PDE5 COMPOSITIONS AND METHODS FOR IMMUNOTHERAPY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to 62/518,078 filed on June 12, 2017 entitled PDE5 Tunable Protein Regulation, 62/523,850 filed on June 23, 2017 entitled PDE5 Tunable Protein Regulation, 62/523,862 filed on June 23, 2017 entitled PDE5 Compositions and Methods for Immunotherapy, 62/555,313 filed on September 7, 2017 entitled PDE5 Tunable Protein Regulation, the contents of each of which are herein incorporated by reference in their entirety.

REFERENCE TO SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 2095_1003PCT_SL.txt, created on June 12, 2018, which is 18,074,972 bytes in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present invention relates to tunable biocircuit systems for the development of controlled and/or regulated therapeutic systems. In particular, regulatable biocircuits containing destabilizing domains (DD) derived from mutant human cGMP-specific phosphodiesterase type 5 (PDE5) are disclosed. The present invention also relates to compositions and methods for immunotherapy.

[0004] Provided in the present invention include polypeptides of biocircuit systems, effector modules, stimulus response elements (SREs) and immunotherapeutic agents, polynucleotides encoding the same, vectors and cells containing the polypeptides and/or polynucleotides for use in cancer immunotherapy. In one embodiment, the compositions comprise destabilizing domains (DDs) which tune protein stability.

BACKGROUND OF THE INVENTION

[0005] Safe and effective gene therapy requires tightly regulated expression of a therapeutic transgenic product (e.g., the protein product). Similarly, the analysis of gene function in development, cell differentiation and other physiological activities requires the controllable expression of a protein under investigation. However, current technologies do not allow titration of levels of target protein induced or kinetics of induction. Inadequate exogenous and/or endogenous gene control is a critical issue in numerous settings including *ex vivo* and *in vivo* gene therapy. This lack of tunability also makes it difficult to safely express proteins with narrow or uncertain therapeutic windows or those requiring more titrated, controlled or transient expression.

[0006] One approach to regulated protein expression or function is the use of Destabilizing Domains (DDs). Destabilizing domains are small protein domains that can be appended to a payload such as a protein of interest (POI). DDs render the attached protein of interest (POI) unstable in the absence of a DD-binding ligand such that the protein is rapidly degraded by the ubiquitin-proteasome system of the cell (Stankunas, K., et al., (2003). *Mol. Cell* 12, 1615–1624; Banaszynski, L.A., et al., (2006) *Cell*; 126(5): 995–1004; reviewed in Banaszynski, L.A., and Wandless, T.J. (2006) *Chem. Biol.* 13, 11–21; Iwamoto, M., et al. (2010). *Chem Biol.* 17(9):981-8; Egeler, E.L.et al. (2011). *J Biol Chem.* 286(36):31328-36; and Rakhit R, Navarro R, Wandless TJ (2014) *Chem Biol.* Sep 18;21(9):1238-52; Navarro, R. et al. (2016) *ACS Chem Biol.* 11(8): 2101–2104). In some cases, the protein of interest is not completely processed and may not be secreted or presented on the membrane in the absence of DD-binding ligand (Sellmeyer et al., (2012), doi.org/10.1371/journal.pone.0043297; the contents of which are incorporated by reference in their entirety). However, when a specific small molecule ligand binds its intended DD as a ligand binding partner, the instability is reversed and protein function is restored or, in some cases, processing is restored and the protein of interest is presented on the membrane or secreted. Such a system is herein referred to as a biocircuit, with the canonical DD-containing biocircuit described above being the prototypical model biocircuit

[0007] It is believed that improvements of biocircuits, including those containing DDs can form the basis of a new class of cell and gene therapies that employ tunable and temporal control of gene expression and function. Such novel moieties are described by the present inventors as stimulus response elements (SREs) which act in the context of an effector module to complete a biocircuit arising from a stimulus and ultimately producing a signal or outcome. When properly formatted with a polypeptide payload, and when activated by a particular stimulus, e.g., a small molecule, biocircuit systems can be used to regulate transgene and/or protein levels either up or down by perpetuating a stabilizing signal or destabilizing signal. This approach has many advantages over existing methods of regulating protein function and/or expression, which are currently focused on top level transcriptional regulation via inducible promoters.

[0008] The present invention provides novel protein domains, in particular, destabilizing domains (DDs) derived from mutant human cGMP-specific phosphodiesterase type 5 (PDE5), particularly the catalytic domain of human PDE5, that display small molecule dependent stability, and the biocircuit systems and effector modules comprising such DDs. Methods for tuning transgene functions using the same are also provided.

[0009] Cancer immunotherapy aims to eradicate cancer cells by rejuvenating the tumoricidal functions of tumor-reactive immune cells, predominantly T cells. Strategies of cancer immunotherapy including the recent development of checkpoint blockade, adoptive cell transfer (ACT) and cancer vaccines which can increase the anti-tumor immune effector cells have produced remarkable results in several tumors.

[0010] The impact of host anti-tumor immunity and cancer immunotherapy is impeded by three major hurdles: 1) low number of tumor antigen-specific T cells due to clonal deletion; 2) poor activation of innate immune cells and accumulation of tolerogenic antigen-presenting cells in the tumor microenvironment; and 3) formation of an immunosuppressive tumor microenvironment. Particularly, in solid tumors the therapeutic efficacy of immunotherapeutic regimens remains unsatisfactory due to lack of an effective an anti-tumor response in the immunosuppressive tumor microenvironment. Tumor cells often induce immune tolerance or suppression and such tolerance is acquired because even truly foreign tumor antigens will become tolerated. Such tolerance is also active and dominant because cancer vaccines and adoptive transfer of pre-activated immune effector cells (e.g., T cells), are subject to suppression by inhibitory factors in the tumor microenvironment (TME).

[0011] In addition, administration of engineered T cells could result in on/off target toxicities as well as a cytokine release syndrome (reviewed by Tey *Clin. Transl. Immunol.*, 2014, 3: e17 10.1038).

[0012] Development of a tunable switch that can turn on or off the transgenic immunotherapeutic agent expression is needed in case of adverse events. For example, adoptive cell therapies may have a very long and an indefinite half-life. Since toxicity can be progressive, a safety switch is desired to eliminate the infused cells. Systems and methods that can tune the transgenic protein level and expression window with high flexibility can enhance therapeutic benefit, and reduce potential side effects.

[0013] In an effort to develop regulatable therapeutic agents for disease therapy, in particular cancer immunotherapy, the present invention provides biocircuit systems to control the expression of immunotherapeutic agents. The biocircuit system comprises a stimulus and at least one effector module that responds to the stimulus. The effector module may include a stimulus response element (SRE) that binds and is responsive to a stimulus and an immunotherapeutic agent operably linked to the SRE. In one example, a SRE is a destabilizing domain (DD) which is destabilized in the absence of its specific ligand and can be stabilized by binding to its specific ligand.

SUMMARY OF THE INVENTION

[0014] The present invention provides compositions and methods for immunotherapy. The compositions relate to tunable systems and agents that induce anti-cancer immune responses in a cell or in a subject. The tunable system and agent may be a biocircuit system comprising at least one effector module that is responsive to at least one stimulus. The biocircuit system may be, but is not limited to, a destabilizing domain (DD) biocircuit system, a dimerization biocircuit system, a receptor biocircuit system, and a cell biocircuit system. These systems are further taught in co-owned U.S. Provisional Patent Application No. 62/320,864 filed April 11, 2016, 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587 (the contents of each of which are herein incorporated by reference in their entirety).

[0015] The present invention provides compositions for an inducing immune response in a cell or subject. In some embodiments, the composition may include a stimulus response element (SRE) and at least one payload. In some embodiments, the payload may be attached, appended or associated with the SRE. The SRE may comprise a destabilizing domain (DD). In some embodiments, the DD may comprise, in whole or in part, the cGMP-specific 3', 5'-cyclic phosphodiesterase (hPDE5; SEQ ID NO.1). In some embodiments, the payload may be appended to the SRE.

[0016] In some embodiments, the DD may comprise the catalytic domain of hPDE5 (SEQ ID NO. 3). In some aspects, the catalytic domain may include amino acids 535-860 of hPDE5 (SEQ ID NO. 1). In some embodiments, the DD may include a mutation in the amino acid at position 732 (R732) of SEQ ID NO. 1. The mutation at position R732 may include but is not limited to R732L, R732A, R732G, R732V, R732I, R732P, R732F, R732W, R732Y, R732H, R732S, R732T, R732D, R732E, R732Q, R732N, R732M, R732C, and R732K.

[0017] In some aspects, the DD may be selected from the group including but not limited to hPDE5 (Amino acid 535-860 of WT, R732L) (SEQ ID NO. 12); hPDE5 (Amino acid 535-860 of WT, R732A) (SEQ ID NO. 384); hPDE5 (Amino acid 535-860 of WT, R732G) (SEQ ID NO. 383); hPDE5 (Amino acid 535-860 of WT, R732V) (SEQ ID NO. 385); hPDE5 (Amino acid 535-860 of WT, R732I) (SEQ ID NO. 386); hPDE5 (Amino acid 535-860 of WT, R732P) (SEQ ID NO. 387); hPDE5 (Amino acid 535-860 of WT, R732F) (SEQ ID NO. 388); hPDE5 (Amino acid 535-860 of WT, R732W) (SEQ ID NO. 389); hPDE5 (Amino acid 535-860 of WT, R732Y) (SEQ ID NO. 390); hPDE5 (Amino acid 535-860 of WT, R732H) (SEQ ID NO. 391); hPDE5 (Amino acid 535-860 of WT, R732S) (SEQ ID NO. 392); hPDE5 (Amino acid 535-860 of WT, R732T) (SEQ ID NO. 393); hPDE5 (Amino acid 535-860 of

WT, R732D) (SEQ ID NO. 394); hPDE5 (Amino acid 535-860 of WT, R732E) (SEQ ID NO. 395); hPDE5 (Amino acid 535-860 of WT, R732Q) (SEQ ID NO. 396); hPDE5 (Amino acid 535-860 of WT, R732N) (SEQ ID NO. 397); hPDE5 (Amino acid 535-860 of WT, R732M) (SEQ ID NO. 398); hPDE5 (Amino acid 535-860 of WT, R732C) (SEQ ID NO. 399); and hPDE5 (Amino acid 535-860 of WT, R732K) (SEQ ID NO. 400).

[0018] In some embodiments, the mutation in the amino acid at position R732 may be R732L. In one embodiment, the DD may comprise the amino acid sequence of SEQ ID NO. 12. In some embodiments, the mutation in the amino acid at position R732 may be R732A. In one embodiment, the DD may comprise the amino acid sequence of SEQ ID NO. 384. In some embodiments, the mutation in the amino acid at position R732 may be R732G. In one embodiment, the DD may comprise the amino acid sequence of SEQ ID NO. 383.

[0019] The DDs of the present invention may further comprise one or more mutations independently selected from the group consisting of H653A, F736A, D764A, D764N, Y612F, Y612W, Y612A, W853F, I821A, Y829A, F787A, D656L, Y728L, M625I, E535D, E536G, Q541R, K555R, F559L, F561L, F564L, F564S, K591E, N587S, K604E, K608E, N609H, K630R, K633E, N636S, N661S, Y676D, Y676N, C677R, H678R, D687A, T712S, D724N, D724G, L738H, N742S, A762S, D764G, D764V, S766F, K795E, L797F, I799T, T802P, S815C, M816A, I824T, C839S, K852E, S560G, V585A, I599V, I648V, S663P, L675P, T711A, F744L, L746S, F755L, L804P, M816T, and F840S.

[0020] In one embodiment the DD may include the mutation H653A. In one embodiment, the DD may comprise the amino acid sequence of SEQ ID NO. 509. In one embodiment, the DD may include the mutation F736A. In one embodiment, the DD may comprise the amino acid sequence of SEQ ID NO. 227. In one embodiment, the DD may comprise the mutation D764A. In one embodiment, the DD comprises the amino acid sequence of SEQ ID NO. 510. In one embodiment, the DD may include the mutation Y612F. In one aspect, the DD may comprise the amino acid sequence of SEQ ID NO. 506. In one embodiment, the DD may include the Y612W mutation. In one aspect, the DD may include the amino acid sequence of SEQ ID NO. 507. In one embodiment, the DD may include the mutation Y612A. In one embodiment the DD may comprise the amino acid sequence of SEQ ID NO. 508. In one embodiment, the DD may include the mutation D64N. In some aspects, the DD may comprise the amino acid sequence of SEQ ID NO. 505.

[0021] In some embodiments, the SRE of the present invention may be appended to a payload. In some aspects, the payload may be an immunotherapeutic agent. In some aspects,

the immunotherapeutic agent may be selected from a chimeric antigen receptor (CAR) and a cytokine-cytokine receptor fusion polypeptide.

[0022] In some embodiments the CAR may include an extracellular target moiety, a hinge and transmembrane domain, an intracellular signaling domain; and optionally, one or more co-stimulatory domains. In some embodiments, the CAR may be a standard CAR, a split CAR, an off-switch CAR, an on-switch CAR, a first-generation CAR, a second-generation CAR, a third-generation CAR, or a fourth-generation CAR.

[0023] The extracellular target moiety of the CAR may have an affinity of bind to a target molecule on the surface of the cancer cell. In some aspects, the extracellular target moiety of the CAR may be an scFv. In one aspect, the target molecule may be CD19. In some embodiments, the extracellular target moiety of the CAR is a CD19 scFv (SEQ ID NO. 8233). In some embodiments, wherein the hinge and transmembrane domain of the CAR may be paired. The paired hinge and transmembrane domain may be derived from CD8a, CD5, CD4, CD9, CD16, CD22, CD33, CD28, CD37, CD45, CD64, CD80, CD86, CD148, DAP 10, EpoRI, GITR, LAG3, ICOS, Her2, OX40 (CD134), 4-1BB (CD137), CD152, CD154, PD-1, or CTLA-4. In some embodiments, the paired domain may be derived from a transmembrane region of an alpha, beta or zeta chain of a T-cell receptor; or an immunoglobulin selected from IgG1, IgD, IgG4, and an IgG4 Fc region; or the CD3 epsilon chain of a T-cell receptor. In one embodiment, the paired hinge and transmembrane domain of the CAR may be derived from CD8a. In one aspect, the paired hinge and transmembrane domain may comprise the amino acid sequence of SEQ ID NO. 8235. In some embodiments, the CAR of the present invention may include an intracellular domain. The intracellular domain may be derived from CD3zeta or a cell surface molecule selected from the group consisting of FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d. In some embodiments, the co-stimulatory domain may be present. The costimulatory domain may be derived from 4-1BB (CD137) 2B4, HVEM, ICOS, LAG3, DAP10, DAP12, CD27, CD28, OX40 (CD134), CD30, CD40, ICOS (CD278), glucocorticoid-induced tumor necrosis factor receptor (GITR), lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, and B7-H3. In one aspect the intracellular domain may be derived from CD3 Zeta SEQ ID NO. 8236. In some embodiments, the CAR may include a co-stimulatory domain derived from 4-1BB (SEQ ID NO. 8237). In some aspects, the CAR further may also include a signal sequence. The signal sequence may be derived from CD8α. In some aspects, the signal sequence may comprise the amino acid sequence of SEQ ID NO. 278.

[0024] In some embodiments, the immunotherapeutic agent may be a cytokine-cytokine receptor fusion polypeptide. The cytokine-cytokine receptor fusion polypeptide may include the whole or a portion of IL15, fused to the whole or a portion of IL15Ra to produce a IL15-IL15Ra fusion polypeptide. In one embodiment the cytokine-cytokine receptor fusion polypeptide may include amino acid sequence of SEQ ID NO. 8324 fused to the amino acid sequence of SEQ ID NO. 8324 to produce a fusion polypeptide.

[0025] In some embodiments, the effector module of the invention may be a DD-CD19 CAR fusion polypeptide. The fusion polypeptide may comprise the amino acid sequence of SEQ ID NO. 8283; 8271-8282 or 8284. In some embodiments, the effector module of the invention may be a DD-IL15-IL15Ra fusion polypeptide (SEQ ID NO. 8338; 8334-8337 or 8339-8343).

[0026] In some embodiments, the SRE may be responsive to one or more stimuli. The stimulus may be a small molecule such as but not limited to Tadalafil, Vardenafil, Sildenafil, Avanafil, Lodenafil, Mirodenafil, Udenafil, Benzamidenafil, Dasantafil, and Beminafil. In one aspect, the small molecule may be Tadalafil.

[0027] The present invention also provides a pharmaceutical composition which may include the compositions described herein and a pharmaceutically acceptable excipient.

[0028] The present invention also provides polynucleotides encoding the compositions and the pharmaceutical compositions described herein.

[0029] Also provided herein are immune cells for adoptive transfer. The immune cells may express the compositions, pharmaceutical compositions, the polynucleotides, or the vectors described herein.

[0030] The present invention also provides methods of inducing an immune response in a cell. Such methods may include administering to the cell, a therapeutically effective amount of any of the pharmaceutical composition and administering to the cell, a therapeutically effective amount of a stimulus to modulate the expression of the immunotherapeutic agent. In some embodiments, the stimulus may be a ligand. In some aspects, the immunotherapeutic agent may be capable of inducing an immune response in the cell, in response to the stimulus.

[0031] Methods of reducing tumor burden using the compositions described herein are also provided. Such methods may include administering to the subject a therapeutically effective amount of the immune cells described herein and administering to the subject a therapeutically effective amount of a stimulus. In some embodiments, the stimulus may be a ligand. In some embodiments, the stimulus may be able to modulate the expression of the immunotherapeutic agent, thereby reducing the tumor burden. In some embodiments, the

ligand is Tadalafil. In some aspects the Tadalafil may be administered to the subject at a dose ranging from about 0.1 mg/kg to about 100 mg/kg body weight of the subject. In some aspects, the Tadalafil may be administered to the subject at a dose of 10 mg/kg body weight of the subject. In some aspects, the Tadalafil may be administered to the subject at a dose of 30 mg/kg body weight of the subject. In some aspects, the Tadalafil may be administered to the subject at a dose of 100 mg/kg body weight of the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the invention, as illustrated in the accompanying drawings. The drawings are not necessarily to scale; emphasis instead being placed upon illustrating the principles of various embodiments of the invention.

[0033] Figure 1 shows an overview diagram of a biocircuit system of the invention. The biocircuit comprises a stimulus and at least one effector module responsive to a stimulus, where the response to the stimulus produces a signal or outcome. The effector module comprises at least one stimulus response element (SRE) and one payload.

[0034] Figure 2 shows representative effector modules carrying one payload. The signal sequence (SS), SRE and payload may be located or positioned in various arrangements without (A to F) or with (G to Z, and AA to DD) a cleavage site. An optional linker may be inserted between each component of the effector module.

[0035] Figure 3 shows representative effector modules carrying two payloads without a cleavage site. The two payloads may be either directly linked to each other or separated.

[0036] Figure 4 shows representative effector modules carrying two payloads with a cleavage site. In one embodiment, an SS is positioned at the N-terminus of the construct, while other components: SRE, two payloads and the cleavage site may be located at different positions (A to L). In another embodiment, the cleavage site is positioned at the N-terminus of the construct (M to X). An optional linker may be inserted between each component of the effector module.

[0037] Figure 5 shows effector modules of the invention carrying two payloads, where an SRE is positioned at the N-terminus of the construct (A to L), while SS, two payloads and the cleavage site can be in any configuration. An optional linker may be inserted between each component of the effector module.

[0038] Figure 6 shows effector modules of the invention carrying two payloads, where either the two payloads (A to F) or one of the two payloads (G to X) is positioned at the N-terminus of the construct (A to L), while SS, SRE and the cleavage site can be in any

configuration. An optional linker may be inserted between each component of the effector module.

[0039] Figure 7 depicts representative configurations of the stimulus and effector module within a biocircuit system. A trans-membrane effector module is activated either by a free stimulus (A) or a membrane bound stimulus (B) which binds to SRE. The response to the stimulus causes the cleavage of the intracellular signal/payload, which activates down-stream effector/payload.

[0040] Figure 8 depicts a dual stimulus-dual presenter biocircuit system, where two bound stimuli (A and B) from two different presenters (e.g., different cells) bind to two different effector modules in a single receiver (e.g., another single cell) simultaneously and create a dual-signal to downstream payloads.

[0041] Figure 9 depicts a dual stimulus-single presenter biocircuit system, where two bound stimuli (A and B) from the same presenter (e.g., a single cell) bind to two different effector modules in another single cell simultaneously and create a dual-signal.

[0042] Figure 10 depicts a single-stimulus-bridged receiver biocircuit system. In this configuration, a bound stimulus (A) binds to an effector module in the bridge cell and creates a signal to activate a payload which is a stimulus (B) for another effector module in the final receiver (e.g., another cell).

[0043] Figure 11 depicts a single stimulus-single receiver biocircuit system, wherein the single receiver contains the two effector modules which are sequentially activated by a single stimulus.

[0044] Figure 12 depicts a biocircuit system which requires a dual activation. In this embodiment, one stimulus must bind the transmembrane effector module first to prime the receiver cell being activated by the other stimulus. The receiver only activates when it senses both stimuli (B).

[0045] Figure 13 depicts a standard effector module of a chimeric antigen receptor (CAR) system which comprises an antigen binding domain as an SRE, and signaling domain(s) as payload.

[0046] Figure 14 depicts the structure design of a regulatable CAR system, where the trans-membrane effector modules comprise antigen binding domains sensing an antigen and a first switch domain and the intracellular module comprises a second switch domain and signaling domains. A stimulus (e.g., a dimerization small molecule) can dimerize the first and second switch domains and assemble an activated CAR system.

[0047] Figure 15 shows schematic representation of CAR systems having one (A) or two (B and C) SREs incorporated into the effector module.

[0048] Figure 16 depicts a split CAR design to control T cell activation by a dual stimulus (e.g., an antigen and small molecule). (A) shows normal T cell activation which entails a dual activation of TCR and co-stimulatory receptor. The regular CAR design (B) combines the antigen recognition domain with TCR signaling motif and co-stimulatory motif in a single molecule. The split CAR system separates the components of the regular CAR into two separate effector modules which can be reassembled when a heterodimerizing small molecule (stimulus) is present.

[0049] Figure 17 depicts the positive and negative regulation of CAR engineered T cell activation. The absence or presence of a second stimulus can negatively (A) or positively (B) control T cell activation.

[0050] Figure 18 shows schematic representation of gated activation of CAR engineered T cells. If a normal cell that has no stimulus (e.g., an antigen) (A) or an antigen that cannot bind to the trans-membrane effector module (B), or only an antigen that activates the trans-membrane effector module and primes the receiver T cell to express the second effector (C), the receiver T cell remains inactive. When both stimuli (e.g. two antigens) that bind the trans-membrane effector module and the primed effector, are present on the presenter cell (e.g. a cancer cell), the T cell is activated (D).

[0051] Figure 19A shows the percent of CAR positive cells obtained with cells transduced with different volumes of virus related to the CAR constructs. Figure 19B shows the percentage of CAR positive cells with vardenafil treatment. Figure 19C shows the expression of the CAR with CD3/CD28 bead restimulation. Figure 19D shows the percentage of CAR positive cells with different concentrations of virus and in the presence or absence of CD3/CD28 bead restimulation. Figure 19E shows the dose response of CD19 CAR constructs to sildenafil, vardenafil and tadalafil. Figure 19F shows the response of CD19 CAR constructs to different ligands and with varying the duration of ligand treatment. Figure 19G shows IL2 and IFNγ levels obtained from the supernatants of cocultures of effector and target cells in the presence of vardenafil. Figure 19H shows the percentage of CAR positive T cells obtained with Tadalafil treatment. Figure 19I shows the IL2 and IFNγ levels obtained from the supernatants of cocultures of effector and target cells in the presence of tadalafil. Figure 19J shows the target cell killing by CAR expressing T cells in the presence of vardenafil. Figure 19K shows the proliferation of target cells cocultured with CAR expressing T cells in the presence of vardenafil.

[0052] Figure 20A shows the total flux of Nalm6 luc cells in mice, in the presence of tadalafil. Figure 20B and Figure 20C show the pharmacokinetics of vardenafil and tadalafil in plasma of mice after injections of ligand at indicated doses.

DETAILED DESCRIPTION OF THE INVENTION

[0053] The details of one or more embodiments of the invention are set forth in the accompanying description below. Although any materials and methods similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred materials and methods are now described. Other features, objects and advantages of the invention will be apparent from the description. In the description, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present description will control.

I. INTRODUCTION

Protein regulation

[0054] The ability to conditionally control protein levels is a powerful tool in gene and cell therapy. Techniques to control protein expression on a genetic level have been widely studied. The Cre-Lox technology provides a useful approach to activate or inactivate genes. Tissue or cell specific promoters can be used to control spatial and temporal expression of genes of interest. However, this system is limited in application due to the irreversible nature of the perturbation. The transcription of the gene of interest can be conditionally regulated using tools such as Doxycycline (Dox)-inducible system. Alternatively, the stability of mRNA can be regulated using RNA interference techniques. However, methods targeting DNA or RNA are slow acting, irreversible and have low efficiency.

[0055] Direct manipulation of activities at the protein level provides significant advantages in flexibility, reversibility and speed. Strategies which directly trigger a cell's natural degradation system have been developed. Szostak and colleagues showed that a small peptide sequence could be fused to the N-terminus of a protein of interest to modulate protein stability (Park, E-C., et al., *Proc. Natl. Acad. Sci. U.S.A.* 1992, 89:1249-1252). Varshavsky and coworkers isolated a temperature-sensitive peptide sequence that greatly reduced the half-life of dihydrofolate reductase (DHFR) at the non-permissive temperatures (Dohmen et al. *Science* 1994, 263:1273-1276). These mutants have been widely used to study protein functions in yeast (Labib et al. *Science* 2000, 288:1643-1646; and Kanemaki et al. *Nature* 2003, 423:720-724).

[0056] Subsequently, reversible systems employing a rapamycin derivative for the regulation of GSK-3β kinase fused to an unstable triple-mutant of the FRB domain (FRB*) were developed. The rapamycin derivative induces dimerization of the FRB*-GSK-3β and endogenous FKBP12 and stabilizes the FRB* fusion thus restoring the function of the fused kinase. (Stankunas et al., Mol Cell. 2003; 12:1615–1624 and Liu et al., Nature. 2007; 446:79–82).

[0057] Building on the FRB* domain system, Banaszynski, *et al.*, developed a cell-permeable ligand system using mutants of FKBP12 protein which were engineered to be unstable in the absence of a high-affinity ligand, Shield-1. (Banaszynski et al., Cell. 2006; 126:995–1004). They termed these unstable domains, destabilizing domains (DDs).

[0058] The FKBP/shield-1 tuning system has been successfully used in several studies to control target proteins. For example, Dettwier et al., fused FKBP to tune the express of NADPH P450 oxidoreductase (POR) (Dettwier et al., *PLoS One,* 2014, 9(11): e113540).

[0059] The FKBP DD-shield system has been used in cell lines, transgenic mice, protozoan *Entamoeba histolytica,* the flatworm *Caenorhabditis elegans*, the medaka, and transgenic xenografts to investigate the activity of a protein of interest (Maynard-Smith et al., *J Biol Chem*. 2007, 282(34): 24866–24872; Liu et al., *Int J Parasitol.* 2014, 44(10):729–735; Cho et al., *PLoS One*. 2013, 8(8): e72393); Banaszynski et al. *Nat Med.* 2008, 14(10):1123–1127; Rodriguez and Wolfgang, *Chem Biol.* 2011, 19(3):391–398; and Froschauer et al., *PLoS One*, 2015, 10(7): e0131252), for iPSC reprogramming (Sui et al., Stem cell Reports., 2014, 2(5): 721-733).

[0060] In addition, the destabilizing domain has been used for the conditional knock-down or knock-out of the target gene fused with the destabilizing domain. Park et al achieved this genomic engineering by CRISPR/Cas9-mediated homologous recombination and a donor template coding for a resistance cassette and the DD-tagged TCOF1 sequence (Park et al., *PLoS One*. 2014, 9(4): e95101).

[0061] More recently protein switches useful as biosensors as well as new chimeric antigen receptors and other small molecule stabilization frameworks have been disclosed (An W, et al. *PLoS ONE*, 2015, 10(12): e0145783. doi: 10.1371/journal.pone.0145783; Nicholes, et al., *Protein Engineering, Design & Selection*, 2016, vol. 29 no. 2, pp. 77–85; Nath, et al., *Biochemical and Biophysical Research Communications*, 2016, 470: 411e416); Stevers, et al., *PNAS*, 2016, vol. 119, no. 9, pp. E112-1161; Juillerat, A. et al., *Sci. Rep.* 2016, 6: 18950; Roybal, *Cell*, 2016, vol. 164, pp. 1-10; and Morsut, *Cell,* 2016, vol. 164, pp. 1-12).

[0062] One drawback of the FKBP/Shield-1 is that Shield-1 is a novel drug whose biodistribution is not fully characterized and it is not known to what extent Shield-1 crosses the blood-brain barrier.

[0063] Other DD ligand pairs include estrogen receptor domains which can be regulated by several estrogen receptor antagonists (Miyazaki et al., J Am Chem. Soc., 2012, 134(9): 3942-3945), and fluorescent destabilizing domain (FDD) derived from bilirubin-inducible fluorescent protein, UnaG. A FDD and its cognate ligand bilirubin (BR) can induce degradation of a protein fused to the FDD (Navarro et al., ACS Chem Biol., 2016, June 6, Epub). Other known DDs and their applications in protein stability include those described in U.S. Pat. NO. 8,173,792 and U.S. Pat. NO. 8,530,636, the contents of which are each incorporated herein by reference in their entirety.

[0064] In an orthogonal approach, the destabilizing domains of the bacterial dihydrofolate reductase (ecDHFR) were explored. (Iwamoto et al., *Chem Biol.* 2010, 17(9):981–988; and Tai et al., *PLoS One*. 2012, 7(9): e46269). Numerous inhibitors of DHFR have been developed as drugs and one such inhibitor Trimethoprim (TMP), inhibits ecDHFR much more potently than mammalian DHFR providing specificity to the interaction. Additionally, TMP is commercially available and has desirable pharmacological properties making this protein-ligand pair ideal for development for use as a biocircuit (Iwamoto, et al., Chem Biol. (2010) September 24; 17(9): 981–988).

[0065] The present invention provides novel protein domains displaying small molecule dependent stability. Such protein domains are called destabilizing domains (DDs). In the absence of its binding ligand, the DD is destabilizing and causes degradation of a payload fused to the DD (e.g., a protein of interest (POI), while in the presence of its binding ligand, the fused DD and payload can be stabilized and its stability is dose dependent. Methods for tuning the expression level and activity of a protein of interest using the DDs, effector modules, biocircuit systems and compositions of the invention are also provided. In some embodiments, the SRE may be a destabilizing domain (DD). In some examples, the DD may be a portion or region of human protein PDE5. In this context, the biocircuit system is a DD biocircuit system.

[0066] The present invention expands upon the technology of tuning protein stability using novel destabilizing domains derived from human PDE5 protein. The destabilization and stabilization of a protein of interest, e.g., a transgene for gene therapy, can be controlled by PDE5 mutant DDs having destabilizing or stabilizing properties and their ligands, e.g. Sildenafil and Vardenafil specifically binding to such protein domains. The presence and/or

absence of a small molecule ligand can tune the activity of a payload (e.g., a protein of interest) that is operably linked to the destabilizing domain.

Immunotherapy

[0067] Cancer immunotherapy aims` at the induction or restoration of the reactivity of the immune system towards cancer. Significant advances in immunotherapy research have led to the development of various strategies which may broadly be classified into active immunotherapy and passive immunotherapy. In general, these strategies may be utilized to directly kill cancer cells or to counter the immunosuppressive tumor microenvironment. Active immunotherapy aims at induction of an endogenous, long-lasting tumor-antigen specific immune response. The response can further be enhanced by non-specific stimulation of immune response modifiers such as cytokines. In contrast, passive immunotherapy includes approaches where immune effector molecules such as tumor-antigen specific cytotoxic T cells or antibodies are administered to the host. This approach is short lived and requires multiple applications.

[0068] Despite significant advances, the efficacy of current immunotherapy strategies is limited by associated toxicities. These are often related to the narrow therapeutic window associated with immunotherapy, which in part, emerges from the need to push therapy dose to the edge of potentially fatal toxicity to get a clinically meaningful treatment effect. Further, dose expands *in vivo* since adoptively transferred immune cells continue to proliferate within the patient, often unpredictably.

[0069] A major risk involved in immunotherapy is the on-target but off tumor side effects resulting from T-cell activation in response to normal tissue expression of the tumor associated antigen (TAA). Clinical trials utilizing T cells expressing T-cell receptor against specific TAA reported skin rash, colitis and hearing loss in response to immunotherapy.

[0070] Immunotherapy may also produce on target, on-tumor toxicities that emerge when tumor cells are killed in response to the immunotherapy. The adverse effects include tumor lysis syndrome, cytokine release syndrome and the related macrophage activation syndrome. Importantly, these adverse effects may occur during the destruction of tumors, and thus even a successful on-tumor immunotherapy might result in toxicity. Approaches to regulatably control immunotherapy are thus highly desirable since they have the potential to reduce toxicity and maximize efficacy.

[0071] The present invention provides systems, compositions, immunotherapeutic agents and methods for cancer immunotherapy. These compositions provide tunable regulation of gene expression and function in immunotherapy. The present invention also provides

biocircuit systems, effector modules, stimulus response elements (SREs) and payloads, as well as polynucleotides encoding any of the foregoing. In one aspect, the systems, compositions, immunotherapeutic agents and other components of the invention can be controlled by a separately added stimulus, which provides a significant flexibility to regulate cancer immunotherapy. Further, the systems, compositions and the methods of the present invention may also be combined with therapeutic agents such as chemotherapeutic agents, small molecules, gene therapy, and antibodies.

[0072] The tunable nature of the systems and compositions of the invention has the potential to improve the potency and duration of the efficacy of immunotherapies. Reversibly silencing the biological activity of adoptively transferred cells using compositions of the present invention allows maximizing the potential of cell therapy without irretrievably killing and terminating the therapy.

[0073] In particular, present invention provides methods for fine tuning of immunotherapy after administration to patients. This in turn improves the safety and efficacy of immunotherapy and increases the subject population that may benefit from immunotherapy.

II. COMPOSITIONS OF THE INVENTION

[0074] A variety of strategies that can directly control protein, e.g., a transgene, expression and function are available. The present invention provides novel protein domains displaying small molecule dependent stability. Such protein domains are called destabilizing domains (DDs). In the absence of its binding ligand, the DD causes degradation of a payload such as a protein of interest (POI) that is operably linked to the DD, while in the presence of its binding ligand, the fused DD and payload can be stabilized and its stability is dose dependent.

[0075] According to the present invention, novel destabilizing domains derived from human hPDE5 (cGMP-specific phosphodiesterase type 5; also referred to as cGMP-specific 3',5'-cyclic phosphodiesterase) protein are provided. The destabilizing domain (DD) mutants are derived from the human PDE5 protein, comprising the amino acid sequence of SEQ ID NO. 1 (encoded by the nucleic acid sequence of SEQ ID NO. 2). The hPDE5 DD mutant may also comprise more than one mutation in the catalytic domain of human PDE5 (SEQ ID NO. 3), encoded by nucleic acid sequence of SEQ ID NO.339, e.g., two, three, four, five or more mutations. These hPDE5 DDs can bind to Sildenafil and/or Vardenafil and be stabilized. In some embodiments, the hPDE5 DD may include a methionine appended to the N terminus of catalytic domain (SEQ ID NO. 237), encoded by SEQ ID NO. 4.

[0076] According to the present invention, biocircuit systems are provided which comprise, at their core, at least one effector module system. Such effector module systems comprise at least one effector module having associated, or integral therewith, one or more stimulus response elements (SREs). The overall architecture of a biocircuit system of the invention is illustrated in Figure 1. In general, a stimulus response element (SRE) may be operably linked to a payload construct which could be any protein of interest (POI) (e.g., an immunotherapeutic agent), to form an effector module. The SRE, when activated by a particular stimulus, e.g., a small molecule, can produce a signal or outcome, to regulate transcription and/or protein levels of the linked payload either up or down by perpetuating a stabilizing signal or destabilizing signal, or any other types of regulation. A much-detailed description of a biocircuit system can be found in co-owned U.S. Provisional Patent Application No. 62/320,864 filed April 11, 2016, 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587 (the contents of each of which are herein incorporated by reference in their entirety). In accordance with the present invention, biocircuit systems, effector modules, SREs and components that tune expression levels and activities of any agents used for immunotherapy are provided. In particular, biocircuit systems and effector modules comprising the novel hPDE5 destabilizing domains discussed herein are provided.

[0077] As used herein, a "biocircuit" or "biocircuit system" is defined as a circuit within or useful in biologic systems comprising a stimulus and at least one effector module responsive to a stimulus, where the response to the stimulus produces at least one signal or outcome within, between, as an indicator of, or on a biologic system. Biologic systems are generally understood to be any cell, tissue, organ, organ system or organism, whether animal, plant, fungi, bacterial, or viral. It is also understood that biocircuits may be artificial circuits which employ the stimuli or effector modules taught by the present invention and effect signals or outcomes in acellular environments such as with diagnostic, reporter systems, devices, assays or kits. The artificial circuits may be associated with one or more electronic, magnetic, or radioactive components or parts.

[0078] In accordance with the present invention, a biocircuit system may be a destabilizing domain (DD) biocircuit system, a dimerization biocircuit system, a receptor biocircuit system, and a cell biocircuit system. Any of these systems may act as a signal to any other of these biocircuit systems. In some embodiments, the present invention provides biocircuit systems, effector modules and compositions comprising the DDs of the present invention. In one aspect, the biocircuit system is a DD biocircuit system.

[0079] In one aspect of the present invention, the biocircuit system is a DD biocircuit system. The DD is a hPDE5 derived DD.

Effector Modules and SREs for Immunotherapy

[0080] In accordance with the present invention, biocircuit systems, effector modules, SREs, and components that tune expression levels and activities of any agents used for immunotherapy are provided. As non-limiting examples, an immunotherapeutic agent may be an antibody and fragments and variants thereof, a cancer specific T cell receptor (TCR) and variants thereof, an anti-tumor specific chimeric antigen receptor (CAR), a chimeric switch receptor, an inhibitor of a co-inhibitory receptor or ligand, an agonist of a co-stimulatory receptor and ligand, a cytokine, chemokine, a cytokine receptor, a chemokine receptor, a soluble growth factor, a metabolic factor, a suicide gene, a homing receptor, or any agent that induces an immune response in a cell and a subject.

[0081] As stated, the biocircuits of the invention include at least one effector module as a component of an effector module system. As used herein, an "effector module" is a single or multi-component construct or complex comprising at least (a) one or more stimulus response elements (SREs) and (b) one or more payloads (i.e. proteins of interest (POIs)). In the context of the present invention, the SRE is a DD derived from human PDE5 protein.

[0082] As used herein a "stimulus response element (SRE)" is a component of an effector module which is joined, attached, linked to or associated with one or more payloads of the effector module and in some instances, is responsible for the responsive nature of the effector module to one or more stimuli. As used herein, the "responsive" nature of an SRE to a stimulus may be characterized by a covalent or non-covalent interaction, a direct or indirect association or a structural or chemical reaction to the stimulus. Further, the response of any SRE to a stimulus may be a matter of degree or kind. The response may be a partial response. The response may be a reversible response. The response may ultimately lead to a regulated signal or output. Such output signal may be of a relative nature to the stimulus, e.g., producing a modulatory effect of between 1% and 100% or a factored increase or decrease such as 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more.

[0083] In some embodiments, the biocircuit system of the present invention comprising a stimulus and an effector module of the invention. The DD of the effector module binds to the stimulus and regulates the stability of the linked payload. The DD may destabilize the protein of interest by a destabilization ratio between 0, and 0.09, wherein the destabilization ratio comprises the ratio of expression, function or level of a protein of interest in the absence of the stimulus specific to the DD to the expression, function or level of the protein of interest

that is expressed constitutively, and in the absence of the stimulus specific to the DD. In some embodiments, the DD may stabilize the protein of interest by a stabilization ratio of 1 or more, wherein the stabilization ratio comprises the ratio of expression, function or level of a protein of interest in the presence of the stimulus to the expression, function or level of the protein of interest in the absence of the stimulus.

[0084] In some embodiments, the present invention provides methods for modulating protein expression, function or level. In some aspects, the modulation of protein expression, function or level refers to modulation of expression, function or level by at least about 20%, such as by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%.

[0085] According to the present invention, biocircuit systems and effector modules of the invention can be used to regulate the expression and activity of a payload in response to the presence or absence of a ligand that specifically binds to the DD integrated within the biocircuit system and effector module.

[0086] In some aspects, DDs, effector modules and biocircuit systems of the invention may be used to regulate the expression, function and activity of a payload in a cell or a subject. The regulation refers to a level of change of its expression, function and activity, by at least about 10%, or at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%.

[0087] In some embodiments, the mutation co-efficient of the biocircuits of the invention may also be measured as a way of evaluating the ability of the DD to modulate protein expression, function or level. As used herein, the "mutation co-efficient" refers to the expression, function or level or a protein of interest, appended to a particular DD mutant, in the absence of the stimulus specific to the SRE; to the protein expression, function or level of

the protein of interest, appended to the corresponding wildtype sequence from which the particular DD mutant is derived and in the absence of the stimulus. The mutation co-efficient is indicative of the contribution of the destabilizing mutations towards the basal expression of the protein independent of the whether the corresponding wildtype protein can be destabilized without any mutations. In some aspects, the mutation co-efficient ratio is at least 0, such as by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or at least, 0-0.1, 0-0.2, 0 -0.3, 0-0.4, 0-0.5, 0-0.6, 0-0.7, 0-0.8, 0-0.9, 0.1-0.2, 0.1 -0.3, 0.1-0.4, 0.1-0.5, 0.1-0.6, 0.1-0.7, 0.1-0.8, 0.1-0.9, 0.2 -0.3, 0.2-0.4, 0.2-0.5, 0.2-0.6, 0.2-0.7, 0.2-0.8, 0.2-0.9, 0.3-0.4, 0.3-0.5, 0.3-0.6, 0.3-0.7, 0.3-0.8, 0.3-0.9, 0.4-0.5, 0.4-0.6, 0.4-0.7, 0.4-0.8, 0.4-0.9, 0.5-0.6, 0.5-0.7, 0.5-0.8, 0.5-0.9, 0.6-0.7, 0.6-0.8, 0.6-0.9,0.7-0.8, 0.7-0.9 or 0.8-0.9.

[0088] In some embodiments, the present invention provides methods for modulating protein, expression, function or level by measuring the stabilization ratio, destabilization ratio, and/or destabilizing mutation co-efficient. As used herein, the "stabilization ratio" is the ratio of expression, function or level of a protein of interest in response to the stimulus to the expression, function or level of the protein of interest in the absence of the stimulus specific to the SRE. In some aspects, the stabilization ratio is at least 1, such as by at least 1-10, 1-20, 1 -30, 1-40, 1-50, 1- 60, 1-70, 1-80, 1- 90, 1-100, 20-30, 20-40, 20-50, 20-60, 20-70, 20-80, 20-90, 20-95, 20-100, 30-40, 30-50, 30-60, 30-70, 30-80, 30-90, 30-95, 30-100, 40-50, 40-60, 40-70, 40-80, 40-90, 40-95, 40-100, 50-60, 50-70, 50-80, 50-90, 50-95, 50-100, 60-70, 60-80, 60-90, 60-95, 60-100, 70-80, 70-90, 70-95, 70-100, 80-90, 80-95, 80-100, 90-95, 90-100 or 95-100. As used herein, the "destabilization ratio" is the ratio of expression, function or level of a protein of interest in the absence of the stimulus specific to the effector module to the expression, function or level of the protein of interest, that is expressed constitutively and in the absence of the stimulus specific to the SRE. As used herein "constitutively" refers to the expression, function or level a protein of interest that is not linked to an SRE, and is therefore expressed both in the presence and absence of the stimulus to the SRE. As used herein, the "destabilizing mutation co-efficient" may be defined as the ratio of expression or level of a protein of interest that is appended to a DD, in the absence of the stimulus specific to the effector module to the expression, function or level of the protein that is appended to the wild type protein from which the DD is derived. In some aspects, the destabilization ratio and/or the destabilizing mutation co-efficient is at least 0, such as by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or at least, 0-0.1, 0-0.2, 0 -0.3, 0-0.4, 0-0.5, 0-0.6, 0-0.7, 0-0.8, 0-0.9, 0.1-0.2, 0.1 -0.3, 0.1-0.4, 0.1-0.5, 0.1-0.6, 0.1-0.7, 0.1-0.8, 0.1-0.9, 0.2 -0.3, 0.2-0.4, 0.2-0.5, 0.2-0.6, 0.2-0.7, 0.2-0.8, 0.2-0.9, 0.3-0.4, 0.3-0.5, 0.3-0.6, 0.3-0.7, 0.3-0.8, 0.3-0.9, 0.4-0.5, 0.4-

0.6, 0.4-0.7, 0.4-0.8, 0.4-0.9, 0.5-0.6, 0.5-0.7, 0.5-0.8, 0.5-0.9, 0.6-0.7, 0.6-0.8, 0.6-0.9,0.7-0.8, 0.7-0.9 or 0.8-0.9.

[0089] The SRE of the effector module may be selected from, but is not limited to, a peptide, peptide complex, peptide-protein complex, protein, fusion protein, protein complex, protein-protein complex. The SRE may comprise one or more regions derived from any natural or mutated protein, or antibody. In this aspect, the SRE is an element, when responding to a stimulus, can tune intracellular localization, intramolecular activation, and/or degradation of payloads.

[0090] In some embodiments, effector modules of the present invention may comprise additional features that facilitate the expression and regulation of the effector module, such as one or more signal sequences (SSs), one or more cleavage and/or processing sites, one or more targeting and/or penetrating peptides, one or more tags, and/or one or more linkers. Additionally, effector modules of the present invention may further comprise other regulatory moieties such as inducible promoters, enhancer sequences, microRNA sites, and/or microRNA targeting sites. Each aspect or tuned modality may bring to the effector module or biocircuit a differentially tuned feature. For example, an SRE may represent a destabilizing domain, while mutations in the protein payload may alter its cleavage sites or dimerization properties or half-life and the inclusion of one or more microRNA or microRNA binding site may impart cellular detargeting or trafficking features. Consequently, the present invention embraces biocircuits which are multifactorial in their tenability. Such biocircuits may be engineered to contain one, two, three, four or more tuned features.

[0091] As shown in Figure 2, representative effector module embodiments comprising one payload, i.e. one immunotherapeutic agent are illustrated. Each components of the effector module may be located or positioned in various arrangements without (A to F) or with (G to Z, and AA to DD) a cleavage site. An optional linker may be inserted between each component of the effector module.

[0092] Figures 3 to 6 illustrate representative effector module embodiments comprising two payloads, i.e. two immunotherapeutic agents. In some aspects, more than two immunotherapeutic agents (payloads) may be included in the effector module under the regulation of the same SRE (e.g., the same DD). The two or more agents may be either directly linked to each other or separated (Figure 3). The SRE may be positioned at the N-terminus of the construct, or the C-terminus of the construct, or in the internal location.

[0093] In some aspects, the two or more immunotherapeutic agents may be the same type such as two antibodies, or different types such as a CAR construct and a cytokine IL12. Biocircuits and components utilizing such effector molecules are given in Figures 7-12.

[0094] As used herein a "payload" or "target payload" is defined as any protein or nucleic acid whose function is to be altered. Payloads may include any coding or non-coding gene or any protein or fragment thereof, or fusion constructs, or antibodies.

[0095] Payloads are often associated with one or more SREs (e.g., DDs) and may be encoded alone or in combination with one or more DD in a polynucleotide of the invention. Payloads themselves may be altered (at the protein or nucleic acid level) thereby providing for an added layer of tenability of the effector module. For example, payloads may be engineered or designed to contain mutations, single or multiple, which affect the stability of the payload or its susceptibility to degradation, cleavage or trafficking. The combination of a DD which can have a spectrum of responses to a stimulus with a payload which is altered to exhibit a variety of responses or gradations of output signals, e.g., expression levels, produce biocircuits which are superior to those in the art. For example, mutations or substitutional designs such as those created for IL12 in WO2016048903 (specifically in Example 1 therein), the contents of which are incorporated herein by reference in their entirety, may be used in any protein payload in conjunction with a DD of the present invention to create dual tunable biocircuits. The ability to independently tune both the DD and the payload greatly increases the scope of uses of the effector modules of the present invention.

[0096] Effector modules may be designed to include one or more payloads, one or more DDs, one or more cleavage sites, one or more signal sequences, one or more tags, one or more targeting peptides, and one or more additional features including the presence or absence of one or more linkers. Representative effector module embodiments of the invention are illustrated in Figures 2-6. In some aspects, the DD can be positioned at the N-terminal end, or the C-terminal end, or internal of the effector module construct. Different components of an effector module such as DDs, payloads and additional features are organized linearly in one construct, or are separately constructed in separate constructs.

[0097] Additionally, effector modules of the present invention may further comprise other regulatory moieties such as inducible promoters, enhancer sequences, microRNA sites, and/or microRNA targeting sites that provide flexibility on controlling the activity of the payload. The payloads of the present invention may be any natural proteins and their variants, or fusion polypeptides, antibodies and variants thereof, transgenes and therapeutic agents.

[0098] The stimulus of the biocircuit system may be, but is not limited to, a ligand, a small molecule, an environmental signal (e.g., pH, temperature, light and subcellular location), a peptide or a metabolite. In one aspect of the present invention, the stimulus is a hPDE5 DD binding ligand including Sildenafil and Vardenafil.

[0099] Polypeptides of DDs, biocircuit systems and effector modules comprising such DDs and payload constructs, other components, polynucleotides encoding these polypeptides and variants thereof, vectors comprising these polynucleotides, are provided in the present invention. The vector may be a plasmid or a viral vector including but not limited to a lentiviral vector, a retroviral vector, a recombinant AAV vector and oncolytic viral vector.

[0100] The position of the payload with respect to the DD, within the SRE may be varied to achieve optimal DD regulation. In some embodiments, the payload may be fused to the N terminus of the DD. In another embodiment, the payload may be fused to the C terminus of the DDs. An optional start codon nucleotide sequence encoding for methionine may be added to the DD and/or payload.

[0101] In some embodiments, more than one biocircuit system may be used in combination to control various protein functions in the same cell or organism, each of which uses different DD and ligand pair and can be regulated separately.

[0102] In some embodiments, biocircuits of the invention may be modified to reduce their immunogenicity. Immunogenicity is the result of a complex series of responses to a substance that is perceived as foreign and may include the production of neutralizing and non-neutralizing antibodies, formation of immune complexes, complement activation, mast cell activation, inflammation, hypersensitivity responses, and anaphylaxis. Several factors can contribute to protein immunogenicity, including, but not limited to protein sequence, route and frequency of administration and patient population. In a preferred embodiment, protein engineering may be used to reduce the immunogenicity of the compositions of the invention. In some embodiments, modifications to reduce immunogenicity may include those that reduce binding of the processed peptides derived from the sequence of the compositions of the invention, to the MHC proteins. For example, amino acid may be modified such that virtually none or a minimal of number of immune epitopes predicted to bind to any prevalent MHC alleles are present in the compositions of the invention. Several methods to identify MHC binding epitopes of known protein sequences are known in the art and may be used to score epitopes in the compositions of the present invention. Such methods are disclosed in US Patent Publication No. US20020119492, US20040230380, and US 20060148009; the contents of each of which are incorporated by reference in their entirety.

[0103] Epitope identification and subsequent sequence modification may be applied to reduce immunogenicity. The identification of immunogenic epitopes may be achieved either physically or computationally. Physical methods of epitope identification may include, for example, mass spectrometry and tissue culture/cellular techniques. Computational approaches that utilize information related to antigen processing, loading and display, structural and/or proteomic data for identifying peptides that may result from antigen processing, and that are likely to have good binding characteristics in the groove of the MHC may also be utilized. One or more mutations may be introduced into the biocircuits of the invention to render the identified epitope less or non-immunogenic, while maintaining functionality.

[0104] In some embodiments, protein modifications engineered into the structure of the compositions of the invention to interfere with antigen processing and peptide loading such as glycosylation and PEGylation, may also be useful in the present invention. Compositions of the invention may also be engineered to include non-classical amino acid sidechains. Any of the methods discussed in International Patent Publication No. WO2005051975 for reducing immunogenicity may be useful in the present invention (the contents of which are incorporated by reference in their entirety).

[0105] In one embodiment, patients may also be stratified according to the immunogenic peptides presented by their immune cells and may be utilized as a parameter to determine patient cohorts that may therapeutically benefit from the compositions of the invention.

[0106] In some embodiments, reduced immunogenicity may be achieved by limiting immunoproteasome processing. The proteasome is an important cellular protease that is found in two forms: the constitutive proteasome, which is expressed in all cell types and which contains catalytic subunits and the immunoproteasome that is expressed in cells of the hematopoietic lineage, and which contains different active subunits termed low molecular weight proteins (LMP) namely LMP-2, LMP- 7 and LMP-10. Immunoproteasomes exhibit altered peptidase activities and cleavage site preferences that result in more efficient liberation of many MHC class I epitopes. A well described function of the immunoproteasome is to generate peptides with hydrophobic C terminus that can be processed to fit in the groove of MHC class I molecules. Deol P et al. have shown that immunoproteasomes may lead to a frequent cleavage of specific peptide bonds and thereby to a faster appearance of a certain peptide on the surface of the antigen presenting cells; and enhanced peptide quantities (Deol P et al. (2007) *J Immunol* 178 (12) 7557-7562; the contents of which are incorporated herein reference in its entirety). This study indicates that reduced immunoproteasome processing may be accompanied by reduced immunogenicity. In

some embodiments, immunogenicity of the compositions of the invention may be reduced by modifying the sequence encoding the compositions of the invention to prevent immunoproteasome processing. Biocircuits of the present invention may also be combined with immunoproteasome-selective inhibitors to achieve the same effects. Examples of inhibitors useful in the present invention include UK-101 (B1i selective compound), IPSI-001, ONX 0914 (PR-957), and PR-924 (IPSI).

[0107] In some embodiments, effector modules of the present invention may include one or more degrons to tune expression. As used herein, a "degron" refers to a minimal sequence within a protein that is sufficient for the recognition and the degradation by the proteolytic system. An important property of degrons is that they are transferrable, that is, appending a degron to a sequence confers degradation upon the sequence. In some embodiments, the degron may be appended to the destabilizing domains, the payload or both. Incorporation of the degron within the effector module of the invention, confers additional protein instability to the effector module and may be used to reduce basal expression. In some embodiments, the degron may be an N-degron, a phospho degron, a heat inducible degron, a photosensitive degron, an oxygen dependent degron. As a non-limiting example, the degron may be an Ornithine decarboxylase degron as described by Takeuchi et al. (Takeuchi J et al. (2008). Biochem J. 2008 Mar 1; 410(2):401-7; the contents of which are incorporated by reference in their entirety). Other examples of degrons useful in the present invention include degrons described in International patent publication Nos. WO2017004022, WO2016210343, and WO2011062962; the contents of each of which are incorporated by reference in their entirety.

[0108] In some embodiments, the effector modules of the present invention may include degrons at their C termini. The degrons may comprise -GG, -RG, -KG, -QG, -WG, -PG, and -AG as the penultimate and the ultimate amino acids of the SREs. Furthermore, certain -2 amino acids (D, E, V, I and L) may be more enriched in the C terminus of the of the effector modules. Other degrons include, but are not limited, to RxxG motif, wherein x is any amino acid, C-terminal twin glutamic acid (EE) motif, and motifs that comprise an arginine at the -3 positions. Degrons may also be selected from the R-3 motif, G-end, R at -3, A-end, A at -2, V at -2 positions. Any of the degrons described in Koren et al., 2018, Cell 173, 1–14, may be useful in the present invention (the contents of which are incorporated by reference in their entirety). In some aspects, the expression of the effector module may be tuned by altering its overall amino acid composition. In some aspects, the amino acid composition of the effector module may be tuned to reduce basal expression. In some embodiments, basal expression may be tuned by increasing the number of bulky aromatic residues such as tryptophan (W),

phenylalanine (F), and tyrosine (Y) in the effector module. Such bulky amino acids are known to reduce protein stability. In some embodiments, the amino acid composition of the SREs may be enriched with acidic residues such as, but not limited to, aspartic acid (D) and glutamic acid (E), and positively charged lysine (K), if an increase in the basal expression of the SRE is desired.

[0109] In some embodiments, the endoplasmic reticulum associated degradation (ERAD) pathway may be used to optimize degradation of the payloads described herein e.g. secreted and membrane cargos. In one embodiment, the effector modules of the invention may be directed to the ER E3 ligases by using adaptor proteins or protein domains. The endoplasmic reticulum is endowed with a specialized machinery to ensure proteins deployed to the distal secretory pathway are correctly folded and assembled into native oligomeric complexes. Proteins failing to meet this conformational standard are degraded by the ERAD pathway, a process through which folding defective proteins are selected and ultimately degraded by the ubiquitin proteasome system. ERAD proceeds through four main steps involving substrate selection, dislocation across the ER membrane, covalent conjugation with polyubiquitin, and proteasome degradation. Any of these steps may be modulated to optimize the degradation of the payloads and the effector modules described herein. Protein adaptors within the ER membrane, link substrate recognition to the ERAD machinery (herein referred to as the "dislocon"), which causes the dislocation of the proteins from the ER. Non-limiting examples of protein adaptors that may be used to optimize ERAD pathway degradation include, but are not limited to SEL1L (an adaptor that links glycan recognition to the dislocon), Erlins (intermembrane substrate adaptors), Insigs (client specific adaptors), F-Box proteins (act as adaptors for dislocated glycoproteins in the cytoplasm) and viral-encoded adaptors.

[0110] According to the present invention, novel destabilizing domains derived from human hPDE5 (cGMP-specific phosphodiesterase type 5) protein are provided. The destabilizing mutants are derived from the human PDE5 protein, comprising the amino acid sequence of SEQ ID NO. 1 (encoded by the nucleic acid sequence of SEQ ID NO: 2). The hPDE5 DD mutant may also comprise more than one mutation in the catalytic domain of human PDE5 of SEQ ID NO. 3 (encoded by nucleic acid sequence of SEQ ID NO. 339), e.g., two, three, four, five or more mutations. These hPDE5 DDs can bind to Sildenafil and/or Vardenafil and be stabilized.

Destabilizing Domains (DDs)

[0111] As used herein, the term “destabilizing domains (DDs)” refers to protein domains that are unstable and degraded in the absence of ligand, but whose stability is rescued by

binding to a high affinity cell-permeable ligand. Destabilizing domains (DDs) can be appended to a target protein of interest (POI) and can convey its destabilizing property to the protein of interest, causing protein degradation. The presence, absence or an amount of a small molecule ligand that binds to or interacts with the DD, can, upon such binding or interaction modulate the stability of the payload(s) and consequently the function of the payload. A protein domain with destabilizing property (e.g. a DD) is used in conjunction with a cell-permeable ligand to regulate any protein of interest when it is fused with the destabilizing domain. DDs render the attached protein of interest unstable in the absence of a DD-binding ligand such that the protein is rapidly degraded by the ubiquitin-proteasome system of the cell. However, when a specific small molecule ligand binds its intended DD as a ligand binding partner, the instability is reversed and protein function is restored. The conditional nature of DD stability allows a rapid and non-perturbing switch from stable protein to unstable substrate for degradation. Moreover, its dependency on the concentration of its ligand further provides tunable control of degradation rates. Depending on the degree of binding and/or interaction the altered function of the payload may vary, hence providing a "tuning" of the payload function.

[0112] Due to its reversibility, specificity and the fast and easy regulation on protein level, the post-transcriptional tuning system provides a useful system for gene regulation. Furthermore, the regulation may be dose-dependent, thereby altering the protein-turnover rate to transform a short-lived or no detectable protein into a protein that functions for a precisely controlled period of time (Iwamoto et al., *Chem. Biol.* 2010, 17: 981–988).

[0113] In some embodiments, the desired characteristics of the DDs may include, but are not limited to, low protein levels in the absence of a ligand of the DD (i.e. low basal stability), large dynamic range, robust and predictable dose-response behavior, and rapid kinetics of degradation. Candidate DDs that bind to a desired ligand but not endogenous molecules may be preferred.

[0114] Candidate destabilizing domain sequence identified from protein domains of known wildtype proteins (as a template) may be mutated to generate libraries of mutants based on the template candidate domain sequence. Mutagenesis strategies used to generate DD libraries may include site-directed mutagenesis e.g. by using structure guided information, or random mutagenesis e.g. using error-prone PCR, or a combination of both. In some embodiments, destabilizing domains identified using random mutagenesis may be used to identify structural properties of the candidate DDs that may be required for destabilization,

which may then be used to further generate libraries of mutations using site directed mutagenesis.

[0115] In some embodiments, novel DDs may be identified by mutating one or more amino acids in the candidate destabilizing domain to an amino acid that is vicinal to the mutation site. As used herein a vicinal amino acid refers to an amino acid that is located 1, 2, 3, 4, 5 or more amino acids upstream or downstream of the mutation site in the linear sequence and/or the crystal structure of the candidate destabilizing domain. In some embodiments, the vicinal amino acid may be a conserved amino acid (with similar physicochemical properties as the amino acid at the mutation site), a semi-conserved amino acid (e.g. negatively to positively charge amino acid) or a non-conserved amino acid (with different physicochemical properties than the amino acid at the mutation site).

[0116] In some embodiments, DD mutant libraries may be screened for mutations with altered, preferably higher binding affinity to the ligand, as compared to the wild type protein. DD libraries may also be screened using two or more ligands and DD mutations that are stabilized by some ligands but not others may be preferentially selected. DD mutations that bind preferentially to the ligand compared to a naturally occurring protein may also be selected. Such methods may be used to optimize ligand selection and ligand binding affinity of the DD. Additionally, such approaches can be used to minimize deleterious effects caused by off-target ligand binding.

[0117] In some embodiments, suitable DDs may be identified by screening mutant libraries using barcodes. Such methods may be used to detect, identify and quantify individual mutant clones within the heterogeneous mutant library. Each DD mutant within the library may have distinct barcode sequences (with respect to each other). In other instances, the polynucleotides can also have different barcode sequences with respect to 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleic acid bases. Each DD mutant within the library may also comprise a plurality of barcode sequences. When used in plurality barcodes may be used such that each barcode is unique to any other barcode. Alternatively, each barcode used may not be unique, but the combination of barcodes used may create a unique sequence that can be individually tracked. The barcode sequence may be placed upstream of the SRE, downstream of the SRE, or in some instances may be placed within the SRE. DD mutants may be identified by barcodes using sequencing approaches such as Sanger sequencing, and next generation sequencing, but also by polymerase chain reaction and quantitative polymerase chain reaction. In some embodiments, polymerase chain reaction primers that amplify a different size product for each barcode may be used to identify each barcode on an agarose

gel. In other instances, each barcode may have a unique quantitative polymerase chain reaction probe sequence that enables targeted amplification of each barcode.

[0118] Inventors of the present invention investigated several human proteins and identified novel human DDs which can confer its instability features to the fused payload and facilitate the rapid degradation of the fusion polypeptide in the absence of its ligand but stabilize the fused payload in response to the binding to its ligand. Specifically, the new DDs are derived from human PDE5 protein.

Human PDE5 mutants

[0119] In some embodiments, DDs of the invention may be derived from human cGMP-specific phosphodiesterase type 5 (PDE5); gene name: PDE5A (herein referred to as "hPDE5"). hPDE5 (phosphodiesterase 5) is a member of the 3,5′-cyclic nucleotide phosphodiesterase family which degrades/hydrolyzes cyclic GMP (cGMP) into its inactive form, GMP, and regulates cGMP signaling. The cGMP/PDE 5 signaling contributes to the development of hypertension in the vasculature, the central nervous system, and the kidney. hPDE5 is known to bind to small molecule such as Sildenafil, Vardenafil, Tadalafil, Avanafil, Lodenafil, Mirodenafil, Udenafil, Benzamidenafil, Dasantafil, Beminafil, SLx-2101, LAS 34179, UK-343,664, UK-357903, UK-371800, and BMS-341400. Sildenafil, Vardenafil, Avanafil, and Tadalafil are hPDE5 inhibitors clinically approved for the treatment of erectile dysfunction. In particular, the binding of these small molecules to hPDE5 occurs within the catalytic domain. In some embodiments, the DDs of the invention may be derived from the catalytic domain of hPDE5 (SEQ ID NO. 3) which includes of residues 535 to 860 of hPDE5 (SEQ ID NO. 1; GenBank Access NO. 076074.2) which may be stabilized by ligands such as small molecule inhibitors of hPDE5 e.g. Sildenafil and Vardenafil. As used herein the term "PDE5 WT" or "hPDE5 WT", refers to the human wildtype PDE5 protein sequence, which is defined as SEQ ID NO. 1, with the GenBank Access NO. 076074.2. In some embodiments, DDs of the present invention may be identified by utilizing a cocktail of hPDE5 inhibitors. In other instances, the suitable DDs may be identified by screening first with one hPDE5 inhibitor and subsequently screening with a second hPDE5 inhibitor.

