln	Val	Glu	Thr	Ile

eo1f-seq1

500

505

510

Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val
515 520 525

Val His Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser
530 535 540

Arg Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val
545 550 555 560

Ile Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg
565 570 575

Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His
580 585 590

Pro Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu
595 600 605

Leu Lys Leu Glu Glu
610

<210> 108

<211> 601

<212> PRT

<213> artificial sequence

<220>

<223> CD123-sccAR-intraCID-n°2

<400> 108

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
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His Ala Ala Arg Pro Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Thr Asp Tyr Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys
50 55 60

Ala Leu Glu Trp Leu Ala Leu Ile Arg Ser Lys Ala Asp Gly Tyr Thr
65 70 75 80

Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Leu Ser Arg Asp
85 90 95

Asp Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn Ala Leu Arg Pro Glu
100 105 110

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Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Asp Ala Ala Tyr Tyr Ser Tyr
 115 120 125
 Tyr Ser Pro Glu Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
 130 135 140
 Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
 145 150 155 160
 Gly Gly Ser Met Ala Asp Tyr Lys Asp Ile Val Met Thr Gln Ser His
 165 170 175
 Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Asn Ile Thr Cys Lys
 180 185 190
 Ala Ser Gln Asn Val Asp Ser Ala Val Ala Trp Tyr Gln Gln Lys Pro
 195 200 205
 Gly Gln Ser Pro Lys Ala Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser
 210 215 220
 Gly Val Pro Asp Arg Phe Thr Gly Arg Gly Ser Gly Thr Asp Phe Thr
 225 230 235 240
 Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys
 245 250 255
 Gln Gln Tyr Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
 260 265 270
 Glu Ile Lys Arg Ser Asp Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
 275 280 285
 Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
 290 295 300
 Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
 305 310 315 320
 Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
 325 330 335
 Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Arg Gly Arg
 340 345 350
 Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
 355 360 365
 Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
 370 375 380

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Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
385 390 395 400

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
405 410 415

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
420 425 430

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
435 440 445

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
450 455 460

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
465 470 475 480

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
485 490 495

Gln Ala Leu Pro Pro Arg Ser Ser Gly Gly Arg Val Ala Ile Leu Trp
500 505 510

His Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg Leu Tyr Phe
515 520 525

Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro Leu His
530 535 540

Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser Phe Asn
545 550 555 560

Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys Arg Lys
565 570 575

Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala Trp Asp Leu
580 585 590

Tyr Tyr His Val Phe Arg Arg Ile Glu
595 600

<210> 109

<211> 624

<212> PRT

<213> artificial sequence

<220>

<223> CD123-sccAR-intraCID-n°3

<400> 109

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
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His	Ala	Ala	Arg	Pro	Glu	Val
			20			
Lys	Leu	Val	Glu	Ser	Gly	Gly
	25				30	
Leu	Val	Glu	Ser	Gly	Gly	Leu
Val	Gln	Pro	Gly	Gly	Ser	Leu
		35				
Ser	Leu	Ser	Leu	Ser	Cys	Ala
		40				45
Ala	Ala	Ser	Gly	Phe		
Thr	Phe	Thr	Asp	Tyr	Tyr	Met
	50					55
Ser	Trp	Val	Arg	Gln	Pro	Pro
				60		
Gly	Lys					
Ala	Leu	Glu	Trp	Leu	Ala	Leu
					70	
Ile	Arg	Ser	Lys	Ala	Asp	Gly
			75			
Tyr	Thr					
Thr	Glu	Tyr	Ser	Ala	Ser	Val
				85		
Lys	Gly	Arg	Phe	Thr	Leu	Ser
		90				
Arg	Asp					
Asp	Ser	Gln	Ser	Ile	Leu	Tyr
			100			
Leu	Gln	Met	Asn	Ala	Leu	Arg
		105				110
Pro	Glu					
Asp	Ser	Ala	Thr	Tyr	Tyr	Cys
		115				
Ala	Arg	Asp	Ala	Ala	Tyr	Tyr
			120		125	
Ser	Tyr					
Tyr	Ser	Pro	Glu	Gly	Ala	Met
	130					135
Asp	Tyr	Trp	Gly	Gln	Gly	Thr
				140		
Ser	Val					
Thr	Val	Ser	Ser	Gly	Gly	Gly
				150		
Ser	Gly	Gly	Ser	Gly	Gly	Gly
				155		
Ser	Gly	Gly	Ser	Gly	Gly	Gly
						160
Gly	Gly	Ser	Met	Ala	Asp	Tyr
			165			
Lys	Asp	Tyr	Lys	Asp	Ile	Val
					170	
Met	Thr	Gln	Ser	His		
Lys	Phe	Met	Ser	Thr	Ser	Val
			180			
Gly	Asp	Arg	Val	Asn	Ile	Thr
	185					190
Cys	Lys					
Ala	Ser	Gln	Asn	Val	Asp	Ser
		195				
Ala	Val	Ala	Trp	Tyr	Gln	Gln
		200			205	
Lys	Pro					
Gly	Gln	Ser	Pro	Lys	Ala	Leu
	210					215
Ile	Tyr	Ser	Ala	Ser	Tyr	Arg
				220		
Tyr	Ser					
Gly	Val	Pro	Asp	Arg	Phe	Thr
					230	
Thr	Gly	Arg	Gly	Ser	Gly	Thr
				235		
Asp	Phe	Thr				
						240
Leu	Thr	Ile	Ser	Ser	Val	Gln
				245		
Ala	Glu	Asp	Leu	Ala	Val	Tyr
		250				
Tyr	Cys					
						255
Gln	Gln	Tyr	Tyr	Ser	Thr	Pro
			260			
Trp	Thr	Phe	Gly	Gly	Gly	Thr
			265			270
Lys	Leu					
Glu	Ile	Lys	Arg	Ser	Asp	Pro
Thr	Thr	Thr	Pro	Ala	Pro	Arg
Pro	Pro					