[0120] In one embodiment, the hPDE5 derived DD may comprise the amino acid sequence of UniProt ID: O76074 (SEQ ID NO. 1) or a portion or a fragment thereof. In another embodiment, the hPDE5 derived DD may comprise the catalytic domain of UniProt ID: O76074, spanning from amino acid position 535 to position 860 (SEQ ID NO. 3); encoded by SEQ ID NO. 339. In addition to the catalytic domain, hPDE5 derived DDs may

also comprise one or more GAF domains and/or the C terminal portion that extends beyond the catalytic domain. In some embodiment, the hPDE5 derived DD may be identified by testing constructs generated by truncating the 5' and/or the 3' end of hPDE5. In one embodiment, the hPDE5 derived DD may be truncated and the smallest hPDE5 based DD may be identified. In another embodiment, the hPDE5 derived DD may include amino acids from position 535 to 836 of SEQ ID NO. 1 which removes the C terminal helix. In another embodiment, the hPDE5 derived DD may consist of amino acids from position 567 to 860 of UniProt ID: O76074 (SEQ ID NO. 1), or position 590 to 860 of UniProt ID: O76074 (SEQ ID NO. 1), which removes a portion of the N terminal domain. In another embodiment, the hPDE5 derived DD may consist of amino acids from position 590 to 836 of UniProt ID: O76074 (SEQ ID NO. 1), which removes a portion of the N terminal domain and the C terminal helix. The DD may include amino acids from position 535 to position 875 of UniProt ID: O76074 (SEQ ID NO. 1). In another embodiment, the hPDE5 derived DD may consist of amino acids from position 466 to 875 of UniProt ID: O76074 (SEQ ID NO. 1) or position 420 to 875 of UniProt ID: O76074 (SEQ ID NO. 1).

[0121] According to the present invention, several hPDE5 destabilizing mutations were discovered by site directed mutagenesis of the catalytic domain of wildtype human PDE5 using site directed mutagenesis. The destabilization of the mutants in the absence of its binding ligands is tested. Binding to hPDE5 ligands, Sildenafil, Tadalafil and Vardenafil to human PDE5 was tested and ligand dependent stabilization was characterized. Based on the structural analysis of hPDE5 bound to Sildenafil, several residues were selected for mutagenesis. In some embodiments one or more of the residues described herein may be mutagenized to obtain hPDE5 derived DDs. The tryptophan at position 853 of SEQ ID NO.1 may be mutated to phenylalanine to induce hydrophobic packing near binding site, while maintaining pi bond with the nearby tryptophan at position 772. The isoleucine at position 821 may be mutated to valine or alanine, which results in hydrophobic packing near binding site. The tyrosine at position 829 may be mutated to isoleucine, valine or alanine, which results in hydrophobic packing near binding site. The aspartate at position 656 may be mutated to asparagine or leucine to break up the charge and the salt bridge on loop/helix. The tyrosine at position 728 may be mutated to phenylalanine or leucine to break the salt bridges at position 732 and to affect hydrophobic packing. Alternatively, the arginine at position 732 may be mutated to lysine or leucine to generate the inverse of the effects of mutating tyrosine at position 728. The methionine at position 625 may be mutated to leucine or isoleucine to

alter packing in away from the binding site. In some embodiments, destabilizing mutations that do not affect ligand binding may be preferentially selected.

[0122] In some embodiments, new destabilizing domains of the present invention are derived from the catalytic domain of human PDE5 protein comprising the amino acid sequence of SEQ ID NO. 3. In some aspects, the destabilizing mutant domain may comprise one, two, three, four, five or more mutations such as, but not limited to, M625I, D656L, Y728L, R732L, F736A, F787A, I821A, Y829A and W853F. The DDs of the invention may further include additional mutations e.g. E535D, E536G, Q541R, K555R, S560G, F559L, F561L, F564L, F564S, S766F, V585A, N587S, K591E, I599V, K604E, K608E, N609H, K630R, K633E, N636S, I648V, N661S, S663P, L675P, Y676D, Y676N, C677R, H678R, D687A, T711A, T712S, D724N, L738H, N742S, F744L, L746S, F755L, A762S, D764V, D764N, D764G, K795E, L797F, I799T, L804P, T802P, S815C, M816A, M816T, I824T, C839S, F840S, and K852E. In some embodiments, any of the mutation sites disclosed herein may be mutated to any of the known amino acids such as Histidine, Alanine, Isoleucine, Arginine, Leucine, Aspartic acid, Lysine, Cysteine, Methionine, Glutamic acid, Phenylalanine, Glutamine, Threonine, Glycine, Tryptophan, Proline, Valine, Serine, Tyrosine, Asparagine, Selenocysteine, Pyrrolysine. In some embodiments, DDs of the present invention may be stabilized by ligands such as Sildenafil, Vardenafil, Tadalafil, Avanafil, Lodenafil, Mirodenafil, Udenafil, Benzamidenafil, Dasantafil, and Beminafil.

[0123] The amino acid sequences of the destabilizing domains encompassed in the invention have at least about 40%, 50 or 60% identity, further at least about 70% identity, preferably at least about 75% or 80% identity, more preferably at least about 85%, 86%, 87%, 88%, 89% or 90% identity, and further preferably at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to the amino acid sequence set forth therein. Percent identity may be determined, for example, by comparing sequence information using the advanced BLAST computer program, including version Magic-BLAST 1.2.0, available from the National Institutes of Health. The BLAST program is based on the alignment method discussed in Karl and Altschul (1990) Proc. Natl. Acad. Sci USA, 87:2264-68 (the contents of which are incorporated by reference in their entirety).

[0124] Several hPDE5 destabilizing mutants were identified and are provided in Table 1. The position of the mutated amino acids listed in Table 1 is relative to the full length hPDE5 of SEQ ID NO. 1. The domains described in Table 1 include the catalytic domain of hPDE5 (e.g., 535-860 of SEQ ID NO. 1). In some embodiments, the hPDE5 DDs described in Table

1 may include a methionine at the N terminal of the catalytic domain of hPDE5, i.e. amino acid 535-860 of PDE5 WT. In Table 1, the mutated amino acids are in bold and underlined.

Table 1: hPDE5 DDs

hPDE5 mutant description	Amino Acid Sequence	AA SEQ ID NO	NA SEQ ID NO
hPDE5 (Amino acid 535-860 of WT, W853F)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEFF ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQ RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQK**F**QAL AEQQ	5	350
hPDE5 (Amino acid 535-860 of WT, I821A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEFF ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQ RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGF**A**DAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ	6	351
hPDE5 (Amino acid 535-860 of WT, Y829A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEFF ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQ RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQL**A**EALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ	7	352
hPDE5 (Amino acid 535-860 of WT, F787A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEFF ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQ RIAELVATEF**A**DQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ	8	353
hPDE5 (Amino acid 535-860 of WT, F736A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEF **A**ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQ QRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ	9	354; 355
hPDE5 (Amino acid 535-860 of WT, D656L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DL**L**HRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEFF ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQ	10	356

	RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ		
hPDE5 (Amino acid 535-860 of WT, Y728L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLAL**L**IKRRGEFF ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQ RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ	11	357
hPDE5 (Amino acid 535-860 of WT, R732L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKR**L**GEFF ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQ RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ	12	358; 359
hPDE5 (Amino acid 535-860 of WT, M625I)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQC**I**FAALKAGKIQNKLTDLEILALLIAALSHD LDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILN SPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEFFE LIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRI AELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQV GFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQALAE QQ	13	360
Methionine; hPDE5 (Amino acid 535-860 of WT; W853F)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQK**F** QALAEQQ	340	14
Methionine; hPDE5 (Amino acid 535-860 of WT, I821A)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGF**A**DAICLQLYEALTHVSEDCFPLLDGCRKNRQK WQALAEQQ	341	15
Methionine; hPDE5 (Amino acid 535-860 of WT, Y829A)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQL**A**EALTHVSEDCFPLLDGCRKNRQKW QALAEQQ	342	16
Methionine; hPDE5 (Amino acid	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL	343	17

535-860 of WT, F787A)	SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEF**A**DQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQ		
Methionine; hPDE5 (Amino acid 535-860 of WT, F736A)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEF**A**ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQ	344	18
Methionine; hPDE5 (Amino acid 535-860 of WT, D656L)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDL**L**HRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQ	345	19
Methionine; hPDE5 (Amino acid 535-860 of WT, Y728L)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLAL**L**IKRRG EFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPI QQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ	346	20
Methionine; hPDE5 (Amino acid 535-860 of WT, R732L)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKR**L** GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQ	238	21
Methionine; hPDE5 (Amino acid 535-860 of WT, M625I)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQC**I**FAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMI LNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEF FELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQ QRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ	347	22
hPDE5 (Amino acid 535-860 of WT, H653A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSA DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEFF ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQ RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ	348	361

hPDE5 (Amino acid 535-860 of WT, D764A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEFF ELIRKNQFNLEDPHQKELFLAMLMTACALSAITKPWPIQQ RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ	349	362

[0125] In some embodiments, DDs derived from hPDE5 may include one, two, three, four, five, or more of the mutations described in the previous Table (Table 1).

[0126] In some embodiments, DDs derived from hPDE5 may further comprise one, two, three, four, five or more mutations to the catalytic domain of hPDE5 and may be selected from E535D, E536G, Q541R, K555R, S560G, F559L, F561L, F564L, F564S, S766F, V585A, N587S, K591E, I599V, K604E, K608E, N609H, K630R, K633E, N636S, I648V, N661S, S663P, L675P, Y676D, Y676N, C677R, H678R, D687A, T711A, T712S, D724N, L738H, N742S, F744L, L746S, F755L, A762S, D764V, D764N, D764G, K795E, L797F, I799T, L804P, T802P, S815C, M816A, M816T, I824T, C839S, F840S, and K852E (as listed in Table 2). The position of the mutated amino acid is with respect to the hPDE5 of SEQ ID NO. 1. In Table 2, the mutated amino acids are underlined and in bold. The position of the mutated amino acids listed in Table 2 is relative to the full length hPDE5 of SEQ ID NO.1

Table 2: Additional hPDE5 DDs

hPDE5 mutant description	**Amino Acid Sequence**	**AA SEQ ID NO**
hPDE5 (Amino acid 535-860 of WT, E535D)	**D**ETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	23
hPDE5 (Amino acid 535-860 of WT, E536G)	E**G**TRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	24
hPDE5 (Amino acid 535-860 of WT, Q541R)	EETREL**R**SLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	25

hPDE5 (Amino acid 535-860 of WT, K555R)	EETRELQSLAAAVVPSAQTL**R**ITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	26
hPDE5 (Amino acid 535-860 of WT, F559L)	EETRELQSLAAAVVPSAQTLKITD**L**SFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	27
hPDE5 (Amino acid 535-860 of WT, F561L)	EETRELQSLAAAVVPSAQTLKITDFS**L**SDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	28
hPDE5 (Amino acid 535-860 of WT, F564L)	EETRELQSLAAAVVPSAQTLKITDFSFSD**L**ELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	29
hPDE5 (Amino acid 535-860 of WT, F564S)	EETRELQSLAAAVVPSAQTLKITDFSFSD**S**ELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	30
hPDE5 (Amino acid 535-860 of WT, K591E)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQM**E**HEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	31
hPDE5 (Amino acid 535-860 of WT, N587S)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQ**S**FQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTA QCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQ RSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFLA MLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPT DLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGC RKNRQKWQALAEQQ	32
hPDE5 (Amino acid 535-860 of WT, K604E)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVK**E**NYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK	33

	TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	
hPDE5 (Amino acid 535-860 of WT, K608E)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYR**E**NVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	34
hPDE5 (Amino acid 535-860 of WT, N609H)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRK**H**VAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	35
hPDE5 (Amino acid 535-860 of WT, K630R)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAAL**R**AGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	36
hPDE5 (Amino acid 535-860 of WT, K633E)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAG**E**IQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	37
hPDE5 (Amino acid 535-860 of WT, N636S)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQ**S**KLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	38
hPDE5 (Amino acid 535-860 of WT, N661S)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGV**S**NSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	39
hPDE5 (Amino acid 535-860 of WT, Y676D)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQL**D**CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	40

hPDE5 (Amino acid 535-860 of WT, Y676N)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQL**N**CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	41
hPDE5 (Amino acid 535-860 of WT, C677R)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLY**R**HSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	42
hPDE5 (Amino acid 535-860 of WT, H678R)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYC**R**SIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	43
hPDE5 (Amino acid 535-860 of WT, D687A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHF**A**QCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	44
hPDE5 (Amino acid 535-860 of WT, T712S)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK T**S**LKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	45
hPDE5 (Amino acid 535-860 of WT, D724N)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILAT**N**LALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	46
hPDE5 (Amino acid 535-860 of WT, D724G)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILAT**G**LALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	47
hPDE5 (Amino acid 535-860 of WT, L738H)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK	48

	TTLKIIKQAILATDLALYIKRRGEFFE**H**IRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	
hPDE5 (Amino acid 535-860 of WT, N742S)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRK**S**QFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	49
hPDE5 (Amino acid 535-860 of WT, A762S)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMT**S**CDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	50
hPDE5 (Amino acid 535-860 of WT, D764N)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTAC**N**LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	51
hPDE5 (Amino acid 535-860 of WT, D764G)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTAC**G**LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	52
hPDE5 (Amino acid 535-860 of WT, D764V)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTAC**V**LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	53
hPDE5 (Amino acid 535-860 of WT, S766F)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDL**F**AITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	54
hPDE5 (Amino acid 535-860 of WT, K795E)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRER**E**ELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	55

hPDE5 (Amino acid 535-860 of WT, L797F)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKE**F**NIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	56
hPDE5 (Amino acid 535-860 of WT, I799T)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELN**T**E PTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLD GCRKNRQKWQALAEQQ	57
hPDE5 (Amino acid 535-860 of WT, T802P)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP **P**DLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	58
hPDE5 (Amino acid 535-860 of WT, S815C)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIP**C**MQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	59
hPDE5 (Amino acid 535-860 of WT, M816A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPS**A**QVGFIDAICLQLYEALTHVSEDCFPLLDGC RKNRQKWQALAEQQ	60
hPDE5 (Amino acid 535-860 of WT, I824T)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDA**T**CLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	61
hPDE5 (Amino acid 535-860 of WT, C839S)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSED**S**FPLLDG CRKNRQKWQALAEQQ	62
hPDE5 (Amino acid 535-860 of WT, K852E)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK	63

	TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQ**E**WQALAEQQ	
hPDE5 (Amino acid 535-860 of WT, S560G)	EETRELQSLAAAVVPSAQTLKITDF**G**FSDFELSDLETALCTIRMF TDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	64
hPDE5 (Amino acid 535-860 of WT, V585A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNL**A**QNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	65
hPDE5 (Amino acid 535-860 of WT, I599V)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRW**V**LSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	66
hPDE5 (Amino acid 535-860 of WT, I648V)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALL**V**AALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	67
hPDE5 (Amino acid 535-860 of WT, S663P)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNN**P**YI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	68
hPDE5 (Amino acid 535-860 of WT, L675P)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQ**P**YCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	69
hPDE5 (Amino acid 535-860 of WT, T711A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK **A**TLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	70

hPDE5 (Amino acid 535-860 of WT, F744L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQ**L**NLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	71
hPDE5 (Amino acid 535-860 of WT, L746S)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFN**S**EDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	72
hPDE5 (Amino acid 535-860 of WT, F755L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKEL**L**L AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	73
hPDE5 (Amino acid 535-860 of WT, L804P)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TD**P**MNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	74
hPDE5 (Amino acid 535-860 of WT, M816T)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPS**T**QVGFIDAICLQLYEALTHVSEDCFPLLDGC RKNRQKWQALAEQQ	75
hPDE5 (Amino acid 535-860 of WT, F840S)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDC**S**PLLDG CRKNRQKWQALAEQQ	76

[0127] In some embodiments, DDs derived from hPDE5 may include the combination of at least one, two, three, four or five mutations listed in Table 1 with at least 0, 1, 2, 3, 4, 5 or more mutations listed in Table 2.

[0128] In some embodiments, the DDs may be derived from hPDE5 (SEQ ID NO. 3), by mutating one or more amino acids residues between positions 530 -550, 550-570, 570-590, 590-610, 620- 640, 640-660, 660-680, 680-700, 710- 730, 730- 750, 750- 770, 770-790, 790-

810- 830, 830- 850, 850-860 of the catalytic domain of human PDE5 (SEQ ID NO. 1). In some embodiments, the mutation may be a conserved (with similar physicochemical properties as the amino acid at the mutation site), a semi conserved (e.g., negatively to positively charge amino acid) or a non-conserved (amino acid with different physicochemical properties than the amino acid at the mutation site). In some embodiments, the amino acid lysine may be mutated to glutamic acid or arginine; the amino acid phenylalanine may be mutated to leucine; the amino acid leucine may be mutated to phenylalanine; or the amino acid asparagine may be mutated to serine. Regions or portions or domains of wild type proteins may be utilized as SREs/DDs in whole or in part. They may be combined or rearranged to create new peptides, proteins, regions or domains of which any may be used as SREs/DDs or the starting point for the design of further SREs and/or DDs.

[0129] In some embodiments, DDs may be derived from hPDE5 by mutating amino acid residues conserved within all members of the PDE family. Exemplary conserved residues include but are not limited to, E682, H613, H617, H653, D654, and H657 residues of full length human PDE5 (SEQ ID NO. 1) and are taught in Sung et al. Nature (2003) 425, 98-102 (the contents of which are incorporated herein by reference in their entirety). In other embodiments, residues that are critical for binding to metals such as zinc and magnesium may be mutated to identify novel hPDE5 DDs. In some embodiments, hPDE5 derived DDs may be identified from a library of mutants of hPDE5 catalytic domain generated using a combination of error-prone PCR and nucleotide analog mutagenesis through random mutagenesis. Any of the mutations identified by site directed mutagenesis may be combined with the mutations identified by random mutagenesis. In some embodiments, DDs described herein may be derived by mutating the Y612 amino acid of hPDE5 (SEQ ID NO.1). In some embodiments, the mutations to the Y612 amino acid may be combined with any of the mutations described herein. Independent co-crystals of hPDE5 with vardenafil and with sildenafil, have demonstrated that one of the rings of the both ligand, interacts with Y612 of hPDE5, an amino acid located within the catalytic site of hPDE5. Interactions occur via a hydrogen bond with a water molecule and via hydrophobic bonds. Y612F mutation, which ablates the hydrogen bonding potential, increases the inhibition of hPDE5 activity by both ligands. The Y612A mutation, which leads to the ablation of both hydrogen bonding and hydrophobic bonding potential has been shown to weaken the inhibition of hPDE5 catalytic activity by vardenafil and sildenafil to a lesser extent. These studies suggest that hydrophobic bonding involving Y612 is stronger for vardenafil than for sildenafil (Corbin et al. 2006,

International Journal of Impotence Research 18, 251-257; the contents of which are incorporated by reference in their entirety).

[0130] The destabilization domains described herein may also include amino acid and nucleotide substitutions that do not affect stability, including conservative, non-conservative substitutions and or polymorphisms.

[0131] In some embodiments, hPDE5 DDs described herein may also be fragments of the above destabilizing domains, including fragments containing variant amino acid sequences. Preferred fragments are unstable in the absence of the stimulus and stabilized upon addition of the stimulus. Preferred fragments retain the ability to interact with the stimulus with similar efficiency as the DDs described herein.

[0132] In one embodiment, hPDE5 mutants are fused to AcGFP through a linker sequence at either the N-terminal or the C-terminal end of the fusion constructs. The AcGFP of Uniprot ID BAE93141 (SEQ ID NO. 363), may be used as the GFP template and is referred to as the wildtype or "WT" version of AcGFP. In some embodiments, the hPDE5 mutants described herein may also be operably linked to a luciferase (luc) gene, such as the firefly luciferase (Fluc) or Renilla luciferase (Rluc). The position of the mutations in the Fluc protein sequence described herein are based on the comparison of the SEQ ID NO. 223 with the wildtype luciferase sequence of Photinus pyralis (Uniprot ID: P08659.1) or "Fluc WT", comprising the amino acid sequence of SEQ ID NO. 364. The destabilizing and ligand dependent stabilization properties of the fusion proteins may be evaluated by methods such as western blotting, and FACS. hPDE5 mutants that are fused to the N terminus of GFP are provided in Table 3. All constructs may be cloned into any vector known in the art and/or described herein such as, but not limited to, pLVX.IRES Puro vectors. OT-hPDE5C-036 (OT-001232) was placed under the transcriptional control of the EF1a promoter, while the other constructs described in Table 3 were placed under the transcriptional control of CMV promoter. In Table 3, and asterisk indicates the translation of the stop codon. Table 3 also provides alternate aliases for a given construct ID. These aliases are identified by the prefix OT.

Table 3: hPDE5-AcGFP constructs

Construct ID/ Description	Amino Acid Sequence	AA SEQ ID NO.	NA SEQ ID NO.
Linker	GGSGGGSGG	77	92
Linker	GGSGGG	78	93; 300
Linker	SG	-	AGT GGT

AcGFP (Amino acid 2-239 of WT)	VSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYG KLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQ HDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLV NRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAKN GIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDNH YLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELYK	79	372
AcGFP (Amino acid 1-239 of WT)	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATY GKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTL VNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDN HYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY K	365	94, 373
Fluc (Amino acid 2-549 of WT, N50D, N119G, S548I, K549A, L550V)	EDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTI AFTDAHIEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIV VCSENSLQFFMPVLGALFIGVAVAPANDIYNERELLNSMG ISQPTVVFVSKKGLQKILNVQKKLPIIQKIIIMDSKTDYQGF QSMYTFVTSHLPPGFNEYDFVPESFDRDKTIALIMNSSGST GLPKGVALPHRTACVRFSHARDPIFGNQIIPDTAILSVVPFH HGFGMFTTLGYLICGFRVVLMYRFEEELFLRSLQDYKIQS ALLVPTLFSFFAKSTLIDKYDLSNLHEIASGGAPLSKEVGE AVAKRFHLPGIRQGYGLTETTSAILITPEGDDKPGAVGKV VPFFEAKVVDLDTGKTLGVNQRGELCVRGPMIMSGYVNN PEATNALIDKDGWLHSGDIAYWDEDEHFFIVDRLKSLIKY KGYQVAPAELESILLQHPNIFDAGVAGLPDDDAGELPAAV VVLEHGKTMTEKEIVDYVASQVTTAKKLRGGVVFVDEVP KGLTGKLDARKIREILIKAKKGGKIAV	366	374
OT-hPDE5N-001 (OT-001075, OT-hPDE5-001) Methionine; hPDE5 (Amino acid 535-860 of WT); linker (GGSGGGSGG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQGGSGGGSGGVSKGAELFTGIVPILIELNGDVNG HKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTL SYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDG NYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEY NYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHY QQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFG FVTAAAITHGMDELYK*	80	95
OT-hPDE5N-002 (OT-001078, OT-hPDE5-002) Methionine; hPDE5 (Amino acid 535-860 of WT, W853F); linker (GGSGGGSGG); AcGFP (Amino acid 2-239 of WT); stop)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKF QALAEQQGGSGGGSGGVSKGAELFTGIVPILIELNGDVNG HKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTL SYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDG NYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEY NYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHY QQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFG FVTAAAITHGMDELYK*	81	96
OT-hPDE5N-003 (OT-	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL	82	97

001080, OT-hPDE5-003) Methionine; hPDE5 (Amino acid 535-860 of WT, I821A); linker (GGSGGGSGG); AcGFP (Amino acid 2-239 of WT); stop	SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFADAICLQLYEALTHVSEDCFPLLDGCRKNRQK WQALAEQQGGSGGGSGGVSKGAELFTGIVPILIELNGDVN GHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTT LSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDD GNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKME YNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADH YQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*		
OT-hPDE5N-004 (OT-001081, OT-hPDE5-004) Methionine; hPDE5 (Amino acid 535-860 of WT, Y829A); linker (GGSGGGSGG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLAEALTHVSEDCFPLLDGCRKNRQKW QALAEQQGGSGGGSGGVSKGAELFTGIVPILIELNGDVNG HKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTL SYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDG NYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEY NYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHY QQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFG FVTAAAITHGMDELYK*	83	98
OT-hPDE5N-005 (OT-001074, OT-hPDE5-005) Methionine; hPDE5 (Amino acid 535-860 of WT, F787A); linker (GGSGGGSGG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFADQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQGGSGGGSGGVSKGAELFTGIVPILIELNGDVNG HKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTL SYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDG NYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEY NYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHY QQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFG FVTAAAITHGMDELYK*	84	99
OT-hPDE5N-006 (OT-001076, OT-hPDE5-006) Methionine; hPDE5 (Amino acid 535-860 of WT, F736A); linker (GGSGGGSGG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFAELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQGGSGGGSGGVSKGAELFTGIVPILIELNGDVNG HKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTL SYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDG NYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEY NYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHY QQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFG FVTAAAITHGMDELYK*	85	100
OT-hPDE5N-007 (OT-	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY	86	101

001082, OT-hPDE5-007) Methionine; hPDE5 (Amino acid 535-860 of WT, D656L); linker (GGSGGGSGG); AcGFP (Amino acid 2-239 of WT); stop	HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLLHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQGGSGGGSGGVSKGAELFTGIVPILIELNGDVNG HKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTL SYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDG NYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEY NYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHY QQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFG FVTAAAITHGMDELYK*		
OT-hPDE5N-008 (OT-001083, OT-hPDE5-008) Methionine; hPDE5 (Amino acid 535-860 of WT, Y728L); linker (GGSGGGSGG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALLIKRRG EFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPI QQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQGGSGGGSGGVSKGAELFTGIVPILIELNGDVNGH KFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTLS YGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDGN YKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEYN YNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGF VTAAAITHGMDELYK*	87	102
OT-hPDE5N-009 (OT-001084, OT-hPDE5-009) Methionine; hPDE5 (Amino acid 535-860 of WT, R732L); linker (GGSGGGSGG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPI QQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQGGSGGGSGGVSKGAELFTGIVPILIELNGDVNGH KFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTLS YGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDGN YKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEYN YNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGF VTAAAITHGMDELYK*	88	103
OT-hPDE5N-010 (OT-001070, OT-hPDE5-010) Methionine; hPDE5 (Amino acid 535-860 of WT, M625I); linker (GGSGGGSGG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCIFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMI LNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEF FELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQ QRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQGGSGGGSGGVSKGAELFTGIVPILIELNGDVNGH KFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTLS YGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDGN YKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEYN YNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGF VTAAAITHGMDELYK*	89	104

OT-hPDE5-028 (OT-001224) Methionine; hPDE5 (Amino acid 535-860 of WT); linker (GGSGGG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQGGSGGGVSKGAELFTGIVPILIELNGDVNGHKF SVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTLSYG VQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDGNYK SRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEYNYN AHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQQN TPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVT AAAITHGMDELYK*	90	105
OT-hPDE5C-036 (OT-001232; OT-hPDE5-036) AcGFP (Amino acid 1-239 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATY GKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTL VNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDN HYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY KSGEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETA LCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA YHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA LSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQ*	91	106
OT-hPDE5-031 (OT-001227) Methionine; hPDE5 (Amino acid 535-860 of WT); linker (SG); Fluc (N50D, N119G, S548I, K549A, L550V); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQSGEDAKNIKKGPAPFYPLEDGTAGEQLHKAMK RYALVPGTIAFTDAHIEVDITYAEYFEMSVRLAEAMKRYG LNTNHRIVVCSENSLQFFMPVLGALFIGVAVAPANDIYNE RELLNSMGISQPTVVFVSKKGLQKILNVQKKLPIIQKIIIMD SKTDYQGFQSMYTFVTSHLPPGFNEYDFVPESFDRDKTIA LIMNSSGSTGLPKGVALPHRTACVRFSHARDPIFGNQIIPD TAILSVVPFHHGFGMFTTLGYLICGFRVVLMYRFEEELFLR SLQDYKIQSALLVPTLFSFFAKSTLIDKYDLSNLHEIASGG APLSKEVGEAVAKRFHLPGIRQGYGLTETTSAILITPEGDD KPGAVGKVVPFFEAKVVDLDTGKTLGVNQRGELCVRGP MIMSGYVNNPEATNALIDKDGWLHSGDIAYWDEDEHFFI VDRLKSLIKYKGYQVAPAELESILLQHPNIFDAGVAGLPD DDAGELPAAVVVLEHGKTMTEKEIVDYVASQVTTAKKLR GGVVFVDEVPKGLTGKLDARKIREILIKAKKGGKIAV*	367	375
OT-hPDE5-032 (OT-001228) Methionine; hPDE5 (Amino acid 535-860 of WT, F736A);	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFAELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW	368	376

linker (SG); Fluc (N50D, N119G, S548I, K549A, L550V); stop	QALAEQQSGEDAKNIKKGPAPFYPLEDGTAGEQLHKAMK RYALVPGTIAFTDAHIEVDITYAEYFEMSVRLAEAMKRYG LNTNHRIVVCSENSLQFFMPVLGALFIGVAVAPANDIYNE RELLNSMGISQPTVVFVSKKGLQKILNVQKKLPIIQKIIIMD SKTDYQGFQSMYTFVTSHLPPGFNEYDFVPESFDRDKTIA LIMNSSGSTGLPKGVALPHRTACVRFSHARDPIFGNQIIPD TAILSVVPFHHGFGMFTTLGYLICGFRVVLMYRFEEELFLR SLQDYKIQSALLVPTLFSFFAKSTLIDKYDLSNLHEIASGG APLSKEVGEAVAKRFHLPGIRQGYGLTETTSAILITPEGDD KPGAVGKVVPFFEAKVVDLDTGKTLGVNQRGELCVRGP MIMSGYVNNPEATNALIDKDGWLHSGDIAYWDEDEHFFI VDRLKSLIKYKGYQVAPAELESILLQHPNIFDAGVAGLPD DDAGELPAAVVVLEHGKTMTEKEIVDYVASQVTTAKKLR GGVVFVDEVPKGLTGKLDARKIREILIKAKKGGKIAV*		
OT-hPDE5-033 (OT-001229) Methionine; hPDE5 (Amino acid 535-860 of WT, R732L); Linker (SG); Fluc (N50D, N119G, S548I, K549A, L550V); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPI QQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQSGEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKR YALVPGTIAFTDAHIEVDITYAEYFEMSVRLAEAMKRYGL NTNHRIVVCSENSLQFFMPVLGALFIGVAVAPANDIYNER ELLNSMGISQPTVVFVSKKGLQKILNVQKKLPIIQKIIIMDS KTDYQGFQSMYTFVTSHLPPGFNEYDFVPESFDRDKTIALI MNSSGSTGLPKGVALPHRTACVRFSHARDPIFGNQIIPDTA ILSVVPFHHGFGMFTTLGYLICGFRVVLMYRFEEELFLRSL QDYKIQSALLVPTLFSFFAKSTLIDKYDLSNLHEIASGGAP LSKEVGEAVAKRFHLPGIRQGYGLTETTSAILITPEGDDKP GAVGKVVPFFEAKVVDLDTGKTLGVNQRGELCVRGPMI MSGYVNNPEATNALIDKDGWLHSGDIAYWDEDEHFFIVD RLKSLIKYKGYQVAPAELESILLQHPNIFDAGVAGLPDDD AGELPAAVVVLEHGKTMTEKEIVDYVASQVTTAKKLRGG VVFVDEVPKGLTGKLDARKIREILIKAKKGGKIAV*	369	377
OT-hPDE5-086 (OT-001211) AcGFP (Amino acid 1-239 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT, H653A); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATY GKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTL VNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDN HYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY KSGEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETA LCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA YHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA LSADLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQ*	370	378
OT-hPDE5-087 (OT-001208) AcGFP (Amino acid 1-239 of WT); linker (SG); hPDE5 (Amino acid	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATY GKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTL VNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDN HYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY KSGEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETA LCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA YHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA	371	379

535-860 of WT, D764A); stop	LSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACALSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQ*		

[0133] In addition to human PDE5, other phosphodiesterases may also be used to generate novel destabilizing domains. The human PDE superfamily includes 11 structurally related but functionally distinct gene families (hPDE1 to hPDE11). These differ in their cellular functions, primary structures, affinities for cAMP and cGMP, catalytic properties and response to specific activators, inhibitors, effectors and mechanisms of regulation. As modular proteins, hPDEs exhibit a common structural organization with divergent amino-terminal regulatory regions and conserved carboxy-terminal catalytic core. The hPDE family proteins contain an N terminal regulatory region and a C terminal catalytic region. The N-terminal regulatory regions contain structural determinants that target individual hPDEs to different subcellular locations, and allow individual hPDEs to specifically respond to different post translational modification. The structural elements include dimerization domains, auto-inhibitory modules, binding sites for ligands and allosteric effectors. In contrast, the X ray crystal structure isolated catalytic domains of nine hPDE families (hPDE1 to hPDE5 and hPDE7 to hPDE10) have demonstrated that the catalytic domains of hPDEs share a similar topography, composed of ~350 amino acids folded into 16 helices. Across the hPDE families, the active site forms a deep hydrophobic pocket that contains a hPDE specific, histidine-containing signature motif, HD(X_2) H(X_4) N (SEQ ID NO: 8377), and binding sites for two divalent metal ions that are essential for catalytic function. The affinity of hPDEs to specific cyclic nucleotides varies within the family-some hPDEs specifically hydrolyze cAMP (hPDE4, hPDE7 and hPDE8), whereas others hydrolyze cGMP (hPDE5, hPDE6 and hPDE9), and some hydrolyze both cAMP and cGMP (hPDE1, hPDE2, hPDE3, hPDE10 and hPDE11).

[0134] Similar to hPDE5, the catalytic domain or other functional domain of any hPDE family member may be mutagenized and screened for destabilizing mutations. Known inhibitors for each hPDE protein may also be tested for ligand-dependent stabilization.

[0135] In some embodiments, known mutations in phosphodiesterases that affect protein stability may be utilized to identify novel hPDE derived DDs. Mutations previously identified include, but are not limited to, hPDE5 (I778T), or hPDE6C (H602L), hPDE6C (E790K), hPDE6C (R104W), hPDE6C (Y323N), and hPDE6C (P391L) or hPDE4D (S752A), hPDE4D

(S754A), hPDE4D (S752A, S754A), and hPDE4D (E757A, E758A, D759A) (Zhu et al. (2010) Mol Cell Biol. 4379-4390; Alexandre et al. (2015). Endocr. Relat. Cancer 22(4):519-30; Cheguru P. et al. (2015) Mol Cell Neurosci; 64: 1–8; the contents of each of which are incorporated herein by reference in their entirety).

[0136] In some embodiments, novel DDs may be generated from hPDE1 which is also known as calcium and calmodulin dependent phosphodiesterase. It has three subtypes hPDE1A, hPDE1B and hPDE1C. The enzyme contains three functional domains; a conserved catalytic core, a regulatory N-terminus and a C-terminus. The catalytic domains of hPDE1 have three helical subdomains; an N-terminal cyclin fold region, a linker region and a C-terminal helical bundle. Vinpocetine is a known inhibitor of hPDE1.

[0137] In some embodiments, novel DDs may be generated from hPDE2, a dual substrate enzyme that hydrolyzes both cAMP and cGMP. The distinguishing feature of this hPDE is that it is allosterically stimulated by cGMP binding to one of its GAF domains. The crystal structure of hPDE2 GAF-B domain reveals that the GAF-B domain binds cGMP with high affinity and selectivity. Exemplary hPDE2 inhibitors include EHNA (erythro-9-(2-hydroxy-3-nonyl) adenine), Oxindole, PDP and BAY 60-7550. Inhibitors that selectively inhibit a hPDE2 isoform may also be used, for example, substituted pyrido (2,3-b) pyrazines having a hPDE2A selective inhibitory action (See, e.g., US Pat. NO.: 9,527,841; the contents of which are incorporated by reference in its entirety.)

[0138] In some embodiments, novel DDs may be generated from hPDE3 which preferentially hydrolyses cAMP. Like other hPDE family members, it comprises three functional domains, a conserved catalytic core, a regulatory terminus and the C-terminus. The catalytic core of hPDE is characterized by a unique 44-amino acid insert. Amrinone, Cilostazol, Milrinone, Enoximone and Pimobendan are inhibitors for hPDE3 enzyme.

[0139] In some embodiments, novel DDs may be generated from hPDE4, the principal second messenger for immune response regulation and is responsible for the hydrolysis of cAMP. Four isoforms of hPDE4 exist with each isoform having a unique N terminal region that specifies cellular localization by mediating interactions with scaffolding proteins which may further comprise upstream conserved regions (UCRs). All isoforms share invariant catalytic domain. The catalytic pocket is lined with highly conserved and invariant residues, including an invariant glutamine (Q369) that forms crucial hydrogen bond with substrates. Analyses of crystal structure of hPDE-inhibitor complexes suggest that two conserved residues are essential for inhibitor binding. The formation of hydrogen bonds with invariant glutamine determines the orientation of the inhibitors and conserved hydrophobic residues

(I336 and F340) form a hydrophobic clamp that anchors inhibitors in the pocket. A number of small molecules can inhibit hPDE 4 activity, some of which are FDA approved such as AN2728 (4-[(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-5-yl) oxy]benzonitrile), Apremilast/ CC10004 (N-{2-[(1S)-1-(3-Ethoxy-4-methoxyphenyl)-2-(methyl sulfonyl) ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl}acetamide), and Roflumilast. Other small molecules that inhibit hPDE4 also include E6005/RVT501, Cilomilast/SB-207,499, Ibudilast (AV-411 or MN-166), Mesembrenone, Piclamilast / RP 73401, Rolipram, Atizoram / CP-80633, Arofylline, CC-1088, Catramilast, CGH-2466, Cipamfylline, Drotaverine, Filaminast/WAY-PDA 641, HT-0712, DNS-001, ICI-63197, Indimilast, Irsogladine/MN 1695, Lirimilast/ BAY 19-8004, Oglemilast, Revamilast, Ro 20-1724, Ronomilast, GSK256066, DC-TA-46, AWD 12–281 and YM-976.

[0140] In some embodiments, novel DDs may be generated from hPDE6. This holoenzyme includes hPDE6 alpha, hPDE6 beta and/or two identical inhibitory subunits of hPDE6 gamma. hPDE6 alpha and beta forms comprise three domains: two N-terminal GAF domains and one C-terminal catalytic domain. The non-catalytic GAF domains are responsible for cGMP binding.

[0141] In some embodiments, novel DDs may be generated from hPDE7, a cAMP specific hPDE which consists of two genes, hPDE7A and hPDE7B. There are no known regulatory domains on the N terminus as established for most of the other hPDE families, although consensus PKA phosphorylation sites exist in this region. Several small molecules can inhibit PDE7, including BRL-50481(N, N,2-Trimethyl-5-nitrobenzenesulfonamide) and ASB16165 (1H-Thieno(2,3-C) pyrazole-5-carboxamide, 1-cyclohexyl-N-(6-(4-hydroxy-1-piperidinyl)-3-pyridinyl)-3-methyl).

[0142] In some embodiments, novel DDs may be generated from hPDE8. Two subfamilies of hPDE8 exist and both they have very high affinity for the substrate cAMP and are insensitive to the non-specific PDE inhibitor IBMX. Each protein contains a catalytic core, a PAS (Per, Arnt and Sim) and a REC (receiver) domain. The crystal structure of the catalytic core of hPDE8 identified Tyr748 residue as a unique residue that distinguishes hPDE8 inhibitor binding from other hPDE proteins bound to inhibitors. PF-04957325 (Pfizer) is a small molecule inhibitor of hPDE8.

[0143] In some embodiments, novel DDs may be generated from hPDE9, which has the highest affinity for cGMP. The primary structure of hPDE9A is simple as it does not appear to contain any GAF domains or other N-terminal regulatory sequences found in other hPDEs. The catalytic pocket is lined with highly conserved and invariant residues, including an

invariant glutamine Gln 453 in hPDE9A2 that forms crucial hydrogen bond with substrates. The formation of hydrogen bonds with invariant glutamine determines the orientation of the inhibitors and conserved hydrophobic residues form a hydrophobic clamp that anchors inhibitors in the pocket and wedges their ring structures against F456 in hPDE9A. Tested hPDE9 inhibitors may include BAY73-6691 (1-(2-chlorophenyl)-6-[(2R)-3,3,3-trifluoro-2-methylpropyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one), PF-04447943 (6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-1-(oxan-4-yl)-2H-pyrazolo[3,4-d]pyrimidin-4-one) and WYQ-C28L.

[0144] In some embodiments, novel DDs may be generated from hPDE10, which can hydrolyze both cAMP and cGMP. Like some other hPDE family proteins, hPDE10 comprises 2 GAF domains in the N terminal region, a Protein Kinase A phosphorylation site and a catalytic domain. The catalytic pocket is lined with highly conserved and invariant residues, including an invariant glutamine Q726 in hPDE10A2 that forms crucial hydrogen bond with substrates. Several PDE10 inhibitors are under clinical trials including OMS 824, Papaverine and PF-2545920 (2-(4-(1-methyl-4-pyridin-4-yl-1H-pyrazol-3-yl) phenoxymethyl) quinolone).

[0145] In some embodiments, novel DDs may be generated from hPDE11. Like hPDE10, the recently discovered hPDE11 can hydrolyze both cAMP and cGMP. It comprises of only one gene with four isoform variants. The longest variant, hPDE11A4, has two N-terminal GAF domains, whereas the other variants are truncations of this variant of varying lengths.

[0146] In some embodiments, any of the destabilizing mutations related to hPDE5 described herein may be structurally mapped onto other phosphodiesterases to generate destabilizing domains. In one embodiment, mutations that destabilize hPDE5, and which subsequently result in stabilization in the presence of sildenafil and/or vardenafil may be engineered onto hPDE6. In one embodiment, mutations that destabilize hPDE5, and which subsequently result in stabilization in the presence of Tadalafil may be engineered onto hPDE11.

[0147] The full length hPDEs and their catalytic domains that may be utilized to derive novel DDs are listed in Table 4.

Table 4: Sequences of human PDE proteins and their catalytic domains

PDE protein (Uniprot ID or domain description)	Amino Acid sequence	AA SEQ ID NO.
hPDE1A (Uniprot ID: P54750)	MDDHVTIRKKHLQRPIFRLRCLVKQLERGDVNVVDLKKNIEYAA SVLEAVYIDETRRLLDTEDELSDIQTDSVPSEVRDWLASTFTRKM GMTKKKPEEKPKFRSIVHAVQAGIFVERMYRKTYHMVGLAYPA AVIVTLKDVDKWSFDVFALNEASGEHSLKFMIYELFTRYDLINRF KIPVSCLITFAEALEVGYSKYKNPYHNLIHAADVTQTVHYIMLHT GIMHWLTELEILAMVFAAAIHDYEHTGTTNNFHIQTRSDVAILYN DRSVLENHHVSAAYRLMQEEEMNILINLSKDDWRDLRNLVIEMV LSTDMSGHFQQIKNIRNSLQQPEGIDRAKTMSLILHAADISHPAKS WKLHYRWTMALMEEFFLQGDKEAELGLPFSPLCDRKSTMVAQS QIGFIDFIVEPTFSLLTDSTEKIVIPLIEEASKAETSSYVASSSTTIVG LHIADALRRSNTKGSMSDGSYSPDYSLAAVDLKSFKNNLVDIIQQ NKERWKELAAQEARTSSQKCEFIHQ	107
hPDE1A Catalytic domain (Amino acid 193 – 515 of PDE1A)	FKIPVSCLITFAEALEVGYSKYKNPYHNLIHAADVTQTVHYIMLH TGIMHWLTELEILAMVFAAAIHDYEHTGTTNNFHIQTRSDVAILY NDRSVLENHHVSAAYRLMQEEEMNILINLSKDDWRDLRNLVIEM VLSTDMSGHFQQIKNIRNSLQQPEGIDRAKTMSLILHAADISHPAK SWKLHYRWTMALMEEFFLQGDKEAELGLPFSPLCDRKSTMVAQ SQIGFIDFIVEPTFSLLTDSTEKIVIPLIEEASKAETSSYVASSSTTIVG LHIADALRRSNTKGSMSDGSYSPDYSLAAVDLKSFKNNLVDIIQQ NKERW	108
hPDE1B (Uniprot ID: Q01064)	MELSPRSPPEMLEESDCPSPLELKSAPSKKMWIKLRSLLRYMVKQ LENGEINIEELKKNLEYTASLLEAVYIDETRQILDTEDELQELRSD AVPSEVRDWLASTFTQQARAKGRRAEEKPKFRSIVHAVQAGIFV ERMFRRTYTSVGPTYSTAVLNCLKNLDLWCFDVFSLNQAADDH ALRTIVFELLTRHNLISRFKIPTVFLMSFLDALETGYGKYKNPYHN QIHAADVTQTVHCFLLRTGMVHCLSEIELLAIIFAAAIHDYEHTGT TNSFHIQTKSECAIVYNDRSVLENHHISSVFRLMQDDEMNIFINLT KDEFVELRALVIEMVLATDMSCHFQQVKTMKTALQQLERIDKPK ALSLLLHAADISHPTKQWLVHSRWTKALMEEFFRQGDKEAELGL PFSPLCDRTSTLVAQSQIGFIDFIVEPTFSVLTDVAEKSVQPLADED SKSKNQPSFQWRQPSLDVEVGDPNPDVVSFRSTWVKRIQENKQK WKERAASGITNQMSIDELSPCEEEAPPSPAEDEHNQNGNLD	109
hPDE1B Catalytic domain (Amino acid 197 – 496 of PDE1B)	FKIPTVFLMSFLDALETGYGKYKNPYHNQIHAADVTQTVHCFLLR TGMVHCLSEIELLAIIFAAAIHDYEHTGTTNSFHIQTKSECAIVYND RSVLENHHISSVFRLMQDDEMNIFINLTKDEFVELRALVIEMVLA TDMSCHFQQVKTMKTALQQLERIDKPKALSLLLHAADISHPTKQ WLVHSRWTKALMEEFFRQGDKEAELGLPFSPLCDRTSTLVAQSQ IGFIDFIVEPTFSVLTDVAEKSVQPLADEDSKSKNQPSFQWRQPSL DVEVGDPNPDVVSFRSTWVKRIQENKQKW	110
hPDE1C (Uniprot ID: Q14123)	MESPTKEIEEFESNSLKYLQPEQIEKIWLRLRGLRKYKKTSQRLRS LVKQLERGEASVVDLKKNLEYAATVLESVYIDETRRLLDTEDELS DIQSDAVPSEVRDWLASTFTRQMGMMLRRSDEKPRFKSIVHAVQ AGIFVERMYRRTSNMVGLSYPPAVIEALKDVDKWSFDVFSLNEA SGDHALKFIFYELLTRYDLISRFKIPISALVSFVEALEVGYSKHKNP YHNLMHAADVTQTVHYLLYKTGVANWLTELEIFAIIFSAAIHDYE HTGTTNNFHIQTRSDPAILYNDRSVLENHHLSAAYRLLQDDEEM NILINLSKDDWREFRTLVIEMVMATDMSCHFQQIKAMKTALQQP EAIEKPKALSLMLHTADISHPAKAWDLHHRWTMSLLEEFFRQGD REAELGLPFSPLCDRKSTMVAQSQVGFIDFIVEPTFTVLTDMTEKI VSPLIDETSQTGGTGQRRSSLNSISSSDAKRSGVKTSGSEGSAPINN SVISVDYKSFKATWTEVVHINRERWRAKVPKEEKAKKEAEEKAR LAAEEQQKEMEAKSQAEEGASGKAEKKTSGETKNQVNGTRANK SDNPRGKNSKAEKSSGEQQQNGDFKDGKNKTDKKDHSNIGNDS	111

	KKTDGTKQRSHGSPAPSTSSTCRLTLPVIKPPLRHFKRPAYASSSY APSVSKKTDEHPARYKMLDQRIKMKKIQNISHNWNRK	
hPDE1C Catalytic domain (Amino acid 202 – 521 of PDE1C)	FKIPISALVSFVEALEVGYSKHKNPYHNLMHAADVTQTVHYLLY KTGVANWLTELEIFAIIFSAAIHDYEHTGTTNNFHIQTRSDPAILYN DRSVLENHHLSAAYRLLQDDEEMNILINLSKDDWREFRTLVIEM VMATDMSCHFQQIKAMKTALQQPEAIEKPKALSLMLHTADISHP AKAWDLHHRWTMSLLEEFFRQGDREAELGLPFSPLCDRKSTMV AQSQVGFIDFIVEPTFTVLTDMTEKIVSPLIDETSQTGGTGQRRSSL NSISSSDAKRSGVKTSGSEGSAPINNSVISVDYKSFKATWTEVVHI NRERW	112
hPDE2A (Uniprot ID: O00408)	MGQACGHSILCRSQQYPAARPAEPRGQQVFLKPDEPPPPPQPCAD SLQDALLSLGSVIDISGLQRAVKEALSAVLPRVETVYTYLLDGES QLVCEDPPHELPQEGKVREAIISQKRLGCNGLGFSDLPGKPLARL VAPLAPDTQVLVMPLADKEAGAVAAVILVHCGQLSDNEEWSLQ AVEKHTLVALRRVQVLQQRGPREAPRAVQNPPEGTAEDQKGGA AYTDRDRKILQLCGELYDLDASSLQLKVLQYLQQETRASRCCLL LVSEDNLQLSCKVIGDKVLGEEVSFPLTGCLGQVVEDKKSIQLKD LTSEDVQQLQSMLGCELQAMLCVPVISRATDQVVALACAFNKLE GDLFTDEDEHVIQHCFHYTSTVLTSTLAFQKEQKLKCECQALLQV AKNLFTHLDDVSVLLQEIITEARNLSNAEICSVFLLDQNELVAKVF DGGVVDDESYEIRIPADQGIAGHVATTGQILNIPDAYAHPLFYRG VDDSTGFRTRNILCFPIKNENQEVIGVAELVNKINGPWFSKFDEDL ATAFSIYCGISIAHSLLYKKVNEAQYRSHLANEMMMYHMKVSDD EYTKLLHDGIQPVAAIDSNFASFTYTPRSLPEDDTSMAILSMLQD MNFINNYKIDCPTLARFCLMVKKGYRDPPYHNWMHAFSVSHFC YLLYKNLELTNYLEDIEIFALFISCMCHDLDHRGTNNSFQVASKS VLAALYSSEGSVMERHHFAQAIAILNTHGCNIFDHFSRKDYQRML DLMRDIILATDLAHHLRIFKDLQKMAEVGYDRNNKQHHRLLLCL LMTSCDLSDQTKGWKTTRKIAELIYKEFFSQGDLEKAMGNRPME MMDREKAYIPELQISFMEHIAMPIYKLLQDLFPKAAELYERVASN REHWTKVSHKFTIRGLPSNNSLDFLDEEYEVPDLDGTRAPINGCC SLDAE	113
hPDE2A Catalytic domain (Amino acid 633 – 891 of PDE2A)	KIDCPTLARFCLMVKKGYRDPPYHNWMHAFSVSHFCYLLYKNL ELTNYLEDIEIFALFISCMCHDLDHRGTNNSFQVASKSVLAALYSS EGSVMERHHFAQAIAILNTHGCNIFDHFSRKDYQRMLDLMRDIIL ATDLAHHLRIFKDLQKMAEVGYDRNNKQHHRLLLCLLMTSCDL SDQTKGWKTTRKIAELIYKEFFSQGDLEKAMGNRPMEMMDREK AYIPELQISFMEHIAMPIYKLLQDLFPKAAELYERVASN	114
hPDE3A (Uniprot ID: Q14432)	MAVPGDAARVRDKPVHSGVSQAPTAGRDCHHRADPASPRDSGC RGCWGDLVLQPLRSSRKLSSALCAGSLSFLLALLVRLVRGEVGC DLEQCKEAAAAEEEEAAPGAEGGVFPGPRGGAPGGGARLSPWL QPSALLFSLLCAFFWMGLYLLRAGVRLPLAVALLAACCGGEALV QIGLGVGEDHLLSLPAAGVVLSCLAAATWLVLRLRLGVLMIALT SAVRTVSLISLERFKVAWRPYLAYLAGVLGILLARYVEQILPQSA EAAPREHLGSQLIAGTKEDIPVFKRRRRSSSVVSAEMSGCSSKSHR RTSLPCIPREQLMGHSEWDHKRGPRGSQSSGTSITVDIAVMGEAH GLITDLLADPSLPPNVCTSLRAVSNLLSTQLTFQAIHKPRVNPVTS LSENYTCSDSEESSEKDKLAIPKRLRRSLPPGLLRRVSSTWTTTTS ATGLPTLEPAPVRRDRSTSIKLQEAPSSSPDSWNNPVMMTLTKSR SFTSSYAISAANHVKAKKQSRPGALAKISPLSSPCSSPLQGTPASSL VSKISAVQFPESADTTAKQSLGSHRALTYTQSAPDLSPQILTPPVIC SSCGRPYSQGNPADEPLERSGVATRTPSRTDDTAQVTSDYETNNN SDSSDIVQNEDETECLREPLRKASACSTYAPETMMFLDKPILAPEP LVMDNLDSIMEQLNTWNFPIFDLVENIGRKCGRILSQVSYRLFED MGLFEAFKIPIREFMNYFHALEIGYRDIPYHNRIHATDVLHAVWY LTTQPIPGLSTVINDHGSTSDSDSDSGFTHGHMGYVFSKTYNVTD DKYGCLSGNIPALELMALYVAAAMHDYDHPGRTNAFLVATSAP QAVLYNDRSVLENHHAAAAWNLFMSRPEYNFLINLDHVEFKHF RFLVIEAILATDLKKHFDFVAKFNGKVNDDVGIDWTNENDRLLV CQMCIKLADINGPAKCKELHLQWTDGIVNEFYEQGDEEASLGLPI	115

	SPFMDRSAPQLANLQESFISHIVGPLCNSYDSAGLMPGKWVEDSD ESGDTDDPEEEEEEAPAPNEEETCENNESPKKKTFKRRKIYCQITQ HLLQNHKMWKKVIEEEQRLAGIENQSLDQTPQSHSSEQIQAIKEE EEEKGKPRGEEIPTQKPDQ	
hPDE3A Catalytic domain (Amino acid 728 – 1086 of PDE3A)	FKIPIREFMNYFHALEIGYRDIPYHNRIHATDVLHAVWYLTTQPIP GLSTVINDHGSTSDSDSDSGFTHGHMGYVFSKTYNVTDDKYGCL SGNIPALELMALYVAAAMHDYDHPGRTNAFLVATSAPQAVLYN DRSVLENHHAAAAWNLFMSRPEYNFLINLDHVEFKHFRFLVIEAI LATDLKKHFDFVAKFNGKVNDDVGIDWTNENDRLLVCQMCIKL ADINGPAKCKELHLQWTDGIVNEFYEQGDEEASLGLPISPFMDRS APQLANLQESFISHIVGPLCNSYDSAGLMPGKWVEDSDESGDTDD PEEEEEEAPAPNEEETCENNESPKKKTFKRRKIYCQITQHLLQNHK MW	116
hPDE3B (Uniprot ID: Q13370)	MRRDERDAKAMRSLQPPDGAGSPPESLRNGYVKSCVSPLRQDPP RGFFFHLCRFCNVELRPPPASPQQPRRCSPFCRARLSLGALAAFVL ALLLGAEPESWAAGAAWLRTLLSVCSHSLSPLFSIACAFFFLTCFL TRTKRGPGPGRSCGSWWLLALPACCYLGDFLVWQWWSWPWGD GDAGSAAPHTPPEAAAGRLLLVLSCVGLLLTLAHPLRLRHCVLV LLLASFVWWVSFTSLGSLPSALRPLLSGLVGGAGCLLALGLDHFF QIREAPLHPRLSSAAEEKVPVIRPRRRSSCVSLGETAASYYGSCKIF RRPSLPCISREQMILWDWDLKQWYKPHYQNSGGGNGVDLSVLN EARNMVSDLLTDPSLPPQVISSLRSISSLMGAFSGSCRPKINPLTPF PGFYPCSEIEDPAEKGDRKLNKGLNRNSLPTPQLRRSSGTSGLLPV EQSSRWDRNNGKRPHQEFGISSQGCYLNGPFNSNLLTIPKQRSSS VSLTHHVGLRRAGVLSSLSPVNSSNHGPVSTGSLTNRSPIEFPDTA DFLNKPSVILQRSLGNAPNTPDFYQQLRNSDSNLCNSCGHQMLK YVSTSESDGTDCCSGKSGEEENIFSKESFKLMETQQEEETEKKDSR KLFQEGDKWLTEEAQSEQQTNIEQEVSLDLILVEEYDSLIEKMSN WNFPIFELVEKMGEKSGRILSQVMYTLFQDTGLLEIFKIPTQQFMN YFRALENGYRDIPYHNRIHATDVLHAVWYLTTRPVPGLQQIHNG CGTGNETDSDGRINHGRIAYISSKSCSNPDESYGCLSSNIPALELM ALYVAAAMHDYDHPGRTNAFLVATNAPQAVLYNDRSVLENHH AASAWNLYLSRPEYNFLLHLDHVEFKRFRFLVIEAILATDLKKHF DFLAEFNAKANDVNSNGIEWSNENDRLLVCQVCIKLADINGPAK VRDLHLKWTEGIVNEFYEQGDEEANLGLPISPFMDRSSPQLAKLQ ESFITHIVGPLCNSYDAAGLLPGQWLEAEEDNDTESGDDEDGEEL DTEDEEMENNLNPKPPRRKSRRRIFCQLMHHLTENHKIWKEIVEE EEKCKADGNKLQVENSSLPQADEIQVIEEADEEE	117
hPDE3B Catalytic domain (Amino acid 713 – 1072 of PDE3B)	FKIPTQQFMNYFRALENGYRDIPYHNRIHATDVLHAVWYLTTRP VPGLQQIHNGCGTGNETDSDGRINHGRIAYISSKSCSNPDESYGCL SSNIPALELMALYVAAAMHDYDHPGRTNAFLVATNAPQAVLYN DRSVLENHHAASAWNLYLSRPEYNFLLHLDHVEFKRFRFLVIEAI LATDLKKHFDFLAEFNAKANDVNSNGIEWSNENDRLLVCQVCIK LADINGPAKVRDLHLKWTEGIVNEFYEQGDEEANLGLPISPFMDR SSPQLAKLQESFITHIVGPLCNSYDAAGLLPGQWLEAEEDNDTES GDDEDGEELDTEDEEMENNLNPKPPRRKSRRRIFCQLMHHLTEN HKIW	118
hPDE4A (Uniprot ID: P27815)	MEPPTVPSERSLSLSLPGPREGQATLKPPPQHLWRQPRTPIRIQQR GYSDSAERAERERQPHRPIERADAMDTSDRPGLRTTRMSWPSSFH GTGTGSGGAGGGSSRRFEAENGPTPSPGRSPLDSQASPGLVLHAG AATSQRRESFLYRSDSDYDMSPKTMSRNSSVTSEAHAEDLIVTPF AQVLASLRSVRSNFSLLTNVPVPSNKRSPLGGPTPVCKATLSEETC QQLARETLEELDWCLEQLETMQTYRSVSEMASHKFKRMLNREL THLSEMSRSGNQVSEYISTTFLDKQNEVEIPSPTMKEREKQQAPRP RPSQPPPPPVPHLQPMSQITGLKKLMHSNSLNNSNIPRFGVKTDQE ELLAQELENLNKWGLNIFCVSDYAGGRSLTCIMYMIFQERDLLK KFRIPVDTMVTYMLTLEDHYHADVAYHNSLHAADVLQSTHVLL ATPALDAVFTDLEILAALFAAAIHDVDHPGVSNQFLINTNSELAL MYNDESVLENHHLAVGFKLLQEDNCDIFQNLSKRQRQSLRKMVI DMVLATDMSKHMTLLADLKTMVETKKVTSSGVLLLDNYSDRIQ	119

	VLRNMVHCADLSNPTKPLELYRQWTDRIMAEFFQQGDRERERG MEISPMCDKHTASVEKSQVGFIDYIVHPLWETWADLVHPDAQEIL DTLEDNRDWYYSAIRQSPSPPPEEESRGPGHPPLPDKFQFELTLEE EEEEEISMAQIPCTAQEALTAQGLSGVEEALDATIAWEASPAQESL EVMAQEASLEAELEAVYLTQQAQSTGSAPVAPDEFSSREEFVVA VSHSSPSALALQSPLLPAWRTLSVSEHAPGLPGLPSTAAEVEAQR EHQAAKRACSACAGTFGEDTSALPAPGGGGSGGDPT	
hPDE4A Catalytic domain (Amino acid 330-723 of PDE4A)	QPMSQITGLKKLMHSNSLNNSNIPRFGVKTDQEELLAQELENLNK WGLNIFCVSDYAGGRSLTCIMYMIFQERDLLKKFRIPVDTMVTY MLTLEDHYHADVAYHNSLHAADVLQSTHVLLATPALDAVFTDL EILAALFAAAIHDVDHPGVSNQFLINTNSELALMYNDESVLENHH LAVGFKLLQEDNCDIFQNLSKRQRQSLRKMVIDMVLATDMSKH MTLLADLKTMVETKKVTSSGVLLLDNYSDRIQVLRNMVHCADL SNPTKPLELYRQWTDRIMAEFFQQGDRERERGMEISPMCDKHTA SVEKSQVGFIDYIVHPLWETWADLVHPDAQEILDTLEDNRDWYY SAIRQSPSPPPEEESRGPGHPPLPDKFQFELTLEEEEEEEEISM	120
hPDE4B (Uniprot ID: Q07343)	MKKSRSVMTVMADDNVKDYFECSLSKSYSSSSNTLGIDLWRGRR CCSGNLQLPPLSQRQSERARTPEGDGISRPTTLPLTTLPSIAITTVSQ ECFDVENGPSPGRSPLDPQASSSAGLVLHATFPGHSQRRESFLYRS DSDYDLSPKAMSRNSSLPSEQHGDDLIVTPFAQVLASLRSVRNNF TILTNLHGTSNKRSPAASQPPVSRVNPQEESYQKLAMETLEELDW CLDQLETIQTYRSVSEMASNKFKRMLNRELTHLSEMSRSGNQVS EYISNTFLDKQNDVEIPSPTQKDREKKKKQQLMTQISGVKKLMHS SSLNNTSISRFGVNTENEDHLAKELEDLNKWGLNIFNVAGYSHNR PLTCIMYAIFQERDLLKTFRISSDTFITYMMTLEDHYHSDVAYHNS LHAADVAQSTHVLLSTPALDAVFTDLEILAAIFAAAIHDVDHPGV SNQFLINTNSELALMYNDESVLENHHLAVGFKLLQEEHCDIFMNL TKKQRQTLRKMVIDMVLATDMSKHMSLLADLKTMVETKKVTSS GVLLLDNYTDRIQVLRNMVHCADLSNPTKSLELYRQWTDRIMEE FFQQGDKERERGMEISPMCDKHTASVEKSQVGFIDYIVHPLWET WADLVQPDAQDILDTLEDNRNWYQSMIPQSPSPPLDEQNRDCQG LMEKFQFELTLDEEDSEGPEKEGEGHSYFSSTKTLCVIDPENRDSL GETDIDIATEDKSPVDT	121
hPDE4B Catalytic domain (Amino acid 330-682 of PDE4B)	VNTENEDHLAKELEDLNKWGLNIFNVAGYSHNRPLTCIMYAIFQ ERDLLKTFRISSDTFITYMMTLEDHYHSDVAYHNSLHAADVAQS THVLLSTPALDAVFTDLEILAAIFAAAIHDVDHPGVSNQFLINTNS ELALMYNDESVLENHHLAVGFKLLQEEHCDIFMNLTKKQRQTLR KMVIDMVLATDMSKHMSLLADLKTMVETKKVTSSGVLLLDNYT DRIQVLRNMVHCADLSNPTKSLELYRQWTDRIMEEFFQQGDKER ERGMEISPMCDKHTASVEKSQVGFIDYIVHPLWETWADLVQPDA QDILDTLEDNRNWYQSMIPQSPSPPLDEQNRDCQGLMEKFQFEL	122
hPDE4C (Uniprot ID: Q08493)	MENLGVGEGAEACSRLSRSRGRHSMTRAPKHLWRQPRRPIRIQQ RFYSDPDKSAGCRERDLSPRPELRKSRLSWPVSSCRRFDLENGLS CGRRALDPQSSPGLGRIMQAPVPHSQRRESFLYRSDSDYELSPKA MSRNSSVASDLHGEDMIVTPFAQVLASLRTVRSNVAALARQQCL GAAKQGPVGNPSSSNQLPPAEDTGQKLALETLDELDWCLDQLET LQTRHSVGEMASNKFKRILNRELTHLSETSRSGNQVSEYISRTFLD QQTEVELPKVTAEEAPQPMSRISGLHGLCHSASLSSATVPRFGVQ TDQEEQLAKELEDTNKWGLDVFKVAELSGNRPLTAIIFSIFQERDL LKTFQIPADTLATYLLMLEGHYHANVAYHNSLHAADVAQSTHV LLATPALEAVFTDLEILAALFASAIHDVDHPGVSNQFLINTNSELA LMYNDASVLENHHLAVGFKLLQAENCDIFQNLSAKQRLSLRRM VIDMVLATDMSKHMNLLADLKTMVETKKVTSLGVLLLDNYSDR IQVLQNLVHCADLSNPTKPLPLYRQWTDRIMAEFFQQGDRERES GLDISPMCDKHTASVEKSQVGFIDYIAHPLWETWADLVHPDAQD LLDTLEDNREWYQSKIPRSPSDLTNPERDGPDRFQFELTLEEAEEE DEEEEEEGEETALAKEALELPDTELLSPEAGPDPGDLPLDNQRT	123
hPDE4C Catalytic domain (Amino	VQTDQEEQLAKELEDTNKWGLDVFKVAELSGNRPLTAIIFSIFQE RDLLKTFQIPADTLATYLLMLEGHYHANVAYHNSLHAADVAQST HVLLATPALEAVFTDLEILAALFASAIHDVDHPGVSNQFLINTNSE	124

acid 312-677 of PDE4C)	LALMYNDASVLENHHLAVGFKLLQAENCDIFQNLSAKQRLSLRR MVIDMVLATDMSKHMNLLADLKTMVETKKVTSLGVLLLDNYS DRIQVLQNLVHCADLSNPTKPLPLYRQWTDRIMAEFFQQGDRER ESGLDISPMCDKHTASVEKSQVGFIDYIAHPLWETWADLVHPDA QDLLDTLEDNREWYQSKIPRSPSDLTNPERDGPDRFQFELTLEEA EEEDEEEEEEGE	
hPDE4D (Uniprot ID: Q08499)	MEAEGSSAPARAGSGEGSDSAGGATLKAPKHLWRHEQHHQYPL RQPQFRLLHPHHHLPPPPPPSPQPQPQCPLQPPPPPPLPPPPPPPGAA RGRYASSGATGRVRHRGYSDTERYLYCRAMDRTSYAVETGHRP GLKKSRMSWPSSFQGLRRFDVDNGTSAGRSPLDPMTSPGSGLILQ ANFVHSQRRESFLYRSDSDYDLSPKSMSRNSSIASDIHGDDLIVTP FAQVLASLRTVRNNFAALTNLQDRAPSKRSPMCNQPSINKATITE EAYQKLASETLEELDWCLDQLETLQTRHSVSEMASNKFKRMLNR ELTHLSEMSRSGNQVSEFISNTFLDKQHEVEIPSPTQKEKEKKKRP MSQISGVKKLMHSSSLTNSSIPRFGVKTEQEDVLAKELEDVNKW GLHVFRIAELSGNRPLTVIMHTIFQERDLLKTFKIPVDTLITYLMTL EDHYHADVAYHNNIHAADVVQSTHVLLSTPALEAVFTDLEILAAI FASAIHDVDHPGVSNQFLINTNSELALMYNDSSVLENHHLAVGFK LLQEENCDIFQNLTKKQRQSLRKMVIDIVLATDMSKHMNLLADL KTMVETKKVTSSGVLLLDNYSDRIQVLQNMVHCADLSNPTKPLQ LYRQWTDRIMEEFFRQGDRERERGMEISPMCDKHNASVEKSQVG FIDYIVHPLWETWADLVHPDAQDILDTLEDNREWYQSTIPQSPSP APDDPEEGRQGQTEKFQFELTLEEDGESDTEKDSGSQVEEDTSCS DSKTLCTQDSESTEIPLDEQVEEEAVGEEEESQPEACVIDDRSPDT	125
hPDE4D Catalytic domain (Amino acid 386-751 of PDE4D)	VKTEQEDVLAKELEDVNKWGLHVFRIAELSGNRPLTVIMHTIFQE RDLLKTFKIPVDTLITYLMTLEDHYHADVAYHNNIHAADVVQST HVLLSTPALEAVFTDLEILAAIFASAIHDVDHPGVSNQFLINTNSEL ALMYNDSSVLENHHLAVGFKLLQEENCDIFQNLTKKQRQSLRKM VIDIVLATDMSKHMNLLADLKTMVETKKVTSSGVLLLDNYSDRI QVLQNMVHCADLSNPTKPLQLYRQWTDRIMEEFFRQGDRERER GMEISPMCDKHNASVEKSQVGFIDYIVHPLWETWADLVHPDAQD ILDTLEDNREWYQSTIPQSPSPAPDDPEEGRQGQTEKFQFELTLEE DGESDTEKD	126
hPDE6A (Uniprot ID: P16499)	MGEVTAEEVEKFLDSNIGFAKQYYNLHYRAKLISDLLGAKEAAV DFSNYHSPSSMEESEIIFDLLRDFQENLQTEKCIFNVMKKLCFLLQ ADRMSLFMYRTRNGIAELATRLFNVHKDAVLEDCLVMPDQEIVF PLDMGIVGHVAHSKKIANVPNTEEDEHFCDFVDILTEYKTKNILA SPIMNGKDVVAIIMAVNKVDGSHFTKRDEEILLKYLNFANLIMKV YHLSYLHNCETRRGQILLWSGSKVFEELTDIERQFHKALYTVRAF LNCDRYSVGLLDMTKQKEFFDVWPVLMGEVPPYSGPRTPDGREI NFYKVIDYILHGKEDIKVIPNPPPDHWALVSGLPAYVAQNGLICNI MNAPAEDFFAFQKEPLDESGWMIKNVLSMPIVNKKEEIVGVATF YNRKDGKPFDEMDETLMESLTQFLGWSVLNPDTYESMNKLENR KDIFQDIVKYHVKCDNEEIQKILKTREVYGKEPWECEEEELAEILQ AELPDADKYEINKFHFSDLPLTELELVKCGIQMYYELKVVDKFHI PQEALVRFMYSLSKGYRKITYHNWRHGFNVGQTMFSLLVTGKL KRYFTDLEALAMVTAAFCHDIDHRGTNNLYQMKSQNPLAKLHG SSILERHHLEFGKTLLRDESLNIFQNLNRRQHEHAIHMMDIAIIAT DLALYFKKRTMFQKIVDQSKTYESEQEWTQYMMLEQTRKEIVM AMMMTACDLSAITKPWEVQSQVALLVAAEFWEQGDLERTVLQQ NPIPMMDRNKADELPKLQVGFIDFVCTFVYKEFSRFHEEITPMLD GITNNRKEWKALADEYDAKMKVQEEKKQKQQSAKSAAAGNQP GGNPSPGGATTSKSCCIQ	127
hPDE6A Catalytic domain (Amino acid 483-819 of PDE6A)	EEEELAEILQAELPDADKYEINKFHFSDLPLTELELVKCGIQMYYE LKVVDKFHIPQEALVRFMYSLSKGYRKITYHNWRHGFNVGQTM FSLLVTGKLKRYFTDLEALAMVTAAFCHDIDHRGTNNLYQMKSQ NPLAKLHGSSILERHHLEFGKTLLRDESLNIFQNLNRRQHEHAIH MMDIAIIATDLALYFKKRTMFQKIVDQSKTYESEQEWTQYMMLE QTRKEIVMAMMMTACDLSAITKPWEVQSQVALLVAAEFWEQGD	128

	LERTVLQQNPIPMMDRNKADELPKLQVGFIDFVCTFVYKEFSRFH EEITPMLDGITNNRKEWKALADEYDAK	
hPDE6B (Uniprot ID: P35913)	MSLSEEQARSFLDQNPDFARQYFGKKLSPENVAAACEDGCPPDC DSLRDLCQVEESTALLELVQDMQESINMERVVFKVLRRLCTLLQ ADRCSLFMYRQRNGVAELATRLFSVQPDSVLEDCLVPPDSEIVFP LDIGVVGHVAQTKKMVNVEDVAECPHFSSFADELTDYKTKNML ATPIMNGKDVVAVIMAVNKLNGPFFTSEDEDVFLKYLNFATLYL KIYHLSYLHNCETRRGQVLLWSANKVFEELTDIERQFHKAFYTVR AYLNCERYSVGLLDMTKEKEFFDVWSVLMGESQPYSGPRTPDGR EIVFYKVIDYVLHGKEEIKVIPTPSADHWALASGLPSYVAESGFIC NIMNASADEMFKFQEGALDDSGWLIKNVLSMPIVNKKEEIVGVA TFYNRKDGKPFDEQDEVLMESLTQFLGWSVMNTDTYDKMNKLE NRKDIAQDMVLYHVKCDRDEIQLILPTRARLGKEPADCDEDELG EILKEELPGPTTFDIYEFHFSDLECTELDLVKCGIQMYYELGVVRK FQIPQEVLVRFLFSISKGYRRITYHNWRHGFNVAQTMFTLLMTGK LKSYYTDLEAFAMVTAGLCHDIDHRGTNNLYQMKSQNPLAKLH GSSILERHHLEFGKFLLSEETLNIYQNLNRRQHEHVIHLMDIAIIAT DLALYFKKRAMFQKIVDESKNYQDKKSWVEYLSLETTRKEIVMA MMMTACDLSAITKPWEVQSKVALLVAAEFWEQGDLERTVLDQQ PIPMMDRNKAAELPKLQVGFIDFVCTFVYKEFSRFHEEILPMFDRL QNNRKEWKALADEYEAKVKALEEKEEEERVAAKKVGTEICNGG PAPKSSTCCIL	129
hPDE6B Catalytic domain (Amino acid 476-817 of PDE6B)	PADCDEDELGEILKEELPGPTTFDIYEFHFSDLECTELDLVKCGIQ MYYELGVVRKFQIPQEVLVRFLFSISKGYRRITYHNWRHGFNVA QTMFTLLMTGKLKSYYTDLEAFAMVTAGLCHDIDHRGTNNLYQ MKSQNPLAKLHGSSILERHHLEFGKFLLSEETLNIYQNLNRRQHE HVIHLMDIAIIATDLALYFKKRAMFQKIVDESKNYQDKKSWVEY LSLETTRKEIVMAMMMTACDLSAITKPWEVQSKVALLVAAEFW EQGDLERTVLDQQPIPMMDRNKAAELPKLQVGFIDFVCTFVYKE FSRFHEEILPMFDRLQNNRKEWKALADEYEAK	130
hPDE6C (Uniprot ID: P51160)	MGEINQVAVEKYLEENPQFAKEYFDRKLRVEVLGEIFKNSQVPV QSSMSFSELTQVEESALCLELLWTVQEEGGTPEQGVHRALQRLA HLLQADRCSMFLCRSRNGIPEVASRLLDVTPTSKFEDNLVGPDKE VVFPLDIGIVGWAAHTKKTHNVPDVKKNSHFSDFMDKQTGYVT KNLLATPIVVGKEVLAVIMAVNKVNASEFSKQDEEVFSKYLNFV SIILRLHHTSYMYNIESRRSQILMWSANKVFEELTDVERQFHKAL YTVRSYLNCERYSIGLLDMTKEKEFYDEWPIKLGEVEPYKGPKTP DGREVNFYKIIDYILHGKEEIKVIPTPPADHWTLISGLPTYVAENGF ICNMMNAPADEYFTFQKGPVDETGWVIKNVLSLPIVNKKEDIVG VATFYNRKDGKPFDEHDEYITETLTQFLGWSLLNTDTYDKMNKL ENRKDIAQEMLMNQTKATPEEIKSILKFQEKLNVDVIDDCEEKQL VAILKEDLPDPRSAELYEFRFSDFPLTEHGLIKCGIRLFFEINVVEK FKVPVEVLTRWMYTVRKGYRAVTYHNWRHGFNVGQTMFTLLM TGRLKKYYTDLEAFAMLAAAFCHDIDHRGTNNLYQMKSTSPLA RLHGSSILERHHLEYSKTLLQDESLNIFQNLNKRQFETVIHLFEVAI IATDLALYFKKRTMFQKIVDACEQMQTEEEAIKYVTVDPTKKEII MAMMMTACDLSAITKPWEVQSQVALMVANEFWEQGDLERTVL QQQPIPMMDRNKRDELPKLQVGFIDFVCTFVYKEFSRFHKEITPM LSGLQNNRVEWKSLADEYDAKMKVIEEEAKKQEGGAEKAAEDS GGGDDKKSKTCLML	131
hPDE6C Catalytic domain (Amino acid 483-822 of PDE6C)	DDCEEKQLVAILKEDLPDPRSAELYEFRFSDFPLTEHGLIKCGIRLF FEINVVEKFKVPVEVLTRWMYTVRKGYRAVTYHNWRHGFNVG QTMFTLLMTGRLKKYYTDLEAFAMLAAAFCHDIDHRGTNNLYQ MKSTSPLARLHGSSILERHHLEYSKTLLQDESLNIFQNLNKRQFET VIHLFEVAIIATDLALYFKKRTMFQKIVDACEQMQTEEEAIKYVT VDPTKKEIIMAMMMTACDLSAITKPWEVQSQVALMVANEFWEQ GDLERTVLQQQPIPMMDRNKRDELPKLQVGFIDFVCTFVYKEFSR FHKEITPMLSGLQNNRVEWKSLADEYDAK	132

hPDE7A (Uniprot ID: Q13946)	MEVCYQLPVLPLDRPVPQHVLSRRGAISFSSSSALFGCPNPRQLSQ RRGAISYDSSDQTALYIRMLGDVRVRSRAGFESERRGSHPYIDFRI FHSQSEIEVSVSARNIRRLLSFQRYLRSSRFFRGTAVSNSLNILDDD YNGQAKCMLEKVGNWNFDIFLFDRLTNGNSLVSLTFHLFSLHGLI EYFHLDMMKLRRFLVMIQEDYHSQNPYHNAVHAADVTQAMHC YLKEPKLANSVTPWDILLSLIAAATHDLDHPGVNQPFLIKTNHYL ATLYKNTSVLENHHWRSAVGLLRESGLFSHLPLESRQQMETQIG ALILATDISRQNEYLSLFRSHLDRGDLCLEDTRHRHLVLQMALKC ADICNPCRTWELSKQWSEKVTEEFFHQGDIEKKYHLGVSPLCDR HTESIANIQIGFMTYLVEPLFTEWARFSNTRLSQTMLGHVGLNKA SWKGLQREQSSSEDTDAAFELNSQLLPQENRLS	133
hPDE7A Catalytic domain (Amino acid 187-451 of PDE7A)	FHLDMMKLRRFLVMIQEDYHSQNPYHNAVHAADVTQAMHCYL KEPKLANSVTPWDILLSLIAAATHDLDHPGVNQPFLIKTNHYLAT LYKNTSVLENHHWRSAVGLLRESGLFSHLPLESRQQMETQIGALI LATDISRQNEYLSLFRSHLDRGDLCLEDTRHRHLVLQMALKCADI CNPCRTWELSKQWSEKVTEEFFHQGDIEKKYHLGVSPLCDRHTE SIANIQIGFMTYLVEPLFTEWARFSNTRLSQTMLGHVGLNKASW	134
hPDE7B (Uniprot ID: Q9NP56)	MSCLMVERCGEILFENPDQNAKCVCMLGDIRLRGQTGVRAERRG SYPFIDFRLLNSTTYSGEIGTKKKVKRLLSFQRYFHASRLLRGIIPQ APLHLLDEDYLGQARHMLSKVGMWDFDIFLFDRLTNGNSLVTLL CHLFNTHGLIHHFKLDMVTLHRFLVMVQEDYHSQNPYHNAVHA ADVTQAMHCYLKEPKLASFLTPLDIMLGLLAAAAHDVDHPGVN QPFLIKTNHHLANLYQNMSVLENHHWRSTIGMLRESRLLAHLPK EMTQDIEQQLGSLILATDINRQNEFLTRLKAHLHNKDLRLEDAQD RHFMLQIALKCADICNPCRIWEMSKQWSERVCEEFYRQGELEQK FELEISPLCNQQKDSIPSIQIGFMSYIVEPLFREWAHFTGNSTLSEN MLGHLAHNKAQWKSLLPRQHRSRGSSGSGPDHDHAGQGTESEE QEGDSP	135
hPDE7B Catalytic domain (Amino acid 172-410 of PDE7B)	YHNAVHAADVTQAMHCYLKEPKLASFLTPLDIMLGLLAAAAHD VDHPGVNQPFLIKTNHHLANLYQNMSVLENHHWRSTIGMLRESR LLAHLPKEMTQDIEQQLGSLILATDINRQNEFLTRLKAHLHNKDL RLEDAQDRHFMLQIALKCADICNPCRIWEMSKQWSERVCEEFYR QGELEQKFELEISPLCNQQKDSIPSIQIGFMSYIVEPLFREWAHFTG NSTLSENMLGHLAHNK	136
hPDE8A (Uniprot ID: O60658)	MGCAPSIHISERLVAEDAPSPAAPPLSSGGPRLPQGQKTAALPRTR GAGLLESELRDGSGKKVAVADVQFGPMRFHQDQLQVLLVFTKE DNQCNGFCRACEKAGFKCTVTKEAQAVLACFLDKHHDIIIIDHRN PRQLDAEALCRSIRSSKLSENTVIVGVVRRVDREELSVMPFISAGF TRRYVENPNIMACYNELLQLEFGEVRSQLKLRACNSVFTALENSE DAIEITSEDRFIQYANPAFETTMGYQSGELIGKELGEVPINEKKAD LLDTINSCIRIGKEWQGIYYAKKKNGDNIQQNVKIIPVIGQGGKIR HYVSIIRVCNGNNKAEKISECVQSDTHTDNQTGKHKDRRKGSLD VKAVASRATEVSSQRRHSSMARIHSMTIEAPITKVINIINAAQESSP MPVTEALDRVLEILRTTELYSPQFGAKDDDPHANDLVGGLMSDG LRRLSGNEYVLSTKNTQMVSSNIITPISLDDVPPRIARAMENEEYW DFDIFELEAATHNRPLIYLGLKMFARFGICEFLHCSESTLRSWLQII EANYHSSNPYHNSTHSADVLHATAYFLSKERIKETLDPIDEVAALI AATIHDVDHPGRTNSFLCNAGSELAILYNDTAVLESHHAALAFQL TTGDDKCNIFKNMERNDYRTLRQGIIDMVLATEMTKHFEHVNKF VNSINKPLATLEENGETDKNQEVINTMLRTPENRTLIKRMLIKCA DVSNPCRPLQYCIEWAARISEEYFSQTDEEKQQGLPVVMPVFDRN TCSIPKSQISFIDYFITDMFDAWDAFVDLPDLMQHLDNNFKYWKG LDEMKLRNLRPPPE	137
hPDE8A Catalytic domain (Amino acid 531-813 of PDE8A)	LHCSESTLRSWLQIIEANYHSSNPYHNSTHSADVLHATAYFLSKE RIKETLDPIDEVAALIAATIHDVDHPGRTNSFLCNAGSELAILYND TAVLESHHAALAFQLTTGDDKCNIFKNMERNDYRTLRQGIIDMV LATEMTKHFEHVNKFVNSINKPLATLEENGETDKNQEVINTMLR TPENRTLIKRMLIKCADVSNPCRPLQYCIEWAARISEEYFSQTDEE KQQGLPVVMPVFDRNTCSIPKSQISFIDYFITDMFDAWDAFVDLP DLMQHLDNNFKYW	138

hPDE8B (Uniprot ID: O95263)	MGCAPSIHVSQSGVIYCRDSDESSSPRQTTSVSQGPAAPLPGLFVQ TDAADAIPPSRASGPPSVARVRRARTELGSGSSAGSAAPAATTSR GRRRHCCSSAEAETQTCYTSVKQVSSAEVRIGPMRLTQDPIQVLLI FAKEDSQSDGFWWACDRAGYRCNIARTPESALECFLDKHHEIIVI DHRQTQNFDAEAVCRSIRATNPSEHTVILAVVSRVSDDHEEASVL PLLHAGFNRRFMENSSIIACYNELIQIEHGEVRSQFKLRACNSVFT ALDHCHEAIEITSDDHVIQYVNPAFERMMGYHKGELLGKELADL PKSDKNRADLLDTINTCIKKGKEWQGVYYARRKSGDSIQQHVKI TPVIGQGGKIRHFVSLKKLCCTTDNNKQIHKIHRDSGDNSQTEPHS FRYKNRRKESIDVKSISSRGSDAPSLQNRRYPSMARIHSMTIEAPIT KVINIINAAQENSPVTVAEALDRVLEILRTTELYSPQLGTKDEDPH TSDLVGGLMTDGLRRLSGNEYVFTKNVHQSHSHLAMPITINDVPP CISQLLDNEESWDFNIFELEAITHKRPLVYLGLKVFSRFGVCEFLN CSETTLRAWFQVIEANYHSSNAYHNSTHAADVLHATAFFLGKER VKGSLDQLDEVAALIAATVHDVDHPGRTNSFLCNAGSELAVLYN DTAVLESHHTALAFQLTVKDTKCNIFKNIDRNHYRTLRQAIIDMV LATEMTKHFEHVNKFVNSINKPMAAEIEGSDCECNPAGKNFPEN QILIKRMMIKCADVANPCRPLDLCIEWAGRISEEYFAQTDEEKRQ GLPVVMPVFDRNTCSIPKSQISFIDYFITDMFDAWDAFAHLPALM QHLADNYKHWKTLDDLKCKSLRLPSDS	139
hPDE8B Catalytic domain (Amino acid 590-868 of PDE8B)	LNCSETTLRAWFQVIEANYHSSNAYHNSTHAADVLHATAFFLGK ERVKGSLDQLDEVAALIAATVHDVDHPGRTNSFLCNAGSELAVL YNDTAVLESHHTALAFQLTVKDTKCNIFKNIDRNHYRTLRQAIID MVLATEMTKHFEHVNKFVNSINKPMAAEIEGSDCECNPAGKNFP ENQILIKRMMIKCADVANPCRPLDLCIEWAGRISEEYFAQTDEEK RQGLPVVMPVFDRNTCSIPKSQISFIDYFITDMFDAWDAFAHLPAL MQHLADNYKHW	140
hPDE9A (Uniprot ID: O76083)	MGSGSSSYRPKAIYLDIDGRIQKVIFSKYCNSSDIMDLFCIATGLPR NTTISLLTTDDAMVSIDPTMPANSERTPYKVRPVAIKQLSAGVED KRTTSRGQSAERPLRDRRVVGLEQPRREGAFESGQVEPRPREPQG CYQEGQRIPPEREELIQSVLAQVAEQFSRAFKINELKAEVANHLA VLEKRVELEGLKVVEIEKCKSDIKKMREELAARSSRTNCPCKYSF LDNHKKLTPRRDVPTYPKYLLSPETIEALRKPTFDVWLWEPNEM LSCLEHMYHDLGLVRDFSINPVTLRRWLFCVHDNYRNNPFHNFR HCFCVAQMMYSMVWLCSLQEKFSQTDILILMTAAICHDLDHPGY NNTYQINARTELAVRYNDISPLENHHCAVAFQILAEPECNIFSNIPP DGFKQIRQGMITLILATDMARHAEIMDSFKEKMENFDYSNEEHM TLLKMILIKCCDISNEVRPMEVAEPWVDCLLEEYFMQSDREKSEG LPVAPFMDRDKVTKATAQIGFIKFVLIPMFETVTKLFPMVEEIML QPLWESRDRYEELKRIDDAMKELQKKTDSLTSGATEKSRERSRD VKNSEGDCA	141
hPDE9A Catalytic domain (Amino acid 288-550 of PDE9A)	FSINPVTLRRWLFCVHDNYRNNPFHNFRHCFCVAQMMYSMVWL CSLQEKFSQTDILILMTAAICHDLDHPGYNNTYQINARTELAVRY NDISPLENHHCAVAFQILAEPECNIFSNIPPDGFKQIRQGMITLILAT DMARHAEIMDSFKEKMENFDYSNEEHMTLLKMILIKCCDISNEV RPMEVAEPWVDCLLEEYFMQSDREKSEGLPVAPFMDRDKVTKA TAQIGFIKFVLIPMFETVTKLFPMVEEIMLQPLWESRDRY	142

hPDE10A (Uniprot ID: Q9Y233)	MRIEERKSQHLTGLTDEKVKAYLSLHPQVLDEFVSESVSAETVEK WLKRKNNKSEDESAPKEVSRYQDTNMQGVVYELNSYIEQRLDT GGDNQLLLYELSSIIKIATKADGFALYFLGECNNSLCIFTPPGIKEG KPRLIPAGPITQGTTVSAYVAKSRKTLLVEDILGDERFPRGTGLES GTRIQSVLCLPIVTAIGDLIGILELYRHWGKEAFCLSHQEVATANL AWASVAIHQVQVCRGLAKQTELNDFLLDVSKTYFDNIVAIDSLLE HIMIYAKNLVNADRCALFQVDHKNKELYSDLFDIGEEKEGKPVF KKTKEIRFSIEKGIAGQVARTGEVLNIPDAYADPRFNREVDLYTG YTTRNILCMPIVSRGSVIGVVQMVNKISGSAFSKTDENNFKMFAV FCALALHCANMYHRIRHSECIYRVTMEKLSYHSICTSEEWQGLM QFTLPVRLCKEIELFHFDIGPFENMWPGIFVYMVHRSCGTSCFELE KLCRFIMSVKKNYRRVPYHNWKHAVTVAHCMYAILQNNHTLFT DLERKGLLIACLCHDLDHRGFSNSYLQKFDHPLAALYSTSTMEQ HHFSQTVSILQLEGHNIFSTLSSSEYEQVLEIIRKAIIATDLALYFGN RKQLEEMYQTGSLNLNNQSHRDRVIGLMMTACDLCSVTKLWPV TKLTANDIYAEFWAEGDEMKKLGIQPIPMMDRDKKDEVPQGQL GFYNAVAIPCYTTLTQILPPTEPLLKACRDNLSQWEKVIRGEETAT WISSPSVAQKAAASED	143
hPDE10A Catalytic domain (Amino acid 458-760 of PDE10A)	CKEIELFHFDIGPFENMWPGIFVYMVHRSCGTSCFELEKLCRFIMS VKKNYRRVPYHNWKHAVTVAHCMYAILQNNHTLFTDLERKGLL IACLCHDLDHRGFSNSYLQKFDHPLAALYSTSTMEQHHFSQTVSI LQLEGHNIFSTLSSSEYEQVLEIIRKAIIATDLALYFGNRKQLEEMY QTGSLNLNNQSHRDRVIGLMMTACDLCSVTKLWPVTKLTANDIY AEFWAEGDEMKKLGIQPIPMMDRDKKDEVPQGQLGFYNAVAIP CYTTLTQILPPTEPLLKACRDNLSQWEKVIRGEE	144
hPDE11A (Uniprot ID: Q9HCR9)	MAASRLDFGEVETFLDRHPELFEDYLMRKGKQEMVEKWLQRHS QGQGALGPRPSLAGTSSLAHSTCRGGSSVGGGTGPNGSAHSQPLP GGGDCGGVPLSPSWAGGSRGDGNLQRRASQKELRKSFARSKAIH VNRTYDEQVTSRAQEPLSSVRRRALLRKASSLPPTTAHILSALLES RVNLPRYPPTAIDYKCHLKKHNERQFFLELVKDISNDLDLTSLSY KILIFVCLMVDADRCSLFLVEGAAAGKKTLVSKFFDVHAGTPLLP CSSTENSNEVQVPWGKGIIGYVGEHGETVNIPDAYQDRRFNDEID KLTGYKTKSLLCMPIRSSDGEIIGVAQAINKIPEGAPFTEDDEKVM QMYLPFCGIAISNAQLFAASRKEYERSRALLEVVNDLFEEQTDLE KIVKKIMHRAQTLLKCERCSVLLLEDIESPVVKFTKSFELMSPKCS ADAENSFKESMEKSSYSDWLINNSIAELVASTGLPVNISDAYQDP RFDAEADQISGFHIRSVLCVPIWNSNHQIIGVAQVLNRLDGKPFDD ADQRLFEAFVIFCGLGINNTIMYDQVKKSWAKQSVALDVLSYHA TCSKAEVDKFKAANIPLVSELAIDDIHFDDFSLDVDAMITAALRM FMELGMVQKFKIDYETLCRWLLTVRKNYRMVLYHNWRHAFNV CQLMFAMLTTAGFQDILTEVEILAVIVGCLCHDLDHRGTNNAFQ AKSGSALAQLYGTSATLEHHHFNHAVMILQSEGHNIFANLSSKEY SDLMQLLKQSILATDLTLYFERRTEFFELVSKGEYDWNIKNHRDI FRSMLMTACDLGAVTKPWEISRQVAELVTSEFFEQGDRERLELK LTPSAIFDRNRKDELPRLQLEWIDSICMPLYQALVKVNVKLKPML DSVATNRSKWEELHQKRLLASTASSSPASVMVAKEDRN	145
hPDE11A Catalytic Domain (Amino acid 640-905 of PDE11A)	FKIDYETLCRWLLTVRKNYRMVLYHNWRHAFNVCQLMFAMLT TAGFQDILTEVEILAVIVGCLCHDLDHRGTNNAFQAKSGSALAQL YGTSATLEHHHFNHAVMILQSEGHNIFANLSSKEYSDLMQLLKQS ILATDLTLYFERRTEFFELVSKGEYDWNIKNHRDIFRSMLMTACD LGAVTKPWEISRQVAELVTSEFFEQGDRERLELKLTPSAIFDRNRK DELPRLQLEWIDSICMPLYQALVKVNVKLKPMLDSVATNRSKW	146

[0148] In some embodiments, the hPDE5 derived destabilizing domains may be derived from variants, and/or isoforms of hPDE5. The three isoforms hPDE5 Isoform 1, hPDE5 Isoform 2, and hPDE5 Isoform 3 differ at their N terminal regions, and all 3 have unique first exons followed by a common sequence of 823 amino acids. Accordingly, hPDE5 derived

DDs may be derived from hPDE5 Isoform 1 (SEQ ID NO. 1; encoded by the nucleotide sequence of SEQ ID NO. 2; hPDE5 Isoform 2 (SEQ ID NO. 147; encoded by the nucleotides 113- 2611 of the nucleotide sequence of SEQ ID NO. 148 or the nucleotide sequence of SEQ ID NO. 380) and/or hPDE5 Isoform 3 (SEQ ID NO. 149; encoded by the nucleotides 95-2563 of nucleotide sequence of SEQ ID NO. 150 or SEQ ID NO. 381). In some embodiments, the hPDE5 DDs may be derived from hPDE5 Isoform X1 (SEQ ID NO. 382).

[0149] In some embodiments, the DD mutations identified herein may be mapped back to the hPDE5 sequence to identify DD hotspots. DD hotspots as used herein refer to amino acids within the hPDE5 of SEQ ID NO. 1 whose mutation results in the "responsive" nature of the stimulus responsive element generated from hPDE5.The DD characteristics may be improved by saturation mutagenesis, which involves mutating the amino acids at the hotspot position to any of the known amino acids, including, but not limited to lysine, aspartic acid, glutamic acid, glutamine, asparagine, histidine, serine, threonine, tyrosine, cysteine, methionine, tryptophan, alanine, isoleucine, leucine, phenylalanine, valine, proline, and glycine. In some instances, a library of hotspot mutations may be generated by site directed mutagenesis and each of the mutants in the library is fused to a reporter protein e.g. AcGFP (SEQ ID NO. 79) via a linker such as SG. The properties of the DDs may be analyzed in the presence and absence of ligands such as Sildenafil, Vardenafil and Tadalafil. In some embodiments, the arginine at position 732 (also referred to as R732) of the hPDE5 of SEQ ID NO. 1, may be mutated to any of the known amino acids and are provided in Table 5A. The mutations of the amino acid R732 may include but are not limited to R732L, R732A, R732G, R732V, R732I, R732P, R732F, R732W, R732Y, R732H, R732S, R732T, R732D, R732E, R732Q, R732N, R732M, R732C, and R732K. The hPDE5 mutants fused either at the N terminus or the C terminus to a linker and GFP are provided in Table 6. In Table 5A, the mutations are in bold. Table 5B provides the additional components that may be combined with the mutants listed in Table 5A to generate the constructs described in Table 6. In Table 6, asterisk indicates the translation of the stop codon. Table 6 also provides alternate aliases for a given construct ID. These aliases are identified by the prefix OT.

Table 5A: hPDE5 R732 mutants

Construct ID/ Description	Sequence	AA SEQ ID NO.	NA SEQ ID NO.
hPDE5 (Amino acid 590-836 of WT, R732G)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**G**GEFFELIRKNQFNLEDPHQKEL	151	169

	FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS		
hPDE5 (Amino acid 590-836 of WT, R732A)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**A**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	152	170
hPDE5 (Amino acid 590-836 of WT, R732V)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**V**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	153	171
hPDE5 (Amino acid 590-836 of WT, R732I)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**I**GEFFELIRKNQFNLEDPHQKELF LAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKE LNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	154	172
hPDE5 (Amino acid 590-836 of WT, R732P)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**P**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	155	173
hPDE5 (Amino acid 590-836 of WT, R732F)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**F**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	156	174
hPDE5 (Amino acid 590-836 of WT, R732W)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**W**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	157	175
hPDE5 (Amino acid 590-836 of WT, R732Y)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**Y**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	158	176
hPDE5 (Amino acid 590-836 of WT, R732H)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**H**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	159	177
hPDE5 (Amino acid 590-836 of WT, R732S)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**S**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	160	178
hPDE5 (Amino acid 590-836 of WT, R732T)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**T**GEFFELIRKNQFNLEDPHQKEL	161	179

	FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS		
hPDE5 (Amino acid 590-836 of WT, R732D)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**D**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	162	180
hPDE5 (Amino acid 590-836 of WT, R732E)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**E**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	163	181
hPDE5 (Amino acid 590-836 of WT, R732Q)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**Q**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	164	182
hPDE5 (Amino acid 590-836 of WT, R732N)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**N**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	165	183
hPDE5 (Amino acid 590-836 of WT, R732M)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**M**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	166	184
hPDE5 (Amino acid 590-836 of WT, R732C)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**C**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	167	185
hPDE5 (Amino acid 590-836 of WT, R732K)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSE HPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKT TLKIIKQAILATDLALYIKR**K**GEFFELIRKNQFNLEDPHQKEL FLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERK ELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	168	186
hPDE5 (Amino acid 535-860 of WT, R732G)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRGGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	383	401; 402
hPDE5 (Amino acid 535-860 of WT, R732A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRAGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	384	403; 404

hPDE5 (Amino acid 535-860 of WT, R732L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	12	405
hPDE5 (Amino acid 535-860 of WT, R732V)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRVGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	385	406; 407
hPDE5 (Amino acid 535-860 of WT, R732I)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRIGEFFELIRKNQ FNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATE FFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQ LYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	386	408
hPDE5 (Amino acid 535-860 of WT, R732P)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRPGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	387	409; 410
hPDE5 (Amino acid 535-860 of WT, R732F)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRFGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	388	411
hPDE5 (Amino acid 535-860 of WT, R732W)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRWGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	389	412
hPDE5 (Amino acid 535-860 of WT, R732Y)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRYGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	390	413; 414
hPDE5 (Amino acid 535-860 of	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN	391	415; 416

WT, R732H)	QILSGLSIEEYKTTLKIIKQAILATDLALYIKRHGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ		
hPDE5 (Amino acid 535-860 of WT, R732S)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRSGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	392	417; 418
hPDE5 (Amino acid 535-860 of WT, R732T)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRTGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	393	419
hPDE5 (Amino acid 535-860 of WT, R732D)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRDGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	394	420; 421
hPDE5 (Amino acid 535-860 of WT, R732E)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKREGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	395	422; 423
hPDE5 (Amino acid 535-860 of WT, R732Q)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRQGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	396	424; 425
hPDE5 (Amino acid 535-860 of WT, R732N)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRNGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	397	426
hPDE5 (Amino acid 535-860 of WT, R732M)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRMGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	398	427

hPDE5 (Amino acid 535-860 of WT, R732C)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRCGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	399	428
hPDE5 (Amino acid 535-860 of WT, R732K)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWR HAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDH RGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGN QILSGLSIEEYKTTLKIIKQAILATDLALYIKRKGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVA TEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	400	429

Table 5B: Additional hPDE5 R732 construct components

Component	Amino Acid Sequence	AA SEQ ID NO	NA SEQ ID NO
AcGFP (Amino acid 2-239 of WT)	VSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDA TYGKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRY PDHMKQHDFFKSAMPEGYIQERTIFFEDDGNYKSRA EVKFEGDTLVNRIELTGTDFKEDGNILGNKMEYNYN AHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHY QQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMI YFGFVTAAAITHGMDELYK	79	372
AcGFP (Amino acid 1-239 of WT)	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGD ATYGKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSR YPDHMKQHDFFKSAMPEGYIQERTIFFEDDGNYKSR AEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEYNY NAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADH YQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDH MIYFGFVTAAAITHGMDELYK	365	373
linker (SG)	SG	-	AGTGGT
linker (GS)	GS	-	GGATCC

Table 6: hPDE5 R732 constructs

Construct ID/ Description	Sequence	AA SEQ ID NO.	NA SEQ ID NO.
OT-hPDE5N-037 (OT-001233, OT-hPDE5-037) hPDE5 (Amino acid 590-836 of WT, R732G); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRGGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	187	205

OT-hPDE5N-038 (OT-001234, OT-hPDE5-038) hPDE5 (Amino acid 590-836 of WT, R732A); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRAGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVS**SG**VSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	188	206
OT-hPDE5N-039 (OT-001235, OT-hPDE5-039) hPDE5 (Amino acid 590-836 of WT, R732V); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRVGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVS**SG**VSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	189	207
OT-hPDE5N-040 (OT-001236, OT-hPDE5-040) hPDE5 (Amino acid 590-836 of WT, R732I); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRIGEFFELIRKNQFNLEDPHQKELFLAMLMT ACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLM NREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFTGI VPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLP VPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQER TIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGN KMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLAD HYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGF VTAAAITHGMDELYK*	190	208
OT-hPDE5N-041 (OT-001237, OT-hPDE5-041) hPDE5 (Amino acid 590-836 of WT, R732P); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRPGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	191	209
OT-hPDE5N-042 (OT-001238, OT-hPDE5-042) hPDE5 (Amino acid 590-836 of WT, R732F);	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRFGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE	192	210

linker (SG); AcGFP (Amino acid 2-239 of WT); stop	RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*		
OT-hPDE5N-043 (OT-001239, OT-hPDE5-043) hPDE5 (Amino acid 590-836 of WT, R732W); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRWGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	193	211
OT-hPDE5N-044 (OT-001240, OT-hPDE5-044) hPDE5 (Amino acid 590-836 of WT, R732Y); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRYGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	194	212
OT-hPDE5N-045 (OT-001241, OT-hPDE5-045) hPDE5 (Amino acid 590-836 of WT, R732H); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRHGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	195	213
OT-hPDE5N-046 (OT-001242, OT-hPDE5-046) hPDE5 (Amino acid 590-836 of WT, R732S); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRSGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	196	214
OT-hPDE5N-047 (OT-	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK	197	215

001243, OT-hPDE5-047) hPDE5 (Amino acid 590-836 of WT, R732T); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	QAILATDLALYIKRTGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*		
OT-hPDE5N-048 (OT-001244, OT-hPDE5-048) hPDE5 (Amino acid 590-836 of WT, R732D); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRDGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	198	216
OT-hPDE5N-049 (OT-001245, OT-hPDE5-049) hPDE5 (Amino acid 590-836 of WT, R732E); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKREGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	199	217
OT-hPDE5N-050 (OT-001246, OT-hPDE5-050) hPDE5 (Amino acid 590-836 of WT, R732Q); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRQGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	200	218
OT-hPDE5N-051 (OT-001247, OT-hPDE5-051) hPDE5 (Amino acid 590-836 of WT, R732N); linker (SG); AcGFP	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRNGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA	201	219

(Amino acid 2-239 of WT); stop	DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*		
OT-hPDE5N-052 (OT-001248, OT-hPDE5-052) hPDE5 (Amino acid 590-836 of WT, R732M); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRMGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	202	220
OT-hPDE5N-053 (OT-001249, OT-hPDE5-053) hPDE5 (Amino acid 590-836 of WT, R732C); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRCGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	203	221
OT-hPDE5N-054 (OT-001250, OT-hPDE5-054) hPDE5 (Amino acid 590-836 of WT, R732K); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAAL KAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPL AQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRKGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAELFT GIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKL PVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQE RTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILG NKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLA DHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	204	222
OT-hPDE5-064 (OT-001186) Methionine; hPDE5 (Amino acid 535-860 of WT, R732G); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRGGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	430	467
OT-hPDE5-065 (OT-001187) Methionine;	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS	431	468

hPDE5 (Amino acid 535-860 of WT, R732A); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	GLSIEEYKTTLKIIKQAILATDLALYIKRAGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*		
OT-hPDE5-066 (OT-001188) Methionine; hPDE5 (Amino acid 535-860 of WT, R732V); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRVGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	432	469
OT-hPDE5-067 (OT-001189) Methionine; hPDE5 (Amino acid 535-860 of WT, R732I); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRIGEFFELIRKNQFNLED PHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGD RERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTH VSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVPIL IELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWP TLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFE DDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEY NYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQQ NTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTAA AITHGMDELYK*	433	470
OT-hPDE5-068 (OT-001190) Methionine; hPDE5 (Amino acid 535-860 of WT, R732P); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRPGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	434	471
OT-hPDE5-069 (OT-001191) Methionine; hPDE5 (Amino acid 535-860 of WT, R732F);	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRFGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP	435	472

linker (SG); AcGFP (Amino acid 2-239 of WT); stop	ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*		
OT-hPDE5-070 (OT-001192) Methionine; hPDE5 (Amino acid 535-860 of WT, R732W); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRWGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	436	473
OT-hPDE5-071 (OT-001193) Methionine; hPDE5 (Amino acid 535-860 of WT, R732Y); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRYGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	437	474
OT-hPDE5-072 (OT-001195) Methionine; hPDE5 (Amino acid 535-860 of WT, R732H); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRHGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	438	475
OT-hPDE5-073 (OT-001196) Methionine; hPDE5 (Amino acid 535-860 of WT, R732S); linker (SG); AcGFP (Amino acid 2-	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRSGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ	439	476

239 of WT); stop	QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*		
OT-hPDE5-074 (OT-001197) Methionine; hPDE5 (Amino acid 535-860 of WT, R732T); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRTGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	440	477
OT-hPDE5-075 (OT-001198) Methionine; hPDE5 (Amino acid 535-860 of WT, R732D); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRDGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	441	478
OT-hPDE5-076 (OT-001199) Methionine; hPDE5 (Amino acid 535-860 of WT, R732E); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKREGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	442	479
OT-hPDE5-077 (OT-001200) Methionine; hPDE5 (Amino acid 535-860 of WT, R732Q); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRQGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	443	480
OT-hPDE5-078 (OT-	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH	444	481

001201) Methionine; hPDE5 (Amino acid 535-860 of WT, R732N); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRNGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*		
OT-hPDE5-079 (OT-001202) Methionine; hPDE5 (Amino acid 535-860 of WT, R732M); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRMGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	445	482
OT-hPDE5-080 (OT-001203) Methionine; hPDE5 (Amino acid 535-860 of WT, R732C); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRCGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	446	483
OT-hPDE5-081 (OT-001204) Methionine; hPDE5 (Amino acid 535-860 of WT, R732K); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIR MFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRH AFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRG VNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRKGEFFELIRKNQFNLE DPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFDQG DRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIVP ILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVP WPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIF FEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKM EYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTA AAITHGMDELYK*	447	484
OT-hPDE5-096 (OT-001279) AcGFP (Amino acid 1-239 of WT);	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV	448	485

linker (GS); hPDE5 (Amino acid 535-860 of WT, R732G); Xba I site (TCTAGA); stop	PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRGGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*		
OT-hPDE5-097 (OT-001280) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732A); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRAGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	449	486
OT-hPDE5-098 (OT-001281) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732L); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	450	487
OT-hPDE5-099 (OT-001282) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732M); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRMGEFFELIRKNQFNLEDPHQKELFLAMLMTAC DLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNR EKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNR QKWQALAEQQSR*	451	488
OT-hPDE5-100 (OT-001283) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL	452	489

WT, R732F); Xba I site (TCTAGA); stop	ATDLALYIKRFGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*		
OT-hPDE5-101 (OT-001284) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732W); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRWGEFFELIRKNQFNLEDPHQKELFLAMLMTAC DLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNR EKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNR QKWQALAEQQSR*	453	490
OT-hPDE5-102 (OT-001285) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732K); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRKGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	454	491
OT-hPDE5-103 (OT-001286) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732Q); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRQGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	455	492
OT-hPDE5-104 (OT-001287) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732E); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKREGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	456	493

OT-hPDE5-105 (OT-001288) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732S); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRSGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	457	494
OT-hPDE5-106 (OT-001289) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732P); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRPGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	458	495
OT-hPDE5-107 (OT-001290) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732V); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRVGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	459	496
OT-hPDE5-108 (OT-001291) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732I); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRIGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	460	497
OT-hPDE5-109 (OT-001292) AcGFP	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH	461	498

(Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732C); Xba I site (TCTAGA); stop	NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRCGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*		
OT-hPDE5-110 (OT-001293) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732Y); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRYGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	462	499
OT-hPDE5-111 (OT-001294) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732H); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRHGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	463	500
OT-hPDE5-112 (OT-001295) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732N); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRNGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	464	501
OT-hPDE5-113 (OT-001296) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG	465	502

(Amino acid 535-860 of WT, R732D); Xba I site (TCTAGA); stop	KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRDGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*		
OT-hPDE5-114 (OT-001297) AcGFP (Amino acid 1-239 of WT); linker (GS); hPDE5 (Amino acid 535-860 of WT, R732T); Xba I site (TCTAGA); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKL TLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFK SAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGT DFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRH NIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYKGSEETRELQSLAAAVV PSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALKAG KIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRTGEFFELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNRE KKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQSR*	466	503

[0150] In some embodiments, any of the mutations taught in Tables 1, 2, and 5A may be combined. In one embodiment, the combination mutations are provided in Table 7. Combination mutations may be linked to AcGFP (Amino acid 2-239 of WT) (SEQ ID NO. 79); encoded by the nucleotide sequence of SEQ ID NO. 372; AcGFP (Amino acid 1-239 of WT) (SEQ ID NO. 365); encoded by the nucleotide sequence of SEQ ID NO. 94; or firefly luciferase, Fluc (N50D, N119G, S548I, K549A, L550V) (SEQ ID NO. 223) encoded by the nucleotide sequence of SEQ ID NO. 224. In some embodiments, the portions of the construct may be linked through a linker e.g. SG linker, encoded by the nucleotide sequence (AGTGGT). In some embodiments, the constructs described in Table 7 may comprise an Xba I restriction site, SR, encoded by the nucleotide sequence, TCTAGA. Table 7 provides the constructs comprising the combination mutations. In Table 7, translation of the stop codon is indicated by asterisk. Also provided in Table7 are alternate aliases for a given construct ID. These aliases are identified by the prefix OT.

Table 7: hPDE5 combination mutations

Construct ID/ Description	**Sequence**	**AA SEQ ID NO.**	**NA SEQ ID NO.**
hPDE5 (Amino acid 535-860 of WT, F736A, D764N)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCT IRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYH NWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLM ILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRRG EFAELIRKNQFNLEDPHQKELFLAMLMTACNLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNK IPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQK WQALAEQQ	504	519

Methionine; hPDE5 (Amino acid 535-860 of WT, F736A, D764N)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETAL CTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA YHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA LSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQC LMILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKR RGEFAELIRKNQFNLEDPHQKELFLAMLMTACNLSAITKP WPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKN KIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQ	225	231
hPDE5 (Amino acid 535-860 of WT, R732L, D764N)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCT IRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYH NWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLM ILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFFELIRKNQFNLEDPHQKELFLAMLMTACNLSAITKPWP IQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQK WQALAEQQ	505	520
Methionine; hPDE5 (Amino acid 535-860 of WT, R732L, D764N)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETAL CTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA YHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA LSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQC LMILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKR LGEFFELIRKNQFNLEDPHQKELFLAMLMTACNLSAITKP WPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKN KIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQ	226	232
hPDE5 (Amino acid 535-860 of WT, R732L, F736A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEF AELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQ QRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ	227	233
hPDE5 (Amino acid 535-860 of WT, Y612F, R732L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAFHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEFF ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQ RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ	506	521
hPDE5 (Amino acid 535-860 of WT, Y612W, R732L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAWH NWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMI LNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEF FELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQ QRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ	507	522
hPDE5 (Amino acid 535-860 of WT, Y612A, R732L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAAHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEFF ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQ	508	523

	RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ		
hPDE5 (Amino acid 535-860 of WT, H653A, R732L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSA DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEFF ELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQ RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ	509	524
hPDE5 (Amino acid 535-860 of WT, R732L, D764A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHN WRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALSH DLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMIL NSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEFF ELIRKNQFNLEDPHQKELFLAMLMTACALSAITKPWPIQQ RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPSM QVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQA LAEQQ	510	525
OT-hPDE5N-025 (OT-001222, OT-hPDE5-025) Methionine; hPDE5 (Amino acid 535-860 of WT, F736A, D764N); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFAELIRKNQFNLEDPHQKELFLAMLMTACNLSAITKPW PIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQSGVSKGAELFTGIVPILIELNGDVNGHKFSVSGE GEGDATYGKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFS RYPDHMKQHDFFKSAMPEGYIQERTIFFEDDGNYKSRAE VKFEGDTLVNRIELTGTDFKEDGNILGNKMEYNYNAHNV YIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIGD GPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTAAAIT HGMDELYK*	228	234
OT-hPDE5N-026 (OT-001223, OT-hPDE5-026) Methionine; hPDE5 (Amino acid 535-860 of WT, R732L, D764N); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFFELIRKNQFNLEDPHQKELFLAMLMTACNLSAITKPWPI QQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQSGVSKGAELFTGIVPILIELNGDVNGHKFSVSGEG EGDATYGKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSR YPDHMKQHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEV KFEGDTLVNRIELTGTDFKEDGNILGNKMEYNYNAHNVY IMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDG PVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTAAAITH GMDELYK*	229	235
OT-hPDE5C-035 (OT-001231, OT-hPDE5-035) Fluc (N50D, N119G, S548I, K549A,	MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGT IAFTDAHIEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIV VCSENSLQFFMPVLGALFIGVAVAPANDIYNERELLNSMG ISQPTVVFVSKKGLQKILNVQKKLPIIQKIIIMDSKTDYQGF QSMYTFVTSHLPPGFNEYDFVPESFDRDKTIALIMNSSGST GLPKGVALPHRTACVRFSHARDPIFGNQIIPDTAILSVVPFH HGFGMFTTLGYLICGFRVVLMYRFEEELFLRSLQDYKIQS ALLVPTLFSFFAKSTLIDKYDLSNLHEIASGGAPLSKEVGE AVAKRFHLPGIRQGYGLTETTSAILITPEGDDKPGAVGKV	230	236

L550V); linker (SG); hPDE5 (Amino acid 535-860 of WT, R732L; F736A); stop	VPFFEAKVVDLDTGKTLGVNQRGELCVRGPMIMSGYVNN PEATNALIDKDGWLHSGDIAYWDEDEHFFIVDRLKSLIKY KGYQVAPAELESILLQHPNIFDAGVAGLPDDDAGELPAAV VVLEHGKTMTEKEIVDYVASQVTTAKKLRGGVVFVDEVP KGLTGKLDARKIREILIKAKKGGKIAV**SG**EETRELQSLAA AVVPSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQ NFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQ CMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNS YIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGL SIEEYKTTLKIIKQAILATDLALYIKRLGEFAELIRKNQFNL EDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEF FDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICL QLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ*		
OT-hPDE5-029 (OT-001225) Methionine; hPDE5 (Amino acid 535-860 of WT, R732L, F736A); Linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALC TIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAY HNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFAELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWP IQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIP SMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQSGVSKGAELFTGIVPILIELNGDVNGHKFSVSGE GEGDATYGKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFS RYPDHMKQHDFFKSAMPEGYIQERTIFFEDDGNYKSRAE VKFEGDTLVNRIELTGTDFKEDGNILGNKMEYNYNAHNV YIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIGD GPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTAAAIT HGMDELYK*	511	526
OT-hPDE5-030 (OT-001226) AcGFP (Amino acid 1-239 of WT); linker (SG); PDE5 (Amino acid 535-860 of WT, R732L, F736A); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATY GKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTL VNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDN HYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY KSGEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETA LCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA YHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA LSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFAELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWP IQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIP SMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKW QALAEQQ*	512	527
OT-hPDE5-083 (OT-001205) AcGFP (Amino acid 1-239 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT, Y612F, R732L); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATY GKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTL VNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDN HYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY KSGEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETA LCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA FHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA LSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPI QQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ*	513	528
OT-hPDE5-084 (OT-	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATY GKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK	514	529

001206) AcGFP (Amino acid 1-239 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT, Y612W, R732L); stop	QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTL VNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDN HYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY KSGEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETA LCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA WHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA LSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPI QQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ*		
OT-hPDE5-085 (OT-001207) AcGFP (Amino acid 1-239 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT, Y612A, R732L); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATY GKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTL VNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDN HYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY KSGEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETA LCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA AHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA LSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPI QQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ*	515	530
OT-hPDE5-090 (OT-001212) AcGFP (Amino acid 1-239 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT, H653A, R732L); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATY GKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTL VNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDN HYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY KSGEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETA LCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA YHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA LSADLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPI QQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ*	516	531
OT-hPDE5-091 (OT-001213) AcGFP (Amino acid 1-239 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT, R732L, D764A); stop	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATY GKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTL VNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDN HYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY KSGEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETA LCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA YHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA LSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFFELIRKNQFNLEDPHQKELFLAMLMTACALSAITKPWPI QQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ*	517	532
OT-hPDE5-094 (OT-	MVSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATY GKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK	518	533

001253) AcGFP (Amino acid 1-239 of WT); linker (SG); hPDE5(Amino acid 535-860 of WT; R732L); Xba I site (TCTAGA); stop	QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTL VNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDN HYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY KSGEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETA LCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVA YHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAA LSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLG EFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPI QQRIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQSR*		

[0151] In some embodiments, any of the mutations described herein may be tested in the context of the truncated hPDE5 domains. As used herein truncated hPDE5 domains refers to regions and/or portions of hPDE5 of SEQ ID NO. 1, and are exemplified in Table 8. Also provided in Table 8 are the constructs utilizing the regions or portions of hPDE5, fused to AcGFP via linkers. In Table 8, translation of the stop codon is indicated by asterisk. Table 8 also provides alternate aliases for a given construct ID. These aliases are identified by the prefix OT.

Table 8: hPDE5 truncation constructs and its components

Construct ID/ Description	Sequence	AA SEQ ID NO	NA SEQ ID NO
Methionine; hPDE5 (Amino acid 535-860 of WT)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRM FTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFN TAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	237	4
Methionine; hPDE5 (Amino acid 535-860 of WT, R732L)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRM FTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFN TAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	238	250
Methionine; hPDE5 (Amino acid 535-836 of WT, R732L)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRM FTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFN TAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	239	251
Methionine; hPDE5 (Amino acid	MSDLETALCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRK NVAYHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNS PGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEFFELIRKN	240	252

567-860 of WT, R732L)	QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFF DQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEA LTHVSEDCFPLLDGCRKNRQKWQALAEQQ		
hPDE5 (Amino acid 590-860 of WT, R732L)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALK AGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQL YCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFLAMLMTACDL SAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ	241	253
hPDE5 (Amino acid 590-836 of WT, R732L)	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALK AGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQL YCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFLAMLMTACDL SAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVS	242	254
hPDE5 (Amino acid 535-860 of WT)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	3	339
hPDE5 (Amino acid 535-860 of WT, R732L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQ	12	536
hPDE5 (Amino acid 535-836 of WT, R732L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRMFT DLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNT AQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYI QRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVS	534	537
hPDE5 (Amino acid 567-860 of WT, R732L)	SDLETALCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKN VAYHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSP GNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEFFELIRKNQ FNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFD QGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALT HVSEDCFPLLDGCRKNRQKWQALAEQQ	535	538
Linker (SG)	SG	-	AGT GGT
AcGFP	VSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLK FICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMP EGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDG NILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQ LADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK	79	372
OT-hPDE5N-019 (OT-001216, OT-hPDE5-019)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRM FTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFN TAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP	243	255

Methionine; hPDE5 (Amino acid 535-860 of WT); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQSGVSKGAELFTGIVPILIELNGDVNGHKF SVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTLSYGVQCF SRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFE GDTLVNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLS TQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELYK*		
OT-hPDE5N-020 (OT-001217, OT-hPDE5-020) Methionine; hPDE5 (Amino acid 535-860 of WT, R732L); linker (SG); AcGFP; stop (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRM FTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFN TAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDG CRKNRQKWQALAEQQSGVSKGAELFTGIVPILIELNGDVNGHKF SVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTLSYGVQCF SRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFE GDTLVNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAK NGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLS TQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELYK*	244	256
OT-hPDE5N-021 (OT-001218, OT-hPDE5-021) Methionine; hPDE5 (Amino acid 535-836 of WT, R732L); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTIRM FTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFN TAQCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYK TTLKIIKQAILATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFL AMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSSGVSKGAEL FTGIVPILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGK LPVPWPTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQER TIFFEDDGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNK MEYNYNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQ QNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTAA AITHGMDELYK*	245	257
OT-hPDE5N-022 (OT-001219, OT-hPDE5-022) Methionine; hPDE5 (Amino acid 567-860 of WT, R732L); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MSDLETALCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRK NVAYHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAAL SHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNS PGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEFFELIRKN QFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFF DQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEA LTHVSEDCFPLLDGCRKNRQKWQALAEQQSGVSKGAELFTGIV PILIELNGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPW PTLVTTLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFED DGNYKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEYNY NAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIG DGPVLLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGM DELYK*	246	258
OT-hPDE5N-	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALK AGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQL	247	259

023 (OT-001220, OT-hPDE5-023) hPDE5 (Amino acid 590-860 of WT, R732L); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	YCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFLAMLMTACDL SAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ**SG**VSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGD ATYGKLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMKQ HDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDTLVNRIEL TGTDFKEDGNILGNKMEYNYNAHNVYIMTDKAKNGIKVNFKIR HNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPN EKRDHMIYFGFVTAAAITHGMDELYK*		
OT-hPDE5N-024 (OT-001221, OT-hPDE5-024) hPDE5 (Amino acid 590-836 of WT, R732L); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFAALK AGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQL YCHSIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFLAMLMTACDL SAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVS**SG**VSKGAELFTGIVPILIEL NGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVT TLSYGVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDGNY KSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEYNYNAHN VYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPV LLPDNHYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDELY K*	248	260

Stimulus

[0152] Biocircuits of the invention are triggered by one or more stimuli. Stimuli may be selected from a ligand, an externally added or endogenous metabolite, the presence or absence of a defined ligand, pH, temperature, light, ionic strength, radioactivity, cellular location, subject site, microenvironment, the presence or the concentration of one or more metal ions.

[0153] In some embodiments, the stimulus is a ligand. Ligands may be nucleic acid-based, protein-based, lipid based, organic, inorganic or any combination of the foregoing. In some embodiments, the ligand is selected from the group consisting of a protein, peptide, nucleic acid, lipid, lipid derivative, sterol, steroid, metabolite derivative and a small molecule. In some embodiments, the stimulus is a small molecule. In some embodiments, the small molecules are cell permeable. Ligands useful in the present invention include without limitation, any of those taught in Table 2 of co-owned U.S. Provisional Patent Application No. 62/320,864 filed April 11, 2016, 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587 (the contents of each of which are herein incorporated by reference in their entirety). In some embodiments, the small molecules are FDA-approved, safe and orally administered.

[0154] In some embodiments, the ligand binds to phosphodiesterases. In some embodiments, the ligand binds to and inhibits phosphodiesterase function and is herein referred to as a phosphodiesterase inhibitor.

[0155] In some embodiments, the ligand is a small molecule that binds to phosphodiesterase 5. In one embodiment, the small molecule is a hPDE5 inhibitor. Examples of hPDE5 inhibitors include, but are not limited to, Sildenafil, Vardenafil, Tadalafil, Avanafil, Lodenafil, Mirodenafil, Udenafil, Benzamidenafil, Dasantafil, Beminafil, SLx-2101, LAS 34179, UK-343,664, UK-357903, UK-371800, and BMS-341400.

[0156] In some embodiments, ligands include sildenafil-derived ligands containing portions of the ligand known to mediate binding to hPDE5. Ligands may also be modified to reduce off-target binding to Phosphodiesterases and increase specific binding to hPDE5.

[0157] hPDE5 inhibitors cover a broad pharmacokinetic space with respect to the approved dose and their duration of action and is described in Table 9. In Table 9, PO stands for *per os* (i.e. by mouth); QD represents *quaque die* (i.e. every day); IV represents intravenous; TID represents *ter un die* (i.e. three times a day); and Cmax represents the peak serum concentration that a drug achieves after its administration.

Table 9: Pharmacokinetics of hPDE5 inhibitors

Drug	Approved Dose	Cmax	Duration of action
Sildenafil	PO: 100 mg QD or 20 mg TID IV: 10 mg TID	PO: 1 μM IV: 1 μM	4-8 hrs
Vardenafil	PO: 20 mg QD	0.1 μM	2-8 hrs
Tadalafil	PO: 40 QD	1.5 μM	24-36 hrs

[0158] In some embodiments, the ligand selection is determined by the magnitude and duration of expression of the effector modules of the invention using the PK parameters described in Table 9. In some embodiments, high levels of expression of the payload for a short duration of time may be desired. In such instances, vardenafil may be selected as the ligand. In some embodiments, high levels of expression of the payload may be desired for a long duration. In such instances, the ligand, Tadalafil may be selected. In some embodiments, low levels of expression of the payload may be desired for a long duration of time. In such instances, Sildenafil may be selected as the ligand.

[0159] In some embodiments, additional hPDE5 inhibitors may be developed to show selectivity towards a specific phosphodiesterase protein; to reduce or increase the duration of treatment with the ligand; and to improve the rate of onset of the ligand.

[0160] Ligands may also be selected from the analysis of the dependence of a known hPDE5 ligand's activity on its molecular/ chemical structure, through Structure Activity Relationships (SAR) study. Any of the methods related to SAR, known in art may be utilized to identify stabilizing ligands of the invention. SAR may be utilized to improve properties of the ligand such as specificity, potency, pharmacokinetics, bioavailability, and safety. SAR analysis of known hPDE5 inhibitors may also be combined with high resolution X ray structures of hPDE5 complexed with ligands. The X ray structure of hPDE5 co-crystallized with Sildenafil, Tadalafil, and Vardenafil have been studied and the binding mode of the inhibitors has been identified (Zhang, K. Y. J. et al. (2004) Mol. Cell., 15, 279; Card, G.L. et al. (2004) Structure.12, 2233; the contents of each of which are incorporated herein by reference in their entirety). There are several classes of hPDE5 inhibitors described. These include aryl, beryl, heteroaryl or heterobiaryl classes with different scaffold structures. The aryl class includes substituted nitroanilines and the biaryl class includes substituted naphthalenes. The heterobiaryl and heterotriaryl are further sub classified based on its fused system into pyrazolopyrimidinones, triazolopyrimidinones, imidazotriazines, purines, pyrrolopyrimidinones, triazolotrizinones, isoxazolopyrimidinones, β-carbolines, pyrroloquinolones, isoquinolines, quinazolines, imidazoquinazolinones, pyrazolopyridines, pyrazolopyridopyrimidinones. These widely different chemical structures are suggested to have different orientation in the binding site of hPDE5 enzyme. Sildenafil has three main chemical groups, the pyrazolopyrimidinone ring, the ethoxyphenyl ring and the methylpiperazine ring. The pyrazolopyrimidinone group is responsible for the binding of the drug to its active binding site of hPDE5.