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275

280

285

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
 290 295 300

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
 305 310 315 320

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
 325 330 335

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Gly Arg Lys
 340 345 350

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
 355 360 365

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
 370 375 380

Gly Gly Cys Glu Leu Gly Ser Gly Ser Gly Ser Gly Ser Ser Gly Gly
 385 390 395 400

Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys
 405 410 415

Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp Gly
 420 425 430

Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met
 435 440 445

Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln
 450 455 460

Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala
 465 470 475 480

Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu
 485 490 495

Val Phe Asp Val Glu Leu Leu Lys Leu Glu Gly Ser Gly Ser Gly Arg
 500 505 510

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
 515 520 525

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
 530 535 540

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro

eolfs-seql															
545				550				555				560			
Arg	Arg	Lys	Asn	Pro 565	Gln	Glu	Gly	Leu	Tyr 570	Asn	Glu	Leu	Gln	Lys 575	Asp
Lys	Met	Ala	Glu 580	Ala	Tyr	Ser	Glu	Ile 585	Gly	Met	Lys	Gly	Glu 590	Arg	Arg
Arg	Gly	Lys 595	Gly	His	Asp	Gly	Leu 600	Tyr	Gln	Gly	Leu	Ser 605	Thr	Ala	Thr
Lys	Asp 610	Thr	Tyr	Asp	Ala	Leu 615	His	Met	Gln	Ala	Leu 620	Pro	Pro	Arg	Glu

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<212> PRT
<213> artificial sequence

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35 40 45
Thr Phe Thr Asp Tyr Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys
50 55 60
Ala Leu Glu Trp Leu Ala Leu Ile Arg Ser Lys Ala Asp Gly Tyr Thr
65 70 75 80
Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Leu Ser Arg Asp
85 90 95
Asp Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn Ala Leu Arg Pro Glu
100 105 110
Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Asp Ala Ala Tyr Tyr Ser Tyr
115 120 125
Tyr Ser Pro Glu Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
130 135 140

eo1f-seq1

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145 150 155 160

Gly Gly Ser Met Ala Asp Tyr Lys Asp Ile Val Met Thr Gln Ser His
165 170 175

Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Asn Ile Thr Cys Lys
180 185 190

Ala Ser Gln Asn Val Asp Ser Ala Val Ala Trp Tyr Gln Gln Lys Pro
195 200 205

Gly Gln Ser Pro Lys Ala Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser
210 215 220

Gly Val Pro Asp Arg Phe Thr Gly Arg Gly Ser Gly Thr Asp Phe Thr
225 230 235 240

Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys
245 250 255

Gln Gln Tyr Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
260 265 270

Glu Ile Lys Arg Ser Asp Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
275 280 285

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
290 295 300

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
305 310 315 320

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
325 330 335

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Gly Arg Lys
340 345 350

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
355 360 365

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
370 375 380

Gly Gly Cys Glu Leu Gly Ser Gly Ser Gly Ser Gly Ser Ser Gly Gly
385 390 395 400

Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu Glu
405 410 415

eo1f-seq1

Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu
420 425 430

Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu
435 440 445

Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala
450 455 460

Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu
465 470 475 480

Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Gly Ser
485 490 495

Gly Ser Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
500 505 510

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
515 520 525

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
530 535 540

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
545 550 555 560

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
565 570 575

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
580 585 590

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
595 600 605

Pro Pro Arg Glu
610

<210> 111

<211> 617

<212> PRT

<213> artificial sequence

<220>

<223> CD123-sccAR-intraCID-n°5

<400> 111

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

His Ala Ala Arg Pro Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu
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eo1f-seq1

20

25

30

Val Gln Pro Gly Gly Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Thr Asp Tyr Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys
50 55 60

Ala Leu Glu Trp Leu Ala Leu Ile Arg Ser Lys Ala Asp Gly Tyr Thr
65 70 75 80

Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Leu Ser Arg Asp
85 90 95

Asp Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn Ala Leu Arg Pro Glu
100 105 110

Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Asp Ala Ala Tyr Tyr Ser Tyr
115 120 125

Tyr Ser Pro Glu Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
130 135 140

Thr val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly
145 150 155 160

Gly Gly Ser Met Ala Asp Tyr Lys Asp Ile Val Met Thr Gln Ser His
165 170 175

Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Asn Ile Thr Cys Lys
180 185 190

Ala Ser Gln Asn Val Asp Ser Ala Val Ala Trp Tyr Gln Gln Lys Pro
195 200 205

Gly Gln Ser Pro Lys Ala Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser
210 215 220

Gly Val Pro Asp Arg Phe Thr Gly Arg Gly Ser Gly Thr Asp Phe Thr
225 230 235 240

Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys
245 250 255

Gln Gln Tyr Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
260 265 270

Glu Ile Lys Arg Ser Asp Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
275 280 285

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu

eo1f-seq1
300

290

295

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
305 310 315 320

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
325 330 335

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Gly Gly
340 345 350

Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys
355 360 365

Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp Gly
370 375 380

Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met
385 390 395 400

Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln
405 410 415

Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala
420 425 430

Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu
435 440 445

Val Phe Asp Val Glu Leu Leu Lys Leu Glu Gly Ser Gly Ser Ser Arg
450 455 460

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
465 470 475 480

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
485 490 495

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
500 505 510

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
515 520 525

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
530 535 540

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
545 550 555 560

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser

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565

570

575

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
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Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
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His Met Gln Ala Leu Pro Pro Arg Glu
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His Ala Ala Arg Pro Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu
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Val Gln Pro Gly Gly Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Thr Asp Tyr Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys
50 55 60

Ala Leu Glu Trp Leu Ala Leu Ile Arg Ser Lys Ala Asp Gly Tyr Thr
65 70 75 80

Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Leu Ser Arg Asp
85 90 95

Asp Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn Ala Leu Arg Pro Glu
100 105 110

Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Asp Ala Ala Tyr Tyr Ser Tyr
115 120 125

Tyr Ser Pro Glu Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
130 135 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145 150 155 160

Gly Gly Ser Met Ala Asp Tyr Lys Asp Ile Val Met Thr Gln Ser His
165 170 175

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Lys Phe Met Ser Thr Ser Val Gly Asp Arg Val Asn Ile Thr Cys Lys
 180 185 190
 Ala Ser Gln Asn Val Asp Ser Ala Val Ala Trp Tyr Gln Gln Lys Pro
 195 200 205
 Gly Gln Ser Pro Lys Ala Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser
 210 215 220
 Gly Val Pro Asp Arg Phe Thr Gly Arg Gly Ser Gly Thr Asp Phe Thr
 225 230 235 240
 Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys
 245 250 255
 Gln Gln Tyr Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
 260 265 270
 Glu Ile Lys Arg Ser Asp Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
 275 280 285
 Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
 290 295 300
 Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
 305 310 315 320
 Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
 325 330 335
 Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Gly Gly
 340 345 350
 Arg Val Ala Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu Glu
 355 360 365
 Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu
 370 375 380
 Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu
 385 390 395 400
 Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala
 405 410 415
 Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu
 420 425 430
 Thr Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Gly Ser
 435 440 445

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Gly	Ser	Ser	Arg	Gly	Arg	Lys	Lys	Leu	Leu	Tyr	Ile	Phe	Lys	Gln	Pro
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Phe	Met	Arg	Pro	Val	Gln	Thr	Thr	Gln	Glu	Glu	Asp	Gly	Cys	Ser	Cys
465					470					475					480
Arg	Phe	Pro	Glu	Glu	Glu	Glu	Gly	Gly	Cys	Glu	Leu	Arg	Val	Lys	Phe
			485						490					495	
Ser	Arg	Ser	Ala	Asp	Ala	Pro	Ala	Tyr	Gln	Gln	Gly	Gln	Asn	Gln	Leu
			500					505					510		
Tyr	Asn	Glu	Leu	Asn	Leu	Gly	Arg	Arg	Glu	Glu	Tyr	Asp	Val	Leu	Asp
	515						520					525			
Lys	Arg	Arg	Gly	Arg	Asp	Pro	Glu	Met	Gly	Gly	Lys	Pro	Arg	Arg	Lys
	530					535					540				
Asn	Pro	Gln	Glu	Gly	Leu	Tyr	Asn	Glu	Leu	Gln	Lys	Asp	Lys	Met	Ala
545					550					555					560
Glu	Ala	Tyr	Ser	Glu	Ile	Gly	Met	Lys	Gly	Glu	Arg	Arg	Arg	Gly	Lys
				565					570					575	
Gly	His	Asp	Gly	Leu	Tyr	Gln	Gly	Leu	Ser	Thr	Ala	Thr	Lys	Asp	Thr
			580					585					590		
Tyr	Asp	Ala	Leu	His	Met	Gln	Ala	Leu	Pro	Pro	Arg	Glu			
		595					600					605			