[0161] Many hPDE inhibitors act by competing with the substrate, cGMP, for the catalytic site of the enzyme. Sildenafil and Vardenafil differ in the heterocyclic ring system used to mimic the purine ring of cGMP. They also differ in the substituent (ethyl/methyl) of a piperazine side chain. Although these are the only structural differences, Vardenafil is more potent than Sildenafil. In some embodiments, the structural differences between different know inhibitors of hPDE may be utilized to design better hPDE inhibitor based ligands. For example, Corbin et al. synthesized an analog of sildenafil that contained the sildenafil ring system but with the appended ethyl group found in vardenafil; and an analog of vardenafil (dimethyl-vardenafil) that contained the vardenafil ring system but with the appended methyl group found in sildenafil was also generated. These studies identified that the ring systems play a critical role in higher potency of vardenafil over sildenafil (Corbin JD et al. (2004) Neurochem Int ;45(6):859-63; the contents of which are incorporated herein by reference in

their entirety). Based on the X ray crystal structure of hPDE complexed with sildenafil, the active site region was defined as a sphere within the 6.5 Angstrom from the reference ligand, sildenafil. Surface hydrophobicity (lipophilicity) potential physicochemical property map of the hPDE5 active site may be generated based on this information. The ethoxyphenyl group of sildenafil fits into the hydrophobic pocket formed by Phe 786, Ala783, Leu804, and Val782, and the pyrazolopyrimidinone ring also forms hydrophobic interaction with the side chains of Val782, Tyr612, and Phe820 in the binding pocket.

[0162] New hPDE5 inhibitors may also be developed using a series of analogs of known hPDE5 inhibitors. 3D-Quantitative Structure activity analysis (QSAR), CoMFA (comparative molecular field analysis) and CoMSIA (comparative molecular similarity indices analysis) may be implemented for this purpose. In one embodiment, the structure of hPDE5 inhibitor may preferentially incorporate an N ethyl group in the pyrrolopyrimidinone ring at N5 position; and a propoxyphenyl group, which bear a substituent; one methylene unit longer, respectively in comparison with the corresponding positions of sildenafil. Any of the modifications to Sildenafil structure taught by Koo J et al. may be useful in the present invention (Koo J et al. (2007) Bioorg. & Med. Chem Lett 17; 4271–4274; the contents of which are incorporated by reference in their entirety).

[0163] In some embodiments, the stimulus may be a ligand that binds to more than one phosphodiesterase. In one embodiment, the stimulus is a pan phosphodiesterase inhibitor that may bind to two or more hPDEs such as Aminophyline, Paraxanthine, Pentoxifylline, Theobromine, Dipyridamole, Theophyline, Zaprinast, Icariin, CDP-840, Etazolate and Glaucine.

[0164] In some embodiments, the ligand is a hPDE1 inhibitor. Exemplary hPDE1 inhibitor, Vinpocetine may in some instances be used as the ligand in the present invention. In some embodiments, the ligand is a hPDE2 inhibitor. Exemplary hPDE2 inhibitors include EHNA (erythro-9-(2-hydroxy-3-nonyl) adenine), Oxindole, PDP and BAY 60-7550. Inhibitors that selectively inhibit a hPDE2 isoform may also be used, for example, substituted pyrido (2,3-b) pyrazines having a hPDE2A selective inhibitory action (See, e.g., US Pat. NO.: 9,527,841; the contents of which are incorporated by reference in its entirety). In some embodiments, the ligand is a hPDE3 inhibitor. hPDE3 inhibitors useful in the invention include, but are not limited to Amrinone, Cilostazol, Milrinone, Enoximone, and Pimobendan. In some embodiments, the ligand is a hPDE4 inhibitor. Exemplary hPDE4 inhibitors include FDA approved small molecules such as, but not limited to AN2728 (4-[(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-5-yl) oxy]benzonitrile), Apremilast/ CC10004 (N-{2-

[(1S)-1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl}acetamide), and Roflumilast. Other exemplary hPDE4 inhibitors include Other small molecules that inhibit hPDE4 also include E6005/RVT501, Cilomilast/SB-207,499, Ibudilast (AV-411 or MN-166), Mesembrenone, Piclamilast / RP 73401, Rolipram, Atizoram / CP-80633, Arofylline, CC-1088, Catramilast, CGH-2466, Cipamfylline, Drotaverine, Filaminast/WAY-PDA 641, HT-0712, DNS-001, ICI-63197, Indimilast, Irsogladine/MN 1695, Lirimilast/ BAY 19-8004, Oglemilast, Revamilast, Ro 20-1724, Ronomilast, GSK256066, DC-TA-46, AWD 12–281 and YM-976. Any of the hPDE4 inhibitors described in International Patent Publication No. WO2014078220A1 and US Patent Publication No. US20170129887A1 may be useful in the present invention (the contents of each of which are incorporated by reference in their entirety). In some embodiments, the ligand is a hPDE6 inhibitor. In some embodiments, the ligand is a hPDE7 inhibitor. Exemplary hPDE7 inhibitors, include BRL-50481(N, N,2-Trimethyl-5-nitrobenzenesulfonamide) and ASB16165 (1H-Thieno(2,3-C) pyrazole-5-carboxamide, 1-cyclohexyl-N-(6-(4-hydroxy-1-piperidinyl)-3-pyridinyl)-3-methyl). In some embodiments, the ligand is a hPDE8 inhibitor such as PF-04957325 (Pfizer). In some embodiments, the ligand is a hPDE9 inhibitor. Exemplary hPDE9 inhibitors include, but are not limited to BAY73-6691 (1-(2-chlorophenyl)-6-[(2R)-3,3,3-trifluoro-2-methylpropyl]-1,5-dihydro-4H-pyrazolo[3,4-d] pyrimidine-4-one), PF-04447943 (6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-1-(oxan-4-yl)-2H-pyrazolo[3,4-d]pyrimidin-4-one) and WYQ-C28L. In some embodiments, the ligand is a hPDE10 inhibitor. Exemplary PDE10 inhibitors include, but are not limited to OMS 824, Papaverine and PF-2545920 (2-(4-(1-methyl-4-pyridin-4-yl-1H-pyrazol-3-yl) phenoxymethyl) quinolone), and GS-5759 (Gilead).

[0165] In one embodiment, the stimuli of the present invention may be FDA approved ligands capable of binding to the specific DDs or target regions within the DDs. In other embodiments, FDA approved ligands may be used to screen potential binders in the human protein. DDs may be designed based on the positive hits from the screen using the portion of the protein that binds to the ligand. In one embodiment, proteins that bind to FDA approved ligands as off target interactions may be used to design DDs of the present invention.

[0166] In some embodiments, ligands that do not affect the activity of the immune cell, and/or the chimeric antigen receptor, in the absence of the SREs may be preferably selected.

Stabilizing Domains

[0167] In some embodiments, the stimulus response element may be stabilized in the absence of the stimulus but destabilized by the stimulus. In some embodiments, SREs may be

derived from protein complexes that comprise at least one protein-protein interaction. In other aspects, the SRE may form a protein-protein interaction with a natural protein within the cell. Protein complexes reduce the exposure of the constituent proteins to the risk of undesired oligomerization by reducing the concentration of the free monomeric state. Payloads appended to such SREs may stabilized in the absence of the stimulus. In some aspects, the stimulus may be a small molecule that is capable of interrupting or disrupting the protein-protein interactions related to the SRE. In such instances, addition of the stimulus, results in the reduced expression and/or function of the payload. In some embodiments, stimuli that induce conformational change of the SRE may be utilized. In one aspect, the SRE may be stabilized by the conformational change. In another aspect, the SRE may be destabilized by the conformational change. The stimuli may also be small molecules that disrupt post translational modification of SREs which may result in the disruption of the protein-protein interaction related to the SRE. In some embodiments, SREs may be identified using protein interactomic techniques known in the art. Such methods may enable the identification of protein interactions that are therapeutically relevant. Any of the large-scale quantitative proteomics methods described in International Patent Publication NOs. WO2017210427A1, WO2016196994A9, and WO2014200987A3 may be useful in the present invention (the contents of each of which are incorporated by reference in their entirety).

Payloads

[0168] In some embodiments, payloads can be any natural protein in an organism genome, a fusion polypeptide, an antibody, or variants, mutants and derivatives thereof. In some embodiments, the effector module of the present invention is a fusion construct comprising a DD of the invention operably linked to at least one payload. In one aspect, the payload may be any natural protein of interest (POI) or variants thereof, an antibody or fragments thereof, a therapeutic agent, or any artificial peptide or polypeptide.

[0169] In some embodiments, payloads of the present invention may be immunotherapeutic agents. As used herein, an immunotherapeutic agent is any agent that induces immune responses in an organism. An immunotherapeutic agent may be a natural protein in an organism or it may be an artificial protein such as a fusion protein or an antibody. The immunotherapeutic agent may be, but is not limited to, an antibody and fragments and variants thereof, a MHC molecule, an antigen and fragments thereof, a T cell receptor (TCR) such as a tumor specific TCR and variants thereof, a chimeric antigen receptor (CAR), a chimeric switch receptor, a co-stimulatory molecule, a co-inhibitory

molecule, an inhibitor of a co-inhibitory receptor or ligand, an agonist of a co-stimulatory receptor and ligand, a cytokine, chemokine, a cytokine receptor, a chemokine receptor, a soluble growth factor, a metabolic factor, a homing receptor, a safety switch (e.g., a suicide gene), or any agent that induces an immune response. In one embodiment, the immunotherapeutic agent induces an anti-cancer immune response in a cell, or in a subject. In some aspects, the immunotherapeutic agent reduces the tumor burden in a subject.

[0170] The payload may be any immunotherapeutic agent used for cancer immunotherapy such as a T cell receptor (TCR), a chimeric agent receptor (CAR) such as CD19 CAR that targets any molecule of tumor cells, an antibody, an antigen binding domain or combination of antigen binding domains, a cytokine such as IL2, IL12, IL15 or IL15/IL15Ra fusion, an antagonist of an immune checkpoint, an agonist of co-stimulatory molecule, a chimeric switch receptor, a safety switch, a metabolic factor, a growth factor, a chemokine, a chemokine receptor, a homing receptor, or any agent that can induce an immune response. The SRE and payload may be operably linked through one or more linkers and the positions of components may vary within the effector module.

1. Protein of Interest

[0171] In some embodiments, payloads of the invention may be a natural protein in an organism genome, or variants, mutants, derivatives thereof. The natural protein may be from, for example, a mammalian organism, a bacterium, and a virus.

[0172] In one example, the payload may be a protein of interest, or a polypeptide from human genome.

2. Antibodies

[0173] In some embodiments, antibodies, fragments and variants thereof are payloads of the present invention. The antibody may be an intact antibody, an antibody light chain, antibody heavy chain, an antibody fragment, an antibody variant, or an antibody derivative.

[0174] In some embodiments, payloads of the invention may be an antibody or fragments thereof. Antibodies useful in this method include without limitation, any of those taught in co-owned U.S. Provisional Patent Application No. 62/320,864 filed April 11, 2016, 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587 (the contents of each of which are herein incorporated by reference in their entirety).

Antibody fragments and variants

[0175] In some embodiments, antibody fragments and variants may comprise antigen binding regions from intact antibodies. Examples of antibody fragments and variants may include, but are not limited to Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear

antibodies; single-chain antibody molecules such as single chain variable fragment (scFv); and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site. Also produced is a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an F(ab')2 fragment that has two antigen-binding sites and is still capable of cross-linking with the antigen. Pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention may comprise one or more of these fragments.

[0176] For the purposes herein, an "antibody" may comprise a heavy and light variable domain as well as an Fc region. As used herein, the term "native antibody" usually refers to a heterotetrameric glycoprotein of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Genes encoding antibody heavy and light chains are known and segments making up each have been well characterized and described (Matsuda et al., *The Journal of Experimental Medicine*. 1998, 188(11): 2151-62 and Li et al., *Blood*, 2004, 103(12): 4602-4609; the content of each of which are herein incorporated by reference in their entirety). Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[0177] As used herein, the term "variable domain" refers to specific antibody domains found on both the antibody heavy and light chains that differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. Variable domains comprise hypervariable regions. As used herein, the term "hypervariable region" refers to a region within a variable domain comprising amino acid residues responsible for antigen binding. The amino acids present within the hypervariable regions determine the structure of the complementarity determining regions (CDRs) that become part of the antigen-binding site of the antibody. As used herein, the term “CDR” refers to a region of an antibody comprising a structure that is complimentary to its target antigen or epitope. Other portions of the variable domain, not interacting with the antigen, are referred to as framework (FW) regions. The antigen-binding site (also known as

the antigen combining site or paratope) comprises the amino acid residues necessary to interact with a particular antigen. The exact residues making up the antigen-binding site are typically elucidated by co-crystallography with bound antigen, however computational assessments based on comparisons with other antibodies can also be used (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety). Determining residues that make up CDRs may include the use of numbering schemes including, but not limited to, those taught by Kabat (Wu et al., *JEM*, 1970, 132(2):211-250 and Johnson et al., *Nucleic Acids Res.* 2000, 28(1): 214-218, the contents of each of which are herein incorporated by reference in their entirety), Chothia (Chothia and Lesk, J. *Mol. Biol.* 1987, 196, 901, Chothia et al., *Nature,* 1989, 342, 877, and Al-Lazikani et al., *J. Mol. Biol.* 1997, 273(4): 927-948, the contents of each of which are herein incorporated by reference in their entirety), Lefranc (Lefranc et al., *Immunome Res.* 2005, 1:3) and Honegger (Honegger and Pluckthun, *J. Mol. Biol.* 2001, 309(3): 657-70, the contents of which are herein incorporated by reference in their entirety).

[0178] VH and VL domains have three CDRs each. VL CDRs are referred to herein as CDR-L1, CDR-L2 and CDR-L3, in order of occurrence when moving from N- to C- terminus along the variable domain polypeptide. VH CDRs are referred to herein as CDR-H1, CDR-H2 and CDR-H3, in order of occurrence when moving from N- to C- terminus along the variable domain polypeptide. Each of CDRs has favored canonical structures with the exception of the CDR-H3, which comprises amino acid sequences that may be highly variable in sequence and length between antibodies resulting in a variety of three-dimensional structures in antigen-binding domains (Nikoloudis, et al., *PeerJ.* 2014, 2: e456). In some cases, CDR-H3s may be analyzed among a panel of related antibodies to assess antibody diversity. Various methods of determining CDR sequences are known in the art and may be applied to known antibody sequences (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety).

[0179] As used herein, the term "Fv" refers to an antibody fragment comprising the minimum fragment on an antibody needed to form a complete antigen-binding site. These regions consist of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. Fv fragments can be generated by proteolytic cleavage, but are largely unstable. Recombinant methods are known in the art for generating stable Fv fragments, typically through insertion of a flexible linker between the light chain variable

domain and the heavy chain variable domain (to form a single chain Fv (scFv)) or through the introduction of a disulfide bridge between heavy and light chain variable domains (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p46-47, the contents of which are herein incorporated by reference in their entirety).

[0180] As used herein, the term "light chain" refers to a component of an antibody from any vertebrate species assigned to one of two clearly distinct types, called kappa and lambda based on amino acid sequences of constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains, antibodies can be assigned to different classes. There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

[0181] As used herein, the term "single chain Fv" or "scFv" refers to a fusion protein of VH and VL antibody domains, wherein these domains are linked together into a single polypeptide chain by a flexible peptide linker. In some embodiments, the Fv polypeptide linker enables the scFv to form the desired structure for antigen binding. In some embodiments, scFvs are utilized in conjunction with phage display, yeast display or other display methods where they may be expressed in association with a surface member (e.g. phage coat protein) and used in the identification of high affinity peptides for a given antigen.

[0182] Using molecular genetics, two scFvs can be engineered in tandem into a single polypeptide, separated by a linker domain, called a “tandem scFv” (tascFv). Construction of a tascFv with genes for two different scFvs yields a “bispecific single-chain variable fragments” (bis-scFvs). Only two tascFvs have been developed clinically by commercial firms; both are bispecific agents in active early phase development by Micromet for oncologic indications, and are described as “Bispecific T-cell Engagers (BiTE).” Blinatumomab is an anti-CD19/anti-CD3 bispecific tascFv that potentiates T-cell responses to B-cell non-Hodgkin lymphoma in Phase 2. MT110 is an anti-EP-CAM/anti-CD3 bispecific tascFv that potentiates T-cell responses to solid tumors in Phase 1. Bispecific, tetravalent “TandAbs” are also being researched by Affimed (Nelson, A. L., MAbs., 2010, Jan-Feb; 2(1):77–83). maxibodies (bivalent scFv fused to the amino terminus of the Fc (CH2-CH3 domains) of IgG may also be included.

[0183] As used herein, the term “bispecific antibody” refers to an antibody capable of binding two different antigens. Such antibodies typically comprise regions from at least two different antibodies. Bispecific antibodies may include any of those described in Riethmuller, G. *Cancer Immunity*. 2012, 12:12-18, Marvin et al., 2005. *Acta Pharmacologica Sinica*.

2005, 26(6): 649-658 and Schaefer et al., *PNAS*. 2011, 108(27):11187-11192, the contents of each of which are herein incorporated by reference in their entirety. In some aspects, bispecific antibodies may be trifunctional antibodies (3funct) and BiTE (bi-specific T cell engager).

[0184] As used herein, the term "diabody" refers to a small antibody fragment with two antigen-binding sites. Diabodies are functional bispecific single-chain antibodies (bscAb). Diabodies comprise a heavy chain variable domain VH connected to a light chain variable domain VL in the same polypeptide chain. By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al. (Hollinger, P. et al., "Diabodies": Small bivalent and bispecific antibody fragments. *PNAS*, 1993. 90: 6444-6448); the contents of each of which are incorporated herein by reference in their entirety.

[0185] The term "intrabody" refers to a form of antibody that is not secreted from a cell in which it is produced, but instead targets one or more intracellular proteins. Intrabodies may be used to affect a multitude of cellular processes including, but not limited to intracellular trafficking, transcription, translation, metabolic processes, proliferative signaling and cell division. In some embodiments, methods of the present invention may include intrabody-based therapies. In some such embodiments, variable domain sequences and/or CDR sequences disclosed herein may be incorporated into one or more constructs for intrabody-based therapy.

[0186] As used herein, the term "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous cells (or clones), i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variants that may arise during production of the monoclonal antibodies, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen.

[0187] The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. The monoclonal antibodies herein include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in

antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies.

[0188] As used herein, the term "humanized antibody" refers to a chimeric antibody comprising a minimal portion from one or more non-human (e.g., murine) antibody source(s) with the remainder derived from one or more human immunoglobulin sources. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from the hypervariable region from an antibody of the recipient are replaced by residues from the hypervariable region from an antibody of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and/or capacity. In one embodiment, the antibody may be a humanized full-length antibody. As a non-limiting example, the antibody may have been humanized using the methods taught in US Patent Publication NO. US20130303399, the contents of which are herein incorporated by reference in its entirety.

[0189] As used herein, the term “antibody variant” refers to a modified antibody (in relation to a native or starting antibody) or a biomolecule resembling a native or starting antibody in structure and/or function (e.g., an antibody mimetic). Antibody variants may be altered in their amino acid sequence, composition or structure as compared to a native antibody. Antibody variants may include, but are not limited to, antibodies with altered isotypes (e.g., IgA, IgD, IgE, IgG1, IgG2, IgG3, IgG4, or IgM), humanized variants, optimized variants, multispecific antibody variants (e.g., bispecific variants), and antibody fragments.

[0190] In some embodiments, pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention may be antibody mimetics. As used herein, the term “antibody mimetic” refers to any molecule which mimics the function or effect of an antibody and which binds specifically and with high affinity to their molecular targets. In some embodiments, antibody mimetics may be monobodies, designed to incorporate the fibronectin type III domain (Fn3) as a protein scaffold (US 6,673,901; US 6,348,584). In some embodiments, antibody mimetics may be those known in the art including, but are not limited to affibody molecules, affilins, affitins, anticalins, avimers, Centyrins, DARPINSTM, Fynomers and Kunitz and domain peptides. In other embodiments, antibody mimetics may include one or more non-peptide regions.

[0191] In one embodiment, the antibody may comprise a modified Fc region. As a non-limiting example, the modified Fc region may be made by the methods or may be any of the regions described in US Patent Publication NO. US20150065690, the contents of which are herein incorporated by reference in its entirety.

[0192] In some embodiments, payloads of the invention may encode multispecific antibodies that bind more than one epitope. As used herein, the terms "multibody" or "multispecific antibody" refer to an antibody wherein two or more variable regions bind to different epitopes. The epitopes may be on the same or different targets. In one embodiment, the multispecific antibody may be generated and optimized by the methods described in International Patent Publication NO. WO2011109726 and US Patent Publication NO. US20150252119, the contents of which each of which are herein incorporated by reference in their entirety. These antibodies are able to bind to multiple antigens with high specificity and high affinity.

[0193] In certain embodiments, a multi-specific antibody is a "bispecific antibody" which recognizes two different epitopes on the same or different antigens. In one aspect, bispecific antibodies are capable of binding two different antigens. Such antibodies typically comprise antigen-binding regions from at least two different antibodies. For example, a bispecific monoclonal antibody (BsMAb, BsAb) is an artificial protein composed of fragments of two different monoclonal antibodies, thus allowing the BsAb to bind to two different types of antigen. Bispecific antibody frameworks may include any of those described in Riethmuller, G., 2012. Cancer Immunity, 2012, 12:12-18; Marvin et al., Acta Pharmacologica Sinica. 2005, 26(6):649-658; and Schaefer et al., PNAS. 2011, 108(27): 11187-11192, the contents of each of which are herein incorporated by reference in their entirety. New generations of BsMAb, called "trifunctional bispecific" antibodies, have been developed. These consist of two heavy and two light chains, one each from two different antibodies, where the two Fab regions (the arms) are directed against two antigens, and the Fc region (the foot) comprises the two heavy chains and forms the third binding site.

[0194] In some embodiments, payloads may encode antibodies comprising a single antigen-binding domain. These molecules are extremely small, with molecular weights approximately one-tenth of those observed for full-sized mAbs. Further antibodies may include "nanobodies" derived from the antigen-binding variable heavy chain regions (VHHs) of heavy chain antibodies found in camels and llamas, which lack light chains (Nelson, A. L., MAbs.2010. Jan-Feb; 2(1):77–83).

[0195] In some embodiments, the antibody may be "miniaturized". Among the best examples of mAb miniaturization are the small modular immunopharmaceuticals (SMIPs) from Trubion Pharmaceuticals. These molecules, which can be monovalent or bivalent, are recombinant single-chain molecules containing one VL, one VH antigen-binding domain, and one or two constant "effector" domains, all connected by linker domains. Presumably, such a molecule might offer the advantages of increased tissue or tumor penetration claimed by fragments while retaining the immune effector functions conferred by constant domains. At least three "miniaturized" SMIPs have entered clinical development. TRU-015, an anti-CD20 SMIP developed in collaboration with Wyeth, is the most advanced project, having progressed to Phase 2 for rheumatoid arthritis (RA). Earlier attempts in systemic lupus erythrematosus (SLE) and B cell lymphomas were ultimately discontinued. Trubion and Facet Biotechnology are collaborating in the development of TRU-016, an anti-CD37 SMIP, for the treatment of CLL and other lymphoid neoplasias, a project that has reached Phase 2. Wyeth has licensed the anti-CD20 SMIP SBI-087 for the treatment of autoimmune diseases, including RA, SLE and possibly multiple sclerosis, although these projects remain in the earliest stages of clinical testing. (Nelson, A. L., MAbs, 2010. Jan-Feb; 2(1):77–83).

[0196] On example of miniaturized antibodies is called "unibody" in which the hinge region has been removed from IgG4 molecules. While IgG4 molecules are unstable and can exchange light-heavy chain heterodimers with one another, deletion of the hinge region prevents heavy chain-heavy chain pairing entirely, leaving highly specific monovalent light/heavy heterodimers, while retaining the Fc region to ensure stability and half-life in vivo. This configuration may minimize the risk of immune activation or oncogenic growth, as IgG4 interacts poorly with FcRs and monovalent unibodies fail to promote intracellular signaling complex formation (see, e.g., Nelson, A. L., MAbs, 2010. Jan-Feb; 2(1):77–83).

[0197] In some embodiments, payloads of the invention may encode single-domain antibodies (sdAbs, or nanobodies) which are antibody fragment consisting of a single monomeric variable antibody domain. Like a whole antibody, it is able to bind selectively to a specific antigen. In one aspect, a sdAb may be a "Camel Ig or "camelid VHH". As used herein, the term "camel Ig" refers to the smallest known antigen-binding unit of a heavy chain antibody (Koch-No lte, et al, *FASEB J.*, 2007, 21: 3490- 3498). A "heavy chain antibody" or a "camelid antibody" refers to an antibody that contains two VH domains and no light chains (Riechmann L. et al, *J. Immunol. Methods*, 1999, 231: 25-38; International patent publication NOs.: WO1994/04678 and W01994/025591; and U.S. Patent No. 6,005,079). In another aspect, a sdAb may be a "immunoglobulin new antigen receptor" (IgNAR). As used

herein, the term "immunoglobulin new antigen receptor" refers to class of antibodies from the shark immune repertoire that consist of homodimers of one variable new antigen receptor (VNAR) domain and five constant new antigen receptor (CNAR) domains. IgNARs represent some of the smallest known immunoglobulin-based protein scaffolds and are highly stable and possess efficient binding characteristics. The inherent stability can be attributed to both (i) the underlying Ig scaffold, which presents a considerable number of charged and hydrophilic surface exposed residues compared to the conventional antibody VH and VL domains found in murine antibodies; and (ii) stabilizing structural features in the complementary determining region (CDR) loops including inter-loop disulphide bridges, and patterns of intra-loop hydrogen bonds.

[0198] In some embodiments, payloads of the invention may encode intrabodies. Intrabodies are a form of antibody that is not secreted from a cell in which it is produced, but instead targets one or more intracellular proteins. Intrabodies are expressed and function intracellularly, and may be used to affect a multitude of cellular processes including, but not limited to intracellular trafficking, transcription, translation, metabolic processes, proliferative signaling and cell division. In some embodiments, methods described herein include intrabody-based therapies. In some such embodiments, variable domain sequences and/or CDR sequences disclosed herein are incorporated into one or more constructs for intrabody-based therapy. For example, intrabodies may target one or more glycated intracellular proteins or may modulate the interaction between one or more glycated intracellular proteins and an alternative protein.

[0199] The intracellular expression of intrabodies in different compartments of mammalian cells allows blocking or modulation of the function of endogenous molecules (Biocca, et al., *EMBO J.* 1990, 9: 101-108; Colby et al., *Proc. Natl. Acad. Sci. U.S.A.* 2004, 101: 17616-17621). Intrabodies can alter protein folding, protein-protein, protein-DNA, protein-RNA interactions and protein modification. They can induce a phenotypic knockout and work as neutralizing agents by direct binding to the target antigen, by diverting its intracellular trafficking or by inhibiting its association with binding partners. With high specificity and affinity to target antigens, intrabodies have advantages to block certain binding interactions of a particular target molecule, while sparing others.

[0200] Sequences from donor antibodies may be used to develop intrabodies. Intrabodies are often recombinantly expressed as single domain fragments such as isolated VH and VL domains or as a single chain variable fragment (scFv) antibody within the cell. For example, intrabodies are often expressed as a single polypeptide to form a single chain antibody

comprising the variable domains of the heavy and light chains joined by a flexible linker polypeptide. Intrabodies typically lack disulfide bonds and are capable of modulating the expression or activity of target genes through their specific binding activity. Single chain intrabodies are often expressed from a recombinant nucleic acid molecule and engineered to be retained intracellularly (e.g., retained in the cytoplasm, endoplasmic reticulum, or periplasm). Intrabodies may be produced using methods known in the art, such as those disclosed and reviewed in: (Marasco et al., *PNAS*, 1993, 90: 7889-7893; Chen et al., *Hum. Gene Ther*. 1994, 5:595-601; Chen et al., 1994, *PNAS*, 91: 5932-5936; Maciejewski et al., 1995, *Nature Med*., 1: 667-673; Marasco, 1995, *Immunotech*, 1: 1-19; Mhashilkar, et al., 1995, *EMBO J*. 14: 1542-51; Chen et al., 1996, *Hum. Gene Therap*., 7: 1515-1525; Marasco, *Gene Ther*. 4:11-15, 1997; Rondon and Marasco, 1997, Annu. Rev. Microbiol. 51:257-283; Cohen, et al., 1998, Oncogene 17:2445-56; Proba et al., 1998, J. Mol. Biol. 275:245-253; Cohen et al., 1998, Oncogene 17:2445-2456; Hassanzadeh, et al., 1998, FEBS Lett. 437:81-6; Richardson et al., 1998, Gene Ther. 5:635-44; Ohage and Steipe, 1999, J. Mol. Biol. 291:1119-1128; Ohage et al., 1999, J. Mol. Biol. 291:1129-1134; Wirtz and Steipe, 1999, Protein Sci. 8:2245-2250; Zhu et al., 1999, J. Immunol. Methods 231:207-222; Arafat et al., 2000, Cancer Gene Ther. 7:1250-6; der Maur et al., 2002, J. Biol. Chem. 277:45075-85; Mhashilkar et al., 2002, Gene Ther. 9:307-19; and Wheeler et al., 2003, FASEB J. 17: 1733-5; and references cited therein).

[0201] In some embodiments, payloads of the invention may encode biosynthetic antibodies as described in U.S. Patent No. 5,091,513, the contents of which are herein incorporated by reference in their entirety. Such antibody may include one or more sequences of amino acids constituting a region which behaves as a biosynthetic antibody binding site (BABS). The sites comprise 1) non-covalently associated or disulfide bonded synthetic VH and VL dimers, 2) VH-VL or VL-VH single chains wherein the VH and VL are attached by a polypeptide linker, or 3) individuals VH or VL domains. The binding domains comprise linked CDR and FR regions, which may be derived from separate immunoglobulins. The biosynthetic antibodies may also include other polypeptide sequences which function, e.g., as an enzyme, toxin, binding site, or site of attachment to an immobilization media or radioactive atom. Methods are disclosed for producing the biosynthetic antibodies, for designing BABS having any specificity that can be elicited by in vivo generation of antibody, and for producing analogs thereof.

[0202] In some embodiments, payloads may encode antibodies with antibody acceptor frameworks taught in U.S. Patent No. 8,399,625. Such antibody acceptor frameworks may be particularly well suited accepting CDRs from an antibody of interest.

[0203] In one embodiment, the antibody may be a conditionally active biologic protein. An antibody may be used to generate a conditionally active biologic protein which are reversibly or irreversibly inactivated at the wild type normal physiological conditions as well as to such conditionally active biologic proteins and uses of such conditional active biologic proteins are provided. Such methods and conditionally active proteins are taught in, for example, International Publication No. WO2015175375 and WO2016036916 and US Patent Publication No. US20140378660, the contents of each of which are incorporated herein by reference in their entirety.

Antibody preparations

[0204] The preparation of antibodies, whether monoclonal or polyclonal, is known in the art. Techniques for the production of antibodies are well known in the art and described, e.g. in Harlow and Lane "Antibodies, A Laboratory Manual", Cold Spring Harbor Laboratory Press, 1988; Harlow and Lane "Using Antibodies: A Laboratory Manual" Cold Spring Harbor Laboratory Press, 1999 and "Therapeutic Antibody Engineering: Current and Future Advances Driving the Strongest Growth Area in the Pharmaceutical Industry" Woodhead Publishing, 2012.

[0205] The antibodies and fragments and variants thereof as described herein can be produced using recombinant polynucleotides. In one embodiment, the polynucleotides have a modular design to encode at least one of the antibodies, fragments or variants thereof. As a non-limiting example, the polynucleotide construct may encode any of the following designs: (1) the heavy chain of an antibody, (2) the light chain of an antibody, (3) the heavy and light chain of the antibody, (4) the heavy chain and light chain separated by a linker, (5) the VH1, CH1, CH2, CH3 domains, a linker and the light chain or (6) the VH1, CH1, CH2, CH3 domains, VL region, and the light chain. Any of these designs may also comprise optional linkers between any domain and/or region. The polynucleotides of the present invention may be engineered to produce any standard class of immunoglobulins using an antibody described herein or any of its component parts as a starting molecule.

Antibodies used for immunotherapy

[0206] In some embodiments, payloads of the present invention may be antibodies, fragments and variants thereof which are specific to tumor specific antigens (TSAs) and tumor associated antigens (TAAs). Antibodies circulate throughout the body until they find

and attach to the TSA/TAA. Once attached, they recruit other parts of the immune system, increasing ADCC (antibody dependent cell-mediated cytotoxicity) and ADCP (antibody dependent cell-mediated phagocytosis) to destroy tumor cells. As used herein, the term "tumor specific antigen (TSA)" means an antigenic substance produced in tumor cells, which can trigger an anti-tumor immune response in a host organism. In one embodiment, a TSA may be a tumor neoantigen. The tumor antigen specific antibody mediates complement-dependent cytotoxic response against tumor cells expressing the same antigen.

[0207] Of particular interest is a TSA that is a breast cancer antigen, an ovarian cancer antigen, a prostate cancer antigen, a cervical cancer antigen, a pancreatic carcinoma antigen, a lung cancer antigen, a bladder cancer antigen, a colon cancer antigen, a testicular cancer antigen, a glioblastoma cancer antigen, an antigen associated with a B cell malignancy, an antigen associated with multiple myeloma, an antigen associated with non-Hodgkins lymphoma, or an antigen associated with chronic lymphocytic leukemia.

[0208] Suitable antibodies which can immunoactively bind to a TSA may include, but are not limited to, those specific to 5T4, 707-AP, A33, AFP (α-fetoprotein), AKAP-4 (A kinase anchor protein 4), ALK, α5β1-integrin, androgen receptor, annexin II, alpha- actinin-4, ART-4, B1, B7H3, B7H4, BAGE (B melanoma antigen), BCMA, BCR-ABL fusion protein, beta-catenin, BKT-antigen, BTAA, CA-I (carbonic anhydrase I), CA50 (cancer antigen 50), CA125, CA15-3, CA195, CA242, calretinin, CAIX (carbonic anhydrase), CAMEL (cytotoxic T-lymphocyte recognized antigen on melanoma), CAM43, CAP-1, Caspase-8/m, CD4, CD5, CD7, CD19, CD20, CD22, CD23, CD25, CD27/m, CD28, CD30, CD33, CD34, CD36, CD38, CD40/CD154, CD41, CD44v6, CD44v7/8, CD45,CD49f, CD56, CD68\KP1, CD74, CD79a/CD79b, CD103, CD123, CD133, CD138, CD171, cdc27/m, CDK4 (cyclin dependent kinase 4), CDKN2A, CDS, CEA (carcinoembryonic antigen), CEACAM5, CEACAM6, chromogranin, c-Met, c-Myc, coa-1, CSAp, CT7, CT10, cyclophilin B, cyclin B1, cytoplasmic tyrosine kinases, cytokeratin, DAM-10, DAM-6, dek-can fusion protein, desmin, DEPDC1 (DEP domain containing 1), E2A-PRL, EBNA, EGF-R (epidermal growth factor receptor), EGP-1(epithelial glycoprotein -1) (TROP-2), EGP-2, EGP-40, EGFR (epidermal growth factor receptor), EGFRvIII, EF-2, ELF2M, EMMPRIN, EpCAM (epithelial cell adhesion molecule), EphA2, Epstein Barr virus antigens, Erb (ErbB1; ErbB3; ErbB4), ETA (epithelial tumor antigen), ETV6-AML1 fusion protein, FAP (fibroblast activation protein), FBP (folate-binding protein), FGF-5, folate receptor α, FOS related antigen 1, fucosyl GM1, G250, GAGE (GAGE-1; GAGE-2), galactin, GD2 (ganglioside), GD3, GFAP (glial fibrillary

acidic protein), GM2 (oncofetal antigen- immunogenic-1; OFA-I-1), GnT-V, Gp100, H4-RET, HAGE (helicase antigen), HER-2/neu, HIFs (hypoxia inducible factors), HIF-1α, HIF-2α, HLA-A2, HLA-A*0201-R170I, HLA-Al l, HMWMAA, Hom/Mel-40, HSP70-2M (Heat shock protien 70), HST-2, HTgp-175, hTERT (or hTRT), human papillomavirus-E6/human papillomavirus-E7 and E6, iCE (immune-capture EIA), IGF-1R, IGH-IGK, IL2R, IL5, ILK (integrin-linked kinase), IMP3 (insulin-like growth factor II mRNA-binding protein 3), IRF4 (interferon regulatory factor 4), KDR (kinase insert domain receptor), KIAA0205, KRAB-zinc finger protein (KID)-3; KID31, KSA (17-1A), K-ras, LAGE, LCK, LDLR/FUT (LDLR-fucosyltransferaseAS fusion protein), LeY (Lewis Y), MAD-CT-1, MAGE (tyrosinase, melanoma-associated antigen) (MAGE-1; MAGE-3), melan-A tumor antigen (MART), MART-2/Ski, MC1R (melanocortin 1 receptor), MDM2, mesothelin, MPHOSPH1, MSA(muscle-specific actin), mTOR (mammalian targets of rapamycin), MUC-1, MUC-2, MUM-1 (melanoma associated antigen (mutated) 1), MUM-2, MUM-3, Myosin/m, MYL-RAR, NA88-A, N-acetylglucosaminyltransferase, neo-PAP, NF-KB (nuclear factor-kappa B), neurofilament, NSE (neuron- specific enolase), Notch receptors, NuMa, N-Ras, NY-BR-1, NY- CO-1, NY-ESO-1, Oncostatin M, OS-9, OY-TES1, p53 mutants, p190 minor bcr-abl, pl5(58), pl85erbB2, pl80erbB-3, PAGE (prostate associated gene), PAP (prostatic acid phosphatase), PAX3, PAX5, PDGFR (platelet derived growth factor receptor), cytochrome P450 involved in piperidine and pyrrolidine utilization (PIPA), Pml-RAR alpha fusion protein, PR-3 (proteinase 3), PSA (prostate specific antigen), PSM, PSMA (Prostate stem cell antigen), PRAME (preferentially expressed antigen of melanoma), PTPRK, RAGE (renal tumor antigen), Raf (A-Raf, B-Raf and C-Raf), Ras, receptor tyrosine kinases, RCAS1, RGSS, ROR1 (receptor tyrosine kinase-like orphan receptor 1), RU1, RU2, SAGE, SART-1, SART-3, SCP-1, SDCCAG16, SP-17 (sperm protein 17), src-family, SSX (synovial sarcoma X breakpoint)-1, SSX-2(HOM-MEL-40), SSX-3, SSX-4, SSX-5, STAT-3, STAT-5, STAT-6, STEAD, STn, survivin, syk-ZAP70, TA-90 (Mac-2 binding protein\cyclophilin C-associated protein), TAAL6, TACSTD1 (tumor associated calcium signal transducer 1), TACSTD2, TAG-72-4, TAGE, TARP (T cell receptor gamma alternate reading frame protein), TEL/AML1 fusion protein, TEM1, TEM8 (endosialin or CD248), TGFβ, TIE2, TLP, TMPRSS2 ETS fusion gene, TNF-receptor (TNF-α receptor, TNF-β receptor; or TNF-γ receptor), transferrin receptor, TPS, TRP-1 (tyrosine related protein 1), TRP-2, TRP-2/INT2, TSP-180, VEGF receptor, WNT, WT-1 (Wilm's tumor antigen) and XAGE.

[0209] In one embodiment, the payload of the present invention may be an anti-CD47 antibody. CD47 is a ubiquitously expressed immunoregulatory protein that prevents phagocytic removal of healthy cells by the immune system. CD47 is expressed on the surface of many types of cancer cells, thereby disrupting anti-cancer immune responses. CD 47 is also involved in various other important cellular processes, such as angiogenesis, cancer cell death and regulation of T-cell immunity. Anti-CD47 antibodies in several pre-clinical studies have shown therapeutic benefit in solid cancers and most notably B-cell malignancies.

[0210] In one embodiment, the payload of the present invention may be an anti-CD22 antibody. As a non-limiting example, the anti-CD22 antibody is any of the antibodies, fragments or variants thereof described in US Patent Publication No. US20150086562. The anti-CD22 antibody may comprise a heavy chain variable region having the amino acid sequences of SEQ ID NO: 49-64 in US20150086562, and/or a light chain variable region having the amino acid sequence of SEQ ID NO: 17-32 in US20150086562; the contents of which are incorporated herein by reference in their entirety.

[0211] In some embodiments, payloads of the present invention may be antibodies, fragments and variants thereof which can specifically block an immunoinhibitory signal. These blocking antibodies (also referred to as antagonists) bind to co-inhibitory receptors, therefore blocking their signal transduction. As non-limiting examples, the blocking antibodies may be specific to CTLA-4, PD-1, and PD-L1/L2. In one embodiment, the anti-CTLA-4 antibody is Ipilimumab. In another embodiment, the anti-PD-1 antibody is Nivolumab. Antibodies that bind to PD-L1 and enhance T cell immune response may include antibodies taught in US patent publication NO.: 2016/0108123; the contents of which are incorporated by reference herein in their entirety. Other inhibitory immunomodulatory targets may include B7-H3, which can increase cancer cell metabolism such as glucose uptakes and lactate production (Lim et al., *Cancer Res.*, 2016, 76(8): 1-12). Antibodies that block B7-H3 are disclosed in US Pat. NO.: 9,150,656; the contents of which are incorporated by reference herein in their entirety.

[0212] In one aspect, payloads of the present invention may be antagonistic antibodies specific to VSIG8 (v-set and immunoglobulin domain containing 8) comprising the amino acid sequences of SEQ ID NOs: 1, 2 and 3 in US patent publication NO.: US2016/0159927; the contents of which are incorporated by reference herein in their entirety. Antagonistic antibodies may also include a chimeric IL2 receptor (CD25) antibody (Basiliximab) (US Patent Publication NO.: 20080171017; the contents of which are incorporated herein by reference in their entirety), and antagonizing antibodies which bind to human TIM-3 (US

patent publication NO.: US2015/0218274; the contents of which are incorporated herein by reference in their entirety), BTLA, VISTA and LAG-3 (See, e.g., US patent publication NO.: US2015/0259420; the contents of which are incorporated herein by reference in their entirety).

[0213] In one aspect, the payload of the present invention may be an anti-CSF-IR antibody, which is characterized in binding to the dimerization domains D4 to D5 of the extracellular domain of human CSF-IR. This antibody inhibitor can inhibit cell proliferation and survival in CSF-IR ligand-dependent and CSF-1 ligand-independent CSF-IR expressing tumor cells, monocytes and infiltrating macrophages (See, e.g., International Patent Publication NO.: WO2013/132044; the contents of which are incorporated herein by reference in their entirety).

[0214] In another aspect, the payload of the present invention may be an antagonistic antibody against CXCL12. The anti-CXCL12 antibody blocks the interaction of CXCL12 with its receptor CXCR4, thereby inhibiting CXCR4 signaling. The CXCR4 signaling inhibitor increases the proximity or the frequency of T-cells among cancer cells in the tumor tissue (See, International Patent Publication NO.: WO 2015/019284; the contents of which are incorporated by reference herein in their entirety).

[0215] In some embodiments, payloads of the present invention may be agonistic antibodies, fragments and variants thereof, which trigger immune responses, including antibodies specific to co-stimulatory molecules, including but not limited to 4-1BB (CD137), OX40 (CD134), CD40, GITR and CD27.

[0216] In one embodiment, the payload of the present invention may be an agonistic CD40 antibody. In another embodiment, the agonistic antibody specific to 4-1BB (CD137) may be Uremab, a fully human IgG4 monoclonal antibody which specifically binds to and activates 4-1BB (CD137) expressing immune cells, stimulating an immune response, in particular a cytotoxic T cell response, against tumor cells; or Utomilumab, a fully human IgG2 monoclonal antibody; or anti-CD137 antibody described in International Patent Publication NO.: WO2006/088447; the contents of which are incorporated herein by reference in their entirety.

[0217] In some embodiments, the payload of the present invention may be an antagonistic antibody against Amphiregulin. Amphiregulin (AREG) is an EGF-like growth factor which binds to the EGFR receptor and enhances T regulatory cell function. AREG is produced in a phenotypically and functionally distinct subtype of $CD4^+$ regulatory T cells (Tregs) which have a distinct T cell receptor (TCR) repertoire and express the IL33R. AREG promotes

immune suppression in the tumor environment. The anti-Amphiregulin antibody may comprise a heavy chain variable region having the amino acid sequences of SEQ ID NO.: 2,4, and 12 in U.S. Patent No. 7,223,393, and/or a light chain variable region having the amino acid sequence of SEQ ID NO.: 3, 5, and 14 in U.S. Patent No. 7,223,393; the contents of which are incorporated herein by reference in their entirety.

[0218] In some embodiments, antibodies specific to co-inhibitory molecules and co-stimulatory molecules may be secreted scFv antibodies.

[0219] In some embodiments, antibody payloads of the present invention may be T-cell bispecific antibodies (e.g. T cell-engaging BiTE™ antibodies CDS- CD 19, CD3-EpCam, and CD3-EGFR). Other bispecific antibodies used for immunotherapy may also be included as payloads of the present invention, for example, bispecific anti-TNF-α and anti- IL6 antibody (EP3062818), bispecific antibodies to an immune cell antigen and TAG-72 (WO2016/089610), anti-ovarian and D3 bispecific antibodies in US. Pat. No. 7,262,276; bispecific antibodies against CD133 and CD3 in WO2014/128185; bispecific antibodies against CTLA-4 and PD-1 discussed in US2016/0145355, bispecific antibodies against CD3 and CD19 disclosed in WO2015/006749, and US. Pat. NOs. 7, 635,472; 7, 112, 324; bispecific antibodies against Her2 and CD3 in US2014/0170149; bispecific antibodies against CD19 and CD16 in US2005/0089519; the contents of each of which are incorporated by reference herein in their entirety.

[0220] In some embodiments, antibodies with decreased affinity may be selected over antibodies with high affinity for the same antigen. Such low affinity antibodies are more effective in discriminating tumors which express high levels of the antigen and normal tissues that express the same antigen at lower levels, while maintaining similar antitumor response.

[0221] In some embodiments, the targeting moieties of the present invention may include variable heavy chain and variable light chain comprising the amino acid sequences selected from those in Table 10.

Table 10: Variable Heavy and Light Chain Sequences

Target	Antibody chain	SEQ ID NO	Source
5T4	VH	539	SEQ ID NO. 2 in WO2016022939
5T4	VH	540	SEQ ID NO. 4 in WO2016022939
AGR2	VH	541	SEQ ID NO. 10 in WO2016040321
AGR2	VH	542	SEQ ID NO. 18 in WO2016040321
ALK	VH	543	SEQ ID NO. 11 in WO2015069922
ALK	VH	544	SEQ ID NO. 13 in WO2015069922
ALK	VH	545	SEQ ID NO. 15 in WO2015069922
ALK	VH	546	SEQ ID NO. 7 in WO2015069922
ALK	VH	547	SEQ ID NO. 9 in WO2015069922

ALK	VH	548	SEQ ID NO: 1 in US20160280798A1
ALK	VH	549	SEQ ID NO: 11 in US20160280798A1
ALK	VH	550	SEQ ID NO: 13 in US20160280798A1
ALK	VH	551	SEQ ID NO: 15 in US20160280798A1
ALK	VH	552	SEQ ID NO: 3 in US20160280798A1
ALK	VH	553	SEQ ID NO: 5 in US20160280798A1
ALK	VH	554	SEQ ID NO: 7 in US20160280798A1
ALK	VH	555	SEQ ID NO: 9 in US20160280798A1
ALK	VH	556	SEQ ID NO. 1 in WO2015069922
ALK	VH	557	SEQ ID NO. 3 in WO2015069922
ALK	VH	558	SEQ ID NO. 5 in WO2015069922
AMC	VH	559	SEQ ID NO. 17 in WO2016161390
AMC	VH	560	SEQ ID NO. 18 in WO2016161390
AMC	VH	561	SEQ ID NO. 19 in WO2016161390
AMC	VH	562	SEQ ID NO. 20 in WO2016161390
AMC	VH	563	SEQ ID NO. 21 in WO2016161390
AMC	VH	564	SEQ ID NO. 22 in WO2016161390
AMC	VH	565	SEQ ID NO. 23 in WO2016161390
AMC	VH	566	SEQ ID NO. 24 in WO2016161390
AMC	VH	567	SEQ ID NO. 25 in WO2016161390
AMC	VH	568	SEQ ID NO. 26 in WO2016161390
ANG2	VH	569	SEQ ID NO.1 in WO2015091655
ANG2	VH	570	SEQ ID NO. 3 in WO2015091655
APCDD1	VH	571	SEQ ID NO:10 in WO2012019061
APCDD1	VH	572	SEQ ID NO:102 in WO2012019061
APCDD1	VH	573	SEQ ID NO:106 in WO2012019061
APCDD1	VH	574	SEQ ID NO:110 in WO2012019061
APCDD1	VH	575	SEQ ID NO:114 in WO2012019061
APCDD1	VH	576	SEQ ID NO:118 in WO2012019061
APCDD1	VH	577	SEQ ID NO:122 in WO2012019061
APCDD1	VH	578	SEQ ID NO:126 in WO2012019061
APCDD1	VH	579	SEQ ID NO:130 in WO2012019061
APCDD1	VH	580	SEQ ID NO:134 in WO2012019061
APCDD1	VH	581	SEQ ID NO:14 in WO2012019061
APCDD1	VH	582	SEQ ID NO:6 in WO2012019061
APCDD1	VH	583	SEQ ID NO:98 in WO2012019061
APRIL	VH	584	SEQ ID NO. 12 in US20160264674
APRIL	VH	585	SEQ ID NO. 14 in US20160264674
APRIL	VH	586	SEQ ID NO. 16 in US20160264674
APRIL	VH	587	SEQ ID NO. 18 in US20160264674
APRIL	VH	588	SEQ ID NO. 3 in US20160264674
APRIL	VH	589	SEQ ID NO. 32 in US20160264674
APRIL	VH	590	SEQ ID NO. 34 in US20160264674
APRIL	VH	591	SEQ ID NO. 36 in US20160264674
APRIL	VH	592	SEQ ID NO. 38 in US20160264674
APRIL	VH	593	SEQ ID NO. 40 in US20160264674
APRIL	VH	594	SEQ ID NO. 42 in US20160264674
APRIL	VH	595	SEQ ID NO. 44 in US20160264674
APRIL	VH	596	SEQ ID NO. 46 in US20160264674
APRIL	VH	597	SEQ ID NO. 48 in US20160264674
APRIL	VH	598	SEQ ID NO. 52 in US20160264674
AXL	VH	599	SEQ ID NO. 21 in WO2016097370
AXL	VH	600	SEQ ID NO. 3 in WO2016097370
AXL	VH	601	SEQ ID NO. 45 in WO2016097370
B2MG	VH	602	SEQIDNO:28 in WO2016126213A1
B7H1	VH	603	SEQ ID NO: 12 in US20130034559
B7H1	VH	604	SEQ ID NO: 32 in US20130034559
B7H1	VH	605	SEQ ID NO: 42 in US20130034559

B7H1	VH	606	SEQ ID NO: 52 in US20130034559
B7H1	VH	607	SEQ ID NO: 72 in US20130034559
B7H1	VH	608	SEQ ID NO: 2 in US20130034559
B7H1	VH	609	SEQ ID NO: 62 in US20130034559
B7H3	VH	610	SEQ ID NO. 10 in WO2016033225
B7H3	VH	611	SEQ ID NO. 11 in WO2016033225
B7H3	VH	612	SEQ ID NO. 12 in WO2016033225
B7H3	VH	613	SEQ ID NO. 13 in WO2016033225
B7H3	VH	614	SEQ ID NO. 14 in WO2016033225
B7H3	VH	615	SEQ ID NO. 15 in WO2016033225
B7H3	VH	616	SEQ ID NO. 16 in WO2016033225
B7H3	VH	617	SEQ ID NO. 9 in WO2016033225
B7H3(CD276)	VH	618	SEQ ID NO. 17 in WO2016044383
B7H3(CD276)	VH	619	SEQ ID NO. 26 in WO2016044383
B7H3(CD276)	VH	620	SEQ ID NO. 7 in WO2016044383
B7H4	VH	621	SEQ ID NO. 100 in US20160159910
B7H4	VH	622	SEQ ID NO. 101 in US20160159910
B7H4	VH	623	SEQ ID NO. 102 in US20160159910
B7H4	VH	624	SEQ ID NO. 103 in US20160159910
B7H4	VH	625	SEQ ID NO. 107 in US20160159910
B7H4	VH	626	SEQ ID NO. 108 in US20160159910
B7H4	VH	627	SEQ ID NO. 109 in US20160159910
B7H4	VH	628	SEQ ID NO. 110 in US20160159910
B7H4	VH	629	SEQ ID NO. 111 in US20160159910
B7H4	VH	630	SEQ ID NO. 112 in US20160159910
B7H4	VH	631	SEQ ID NO. 113 in US20160159910
B7H4	VH	632	SEQ ID NO. 114 in US20160159910
B7H4	VH	633	SEQ ID NO. 12 in US20160159910
B7H4	VH	634	SEQ ID NO. 127 in US20160159910
B7H4	VH	635	SEQ ID NO. 13 in WO2016160620
B7H4	VH	636	SEQ ID NO. 130 in US20160159910
B7H4	VH	637	SEQ ID NO. 131 in US20160159910
B7H4	VH	638	SEQ ID NO. 132 in US20160159910
B7H4	VH	639	SEQ ID NO. 133 in US20160159910
B7H4	VH	640	SEQ ID NO. 137 in US20160159910
B7H4	VH	641	SEQ ID NO. 2 in US20160159910
B7H4	VH	642	SEQ ID NO. 20 in US20160159910
B7H4	VH	643	SEQ ID NO. 28 in US20160159910
B7H4	VH	644	SEQ ID NO. 36 in US20160159910
B7H4	VH	645	SEQ ID NO. 37 in US20160159910
B7H4	VH	646	SEQ ID NO. 38 in US20160159910
B7H4	VH	647	SEQ ID NO. 4 in US20160159910
B7H4	VH	648	SEQ ID NO. 56 in US20160159910
B7H4	VH	649	SEQ ID NO. 99 in US20160159910
B7H4	VH	650	SEQ ID NO. 144 in US20160159910
B7H4	VH	651	SEQ ID NO.15 in WO2016160620
B7H4	VH	652	SEQ ID NO.17 in WO2016160620
BAT1	VH	653	SEQ ID NO. 5 in WO2013014668
BAT1	VH	654	SEQ ID NO.6 in WO2013014668
BAT1	VH	655	SEQ ID NO.7 in WO2013014668
BAT1	VH	656	SEQ ID NO.8 in WO2013014668
BAT1	VH	657	SEQ ID NO.9 in WO2013014668
BCMA	VH	658	SEQ ID NO: 26 in WO2016168773A3
BCMA	VH	659	SEQ ID NO:142 in WO2016168595A1
BCMA	VH	660	SEQ ID NO:148 in WO2016168595A1
BCMA	VH	661	SEQ ID NO:154 in WO2016168595A1
BCMA	VH	662	SEQ ID NO:160 in WO2016168595A1
BCMA	VH	663	SEQ ID NO:166 in WO2016168595A1

BCMA	VH	664	SEQ ID NO:172 in WO2016168595A1
BCMA	VH	665	SEQ ID NO:178 in WO2016168595A1
BCMA	VH	666	SEQ ID NO:184 in WO2016168595A1
BCMA	VH	667	SEQ ID NO:190 in WO2016168595A1
BCMA	VH	668	SEQ ID NO:196 in WO2016168595A1
BCMA	VH	669	SEQ ID NO:202 in WO2016168595A1
BCMA	VH	670	SEQ ID NO:208 in WO2016168595A1
BCMA	VH	671	SEQ ID NO:214 in WO2016168595A1
BCMA	VH	672	SEQ ID NO:220 in WO2016168595A1
BCMA	VH	673	SEQ ID NO:226 in WO2016168595A1
BCMA	VH	674	SEQ ID NO:232 in WO2016168595A1
BCMA	VH	675	SEQ ID NO:238 in WO2016168595A1
BCMA	VH	676	SEQ ID NO:244 in WO2016168595A1
BCMA	VH	677	SEQ ID NO:250 in WO2016168595A1
BCMA	VH	678	SEQ ID NO:256 in WO2016168595A1
BCMA	VH	679	SEQ ID NO:262 in WO2016168595A1
BCMA	VH	680	SEQ ID NO:268 in WO2016168595A1
BCMA	VH	681	SEQ ID NO:274 in WO2016168595A1
BCMA	VH	682	SEQ ID NO:280 in WO2016168595A1
BCMA	VH	683	SEQ ID NO:286 in WO2016168595A1
BCMA	VH	684	SEQ ID NO:292 in WO2016168595A1
BCMA	VH	685	SEQ ID NO:298 in WO2016168595A1
BCMA	VH	686	SEQ ID NO:304 in WO2016168595A1
BCMA	VH	687	SEQ ID NO:310 in WO2016168595A1
BCMA	VH	688	SEQ ID NO:316 in WO2016168595A1
BCMA	VH	689	SEQ ID NO:322 in WO2016168595A1
BCMA	VH	690	SEQ ID NO:328 in WO2016168595A1
BCMA	VH	691	SEQ ID NO:334 in WO2016168595A1
BCMA	VH	692	SEQ ID NO:340 in WO2016168595A1
BCMA	VH	693	SEQ ID NO:346 in WO2016168595A1
BCMA	VH	694	SEQ ID NO:352 in WO2016168595A1
BCMA	VH	695	SEQ ID NO: 8 in WO2016094304A3
BCMA	VH	696	SEQ ID NO. 171 WO2016014565
BCMA	VH	697	SEQ ID NO. 172 WO2016014565
BCMA	VH	698	SEQ ID NO. 173 WO2016014565
BCMA	VH	699	SEQ ID NO. 174 WO2016014565
BCMA	VH	700	SEQ ID NO. 175 WO2016014565
BCMA	VH	701	SEQ ID NO. 176 WO2016014565
BCMA	VH	702	SEQ ID NO. 177 WO2016014565
BCMA	VH	703	SEQ ID NO. 178 WO2016014565
BCMA	VH	704	SEQ ID NO. 179 WO2016014565
BCMA	VH	705	SEQ ID NO. 180 WO2016014565
BCMA	VH	706	SEQ ID NO. 181 WO2016014565
BCMA	VH	707	SEQ ID NO. 182 WO2016014565
BCMA	VH	708	SEQ ID NO. 183 WO2016014565
BCMA	VH	709	SEQ ID NO. 184 WO2016014565
BCMA	VH	710	SEQ ID NO. 185 WO2016014565
BCMA	VH	711	SEQ ID NO. 186 WO2016014565
BCMA	VH	712	SEQ ID NO. 187 WO2016014565
BCMA	VH	713	SEQ ID NO. 190 WO2016014565
BCMA	VH	714	SEQ ID NO. 255 WO2016014565
BCMA	VH	715	SEQ ID NO. 257 WO2016014565
BCMA	VH	716	SEQ ID NO. 258 WO2016014565
BCMA	VH	717	SEQ ID NO. 69WO2016014565
BCMA	VH	718	SEQ ID NO. 70WO2016014565
BCMA	VH	719	SEQ ID NO. 71 WO2016014565
BCMA	VH	720	SEQ ID NO. 72 WO2016014565
BCMA	VH	721	SEQ ID NO. 73 WO2016014565

BCMA	VH	722	SEQ ID NO. 74 WO2016014565
BCMA	VH	723	SEQ ID NO. 75 WO2016014565
BCMA	VH	724	SEQ ID NO. 76 WO2016014565
BCMA	VH	725	SEQ ID NO. 77 WO2016014565
BCMA	VH	726	SEQ ID NO. 78 WO2016014565
BCMA	VH	727	SEQ ID NO. 79 WO2016014565
BCMA	VH	728	SEQ ID NO. 80 WO2016014565
BCMA	VH	729	SEQ ID NO. 81 WO2016014565
BCMA	VH	730	SEQ ID NO: 38 in EP3057994A1
BCMA	VH	731	SEQ ID NO: 55 in WO2016187349A1
BCMA	VH	732	SEQ ID NO. 1 in WO2016090320
BCMA	VH	733	SEQ ID NO. 10 in WO2016014789
BCMA	VH	734	SEQ ID NO. 101 in WO2016120216
BCMA	VH	735	SEQ ID NO. 11 in WO2015158671A1
BCMA	VH	736	SEQ ID NO. 11 in WO2016014789
BCMA	VH	737	SEQ ID NO. 12 in WO2016014789
BCMA	VH	738	SEQ ID NO. 13 in WO2016014789
BCMA	VH	739	SEQ ID NO. 13 in WO2016090320
BCMA	VH	740	SEQ ID NO. 14 in WO2016014789
BCMA	VH	741	SEQ ID NO. 17 in WO2015158671A1
BCMA	VH	742	SEQ ID NO. 17 in WO2016090320
BCMA	VH	743	SEQ ID NO. 174 in WO2016120216
BCMA	VH	744	SEQ ID NO. 21 in WO2016090320
BCMA	VH	745	SEQ ID NO. 25 in WO2016090320
BCMA	VH	746	SEQ ID NO. 29 in WO2016090320
BCMA	VH	747	SEQ ID NO. 33 in WO2016090320
BCMA	VH	748	SEQ ID NO. 37 in WO2016090320
BCMA	VH	749	SEQ ID NO. 41 in WO2016090320
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EGFRvIII	VH	2148	SEQ ID NO: 24 in WO2016168773A3
EGFRvIII	VH	2149	SEQ ID NO. 34 in US20160304615
EGFRvIII	VH	2150	SEQ ID NO: 2 in US20160200819A1
Endoglin	VH	2151	SEQ ID NO. 41 in US20160009811
Endoglin	VH	2152	SEQ ID NO. 42 in US20160009811
Endoglin	VH	2153	SEQ ID NO. 43 in US20160009811
Endoglin	VH	2154	SEQ ID NO. 71 in US20160009811
Endoglin	VH	2155	SEQ ID NO. 73 in US20160009811
Endoglin	VH	2156	SEQ ID NO. 75 in US20160009811
Endoglin	VH	2157	SEQ ID NO. 88 in US20160009811
Endoglin	VH	2158	SEQ ID NO. 89 in US20160009811
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Endoglin	VH	2160	SEQ ID NO. 91 in US20160009811
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EphA2receptor	VH	2164	US20150274824 SEQ ID NO: 24
EphA2receptor	VH	2165	US20150274824 SEQ ID NO: 32
EphA2receptor	VH	2166	US20150274824 SEQ ID NO: 34
EphA2receptor	VH	2167	US20150274824 SEQ ID NO: 36
EphA2receptor	VH	2168	US20150274824 SEQ ID NO: 37
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EphA2receptor	VH	2170	US20150274824 SEQ ID NO: 40
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EphA2receptor	VH	2173	US20150274824 SEQ ID NO: 45
EphA2receptor	VH	2174	US20150274824 SEQ ID NO: 74
EphA2receptor	VH	2175	US20150274824 SEQ ID NO: 76
ERBB2	VH	2176	US20110129464 SEQ ID NO: 2
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ERBB2	VH	2178	US20130089544 SEQ ID NO: 10
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ERBB2	VH	2189	US20130089544 SEQ ID NO: 57
ERBB2	VH	2190	US20130089544 SEQ ID NO: 58
ERBB2	VH	2191	US20130089544 SEQ ID NO: 6
ERBB2	VH	2192	US20130266564 SEQ ID NO: 8
ERBB2	VH	2193	US20150104443 SEQ ID NO: 1
FactorD	VH	2194	SEQ ID NO. 17 in US20160017052
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FactorD	VH	2201	SEQ ID NO. 33 in US20160017052
FactorD	VH	2202	SEQ ID NO. 4 in US20160017052
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FAP	VH	2204	SEQ ID NO. 1 in WO2015118030
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FAP	VH	2207	SEQ ID NO. 172 in WO2016120216
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FcRL5(FcReceptorLike5)	VH	2220	SEQ ID NO: 915 WO2016090337
FcRL5(FcReceptorLike5)	VH	2221	SEQ ID NO: 919 WO2016090337
FGFR3	VH	2222	SEQ ID NO. 132 in US9499623
FGFR3	VH	2223	SEQ ID NO. 134 in US9499623
FGFR3	VH	2224	SEQ ID NO. 136 in US9499623
FGFR4	VH	2225	SEQ ID NO.7 in US20160237157
Frizzled Receptor	VH	2226	SEQ ID NO. 10 in WO2010037041
GAH	VH	2227	SEQ ID NO 7 in US20060057147A1
GCC1	VH	2228	SEQ ID NO. 1 in US20160030595A1
GD2	VH	2229	SEQ ID NO. 10 in WO2015132604

GD2	VH	2230	SEQ ID NO. 3 in US20130216528
GD2	VH	2231	SEQ ID NO. 4 in US20130216528
GD2	VH	2232	SEQ ID NO. 6 in US20130216528
GD2	VH	2233	SEQ ID NO. 8 in US20130216528
GD2	VH	2234	SEQ ID NO. 9 in WO2015132604
GD3	VH	2235	SEQ ID NO: 11 in WO2016185035A1
GD3	VH	2236	SEQ ID NO: 13 in WO2016185035A1
GD3	VH	2237	SEQ ID NO: 15 in WO2016185035A1
GD3	VH	2238	SEQ ID NO: 17 in WO2016185035A1
Glyco epitope and ErbBB I Specific	VH	2239	SEQ ID No. 7 in WO2012007167A1
Glyco epitope and ErbBBI Specific	VH	2240	SEQ ID No. 9 in WO2012007167A1
GM2	VH	2241	US20090028877 SEQ ID NO: 20
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GM2	VH	2243	US20090028877 SEQ ID NO: 23
GM2	VH	2244	US20090028877 SEQ ID NO: 26
GM2	VH	2245	US20090028877 SEQ ID NO: 27
GM2	VH	2246	US20090028877 SEQ ID NO: 28
GM2	VH	2247	US20090028877 SEQ ID NO: 29
GM2	VH	2248	US20090028877 SEQ ID NO: 30
GPC3	VH	2249	SEQ ID NO: 10 in US20160208015A1
GPC3	VH	2250	SEQ ID NO: 14 in US20160208015A1
GPC3	VH	2251	SEQ ID NO: 2 in US20160208015A1
GPC3	VH	2252	SEQ ID NO: 3 in US20160208015A1
GPC3	VH	2253	SEQ ID NO: 4 in US20160208015A1
GPC3	VH	2254	SEQ ID NO: 5 in US20160208015A1
GPC3	VH	2255	SEQ ID NO: 6 in US20160208015A1
GPC3	VH	2256	SEQ ID NO: 7 in US20160208015A1
GPC3	VH	2257	SEQ ID NO: 8 in US20160208015A1
GPC3	VH	2258	SEQ ID NO: 9 in US20160208015A1
GPRC5D	VH	2259	SEQ ID NO. 13 in WO2016090312
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GPRC5D	VH	2264	SEQ ID NO. 314 in WO2016090312
GPRC5D	VH	2265	SEQ ID NO. 326 in WO2016090312
GPRC5D	VH	2266	SEQ ID NO. 33 in WO2016090312
GPRC5D	VH	2267	SEQ ID NO. 338 in WO2016090312
GPRC5D	VH	2268	SEQ ID NO. 350 in WO2016090312
GPRC5D	VH	2269	SEQ ID NO. 362 in WO2016090312
GPRC5D	VH	2270	SEQ ID NO. 37 in WO2016090312
GPRC5D	VH	2271	SEQ ID NO. 374 in WO2016090312
GPRC5D	VH	2272	SEQ ID NO. 386 in WO2016090312
GPRC5D	VH	2273	SEQ ID NO. 41 in WO2016090312
GPRC5D	VH	2274	SEQ ID NO. 45 in WO2016090312
GPRC5D	VH	2275	SEQ ID NO. 49 in WO2016090312
GPRC5D	VH	2276	SEQ ID NO. 5 in WO2016090312
GPRC5D	VH	2277	SEQ ID NO. 53 in WO2016090312
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GPRC5D	VH	2286	SEQ ID NO. 89 in WO2016090312
GPRC5D	VH	2287	SEQ ID NO. 93 in WO2016090312
GPRC5D	VH	2288	SEQ ID NO.1 in WO2016090312
GPRC5D	VH	2289	SEQ ID NO.9 in WO2016090312
Her1/her3	VH	2290	SEQ ID NO: 8 of WO2016073629
Her2	VH	2291	SEQ ID NO: 141 in WO2016054555A2
Her2	VH	2292	SEQ ID NO: 262 in WO2016168773A3
Her2	VH	2293	SEQ ID NO: 264 in WO2016168773A3
Her2	VH	2294	SEQ ID NO: 266 in WO2016168773A3
Her2	VH	2295	SEQ ID NO: 268 in WO2016168773A3
Her2	VH	2296	SEQ ID NO: 270 in WO2016168773A3
HER2	VH	2297	SEQ ID NO. 11 in US9518118
HER2	VH	2298	SEQ ID NO: 62 in US20160333114A1
HLAG	VH	2299	SEQ ID NO. 10 in WO2016160622A2
HLAG	VH	2300	SEQ ID NO. 8 in WO2016160622A2
HSP70	VH	2301	SEQ ID NO. 11 in WO2016120217
HSP70	VH	2302	SEQ ID NO. 12 in WO2016120217
humanCD79b	VH	2303	SEQ ID NO.27 in WO2016112870
humanCD79b	VH	2304	SEQ ID NO.29 in WO2016112870
Human chorionic gonadotropin	VH	2305	SEQ ID NO. 2 in WO2007019541
Human chorionic gonadotropin	VH	2306	SEQ ID NO. 4 in WO2007019541
Human chorionic gonadotropin	VH	2307	SEQ ID NO. 6 in WO2007019541
Human collagen VII	VH	2308	SEQ ID NO.31 in WO2016112870
humanERBB3	VH	2309	SEQ ID NO: 19 in WO2013052745
humanERBB3	VH	2310	SEQ ID NO: 29 in WO2013052745
humanERBB3	VH	2311	SEQ ID NO: 38 in WO2013052745
humanERBB3	VH	2312	SEQ ID NO: 45 in WO2013052745
humanERBB3	VH	2313	SEQ ID NO: 55 in WO2013052745
humanERBB3	VH	2314	SEQ ID NO: 61 in WO2013052745
humanERBB3	VH	2315	SEQ ID NO: 9 in WO2013052745
ICOS	VH	2316	SEQ ID NO. 15 in US20160215059
ICOS	VH	2317	SEQ ID NO. 16 in US20160215059
ICOS	VH	2318	SEQ ID NO. 19 in US20160215059
ICOS	VH	2319	SEQ ID NO. 23 in US20160215059
ICOS	VH	2320	SEQ ID NO. 7 in US20160215059
IGFI	VH	2321	SEQ ID NO. 1 in WO2007118214
IGFI	VH	2322	SEQ ID NO. 3 in WO2007118214
IGFI	VH	2323	SEQ ID NO. 7 in WO2007118214
IGFR1	VH	2324	SEQ ID NO:7 in WO2015073575A2
IL13	VH	2325	SEQ ID NO 302. in US20160168242
IL13Ra2	VH	2326	SEQ ID NO. 7 in WO2016123143
IL13Ra2	VH	2327	SEQ ID NO. 8 in WO2016123143
IL1RAP	VH	2328	SEQ ID NO. 1 in WO2016020502
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IL1RAP	VH	2331	SEQ ID NO. 8 in WO2016020502
IL1RAP	VH	2332	SEQ ID NO. 9 in WO2016020502
IL1RAP	VH	2333	SEQ ID NO: 120 in WO2016179319A1
IL1RAP	VH	2334	SEQ ID NO: 122 in WO2016179319A1
IL1RAP	VH	2335	SEQ ID NO: 124 in WO2016179319A1
IL21	VH	2336	SEQ ID NO. 2 in US20160145332
IL21	VH	2337	SEQ ID NO. 3 in US20160145332
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IL33	VH	2345	SEQ ID NO 216. in US20160168242
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IL33	VH	2358	SEQ ID NO 86. in US20160168242
IL33	VH	2359	SEQ ID NO 88. in US20160168242
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Integrin	VH	2361	SEQ ID NO. 3 in US 20140161794
Integrin	VH	2362	SEQ ID NO. 4 in US 20140161794
Integrin	VH	2363	SEQ ID NO. 5 in US 20140161794
KDR	VH	2364	SEQ ID NO. 20 IN WO2003075840
KDR	VH	2365	SEQ ID NO. 24 IN WO2003075840
KDR	VH	2366	SEQ ID NO. 26 IN WO2003075840
KDR	VH	2367	SEQ ID NO. 29 IN WO2003075840
KDR	VH	2368	SEQ ID NO. 31 IN WO2003075840
KDR	VH	2369	SEQ ID NO. 33 IN WO2003075840
KIR(Lirilumab)	VH	2370	SEQ ID NO. 3 in US20150290316
KIR(Lirilumab)	VH	2371	SEQ ID NO.1 in WO2014055648
KIR2DL1andKIR2DL2/3	VH	2372	SEQIDNO:36 in WO2016126213A1
Klon43	VH	2373	SEQ ID NO: 47 in WO2016097231
KMA	VH	2374	SEQ ID NO: 22 in WO2016172703A2
LAG3	VH	2375	SEQ ID NO. 100 in US20150259420
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LAG3	VH	2377	SEQ ID NO. 108 in US20150259420
LAG3	VH	2378	SEQ ID NO. 28 in US20150259420
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LAG3	VH	2385	SEQ ID NO.1 in WO2015042246
leukocytegenA0	VH	2386	SEQ ID NO.9 in WO2010065962A2
leukocytegenA2	VH	2387	SEQ ID NO.25 in WO2010065962A2
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LGR4	VH	2390	SEQ ID NO. 5 in US20160046723
LGR4	VH	2391	SEQ ID NO. 9 in US20160046723
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LGR5	VH	2398	SEQ ID NO. 24 in US20160102146

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LHR	VH	2407	SEQ ID NO: 7 in WO2016160618A3
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Lymphotoxin beta receptor	VH	2415	SEQ ID NO. 12 in WO2004002431
Lymphotoxin beta receptor	VH	2416	SEQ ID NO. 14 in WO2004002431
Lymphotoxin beta receptor	VH	2417	SEQ ID NO. 16 in WO2004002431
Lymphotoxin beta receptor	VH	2418	SEQ ID NO. 2 in WO2004002431
Lysyloxidaselike2	VH	2419	SEQ ID NO. 42 in WO2011097513
Lysyloxidaselike2	VH	2420	SEQ ID NO. 44 in WO2011097513
Malignant Variable Receptor	VH	2421	SEQ ID NO. 1 in WO2015133817A1
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Mesothelin	VH	2465	SEQ ID NO. 6 WO2015188141
Mesothelin	VH	2466	SEQ ID NO: 119 in US20160333114A1
Mesothelin	VH	2467	SEQ ID NO: 5 in WO2013142034
Mesothelin	VH	2468	SEQ ID NO: 50 in US20160333114A1
Mesothelin	VH	2469	SEQ ID NO: 6 in WO2013142034
Mesothelin	VH	2470	SEQ ID NO: 15 inUS9416190B2
Mesothelin	VH	2471	SEQ ID NO: 2 inUS9416190B2
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MN	VH	2481	SEQ ID NO. 151 in WO2007070538
MPER	VH	2482	SEQ ID NO: 13 in US20160194375A1
MUC1	VH	2483	SEQ ID NO.5 in US20160130357
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NOTCH2/3	VH	2537	SEQ ID NO:29 in WO2013074596
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Olfml3	VH	2541	SEQ ID NO.1 in WO2015054441A1
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Olfml3	VH	2543	SEQ ID NO.3 in WO2015054441A1
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RAS	VH	2741	SEQ ID NO.7 in WO2016154047
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Rituximab	VH	2745	SEQ ID NO: 66 in US20160333114A1

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VEGF	VH	2931	US20160090427 SEQ ID NO: 156
VEGF	VH	2932	US20160090427 SEQ ID NO: 157
VEGF	VH	2933	US20160090427 SEQ ID NO: 158
VEGF	VH	2934	US20160090427 SEQ ID NO: 159
VEGFR2	VH	2935	SEQ ID NO. 100 In WO2017004254
VEGFR2	VH	2936	SEQ ID NO. 101 In WO2017004254
VEGFR2	VH	2937	SEQ ID NO. 102 In WO2017004254
VEGFR2	VH	2938	SEQ ID NO. 103 In WO2017004254
VEGFR2	VH	2939	SEQ ID NO. 114 in WO2017004254
VEGFR2	VH	2940	SEQ ID NO. 115 in WO2017004254
VEGFR2	VH	2941	SEQ ID NO. 116 in WO2017004254
VEGFR2	VH	2942	SEQ ID NO. 117 in WO2017004254
VEGFR2	VH	2943	SEQ ID NO. 118 in WO2017004254
VEGFR2	VH	2944	SEQ ID NO. 119 in WO2017004254
VEGFR2	VH	2945	SEQ ID NO. 120 in WO2017004254
VEGFR2	VH	2946	SEQ ID NO. 121 in WO2017004254
VEGFR2	VH	2947	SEQ ID NO. 122 in WO2017004254
VEGFR2	VH	2948	SEQ ID NO. 123 in WO2017004254
VEGFR2	VH	2949	SEQ ID NO. 124 in WO2017004254
VEGFR2	VH	2950	SEQ ID NO. 95 In WO2017004254
VEGFR2	VH	2951	SEQ ID NO. 96 In WO2017004254
VEGFR2	VH	2952	SEQ ID NO. 97 In WO2017004254
VEGFR2	VH	2953	SEQ ID NO. 98 In WO2017004254
VEGFR2	VH	2954	SEQ ID NO. 99 In WO2017004254
VISTA	VH	2955	SEQ ID NO:37 in WO2015097536
VISTA	VH	2956	SEQ ID NO:38 in WO2015097536
VISTA	VH	2957	SEQ ID NO:39 in WO2015097536
VISTA	VH	2958	SEQ ID NO:40 in WO2015097536
VMS2	VH	2959	FIG. 1 in WO2000058363
WT1/HLA Bi Specific	VH	2960	SEQ ID NO.104 in WO2015070061
WT1/HLA Bi Specific	VH	2961	SEQ ID NO.111 in WO2015070061
WT1/HLA Bi Specific	VH	2962	SEQ ID NO.128 in WO2015070061
WT1/HLA Bi Specific	VH	2963	SEQ ID NO.14 in WO2015070061
WT1/HLA Bi Specific	VH	2964	SEQ ID NO.32 in WO2015070061
WT1/HLA Bi Specific	VH	2965	SEQ ID NO.50 in WO2015070061
WT1/HLA Bi Specific	VH	2966	SEQ ID NO.68 in WO2015070061
WT1/HLA Bi Specific	VH	2967	SEQ ID NO.86 in WO2015070061
CD19	VH	2968	SEQ ID NO. 53 in WO2016120216
CD19	VH	2969	SEQ ID NO. 55 in WO2016120216
CD20(Ofatumumab)	VH	2970	SEQ ID NO. 25 in US20170000900
CD20(Rituximab)	VH	2971	SEQ ID NO. 24 in US20170000900
CD20(Veltuzumab)	VH	2972	SEQ ID NO. 23 in US20170000900
CD22	VH	2973	SEQ ID NO. 3 in WO2013059593

CD22	VH	2974	SEQ ID NO. 4 in WO2013059593
CD28	VH	2975	SEQ ID NO. 19 in WO2015158868
CD33	VH	2976	SEQ ID NO. 65 in WO2016120216
CD33	VH	2977	SEQ ID NO. 67 in WO2016120216
CD33	VH	2978	SEQ ID NO. 69 in WO2016120216
CD33	VH	2979	SEQ ID NO. 71 in WO2016120216
CD33	VH	2980	SEQ ID NO. 77 in WO2016120216
CD33	VH	2981	SEQ ID NO. 79 in WO2016120216
CD33	VH	2982	SEQ ID NO. 81 in WO2016120216
CD33	VH	2983	SEQ ID NO. 83 in WO2016120216
CD33	VH	2984	SEQ ID NO. 84 in WO2016120216
CD37	VH	2985	SEQ ID NO. 11 in US20170000900
CD37	VH	2986	SEQ ID NO. 12 in US20170000900
CD37	VH	2987	SEQ ID NO. 18 in US20170000900
CD73	VH	2988	SEQ ID NO. 100 in US20160145350
CD73	VH	2989	SEQ ID NO. 103 in US20160145350
CD73	VH	2990	SEQ ID NO. 107 in US20160145350
CD73	VH	2991	SEQ ID NO. 109 in US20160145350
CD73	VH	2992	SEQ ID NO. 112 in US20160145350
CD73	VH	2993	SEQ ID NO. 114 in US20160145350
CD73	VH	2994	SEQ ID NO. 116 in US20160145350
CD73	VH	2995	SEQ ID NO. 119 in US20160145350
CD73	VH	2996	SEQ ID NO. 121 in US20160145350
CD73	VH	2997	SEQ ID NO. 16 in US20160145350
CD73	VH	2998	SEQ ID NO. 32 in US20160145350
CD73	VH	2999	SEQ ID NO. 4 in US20160145350
CD73	VH	3000	SEQ ID NO. 52 in US20160145350
CD73	VH	3001	SEQ ID NO. 60 in US20160145350
CD73	VH	3002	SEQ ID NO. 68 in US20160145350
CD73	VH	3003	SEQ ID NO. 80 in US20160145350
CD73	VH	3004	SEQ ID NO. 88 in US20160145350
CD74	VH	3005	SEQ ID NO. 23 in US20130171064
CD74	VH	3006	SEQ ID NO. 27 in US20130171064
CD74	VH	3007	SEQ ID NO. 30 in US20130171064
CD74	VH	3008	SEQ ID NO. 33 in US20130171064
CLDN18.2	VH	3009	SEQ ID No. 12 in US20160347815A1
CLDN18.2	VH	3010	SEQ ID No. 2 in US20160347815A1
CSPG4	VH	3011	SEQ ID NO. 10 in WO2016077638
CSPG4	VH	3012	SEQ ID NO. 16 in WO2016077638
CSPG4	VH	3013	SEQ ID NO. 18 in WO2016077638
CSPG4	VH	3014	SEQ ID NO. 4 in WO2016077638
CSPG4	VH	3015	SEQ ID NO. 6 in WO2016077638
CSPG4	VH	3016	SEQ ID NO. 8 in WO2016077638
EGFRvIII	VH	3017	SEQ ID NO. 91 in WO2016120216
EGFRvIII	VH	3018	SEQ ID NO. 93 in WO2016120216
FAP	VH	3019	SEQ ID NO:8 in US20160326265A1
GD2	VH	3020	SEQ ID NO. 17 in WO2016134284
GPC3	VH	3021	SEQ ID NO. 22 in WO2016049459
GPC3	VH	3022	SEQ ID NO: 12 in US9409994B2
GPC3	VH	3023	SEQ ID NO: 16 in US9409994B2
GPC3	VH	3024	SEQ ID NO: 20 in US9409994B2
GPC3	VH	3025	SEQ ID NO: 37 in US9409994B2
GPC3	VH	3026	SEQ ID NO: 8 in US9409994B2
HER2	VH	3027	SEQ ID NO. 19 in US9518118
HER2	VH	3028	SEQ ID NO. 24 in US9518118
LAG3	VH	3029	SEQ ID NO. 102 in US20150259420
LAG3	VH	3030	SEQ ID NO. 106 in US20150259420
LAG3	VH	3031	SEQ ID NO. 110 in US20150259420

LAG3	VH	3032	SEQ ID NO. 113 in US20150259420
LAG3	VH	3033	SEQ ID NO. 122 in US20150259420
LAG3	VH	3034	SEQ ID NO. 18 in US20150259420
LAG3	VH	3035	SEQ ID NO. 30 in US20150259420
LAG3	VH	3036	SEQ ID NO. 66 in US20150259420
LAG3	VH	3037	SEQ ID NO. 70 in US20150259420
LAG3	VH	3038	SEQ ID NO. 74 in US20150259420
LAG3	VH	3039	SEQ ID NO. 78 in US20150259420
MCAM	VH	3040	SEQ ID NO. 101 in US20150259419
MCAM	VH	3041	SEQ ID NO. 102 in US20150259419
MCAM	VH	3042	SEQ ID NO. 103 in US20150259419
MCAM	VH	3043	SEQ ID NO. 104 in US20150259419
MCAM	VH	3044	SEQ ID NO. 105 in US20150259419
MCAM	VH	3045	SEQ ID NO. 106 in US20150259419
MCAM	VH	3046	SEQ ID NO. 107 in US20150259419
Mesothelin	VH	3047	SEQ ID NO: 13 in US20160229919A1
Mesothelin	VH	3048	SEQ ID NO: 17 in US20160229919A1
Mesothelin	VH	3049	SEQ ID NO: 21 in US20160229919A1
Mesothelin	VH	3050	SEQ ID NO: 25 in US20160229919A1
Mesothelin	VH	3051	SEQ ID NO: 29 in US20160229919A1
Mesothelin	VH	3052	SEQ ID NO: 9 in US20160229919A1
MUC1C/ECD	VH	3053	SEQ ID NO: 15 in US20160340442A1
MUC1C/ECD	VH	3054	SEQ ID NO: 19 in US20160340442A1
MUC1C/ECD	VH	3055	SEQ ID NO: 23 in US20160340442A1
MUC1C/ECD	VH	3056	SEQ ID NO: 60 in US20160340442A1
MUC1C/ECD	VH	3057	SEQ ID NO: 64 in US20160340442A1
MUC1C/ECD	VH	3058	SEQ ID NO: 68 in US20160340442A1
MUC1C/ECD	VH	3059	SEQ ID NO: 72 in US20160340442A1
NYBR1	VH	3060	SEQ ID NO: 19 in US20160333422A1
OTK3	VH	3061	SEQ ID NO. 17 in WO2015158868
OX40	VH	3062	SEQ ID NO. 19 in US8748585
OX40	VH	3063	SEQ ID NO. 21 in US8748585
OX40	VH	3064	SEQ ID NO. 22 in US8748585
OX40	VH	3065	SEQ ID NO. 23 in US8748585
OX40	VH	3066	SEQ ID NO. 29 in US8748585
OX40	VH	3067	SEQ ID NO. 58 in US8748585
OX40	VH	3068	SEQ ID NO. 59 in US8748585
OX40	VH	3069	SEQ ID NO. 7 in US8748585
OX40	VH	3070	SEQ ID NO. 77 in US8748585
OX40	VH	3071	SEQ ID NO. 78 in US8748585
OX40	VH	3072	SEQ ID NO. 79 in US8748585
OX40	VH	3073	SEQ ID NO. 80 in US8748585
PDL1	VH	3074	US20160108123 SEQ ID NO: 358
PDL1	VH	3075	US20160108123 SEQ ID NO: 56
PDL1	VH	3076	US20160108123 SEQ ID NO: 64
PTK7	VH	3077	SEQ ID NO. 1 in US20150315293
PTK7	VH	3078	SEQ ID NO. 25 in US20150315293
PTK7	VH	3079	SEQ ID NO. 49 in US20150315293
TIM3	VH	3080	SEQ ID NO. 102 in US20150086574
TIM3	VH	3081	SEQ ID NO. 112 in US20150086574
TIM3	VH	3082	SEQ ID NO. 12 in US20150086574
TIM3	VH	3083	SEQ ID NO. 2 in US20150086574
TIM3	VH	3084	SEQ ID NO. 22 in US20150086574
TIM3	VH	3085	SEQ ID NO. 32 in US20150086574
TIM3	VH	3086	SEQ ID NO. 42 in US20150086574
TIM3	VH	3087	SEQ ID NO. 52 in US20150086574
TIM3	VH	3088	SEQ ID NO. 62 in US20150086574
TIM3	VH	3089	SEQ ID NO. 72 in US20150086574

TIM3	VH	3090	SEQ ID NO. 82 in US20150086574
TIM3	VH	3091	SEQ ID NO. 92 in US20150086574
CD20(Obinutuzumab)	VH	3092	SEQ ID NO. 26 in US20170000900
GD2		3093	SEQ ID NO. 1 in US20130216528
GPDL1	VH	3094	US20160108123 SEQ ID NO: 20
CD19	VK	3095	SEQ ID NO: 13 US20160319020
CD19	VK	3096	SEQ ID NO: 6 US20160319020
hBAT1	VL	3097	SEQ ID NO.1 in WO2013014668
hBAT1	VL	3098	SEQ ID NO.2 in WO2013014668
hBAT1	VL	3099	SEQ ID NO.3 in WO2013014668
hBAT1	VL	3100	SEQ ID NO.4 in WO2013014668
AGR2	VL	3101	SEQ ID NO. 11 in WO2016040321
AGR2	VL	3102	SEQ ID NO. 19 in WO2016040321
ALK	VL	3103	SEQ ID NO: 10 in US20160280798A1
ALK	VL	3104	SEQ ID NO: 12 in US20160280798A1
ALK	VL	3105	SEQ ID NO: 14 in US20160280798A1
ALK	VL	3106	SEQ ID NO: 16 in US20160280798A1
ALK	VL	3107	SEQ ID NO: 2 in US20160280798A1
ALK	VL	3108	SEQ ID NO: 4 in US20160280798A1
ALK	VL	3109	SEQ ID NO: 6 in US20160280798A1
ALK	VL	3110	SEQ ID NO: 8 in US20160280798A1
AMC	VL	3111	SEQ ID NO. 27 in WO2016161390
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AMC	VL	3113	SEQ ID NO. 29 in WO2016161390
AMC	VL	3114	SEQ ID NO. 31 in WO2016161390
AMC	VL	3115	SEQ ID NO. 32 in WO2016161390
AMC	VL	3116	SEQ ID NO. 33 in WO2016161390
AMC	VL	3117	SEQ ID NO. 34 in WO2016161390
AMC	VL	3118	SEQ ID NO. 35 in WO2016161390
AMC	VL	3119	SEQ ID NO. 36 in WO2016161390
ANG2	VL	3120	SEQ ID NO.2 in WO2015091655
ANG2	VL	3121	SEQ ID NO.4 in WO2015091655
APCDD1	VL	3122	SEQ ID NO:136 in WO2012019061
APCDD1	VL	3123	SEQ ID NO:100 in WO2012019061
APCDD1	VL	3124	SEQ ID NO:104 in WO2012019061
APCDD1	VL	3125	SEQ ID NO:108 in WO2012019061
APCDD1	VL	3126	SEQ ID NO:112 in WO2012019061
APCDD1	VL	3127	SEQ ID NO:116 in WO2012019061
APCDD1	VL	3128	SEQ ID NO:12 in WO2012019061
APCDD1	VL	3129	SEQ ID NO:120 in WO2012019061
APCDD1	VL	3130	SEQ ID NO:124 in WO2012019061
APCDD1	VL	3131	SEQ ID NO:128 in WO2012019061
APCDD1	VL	3132	SEQ ID NO:132 in WO2012019061
APCDD1	VL	3133	SEQ ID NO:16 in WO2012019061
APCDD1	VL	3134	SEQ ID NO:8 in WO2012019061
APRIL	VL	3135	SEQ ID NO. 20 in US20160264674
APRIL	VL	3136	SEQ ID NO. 22 in US20160264674
APRIL	VL	3137	SEQ ID NO. 24 in US20160264674
APRIL	VL	3138	SEQ ID NO. 26 in US20160264674
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APRIL	VL	3140	SEQ ID NO. 30 in US20160264674
APRIL	VL	3141	SEQ ID NO. 4 in US20160264674
APRIL	VL	3142	SEQ ID NO. 50 in US20160264674
AXL	VL	3143	SEQ ID NO. 22 in WO2016097370
AXL	VL	3144	SEQ ID NO. 4 in WO2016097370
B2MG	VL	3145	SEQIDNO:29 in WO2016126213A1
B7H1	VL	3146	SEQ ID NO: 17 in US20130034559
B7H1	VL	3147	SEQ ID NO: 37 in US20130034559

B7H1	VL	3148	SEQ ID NO: 47 in US20130034559
B7H1	VL	3149	SEQ ID NO: 57 in US20130034559
B7H1	VL	3150	SEQ ID NO: 7 in US20130034559
B7H1	VL	3151	SEQ ID NO: 77 in US20130034559
B7H1	VL	3152	SEQ ID NO: 27 in US20130034559
B7H1	VL	3153	SEQ ID NO: 67 in US20130034559
B7H3	VL	3154	SEQ ID NO. 1 in WO2016033225
B7H3	VL	3155	SEQ ID NO. 2 in WO2016033225
B7H3	VL	3156	SEQ ID NO. 3 in WO2016033225
B7H3	VL	3157	SEQ ID NO. 4 in WO2016033225
B7H3	VL	3158	SEQ ID NO. 5 in WO2016033225
B7H3	VL	3159	SEQ ID NO. 6 in WO2016033225
B7H3	VL	3160	SEQ ID NO. 7 in WO2016033225
B7H3	VL	3161	SEQ ID NO. 8 in WO2016033225
B7H3(CD276)	VL	3162	SEQ ID NO. 18 in WO2016044383
B7H3(CD276)	VL	3163	SEQ ID NO. 27 in WO2016044383
B7H3(CD276)	VL	3164	SEQ ID NO. 8 in WO2016044383
B7H4	VL	3165	SEQ ID NO. 104 in US20160159910
B7H4	VL	3166	SEQ ID NO. 11 in US20160159910
B7H4	VL	3167	SEQ ID NO. 126 in US20160159910
B7H4	VL	3168	SEQ ID NO. 134 in US20160159910
B7H4	VL	3169	SEQ ID NO. 138 in US20160159910
B7H4	VL	3170	SEQ ID NO. 19 in US20160159910
B7H4	VL	3171	SEQ ID NO. 27 in US20160159910
B7H4	VL	3172	SEQ ID NO. 3 in US20160159910
B7H4	VL	3173	SEQ ID NO. 35 in US20160159910
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B7H4	VL	3175	SEQ ID NO. 93 in US20160159910
B7H4	VL	3176	SEQ ID NO. 95 in US20160159910
B7H4	VL	3177	SEQ ID NO. 97 in US20160159910
B7H4	VL	3178	SEQ ID NO. 98 in US20160159910
B7H4	VL	3179	SEQ ID NO. 145 in US20160159910
B7H4	VL	3180	SEQ ID NO. 146 in US20160159910
B7H4	VL	3181	SEQ ID NO. 147 in US20160159910
B7H4	VL	3182	SEQ ID NO. 148 in US20160159910
B7H4	VL	3183	SEQ ID NO.29 in WO2016160620
B7H4	VL	3184	SEQ ID NO.31 in WO2016160620
B7H4	VL	3185	SEQ ID NO.33 in WO2016160620
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BCMA	VL	3256	SEQ ID NO: 53 in WO2016187349A1
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BCMA	VL	3258	SEQ ID NO. 10 in WO2016090320
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BCMA	VL	3280	SEQ ID NO. 62 in WO2016090320
BCMA	VL	3281	SEQ ID NO. 66 in WO2016090320
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BCMA	VL	3283	SEQ ID NO. 8 in WO2016014789
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BCMA	VL	3285	SEQ ID NO. 96 in WO2016120216
BCMA	VL	3286	SEQ ID NO. 98 in WO2016120216
BCMA	VL	3287	SEQ ID NO: 14 in WO2016168766A1
CA19.9	VL	3288	SEQ ID NO: 118 in US20160333114A1
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EFNA	VL	4044	SEQ ID NO: 155 in WO2012118547
EFNA	VL	4045	SEQ ID NO: 159 in WO2012118547
EFNA	VL	4046	SEQ ID NO: 163 in WO2012118547
EFNA4	VL	4047	SEQ ID NO. 27 in US20150125472
EFNA4	VL	4048	SEQ ID NO. 53 in US20150125472
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ERBB2	VL	4711	US20130089544 SEQ ID NO: 8
ERBB2	VL	4712	US20130266564 SEQ ID NO: 7
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FactorD	VL	4714	SEQ ID NO. 18 in US20160017052
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FactorD	VL	4716	SEQ ID NO. 26 in US20160017052
FactorD	VL	4717	SEQ ID NO. 3 in US20160017052
FactorXII	VL	4718	SEQ ID NO.17 in WO2014089493
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FAP	VL	4720	SEQ ID NO. 6 in WO2015118030
FAP	VL	4721	SEQ ID NO. 171 in WO2016120216
FAP	VL	4722	SEQ ID NO. 173 in WO2016120216
FAP	VL	4723	SEQ ID NO:9 in US20160326265A1
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FGFR3	VL	4740	SEQ ID NO. 137 in US9499623
FGFR3	VL	4741	SEQ ID NO. 139 in US9499623
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GD2	VL	4748	SEQ ID NO. 11 in WO2015132604
GD2	VL	4749	SEQ ID NO. 12 in WO2015132604
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GD2	VL	4751	SEQ ID NO. 2 in US20130216528
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GD3	VL	4756	SEQ ID NO: 14 in WO2016185035A1
GD3	VL	4757	SEQ ID NO: 16 in WO2016185035A1
GD3	VL	4758	SEQ ID NO: 18 in WO2016185035A1
Glycol epitope and ErbB Bi Specific	VL	4759	SEQ ID No. 10 in WO2012007167A1
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GM2	VL	4761	US20090028877 SEQ ID NO: 24
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GM2	VL	4766	US20090028877 SEQ ID NO: 34
GM2	VL	4767	US20090028877 SEQ ID NO: 35
GPC3	VL	4768	SEQ ID NO: 10 in US9409994B2
GPC3	VL	4769	SEQ ID NO: 14 in US9409994B2
GPC3	VL	4770	SEQ ID NO: 16 in US20160208015A1

GPC3	VL	4771	SEQ ID NO: 18 in US9409994B2
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GPC3	VL	4773	SEQ ID NO: 24 in US9409994B2
GPC3	VL	4774	SEQ ID NO: 26 in US9409994B2
GPC3	VL	4775	SEQ ID NO: 31 in US20160208015A1
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GPRC5D	VL	4806	SEQ ID NO. 94 in WO2016090312
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Her2	VL	4809	SEQ ID NO: 261 in WO2016168773A3
Her2	VL	4810	SEQ ID NO: 263 in WO2016168773A3
Her2	VL	4811	SEQ ID NO: 265 in WO2016168773A3
Her2	VL	4812	SEQ ID NO: 267 in WO2016168773A3
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HSP70	VL	4823	SEQ ID NO. 17 in WO2016120217
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humanCD79b	VL	4825	SEQ ID NO.30 in WO2016112870
Human collagen VII	VL	4826	SEQ ID NO.32 in WO2016112870
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humanERBB3	VL	4828	SEQ ID NO: 20 in WO2013052745

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MUC16	VL	4994	SEQ ID NO. 62 in WO2016149368
MUC16	VL	4995	SEQ ID NO. 82 in WO2016149368
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PD1	VL	5114	SEQ ID NO. 31 in US20130291136
PD1	VL	5115	SEQ ID NO. 32 in US20130291136
PD1	VL	5116	SEQ ID NO. 33 in US20130291136
PD1	VL	5117	SEQ ID NO. 39 in US 20160159905
PD1	VL	5118	SEQ ID NO. 42 in WO2015112900

PD1	VL	5119	SEQ ID NO. 46 in WO2015112900
PD1	VL	5120	SEQ ID NO. 54 in WO2015112900
PD1	VL	5121	SEQ ID NO. 58 in WO2015112900
PD1	VL	5122	SEQ ID NO. 62 in WO2015112900
PD1	VL	5123	SEQ ID NO. 66 in WO2015112900
PD1	VL	5124	SEQ ID NO. 7 in US 20160159905
PD1	VL	5125	SEQ ID NO. 70 in WO2015112900
PD1	VL	5126	SEQ ID NO. 74 in WO2015112900
PD1	VL	5127	SEQ ID NO. 78 in WO2015112900
PD1	VL	5128	SEQ ID NO. 8 in US 20160159905
PD1	VL	5129	SEQ ID NO. 9 in US 20160159905
PD1	VL	5130	SEQ ID NO.18 in WO2014055648
PD1(Nivolumab)	VL	5131	SEQ ID NO. 11 in US20150190506
PD1(Pembrolizumab)	VL	5132	SEQ ID NO. 5 in WO2016040892
PD1(Pembrolizumab)	VL	5133	SEQ ID NO. 13 in US20150190506
PDK1	VL	5134	SEQ ID NO.9 in WO2016090365
PDL1	VL	5135	SEQ ID NO. 22 in WO2016061142
PDL1	VL	5136	SEQ ID NO. 26 in WO2016061142
PDL1	VL	5137	SEQ ID NO. 30 in US20150190506
PDL1	VL	5138	SEQ ID NO. 34 in WO2016061142
PDL1	VL	5139	SEQ ID NO. 42 in WO2016061142
PDL1	VL	5140	SEQ ID NO. 58 in WO2016061142
PDL1	VL	5141	SEQ ID NO. 66 in WO2016061142
PDL1	VL	5142	SEQ ID NO. 7 in US20160319022
PDL1	VL	5143	SEQ ID NO. 74 in WO2016061142
PDL1	VL	5144	SEQ ID NO. 8 in US20150190506
PDL1	VL	5145	SEQ ID NO. 82 in WO2016061142
PDL1	VL	5146	SEQ ID NO. 86 in WO2016061142
PDL1	VL	5147	SEQ ID NO. 9 in US20150190506
PDL1	VL	5148	SEQ ID NO. 9 in US20160319022
PDL1	VL	5149	US20160108123 SEQ ID NO: 17
PDL1	VL	5150	US20160108123 SEQ ID NO: 22
PDL1	VL	5151	US20160108123 SEQ ID NO: 24
PDL1	VL	5152	US20160108123 SEQ ID NO: 249
PDL1	VL	5153	US20160108123 SEQ ID NO: 26
PDL1	VL	5154	US20160108123 SEQ ID NO: 28
PDL1	VL	5155	US20160108123 SEQ ID NO: 309
PDL1	VL	5156	US20160108123 SEQ ID NO: 311
PDL1	VL	5157	US20160108123 SEQ ID NO: 313
PDL1	VL	5158	US20160108123 SEQ ID NO: 320
PDL1	VL	5159	US20160108123 SEQ ID NO: 325
PDL1	VL	5160	US20160108123 SEQ ID NO: 34
PDL1	VL	5161	US20160108123 SEQ ID NO: 340
PDL1	VL	5162	US20160108123 SEQ ID NO: 357
PDL1	VL	5163	US20160108123 SEQ ID NO: 359
PDL1	VL	5164	US20160108123 SEQ ID NO: 36
PDL1	VL	5165	US20160108123 SEQ ID NO: 42
PDL1	VL	5166	US20160108123 SEQ ID NO: 44
PDL1	VL	5167	US20160108123 SEQ ID NO: 58
PDL1	VL	5168	US20160108123 SEQ ID NO: 60
PDL1	VL	5169	US20160108123 SEQ ID NO: 66
PDL1	VL	5170	US20160108123 SEQ ID NO: 68
PDL1	VL	5171	US20160108123 SEQ ID NO: 74
PDL1	VL	5172	US20160108123 SEQ ID NO: 76
PDL1	VL	5173	US20160108123 SEQ ID NO: 8
PDL1	VL	5174	US20160108123 SEQ ID NO: 82
PDL1	VL	5175	US20160108123 SEQ ID NO: 84
PDL1	VL	5176	US20160108123 SEQ ID NO: 86

PDL1	VL	5177	US20160108123 SEQ ID NO: 88
PDL2	VL	5178	SEQ ID NO. 47 in US20130291136
PDL2	VL	5179	SEQ ID NO. 48 in US20130291136
PDL2	VL	5180	SEQ ID NO. 49 in US20130291136
PDL2	VL	5181	SEQ ID NO. 50 in US20130291136
PDL2	VL	5182	SEQ ID NO. 51 in US20130291136
PG16	VL	5183	SEQ ID NO: 12 in EP3074419A2
PG9	VL	5184	SEQ ID NO: 10 in EP3074419A2
PGT2	VL	5185	SEQ ID NO: 16 in EP3074419A2
PGT3	VL	5186	SEQ ID NO: 18 in EP3074419A2
PGT4	VL	5187	SEQ ID NO: 20 in EP3074419A2
PGT5	VL	5188	SEQ ID NO: 22 in EP3074419A2
PRAME	VL	5189	SEQ ID NO: 49 in WO2016191246A2
PRAME	VL	5190	SEQ ID NO: 51 in WO2016191246A2
PRAME	VL	5191	SEQ ID NO: 53 in WO2016191246A2
PRAME	VL	5192	SEQ ID NO: 55 in WO2016191246A2
PRAME	VL	5193	SEQ ID NO: 57 in WO2016191246A2
PRAME	VL	5194	SEQ ID NO: 59 in WO2016191246A2
PRAME	VL	5195	SEQ ID NO: 61 in WO2016191246A2
PRP	VL	5196	SEQ ID NO: 39 in US20160333114A1
PRP	VL	5197	SEQ ID NO: 41 in US20160333114A1
PSMA	VL	5198	SEQ ID NO: 44 in WO2016097231
PTK7	VL	5199	SEQ ID NO. 20 in WO2012112943A1
PTK7	VL	5200	SEQ ID NO. 22 in WO2012112943A1
PTK7	VL	5201	SEQ ID NO. 24 in WO2012112943A1
PTK7	VL	5202	SEQ ID NO. 26 in WO2012112943A1
PTK7	VL	5203	SEQ ID NO. 28 in WO2012112943A1
PTK7	VL	5204	SEQ ID NO. 30 in WO2012112943A1
PTK7	VL	5205	SEQ ID NO. 32 in WO2012112943A1
PTK7	VL	5206	SEQ ID NO. 34 in WO2012112943A1
PTK7	VL	5207	SEQ ID NO. 36 in WO2012112943A1
PTK7	VL	5208	SEQ ID NO. 38 in WO2012112943A1
PTK7	VL	5209	SEQ ID NO. 40 in WO2012112943A1
PTK7	VL	5210	SEQ ID NO. 42 in WO2012112943A1
PTK7	VL	5211	SEQ ID NO. 44 in WO2012112943A1
PTK7	VL	5212	SEQ ID NO. 46 in WO2012112943A1
PTK7	VL	5213	SEQ ID NO. 48 in WO2012112943A1
PTK7	VL	5214	SEQ ID NO. 50 in WO2012112943A1
PTK7	VL	5215	SEQ ID NO. 52 in WO2012112943A1
PTK7	VL	5216	SEQ ID NO. 54 in WO2012112943A1
PTK7	VL	5217	SEQ ID NO. 56 in WO2012112943A1
PTK7	VL	5218	SEQ ID NO. 58 in WO2012112943A1
PTK7	VL	5219	SEQ ID NO. 60 in WO2012112943A1
PTK7	VL	5220	SEQ ID NO. 62 in WO2012112943A1
PTK7	VL	5221	SEQ ID NO. 64 in WO2012112943A1
PTK7	VL	5222	SEQ ID NO. 66 in WO2012112943A1
PTK7	VL	5223	SEQ ID NO. 68 in WO2012112943A1
PTK7	VL	5224	SEQ ID NO. 15 in US20150315293
PTK7	VL	5225	SEQ ID NO. 39 in US20150315293
PTK7	VL	5226	SEQ ID NO. 63 in US20150315293
RAS	VL	5227	SEQ ID NO.19 in WO2016154047
RAS	VL	5228	SEQ ID NO.49 in WO2016154047
RAS	VL	5229	SEQ ID NO.59 in WO2016154047
RAS	VL	5230	SEQ ID NO.69 in WO2016154047
RAS	VL	5231	SEQ ID NO.79 in WO2016154047
RAS	VL	5232	SEQ ID NO.9 in WO2016154047
RHAMM antagonist body light chain	VL	5233	SEQ ID NO 4 in WO2000029447

Rituximab	VL	5234	SEQ ID NO: 63 in US20160333114A1
Rituximab	VL	5235	SEQ ID NO: 65 in US20160333114A1
ROR1	VL	5236	SEQ ID NO. 16 WO2016016343A1
ROR1	VL	5237	SEQ ID NO. 24 WO2016016343A1
ROR1	VL	5238	SEQ ID NO. 32 WO2016016343A1
ROR1	VL	5239	SEQ ID NO. 40 WO2016016343A1
ROR1	VL	5240	SEQ ID NO. 56 WO2016016343A1
ROR1	VL	5241	SEQ ID NO. 64 WO2016016343A1
ROR1	VL	5242	SEQ ID NO. 72 WO2016016343A1
ROR1	VL	5243	SEQ ID NO.36 in WO2016016344A1
ROR1	VL	5244	SEQ ID NO.62 in WO2016016344A1
ROR1	VL	5245	SEQ ID NO.23 in WO2016016344A1
ROR1	VL	5246	SEQ ID NO.49 in WO2016016344A1
ROR1	VL	5247	SEQ ID NO.58 in WO2016016344A1
ROR1	VL	5248	SEQ ID NO. 86 in WO2016120216
ROR1	VL	5249	SEQ ID NO. 88 in WO2016120216
ROR1	VL	5250	SEQ ID NO. 90 in WO2016120216
ROR1	VL	5251	SEQ ID NO: 126 in US20160208018A1
ROR1	VL	5252	SEQ ID NO: 127 in US20160208018A1
ROR1	VL	5253	SEQ ID NO: 234 in US20160208018A1
ROR1	VL	5254	SEQ ID NO: 235 in US20160208018A1
ROR1	VL	5255	SEQ ID NO: 236 in US20160208018A1
ROR1	VL	5256	SEQ ID NO: 237 in US20160208018A1
ROR1	VL	5257	SEQ ID NO: 238 in US20160208018A1
ROR1	VL	5258	SEQ ID NO: 240 in US20160208018A1
ROR1	VL	5259	SEQ ID NO: 241 in US20160208018A1
ROR1	VL	5260	SEQ ID NO: 242 in US20160208018A1
ROR1	VL	5261	SEQ ID NO: 243 in US20160208018A1
ROR1	VL	5262	SEQ ID NO: 244 in US20160208018A1
ROR1	VL	5263	SEQ ID NO: 245 in US20160208018A1
ROR1	VL	5264	SEQ ID NO: 246 in US20160208018A1
ROR1	VL	5265	SEQ ID NO: 247 in US20160208018A1
ROR1	VL	5266	SEQ ID NO: 248 in US20160208018A1
ROR1	VL	5267	SEQ ID NO: 56 in EP3083671A1
ROR1	VL	5268	SEQ ID NO: 103 in WO2016187216A1
ROR1	VL	5269	SEQ ID NO: 111 in WO2016187216A1
ROR1	VL	5270	SEQ ID NO: 127 in WO2016187216A1
ROR1	VL	5271	SEQ ID NO: 135 in WO2016187216A1
ROR1	VL	5272	SEQ ID NO: 143 in WO2016187216A1
ROR1	VL	5273	SEQ ID NO: 15 in WO2016187216A1
ROR1	VL	5274	SEQ ID NO: 151 in WO2016187216A1
ROR1	VL	5275	SEQ ID NO: 159 in WO2016187216A1
ROR1	VL	5276	SEQ ID NO: 167 in WO2016187216A1
ROR1	VL	5277	SEQ ID NO: 175 in WO2016187216A1
ROR1	VL	5278	SEQ ID NO: 183 in WO2016187216A1
ROR1	VL	5279	SEQ ID NO: 191 in WO2016187216A1
ROR1	VL	5280	SEQ ID NO: 199 in WO2016187216A1
ROR1	VL	5281	SEQ ID NO: 207 in WO2016187216A1
ROR1	VL	5282	SEQ ID NO: 215 in WO2016187216A1
ROR1	VL	5283	SEQ ID NO: 223 in WO2016187216A1
ROR1	VL	5284	SEQ ID NO: 23 in WO2016187216A1
ROR1	VL	5285	SEQ ID NO: 231 in WO2016187216A1
ROR1	VL	5286	SEQ ID NO: 239 in WO2016187216A1
ROR1	VL	5287	SEQ ID NO: 247 in WO2016187216A1
ROR1	VL	5288	SEQ ID NO: 255 in WO2016187216A1
ROR1	VL	5289	SEQ ID NO: 263 in WO2016187216A1
ROR1	VL	5290	SEQ ID NO: 271 in WO2016187216A1
ROR1	VL	5291	SEQ ID NO: 279 in WO2016187216A1

ROR1	VL	5292	SEQ ID NO: 287 in WO2016187216A1
ROR1	VL	5293	SEQ ID NO: 295 in WO2016187216A1
ROR1	VL	5294	SEQ ID NO: 303 in WO2016187216A1
ROR1	VL	5295	SEQ ID NO: 31 in WO2016187216A1
ROR1	VL	5296	SEQ ID NO: 311 in WO2016187216A1
ROR1	VL	5297	SEQ ID NO: 319 in WO2016187216A1
ROR1	VL	5298	SEQ ID NO: 327 in WO2016187216A1
ROR1	VL	5299	SEQ ID NO: 335 in WO2016187216A1
ROR1	VL	5300	SEQ ID NO: 343 in WO2016187216A1
ROR1	VL	5301	SEQ ID NO: 351 in WO2016187216A1
ROR1	VL	5302	SEQ ID NO: 359 in WO2016187216A1
ROR1	VL	5303	SEQ ID NO: 39 in WO2016187216A1
ROR1	VL	5304	SEQ ID NO: 47 in WO2016187216A1
ROR1	VL	5305	SEQ ID NO: 55 in WO2016187216A1
ROR1	VL	5306	SEQ ID NO: 63 in WO2016187216A1
ROR1	VL	5307	SEQ ID NO: 7 in WO2016187216A1
ROR1	VL	5308	SEQ ID NO: 71 in WO2016187216A1
ROR1	VL	5309	SEQ ID NO: 79 in WO2016187216A1
ROR1	VL	5310	SEQ ID NO: 87 in WO2016187216A1
ROR1	VL	5311	SEQ ID NO: 95 in WO2016187216A1
SEMAPHORIN4D	VL	5312	SEQ ID NO. 17 in US20160115240A1
SEMAPHORIN4D	VL	5313	SEQ ID NO. 18 in US20160115240A1
SEMAPHORIN4D	VL	5314	SEQ ID NO. 29 in US20160115240A1
TAG73	VL	5315	SEQ ID NO: 116 in US20160333114A1
TCR	VL	5316	SEQ ID NO. 132 in WO2016122701
TEM8	VL	5317	SEQ ID NO: 4 in US20160264662A1
TEM8	VL	5318	SEQ ID NO: 6 in US20160264662A1
TEM8	VL	5319	SEQ ID NO: 8 in US20160264662A1
Tie	VL	5320	SEQ ID NO 724 in US20060057138A1
TIGIT	VL	5321	SEQ ID NO. 130 in US20160355589
TIGIT	VL	5322	SEQ ID NO. 131 in US20160355589
TIGIT	VL	5323	SEQ ID NO. 132 in US20160355589
TIGIT	VL	5324	SEQ ID NO. 133 in US20160355589
TIGIT	VL	5325	SEQ ID NO. 137 in US20160355589
TIGIT	VL	5326	SEQ ID NO. 139 in US20160355589
TIGIT	VL	5327	SEQ ID NO. 145 in US20160355589
TIGIT	VL	5328	SEQ ID NO. 146 in US20160355589
TIGIT	VL	5329	SEQ ID NO. 151 in US20160355589
TIGIT	VL	5330	SEQ ID NO. 152 in US20160355589
TIGIT	VL	5331	SEQ ID NO. 25 in US20160355589
TIGIT	VL	5332	SEQ ID NO. 26 in US20160355589
TIGIT	VL	5333	SEQ ID NO. 27 in US20160355589
TIGIT	VL	5334	SEQ ID NO. 28 in US20160355589
TIGIT	VL	5335	SEQ ID NO. 29 in US20160355589
TIGIT	VL	5336	SEQ ID NO. 30 in US20160355589
TIGIT	VL	5337	SEQ ID NO. 50 in US20160355589
TIGIT	VL	5338	SEQ ID NO. 51 in US20160355589
TIGIT	VL	5339	SEQ ID NO. 52 in US20160355589
TIGIT	VL	5340	SEQ ID NO. 64 in US20160355589
TIGIT	VL	5341	SEQ ID NO. 95 in US20160355589
TIGIT	VL	5342	SEQ ID NO.8 in US20160355589
TIM3	VL	5343	SEQ ID NO:7 in WO2013006490
TIM3	VL	5344	SEQ ID NO. 107 in US20150086574
TIM3	VL	5345	SEQ ID NO. 117 in US20150086574
TIM3	VL	5346	SEQ ID NO. 17 in US20150086574
TIM3	VL	5347	SEQ ID NO. 27 in US20150086574
TIM3	VL	5348	SEQ ID NO. 37 in US20150086574
TIM3	VL	5349	SEQ ID NO. 47 in US20150086574

TIM3	VL	5350	SEQ ID NO. 57 in US20150086574
TIM3	VL	5351	SEQ ID NO. 67 in US20150086574
TIM3	VL	5352	SEQ ID NO. 7 in US20150086574
TIM3	VL	5353	SEQ ID NO. 77 in US20150086574
TIM3	VL	5354	SEQ ID NO. 87 in US20150086574
TIM3	VL	5355	SEQ ID NO. 97 in US20150086574
TIM3	VL	5356	SEQ ID NO: 17 in WO2016179319A1
TIM3	VL	5357	SEQ ID NO: 25 in WO2016179319A1
TIM3	VL	5358	SEQ ID NO: 33 in WO2016179319A1
TIM3	VL	5359	SEQ ID NO: 41 in WO2016179319A1
TIM3	VL	5360	SEQ ID NO: 49 in WO2016179319A1
TIM3	VL	5361	SEQ ID NO: 57 in WO2016179319A1
TIM3	VL	5362	SEQ ID NO: 65 in WO2016179319A1
TIM3	VL	5363	SEQ ID NO: 73 in WO2016179319A1
TIM3	VL	5364	SEQ ID NO: 81 in WO2016179319A1
TIM3	VL	5365	SEQ ID NO: 89 in WO2016179319A1
TIM3	VL	5366	SEQ ID NO: 9 in WO2016179319A1
TIM3	VL	5367	SEQ ID NO: 97 in WO2016179319A1
Tissue factor	VL	5368	SEQ ID NO 25 in US20040229301A1
Tissue factor	VL	5369	SEQ ID NO 31 in US20040229301A1
Tissue factor	VL	5370	SEQ ID NO 12 in WO2004094475
Tissue factor	VL	5371	SEQ ID NO 21 in WO2004094475
Tissue factor	VL	5372	SEQ ID NO 25 in WO2004094475
Tissue factor	VL	5373	SEQ ID NO 31 in WO2004094475
Tissue factor	VL	5374	SEQ ID NO 8 in WO2004094475
Tissue factor	VL	5375	SEQ ID NO: 35 in US20160333114A1
Tissue factor	VL	5376	SEQ ID NO: 37 in US20160333114A1
TRBC1	VL	5377	SEQ ID NO. 2 in WO2015132598
TrophoblastGlycoprotein5T4	VL	5378	SEQ ID NO. 18 in WO2016034666A1
TrophoblastGlycoprotein5T4 VL	VL	5379	SEQ ID NO. 12 in WO2016034666A1
TrophoblastGlycoprotein5T4 VL	VL	5380	SEQ ID NO. 14 in WO2016034666A1
TrophoblastGlycoprotein5T4 VL	VL	5381	SEQ ID NO. 16 in WO2016034666A1
uPAR	VL	5382	SEQ ID NO: 71 in US20160333114A1
uPAR	VL	5383	SEQ ID NO: 73 in US20160333114A1
VEGF	VL	5384	SEQ ID NO 2 in WO2000034337
VEGF	VL	5385	SEQ ID NO 6 in WO2000034337
VEGF	VL	5386	SEQ ID NO.9 in US20030175276A1
VEGF	VL	5387	SEQ ID NO 11 in WO2006012688A1
VEGF	VL	5388	SEQ ID NO 19 in WO2006012688A1
VEGF	VL	5389	SEQ ID NO 27 in WO2006012688A1
VEGF	VL	5390	SEQ ID NO 28 in WO2006012688A1
VEGF	VL	5391	SEQ ID NO 3 in WO2006012688A1
VEGF	VL	5392	SEQ ID NO 43 in WO2006012688A1
VEGF	VL	5393	US20160090427 SEQ ID NO: 160
VEGF	VL	5394	US20160090427 SEQ ID NO: 161
VEGF	VL	5395	US20160090427 SEQ ID NO: 162
VEGF	VL	5396	US20160090427 SEQ ID NO: 163
VEGF	VL	5397	US20160090427 SEQ ID NO: 164
VEGF	VL	5398	US20160090427 SEQ ID NO: 165
VEGF	VL	5399	US20160090427 SEQ ID NO: 166
VEGF	VL	5400	US20160090427 SEQ ID NO: 167
VEGFR2	VL	5401	SEQ ID NO. 107 in WO2017004254
VEGFR2	VL	5402	SEQ ID NO. 108 in WO2017004254
VEGFR2	VL	5403	SEQ ID NO. 109 in WO2017004254
VEGFR2	VL	5404	SEQ ID NO. 110 in WO2017004254

VEGFR2	VL	5405	SEQ ID NO. 111 in WO2017004254
VEGFR2	VL	5406	SEQ ID NO. 112 in WO2017004254
VEGFR2	VL	5407	SEQ ID NO. 113 in WO2017004254
VEGFR2	VL	5408	SEQ ID NO. 86 In WO2017004254
VEGFR2	VL	5409	SEQ ID NO. 87 In WO2017004254
VEGFR2	VL	5410	SEQ ID NO. 88 In WO2017004254
VEGFR2	VL	5411	SEQ ID NO. 89 In WO2017004254
VEGFR2	VL	5412	SEQ ID NO. 90 In WO2017004254
VEGFR2	VL	5413	SEQ ID NO. 91 In WO2017004254
VEGFR2	VL	5414	SEQ ID NO. 92 In WO2017004254
VEGFR2	VL	5415	SEQ ID NO. 93 In WO2017004254
VEGFR2	VL	5416	SEQ ID NO. 94 In WO2017004254
VISTA	VL	5417	SEQ ID NO:41 in WO2015097536
VISTA	VL	5418	SEQ ID NO:42 in WO2015097536
VISTA	VL	5419	SEQ ID NO:43 in WO2015097536
VISTA	VL	5420	SEQ ID NO:44 in WO2015097536
VISTA	VL	5421	SEQ ID NO:45 in WO2015097536
VMS2	VL	5422	FIG. 2 in WO2000058363
WT1/HLA Bi Specific	VL	5423	SEQ ID NO.106 in WO2015070061
WT1/HLA Bi Specific	VL	5424	SEQ ID NO.112 in WO2015070061
WT1/HLA Bi Specific	VL	5425	SEQ ID NO.130 in WO2015070061
WT1/HLA Bi Specific	VL	5426	SEQ ID NO.34 in WO2015070061
WT1/HLA Bi Specific	VL	5427	SEQ ID NO.52 in WO2015070061
WT1/HLA Bi Specific	VL	5428	SEQ ID NO.70 in WO2015070061
WT1/HLA Bi Specific	VL	5429	SEQ ID NO.88 in WO2015070061
5T4	VL	5430	SEQ ID NO. 1 in WO2016022939
5T4	VL	5431	SEQ ID NO. 3 in WO2016022939
ALK	VL	5432	SEQ ID NO. 10 in WO2015069922
ALK	VL	5433	SEQ ID NO. 12 in WO2015069922
ALK	VL	5434	SEQ ID NO. 14 in WO2015069922
ALK	VL	5435	SEQ ID NO. 16 in WO2015069922
ALK	VL	5436	SEQ ID NO. 8 in WO2015069922
ALKVL	VL	5437	SEQ ID NO. 2 in WO2015069922
ALKVL	VL	5438	SEQ ID NO. 4 in WO2015069922
ALKVL	VL	5439	SEQ ID NO. 6 in WO2015069922
CD123	VL	5440	SEQ ID NO. 114 in WO2016120216
CD123	VL	5441	SEQ ID NO. 116 in WO2016120216
CD123	VL	5442	SEQ ID NO. 58 in WO2016120216
CD123	VL	5443	SEQ ID NO. 60 in WO2016120216
CD123	VL	5444	SEQ ID NO. 64 in WO2016120216
CD16	VL	5445	SEQ ID NO. 26 in WO2015158868
CD22	VL	5446	SEQ ID NO. 1 in WO2013059593
CD276	VL	5447	SEQ ID NO. 18 in US20160053017
CD276	VL	5448	SEQ ID NO. 27 in US20160053017
CD28	VL	5449	SEQ ID NO. 20 in WO2015158868
CD73	VL	5450	SEQ ID NO. 101 in US20160145350
CD73	VL	5451	SEQ ID NO. 102 in US20160145350
CD73	VL	5452	SEQ ID NO. 104 in US20160145350
CD73	VL	5453	SEQ ID NO. 106 in US20160145350
CD73	VL	5454	SEQ ID NO. 110 in US20160145350
CD73	VL	5455	SEQ ID NO. 117 in US20160145350
CD73	VL	5456	SEQ ID NO. 118 in US20160145350
CD73	VL	5457	SEQ ID NO. 120 in US20160145350
CD73	VL	5458	SEQ ID NO. 122 in US20160145350
CD74	VL	5459	SEQ ID NO. 25 in US20130171064
CD74	VL	5460	SEQ ID NO. 29 in US20130171064
CD74	VL	5461	SEQ ID NO. 31 in US20130171064
CD74	VL	5462	SEQ ID NO. 35 in US20130171064

CS1	VL	5463	SEQ ID NO. 110 in WO2016120216
CS1	VL	5464	SEQ ID NO. 112 in WO2016120216
CSPG4	VL	5465	SEQ ID NO. 12 in WO2016077638
CSPG4	VL	5466	SEQ ID NO. 14 in WO2016077638
EGFRvIII	VL	5467	SEQ ID NO. 92 in WO2016120216
EGFRvIII	VL	5468	SEQ ID NO. 94 in WO2016120216
ERBB2	VL	5469	US20110129464 SEQ ID NO: 3
GPC3	VL	5470	SEQ ID NO. 23 in WO2016049459
Malignant Variable Receptor	VL	5471	SEQ ID NO. 5 in WO2015133817A1
OX40	VL	5472	SEQ ID NO. 29 in US20160137740
OX40	VL	5473	SEQ ID NO. 37 in US20150190506

Intrabodies

[0222] In some embodiments, payloads of the present invention may be intrabodies against players in regulating immune cells. An intrabody is an antibody that is designed to be expressed intracellularly and can be directed to a specific target antigen present in various subcellular locations including the cytosol, nucleus, endoplasmic reticulum (ER), mitochondria, peroxisomes, plasma membrane and trans-Golgi network (TGN) through in frame fusion with intracellular trafficking/localization peptide sequences. The most commonly used format is a single chain antibody (scFv) created by joining the antigen-binding variable domains of heavy and light chain with a linker, most often the 15-amino acid linker (e.g., $(GGGGS)_3$ (SEQ ID NO: 307)) between the variable heavy (VH) and variable light (VL) chains. The intracellular intrabodies are being developed to bind to, neutralize, or modify the function or localization of cancer-related targets and thereby affect the malignant phenotype.

[0223] Players that modulate immune cells (e.g., T cells) may be any intracellular signaling checkpoint. Exemplary players may include a co-inhibitory ligand, Casitas B-linage lymphoma proto-oncogene-b (Cbl-b) (a E3 ligase), a protein tyrosine phosphatase (PTP) such as Src homology 2 domain-containing protein tyrosine phosphatase 1 (SHP-1), and Ras. For example, an intrabody may be an intrabody against oncogenic form of RAS disclosed in PCT patent publication NO.: WO2004/046186; the contents of which are incorporated by reference in their entirety.

Therapeutic Antibodies

[0224] In some embodiments, antibody payloads of the present invention may be therapeutic antibodies. As non-limiting examples, antibodies and fragments and variants thereof may be specific to tumor associated antigens, or tumor specific antigens, or pathogen antigens. In some aspects, antibodies may be blocking antibodies (also referred to as antagonistic antibodies), for example, blocking antibodies against PD-1, PD-L1, PD-L2,

CTLA-4 and other inhibitory molecules. In other aspects, antibodies may be agonist antibodies such as agonistic antibodies specific to stimulatory molecules, e g., 4-1BB (CD137), OX40 (CD134), CD40, GITR and CD27.

[0225] Other exemplary therapeutic antibodies may include, but are not limited to, Abagovomab, Abcxmab, Abituzumab, Abrilumab, Actoxumab, Adalimumab, Adecatumumab, Afasevikumab, Afelimomab, Afutuzumab, Alacizumab, Alemtuzumab, Alirocumab, Altumomab, Amatuximab, Anetumab, Anifrolumab, Apolizumab, Arcitumomab, Ascrinvacumab, Aselizumab, Atezolizumab, Atinumab, Atlizumab, Atorolimumab, Avelumab, Bapineuzumab, Basiliximab, Bavituximab, Bectumomab, Begelomab, Belimumab, Benralizumab, Bertilimumab, Besilesomab, Bevacizumab, Bezlotoxumab, Biciromab, Bimagrumab, Bimekizumab, Bivatuzumab, Bleselumab, Blinatumomab, Blinatumomab, Blosozumab, Bococizumab, Brentuximab, Briaknumab, Brodalumab, Brolucizumab, Brontictuzumab, Cabiralizumab, Canakinumab, Cantuzumab, Caplacizumab, Capromab, Carlumab, Carotuximab, Catumaxomab, cBR96-doxorubicin immunoconjugate, Cedelizumab, Cergutuzumab, Certolizumab pegol, Cetuximab, Citatuzumab, Cixutumumab, Clazakizumab, Clenoliximab, Clivatuzumab, Codrituzumab, Coltuximab, Contatumumab, Concizumab, Crenezumab, Crotedumab, CR6261, Dacetumab, Daclizumab, Dalotuzumab, Dapirolizumab pegol, Daratumumab, Dectrekumab, Demcizumab, Denintuzumab, Denosumab, Derlotuximab biotin, Detumomab, Dinutuximab, Diridavumab, Domagrozumab, Dorlimomab aritox, Drozitumab, Duligotumab, Dupilumab, Durvalumab, Dusigitumab, Ecromeximab, Eculizumab, Edobacomab, Edrecolomab, Efalizumab, Efungumab, Eldelumab, Elgemtumab, Elotuzumab, Elsilimomab, Emactuzumab, Emibetuzumab, Emicizumab, Enavatuzumab, Enfortumab vedotin, Enlimomab pegol, Enoblituzumab, Enokizumab, Enoticumab, Ensituximab, Epitumomab cituxetan, Epratuzumab, Erlizumab, Ertumaxomab, Etaracizumab, Etrolizumab, Evinacumab, Evolocumab, Exbivirumab, Fanolesomab, Faralimomab, Farletuzumab, Fasinumab, FBTA05, Felvizumab, Fezakinumab, Fibatuzumab, Ficlatuzumab, Figitumumab, Firivumab, Flanvotumab, Fletikumab, Fontolizumab, Foralumab, Foravirumab, Fresolimumab, Fulranumab, Futuximab, Galcanezumab, Galiximab, Ganitumab, Gantenerumab, Gavilimomab, Gemtuzumab ozogamicin, Gevokizumab, Girentuximab, Glembatumumab vedotin, Golimumab, Gomiliximab, Guselkumab, Ibalizumab, Ibritumomab tituxetan, icrucumab, Idarucizumab, Igovomab, IMAB362, Imalumab, Imciromab, Imgatuzumab, Inclacumab, Indatuximab, Indusatumab, Inebilizumab, Infliximab, Intetumumab, Inolimomab, Inotuzumab, Ipilimumab, Iratumumab, Isatuximab, Itolizumab, Ixekizumab,

Keliximab, Labetuzumab, Lambrolizumab, Lampalizumab, Lanadelumab, Landogrozumab, Laprituximab, Lebrikizumab, Lemalesomab, Lendalizumab, Lenzilumab, Lerdelimumab, Lexatumumab, Libivirumab, Lifastuzumab, Ligelizumab, Lilotomab, Lintuzumab, Lirilumab, Lodelcizumab, Lokivetmab, Lorvotuzumab, Lucatumumab, Lulizumab pegol, Lumiliximab, Lumretuzumab, Mapatumumab, Margetuximab, Maslimomab, Mavrilimumab, Matuzumab, Mepolizumab, Metelimumab, Milatuzumab, Minretumomab, Mirvetuximab, Mitumomab, Mogamulizumab, Monalizumab, Morolimumab, Motavizumab, Moxetumomab pasudotox, Muromonab-CD3, nacolomab tafenatox, Namilumab, naptumomab, naratuximab, Narnatumab, Natalizumab, Navicixizumab, Navivumab, Nebacumab, Necitumumab, Nemolizumab, Nerelimomab, Nesvacumab, Nimotuzumab, Nivolumab, Nofetumomab, Obiltoxaximab, Obinutuzumab, Ocaratuzumab, Ocrelizumab, Odulimomab, Ofatumumab, Olaratumab, Olaratumab, Olokizumab, Omalizumab, Onartuzumab, Ontuxizumab, Opicinumab, Oportuzumab monatox, Oregovomab, Orticumab, Otelixizumab, Otlertuzumab, Oxelumab, Ozanezumab, Ozoralizumab, Pagibaximab, Palivizumab, Pamrevlumab, Panitumumab, Pankomab, Panobacumab, Parsatuzumab, Pascolizumab, Pasotuxizumab, Pateclizumab, Patritumab, Pembrolizumab, Pemtumomab, Perakizumab, Pertuzumab, Pexelizumab, Pidilizumab, Pinatuzumab, Pintumomab, Placulumab, Plozalizumab, Pogalizumab, Polatuzumab, Ponezumab, Prezalizumab, Priliximab, Pritoxaximab, Pritumumab, PRO 140, Quilizumab, Racotumomab, Radretumab, Rafivirumab, Ralpancizumab, Ramucirumab, Ranibizumab, Raxibacumab, Refanezumab, Regavirumab, Reslizumab, Rilotumumab, Rinucumab, Risankizumab, Rituximab, Rivabazumab pegol, Robatumumab, Roledumab, Romosozumab, Rontalizumab, Rovalpituzumab, Rovelizumab, Ruplizumab, Sacituzumab, Samalizumab, Sapelizumab, Sarilumab, Satumomab pendetide, Secukinumab, Seribantumab, Setoxaximab, Sevirumab, Sibrotuzumab, SGN-CD19A, SGN-CD33A, Sifalimumab, Siltuximab, Simtuzumab, Siplizumab, Sirukumab, Sofituzumab vedotin, Solanezumab, Solitomab, Sonepcizumab, Sontuzumab, Stamulumab, Sulesomab, Suvizumab, tabalumab, Tacatuzumab, Tadocizumab, Talizumab, Tamtuvetmab, Tanezumab, Taplitumomab, Tarextumab, Tefibazumab, Telimomab aritox, Tenatumomab, Teneliximab, Teplizumab, Teprotumumab, Tesidolumab, Tetulomab, Tezepelumab, TGN1412, Ticilimumab, Tildrakizumab, Tigatuzumab, Timolumab, Tisotumab vedotin, TNX-650, Tocilizumab, Toralizumab, Tosatoxumab, Tositumomab, Tovetumab, Tralokinumab, Trastuzumab, TRBS07, Tregalizumab, Tremelimumab, Trevogrumab, Tucotuzumab, Tuvirumab, Ublituximab, Ulcocuplumab, Urelumab, Urtoxazumab, Ustekinumab, Vadastuximab talirine, Vandortuzumab vedotin, Vantictumab, Vanucizumab, Vapaliximab,

Varlilumab, Vatelizumab, Vedolizumab, Veltuzumab, Vepalimomab, Vesencumab, Visilizumab, Vobarilizumab, Volociximab, Vorsetuzumab, Votumumab, Xentuzumab, Zalutumumab, Zanolimumab, Zatuximab, Ziralimumab and Zolimomab aritox.

Bicistronic and/or Pseudo-bicistronic antibody payloads

[0226] According to the present invention, a bicistronic payload is a polynucleotide encoding a two-protein chain antibody on a single polynucleotide strand. A pseudo-bicistronic payload is a polynucleotide encoding a single chain antibody discontinuously on a single polynucleotide strand. For bicistronic payloads, the encoded two strands or two portions/regions and/or domains (as is the case with pseudo-bicistronic) are separated by at least one nucleotide not encoding the strands or domains. More often the separation comprises a cleavage signal or site or a non-coding region of nucleotides. Such cleavage sites include, for example, furin cleavage sites encoded as an "RKR" site, or a modified furin cleavage site in the resultant polypeptide or any of those taught herein.

[0227] According to the present invention, a single domain payload comprises one or two polynucleotides encoding a single monomeric variable antibody domain. Typically, single domain antibodies comprise one variable domain (VH) of a heavy-chain antibody.

[0228] According to the present invention, a single chain Fv payloads is a polynucleotide encoding at least two coding regions and a linker region. The scFv payload may encode a fusion protein of the variable regions of the heavy (VH) and light chains (VL) of immunoglobulins, connected with a short linker peptide of ten to about 25 amino acids. The linker is usually rich in glycine for flexibility, as well as serine or threonine for solubility, and can either connect the N-terminus of the VH with the C-terminus of the VL, or vice versa. Other linkers include those known in the art and disclosed herein.

[0229] According to the present invention, a bispecific payload is a polynucleotide encoding portions or regions of two different antibodies. Bispecific payloads encode polypeptides which may bind two different antigens. Polynucleotides of the present invention may also encode trispecific antibodies having an affinity for three antigens.

3. Tumor and pathogen specific antigens

[0230] In some embodiments, payloads of the present invention may be tumor specific antigens (TSAs), tumor associated antigens (TAAs), pathogen associated antigens, or fragments thereof. The antigen can be expressed as a peptide or as an intact protein or portion thereof. The intact protein or a portion thereof can be native or mutagenized. Antigens associated with cancers or virus-induced cancers as described herein are well-known in the

art. Such a TSA or TAA may be previously associated with a cancer or may be identified by any method known in the art.

[0231] A tumor specific antigen (TSA) may be a tumor neoantigen. A neoantigen is a mutated antigen that is only expressed by tumor cells because of genetic mutations or alterations in transcription which alter protein coding sequences, therefore creating novel, foreign antigens. The genetic changes result from genetic substitution, insertion, deletion or any other genetic changes of a native cognate protein (i.e. a molecule that is expressed in normal cells).

[0232] As non-limiting examples, neoantigens may include mutated new peptides derived from alpha-actinin-4, ARTC1, BCR-ABL fusion protein (b3a2), B-RAF, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, CML-66, COA-1, connexin 37, dek-can fusion protein, EFTUD2, Elongation factor 2, ETV6-AML1 fusion protein, fibronectin, FLT3-ITD, FN1, GPNM8, LDLR-fucosyltransferase AS fusion protein, HLA-A2, HLA-A11, Hsp-70-1B, MART-2, ME1, MUM-1, MUM-2, MUM-3, Myosin class I, NFYC, neo-PAP, OGT, OS-9, p53, pml-RARalpha fusion protein, PRDX5, PTPRK, K-Ras, N-Ras, RBAF600, sirtuin-2, SNRPD1, SYT-SSX1/SSX2 fusion protein, TGF-beta receptor II, etc. Additional neoantigen peptides may include SF3B1 peptides, MYD peptides, TP53 peptides, Abl peptides, FBXW7 peptides, MAPK peptides, and GNB1 peptides disclosed in US patent publication NO.: 20110293637; the contents of which are incorporated herein by reference in their entirety.

[0233] New neoantigens identified through large-scale sequencing and algorithm calculation may also be included. See, e.g., International Patent Publication NO.: WO2014/168874; Nishimura et al., *Cancer Sci.* 2015, 106(5): 505-511; and Linnemann et al., *Nat. Med.*, 2015, 21(1): 81-85; the contents of each of which are incorporated herein by reference in their entirety.

[0234] A tumor associated antigen (TAA) may be an overexpressed or accumulated antigen that is expressed by both normal and neoplastic tissue, with the level of expression highly elevated in cancer tissues. Numerous proteins (e.g. oncogenes) are up-regulated in tumor tissues, including but not limited to adipophilin, AIM-2, ALDH1A1, BCLX(L), BING-4, CALCA, CD45, CD274, CPSF, cyclin D1, DKK1, ENAH, epCAM, ephA3, EZH2, FGF5, G250, HER-2/neu, HLA-DOB, Hepsin, IDO1, IGFB3, IL13Ralpha2, Intestinal carboxyl esterase, kallikrein 4, KIF20A, lengsin, M-CSF, MCSP, mdm-2, Meloe, Midkine, MMP-2, MMP-7, MUC-1, MUC5AC, p53, Pax5, PBF, PRAME, PSMA, RAGE-1, RGS5, RhoC,

RNF43, RU2A5, SECERNIN 1, SOX10, STEAP1, survivin, Telomerase, TPBG, VEGF, and WT1.

[0235] A TAA may be an oncofetal antigen that is typically only expressed at different stages during the development of the fetus and in cancerous somatic cells. Many proteins are normally expressed during fetal development but are transcriptionally repressed after birth or at early stage of infancy, therefore are not present, or are expressed in significantly lower levels in the corresponding normal adult tissue. Some of these developmental proteins are re-expressed in certain tumor cells and become oncofetal antigens. Examples of oncofetal antigens may include, but are not limited to CEA (carcinoembryonic antigen) in colorectal carcinoma, iLRP/OFA (immature laminin receptor protein/oncofetal antigen) in renal cell carcinoma (RCC), TAG-72 (tumor associated glycoprotein-72) in prostate carcinoma, AFP (alpha-fetoprotein) in hepatocellular carcinoma (HCC), ROR1 (a receptor tyrosine kinase) in many malignant cells such as brain tumors, sperm protein 17, HMGA2 (high mobility group A2) in ovarian carcinoma, oncofetal H19, CR-1 (Cripto-1, a member of epidermal growth factor (EGF)-CFC family), trophoblast glycoprotein precursor and GPC-3 (Glypican-3, a member of heparan sulphate proteoglycans) in HCC.

[0236] A TAA may be a cancer-testis antigen that is expressed only by cancer cells and adult reproductive tissues such as testis and placenta, including, but limited to antigens from BAGE family, CAGE family, HAGE family, GAGE family, MAGE family (e.g., MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A6 and MAGE-A13), SAGE family, XAGE family, MCAK, NA88-A (cancer/testis antigen 88), PSAD1, SSX-2, and SLLP-1.

[0237] A TAA may be a lineage restricted antigen that is expressed largely by a single cancer histotype, such as Melan-A/MART-1, Gp100/pmel17, Tyrosinase, TRP-1/-2, P. polypeptide, MC1R in melanoma; and prostate specific antigen (PSA) in prostate cancer.

[0238] A TAA may be an oncoviral antigen that is encoded by tumorigenic transforming viruses (also called oncogenic viruses). Oncogenic viruses, when they infect host cells, can insert their own DNA (or RNA) into that of the host cells. When the viral DNA or RNA affects the host cell's genes, it can push the cell toward becoming cancer. Oncogenic viruses include, but are not limited to, RNA viruses, and DNA viruses. Some examples of commonly known oncoviruses include human papilloma viruses (HPVs) which are main causes of cervical cancer, Epstein-Barr virus (EBV) which may cause nasopharyngeal cancer, certain types of fast-growing lymphomas (e.g., Burkitt lymphoma) and stomach cancer, hepatitis B, C and D viruses (HBV, HCV and HDV) in hepatocellular carcinoma (HCC), human immunodeficiency virus (HIV) which increases the risk of getting many types of cancer (e.g.,

liver cancer, anal cancer and Hodgkin cancer), Kaposi sarcoma herpes virus (KSHV; also known as human herpes virus 8 (HHV8)) which is linked to lymphoma, human T-lymphotrophic virus (HTLV-1) and merkel cell polymavirus (MCV). A viral antigen can be any defined antigen of a virus that is associated with a cancer in a human. For example, antigens from EBV may include but are not limited to, Epstein-Barr nuclear antigen-1 (EBNA1), latent membrane protein 1 (LMP1), or latent membrane protein 2 (LMP2).

[0239] A TAA may be an idiotypic antigen that is generated from highly polymorphic genes where a tumor cell expresses a specific "clonotype", i.e., as in B cell, T cell lymphoma/leukemia resulting from clonal aberrancies, such as Immunoglobulin and T cell receptors (TCRs). Idiotypic antigens are a class of non-pathogen-associated neoantigens. For example, the malignant B cells express rearranged and multiply mutated surface immunoglobulins (Ig). Tumor specific idiotypes (e.g., immunoglobulin idiotypes) are regarded as particularly attractive tumor-specific antigens that can be successfully targeted by immunotherapy (e.g., Alejandro et al., *Front Oncol.*, 2012, 2: 159).

4. T cell receptors (TCRs)

[0240] In some embodiments, payloads of the present invention may be T cell receptors (TCRs). The TCR may be specific to a cancer antigen, having a specific α chain and β chain which together form a TCR$\alpha\beta$ heterodimer, or having a specific γ chain and δ chain which together form a TCR$\gamma\delta$ heterodimer. The TCR may be a recombinant antigen specific T cell receptor.

[0241] The variable regions of α chain and β chain determine T cell specificity to an antigenic peptide presented by the major histocompatibility complex (MHC) class I and II molecules. The TCR recognition of the tumor antigen on the surface of a tumor cell presented by MHC molecules by TCR triggers T cell activation. The use of TCR gene therapy can equip a subject's own T cells with desired specificities and generate sufficient numbers of T cells to eradicate tumor cells. In some embodiments, a biocircuit or an effector module comprising a tumor specific TCR may be transduced into T cells and TCR-engineered T cells will be infused into cancer patients who have lymphocytopenia or lymphopenia by chemotherapy or irradiation, allowing efficient engraftment but inhibiting immune suppression.

[0242] Sequences encoding tumor antigen recognizing TCR chains can be obtained from tumor-reactive T cells (e.g., tumor-infiltrating lymphocytes isolated from the tumor of a patient).

[0243] According to the present invention, a TCR specific to tumor cells can be produced by methods described in International Patent Publication NO.: WO2014/083173; the contents of which are incorporated herein by reference in their entirety. A host organism expressing a transgene of a human leucocyte antigen (HLA) type which is known or suspected to be able to present a mutated tumor specific antigen (TSA) is transduced to express the un-rearranged human TCR loci. Preferably these loci encode TCR α and β chains, and preferably comprise a plurality, ideally all, of human TCR V, D, J, and/or C genes. The host organism is immunized with a cancer specific TSA or a peptide epitope derived from the TSA and T cells expressing rearranged TCRs specifically against the TSA are isolated and cloned. The TCR from the cloned T cells are sequenced (International Patent Publication NO.: WO2014/083173; the contents of which are incorporated herein by reference in their entirety).

[0244] In some embodiments, payloads of the present invention may be TCRs that specifically recognize TSAs, TAAs, or epitopes thereof, complexed with MHC molecules.

[0245] Exemplary tumor antigens that can be recognized by a TCR may include at least the following: 5T4, 707-AP, A33, AFP (α-fetoprotein), AKAP-4 (A kinase anchor protein 4), ALK, α5β1-integrin, androgen receptor, annexin II, alpha- actinin-4, ART-4, B1, B7H3, B7H4, BAGE (B melanoma antigen), BCMA, BCR-ABL fusion protein, beta-catenin, BKT-antigen, BTAA, CA-I (carbonic anhydrase I), CA50 (cancer antigen 50), CA125, CA15-3, CA195, CA242, calretinin, CAIX (carbonic anhydrase), CAMEL (cytotoxic T-lymphocyte recognized antigen on melanoma), CAM43, CAP-1, Caspase-8/m, CD4, CD5, CD7, CD19, CD20, CD22, CD23, CD25, CD27/m, CD28, CD30, CD33, CD34, CD36, CD38, CD40/CD154, CD41, CD44v6, CD44v7/8, CD45,CD49f, CD56, CD68\KP1, CD74, CD79a/CD79b, CD103, CD123, CD133, CD138, CD171, cdc27/m, CDK4 (cyclin dependent kinase 4), CDKN2A, CDS, CEA (carcinoembryonic antigen), CEACAM5, CEACAM6, chromogranin, c-Met, c-Myc, coa-1, CSAp, CT7, CT10, cyclophilin B, cyclin B1, cytoplasmic tyrosine kinases, cytokeratin, DAM-10, DAM-6, dek-can fusion protein, desmin, DEPDC1 (DEP domain containing 1), E2A-PRL, EBNA, EGF-R (epidermal growth factor receptor), EGP-1(epithelial glycoprotein -1) (TROP-2), EGP-2, EGP-40, EGFR (epidermal growth factor receptor), EGFRvIII, EF-2, ELF2M, EMMPRIN, EpCAM (epithelial cell adhesion molecule), EphA2, Epstein Barr virus antigens, Erb (ErbB1; ErbB3; ErbB4), ETA (epithelial tumor antigen), ETV6-AML1 fusion protein, FAP (fibroblast activation protein), FBP (folate-binding protein), FGF-5, folate receptor α, FOS related antigen 1, fucosyl GM1, G250, GAGE (GAGE-1; GAGE-2), galactin, GD2 (ganglioside), GD3, GFAP (glial fibrillary

acidic protein), GM2 (oncofetal antigen- immunogenic-1; OFA-I-1), GnT-V, Gp100, H4-RET, HAGE (helicase antigen), HER-2/neu, HIFs (hypoxia inducible factors), HIF-1α, HIF-2α, HLA-A2, HLA-A*0201-R170I, HLA-Al l, HMWMAA, Hom/Mel-40, HSP70-2M (Heat shock protein 70), HST-2, HTgp-175, hTERT (or hTRT), human papillomavirus-E6/human papillomavirus-E7 and E6, iCE (immune-capture EIA), IGF-1R, IGH-IGK, IL2R, IL5, ILK (integrin-linked kinase), IMP3 (insulin-like growth factor II mRNA-binding protein 3), IRF4 (interferon regulatory factor 4), KDR (kinase insert domain receptor), KIAA0205, KRAB-zinc finger protein (KID)-3; KID31, KSA (17-1A), K-ras, LAGE, LCK, LDLR/FUT (LDLR-fucosyltransferaseAS fusion protein), LeY (Lewis Y), MAD-CT-1, MAGE (tyrosinase, melanoma-associated antigen) (MAGE-1; MAGE-3), melan-A tumor antigen (MART), MART-2/Ski, MC1R (melanocortin 1 receptor), MDM2, mesothelin, MPHOSPH1, MSA(muscle-specific actin), mTOR (mammalian targets of rapamycin), MUC-1, MUC-2, MUM-1 (melanoma associated antigen (mutated) 1), MUM-2, MUM-3, Myosin/m, MYL-RAR, NA88-A, N-acetylglucosaminyltransferase, neo-PAP, NF-KB (nuclear factor-kappa B), neurofilament, NSE (neuron- specific enolase), Notch receptors, NuMa, N-Ras, NY-BR-1, NY- CO-1, NY-ESO-1, Oncostatin M, OS-9, OY-TES1, p53 mutants, p190 minor bcr-abl, pl5(58), pl85erbB2, pl80erbB-3, PAGE (prostate associated gene), PAP (prostatic acid phosphatase), PAX3, PAX5, PDGFR (platelet derived growth factor receptor), cytochrome P450 involved in piperidine and pyrrolidine utilization (PIPA), Pml-RAR alpha fusion protein, PR-3 (proteinase 3), PSA (prostate specific antigen), PSM, PSMA (Prostate stem cell antigen), PRAME (preferentially expressed antigen of melanoma), PTPRK, RAGE (renal tumor antigen), Raf (A-Raf, B-Raf and C-Raf), Ras, receptor tyrosine kinases, RCAS1, RGSS, ROR1 (receptor tyrosine kinase-like orphan receptor 1), RU1, RU2, SAGE, SART-1, SART-3, SCP-1, SDCCAG16, SP-17 (sperm protein 17), src-family, SSX (synovial sarcoma X breakpoint)-1, SSX-2(HOM-MEL-40), SSX-3, SSX-4, SSX-5, STAT-3, STAT-5, STAT-6, STEAD, STn, survivin, syk-ZAP70, TA-90 (Mac-2 binding protein\cyclophilin C-associated protein), TAAL6, TACSTD1 (tumor associated calcium signal transducer 1), TACSTD2, TAG-72-4, TAGE, TARP (T cell receptor gamma alternate reading frame protein), TEL/AML1 fusion protein, TEM1, TEM8 (endosialin or CD248), TGFβ, TIE2, TLP, TMPRSS2 ETS fusion gene, TNF-receptor (TNF-α receptor, TNF-β receptor; or TNF-γ receptor), transferrin receptor, TPS, TRP-1 (tyrosine related protein 1), TRP-2, TRP-2/INT2, TSP-180, VEGF receptor, WNT, WT-1 (Wilm's tumor antigen) and XAGE.

[0246] In one aspect, the payload of the present invention may be a TCR specifically recognizing Her2/neu epitope which has nucleic acid sequences of α chain and β chain disclosed in U.S. Patent Publication NO.: US20110280894 and International Patent Publication NO. WO2016133779A1; the contents of each of which are incorporated herein by reference in their entirety. In another aspect, the payload of the present invention may be a TCR specific to TSA tyrosinase (See US Pat. NO.: 8, 697,854; the contents of which are incorporated herein by reference in their entirety).

[0247] In other aspects, payloads of the present invention may be TCRs having polypeptide sequences specific to synovial sarcoma X Breakpoint (SSX)-2 antigen (U.S. Pat. NO.: 9,345,748); human papillomavirus (HPV) 16 E6 antigen (International Patent Publication NO.: WO2015/009606); cytomegalovirus (CMV) phosphoprotein pp65 (US Pat. NO.: 8,722,048); and WT-1 specific TCR comprising a TCR α-chain having an amino acid sequence as set forth in any one of SEQ ID NOs.: 5-8, and comprising a TCR β-chain having an amino acid sequence as set forth in SEQ ID NO.: 12 or 13, as disclosed in US patent publication NO.: US2016/0083449; the contents of each of which are incorporated herein by reference in their entirety.

[0248] In some embodiments, the TCR specific to a TSA may be modified to possess a sequence encoding an affinity weakening motif which imparts a reduction in non-specific binding to a TSA. In some embodiments, an affinity weakening motif having a modification to a TCR CDR1 or CDR2 region may be used to weaken the interaction between TCR and HLA proteins (see, International Patent Publication NO.: WO2016/014725; the contents of which are incorporated herein by reference in their entirety).

[0249] In some embodiments, the TCR specific to a TSA may be modified to possess an affinity enhancing motif which imparts an enhancement of binding specificity and affinity for a target antigen. In some embodiments, such high affinity TCRs may be generated by using TCR α-chain to select *de novo* generated TCR β-chains that pair with an antigen specific TCR α-chain during T cell development *in vitro* to form enhanced TCRs (see, International Patent Publication NO.: WO2013/ 166321; the contents of which are incorporated herein by reference in their entirety). In other embodiments, the modified TCR may also possess a sequence encoding an affinity enhancing modification CDR3 region which strengthens the interaction between the TCR and the TSA.

[0250] In one embodiment, the TCR specific to a TSA may be modified using zinc finger nucleases (ZFNs), TALENs or a CRISPR/Cas system. The TCR α chain and β chain may contain target sites of a nuclease. The nuclease can cleave the TCR sequence causing a

certain degree of disruption of the TCR (see US Patent Publication NO.: US2014/0301990; the contents of which are incorporated herein by reference in their entirety).

[0251] In one embodiment, the TCR specific to a TSA may be a soluble single-chain TCR having the structure: Vα2-L-Vβ or Vβ-L-Vα2, wherein L is a linker peptide that links a TCR variable β region (Vβ) with a TCR variable α region of the family 2 (Vα2), as discussed in International Patent Publication NO.: WO2011/044186; the contents of which are incorporated herein by reference in their entirety.

[0252] In one embodiment, the TCR specific to a TSA may be maturated to increase its affinity to the TSA according to methods described in US Patent Publication NO.: US2014/0065111; the contents of which are incorporated herein by reference in their entirety.

[0253] In some embodiments, the TCRs may be specific to the Fc domain of an antibody (e.g. FcgRIa) and utilized to enhance efficacy of antibody mediated therapy, as discussed in International Patent Publication NO.: WO2015/179833; the contents of which are incorporated herein by reference in their entirety.

[0254] In some embodiments, payloads of the present invention may be recombinant constructs which act as trifunctional T-cell signaling couplers (TriTACs) mimicking the naturally signaling through T cell receptors. The TriTACs enhance chimeric receptor activity while retaining MHC unrestricted targeting. In some aspects, the recombinant construct may comprise a target specific binding ligand such as a scFV specific to a TSA or a designed ankyrin repeat (DARPin), a ligand that binds a protein associated with the TCR complex and a TCR signaling domain polypeptide, e.g. as described in the International Patent Application NO.: WO2015/117229; the contents of which are incorporated herein by reference in their entirety. The TCR associated proteins may be selected from CD3, ZAP70 9zeta-chain associated protein kinase 70), TYN and CD247. In some aspects, the ligand of a TriTAC that binds the TCR associated protein may be an antibody or an antibody fragment (e.g., scFv). In other aspects, the TCR signaling domain polypeptide of a TriTAC may comprise the transmembrane and cytoplasmic domain of CD4.

[0255] According to the present invention, the α chain and β chain of the TCR of the present invention may be included in separate constructs, for example as payloads of two effector modules. In other embodiments, the α chain and β chain of the TCR of the present invention may be included in a single effector module as two payloads of the same effector module, for example as illustrated in Figures 3-6.

5. Chimeric antigen receptors (CARs)

[0256] In some embodiments, payloads of the present invention may be a chimeric antigen receptors (CARs) which when transduced into immune cells (e.g., T cells and NK cells), can re-direct the immune cells against the target (e.g., a tumor cell) which expresses a molecule recognized by the extracellular target moiety of the CAR.

[0257] As used herein, the term "chimeric antigen receptor (CAR)" refers to a synthetic receptor that mimics TCR on the surface of T cells. In general, a CAR is composed of an extracellular targeting domain, a transmembrane domain/region and an intracellular signaling/activation domain. In a standard CAR receptor, the components: the extracellular targeting domain, transmembrane domain and intracellular signaling/activation domain, are linearly constructed as a single fusion protein. The extracellular region comprises a targeting domain/moiety (e.g., a scFv) that recognizes a specific tumor antigen or other tumor cell-surface molecules. The intracellular region may contain a signaling domain of TCR complex (e.g., the signal region of CD3ζ), and/or one or more costimulatory signaling domains, such as those from CD28, 4-1BB (CD137) and OX-40 (CD134). For example, a "first-generation CAR" only has the CD3ζ signaling domain, whereas in an effort to augment T-cell persistence and proliferation, costimulatory intracellular domains are added, giving rise to second generation CARs having a CD3ζsignal domain plus one costimulatory signaling domain, and third generation CARs having CD3ζ signal domain plus two or more costimulatory signaling domains. A CAR, when expressed by a T cell, endows the T cell with antigen specificity determined by the extracellular targeting moiety of the CAR. Recently, it is also desirable to add one or more elements such as homing and suicide genes to develop a more competent and safer architecture of CAR, so called the fourth-generation CAR.

[0258] Cells such as T cells engineered to express a CAR can be redirected to attack target cells that express a molecule which can be recognized by the targeting moiety of the CAR.

[0259] In some embodiments, the extracellular targeting domain is joined through the hinge (also called space domain or spacer) and transmembrane regions to an intracellular signaling domain. The hinge connects the extracellular targeting domain to the transmembrane domain which transverses the cell membrane and connects to the intracellular signaling domain. The hinge may need to be varied to optimize the potency of CAR transformed cells toward cancer cells due to the size of the target protein where the targeting moiety binds, and the size and affinity of the targeting domain itself. Upon recognition and binding of the targeting moiety to the target cell, the intracellular signaling domain leads to an activation signal to the CAR T cell, which is further amplified by the "second signal" from

one or more intracellular costimulatory domains. The CAR T cell, once activated, can destroy the target cell.

[0260] In some embodiments, the CAR of the present invention may be split into two parts, each part is linked a dimerizing domain, such that an input that triggers the dimerization promotes assembly of the intact functional receptor. Wu and Lim recently reported a split CAR in which the extracellular CD19 binding domain and the intracellular signaling element are separated and linked to the FKBP domain and the FRB* (T2089L mutant of FKBP-rapamycin binding) domain that heterodimerize in the presence of the rapamycin analog AP21967. The split receptor is assembled in the presence of AP21967 and together with the specific antigen binding, activates T cells (Wu et al., *Science*, 2015, 625(6258): aab4077).

[0261] In some embodiments, the CAR of the present invention may be designed as an inducible CAR. Sakemura et al recently reported the incorporation of a Tet-On inducible system to the CD19 CAR construct. The CD19 CAR is activated only in the presence of doxycycline (Dox). Sakemura reported that Tet-CD19CAR T cells in the presence of Dox were equivalently cytotoxic against $CD19^+$ cell lines and had equivalent cytokine production and proliferation upon CD19 stimulation, compared with conventional CD19CAR T cells (Sakemura et al., *Cancer Immuno. Res.*, 2016, Jun 21, Epub ahead of print). In one example, this Tet-CAR may be the payload of the effector module under the control of SREs (e.g., DDs) of the invention. The dual systems provide more flexibility to turn-on and off the CAR expression in transduced T cells.

[0262] According to the present invention, the payload of the present invention may be a first-generation CAR, or a second-generation CAR, or a third-generation CAR, or a fourth-generation CAR. Representative effector module embodiments comprising CAR constructs are illustrated in Figures 13-18. In some embodiments, the payload of the present invention may be a full CAR construct composed of the extracellular domain, the hinge and transmembrane domain and the intracellular signaling region. In other embodiments, the payload of the present invention may be a component of the full CAR construct including an extracellular targeting moiety, a hinge region, a transmembrane domain, an intracellular signaling domain, one or more co-stimulatory domain, and other additional elements that improve CAR architecture and functionality including but not limited to a leader sequence, a homing element and a safety switch, or the combination of such components.

[0263] CARs regulated by biocircuits and compositions of the present invention are tunable and thereby offer several advantages. The reversible on-off switch mechanism allows

management of acute toxicity caused by excessive CAR-T cell expansion. Pulsatile CAR expression using SREs of the present invention may be achieved by cycling ligand level. The ligand conferred regulation of the CAR may be effective in offsetting tumor escape induced by antigen loss, avoiding functional exhaustion caused by tonic signaling due to chronic antigen exposure and improving the persistence of CAR expressing cells *in vivo*.

[0264] In some embodiments, biocircuits and compositions of the invention may be utilized to down regulate CAR expression to limit on target on tissue toxicity caused by tumor lysis syndrome. Down regulating the expression of the CARs of the present invention following anti-tumor efficacy may prevent (1) On target off tumor toxicity caused by antigen expression in normal tissue. (2) antigen independent activation *in vivo*.

Extracellular targeting domain/moiety

[0265] In accordance with the invention, the extracellular target moiety of a CAR may be any agent that recognizes and binds to a given target molecule, for example, a neoantigen on tumor cells, with high specificity and affinity. The target moiety may be an antibody and variants thereof that specifically binds to a target molecule on tumor cells, or a peptide aptamer selected from a random sequence pool based on its ability to bind to the target molecule on tumor cells, or a variant or fragment thereof that can bind to the target molecule on tumor cells, or an antigen recognition domain from native T- cell receptor (TCR) (e.g. CD4 extracellular domain to recognize HIV infected cells), or exotic recognition components such as a linked cytokine that leads to recognition of target cells bearing the cytokine receptor, or a natural ligand of a receptor.

[0266] In some embodiments, the targeting domain of a CAR may be a Ig NAR, a Fab fragment, a Fab' fragment, a F(ab)'2 fragment, a F(ab)'3 fragment, Fv, a single chain variable fragment (scFv), a bis-scFv, a (scFv)2, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein (dsFv), a unitbody, a nanobody, or an antigen binding region derived from an antibody that specifically recognizes a target molecule, for example a tumor specific antigen (TSA). In one embodiment, the targeting moiety is a scFv antibody. The scFv domain, when it is expressed on the surface of a CAR T cell and subsequently binds to a target protein on a cancer cell, is able to maintain the CAR T cell in proximity to the cancer cell and to trigger the activation of the T cell. A scFv can be generated using routine recombinant DNA technology techniques and is discussed in the present invention.

[0267] In one embodiment, the targeting moiety of a CAR construct may be an aptamer such as a peptide aptamer that specifically binds to a target molecule of interest. The peptide

aptamer may be selected from a random sequence pool based on its ability to bind to the target molecule of interest.

[0268] In some embodiments, the targeting moiety of a CAR construct may be a natural ligand of the target molecule, or a variant and/or fragment thereof capable of binding the target molecule. In some aspects, the targeting moiety of a CAR may be a receptor of the target molecule, for example, a full-length human CD27, as a CD70 receptor, may be fused in frame to the signaling domain of CD3 ζ forming a CD27 chimeric receptor as an immunotherapeutic agent for CD70-positive malignancies (See, e.g., US patent publication NO.: US20130323214; the contents of which are incorporated by reference herein in their entirety).

[0269] In some embodiments, the targeting moiety of a CAR may recognize a tumor specific antigen (TSA), for example a cancer neoantigen which is restrictedly expressed on tumor cells.

[0270] As non-limiting examples, the CAR of the present invention may comprise the extracellular targeting domain capable of binding to a tumor specific antigen selected from 5T4, 707-AP, A33, AFP (α-fetoprotein), AKAP-4 (A kinase anchor protein 4), ALK, α5β1-integrin, androgen receptor, annexin II, alpha- actinin-4, ART-4, B1, B7H3, B7H4, BAGE (B melanoma antigen), BCMA, BCR-ABL fusion protein, beta-catenin, BKT-antigen, BTAA, CA-I (carbonic anhydrase I), CA50 (cancer antigen 50), CA125, CA15-3, CA195, CA242, calretinin, CAIX (carbonic anhydrase), CAMEL (cytotoxic T-lymphocyte recognized antigen on melanoma), CAM43, CAP-1, Caspase-8/m, CD4, CD5, CD7, CD19, CD20, CD22, CD23, CD25, CD27/m, CD28, CD30, CD33, CD34, CD36, CD38, CD40/CD154, CD41, CD44v6, CD44v7/8, CD45,CD49f, CD56, CD68\KP1, CD74, CD79a/CD79b, CD103, CD123, CD133, CD138, CD171, cdc27/m, CDK4 (cyclin dependent kinase 4), CDKN2A, CDS, CEA (carcinoembryonic antigen), CEACAM5, CEACAM6, chromogranin, c-Met, c-Myc, coa-1, CSAp, CT7, CT10, cyclophilin B, cyclin B1, cytoplasmic tyrosine kinases, cytokeratin, DAM-10, DAM-6, dek-can fusion protein, desmin, DEPDC1 (DEP domain containing 1), E2A-PRL, EBNA, EGF-R (epidermal growth factor receptor), EGP-1(epithelial glycoprotein -1) (TROP-2), EGP-2, EGP-40, EGFR (epidermal growth factor receptor), EGFRvIII, EF-2, ELF2M, EMMPRIN, EpCAM (epithelial cell adhesion molecule), EphA2, Epstein Barr virus antigens, Erb (ErbB1; ErbB3; ErbB4), ETA (epithelial tumor antigen), ETV6-AML1 fusion protein, FAP (fibroblast activation protein), FBP (folate-binding protein), FGF-5, folate receptor α, FOS related antigen 1, fucosyl GM1, G250, GAGE (GAGE-1; GAGE-2),

galactin, GD2 (ganglioside), GD3, GFAP (glial fibrillary acidic protein), GM2 (oncofetal antigen- immunogenic-1; OFA-I-1), GnT-V, Gp100, H4-RET, HAGE (helicase antigen), HER-2/neu, HIFs (hypoxia inducible factors), HIF-1α, HIF-2α, HLA-A2, HLA-A*0201-R170I, HLA-Al l, HMWMAA, Hom/Mel-40, HSP70-2M (Heat shock protein 70), HST-2, HTgp-175, hTERT (or hTRT), human papillomavirus-E6/human papillomavirus-E7 and E6, iCE (immune-capture EIA), IGF-1R, IGH-IGK, IL2R, IL5, ILK (integrin-linked kinase), IMP3 (insulin-like growth factor II mRNA-binding protein 3), IRF4 (interferon regulatory factor 4), KDR (kinase insert domain receptor), KIAA0205, KRAB-zinc finger protein (KID)-3; KID31, KSA (17-1A), K-ras, LAGE, LCK, LDLR/FUT (LDLR-fucosyltransferaseAS fusion protein), LeY (Lewis Y), MAD-CT-1, MAGE (tyrosinase, melanoma-associated antigen) (MAGE-1; MAGE-3), melan-A tumor antigen (MART), MART-2/Ski, MC1R (melanocortin 1 receptor), MDM2, mesothelin, MPHOSPH1, MSA(muscle-specific actin), mTOR (mammalian targets of rapamycin), MUC-1, MUC-2, MUM-1 (melanoma associated antigen (mutated) 1), MUM-2, MUM-3, Myosin/m, MYL-RAR, NA88-A, N-acetylglucosaminyltransferase, neo-PAP, NF-KB (nuclear factor-kappa B), neurofilament, NSE (neuron- specific enolase), Notch receptors, NuMa, N-Ras, NY-BR-1, NY- CO-1, NY-ESO-1, Oncostatin M, OS-9, OY-TES1, p53 mutants, p190 minor bcr-abl, pl5(58), pl85erbB2, pl80erbB-3, PAGE (prostate associated gene), PAP (prostatic acid phosphatase), PAX3, PAX5, PDGFR (platelet derived growth factor receptor), cytochrome P450 involved in piperidine and pyrrolidine utilization (PIPA), Pml-RAR alpha fusion protein, PR-3 (proteinase 3), PSA (prostate specific antigen), PSM, PSMA (Prostate stem cell antigen), PRAME (preferentially expressed antigen of melanoma), PTPRK, RAGE (renal tumor antigen), Raf (A-Raf, B-Raf and C-Raf), Ras, receptor tyrosine kinases, RCAS1, RGSS, ROR1 (receptor tyrosine kinase-like orphan receptor 1), RU1, RU2, SAGE, SART-1, SART-3, SCP-1, SDCCAG16, SP-17 (sperm protein 17), src-family, SSX (synovial sarcoma X breakpoint)-1, SSX-2(HOM-MEL-40), SSX-3, SSX-4, SSX-5, STAT-3, STAT-5, STAT-6, STEAD, STn, survivin, syk-ZAP70, TA-90 (Mac-2 binding protein\cyclophilin C-associated protein), TAAL6, TACSTD1 (tumor associated calcium signal transducer 1), TACSTD2, TAG-72-4, TAGE, TARP (T cell receptor gamma alternate reading frame protein), TEL/AML1 fusion protein, TEM1, TEM8 (endosialin or CD248), TGFβ, TIE2, TLP, TMPRSS2 ETS fusion gene, TNF-receptor (TNF-α receptor, TNF-β receptor; or TNF-γ receptor), transferrin receptor, TPS, TRP-1 (tyrosine related protein 1), TRP-2, TRP-2/INT2, TSP-180, VEGF receptor, WNT, WT-1 (Wilm's tumor antigen) and XAGE.

[0271] In some embodiments, the CAR of the present invention may comprise a universal immune receptor which has a targeting moiety capable of binding to a labelled antigen. Methods of generating universal immune receptor CAR are discussed in International Patent Publication NO.: WO2013044225A1; the contents of which are incorporated herein by reference in their entirety.

[0272] In some embodiments, the CAR of the present invention may comprise the targeting moiety capable of binding to a pathogen antigen.

[0273] In some embodiments, the CAR of the present invention may comprise the targeting moiety capable of binding to non-protein molecules such as tumor-associated glycolipids and carbohydrates. TSAs may also be lipid molecules, polysaccharides, saccharides, nucleic acids, haptens, carbohydrate, or the combinations thereof.

[0274] In some embodiments, the CAR of the present invention may comprise the targeting moiety capable of binding to a component within the tumor microenvironment including proteins expressed in various tumor stroma cells including tumor associated macrophages (TAMs), immature monocytes, immature dendritic cells, immunosuppressive $CD4^+CD25^+$ regulatory T cells (Treg) and MDSCs. A recent study using an animal model, demonstrated that after systemic transplantation, T cells expressing VEGFR-2 CAR and IL12 infiltrated the tumors, expanded and persisted within tumor mass leading to tumor regression. The anti-tumor effect was dependent on targeting of IL12–responsive host cells via activation of VEGFR-2 CAR-T cells and release of IL12 (Chinnasamy et al., *Clinical Cancer Research*, 2012, 18: 1672-1683).

[0275] In some embodiments, the CAR of the present invention may comprise the targeting moiety capable of binding to a cell surface adhesion molecule, a surface molecule of an inflammatory cell that appears in an autoimmune disease, or a TCR causing autoimmunity.

[0276] As non-limiting examples, the targeting moiety of the present invention may be a scFv antibody that recognizes a tumor specific antigen (TSA), for example scFvs of antibodies SS, SS1 and HN1 that specifically recognize and bind to human mesothelin (US Pat. NO.: 9,359,447), scFv of antibody of GD2 (US Pat. NO.: 9,315,585), a CD19 antigen binding domain (U.S. Pat. NO.: 9, 328, 156); a NKG2D ligand binding domain (U.S. Pat. NO.: 9, 273,283; US patent publication NO.: US20160311906A1); human anti-mesothelin scFvs comprising the amino acid sequences of SEQ ID Nos.: 11 and 12 of US Pat. 9,272,002; an anti-CS1 binding agent (US patent publication NO.: US20160075784); an anti-BCMA binding domain (International Patent Publication NO.: WO2016/014565); anti-CD19 scFv

antibody of SEQ ID NO.: 20 in US Pat. NO.: 9,102,761; GFR alpha 4 antigen binding fragments having the amino acid sequences of SEQ ID NOs: 59 and 79 of International patent publication NO.: 2016/025880; anti-CLL-1 (C-type lectin-like molecule 1) binding domains having the amino acid sequences of SEQ ID N.O:47, 44, 48, 49, 50, 39, 40, 41, 42, 43, 45, 46, 51, 73, 70, 74, 75, 76, 65, 66, 67, 68, 69, 71, 72, 77, 195, 86, 83, 87, 88, 89, 78, 79, 80, 81, 82, 84, 85, 90 and 196 of International Patent Publication NO.: WO2016014535); CD33 binding domains having the amino acid sequences of SEQ ID NOs: 39-46 of International patent publication NO.: WO2016014576; a GPC3 (glypican-3) binding domain (SEQ ID NO.: 2 and SEQ ID NO.: 4 of International patent publication NO.: WO2016036973); a GFR alpha4 (Glycosyl-phosphatidylinositol (GPI)-linked GDNF family α -receptor 4 cell-surface receptor) binding domain (International Patent Publication NO.: WO2016025880); CD123 binding domains having the amino acid sequences of SEQ ID NOs: 480, 483, 485, 478, 158, 159, 160, 157, 217, 218, 219, 216, 276, 277, 278, and 275 of International patent publication NO.: WO20160258896; an anti-ROR1 antibody or fragments thereof (International patent publication NO.: WO2016016344); scFvs specific to GPC-3 (SEQ ID NOs: 1 and 24 of International patent publication NO.: WO2016049459); scFv for CSPG4 (SEQ ID NO.: 2 of International patent publication NO.: WO2015080981; scFv for folate receptor alpha (US Patent Publication NO.: US20170002072A1); the contents of each of which are incorporated herein by reference in their entirety.

[0277] In some embodiments, natural ligands may be used as the targeting moieties of the CARs of the present invention. Such natural ligands may be capable of binding to the antigens with affinity in the range of the scFvs and can redirect T cells specificity and effector functions to target cells expressing the complementary receptor. In some embodiments, the targeting moiety of the CAR may be neuregulin-1 (NRG1) which is a natural ligand for HER3 and HER4; VEGF which is a natural ligand of VEGFR; IL13 wildtype protein or IL13 mutein e.g E13Y which binds to IL13Ra2; NKG2D ligand, which is a natural ligand of NKG2D receptor; CD70 which is ligand of CD27; and a proliferation-inducing ligand (APRIL) which is a natural high affinity ligand for BCMA8 and transmembrane activator and CAML interactor (TACI). Any of the ligand based BCMA CARs taught in the US Patent Publication No. US20160362467A1, the contents of which are incoporated by reference in their entirety.

[0278] In some embodiments, the targeting moieties of the present invention may be scFv comprising the amino acid sequences in Table 11.

Table 11: scFv sequences

Target	Description	SEQ ID NO	Source
Activated alpha.v. Beta.3 integrin receptor	scFv	5474	SEQ ID NO. 8 in US20090117096A1
Activated alpha.v. Beta.3 integrin receptor	scFv	5475	SEQ ID NO.2 in US20090117096A1
Activated alpha.v. Beta.3 integrin receptor	scFv	5476	SEQ ID NO.4 in US20090117096A1
Adalimumab	scFv	5477	SEQ ID NO. 41 in US20160208021
Adalimumab	scFv	5478	SEQ ID NO.41 in WO2016112870
ALK	scFv	5479	SEQ ID NO. 17 in WO2015069922
ALK	scFv	5480	SEQ ID NO. 18 in WO2015069922
ALK	scFv	5481	SEQ ID NO. 19 in WO2015069922
ALK	scFv	5482	SEQ ID NO. 20 in WO2015069922
ALK	scFv	5483	SEQ ID NO. 21 in WO2015069922
ALK	scFv	5484	SEQ ID NO. 22 in WO2015069922
ALK	scFv	5485	SEQ ID NO. 23 in WO2015069922
ALK	scFv	5486	SEQ ID NO. 17 in US20160280798A1
ALK	scFv	5487	SEQ ID NO. 18 in US20160280798A1
ALK	scFv	5488	SEQ ID NO. 19 in US20160280798A1
ALK	scFv	5489	SEQ ID NO. 20 in US20160280798A1
ALK	scFv	5490	SEQ ID NO. 21 in US20160280798A1
ALK	scFv	5491	SEQ ID NO. 22 in US20160280798A1
ALK	scFv	5492	SEQ ID NO. 23 in US20160280798A1
ALK	scFv	5493	SEQ ID NO. 24 in US20160280798A1
ALK	scFv	5494	SEQ ID NO. 24 in WO2015069922
B7H3	scFv	5495	SEQ ID NO. 100 in WO2016033225
B7H3	scFv	5496	SEQ ID NO. 101 in WO2016033225
B7H3	scFv	5497	SEQ ID NO. 102 in WO2016033225
B7H3	scFv	5498	SEQ ID NO. 103 in WO2016033225
B7H3	scFv	5499	SEQ ID NO. 104 in WO2016033225
B7H3	scFv	5500	SEQ ID NO. 105 in WO2016033225
B7H3	scFv	5501	SEQ ID NO. 17 in WO2016033225
B7H3	scFv	5502	SEQ ID NO. 18 in WO2016033225
B7H3	scFv	5503	SEQ ID NO. 19 in WO2016033225
B7H3	scFv	5504	SEQ ID NO. 20 in WO2016033225
B7H3	scFv	5505	SEQ ID NO. 21 in WO2016033225
B7H3	scFv	5506	SEQ ID NO. 22 in WO2016033225
B7H3	scFv	5507	SEQ ID NO. 23 in WO2016033225
B7H3	scFv	5508	SEQ ID NO. 24 in WO2016033225
B7H3	scFv	5509	SEQ ID NO. 25 in WO2016033225
B7H3	scFv	5510	SEQ ID NO. 26 in WO2016033225
B7H3	scFv	5511	SEQ ID NO. 27 in WO2016033225
B7H3	scFv	5512	SEQ ID NO. 87 in WO2016033225
B7H3	scFv	5513	SEQ ID NO. 88 in WO2016033225
B7H3	scFv	5514	SEQ ID NO. 89 in WO2016033225
B7H3	scFv	5515	SEQ ID NO. 90 in WO2016033225
B7H3	scFv	5516	SEQ ID NO. 91 in WO2016033225
B7H3	scFv	5517	SEQ ID NO. 92 in WO2016033225
B7H3	scFv	5518	SEQ ID NO. 94 in WO2016033225
B7H3	scFv	5519	SEQ ID NO. 95 in WO2016033225
B7H3	scFv	5520	SEQ ID NO. 96 in WO2016033225
B7H3	scFv	5521	SEQ ID NO. 97 in WO2016033225
B7H3	scFv	5522	SEQ ID NO. 98 in WO2016033225

B7H3	scFv	5523	SEQ ID NO. 99 in WO2016033225
B7H4	scFv	5524	SEQ ID NO. 1 in WO2013067492
B7H4	scFv	5525	SEQ ID NO. 2 in WO2013067492
B7H4	scFv	5526	SEQ ID NO. 3 in WO2013067492
B7H4	scFv	5527	SEQ ID NO. 4 in WO2013067492
B7H4	scFv	5528	SEQ ID NO. 1 in US9422351B2
BCMA	scFv	5529	SEQ ID NO.152 in WO2016168595A1
BCMA	scFv	5530	SEQ ID NO.158 in WO2016168595A1
BCMA	scFv	5531	SEQ ID NO.176 in WO2016168595A1
BCMA	scFv	5532	SEQ ID NO.182 in WO2016168595A1
BCMA	scFv	5533	SEQ ID NO.188 in WO2016168595A1
BCMA	scFv	5534	SEQ ID NO.200 in WO2016168595A1
BCMA	scFv	5535	SEQ ID NO.212 in WO2016168595A1
BCMA	scFv	5536	SEQ ID NO.218 in WO2016168595A1
BCMA	scFv	5537	SEQ ID NO.224 in WO2016168595A1
BCMA	scFv	5538	SEQ ID NO.284 in WO2016168595A1
BCMA	scFv	5539	SEQ ID NO.290 in WO2016168595A1
BCMA	scFv	5540	SEQ ID NO.296 in WO2016168595A1
BCMA	scFv	5541	SEQ ID NO.302 in WO2016168595A1
BCMA	scFv	5542	SEQ ID NO.314 in WO2016168595A1
BCMA	scFv	5543	SEQ ID NO.326 in WO2016168595A1
BCMA	scFv	5544	SEQ ID NO.344 in WO2016168595A1
BCMA	scFv	5545	SEQ ID NO. 129 in WO2016014565
BCMA	scFv	5546	SEQ ID NO. 130 in WO2016014565
BCMA	scFv	5547	SEQ ID NO. 131 in WO2016014565
BCMA	scFv	5548	SEQ ID NO. 132 in WO2016014565
BCMA	scFv	5549	SEQ ID NO. 133 in WO2016014565
BCMA	scFv	5550	SEQ ID NO. 134 in WO2016014565
BCMA	scFv	5551	SEQ ID NO. 135 in WO2016014565
BCMA	scFv	5552	SEQ ID NO. 136 in WO2016014565
BCMA	scFv	5553	SEQ ID NO. 138 in WO2016014565
BCMA	scFv	5554	SEQ ID NO. 139 in WO2016014565
BCMA	scFv	5555	SEQ ID NO. 140 in WO2016014565
BCMA	scFv	5556	SEQ ID NO. 141 in WO2016014565
BCMA	scFv	5557	SEQ ID NO. 142 in WO2016014565
BCMA	scFv	5558	SEQ ID NO. 143 in WO2016014565
BCMA	scFv	5559	SEQ ID NO. 144 in WO2016014565
BCMA	scFv	5560	SEQ ID NO. 145 in WO2016014565
BCMA	scFv	5561	SEQ ID NO. 146 in WO2016014565
BCMA	scFv	5562	SEQ ID NO. 147 in WO2016014565
BCMA	scFv	5563	SEQ ID NO. 148 in WO2016014565
BCMA	scFv	5564	SEQ ID NO. 149 in WO2016014565
BCMA	scFv	5565	SEQ ID NO. 263 in WO2016014565
BCMA	scFv	5566	SEQ ID NO. 264 in WO2016014565
BCMA	scFv	5567	SEQ ID NO. 265 in WO2016014565
BCMA	scFv	5568	SEQ ID NO. 266 in WO2016014565
BCMA	scFv	5569	SEQ ID NO. 271 in WO2016014565
BCMA	scFv	5570	SEQ ID NO. 273 in WO2016014565
BCMA	scFv	5571	SEQ ID NO. 273 in WO2016014565
BCMA	scFv	5572	SEQ ID NO. 39 in WO2016014565
BCMA	scFv	5573	SEQ ID NO. 40 in WO2016014565
BCMA	scFv	5574	SEQ ID NO. 41 in WO2016014565
BCMA	scFv	5575	SEQ ID NO. 42 in WO2016014565
BCMA	scFv	5576	SEQ ID NO. 43 in WO2016014565
BCMA	scFv	5577	SEQ ID NO. 44 in WO2016014565
BCMA	scFv	5578	SEQ ID NO. 45 in WO2016014565
BCMA	scFv	5579	SEQ ID NO. 46 in WO2016014565
BCMA	scFv	5580	SEQ ID NO. 47 in WO2016014565

BCMA	scFv	5581	SEQ ID NO. 48 in WO2016014565
BCMA	scFv	5582	SEQ ID NO. 49 in WO2016014565
BCMA	scFv	5583	SEQ ID NO. 50 in WO2016014565
BCMA	scFv	5584	SEQ ID NO. 51 in WO2016014565
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CD276	scFv	5926	SEQ ID NO. 19 in US20160053017
CD276	scFv	5927	SEQ ID NO. 28 in US20160053017
CD3	scFv	5928	SEQ ID NO. 46 in WO2015153912A1

CD3	scFv	5929	SEQ ID NO. 47 in WO2015153912A1
CD30	scFv	5930	SEQ ID NO 20 in WO2016116035A1
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CD33	scFv	5933	SEQ ID NO. 263 in WO2016014576
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CD33	scFv	5939	SEQ ID NO. 37 in WO2015092024A2
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CD33	scFv	5958	SEQ ID NO. 161 in WO2016115482A1
CD33	scFv	5959	SEQ ID NO. 162 in WO2016115482A1
CD33	scFv	5960	SEQ ID NO. 163 in WO2016115482A1
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CD33/CD3sBiSpecifc	scFv	5962	SEQ ID NO.34 in WO2014144722A2
CD33/CD3sBiSpecifc	scFv	5963	SEQ ID NO.84 in WO2014144722A2
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CD37		5965	SEQ ID NO. 22 in US20170000900
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CEA	scFv	5993	SEQ ID NO. 22 in US20140242701A1
CEA	scFv	5994	SEQ ID NO. 22 in US20140242701A1
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Centuximab	scFv	5996	SEQ ID NO. 37 in US20160208021
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Claudin	scFv	5998	SEQ ID NO.17 in WO2014179759A1
Claudin	scFv	5999	SEQ ID NO.5 in WO2016073649A1
Claudin	scFv	6000	SEQ ID NO.7 in WO2016073649A1
Claudin	scFv	6001	SEQ ID NO.9 in WO2016073649A1
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Claudin7	scFv	6003	SEQ ID NO. 165 in WO2016115482A1
Claudin8	scFv	6004	SEQ ID NO. 166 in WO2016115482A1
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CXCR4	scFv	6097	SEQ ID NO. 85 in US20110020218
CXCR4	scFv	6098	SEQ ID NO. 86 in US20110020218
CXCR4	scFv	6099	SEQ ID NO. 89 in US20110020218
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E7MC	scFv	6107	SEQ ID NO.230 in WO2016182957A1
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EGFRvIII	scFv	6158	SEQ ID NO. 174 in US20160311907A1
EGFRvIII	scFv	6159	SEQ ID NO. 38 in US9394368B2
EGFRvIII	scFv	6160	SEQ ID NO. 5 in US20160200819A1

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ERBB2	scFv	6163	SEQ ID NO. 27 in US20110059076A1
ERBB2	scFv	6164	SEQ ID NO. 1 in US7244826
ERBB2	scFv	6165	SEQ ID NO. 2 in US7244826
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FcRL5(FcReceptorLike5)	scFv	6272	SEQ ID NO. 786 in WO2016090337
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FcRL5(FcReceptorLike5)	scFv	6276	SEQ ID NO. 794 in WO2016090337

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FcRL5(FcReceptorLike5)	scFv	6279	SEQ ID NO. 800 in WO2016090337
FcRL5(FcReceptorLike5)	scFv	6280	SEQ ID NO. 802 in WO2016090337
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FcRL5(FcReceptorLike5)	scFv	6282	SEQ ID NO. 806 in WO2016090337
FcRL5(FcReceptorLike5)	scFv	6283	SEQ ID NO. 808 in WO2016090337
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FcRL5(FcReceptorLike5)	scFv	6324	SEQ ID NO. 890 in WO2016090337
FcRL5(FcReceptorLike5)	scFv	6325	SEQ ID NO. 892 in WO2016090337
FcRL5(FcReceptorLike5)	scFv	6326	SEQ ID NO. 894 in WO2016090337
FcRL5(FcReceptorLike5)	scFv	6327	SEQ ID NO. 896 in WO2016090337
FcRL5(FcReceptorLike5)	scFv	6328	SEQ ID NO.650 in WO2016090337
FcRL5(FcReceptorLike5)	scFv	6329	SEQ ID NO.678 in WO2016090337
Folate Receptor	scFv	6330	SEQ ID NO. 15 in US20170002072A1
FOLRl/CD3sBiSpecific	scFv	6331	SEQ ID NO.90 in WO2014144722A2
GCN4	scFv	6332	SEQ ID NO. 165 in WO2016168773A3
GCN4	scFv	6333	SEQ ID NO. 166 in WO2016168773A3
GCN4	scFv	6334	SEQ ID NO. 167 in WO2016168773A3

GCN4	scFv	6335	SEQ ID NO. 168 in WO2016168773A3
GCN4	scFv	6336	SEQ ID NO. 169 in WO2016168773A3
GCN4	scFv	6337	SEQ ID NO. 170 in WO2016168773A3
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GD2	scFv	6339	SEQ ID NO. 20 in WO2016134284
GD2	scFv	6340	SEQ ID NO. 21 in WO2016134284
GD2	scFv	6341	SEQ ID NO. 7 in WO2015132604
GD2	scFv	6342	SEQ ID NO. 8 in WO2015132604
GPC3	scFv	6343	SEQ ID NO. 1 in WO2016049459
GPC3	scFv	6344	SEQ ID NO. 12 in US20160208015A1
GPC4	scFv	6345	SEQ ID NO. 24 in WO2016049459
GPRC5D	scFv	6346	SEQ ID NO. 100 in WO2016090312
GPRC5D	scFv	6347	SEQ ID NO. 101 in WO2016090312
GPRC5D	scFv	6348	SEQ ID NO. 102 in WO2016090312
GPRC5D	scFv	6349	SEQ ID NO. 103 in WO2016090312
GPRC5D	scFv	6350	SEQ ID NO. 104 in WO2016090312
GPRC5D	scFv	6351	SEQ ID NO. 105 in WO2016090312
GPRC5D	scFv	6352	SEQ ID NO. 106 in WO2016090312
GPRC5D	scFv	6353	SEQ ID NO. 107 in WO2016090312
GPRC5D	scFv	6354	SEQ ID NO. 108 in WO2016090312
GPRC5D	scFv	6355	SEQ ID NO. 109 in WO2016090312
GPRC5D	scFv	6356	SEQ ID NO. 110 in WO2016090312
GPRC5D	scFv	6357	SEQ ID NO. 111 in WO2016090312
GPRC5D	scFv	6358	SEQ ID NO. 112 in WO2016090312
GPRC5D	scFv	6359	SEQ ID NO. 113 in WO2016090312
GPRC5D	scFv	6360	SEQ ID NO. 114 in WO2016090312
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GPRC5D	scFv	6371	SEQ ID NO. 313 in WO2016090312
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GPRC5D	scFv	6373	SEQ ID NO. 337 in WO2016090312
GPRC5D	scFv	6374	SEQ ID NO. 349 in WO2016090312
GPRC5D	scFv	6375	SEQ ID NO. 361 in WO2016090312
GPRC5D	scFv	6376	SEQ ID NO. 373 in WO2016090312
GPRC5D	scFv	6377	SEQ ID NO. 385 in WO2016090312
HER2/CD3	scFv	6378	SEQ ID N0.9 in WO2014144722A2
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Human collagen VII	scFv	6380	SEQ ID NO.34 in WO2016112870
Integrin Bivalent	scFv	6381	SEQ ID N0.2 in WO2009070753
Integrin Bivalent	scFv	6382	SEQ ID NO. 1 in WO2009070753
Ipilimumab	scFv	6383	SEQ ID NO. 39 in US20160208021
Ipilimumab	scFv	6384	SEQ ID NO.39 in WO2016112870
lL4	scFv	6385	SEQ ID NO. 17 in WO2009121847
lL4R	scFv	6386	SEQ ID NO. 16 in WO2009121847
Mec/CD3sBispecific	scFv	6387	SEQ ID NO.78 in WO2014144722A2
Mesothelin	scFv	6388	SEQ ID NO. 7 WO2015188141
Mesothelin	scFv	6389	SEQ ID NO 47 in WO2016090034
Mesothelin	scFv	6390	SEQ ID NO in 46 in WO2016090034
Mesothelin	scFv	6391	SEQ ID NO in 57 in WO2016090034
Mesothelin	scFv	6392	SEQ ID NO. 48 in WO2016090034

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Mesothelin	scFv	6396	SEQ ID NO. 53 in WO2016090034
Mesothelin	scFv	6397	SEQ ID NO. 54 in WO2016090034
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Mesothelin	scFv	6400	SEQ ID NO. 58 in WO2016090034
Mesothelin	scFv	6401	SEQ ID NO. 59 WO2016090034
Mesothelin	scFv	6402	SEQ ID NO. 62 in WO2016090034
Mesothelin	scFv	6403	SEQ ID NO. 64 in WO2016090034
Mesothelin	scFv	6404	SEQ ID NO. 65 in WO2016090034
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Mesothelin	scFv	6406	SEQ ID NO. 67 in WO2016090034
Mesothelin	scFv	6407	SEQ ID NO. 68 in WO2016090034
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Mesothelin	scFv	6409	SEQ ID NO. 7 WO2015188141
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Mesothelin	scFv	6417	SEQ ID NO. 12 in WO2013142034
Mesothelin	scFv	6418	SEQ ID NO.11 in WO2013063419
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MUC2	scFv	6420	SEQ ID NO.17 in US20160130357
MUC3	scFv	6421	SEQ ID NO.15 in US20160130357
MUC4	scFv	6422	SEQ ID NO.17 in US20160130357
Nivolumab	scFv	6423	SEQ ID NO. 38 in US20160208021
Nivolumab	scFv	6424	SEQ ID NO.38 in WO2016112870
NYBR1	scFv	6425	SEQ ID NO. 21 in US20160333422A1
NYBR1	scFv	6426	SEQ ID NO. 21 in WO2015112830
NYBR1		6427	SEQ ID NO. 18 in WO2015112830
NYBR1		6428	SEQ ID NO. 19 in WO2015112830
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O acetylated GD2 ganglioside	scFv	6430	SEQ ID NO. 31 in US20150140023
OX40	scFv	6431	SEQ ID NO. 33 in US20150190506
PD1	scFv	6432	SEQ ID NO.39 in US20160311917A1
PD1	scFv	6433	SEQ ID NO.40 in US20160311917A1
PD1	scFv	6434	SEQ ID NO.41 in US20160311917A1
PD1	scFv	6435	SEQ ID NO.42 in US20160311917A1
PD1	scFv	6436	SEQ ID NO.43 in US20160311917A1
PD1	scFv	6437	SEQ ID NO.44 in US20160311917A1
PD1	scFv	6438	SEQ ID NO.45 in US20160311917A1
PD1	scFv	6439	SEQ ID NO.46 in US20160311917A1
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PD1	scFv	6449	SEQ ID NO.56 in US20160311917A1
PD1	scFv	6450	SEQ ID NO.57 in US20160311917A1

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PD1	scFv	6452	SEQ ID NO.59 in US20160311917A1
PD1	scFv	6453	SEQ ID NO.60 in US20160311917A1
PD1	scFv	6454	SEQ ID NO.61 in US20160311917A1
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PDL1	Nanobody	6456	SEQ ID NO.22 in US20110129458
PDL1	Nanobody	6457	SEQ ID NO.23 in US20110129458
PDL1	Nanobody	6458	SEQ ID NO.24 in US20110129458
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PDL1	Nanobody	6460	SEQ ID NO.26 in US20110129458
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PDL2	Nanobody	6467	SEQ ID NO.33 in US20110129458
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PRAME	scFv	6474	SEQ ID NO. 69 in WO2016191246A2
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PSMA	scFv	6476	SEQ ID NO.21 in WO2012145714
PSMA	scFv	6477	SEQ ID NO.30 in WO2012145714
PSMA	scFv	6478	SEQ ID NO.31 in WO2012145714
PSMA	scFv	6479	SEQ ID NO.34 in WO2012145714
PSMA	scFv	6480	SEQ ID NO.35 in WO2012145714
PSMA	Diabody	6481	SEQ ID NO.12 in WO2011069019
PSMA	Diabody	6482	SEQ ID NO.13 in WO2011069019
PSMA	Diabody	6483	SEQ ID NO.14 in WO2011069019
PSMA	Diabody	6484	SEQ ID NO.15 in WO2011069019
radiation inducible neoantigen	scFv	6485	SEQ ID NO 22 in WO2005042780A1
radiation inducible neoantigen	scFv	6486	SEQ ID NO 24 in WO2005042780A1
Ranibizuman	scFv	6487	SEQ ID NO. 40 in US20160208021
Ranibizuman	scFv	6488	SEQ ID NO.40 in WO2016112870
RAS	scFv	6489	SEQ ID NO.81 in WO2016154047
Rituximab	scFv	6490	SEQ ID NO. 36 in US20160208021
Rituximab	scFv	6491	SEQ ID NO.36 in WO2016112870
RORI	scFv	6492	SEQ ID NO. 34 in EP3083691A2
RORI	scFv	6493	SEQ ID NO. 249 in US20160208018A1
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RORI	scFv	6513	SEQ ID NO. 57 in EP3083671A1
RORI	scFv	6514	SEQ ID NO. 1 in US20160304619A1
RORI	scFv	6515	SEQ ID NO. 2 in US20160304619A1
RORI	scFv	6516	SEQ ID NO. 34 in WO2015092024A2
Teplizumab	scFv	6517	SEQ ID NO.42 in WO2016112870
Teplizumab(mutated)	scFv	6518	SEQ ID NO. 42 in US20160208021
TOSO	scFv	6519	SEQ ID No. 2 in EP3098237A1
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TRBC1	scFv	6523	SEQ ID NO. 14 in WO2015132598
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TRBC2	scFv	6542	SEQ ID NO. 32 in WO2015132598
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TSLPR	scFv	6544	SEQ ID NO. 2 in US20160311910A1
TSLPR	scFv	6545	SEQ ID NO. 1 in WO2015084513
TSLPR	scFv	6546	SEQ ID NO. 2 in WO2015084513
VEGF	scFv	6547	SEQ ID NO. 168 in US20160090427
VEGF	scFv	6548	SEQ ID NO. 169 in US20160090427
VEGF	scFv	6549	SEQ ID NO. 170 in US20160090427
VEGF	scFv	6550	SEQ ID NO. 171 in US20160090427
VEGF	scFv	6551	SEQ ID NO. 172 in US20160090427
VEGF	scFv	6552	SEQ ID NO. 173 US20160090427
VEGF	scFv	6553	SEQ ID NO. 174 in US20160090427
VEGF	scFv	6554	SEQ ID NO. 175 in US20160090427
VEGFR	scFv	6555	SEQ ID NO.498 in US20110177074A1
VEGFR	scFv	6556	SEQ ID NO.500 in US20110177074A1
VEGFR	scFv	6557	SEQ ID NO.502 in US20110177074A1
VEGFR	scFv	6558	SEQ ID NO.504 in US20110177074A1
VEGFR	scFv	6559	SEQ ID NO.506 in US20110177074A1
VEGFR	scFv	6560	SEQ ID NO.508 in US20110177074A1
VEGFR2	scFv	6561	SEQ ID NO. 1 in US20120213783
VEGFR2	scFv	6562	SEQ ID NO. 2 in US20120213783
WT1/HLA Bispecific	scFv	6563	SEQ ID NO.108 in WO2015070061
WT1/HLA Bispecific	scFv	6564	SEQ ID NO.113 in WO2015070061
WT1/HLA Bispecific	scFv	6565	SEQ ID NO.18 in WO2015070061
WT1/HLA Bispecific	scFv	6566	SEQ ID NO.36 in WO2015070061

WT1/HLA Bispecific	scFv	6567	SEQ ID NO.54 in WO2015070061
WT1/HLA Bispecific	scFv	6568	SEQ ID NO.72 in WO2015070061
WT1/HLA Bispecific	scFv	6569	SEQ ID NO.90 in WO2015070061
αfolate receptor(FRα)	scFv	6570	SEQ ID NO. 15 in WO2012099973
αfolate receptor(FRα)	scFv	6571	SEQ ID NO. 23 in WO2012099973

[0279] In one embodiment, the targeting moiety of the CAR may recognize CD19. CD19 is a well-known B cell surface molecule, which upon B cell receptor activation enhances B-cell antigen receptor induced signaling and expansion of B cell populations. CD19 is broadly expressed in both normal and neoplastic B cells. Malignancies derived from B cells such as chronic lymphocytic leukemia, acute lymphocytic leukemia and many non-Hodgkin lymphomas frequently retain CD19 expression. This near universal expression and specificity for a single cell lineage has made CD19 an attractive target for immunotherapies. Human CD19 has 14 exons wherein exon 1-4 encode the extracellular portion of the CD19, exon 5 encodes the transmembrane portion of CD19 and exons 6-14 encode the cytoplasmic tail. In one embodiment, the targeting moiety may comprise scFvs derived from the variable regions of the FMC63 antibody. FMC63 is an IgG2a mouse monoclonal antibody clone specific to the CD19 antigen that reacts with CD19 antigen on cells of the B lineage. The epitope of CD19 recognized by the FMC63 antibody is in exon 2 (Sotillo et al (2015) Cancer Discov ;5(12):1282-95; the contents of which are incorporated by reference in their entirety). In some embodiments, the targeting moiety of the CAR may be derived from the variable regions of other CD19 monoclonal antibody clones including but not limited to 4G7, SJ25C1, CVID3/429, CVID3/155, HIB19, and J3-119.

[0280] In some embodiments, the targeting moiety of a CAR may recognize a tumor specific antigen (TSA), for example a cancer neoantigen that is only expressed by tumor cells because of genetic mutations or alterations in transcription which alter protein coding sequences, therefore creating novel, foreign antigens. The genetic changes result from genetic substitution, insertion, deletion or any other genetic changes of a native cognate protein (i.e. a molecule that is expressed in normal cells). In the context of CD19, TSAs may include a transcript variant of human CD19 lacking exon 2 or lacking exon 5-6 or both (see International patent publication No. WO2016061368; the contents of which are incorporated herein by reference in their entirety). Since FMC63 binding epitope is in exon 2, CD19 lacking exon 2 is not recognized by FMC63 antibody. Thus, in some embodiments, the targeting moiety of the CAR may be an FMC63-distinct scFV. As used herein "FMC63-distinct" refers, to an antibody, scFv or a fragment thereof that is immunologically specific and binds to an epitope of the CD19 antigen that is different or unlike the epitope of CD19

antigen that is bound by FMC63. In some instances, targeting moiety may recognize a CD19 antigen lacking exon2. In one embodiment, the targeting moiety recognizes a fragment of CD19 encoded by exon 1, 3 and/or 4. In one example, the targeting moiety recognizes the epitope that bridges the portion of CD19 encoded by exon 1 and the portion of CD19 encoded by exon 3.

Intracellular signaling domains

[0281] The intracellular domain of a CAR fusion polypeptide, after binding to its target molecule, transmits a signal to the immune effector cell, activating at least one of the normal effector functions of immune effector cells, including cytolytic activity (e.g., cytokine secretion) or helper activity. Therefore, the intracellular domain comprises an "intracellular signaling domain" of a T cell receptor (TCR).

[0282] In some aspects, the entire intracellular signaling domain can be employed. In other aspects, a truncated portion of the intracellular signaling domain may be used in place of the intact chain as long as it transduces the effector function signal.

[0283] In some embodiments, the intracellular signaling domain of the present invention may contain signaling motifs which are known as immunoreceptor tyrosine-based activation motifs (ITAMs). Examples of ITAM containing cytoplasmic signaling sequences include those derived from TCR CD3zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d. In one example, the intracellular signaling domain is a CD3 zeta (CD3ζ) signaling domain.

[0284] In some embodiments, the intracellular region of the present invention further comprises one or more costimulatory signaling domains which provide additional signals to the immune effector cells. These costimulatory signaling domains, in combination with the signaling domain can further improve expansion, activation, memory, persistence, and tumor-eradicating efficiency of CAR engineered immune cells (e.g., CAR T cells). In some cases, the costimulatory signaling region contains 1, 2, 3, or 4 cytoplasmic domains of one or more intracellular signaling and /or costimulatory molecules. The costimulatory signaling domain may be the intracellular/cytoplasmic domain of a costimulatory molecule, including but not limited to CD2, CD7, CD27, CD28, 4-1BB (CD137), OX40 (CD134), CD30, CD40, ICOS (CD278), GITR (glucocorticoid-induced tumor necrosis factor receptor), LFA-1 (lymphocyte function-associated antigen- 1), LIGHT, NKG2C, B7-H3. In one example, the costimulatory signaling domain is derived from the cytoplasmic domain of CD28. In another example, the costimulatory signaling domain is derived from the cytoplasmic domain of 4-1BB (CD137). In another example, the co-stimulatory signaling domain may be an intracellular domain of

GITR as taught in U.S. Pat. NO.: 9, 175, 308; the contents of which are incorporated herein by reference in its entirety.

[0285] In some embodiments, the intracellular region of the present invention may comprise a functional signaling domain from a protein selected from the group consisting of an MHC class I molecule, a TNF receptor protein, an immunoglobulin-like protein, a cytokine receptor, an integrin, a signaling lymphocytic activation protein (SLAM) such as CD48, CD229, 2B4, CD84, NTB-A, CRACC, BLAME,CD2F-10, SLAMF6, SLAMF7, an activating NK cell receptor, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, IL15Ra, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, NKD2C SLP76, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, CD270 (HVEM), GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, DAP 10, TRIM, ZAP70, Killer immunoglobulin receptors (KIRs) such as KIR2DL1, KIR2DL2/L3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1/S1, KIR3DL2, KIR3DL3, and KIR2DP1; lectin related NK cell receptors such as Ly49, Ly49A, and Ly49C.

[0286] In some embodiments, the intracellular signaling domain of the present invention may contain signaling domains derived from JAK-STAT. In other embodiments, the intracellular signaling domain of the present invention may contain signaling domains derived from DAP-12 (Death associated protein 12) (Topfer et al., *Immunol.*, 2015, 194: 3201-3212; and Wang et al., Cancer Immunol., 2015, 3: 815-826). DAP-12 is a key signal transduction receptor in NK cells. The activating signals mediated by DAP-12 play important roles in triggering NK cell cytotoxicity responses toward certain tumor cells and virally infected cells. The cytoplasmic domain of DAP12 contains an Immunoreceptor Tyrosine-based Activation Motif (ITAM). Accordingly, a CAR containing a DAP12-derived signaling domain may be used for adoptive transfer of NK cells.

[0287] In some embodiments, T cells engineered with two or more CARs incorporating distinct co-stimulatory domains and regulated by distinct DD may be used to provide kinetic control of downstream signaling.

[0288] In some embodiments, the payload of the invention may be any of the co-stimulatory molecules and/or intracellular domains described herein. In some embodiments, one or more co-stimulatory molecules, each under the control of different SRE may be used in the present invention. SRE regulated co- stimulatory molecules may also be expressed in conjunction with a first-generation CAR, a second-generation CAR, a third-generation CAR, a fourth-generation, or any other CAR design described herein.

[0289] In some embodiments, the intracellular domain of the present invention may comprise amino acid sequences of Table 12.

Table 12: Intracellular signaling and co-stimulatory domains

Domain	Amino Acid Sequence	SEQ ID NO.
2B4 co-stimulatory domain	WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTF PGGGSTIYSMIQSQSSAPTSQEPAYTLYSLIQPSRKSGSRK RNHSPSFNSTIYEVIGKSQPKAQNPARLSRKELENFDVYS	6572
CD27 co-stimulatory domain	HQRRKYRSNKGESPVEPAEPCRYSCPREEEGSTIPIQEDY RKPEPACSP	6573
CD272 (BTLA1) co-stimulatory domain	RRHQGKQNELSDTAGREINLVDAKLKSEQTEASTRQNSQ VLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEENKPGIVY ASLNHSVIGPNSRLARNVKEAPTEYASICVRS	6574
CD272 (BTLA1) co-stimulatory domain	CCLRRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQ NSQVLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEENKP GIVYASLNHSVIGPNSRLARNVKEAPTEYASICVRS	6575
CD28 co-stimulatory	FWVLVVVGGVLACYSLLVTVAFIIFWV	6576
CD28 co-stimulatory domain	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGG CEL	6577
CD28 co-stimulatory domain	FWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRD FAAYRS	6578
CD28 co-stimulatory domain	RSKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAA YRS	6579
CD28 co-stimulatory domain	RSKRSRGGHSDYIVINMTPRRPGPTRKHYQPYAPPRDFA AYRS	6580
CD28 co-stimulatory signaling region	MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAVNLS CKYSYNLFSREFRASLHKGLDSAVEVCVVYGNYSQQLQ VYSKTGFNCDGKLGNESVTFYLQNLYVNQTDIYFCKIEV MYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVL VVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNM TPRRPGPTRKHYQPYAPPRDFAAYRS	6581
CD30 co-stimulatory domain	RRACRKRIRQKLHLCYPVQTSQPKLELVDSRPRRSSTQLR SGASVTEPVAEERGLMSQPLMETCHSVGAAYLESLPLQD ASPAGGPSSPRDLPEPRVSTEHTNNKIEKIYIMKADTVIVG TVKAELPEGRGLAGPAEPELEEELEADHTPHYPEQETEPP LGSCSDVMLSVEEEGKEDPLPTAASGK	6582
CD30 co-stimulatory domain	RRACRKRIRQKLHLCYPVQTSQPKLELVDSRPRRSSTQLR SGASVTEPVAEERGLMSQPLMETCHSVGAAYLESLPLQD ASPAGGPSSPRDLPEPRVSTEHTNNKIEKIYIMKADTVIVG	6583

	TVKAELPEGRGLAGPAEPELEEELEADHTPHYPEQETEPP LGSCSDVMLSVEEEGKEDPLPTAASGK	
GITR co-stimulatory domain	HIWQLRSQCMWPRETQLLLEVPPSTEDARSCQFPEEERG ERSAEEKGRLGDLWV	6584
HVEM co-stimulatory domain	CVKRRKPRGDVVKVIVSVQRKRQEAEGEATVIEALQAPP DVTTVAVEETIPSFTGRSPNH	6585
ICOS co-stimulatory domain	TKKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL	6586
ICOS co-stimulatory signaling domain	CWLTKKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVT L	6587
LAG-3 co-stimulatory region	HLWRRQWRPRRFSALEQGIHPPQAQSKIEELEQEPEPEPE PEPEPEPEPEPEQL	6588
OX40 co-stimulatory domain	ALYLLRRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTL AKI	6589
OX40 co-stimulatory domain	RRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI	6590
4-1BB intracellular domain	KRGRKKLLYIFKQPFMRPVQTIQEEDGCSCRFPEEEEGGC EL	6591
4-1BB signaling domain	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGG YEL	6592
4-1BB-CD3Zeta intracellular domain	TGTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLL YIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSR SADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR RGKGHDGLYQGLSTATKDTYDALHMQALPPR	6593
4-1BB-Z endodomain fusion	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGG CELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYS EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP PR	6594
CD127 intracellular domain	KRIKPIVWPSLPDHKKTLEHLCKKPRKNLNVSFNPESFLD CQIHRVDDIQARDEVEGFLQDTFPQQLEESEKQRLGGDV QSPNCPSEDVVITPESFGRDSSLTCLAGNVSACDAPILSSS RSLDCRESGKNGPHVYQDLLLSLGTTNSTLPPPFSLQSGIL TLNPVAQGQPILTSLGSNQEEAYVTMSSFYQNQ	6595
CD137 intracellular domain	RFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCEL	6596
CD148 intracellular domain	RKKRKDAKNNEVSFSQIKPKKSKLIRVENFEAYFKKQQA DSNCGFAEEYEDLKLVGISQPKYAAELAENRGKNRYNN VLPYDISRVKLSVQTHSTDDYINANYMPGYHSKKDFIAT QGPLPNTLKDFWRMVWEKNVYAIIMLTKCVEQGRTKCE EYWPSKQAQDYGDITVAMTSEIVLPEWTIRDFTVKNIQTS ESHPLRQFHFTSWPDHGVPDTTDLLINFRYLVRDYMKQS PPESPILVHCSAGVGRTGTFIAIDRLIYQIENENTVDVYGI VYDLRMHRPLMVQTEDQYVFLNQCVLDIVRSQKDSKVD LIYQNTTAMTIYENLAPVTTFGKTNGYIA	6597
CD27 intracellular domain	QRRKYRSNKGESPVEPAEPCHYSCPREEEGSTIPIQEDYR KPEPACSP	6598
CD28 intracellular domain	FAAYRS	6599
CD28 signaling chain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY MNMTPRRPGPTRKHYQPYAPPRDFAAYRS	6600
CD28 signaling domain	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAA YRS	6601
CD28 signaling domain	SKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAY RS	6602
CD28 signaling domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPF WVLVVVGGVLACYSLLVTVAFIIFWRSKRSRLLHSDYM NMTPRRPGPTRKHYQPYAPPRDFAAYRS	6603

CD28, 4-1BB, and/or CD3ζ signaling domain	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAA YRSRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCR FPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR	6604
CD28/CD3C	AAAIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPS KPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHS DYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRS ADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR RGKGHDGLYQGLSTATKDTYDALHMQALPPR	6605
CD28-0XZ intracellular domain	RSKRSRLLHSDYNMTPRRPGPTRKHYQPYAPPRDFAAYR SRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKIRVK FSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGR DPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	6606
CD28-4-1BB intracellular domain	MFWVLVVVGGVLACYSLLVTVAFIIFWVKRGRKKLLYIF KQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL	6607
CD28-4-1BB intracellular domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPF WVLVVVGGVLACYSLLVTVAFIIFWVKRGRKKLLYIFKQ PFMRPVQTTQEEDGCSCRFPEEEEGGCEL	6608
CD28-CD3 Zeta intracellular domain	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAA YRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYS EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP PR	6609
CD28-CD3Zeta intracellular domain	KRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYR SRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	6610
CD3 delta chain intracellular signaling domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSI TWVEGTVGTLLSDITRLDLGKRILDPRGIYRCNGTDIYKD KESTVQVHYRMCQSCVELDPATVAGIIVTDVIATLLLAL GVFCFAGHETGRLSGAADTQALLRNDQVYQPLRDRDDA QYSHLGGNWARNK	6611
CD3 delta chain intracellular signaling domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSI TWVEGTVGTLLSDITRLDLGKRILDPRGIYRCNGTDIYKD KESTVQVHYRTADTQALLRNDQVYQPLRDRDDAQYSHL GGNWARNK	6612
CD3 delta chain intracellular signaling domain	DQVYQPLRDRDDAQYSHLGGN	6613
CD3 delta intracellular domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSI TWVEGTVGTLLSDITRLDLGKRILDPRGIYRCNGTDIYKD KESTVQVHYRMCQSCVELDPATVAGIIVTDVIATLLLAL GVFCFAGHETGRLSGAADTQALLRNDQVYQPLRDRDDA QYSHLGGNWARNK	6614
CD3 delta intracellular domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSI TWVEGTVGTLLSDITRLDLGKRILDPRGIYRCNGTDIYKD KESTVQVHYRTADTQALLRNDQVYQPLRDRDDAQYSHL GGNWARNK	6615
CD3 delta intracellular domain	DQVYQPLRDRDDAQYSHLGGN	6616
CD3 epsilon intracellular domain	MQSGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYK VSISGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIGS DEDHLSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRA RVCENCMEMDVMSVATIVIVDICITGGLLLLVYYWSKNR KAKAKPVTRGAGAGGRQRGQNKERPPPVPNPDYEPIRK GQRDLYSGLNQRRI	6617

CD3 epsilon intracellular domain	NPDYEPIRKGQRDLYSGLNQR	6618
CD3 gamma intracellular domain	MEQGKGLAVLILAIILLQGTLAQSIKGNHLVKVYDYQED GSVLLTCDAEAKNITWFKDGKMIGFLTEDKKKWNLGSN AKDPRGMYQCKGSQNKSKPLQVYYRMCQNCIELNAATI SGFLFAEIVSIFVLAVGVYFIAGQDGVRQSRASDKQTLLP NDQLYQPLKDREDDQYSHLQGNQLRRN	6619
CD3 gamma intracellular domain	DQLYQPLKDREDDQYSHLQGN	6620
CD3 gamma intracellular domain	DQLYQPLKDREDDQYSHLQGN	6621
CD3 gamma intracellular domain	MEQGKGLAVLILAIILLQGTLAQSIKGNHLVKVYDYQED GSVLLTCDAEAKNITWFKDGKMIGFLTEDKKKWNLGSN AKDPRGMYQCKGSQNKSKPLQVYYRMCQNCIELNAATI SGFLFAEIVSIFVLAVGVYFIAGQDGVRQSRASDKQTLLP NDQLYQPLKDREDDQYSHLQGNQLRRN	6622
CD3 zeta intracellular domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILF IYGVILTALFLRVKFSRSADAPAYQQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR	6623
CD3 zeta intracellular domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILF IYGVILTALFLRVKFSRSADAPAYQQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR	6624
CD3 zeta intracellular domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILF IYGVILTALFLRVKFSRSADAPAYQQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR	6625
CD3 zeta intracellular domain	NQLYNELNLGRREEYDVLDKR	6626
CD3 zeta domain 2 (NM_000734.3)	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	6627
CD3 zeta intracellular domain	DGLYQGLSTATKDTYDALHMQ	6628
CD3 zeta intracellular domain	RVKFSRSAEPPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	6629
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIG MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	6630
CD3 zeta intracellular domain	RSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLD KRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEI GMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPP R	6631
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGEYDVLDKRRGRDPEMGGKPRRK NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGL YQGLSTATKDTYDALHMQALPPR	6632
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEVDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	6633
CD3 zeta intracellular domain	MIPAVVLLLLLLVEQAAALGEPQLCYILDAILFLVGIVLTL LVCRLKIQVRKAAITSYEKSRVKFSRSADAPAYQQGQNQ LYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG LYNELQKDKMAEAVSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR	6634

CD3 zeta intracellular domain	LRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	6635
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPQRRKNPQEGLY	6636
CD3 zeta intracellular domain	LRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEI GMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPP R	6637
CD3 zeta intracellular domain	RRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	6638
CD3 zeta intracellular domain	NQLYNELNLGRREEYDVLDKR	6639
CD3 zeta intracellular domain	EGLYNELQKDKMAEAYSEIGMK	6640
CD3 zeta intracellular domain	DGLYQGLSTATKDTYDALHMQ	6641
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	6642
CD3 zeta intracellular domain	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	6643
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALP	6644
CD3 zeta intracellular domain	DPKLCYLLDGILFIYGVILTALFLRVKFSRSADAPAYQQG QNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRK NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGL YQGLSTATKDTYDALHMQALPPR	6645
CD3 zeta intracellular domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILF IYGVILTALFLRVKFSRSADAPAYQQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR	6646
CD40 intracellular domain	RSRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI	6647
CD79A intracellular domain	MPGGPGVLQALPATIFLLFLLSAVYLGPGCQALWMHKV PASLMVSLGEDAHFQCPHNSSNNANVTWWRVLHGNYT WPPEFLGPGEDPNGTLIIQNVNKSHGGIYVCRVQEGNESY QQSCGTYLRVRQPPPRPFLDMGEGTKNRIITAEGIILLFCA VVPGTLLLFRKRWQNEKLGLDAGDEYEDENLYEGLNLD DCSMYEDISRGLQGTYQDVGSLNIGDVQLEKP	6648
CD79A intracellular domain	MPGGPGVLQALPATIFLLFLLSAVYLGPGCQALWMHKV PASLMVSLGEDAHFQCPHNSSNNANVTWWRVLHGNYT WPPEFLGPGEDPNEPPPRPFLDMGEGTKNRIITAEGIILLF CAVVPGTLLLFRKRWQNEKLGLDAGDEYEDENLYEGLN LDDCSMYEDISRGLQGTYQDVGSLNIGDVQLEKP	6649
CD79A intracellular domain	MPGGPGVLQALPATIFLLFLLSAVYLGPGCQALWMHKV PASLMVSLGEDAHFQCPHNSSNNANVTWWRVLHGNYT WPPEFLGPGEDPNGTLIIQNVNKSHGGIYVCRVQEGNESY QQSCGTYLRVRQPPPRPFLDMGEGTKNRIITAEGIILLFCA VVPGTLLLFRKRWQNEKLGLDAGDEYEDENLYEGLNLD DCSMYEDISRGLQGTYQDVGSLNIGDVQLEKP	6650
CD79A intracellular domain	ENLYEGLNLDDCSMYEDISRG	6651
CD8 intracellular domain	FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAA GGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCN HRNR	6652

CD8 intracellular domain	FVPVFLPAKPITTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNH RNR	6653
CD8a intracellular domain	PTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGL DFACDI	6654
CTLA4 intracellular domain	AVSLSKMLKKRSPLTTGVFVKMAPTEAECEKQFQPYFIPI N	6655
CTLA4 intracellular domain	AVSLSKMLKKRSPLTTGVYMNMTPRRPECEKQFQPYAPP RDFAAYRS	6656
DAP10 intracellular domain	RPRRSPAQDGKVYINMPGRG	6657
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSP GVLAGIVMGDLVLTVLIALAVYFLGRLVPRGRGAAEAA TRKQRITETESPYQELQGQRSDVYSDLNTQRPYYK	6658
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSP GVLAGIVMGDLVLTVLIALAVYFLGRLVPRGRGAAEATR KQRITETESPYQELQGQRSDVYSDLNTQRPYYK	6659
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGD LVLTVLIALAVYFLGRLVPRGRGAAEAATRKQRITETESP YQELQGQRSDVYSDLNTQRPYYK	6660
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGD LVLTVLIALAVYFLGRLVPRGRGAAEATRKQRITETESPY QELQGQRSDVYSDLNTQRPYYK	6661
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSP GVLAGIVMGDLVLTVLIALAVYFLGRLVPRGRGAAEAA TRKQRITETESPYQELQGQRSDVYSDLNTQRPYYK	6662
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSP GVLAGIVMGDLVLTVLIALAVYFLGRLVPRGRGAAEATR KQRITETESPYQELQGQRSDVYSDLNTQRPYYK	6663
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGD LVLTVLIALAVYFLGRLVPRGRGAAEAATRKQRITETESP YQELQGQRSDVYSDLNTQRPYYK	6664
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGD LVLTVLIALAVYFLGRLVPRGRGAAEATRKQRITETESPY QELQGQRSDVYSDLNTQRPYYK	6665
DAP12 intracellular domain	ESPYQELQGQRSDVYSDLNTQ	6666
DAP12 intracellular domain	ESPYQELQGQRSDVYSDLNTQ	6667
GITR intracellular domain	RSQCMWPRETQLLLEVPPSTEDARSCQFPEEERGERSAEE KGRLGDLWV	6668
ICOS intracellular domain	TKKKYSSSVHDPNGEFMFMRAVNTAKKSRLTDVTL	6669
IL 15Ra intracellular domain	KSRQTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHL	6670
OX40-CD3 Zeta intracellular domain	RRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKIRVK FSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGR DPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	6671
ZAP70 intracellular domain	MPDPAAHLPFFYGSISRAEAEEHLKLAGMADGLFLLRQC LRSLGGYVLSLVHDVRFHHFPIERQLNGTYAIAGGKAHC GPAELCEFYSRDPDGLPCNLRKPCNRPSGLEPQPGVFDCL RDAMVRDYVRQTWKLEGEALEQAIISQAPQVEKLIATTA HERMPWYHSSLTREEAERKLYSGAQTDGKFLLRPRKEQ GTYALSLIYGKTVYHYLISQDKAGKYCIPEGTKFDTLWQ LVEYLKLKADGLIYCLKEACPNSSASNASGAAAPTLPAH PSTLTHPQRRIDTLNSDGYTPEPARITSPDKPRPMPMDTS VYESPYSDPEELKDKKLFLKRDNLLIADIELGCGNFGSVR QGVYRMRKKQIDVAIKVLKQGTEKADTEEMMREAQIM HQLDNPYIVRLIGVCQAEALMLVMEMAGGGPLHKFLVG KREEIPVSNVAELLHQVSMGMKYLEEKNFVHRDLAARN VLLVNRHYAKISDFGLSKALGADDSYYTARSAGKWPLK	6672

	WYAPECINFRKFSSRSDVWSYGVTMWEALSYGQKPYKK MKGPEVMAFIEQGKRMECPPECPPELYALMSDCWIYKW EDRPDFLTVEQRMRACYYSLASKVEGPPGSTQKAEAAC A	
CD28 intracellular domain	MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAVNLS CKYSYNLFSREFRASLHKGLDSAVEVCVVYGNYSQQLQ VYSKTGFNCDGKLGNESVTFYLQNLYVNQTDIYFCKIEV MYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVL VVVGGVLACYSLLVTVAFIIFWVR	6673
4-1BB intracellular domain	MGNSCYNIVATLLLVLNFERTRSLQDPCSNCPAGTFCDN NRNQICSPCPPNSFSSAGGQRTCDICRQCKGVFRTRKECS STSNAECDCTPGFHCLGAGCSMCEQDCKQGQELTKKGC KDCCFGTFNDQKRGICRPWTNCSLDGKSVLVNGTKERD VVCGPSPADLSPGASSVTPPAPAREPGHSPQIISFFLALTST ALLFLLFFLTLRFSVVKRGRKKLLYIFKQPFMRPVQTTQE EDG	6674
Fc epsilon Receptor I gamma chain intracellular domain	MIPAVVLLLLLLVEQAAALGEPQLCYILDAILFLYGIVLTL LYCRLKIQVRKAAITSYEKSDGVYTGLSTRNQETYETLK HEKPPQ	6675
Fc epsilon Receptor I gamma chain intracellular domain	DGVYTGLSTRNQETYETLKHE	6676
Fc epsilon Receptor I gamma chain intracellular domain	DPKLCYILDAILFLYGIVLTLLYCRLKIQVRKAAITSYEKS DGVYTGLSTRNQETYETLKHEKPPQ	6677
Fc epsilon Receptor I gamma chain intracellular domain	DGVYTGLSTRNQETYETLKHE	6678

Transmembrane domains

[0290] In some embodiments, the CAR of the present invention may comprise a transmembrane domain. As used herein, the term "Transmembrane domain (TM)" refers broadly to an amino acid sequence of about 15 residues in length which spans the plasma membrane. More preferably, a transmembrane domain includes at least 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 amino acid residues and spans the plasma membrane. In some embodiments, the transmembrane domain of the present invention may be derived either from a natural or from a synthetic source. The transmembrane domain of a CAR may be derived from any naturally membrane-bound or transmembrane protein. For example, the transmembrane region may be derived from (i.e. comprise at least the transmembrane region(s) of) the alpha, beta or zeta chain of the T-cell receptor, CD3 epsilon, CD4, CD5, CD8, CD8α, CD9, CD16, CD22, CD33, CD28, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD152, or CD154.

[0291] Alternatively, the transmembrane domain of the present invention may be synthetic. In some aspects, the synthetic sequence may comprise predominantly hydrophobic residues such as leucine and valine.

[0292] In some embodiments, the transmembrane domain of the present invention may be selected from the group consisting of a CD8α transmembrane domain, a CD4 transmembrane domain, a CD 28 transmembrane domain, a CTLA-4 transmembrane domain, a PD-1

transmembrane domain, and a human Ig_{G4} Fc region. As non-limiting examples, the transmembrane domain may be a CTLA-4 transmembrane domain comprising the amino acid sequences of SEQ ID NOs.: 1-5 of International Patent Publication NO.: WO2014/100385; and a PD-1 transmembrane domain comprising the amino acid sequences of SEQ ID NOs.: 6-8 of International Patent Publication NO.: WO2014100385; the contents of each of which are incorporated herein by reference in their entirety.

[0293] In some embodiments, the CAR of the present invention may comprise an optional hinge region (also called spacer). A hinge sequence is a short sequence of amino acids that facilitates flexibility of the extracellular targeting domain that moves the target binding domain away from the effector cell surface to enable proper cell/cell contact, target binding and effector cell activation (Patel et al., *Gene Therapy*, 1999; 6: 412-419). The hinge sequence may be positioned between the targeting moiety and the transmembrane domain. The hinge sequence can be any suitable sequence derived or obtained from any suitable molecule. The hinge sequence may be derived from all or part of an immunoglobulin (e.g., IgGl, IgG2, IgG3, IgG4) hinge region, i.e., the sequence that falls between the CHI and CH2 domains of an immunoglobulin, e.g., an IgG4 Fc hinge, the extracellular regions of type 1 membrane proteins such as CD8α CD4, CD28 and CD7, which may be a wild type sequence or a derivative. Some hinge regions include an immunoglobulin CH3 domain or both a CH3 domain and a CH2 domain. In certain embodiments, the hinge region may be modified from an IgG1, IgG2, IgG3, or IgG4 that includes one or more amino acid residues, for example, 1, 2, 3, 4 or 5 residues, substituted with an amino acid residue different from that present in an unmodified hinge. Table 13 provides various transmembrane regions that can be used in the CARs described herein.

Table 13: Transmembrane domains

Transmembrane domain	Amino Acid Sequence	SEQ ID NO.
CD8 Transmembrane domain	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDI	6679
4-1BB Transmembrane domain	IISFFLALTSTALLFLLFFLTLRFSVVKRGR	6680
4-1BB Transmembrane domain	IISFFLALTSTALLFLLFFLTLRFSVV	6681
CD134 (OX40) Transmembrane domain	VAAILGLGLVLGLLGPLAILLALYLL	6682
CD148 Transmembrane and intracellular domain	AVFGCIFGALVIVTVGGFIFWRKKRKDAKNNEVSFSQIKP KKSKLIRVENFEAYFKKQQADSNCGFAEEYEDLKLVGISQ PKYAAELAENRGKNRYNNVLPYDISRVKLSVQTHSTDDYI NANYMPGYHSKKDFIATQGPLPNTLKDFWRMVWEKNVY AIIMLTKCVEQGRTKCEEYWPSKQAQDYGDITVAMTSEIV LPEVVTIRDFTVKNIQTSESHPLRQFHFTSWPDHGVPDTTD LLINFRYLVRDYMKQSPPESPILVHCSAGVGRTGTFIAIDR	6683

	LIYQIENENTVDVYGIVYDLRMHRPLMVQTEDQYVFLNQ CVLDIVRSQKDSKVDLIYQNTTAMTIYENLAPVTTFGKTN GYIA	
CD148 Transmembrane domain	AVFGCIFGALVIVTVGGFIFW	6684
CD2 Transmembrane domain	KEITNALETWGALGQDINLDIPSFQMSDDIDDIKWEKTSD KKKIAQFRKEKETFKEKDTYKLFKNGTLKIKHLKTDDQDI YKVSIYDTKGKNVLEKIFDLKIQERVSKPKISWTCINTTLT CEVMNGTDPELNLYQDGKHLKLSQRVITHKWTTSLSAKF KCTAGNKVSKESSVEPVSCPEKGLD	6685
CD28 Transmembrane and intracellular domain	IEVMYPPPYLDNEKSNGTITHVKGKHLCPSPLFPGPSKPFW VLVVVGGVLACYSLLVTVAHIFWVRSKRSRLLHSDYMN MTPRRPGPTRKHYQPYAPPRDFAAYRS	6686
CD28 Transmembrane domain	FWVLVVVGGVLACYSLLVTVAFIIFWV	6687
CD28 Transmembrane domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFW VLVVVGGVLACYSLLVTVAFIIFWV	6688
CD28 Transmembrane domain	IFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRR	6689
CD28 Transmembrane domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY MNMTPRRPGPTRKHYQP YAPPRDFAAYRS	6690
CD28 Transmembrane domain	MFWVLVVVGGVLACYSLLVTVAFIIFWV	6691
CD28 Transmembrane domain	FWVLVVVGGVLACYSLLVTVAFHFWV	6692
CD28 Transmembrane domain	MFWVLVVVGGVLACYSGGVTVAFIIFWV	6693
CD28 Transmembrane domain	WVLVVVGGVLACYSLLVTVAFIIFWV	6694
CD28 Transmembrane domain	PFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY MNMTPRRPGPTRKHYQPYAPPRDFAAYRS	6695
CD28 Transmembrane domain and CD28 and CD3 Zeta intracellular domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY MNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADA PAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQALPPR	6696
CD28 Transmembrane domain and CD28, OX40, and CD3 Zeta intracellular domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY MNMTPRRPGPTRKHYQPYAPPRDFAAYRSRDQRLPPDAH KPPGGGSFRTPIQEEQADAHSTLAKIRVKFSRSADAPAYQ QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPR	6697
CD28 Transmembrane domain and CD3 Zeta intracellular domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRRVKFSRSADAP AYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP RRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD GLYQGLSTATKDTYDALHMQALPPR	6698
CD28 transmembrane-CD3 zeta signaling domain (“28z”)	AAAIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSK PFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY MNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADA PAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQALPPR	6699
CD3 zeta Transmembrane domain	LCYLLDGILFIYGVILTALFLRV	6700
CD3 zeta Transmembrane domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFI YGVILTALFL	6701
CD3 zeta Transmembrane domain	LCYLLDGILFIYGVILTALFL	6702

CD4 Transmembrane domain	ALIVLGGVAGLLLFIGLGIFFCVRC	6703
CD4 Transmembrane domain	MALIVLGGVAGLLLFIGLGIFF	6704
CD45 Transmembrane and intracellular domain	ALIAFLAFLIIVTSIALLVVLYKIYDLHKKRSCNLDEQQELV ERDDEKQLMNVEPIHADILLETYKRKIADEGRLFLAEFQSI PRVFSKFPIKEARKPFNQNKNRYVDILPYDYNRVELSEING DAGSNYINASYIDGFKEPRKYIAAQGPRDETVDDFWRMI WEQKATVIVMVTRCEEGNRNKCAEYWPSMEEGTRAFGD VVVKINQHKRCPDYIIQKLNIVNKKEKATGREVTHIQFTS WPDHGVPEDPHLLLKLRRRVNAFSNFFSGPIWHCSAGVG RTGTYIGIDAMLEGLEAENKVDVYGYVVKLRRQRCLMV QVEAQYILIHQALVEYNQFGETEVNLSELHPYLHNMKKR DPPSEPSPLEAEFQRLPSYRSWRTQHIGNQEENKSKNRNSN VIPYDYNRVPLKHELEMSKESEHDSDESSDDDSDSEEPSK YINASFIMSYWKPEVMIAAQGPLKETIGDFWQMIFQRKVK VIVMLTELKHGDQEICAQYWGEGKQTYGDIEVDLKDTDK SSTYTLRVFELRHSKRKDSRTVYQYQYTNWSVEQLPAEP KELISMIQWKQKLPQKNSSEGNKHHKSTPLLIHCRDGSQQ TGIFCALLNLLESAETEEWDIFQWKALRKARPGMVSTFEQ YQFLYDVIASTYPAQNGQVKKNNHQEDKIEFDNEVDKVK QDANCVNPLGAPEKLPEAKEQAEGSEPTSGTEGPEHSVNG PASPALNQGS	6705
CD62L Transmembrane domain	PLFIPVAVMVTAFSGLAFIIWLA	6706
CD7 Transmembrane domain	ALPAALAVISFLLGLGLGVACVLA	6707
CD8 Transmembrane domain	MALPVTALLLPLALLLHAARP	6708
CD8 Transmembrane domain and CD28 signaling domain	AAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRP AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC NHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRD FAAYRSRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCS CRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNL GRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR	6709
CD8 transmembrane domain-CD137 (4-1BB) signaling domain and CD3 zeta signaling domain (“BBz”)	AAATTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYI FKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSA DAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGK GHDGLYQGLSTATKDTYDALHMQALPPR	6710
CD8a Transmembrane domain	FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHR N	6711
CD8a Transmembrane domain	IWAPLAGTCGVLLLSLVITLYC	6712
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYC	6713
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYCR	6714
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLVCR	6715
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVIT	6716
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLY	6717

CD8b Transmembrane domain	LGLLVAGVLVLLVSLGVAIHLCC	6718
EpoR Transmembrane domain	APVGLVARLADESGHVVLRWLPPPETPMTSHIRYEVDVS AGNGAGSVQRVEILEGRTECVLSNLRGRTRYTFAVRARM AEPSFGGFWSAWSEPVSLLTPSD	6719
FcERI a- Transmembrane domain	MAPAMESPTLLCVALLFFAPDGVLAVPQKPKVSLNPPWN RIFKGENVTLTCNGNNFFEVSSTKWFHNGSLSEETNSSLNI VNAKFEDSGEYKCQHQQVNESEPVYLEVFSDWLLLQASA EVVMEGQPLFLRCHGWRNWDVYKVIYYKDGEALKYWY ENHNISITNATVEDSGTYYCTGKVWQLDYESEPLNITVIKA PREKYWLQFFIPLLVVILFAVDTGLFISTQQQVTFLLKIKRT RKGFRLLNPHPKPNPKNN	6720
FceRIa Transmembrane domain	DIFIPLLVVILFAVDTGLFISTQQQVTFLLKIKRTRKGFRLL NPHPKPNPKNNR	6721
GITR Transmembrane domain	PLGWLTVVLLAVAACVLLLTSAQLGLHIWQL	6722
Her2 Transmembrane domain	SIISAVVGILLVVVLGVVFGILII	6723
Her2 Transmembrane domain	CHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVARCP SGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVDLDDKG CPAEQRASPLTSIISAVVGILLVVVLGVVFGILI	6724
ICOS Transmembrane domain	FWLPIGCAAFVVVCILGCILI	6725
IgG1Transmembrane domain	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKD	6726
OX40 Transmembrane domain	VAAILGLGLVLGLLGPLAILL	6727
Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYC	6728
Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYC	6729

[0294] Hinge region sequences useful in the present invention are provided in Table 14.

Table 14: Hinge regions

Hinge Domain	**Amino Acid Sequence**	**SEQ ID NO.**
Hinge	DKTHT	6730
Hinge	CPPC	6731
Hinge	CPEPKSCDTPPPCPR	6732
Hinge	ELKTPLGDTTHT	6733
Hinge	KSCDKTHTCP	6734
Hinge	KCCVDCP	6735
C233P Hinge	KYGPPCP	6736
C233S Hinge	VEPKSPDKTHTCPPCP	6737
CD28 Hinge	LDPKSSDKTHTCPPCP	6738
CD8a Hinge	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKP	6739
CD8a Hinge	GGAVHTRGLDFA	6740
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACD	6741

CD8a Hinge	AKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACD	6742
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACD	6743
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACD	6744
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDT	6745
CD8a Hinge	PAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIY	6746
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDIYIWAPLAGTCGVLLLSLVITLYC	6747
CD8a Hinge	TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACD	6748
Delta5 Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDIY	6749
EpoR Hinge	LDKTHTCPPCP	6750
FCRIIα Hinge	APVGLVARLADESGHVVLRWLPPPETPMTSHIRYEVDVS AGNGAGSVQRVEILEGRTECVLSNLRGRTRYTFAVRARM AEPSFGGFWSAWSEPVSLLTPSD	6751
FcγRIIIα Hinge	GLAVSTISSFFPPGYQ	6752
Hinge	GLAVSTISSFFPPGYQ	6753
Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	6754
Hinge	YVTVSSQDPAEPKSPDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGKKDPK	6755
Hinge	KPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFA	6756
Hinge	LEPKSCDKTHTCPPCP	6757
Hinge	KPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LD	6758
Hinge	EPKSCDKTHTCPPCP	6759
Hinge	ELKTPLGDTHTCPRCP	6760
Hinge	EPKSCDTPPPCPRCP	6761
Hinge	ESKYGPPCPSCP	6762
Hinge (CH2-CH3)	ERKCCVECPPCP	6763
Hinge (CH3)	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	6764
IgD Hinge	ESKYGPPCPPCPGQPREPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	6765

IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	6766
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLHPSL PPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCEV SGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWA WSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSY VTDH	6767
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMVVLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	6768
IgD Hinge	ESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEE KKKEKEKEEQEERETKTP	6769
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	6770
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	6771
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWA WSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSY VTDH	6772
IgG1 (CH2CH3) Hinge domain	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	6773
IgG1 (CH2CH3) Hinge domain	AEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIART PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE	6774

	QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKD	
IgG1 Hinge	AEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIART PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKD	6775
IgG1 Hinge	AEPKSPDKTHTCPPCPKDPK	6776
IgG1 Hinge	EPKSCDKTHTCPPCP	6777
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEVKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKD	6778
IgG1 Hinge	SVFLFPPKPKDTL	6779
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	6780
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKDPK	6781
IgG1 Hinge (CH2CH3 domain)	VECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK	6782
IgG2 Hinge	DPAEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIA RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKK	6783
IgG3 Hinge	ERKCCVECPPCP	6784
IgG3 Hinge	ELKTPLGDTTHTCPRCP	6785
IgG4 (CH2 and CH3)	ELKTPLGDTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPC PRCPEPKSCDTPPPCPRCP	6786
IgG4 (CH2 and CH3)	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKM	6787
IgG4 Hinge	ESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFQS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA	6788

	VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKM	
IgG4 Hinge	SPNMVPHAHHAQ	6789
IgG4 Hinge	GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK	6790
IgG4 Hinge	ESKYGPPCPPCPGGGSSGGGSGGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLSLGK	6791
IgG4 Hinge	ESKYGPPCPSCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHQAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFVPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	6792
IgG4 Hinge	ESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHQAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFVPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	6793
IgG4 Hinge	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKM	6794
IgG4 Hinge	ESKYGPPCPPCP	6795
IgG4 Hinge	ESKYGPPCPPCPGQPREPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	6796
IgG4 Hinge	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	6797
IgG4 Hinge	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	6798
IgG4 Hinge	YGPPCPPCP	6799
IgG4 Hinge	KYGPPCPPCP	6800
IgG4 Hinge	EVVKYGPPCPPCP	6801
IgG4 Hinge and Linker	ESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDLSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	6802
lgGl Hinge	ESKYGPPCPPCPGGGSSGGGSG	6803
lgGl Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS	6804

	DIAVEWESNGQPENNYKTIPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
IgGl Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTIPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	6805
IgGl Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	6806

[0295] In some embodiments, hinge domains and the transmembrane domains may be paired. The hinge domain may be present at the N terminus of the transmembrane domain, at C terminus of the transmembrane domain or within the transmembrane domain. Hinge and transmembrane region sequences which may be useful in the present invention are provided in Table 15.

Table 15: Paired Hinge and Transmembrane regions

Hinge Domain	Amino Acid Sequence	SEQ ID NO.
CD8a Transmembrane and Hinge	TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYIWAPLAGTCGVLLLSLVITLYC	6807
CD8a Transmembrane and Hinge	DIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQK PGNAPRLLISGATSLETGVPSRFSGSGSGKDYTLSITSLQTE DVATYYCQQYWSTPFTFGSGTKLEIKGGGGSGGGGSGGG GSQVQLKESGPGLVAPSQSLSITSTVSGFSLSRYSVHWVR QPPGKGLEWLGMIWGGGSTDYNSALKSRLSISKDNSKSQ VFLKMNSLQTDDTAMYYCARNEGDTTAGTWFAYWGQG TLVTVSS	6808
CD8a Transmembrane and Hinge	ALSNSIMYFSHFVPVFLPAKPTTTPAPRPPTPAPTIASQPLS LRPEACRPAAGGAVHTRGLD	6809
CD8a Transmembrane and Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDIYIWAPLAGTCGVLLLSLVITLY	6810
CD8a Transmembrane and Hinge	KPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDIYIWAPLAGTCGVLLLSLVITLY	6811

[0296] In some embodiments, the CAR of the present invention may comprise one or more linkers between any of the domains of the CAR. The linker may be between 1-30 amino acids long. In this regard, the linker may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 amino acids in length. In other embodiments, the linker may be flexible.

[0297] In some embodiments, the components including the targeting moiety, transmembrane domain and intracellular signaling domains of the present invention may be constructed in a single fusion polypeptide. The fusion polypeptide may be the payload of an effector module of the invention. In some embodiments, more than one CAR fusion polypeptides may be included in an effector module, for example, two, three or more CARs may be included in the effector module under the control of a single SRE (e.g., a DD). Representative effector modules comprising the CAR payload are illustrated in Figures 2-6.

[0298] In some embodiments, payloads of the present invention may comprise the CAR constructs including the extracellular targeting domain, transmembrane domain and intracellular signaling domains that are taught in the art, for example, a CAR targeting mesothelin (US Pat. NOs: 9,272, 002 and 9, 359,447); EGFRvIII specific CARs in US Pat. NO.: 9,266,960; anti-TAG CARs in US Pat. NO.: 9,233,125; CD19 CARs in US Patent publication NO.: 2016014533; CD19 CAR having the amino acid sequence of SEQ ID NO.: 24 of US Pat. NO.: 9, 328, 156; CD19 CARs in US Pat NOs: 8,911,993; 8,975,071; 9,101,584; 9,102,760; and 9,102,761; BCMA (CD269) specific CARs disclosed in International patent publication NOs: WO2016/014565 (SEQ ID Nos.: 109-113 and 213 to 233) and WO2016/014789; CLL-1(C-type lectin-like molecule 1) CARs comprising the amino acid sequences of SEQ ID NOs: 99, 96, 100, 101, 102, 91, 92, 93, 94, 95, 97, 98, 103, and 197 disclosed in International patent publication NO.: WO2016014535; CD33 specific CARs comprising the amino acid sequences of SEQ ID NOs: 48-56 in International patent publication NO.: WO2016014576; CD33 specific CARs comprising the amino acid sequences of SEQ ID NOs: 19-22, 27-30 and 35-38 in International patent publication NO.: WO2015150526; CD37 specific CARs encoded by the nucleic acids of SEQ ID NOs: 1-5 in US patent publication NO.: US20150329640; GPC3 CAR (International patent publication NO.: WO2016036973), GFR alpha 4 CARs having the amino acid sequences of SEQ ID NOs: 85, 86, 90, 92, 94, 96, 98, 100, 102, and 104 in International patent publication NO.: WO2016025880; CD123 CARs comprising the amino acid sequences of SEQ ID NO: 98, 99, 100 and 101 in International patent publication NOs: WO2016028896; CD123 specific multi-chain CARs in International patent publication NO: WO2015193406; CD123 CARS comprising the amino acid sequences of SEQ ID NO.: 160, 171, 188-197 in International patent publication NO: WO2016/120220; ROR-1 specific CARs comprising the amino acid sequences of SEQ ID NOs: 93, 95 and 117 in International patent publication NO.: WO2016/016344; ROR-1 specific multi-chain CARs in International patent publication NO.: WO2016/016343; trophoblast glycoprotein (5T4, TPBG) specific CARs comprising the

amino acid sequences of SEQ ID NOs: 21, 27, 33, 39, 23, 29, 34, 41, 19, 25, 31, 37, 20, 26, 32, 38, 22, 28, 34, 40, 24, 30, 36 and 42 in International patent publication NO.: WO2016034666; EGFRvIII specific CARs comprising the amino acid sequences of SEQ ID NOs: 15, 17, 24, 25, 26 and 27 in International patent publication NO.: WO2016016341; a TEM 8 CAR comprising the amino acid sequence of SEQ ID NO: 1 in International patent publication NO.: WO2014164544, a TEMl CAR comprising the amino acid sequence of SEQ ID NO:2 in International patent publication NO.: WO2014164544; GPC-3 CAR having the amino acid sequences of SEQ ID NOs: 3 and 26 in International patent publication NO.: WO2016/049459; a chondroitin sulfate proteoglycan-4 (CSPG4) CAR in International patent publication NO.: WO2015/080981; Kappa/lambda CARs in International patent publication NO.: WO2015/164739; GD2 CAR in International patent publication NO.: WO2016/134284; CLL1 CARs in International patent publication NO.: WO2016120218; CLL1 multi-subunit CARs in International patent publication NO.: WO2016120219; Hsp70 CARs in International patent publication NO.: WO2016120217; mAb-driven CARs in International patent publication NO.: WO2016120216; the contents of each of which are incorporated herein by reference in their entirety.

[0299] In some embodiments, the CAR constructs of the present invention may include CAIX (carboxy-anhydrase-IX (CAIX) specific CAR (Lamers et al., *Biochem Soc Trans*, 2016, 44(3): 951-959), HIV-1 specific CAR (Ali et al., *J Virol.*, 2016, May 25, pii: JVI.00805-16), CD20 specific CAR (Rufener et al., *Cancer Immunol. Res.*, 2016, 4(6): 509-519), a CD20/CD19 bispecific CAR (Zah et al., *Cancer Immunol Res.*, 2016, 4(6): 498-508), a CD22/CD19 CAR (International Publication No: WO2016/149578), a CD138/BCMA bi-specific CAR (International Publication No: WO2016/130598) an EGFR specific CARs and anti EGFR viii specific CAR; the contents of each of which are incorporated herein by reference in their entirety.

[0300] In some embodiments, the CAR sequences may be selected from Table 16.

Table 16: CAR sequences

Description	SEQ ID NO	Source
CD70 CAR	6812	SEQ ID NO. 99 in WO2015121454
Acid/Base Leucine zipper zip CAR	6813	SEQ ID NO. 34 in WO2016124930
Acid/Base Leucine zipper zip CAR	6814	SEQ ID NO. 35 in WO2016124930
ALK CAR	6815	SEQ ID NO. 43 in WO2015069922
ALK CAR	6816	SEQ ID NO. 44 in WO2015069922
ALK CAR	6817	SEQ ID NO. 45 in WO2015069922
ALK CAR	6818	SEQ ID NO. 46 in WO2015069922
ALK CAR	6819	SEQ ID NO. 47 in WO2015069922
ALK CAR	6820	SEQ ID NO. 48 in WO2015069922
ALK CAR	6821	SEQ ID NO. 49 in WO2015069922

ALK CAR	6822	SEQ ID NO. 50 in WO2015069922
ALK CAR	6823	SEQ ID NO. 51 in WO2015069922
ALK CAR	6824	SEQ ID NO. 52 in WO2015069922
ALK CAR	6825	SEQ ID NO. 53 in WO2015069922
ALK CAR	6826	SEQ ID NO. 54 in WO2015069922
ALK CAR	6827	SEQ ID NO. 55 in WO2015069922
ALK CAR	6828	SEQ ID NO. 56 in WO2015069922
ALK CAR	6829	SEQ ID NO. 57 in WO2015069922
ALK CAR	6830	SEQ ID NO. 58 in WO2015069922
ALK CAR	6831	SEQ ID NO. 59 in WO2015069922
ALK CAR	6832	SEQ ID NO. 60 in WO2015069922
ALK CAR	6833	SEQ ID NO. 61 in WO2015069922
ALK CAR	6834	SEQ ID NO. 62 in WO2015069922
ALK CAR	6835	SEQ ID NO. 63 in WO2015069922
ALK CAR	6836	SEQ ID NO. 64 in WO2015069922
ALK CAR	6837	SEQ ID NO. 65 in WO2015069922
ALK CAR	6838	SEQ ID NO. 66 in WO2015069922
ALK CAR	6839	SEQ ID NO. 67 in WO2015069922
ALK CAR	6840	SEQ ID NO. 68 in WO2015069922
ALK CAR	6841	SEQ ID NO. 69 in WO2015069922
ALK CAR	6842	SEQ ID NO. 70 in WO2015069922
ALK CAR	6843	SEQ ID NO. 71 in WO2015069922
ALK CAR	6844	SEQ ID NO. 72 in WO2015069922
ALK CAR	6845	SEQ ID NO. 73 in WO2015069922
ALK CAR	6846	SEQ ID NO. 74 in WO2015069922
ALK CAR	6847	SEQ ID NO. 75 in WO2015069922
ALK CAR	6848	SEQ ID NO. 76 in WO2015069922
ALK CAR	6849	SEQ ID NO. 77 in WO2015069922
ALK CAR	6850	SEQ ID NO. 78 in WO2015069922
ALK CAR	6851	SEQ ID NO. 79 in WO2015069922
ALK CAR	6852	SEQ ID NO. 80 in WO2015069922
ALK CAR	6853	SEQ ID NO. 81 in WO2015069922
ALK CAR	6854	SEQ ID NO. 82 in WO2015069922
ALK CAR	6855	SEQ ID NO. 83 in WO2015069922
ALK CAR	6856	SEQ ID NO. 84 in WO2015069922
ALK CAR	6857	SEQ ID NO. 85 in WO2015069922
ALK CAR	6858	SEQ ID NO. 86 in WO2015069922
ALK CAR	6859	SEQ ID NO. 87 in WO2015069922
ALK CAR	6860	SEQ ID NO. 88 in WO2015069922
ALK CAR	6861	SEQ ID NO. 89 in WO2015069922
ALK CAR	6862	SEQ ID NO. 90 in WO2015069922
APRIL IgG1 hinge based CAR	6863	SEQ ID NO: 53 in US20160296562A1
APRIL Fcpvaa based CAR	6864	SEQ ID NO: 52 in US20160296562A1
BCMA CAR	6865	SEQ ID NO:180 in WO2016168595A1
BCMA CAR	6866	SEQ ID NO:180 in WO2016168595A1
BCMA CAR	6867	SEQ ID NO:162 in WO2016168595A1
BCMA CAR	6868	SEQ ID NO:168 in WO2016168595A1
BCMA CAR	6869	SEQ ID NO:174 in WO2016168595A1
BCMA CAR	6870	SEQ ID NO:144 in WO2016168595A1
BCMA CAR	6871	SEQ ID NO:150 in WO2016168595A1
BCMA CAR	6872	SEQ ID NO:186 in WO2016168595A1
BCMA CAR	6873	SEQ ID NO:192 in WO2016168595A1
BCMA CAR	6874	SEQ ID NO:198 in WO2016168595A1
BCMA CAR	6875	SEQ ID NO:204 in WO2016168595A1
BCMA CAR	6876	SEQ ID NO:210 in WO2016168595A1
BCMA CAR	6877	SEQ ID NO:156 in WO2016168595A1
BCMA CAR	6878	SEQ ID NO:216 in WO2016168595A1
BCMA CAR	6879	SEQ ID NO:222 in WO2016168595A1

BCMA CAR	6880	SEQ ID NO:228 in WO2016168595A1
BCMA CAR	6881	SEQ ID NO:234 in WO2016168595A1
BCMA CAR	6882	SEQ ID NO:240 in WO2016168595A1
BCMA CAR	6883	SEQ ID NO:246 in WO2016168595A1
BCMA CAR	6884	SEQ ID NO:252 in WO2016168595A1
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CAR AND gate (CD19 AND CD33) CD148 phosphatase	7079	SEQ ID NO:2 in US20160296562A1
CAR AND gate (CD19 AND CD5)	7080	SEQ ID NO: 43 in US20160296562A1
CAR AND gate (CD19 AND EGFRvIII)	7081	SEQ ID NO: 45 in US20160296562A1
CAR AND gate (CD19 AND GD2)	7082	SEQ ID NO: 41 in US20160296562A1
CAR AND gate (CD19 OR CD33) CD45 phosphatase	7083	SEQ ID NO:3 in US20160296562A1
CAR AND NOT gate (CD19 AND NOT CD33)	7084	SEQ ID NO:4 in US20160296562A1
CAR AND NOT gate (CD19 AND NOT CD33)	7085	SEQ ID NO:5 in US20160296562A1
CAR AND NOT gate 1	7086	SEQ ID NO: 48 in US20160296562A1
CAR AND NOT gate 2	7087	SEQ ID NO: 49 in US20160296562A1
CAR AND NOT gate 3	7088	SEQ ID NO: 50 in US20160296562A1
CAR OR gate (CD19 OR CD33)	7089	SEQ ID NO:1 in US20160296562A1
CAT19 CAR with a CD28Zeta endodomain	7090	SEQ ID NO.12 in WO2016139487
CAT19 CAR with an OX40Zeta endodomain	7091	SEQ ID NO.11 in WO2016139487
CAT19 chimeric gen receptor (CAR) using Campana architecture	7092	SEQ ID NO.10 in WO2016139487
CD123 CAR	7093	SEQ ID NO. 69 in WO2016142532
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CD19 CAR	7336	SEQ ID NO: 25 in US20160333108A1

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CD19 CAR	7406	SEQ ID NO: 56 in US20160250258A1
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CD19 or CD33 CAR (a CAR OR gate which recognizes CD19 OR CD33)	7449	SEQ ID NO. 1 in WO2015075468
CD19CD20 CAR Bispecific CAR	7450	SEQ ID NO: 1308 in WO2016164731A2
CD19CD20 CAR Bispecific CAR	7451	SEQ ID NO: 2 in US9447194B2

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CD19CD20 CAR Bispecific CAR	7453	SEQ ID NO: 11 in US9447194B2
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CD2 CAR	7455	SEQ ID NO. 11 in WO2016138491
CD20 CAR	7456	SEQ ID NO: 25 in WO2015157399A9
CD20 NCAR	7457	SEQ ID NO: 177 in WO2016097231
CD20 NCAR	7458	SEQ ID NO: 181 in WO2016097231
CD20 NCAR	7459	SEQ ID NO: 182 in WO2016097231
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CD22CD19 Bispecific CAR	7544	SEQ ID NO: 1304 in WO2016164731A2
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CD33 CAR	7624	SEQ ID NO. 71 in WO2015150526A2
CD38 CAR	7625	SEQ ID NO: 70 in WO2016097231

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CD38 CAR	7627	SEQ ID NO: 72 in WO2016097231
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CD38 CAR	7631	SEQ ID NO: 67 in WO2016097231
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CD4 CAR	7638	SEQ ID NO. 14 in WO2016138491
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CD435 CAR	7640	SEQ ID NO: 5 in EP3074419A2
CD44 CAR	7641	SEQ ID NO.21 in WO2016042461A1
CD44 CAR	7642	SEQ ID NO.22 in WO2016042461A1
CD44 CAR	7643	SEQ ID NO.23 in WO2016042461A1
CD44 CAR	7644	SEQ ID NO.24 in WO2016042461A1
CD44 CAR	7645	SEQ ID NO.25 in WO2016042461A1
CD44 CAR	7646	SEQ ID NO.26 in WO2016042461A1
CD44 CAR	7647	SEQ ID NO.27 in WO2016042461A1
CD44 CAR	7648	SEQ ID NO.28 in WO2016042461A1
CD44 CAR	7649	SEQ ID NO.31 in WO2016042461A1
CD44 CAR	7650	SEQ ID NO.32 in WO2016042461A1
CD44 CAR	7651	SEQ ID NO.33 in WO2016042461A1
CD44 CAR	7652	SEQ ID NO.34 in WO2016042461A1
CD44 CAR	7653	SEQ ID NO.35 in WO2016042461A1
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CD7 CAR	7658	SEQ ID NO. 17 in WO2016138491
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CD70 CAR	7660	SEQ ID NO. 93 in WO2015121454
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CEA CAR	7670	SEQ ID NO. 30 in US20140242701A
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Chimeric VNARCAR 2	7672	SEQ ID NO: 106 in US20160333094A1
Chimeric VNARCAR 3	7673	SEQ ID NO: 107 in US20160333094A1
Chimeric VNARCAR 4	7674	SEQ ID NO: 108 in US20160333094A1
Chimeric VNARCAR 5	7675	SEQ ID NO: 109 in US20160333094A1
Chimeric VNARCAR 6	7676	SEQ ID NO: 110 in US20160333094A1
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PD1 CAR	8038	SEQ ID NO:73 in US20160311917A1
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PD1 CAR	8040	SEQ ID NO:75 in US20160311917A1
PD1 CAR	8041	SEQ ID NO:76 in US20160311917A1
PD1 CAR	8042	SEQ ID NO:77 in US20160311917A1
PD1 CAR	8043	SEQ ID NO:78 in US20160311917A1
PD1 CAR	8044	SEQ ID NO:79 in US20160311917A1
PD1 CAR	8045	SEQ ID NO:80 in US20160311917A1
PD1 CAR	8046	SEQ ID NO:81 in US20160311917A1
PD1 CAR	8047	SEQ ID NO:82 in US20160311917A1
PD1 CAR	8048	SEQ ID NO:83 in US20160311917A1
PD1 CAR	8049	SEQ ID NO:84 in US20160311917A1
PD1 CAR	8050	SEQ ID NO:85 in US20160311917A1
PD1 CAR	8051	SEQ ID NO:86 in US20160311917A1
PD1 CAR	8052	SEQ ID NO:26 in WO2016172537A1
PD1 CAR	8053	SEQ ID NO:39 in WO2016172537A1
PD1 CAR	8054	SEQ ID NO: 40 in US20160311907A1
PD1 CAR	8055	SEQ ID. NO. 121 in WO2015157252
PD1 CAR	8056	SEQ ID. NO. 119 in WO2015157252
PD1 CAR	8057	SEQ ID NO. 24 (WO2016014565)
PD1 CAR	8058	SEQ ID NO. 22 (WO2016014565)
PD1 FKBP RCAR	8059	SEQ ID NO. 23 (WO2016014565)
PD1 FKBP RCAR	8060	SEQ ID NO. 26 in WO2015142675
PSMA NCAR	8061	SEQ ID NO. 39 in WO2015142675
PSMA NCAR	8062	SEQ ID NO: 28 in US20160311907A1
PSMA NCAR	8063	SEQ ID NO: 29 in US20160311907A1
PSMA NCAR	8064	SEQ ID NO: 140 in WO2016097231
PSMA NCAR	8065	SEQ ID NO: 144 in WO2016097231
PSMA NCAR	8066	SEQ ID NO: 145 in WO2016097231
PSMA NCAR	8067	SEQ ID NO: 146 in WO2016097231
PSMA NCAR	8068	SEQ ID NO: 147 in WO2016097231
PSMA NCAR	8069	SEQ ID NO: 148 in WO2016097231
PSMA NCAR	8070	SEQ ID NO: 149 in WO2016097231
PSMA NCAR	8071	SEQ ID NO: 150 in WO2016097231
PSMA NCAR	8072	SEQ ID NO: 167 in WO2016097231
PSMA NCAR	8073	SEQ ID NO: 168 in WO2016097231
PSMA NCAR	8074	SEQ ID NO: 169 in WO2016097231
PSMA NCAR	8075	SEQ ID NO: 170 in WO2016097231
PSMA NCAR	8076	SEQ ID NO: 171 in WO2016097231
PSMA NCAR	8077	SEQ ID NO: 172 in WO2016097231
PSMA NCAR	8078	SEQ ID NO: 173 in WO2016097231
PSMA NCAR	8079	SEQ ID NO: 174 in WO2016097231
PSMA NCAR	8080	SEQ ID NO: 151 in WO2016097231
PSMA NCAR	8081	SEQ ID NO: 152 in WO2016097231
PSMA NCAR	8082	SEQ ID NO: 153 in WO2016097231
PSMA NCAR	8083	SEQ ID NO: 154 in WO2016097231
PSMA NCAR	8084	SEQ ID NO: 155 in WO2016097231
PSMA NCAR	8085	SEQ ID NO: 156 in WO2016097231
PSMA NCAR	8086	SEQ ID NO: 139 in WO2016097231
PSMA NCAR	8087	SEQ ID NO: 138 in WO2016097231
PSMA NCAR	8088	SEQ ID NO: 175 in WO2016097231
PSMA NCAR	8089	SEQ ID NO: 157 in WO2016097231

PSMA NCAR	8090	SEQ ID NO: 158 in WO2016097231
PSMA NCAR	8091	SEQ ID NO: 159 in WO2016097231
PSMA NCAR	8092	SEQ ID NO: 160 in WO2016097231
PSMA NCAR	8093	SEQ ID NO: 161 in WO2016097231
PSMA NCAR	8094	SEQ ID NO: 162 in WO2016097231
PSMA NCAR	8095	SEQ ID NO: 163 in WO2016097231
PSMA NCAR	8096	SEQ ID NO: 164 in WO2016097231
PSMA NCAR	8097	SEQ ID NO: 165 in WO2016097231
PSMA NCAR	8098	SEQ ID NO: 166 in WO2016097231
PSMA NCAR	8099	SEQ ID NO: 141 in WO2016097231
PSMA NCAR	8100	SEQ ID NO: 142 in WO2016097231
PSMA NCAR	8101	SEQ ID NO: 143 in WO2016097231
PSMA NCAR	8102	SEQ ID NO: 214 in WO2016097231
ROR1 CAR	8103	SEQ ID NO: 216 in WO2016097231
ROR1 CAR	8104	SEQ ID NO: 217 in WO2016097231
ROR1 CAR	8105	SEQ ID NO: 215 in WO2016097231
ROR1 CAR	8106	SEQ ID N0. 79 in WO2016016344A1
ROR1 CAR	8107	SEQ ID N0. 80 in WO2016016344A1
ROR1 CAR	8108	SEQ ID N0. 81 in WO2016016344A1
ROR1 CAR	8109	SEQ ID N0. 82 in WO2016016344A1
ROR1 CAR	8110	SEQ ID N0. 83 in WO2016016344A1
ROR1 CAR	8111	SEQ ID N0. 84 in WO2016016344A1
ROR1 CAR	8112	SEQ ID N0. 85 in WO2016016344A1
ROR1 CAR	8113	SEQ ID N0. 86 in WO2016016344A1
ROR1 CAR	8114	SEQ ID N0. 87 in WO2016016344A1
ROR1 CAR	8115	SEQ ID N0. 88 in WO2016016344A1
ROR1 CAR	8116	SEQ ID N0. 89 in WO2016016344A1
ROR1 CAR	8117	SEQ ID N0. 90 in WO2016016344A1
ROR1 CAR	8118	SEQ ID N0. 91 in WO2016016344A1
ROR1 CAR	8119	SEQ ID N0. 92 in WO2016016344A1
ROR1 CAR	8120	SEQ ID N0. 93 in WO2016016344A1
ROR1 CAR	8121	SEQ ID N0. 94 in WO2016016344A1
ROR1 CAR	8122	SEQ ID N0. 95 in WO2016016344A1
ROR1 CAR	8123	SEQ ID N0. 96 in WO2016016344A1
ROR1 CAR	8124	SEQ ID N0. 103 in WO2016016344A1
ROR1 CAR	8125	SEQ ID N0. 104 in WO2016016344A1
ROR1 CAR	8126	SEQ ID N0. 105 in WO2016016344A1
ROR1 CAR	8127	SEQ ID N0. 106 in WO2016016344A1
ROR1 CAR	8128	SEQ ID N0. 107 in WO2016016344A1
ROR1 CAR	8129	SEQ ID N0. 108 in WO2016016344A1
ROR1 CAR	8130	SEQ ID N0. 109 in WO2016016344A1
ROR1 CAR	8131	SEQ ID N0. 110 in WO2016016344A1
ROR1 CAR	8132	SEQ ID N0. 111 in WO2016016344A1
ROR1 CAR	8133	SEQ ID N0. 112 in WO2016016344A1
ROR1 CAR	8134	SEQ ID N0. 113 in WO2016016344A1
ROR1 CAR	8135	SEQ ID N0. 114 in WO2016016344A1
ROR1 CAR	8136	SEQ ID N0. 115 in WO2016016344A1
ROR1 CAR	8137	SEQ ID N0. 116 in WO2016016344A1
ROR1 CAR	8138	SEQ ID N0. 117 in WO2016016344A1
ROR1 CAR	8139	SEQ ID N0. 118 in WO2016016344A1
ROR1 CAR	8140	SEQ ID N0. 119 in WO2016016344A1
ROR1 CAR	8141	SEQ ID N0. 120 in WO2016016344A1
ROR1 CAR	8142	SEQ ID N0. 127 in WO2016016344A1
ROR1 CAR	8143	SEQ ID N0. 128 in WO2016016344A1
ROR1 CAR	8144	SEQ ID N0. 129 in WO2016016344A1
ROR1 CAR	8145	SEQ ID N0. 130 in WO2016016344A1
ROR1 CAR	8146	SEQ ID N0. 131 in WO2016016344A1
ROR1 CAR	8147	SEQ ID N0. 132 in WO2016016344A1

ROR1 CAR	8148	SEQ ID N0. 133 in WO2016016344A1
ROR1 CAR	8149	SEQ ID N0. 134 in WO2016016344A1
ROR1 CAR	8150	SEQ ID N0. 135 in WO2016016344A1
ROR1 CAR	8151	SEQ ID N0. 136 in WO2016016344A1
ROR1 CAR	8152	SEQ ID N0. 137 in WO2016016344A1
ROR1 CAR	8153	SEQ ID N0. 138 in WO2016016344A1
ROR1 CAR	8154	SEQ ID N0. 97 in WO2016016344A1
ROR1 CAR	8155	SEQ ID N0. 98 in WO2016016344A1
ROR1 CAR	8156	SEQ ID N0. 99 in WO2016016344A1
ROR1 CAR	8157	SEQ ID N0. 100 in WO2016016344A1
ROR1 CAR	8158	SEQ ID N0. 101 in WO2016016344A1
ROR1 CAR	8159	SEQ ID N0. 102 in WO2016016344A1
ROR1 CAR	8160	SEQ ID N0. 121 in WO2016016344A1
ROR1 CAR	8161	SEQ ID N0. 122 in WO2016016344A1
ROR1 CAR	8162	SEQ ID N0. 123 in WO2016016344A1
ROR1 CAR	8163	SEQ ID N0. 124 in WO2016016344A1
ROR1 CAR	8164	SEQ ID N0. 125 in WO2016016344A1
ROR1 CAR	8165	SEQ ID N0. 126 in WO2016016344A1
ROR1 CAR	8166	SEQ ID NO: 386 in WO2016187216A1
ROR1 CAR	8167	SEQ ID NO: 387 in WO2016187216A1
ROR1 CAR	8168	SEQ ID NO: 388 in WO2016187216A1
ROR1 CAR	8169	SEQ ID NO: 389 in WO2016187216A1
ROR1 CAR	8170	SEQ ID NO: 390 in WO2016187216A1
ROR1 CAR	8171	SEQ ID NO: 391 in WO2016187216A1
ROR1 CAR	8172	SEQ ID NO: 392 in WO2016187216A1
ROR1 CAR	8173	SEQ ID NO: 393 in WO2016187216A1
ROR1 CAR	8174	SEQ ID NO: 394 in WO2016187216A1
SNAP CAR	8175	SEQ ID NO: 395 in WO2016187216A1
SSEA4CAR	8176	SEQ ID NO: 396 in WO2016187216A1
SSEA4CAR	8177	SEQ ID NO: 397 in WO2016187216A1
Tan CAR (a CAR AND GATE which recognizes CD19 AND CD33 using a CD45 phosphatase)	8178	SEQ ID NO: 19 in US20160311907A1
Tan CAR (a CAR AND gate which recognizes CD19 AND CD33 using a CD148 phosphatase)	8179	SEQ ID NO.5 in WO2016026742A1
Tan CAR (a CAR AND NOT gate which recognizes CD19 AND NOT CD33 and is based on an ITIM containing endodomain from LAIR1)	8180	SEQ ID NO.6 in WO2016026742A1
Tan CAR (a CAR AND NOT GATE which recognizes CD19 AND NOT CD33 based on PTPN6 phosphatase)	8181	SEQ ID NO. 3 in WO2015075468
Tan CAR (a CAR AND NOT gate which recognizes CD19 AND NOT CD33 and recruits a PTPN6CD148 fusion protein to an ITIM containing endodomain)	8182	SEQ ID NO. 2 in WO2015075468
TOSO CAR	8183	SEQ ID NO. 5 in WO2015075468
TOSO CAR	8184	SEQ ID NO. 4 in WO2015075468
Trophoblast Glycoprotein 5T4 CAR	8185	SEQ ID NO. 6 in WO2015075468
Trophoblast Glycoprotein 5T4 CAR	8186	SEQ ID No. 4 in US20160347854A1
Trophoblast Glycoprotein 5T4 CAR	8187	SEQ ID No. 4 in EP3098237A1
Trophoblast Glycoprotein 5T4 CAR	8188	SEQ ID N0.19 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8189	SEQ ID N0.20 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8190	SEQ ID N0.21 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8191	SEQ ID N0.22 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8192	SEQ ID N0.23 in WO2016034666A1

Trophoblast Glycoprotein 5T4 CAR	8193	SEQ ID N0.24 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8194	SEQ ID N0.25 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8195	SEQ ID N0.26 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8196	SEQ ID N0.27 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8197	SEQ ID N0.28 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8198	SEQ ID N0.29 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8199	SEQ ID N0.30 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8200	SEQ ID N0.31 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8201	SEQ ID N0.32 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8202	SEQ ID N0.33 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8203	SEQ ID N0.34 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8204	SEQ ID N0.35 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8205	SEQ ID N0.36 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8206	SEQ ID N0.37 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8207	SEQ ID N0.38 in WO2016034666A1
Trophoblast Glycoprotein 5T4 CAR	8208	SEQ ID N0.39 in WO2016034666A1
TSLPR CAR	8209	SEQ ID N0.40 in WO2016034666A1
TSLPR CAR	8210	SEQ ID N0.41 in WO2016034666A1
TSLPR CAR	8211	SEQ ID N0.42 in WO2016034666A1
TSLPR CAR	8212	SEQ ID NO. 39 in WO2015084513
TSLPR CAR	8213	SEQ ID NO. 40 in WO2015084513
TSLPR CAR	8214	SEQ ID NO. 41 in WO2015084513
TSLPR CAR	8215	SEQ ID NO. 42 in WO2015084513
TSLPR CAR	8216	SEQ ID NO. 43 in WO2015084513
TSLPR CAR	8217	SEQ ID NO. 44 in WO2015084513
TSLPR CAR	8218	SEQ ID NO. 45 in WO2015084513
TSLPR CAR	8219	SEQ ID NO. 46 in WO2015084513
TSLPR CAR	8220	SEQ ID NO: 39 in US20160311910A1
TSLPR CAR	8221	SEQ ID NO: 40 in US20160311910A1
TSLPR CAR	8222	SEQ ID NO: 41 in US20160311910A1
TSLPR CAR	8223	SEQ ID NO: 42 in US20160311910A1
TSLPR CAR	8224	SEQ ID NO: 43 in US20160311910A1
VEGFR2 CAR	8225	SEQ ID NO: 44 in US20160311910A1
VEGFR2 CAR	8226	SEQ ID NO: 45 in US20160311910A1
VEGFR2 CAR	8227	SEQ ID NO: 46 in US20160311910A1
VEGFR2 CAR	8228	SEQ ID NO. 10 in US20120213783
VEGFR2 CAR	8229	SEQ ID NO. 11 in US20120213783
VEGFR2 CAR	8230	SEQ ID NO. 12 in US20120213783
αfolate receptor (FRα) CAR	8231	SEQ ID NO. 13 in US20120213783
αfolate receptor (FRα) CAR	8232	SEQ ID NO. 14 in US20120213783

[0301] In one embodiment of the present invention, the payload of the invention is a CD19 specific CAR targeting different B cell malignancies and HER2-specific CAR targeting sarcoma, glioblastoma, and advanced Her2-positive lung malignancy.

[0302] In some embodiments, the CAR is a CD19 CAR. The amino acid sequences of CD19 CAR components and CD19 CAR constructs are presented in Table 17A and Table 17B. Table 17B also provides alternate aliases for a given construct ID. These aliases are identified by the prefix OT.

Table 17A CD19 CAR construct components

Description	Amino Acid Sequence	AA SEQ ID NO	NA SEQ ID NO
CD19 scFv	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQ KPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISN LEQEDIATYFCQQGNTLPYTFGGGTKLEITGGGGSGG GGSGGGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSL PDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSR LTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGG SYAMDYWGQGTSVTVSS	8233	8241-8246
CD8α hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACD	8234	8247-8251
CD8α hinge-TM (hinge and transmembrane)	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACDIYIWAPLAGTCGVLLLSLVITLYC	8235	8252-8254
CD3 zeta signaling domain	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLD KRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAY SEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR	8236	8255-8261
4-1BB intracellular signaling domain; CD28 co-stimulatory domain;	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCEL	8237	8262-8267
CD8α leader	MALPVTALLLPLALLLHAARP	278	279-283
hPDE5 (Amino acid 535-860 of WT)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETAL CTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKN VAYHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILA LLIAALSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEH HHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAILA TDLALYIKRRGEFFELIRKNQFNLEDPHQKELFLAML MTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKEL NIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHV SEDCFPLLDGCRKNRQKWQALAEQQ	3	339
hPDE5 (Amino acid 535-860 of WT, R732L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETAL CTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKN VAYHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILA LLIAALSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEH HHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAILA TDLALYIKRLGEFFELIRKNQFNLEDPHQKELFLAML MTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKEL NIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHV SEDCFPLLDGCRKNRQKWQALAEQQ	12	359
hPDE5 (Amino acid 535-860 of WT, R732L, D764N)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETAL CTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKN VAYHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILA LLIAALSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEH HHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAILA TDLALYIKRLGEFFELIRKNQFNLEDPHQKELFLAML MTACNLSAITKPWPIQQRIAELVATEFFDQGDRERKEL NIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHV SEDCFPLLDGCRKNRQKWQALAEQQ	505	520

hPDE5 (Amino acid 535-860 of WT, R732L, F736A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETAL CTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKN VAYHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILA LLIAALSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEH HHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAILA TDLALYIKRLGEFAELIRKNQFNLEDPHQKELFLAML MTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKEL NIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHV SEDCFPLLDGCRKNRQKWQALAEQQ	227	233
hPDE5 (Amino acid 535-860 of WT, H653A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETAL CTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKN VAYHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILA LLIAALSADLDHRGVNNSYIQRSEHPLAQLYCHSIMEH HHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAILA TDLALYIKRRGEFFELIRKNQFNLEDPHQKELFLAML MTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKEL NIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHV SEDCFPLLDGCRKNRQKWQALAEQQ	348	361
hPDE5 (Amino acid 535-860 of WT, R732L, H653A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETAL CTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKN VAYHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILA LLIAALSADLDHRGVNNSYIQRSEHPLAQLYCHSIMEH HHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAILA TDLALYIKRLGEFFELIRKNQFNLEDPHQKELFLAML MTACDLSAITKPWPIQQRIAELVATEFFDQGDRERKEL NIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHV SEDCFPLLDGCRKNRQKWQALAEQQ	509	524
hPDE5 (Amino acid 535-860 of WT, R732L, D764A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETAL CTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKN VAYHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILA LLIAALSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEH HHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAILA TDLALYIKRLGEFFELIRKNQFNLEDPHQKELFLAML MTACALSAITKPWPIQQRIAELVATEFFDQGDRERKEL NIEPTDLMNREKKNKIPSMQVGFIDAICLQLYEALTHV SEDCFPLLDGCRKNRQKWQALAEQQ	510	525
HA Tag	YPYDVPDYA	8238	8268
P2A Cleavable peptide	GATNFSLLKQAGDVEENPGP	8239	8270
mCherry (M1L)	LSKGEEDNMAIIKEFMRFKVHMEGSVNGHEFEIEGEG EGRPYEGTQTAKLKVTKGGPLPFAWDILSPQFMYGSK AYVKHPADIPDYLKLSFPEGFKWERVMNFEDGGVVT VTQDSSLQDGEFIYKVKLRGTNFPSDGPVMQKKTMG WEASSERMYPEDGALKGEIKQRLKLKDGGHYDAEVK TTYKAKKPVQLPGAYNVNIKLDITSHNEDYTIVEQYE RAEGRHSTGGMDELYK	8240	8269
SG LINKER	SG	-	AGTG GT
Linker (GSG) (BamH1-Gly)	GSG	-	GGAT CCGG A
Flexible G/S rich linker; BamH1 Site	GS	-	GGAT CC
Lys-Asp Acid Linker	LD	-	CTAG AT

Table 17B: CD19 CARs constructs

Description	Amino Acid Sequence	AA SEQ ID NO	NA SEQ ID NO
OT-CD19-063 (OT-001407) CD8a leader; CD19 scFv; CD8a Hinge and Transmembrane Domain; 4-1BB intracellular domain; CD3 zeta signaling domain; stop	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLG DRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQ ESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPR KGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVF LKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQG TSVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPR*	8271	8285
OT-CD19-037 (OT-001258) CD8a leader; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain; Linker (GSG), hPDE5 (Amino acid 535-860 of WT, R732L, D764N), stop	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLG DRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQ ESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPR KGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVF LKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQG TSVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPRGSGEETRELQSLAAAVVPSAQTLK ITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMF AALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNS YIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQI LSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEFFELIR KNQFNLEDPHQKELFLAMLMTACNLSAITKPWPIQQ RIAELVATEFFDQGDRERKELNIEPTDLMNREKKNKI PSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNR QKWQALAEQQ*	8272	8286
OT-CD19-045 (OT-001298) CD8a leader; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain; Linker (GSG); hPDE5 (Amino acid 535-860 of WT, R732L, F736A); stop	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLG DRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQ ESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPR KGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVF LKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQG TSVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPRGSGEETRELQSLAAAVVPSAQTLK ITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMF AALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNS	8273	8287

	YIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQI LSGLSIEEYKTTLKIIKQAILATDLALYIKRLGEFAELI RKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQ QRIAELVATEFFDQGDRERKELNIEPTDLMNREKKN KIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRK NRQKWQALAEQQ*		
OT-CD19-051 (OT-001299) CD8a leader; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain; Linker (GSG); hPDE5(Amino acid 535-860 of WT); stop	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLG DRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQ ESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPR KGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVF LKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQG TSVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPRGSGEETRELQSLAAAVVPSAQTLK ITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKH EVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMF AALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNS YIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQI LSGLSIEEYKTTLKIIKQAILATDLALYIKRRGEFFELI RKNQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQ QRIAELVATEFFDQGDRERKELNIEPTDLMNREKKN KIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRK NRQKWQALAEQQ*	8274	8288
OT-CD19-052 (OT-001300) CD8a leader; HA Tag; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain; Linker (SG); hPDE5(Amino acid 535-860 of WT); stop	MALPVTALLLPLALLLHAARPYPYDVPDYADIQMTQ TTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGT VKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQE DIATYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGS GGGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPDY GVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTI IKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSY AMDYWGQGTSVTVSSTTTPAPRPPTPAPTIASQPLSL RPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGV LLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPRSGEETRELQSLAAA VVPSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNL VQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHA FNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDL DHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLM ILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKR RGEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAI TKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLM NREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPL LDGCRKNRQKWQALAEQQ*	8275	8289
OT-CD19-053 (OT-001301) CD8a leader; HA Tag; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain;	MALPVTALLLPLALLLHAARPYPYDVPDYADIQMTQ TTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGT VKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQE DIATYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGS GGGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPDY GVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTI IKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSY AMDYWGQGTSVTVSSTTTPAPRPPTPAPTIASQPLSL	8276	8290

linker (SG); hPDE5 (Amino acid 535-860 of WT, R732L); stop	RPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGV LLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPRSGEETRELQSLAAA VVPSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNL VQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHA FNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDL DHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLM ILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKR LGEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAI TKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLM NREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPL LDGCRKNRQKWQALAEQQ*		
OT-CD19-067 (OT-001302) CD8a leader; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain; linker (GS); hPDE5 (Amino acid 535-860 of WT, R732L, F736A); linker (GS); mCherry (M1L); stop	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLG DRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQ ESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPR KGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVF LKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQG TSVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPRGSEETRELQSLAAAVVPSAQTLKI TDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKHE VLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRLGEFAELIRK NQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRI AELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQGSLSKGEEDNMAIIKEFMRFKVHMEG SVNGHEFEIEGEGEGRPYEGTQTAKLKVTKGGPLPFA WDILSPQFMYGSKAYVKHPADIPDYLKLSFPEGFKW ERVMNFEDGGVVTVTQDSSLQDGEFIYKVKLRGTNF PSDGPVMQKKTMGWEASSERMYPEDGALKGEIKQR LKLKDGGHYDAEVKTTYKAKKPVQLPGAYNVNIKL DITSHNEDYTIVEQYERAEGRHSTGGMDELYK*	8277	8291
OT-CD19-078 (OT-001303) CD8a leader; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain; linker (GS); hPDE5 (Amino acid 535-860 of WT, R732L, F736A); linker (GSG); P2A linker; mCherry (M1L); stop	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLG DRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQ ESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPR KGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVF LKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQG TSVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPRGSEETRELQSLAAAVVPSAQTLKI TDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKHE VLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA	8278	8292

	ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRLGEFAELIRK NQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRI AELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQGSGGATNFSLLKQAGDVEENPGPLSK GEEDNMAIIKEFMRFKVHMEGSVNGHEFEIEGEGEG RPYEGTQTAKLKVTKGGPLPFAWDILSPQFMYGSKA YVKHPADIPDYLKLSFPEGFKWERVMNFEDGGVVTV TQDSSLQDGEFIYKVKLRGTNFPSDGPVMQKKTMG WEASSERMYPEDGALKGEIKQRLKLKDGGHYDAEV KTTYKAKKPVQLPGAYNVNIKLDITSHNEDYTIVEQ YERAEGRHSTGGMDELYK*		
OT-CD19-100 (OT-001304) CD8a leader; HA Tag; CD19 scFV; CD8a-Tm, (4-1BB intracellular domain); CD3zeta signaling domain; linker (GS); hPDE5(Amino acid 535-860 of WT); linker (GS), Spacer (LD); P2A linker; mCherry (M1L); stop	MALPVTALLLPLALLLHAARPYPYDVPDYADIQMTQ TTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGT VKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQE DIATYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGS GGGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPDY GVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTI IKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSY AMDYWGQGTSVTVSSTTTPAPRPPTPAPTIASQPLSL RPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGV LLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPRGSEETRELQSLAAA VVPSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNL VQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHA FNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDL DHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLM ILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKR RGEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAI TKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLM NREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPL LDGCRKNRQKWQALAEQQGSLDGATNFSLLKQAGD VEENPGPLSKGEEDNMAIIKEFMRFKVHMEGSVNGH EFEIEGEGEGRPYEGTQTAKLKVTKGGPLPFAWDILS PQFMYGSKAYVKHPADIPDYLKLSFPEGFKWERVM NFEDGGVVTVTQDSSLQDGEFIYKVKLRGTNFPSDG PVMQKKTMGWEASSERMYPEDGALKGEIKQRLKLK DGGHYDAEVKTTYKAKKPVQLPGAYNVNIKLDITSH NEDYTIVEQYERAEGRHSTGGMDELYK*	8279	8293
OT-CD19-101 (OT-001305) CD8a leader; HA Tag; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain; Linker (GS); hPDE5(Amino acid 535-860 of WT, R732L); Linker (GS), Spacer (LD); P2A linker; mCherry (M1L); stop	MALPVTALLLPLALLLHAARPYPYDVPDYADIQMTQ TTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGT VKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQE DIATYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGS GGGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPDY GVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTI IKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSY AMDYWGQGTSVTVSSTTTPAPRPPTPAPTIASQPLSL RPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGV LLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPRGSEETRELQSLAAA VVPSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNL VQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHA	8280	8294

	FNTAQCMFAALKAGKIQNKLTDLEILALLIAALSHDL DHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCLM ILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKR LGEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAI TKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDLM NREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPL LDGCRKNRQKWQALAEQQGSLDGATNFSLLKQAGD VEENPGPLSKGEEDNMAIIKEFMRFKVHMEGSVNGH EFEIEGEGEGRPYEGTQTAKLKVTKGGPLPFAWDILS PQFMYGSKAYVKHPADIPDYLKLSFPEGFKWERVM NFEDGGVVTVTQDSSLQDGEFIYKVKLRGTNFPSDG PVMQKKTMGWEASSERMYPEDGALKGEIKQRLKLK DGGHYDAEVKTTYKAKKPVQLPGAYNVNIKLDITSH NEDYTIVEQYERAEGRHSTGGMDELYK*		
OT-CD19-111 (OT-001454) CD8a leader; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain; Linker (GS); hPDE5(Amino acid 535-860 of WT, R732L); stop	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLG DRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQ ESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPR KGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVF LKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQG TSVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPRGSEETRELQSLAAAVVPSAQTLKI TDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKHE VLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRLGEFFELIRK NQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRI AELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQ*	8281	8295
OT-CD19-130 (OT-001455) CD8a leader; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain; Linker (GS); hPDE5(Amino acid 535-860 of WT, H653A); stop	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLG DRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQ ESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPR KGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVF LKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQG TSVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPRGSEETRELQSLAAAVVPSAQTLKI TDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKHE VLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSADLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRRGEFFELIRK NQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRI AELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQ*	8282	8296

OT-CD19-131 (OT-001456) CD8a leader; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain; Linker (GS); hPDE5(Amino acid 535-860 of WT, H653A, R732L); stop	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLG DRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQ ESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPR KGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVF LKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQG TSVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPRGSEETRELQSLAAAVVPSAQTLKI TDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKHE VLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSADLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRLGEFFELIRK NQFNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRI AELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQ*	8283	8297
OT-CD19-132 (OT-001457) CD8a leader; CD19 scFV; CD8a-Tm; (4-1BB intracellular domain); CD3zeta signaling domain; Linker (GS); hPDE5 (Amino acid 535-860 of WT, R732L, D764A); stop	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLG DRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQ ESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPR KGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVF LKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQG TSVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPRGSEETRELQSLAAAVVPSAQTLKI TDFSFSDFELSDLETALCTIRMFTDLNLVQNFQMKHE VLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMFA ALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSY IQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILS GLSIEEYKTTLKIIKQAILATDLALYIKRLGEFFELIRK NQFNLEDPHQKELFLAMLMTACALSAITKPWPIQQRI AELVATEFFDQGDRERKELNIEPTDLMNREKKNKIPS MQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNRQ KWQALAEQQ*	8284	8298

Tandem CAR (TanCAR)

[0303] In some embodiments, the CAR of the present invention may be a tandem chimeric antigen receptor (TanCAR) which is able to target two, three, four, or more tumor specific antigens. In some aspects, the CAR is a bispecific TanCAR including two targeting domains which recognize two different TSAs on tumor cells. The bispecific CAR may be further defined as comprising an extracellular region comprising a targeting domain (e.g., an antigen recognition domain) specific for a first tumor antigen and a targeting domain (e.g., an antigen

recognition domain) specific for a second tumor antigen. In other aspects, the CAR is a multispecific TanCAR that includes three or more targeting domains configured in a tandem arrangement. The space between the targeting domains in the TanCAR may be between about 5 and about 30 amino acids in length, for example, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30 amino acids.

Split CAR

[0304] In some embodiments, the components including the targeting moiety, transmembrane domain and intracellular signaling domains of the present invention may be split into two or more parts such that it is dependent on multiple inputs that promote assembly of the intact functional receptor. In one embodiment, the split synthetic CAR system can be constructed in which the assembly of an activated CAR receptor is dependent on the binding of a ligand to the SRE (e.g. a small molecule) and a specific antigen to the targeting moiety. As a non-limiting example, the split CAR consists of two parts that assemble in a small molecule-dependent manner; one part of the receptor features an extracellular antigen binding domain (e.g. scFv) and the other part has the intracellular signaling domains, such as the CD3ζ intracellular domain.

[0305] In other aspects, the split parts of the CAR system can be further modified to increase signal. In one example, the second part of cytoplasmic fragment may be anchored to the plasma membrane by incorporating a transmembrane domain (e.g., CD8α transmembrane domain) to the construct. An additional extracellular domain may also be added to the second part of the CAR system, for instance an extracellular domain that mediates homo-dimerization. These modifications may increase receptor output activity, i.e., T cell activation.

[0306] In some aspects, the two parts of the split CAR system contain heterodimerization domains that conditionally interact upon binding of a heterodimerizing small molecule. As such, the receptor components are assembled in the presence of the small molecule, to form an intact system which can then be activated by antigen engagement. Any known heterodimerizing components can be incorporated into a split CAR system. Other small molecule dependent heterodimerization domains may also be used, including, but not limited to, gibberellin-induced dimerization system (GID1-GAI), trimethoprim-SLF induced ecDHFR and FKBP dimerization (Czlapinski et al., *J Am Chem Soc.*, 2008, 130(40): 13186-13187) and ABA (abscisic acid) induced dimerization of PP2C and PYL domains (Cutler et al., *Annu Rev Plant Biol.* 2010, 61: 651-679). The dual regulation using inducible assembly (e.g., ligand dependent dimerization) and degradation (e.g., destabilizing domain induced

CAR degradation) of the split CAR system may provide more flexibility to control the activity of the CAR modified T cells.

Switchable CAR

[0307] In some embodiments, the CAR of the invention may be a switchable CAR. Juilerat et al (Juilerat et al., *Sci. Rep.*, 2016, 6: 18950; the contents of which are incorporated herein by reference in their entirety) recently reported controllable CARs that can be transiently switched on in response to a stimulus (e.g. a small molecule). In this CAR design, a system is directly integrated in the hinge domain that separate the scFv domain from the cell membrane domain in the CAR. Such system is possible to split or combine different key functions of a CAR such as activation and co-stimulation within different chains of a receptor complex, mimicking the complexity of the TCR native architecture. This integrated system can switch the scFv and antigen interaction between on/off states controlled by the absence/presence of the stimulus.

Reversible CAR

[0308] In other embodiments, the CAR of the invention may be a reversible CAR system. In this CAR architecture, a LID domain (ligand-induced degradation) is incorporated into the CAR system. The CAR can be temporarily down-regulated by adding a ligand of the LID domain. The combination of LID and DD mediated regulation provides tunable control of continuingly activated CAR T cells, thereby reducing CAR mediated tissue toxicity.

Inhibitory CAR (iCAR)

[0309] In some embodiments, payloads of the present invention may be inhibitory CARs. Inhibitory CAR (iCAR) refers to a bispecific CAR design wherein a negative signal is used to enhance the tumor specificity and limit normal tissue toxicity. This design incorporates a second CAR having a surface antigen recognition domain combined with an inhibitory signal domain to limit T cell responsiveness even with concurrent engagement of an activating receptor. This antigen recognition domain is directed towards a normal tissue specific antigen such that the T cell can be activated in the presence of first target protein, but if the second protein that binds to the iCAR is present, the T cell activation is inhibited.

[0310] As a non-limiting example, iCARs against Prostate specific membrane antigen (PMSA) based on CTLA4 and PD1 inhibitory domains demonstrated the ability to selectively limit cytokine secretion, cytotoxicity and proliferation induced by T cell activation (Fedorov V.D, et al., 2013, *Sci Transl Med,*11;5(215):215ra172; the contents of which are incorporated herein in their entirety).

Chimeric switch receptor

[0311] In some embodiments, payloads of the invention may be chimeric switch receptors which can switch a negative signal to a positive signal. As used herein, the term "chimeric switch receptor" refers to a fusion protein comprising a first extracellular domain and a second transmembrane and intracellular domain, wherein the first domain includes a negative signal region and the second domain includes a positive intracellular signaling region. In some aspects, the fusion protein is a chimeric switch receptor that contains the extracellular domain of an inhibitory receptor on T cell fused to the transmembrane and cytoplasmic domain of a co-stimulatory receptor. This chimeric switch receptor may convert a T cell inhibitory signal into a T cell stimulatory signal.

[0312] As a non-limiting example, the chimeric switch receptor may comprise the extracellular domain of PD-1 fused to the transmembrane and cytoplasmic domain of CD28 as taught by Liu et al. (Liu et al., *Cancer Res.*, 2016, 76(6): 1578-1590; the contents of which are incorporated by reference in their entirety). In some aspects, extracellular domains of other inhibitory receptors such as CTLA-4, LAG-3, TIM-3, KIRs and BTLA may also be fused to the transmembrane and cytoplasmic domain derived from costimulatory receptors such as CD28, 4-1BB, CD27, OX40, CD40, GTIR and ICOS. In the context of the present invention, the SRE domain (e.g., DD) may be inserted at the N- or C- terminus of the chimeric switch receptor.

[0313] In some embodiments, chimeric switch receptors of the present invention may include recombinant receptors comprising the extracellular cytokine-binding domain of an inhibitory cytokine receptor (e.g., IL13 receptor α (IL13Rα1), IL10R, and IL4Rα) fused to an intracellular signaling domain of a stimulatory cytokine receptor such as IL2R (IL2Rα, IL2Rβ and IL2Rgamma) and IL7Rα. One example of such chimeric cytokine receptor is a recombinant receptor containing the cytokine-binding extracellular domain of IL4Rα linked to the intracellular signaling domain of IL7Rα (see, US patent publication NO: 2014/0050709; the contents of which are incorporated herein by reference in their entirety).

[0314] In one embodiment, the chimeric switch receptor of the present invention may be a chimeric TGFβ receptor. The chimeric TGFβ receptor may comprise an extracellular domain derived from a TGFβ receptor such as TGFβ receptor 1, TGFβ receptor 2, TGFβ receptor 3, or any other TGFβ receptor or variant thereof; and a non- TGFβ receptor intracellular domain. The non- TGFβ receptor intracellular domain may be the intracellular domain or fragment thereof derived from TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8,

TLR9, TLR10, CD28, 4-1BB (CD137), OX40 (CD134), CD3zeta, CD40, CD27, or a combination thereof. One example of such chimeric TGFβ receptor is discussed in US patent publication NO.: US2016/0075755; the contents of which are incorporated herein by reference in their entirety.

[0315] In some embodiments, payloads of the present invention may be bipartite fusion receptors. In one aspect, the bipartite fusion receptor may comprise an antigen-binding domain that binds to a tumor antigen and an activation domain that binds to one or more cell surface molecules. In some aspects, the antigen binding domain of a bipartite receptor is a scFv antibody. In other aspects, the activation domain that binds to a T cell surface stimulatory molecule may be selected from CD3, CD27, CD 28, CD40, OX40(CD134) and 4-1BB(CD137), or a NK cell surface stimulatory molecule selected from CD16, NKG2D and NKp30. The activation domain may also be a scFv specific to a stimulatory molecule on the surface of immune cells (e.g., T cells and NK cells). Immune cells can be genetically modified to express a bipartite molecule comprising at least one antigen binding domain and an activation domain. The antigen binding domain binds to one or more molecules present on target cells such as cancer cells. Immune cells that express the molecule recognized by the activation domain will be activated and attack the recognized cancer cells. As a non-limiting example, a bipartite molecule may be an engager molecule comprising an antigen recognition scFv specific to CD19 or EphA2, as described in US patent publication NO: US2016/0015749; the contents of which are incorporated by reference herein in their entirety.

Activation-conditional CAR

[0316] In some embodiments, payloads of the invention may be an activation-conditional chimeric antigen receptor, which is only expressed in an activated immune cell. The expression of the CAR may be coupled to activation conditional control region which refers to one or more nucleic acid sequences that induce the transcription and/or expression of a sequence e.g. a CAR under its control. Such activation conditional control regions may be promoters of genes that are upregulated during the activation of the immune effector cell e.g. IL2 promoter or NFAT binding sites. In some embodiments, activation of the immune cell may be achieved by a constitutively expressed CAR (International Publication No: WO 2016126608; the contents of which are incorporated herein by reference in their entirety).

CAR targeting to tumor cells with specific proteoglycan markers

[0317] In some embodiments, payloads of the present invention may be a CAR that targets specific types of cancer cells. Human cancer cells and metastasis may express unique and otherwise abnormal proteoglycans, such as polysaccharide chains (e.g., chondroitin

sulfate (CS), dermatan sulfate (DS or CSB), heparan sulfate (HS) and heparin). Accordingly, the CAR may be fused with a binding moiety that recognizes cancer associated proteoglycans. In one example, a CAR may be fused with VAR2CSA polypeptide (VAR2-CAR) that binds with high affinity to a specific type of chondroitin sulfate A (CSA) attached to proteoglycans. The extracellular ScFv portion of the CAR may be substituted with VAR2CSA variants comprising at least the minimal CSA binding domain, generating CARs specific to chondroitin sulfate A (CSA) modifications. Alternatively, the CAR may be fused with a split-protein binding system to generate a spy-CAR, in which the scFv portion of the CAR is substituted with one portion of a split-protein binding system such as SpyTag and Spy-catcher and the cancer-recognition molecules (e.g. scFv and or VAR2-CSA) are attached to the CAR through the split-protein binding system (See, e.g., PCT publication No.: WO2016/135291; the contents of which are incorporated by reference in their entirety.)

SUPRA CAR

[0318] In some embodiments, the payload of the present invention may be a Split Universal Programmable (SUPRA) CAR. A SUPRA CAR may be a two-component receptor system comprising of a universal receptor (zip CAR) expressed on T cells and a tumor-targeting scFv adaptor. The zip CAR universal receptor may be generated by the fusion of intracellular signaling domains and a leucine zipper as the extracellular domain. The tumor-targeting scFv adaptor molecule or zipFv, may be generated by the fusion of a cognate leucine zipper and an scFv. The scFv of the zipFv may bind to a tumor antigen, and the leucine zipper may bind and activate the zip CAR on the T cells. Unlike the conventional fixed CAR design, the SUPRA CAR modular design allows targeting of multiple antigens without further genetic manipulations of the immune cells. Any of the CAR designs disclosed by Cho et al., 2018, Cell 173, 1–13, may be useful in the present invention (the contents of which are incorporated by reference in their entirety).

6. Cytokines, chemokines and other soluble factors

[0319] In accordance with the present invention, payloads of the present invention may be cytokines, chemokines, growth factors, and soluble proteins produced by immune cells, cancer cells and other cell types, which act as chemical communicators between cells and tissues within the body. These proteins mediate a wide range of physiological functions, from effects on cell growth, differentiation, migration and survival, to a number of effector activities. For example, activated T cells produce a variety of cytokines for cytotoxic function to eliminate tumor cells.

[0320] In some embodiments, payloads of the present invention may be cytokines, and fragments, variants, analogs and derivatives thereof, including but not limited to interleukins, tumor necrosis factors (TNFs), interferons (IFNs), TGF beta and chemokines. In some embodiments, payloads of the present invention may be cytokines that stimulate immune responses. In other embodiments, payloads of the invention may be antagonists of cytokines that negatively impact anti-cancer immune responses.

[0321] In some embodiments, payloads of the present invention may be cytokine receptors, recombinant receptors, variants, analogs and derivatives thereof; or signal components of cytokines.

[0322] In some embodiments, cytokines of the present invention may be utilized to improve expansion, survival, persistence, and potency of immune cells such as CD8+T_{EM}, natural killer cells and tumor infiltrating lymphocytes (TIL) cells used for immunotherapy. In other embodiments, T cells engineered with two or more DD regulated cytokines are utilized to provide kinetic control of T cell activation and tumor microenvironment remodeling. In one aspect, the present invention provides biocircuits and compositions to minimize toxicity related to cytokine therapy. Despite its success in mitigating tumor burden, systemic cytokine therapy often results in the development of severe dose limiting side effects. Two factors contribute to the observed toxicity (a) Pleiotropism, wherein cytokines affect different cells types and sometimes produce opposing effects on the same cells depending on the context (b) Cytokines have short serum half-life and thus need to be administered at high doses to achieve therapeutic effects, which exacerbates the pleiotropic effects. In one aspect, cytokines of the present invention may be utilized to modulate cytokine expression in the event of adverse effects. In some embodiments, cytokines of the present invention may be designed to have prolonged life span or enhanced specificity to minimize toxicity.

[0323] In some embodiments, the payload of the present invention may be an interleukin (IL) cytokine. Interleukins (ILs) are a class of glycoproteins produced by leukocytes for regulating immune responses. As used herein, the term "interleukin (IL)" refers to an interleukin polypeptide from any species or source and includes the full-length protein as well as fragments or portions of the protein. In some aspects, the interleukin payload is selected from IL1, IL1alpha (also called hematopoietin-1), IL1beta (catabolin), IL1 delta, IL1epsilon, IL1eta, IL1 zeta, interleukin-1 family member 1 to 11 (IL1F1 to IL1F11), interleukin-1 homolog 1 to 4 (IL1H1 to IL1H4), IL1 related protein 1 to 3 (IL1RP1 to IL1RP3), IL2, IL3, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL10C, IL10D, IL11, IL11a, IL11b, IL12, IL13, IL14, IL15, IL16, IL17, IL17A, Il17B, IL17C, IL17E, IL17F, IL18, IL19, IL20,

IL20 like (IL20L), Il21, IL22, IL23, IL23A, IL23-p19, IL23-p40, IL24, Il25, IL26, IL27, IL28A, IL28B, IL29, IL30, IL31, IL32, IL33, IL34, IL35, IL36 alpha, IL36 beta, IL36 gamma, IL36RN, IL37, IL37a, IL37b, IL37c, IL37d, IL37e and IL38. In other aspects, the payload of the present invention may be an interleukin receptor selected from CD121a, CDw121b, IL2Rα/CD25, IL2Rβ/CD122, IL2Rγ/CD132, CDw131, CD124, CD131, CDw125, CD126, CD130, CD127, CDw210, IL8RA, IL11Rα, CD212, CD213α1, CD213α2, IL14R, IL15Rα, CDw217, IL18Rα, IL18Rβ, IL20Rα, and IL20Rβ.

[0324] In certain embodiments, a cytokine may be a type I interferons (IFN) including IFN alpha subtypes (IFN α1, IFN α1b, IFN α1c), IFN beta, IFN delta subtypes (IFN delta 1, IFN delta 2, IFN delta 8), IFN gamma, IFN kappa, and IFN epsilon, IFN lambda, IFN omega, IFN tau and IFN zeta. In certain embodiments, a cytokine may be a member of tumor necrosis factor (TNF) superfamily, including TNF-alpha, TNF-beta (also known as lymphotoxin-alpha (LT-α)), lymphotoxin-beta (LT-β), CD40L(CD154), CD27L (CD70), CD30L(CD153), FASL(CD178), 4-1BBL (CD137L), OX40L, TRAIL (TNF-related apoptosis inducing ligand), APRIL (a proliferation-inducing ligand), TWEAK, TRANCE, TALL-1, GITRL, LIGHT and TNFSF1 to TNFSF20 (TNF ligand superfamily member 1 to 20).

[0325] In one embodiment, the payload of the invention may comprise IL2 (SEQ ID NO. 8299, encoded by SEQ ID NO. 8300 and 8301). In one aspect, the effector module of the invention may be a DD-IL2 fusion polypeptide.

[0326] In some aspects of the invention, an IL2 mutein may be used as a payload. As used herein, the term "mutein" is a construct, molecule or sequence of a mutation, change or alteration in a protein and hence is also known as a mutant, e.g., a protein mutant, mutein. Consequently, an "IL2 mutein" is an IL2 mutant. In some embodiments an IL2 mutein is a variant of wild type IL2 protein, where the wildtype IL2 consists of the amino acid sequence of SEQ ID NO. 8299. In some aspects, it refers to an IL2 variant which binds to and activates only cells expressing IL2Rαβγ, but does not significantly bind to or activate cell expressing only IL2Rβγ. In some examples, an IL2 mutein may be an IL2 protein in which residues of IL2 responsible for binding to either IL2Rβ or IL2Rγ are substituted and abolish their interaction. In other examples, an IL2 mutein may be an IL2 protein comprising mutations conferring high affinity for IL2Rα. An IL2 mutein may be an IL2 selective agonist ($IL2_{SA}$) which can preferentially activate the high affinity IL2 receptor (i.e., IL2Rαβγ) which is necessary to selectively activate T cells with respect to NK cells. In some embodiments, the

IL2 mutein may be IL2 protein which preferentially binds to the lower affinity IL2Rβγ but with reduced affinity to CD25.

[0327] In some embodiments, IL2 muteins may be used to preferentially expand or stimulate Treg cells. As used herein "preferentially expand or stimulate Treg cells" means the IL2 muteins promote the proliferation, survival, activation and /or function of T regulatory cells.

[0328] Exemplary IL2 muteins may include, but are not limited to, N88R substitution (Shanafelt et al., *Nature Biotech.*, 2000, 18:1197-1202), an IL2 with a V91K substitution (e.g., US Patent publication NO. US20140286898); V91K substitution, C125A substitution, an IL2 with three mutations: V69A, N71R, Q74P; an IL2 mutein with high affinity for IL2Rα (N29S, Y31H, K35R, T37A, K48E, V69A, N71R, Q74P); an IL2 mutein with high affinity for IL2Rα and reduced signaling activity (N29S, Y31H, K35R, T37A, K48E, V69A, N71R, Q74P, N88D), and D20H, D20I, N88G, N88I, N88R, and Q126L substitutions as described in PCT application NO. 1999060128; the contents of each of which are incorporated herein by reference in their entirety. In other aspects, IL2 muteins may include those described in US Pat.NO.: 4,518,584; *5,116,943; 5,206,344; 6,955*,807; 7,105,653; *7,371,371; 7,803,361; 8,124,066; 8,349,311;* 8,759,486; and 9,206,243; PCT patent publication NOs: WO2005086751 and WO2012088446; EP Pat. NOs: EP0234599 and EP0200280 and Sim, G.C. et al. (2016) Cancer Immunol Res; 4(11):983-994; the contents of each of which are incorporated herein by reference in their entirety.

[0329] In some aspects, the IL2 mutein may be fused to a polypeptide that extends the serum half-life of the IL2 mutein, such as an IgG Fc fragment. Preferred Fc regions are derived from human IgG, which includes IgG1, IgG2, IgG3, and IgG4. In other aspects, the payload of the invention may be an IL2 fusion protein comparing a second functional polypeptide. In a non-limiting example, an IL2 fusion protein may comprise an IL2 or IL2 mutein polypeptide fused with a pro-apoptotic Bcl-2 family polypeptide (such as Bad, Bik/Nbk, Bid, Bim/Bod, Hrk, Bak or Bax); such fusion protein may be capable of inhibiting cell survival, inhibiting cell proliferation, or enhancing cell death or apoptosis of a target cell expressing an IL2 receptor. Alternatively, an IL2 or IL2 mutein polypeptide may be fused with an anti-apoptotic Bcl-2 family polypeptide (such as Bcl-x_L, Bcl-w or Bcl-2). The fusion protein may be capable of enhancing cell survival, enhancing cell proliferation, or inhibiting cell death or apoptosis of a target cell expressing an IL2 receptor. See, e.g., US patent publication NO.: US2016/0229901.

[0330] In addition, the IL2 fusion protein may be a IL2-GMCSF fusion protein which can promote cell-cell interaction; therefore, enhances anti-cancer immune responses (Wen et al., *J. Translational Med.*, 2016, 14: 41).

[0331] In one embodiment, the payload of the invention may comprise IL12. IL12 is a heterodimeric protein of two subunits (p35, p40) that is secreted by antigen presenting cells, such as macrophages and dendritic cells. IL12 is type 1 cytokine that acts on natural killer (NK) cells, macrophages, $CD8^+$ Cytotoxic T cells, and $CD4^+$ T helper cells through STAT4 pathway to induce IFN γ production in these effector immune cells (reviewed by Trinchieri G, *Nat Rev Immunol.* 2003; 3(2): 133–146). IL12 can promote the cytotoxic activity of NK cells and $CD8^+$ T cells, therefore has anti-tumor function. Intravenous injection of recombinant IL12 exhibited modest clinical efficacy in a handful of patients with advanced melanoma and renal cell carcinoma (Gollob et al., *Clin. Cancer Res.* 2000; 6(5):1678–1692). IL12 has been used as an adjuvant to enhance cytotoxic immunity using a melanoma antigen vaccine, or using peptide pulsed peripheral blood mononuclear cells; and to promote NK cell activity in breast cancer with trastuzumab treatment. Local delivery of IL12 to the tumor microenvironment promotes tumor regression in several tumor models. These studies all indicate that locally increased IL12 level can promote anti-tumor immunity. One major obstacle of systemic or local administration of recombinant IL12 protein, or through oncolytic viral vectors is the severe side effects when IL12 is presented at high level. Developing a system that tightly controls IL12 level may provide a safe use of IL12 in cancer treatment.

[0332] In one aspect, the effector module of the invention may be a DD-IL12 fusion polypeptide. This regulatable DD-IL12 fusion polypeptide may be directly used as an immunotherapeutic agent or be transduced into an immune effector cell (T cells and TIL cells) to generate modified T cells with greater *in vivo* expansion and survival capabilities for adoptive cell transfer. The need for harsh preconditioning regimens in current adoptive cell therapies may be minimized using regulated IL12; DD-IL12 may be utilized to modify tumor microenvironment and increase persistence in solid tumors that are currently refractory to tumor antigen targeted therapy. In some embodiments, CAR expressing T cells may be armored with DD regulated IL12 to relieve immunosuppression without systemic toxicity.

[0333] In some embodiments, the IL12 may be a Flexi IL12, wherein both p35 and p40 subunits, are encoded by a single cDNA that produces a single chain polypeptide. In one embodiment, the IL12 may comprise p40 subunit, which includes amino acids 23-328 of wildtype IL12B and comprise the amino acid sequence of SEQ ID NO. 8302 (encoded by

SEQ ID NO. 8303-8312) and a p35 subunit, which includes amino acids 57-253 of wildtype IL12A and comprise the amino acid sequence of SEQ ID NO. 8313 (encoded by SEQ ID NO. 8314-8323). Any portion of IL12 that retains one or more functions of full length or mature IL12 may be useful in the present invention.

[0334] In some embodiments, DD regulated IL12 compositions of the invention may be utilized to minimize the cytotoxicity associated with systemic IL12 administration. Treatment with IL12 has been associated with systemic flu-like symptoms (fever, chills, fatigue, arthromyalgia, headache), toxic effects on the bone marrow, and liver. Hematologic toxicity observed most commonly included neutropenia and thrombocytopenia; hepatic dysfunction manifested in transient (dose dependent) increase in transaminases, hyperbilirubinemia and hypoalbuminemia. In some instances, toxicity is also associated with inflammation of the mucus membranes (oral mucositis, stomatitis or colitis). These toxic effects of IL12 were related to the secondary production of IFNγ, TNF alpha, and chemokines such as IP10, and MIG. In certain aspects of the invention, DD regulated IL12 may be utilized to prevent the toxic effects associated with elevated production of secondary messengers. In some embodiments, DD regulated Flexi-IL12 constructs may be used to improve the efficacy of the CARs, especially in solid tumor settings, by providing a controlled local signal for tumor microenvironment remodeling and epitope spreading. DD regulation also provides rapid, dose dependent, and local production of Flexi IL12.

[0335] The format of the IL12 constructs utilized as payload of the present invention may be optimized. In one embodiment, the payload of the invention may be a bicistronic IL12 containing p40 and p35 subunits separated by an internal ribosome entry site or a cleavage site such as P2A or Furin to allow independent expression of both subunits from a single vector. This results in a configuration of secreted IL12 that is more akin to the naturally occurring IL12 than the flexi IL12 construct, the payload of the invention may be the p40 subunit of the IL12. DD regulated p40 may be co-expressed with constitutive p35 construct to generate "regulatable IL12" expression. Alternatively, the DD regulated p40 may heterodimerize with the endogenous p35. p40 has been shown to stabilize p35 expression and stimulate the export of p35 (Jalah R, et al. (2013). Journal of Biol. Chem. 288, 6763-6776 (the contents of which are incorporated by reference in its entirety).

[0336] In some embodiments, modified forms of IL12 may be utilized as the payload. These modified forms of IL12 may be engineered to have shortened half-life in vivo

compared to the non-modified form of especially when used in combination with tunable systems described herein.

[0337] Human flexi IL12 has a reported half-life of 5-19 hours which, when administered as a therapeutic compound, can result in systemic cytotoxicity (Car et al. (1999) The Toxicology of Interleukin-12: A Review" Toxicologic Path.27 A, 58-63; Robertson et al. (1999) "Immunological Effects of Interleukin 12 Administered by Bolus Intravenous Injection to Patients with Cancer" Clin. Cancer Res. 5:9-16; Atkins et al. (1997)"Phase I Evaluation of Intravenous Recombinant Human Interleukin 12 in Patients with Advance Malignancies" Clin. Cancer Res. 3:409-417). The ligand inducible control of IL12 can regulate production in a dose dependent fashion, the time from cessation of ligand dosing to cessation of protein synthesis and IL12 clearance may be insufficient to prevent toxic accumulation of IL12 in plasma.

[0338] In one embodiment, the modified form of IL12 utilized as the payload may be a Topo-sc IL12 which have the configuration as follows from N to C terminus (i) a first IL12 p40 domain (p40N), (ii) an optional first peptide linker, (iii) an IL12 p35 domain, (iv) an optional second peptide linker, and (v) a second IL12 p40 domain (p40C). In one embodiment, modified topo sc IL12 polypeptides exhibit increased susceptibility to proteolysis. Topo-sc IL12 is described in International Patent Publication No. WO2016048903; the contents of which are incorporated herein by reference in its entirety.

[0339] IL12 polypeptide may also be modified (e.g. genetically, synthetically, or recombinantly engineered) to increase susceptibility to proteinases to reduce the biologically active half-life of the IL12 complex, compared to a corresponding IL12 lacking proteinases susceptibility. Proteinase susceptible forms of IL12 are described in International Patent Publication No. WO2017062953; the contents of which are incorporated by reference in its entirety.

[0340] IL12 systemic toxicity may also be limited or tightly controlled via mechanisms involving tethering IL12 to the cell surface to limit its therapeutic efficacy to the tumor site. Membrane tethered IL12 forms have been described previously using Glycosyl phosphatidylinositol (GPI) signal peptide or using CD80 transmembrane domain (Nagarajan S, et al. (2011) J Biomed Mater Res A. 99(3):410-7; Bozeman EN, et al. (2013) Vaccine. 7;31(20):2449-56; Wen-Yu Pan et al. (2012), Mol. Ther.20:5, 927–937; the contents of each of which are incorporated by reference in their entirety). In some embodiments, transmembrane domains may be selected from any of those described in Table 13, Table 14, and Table 15.

[0341] In some embodiments, the IL12 levels secreted by the immune cells of the invention may approximately be comparable to the IL12 levels secreted by human myeloid dendritic cells (mDC1), when activated with TLR agonists. In one embodiment, the TLR agonist may be the combination of lipopolysaccharide administered with R848.

[0342] In some embodiments, the IFN gamma secreted by IL12 induced activation of the immune cells is at least 5-fold greater in the presence of ligand, compared to the levels in the absence of ligand.

[0343] In some embodiments, regulation of IL12 provides the necessary safety switch. In some embodiments, IL-12 secretion recruit and/or activates effector cells in the tumor microenvironment. In some embodiments, the IL12 regulation provides a benefit to CAR T function without causing toxicity.

[0344] In one embodiment, the payload of the invention may comprise IL15. Interleukin 15 is a potent immune stimulatory cytokine and an essential survival factor for T cells, and Natural Killer cells. Preclinical studies comparing IL2 and IL15, have shown than IL15 is associated with less toxicity than IL2. In some embodiments, the effector module of the invention may be a DD-IL15 fusion polypeptide. IL15 polypeptide may also be modified to increase its binding affinity for the IL15 receptor. For example, the asparagine may be replaced by aspartic acid at position 72 of IL15 (SEQ ID NO. 2 of US patent publication US20140134128A1; the contents of which are incorporated by reference in their entirety). In some aspects, the IL15 comprises amino acid sequence of SEQ ID NO. 8234 (encoded by SEQ ID NO. 8236), which include amino acids 49-162 of wildtype IL15. In some embodiments the IL15 sequence may include a stop codon and may be encoded by the nucleotide sequence of SEQ ID NO.8235, and 8237-8238.

[0345] A unique feature of IL15 mediated activation is the mechanism of trans-presentation in which IL15 is presented as a complex with the alpha subunit of IL15 receptor (IL15Ra) that binds to and activates membrane bound IL15 beta/gamma receptor, either on the same cell or a different cell. The IL15/IL15Ra complex is more effective in activating IL15 signaling, than IL15 by itself. Thus, in some embodiments, the effector module of the invention may include a DD-IL15/IL15Ra fusion polypeptide. In one embodiment, the payload may be IL15/IL15Ra fusion polypeptide described in US Patent Publication NO.: US20160158285A1 (the contents of which are incorporated herein by reference in their entirety). The IL15 receptor alpha comprises an extracellular domain called the sushi domain which contains most of the structural elements necessary for binding to IL15. Thus, in some embodiments, payload may be the IL15/IL15Ra sushi domain fusion polypeptide described in

US Patent Publication NO.: US20090238791A1 (the contents of which are incorporated herein by reference in their entirety).

[0346] Regulated IL15/IL15Ra may be used to promote expansion, survival and potency of CD8T_{EM} cell populations without impacting regulatory T cells, NK cells and TIL cells. In one embodiment, DD-IL15/IL15Ra may be utilized to enhance CD19 directed T cell therapies in B cell leukemia and lymphomas. In one aspect, IL15/IL15Ra may be used as payload of the invention to reduce the need for pre-conditioning regimens in current CAR-T treatment paradigms.

[0347] The effector modules containing DD-IL15, DD-IL15/IL15Ra and/or DD-IL15/IL15Ra sushi domain may be designed to be secreted (using e.g. IL2 signal sequence) or membrane bound (using e.g. IgE or CD8a signal sequence).

[0348] In some embodiments, the IFN gamma secreted by IL15 induced activation of the immune cells is at least 10-fold greater in the presence of ligand, compared to the levels in the absence of ligand.

[0349] In some embodiments, regulation of IL15-IL15Ra fusion proteins provides a safety switch as compared to constitutively expressed IL15-IL15Ra. In some embodiments, IL15-IL15Ra leads to better expansion, and/or persistence of CAR T cells.

[0350] In some aspects, the DD-IL115/IL15Ra comprises the amino acid sequences provided in Table 18. In some embodiments, the linker utilized in Table 18 may be SG linker. In Table 18, asterisk indicates the translation of the stop codon. In some embodiments, the DDs described in Table 18 may contain an additional stop codon. As used herein the wildtype (WT) of IL15 refers to Uniprot ID: P40933 and wildtype (WT) of IL15Ra refers to UniProt ID: Q13261. Table 18 also provides alternate aliases for a given construct ID. These aliases are identified by the prefix OT.

Table 18: DD-IL15-IL15Ra construct sequences

Description/ Construct ID	Amino Acid Sequence	AA SEQ ID NO	NA SEQ ID NO
IL15 (49-162 of WT)	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNV TESGCKECEELEEKNIKEFLQSFVHIVQMFINTS	8324	8326; 8344
IL15Ra (31-267 of WT)	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGS QLMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASAS HQPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKS RQTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHL	8329	8345; 8346

IgE leader	MDWTWILFLVAAATRVHS	276	277
SG3-(SG4)3-SG3-SLQ linker	SGGGSGGGGSGGGGSGGGGSGGGSLQ	323	324
SG Linker	SG	-	AGTGGT
GSGSGS linker	GSGSGS	8330	8347
GSGSGSGS linker	GSGSGSGS	8331	8348
GSGSGGGSGS linker	GSGSGGGSGS	8332	8349
hPDE5 (Amino acid 535-860 of WT)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCT IRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYH NWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKP WPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNR QKWQALAEQQ	3	339
hPDE5 (Amino acid 535-860 of WT, R732L)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCT IRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYH NWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRL GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKP WPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNR QKWQALAEQQ	12	359
hPDE5 (Amino acid 535-860 of WT, R732L, F736A)	EETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCT IRMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYH NWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRL GEFAELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKP WPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNR QKWQALAEQQ	227	233
AcGFP (Amino acid 2-239 of WT)	VSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYG KLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDT LVNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDK AKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLP DNHYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDE LYK	79	372
FLAG-tag	DYKDDDDK	8333	8350
HA Tag	YPYDVPDYA	8238	8351
Modified Furin	ESRRVRRNKRSK	288	291
OT-IL15-031 (OT-001254, OT-IL15-045) IgE signal sequence; IL15 (Amino acid 49-162 of WT); linker (SG3-(SG4)3-SG3-SLQ); IL15Ra	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSSGGGSGGGGSGGGGSGGGGSGGGSLQI TCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSS LTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTV TTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQ LMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASH QPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKSR QTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHLSGE	8334	8352

(Amino acid 31-267 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT, R732L, F736A); stop TGA	ETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYH NWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRL GEFAELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKP WPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNR QKWQALAEQQ*		
OT-IL15-032 (OT-001469) IgE signal sequence; IL15 (Amino acid 49-162 of WT); linker (SG3-(SG4)3-SG3-SLQ); IL15Ra (Amino acid 31-267 of WT); linker (SG); AcGFP (Amino acid 2-239 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT, R732L, F736A); stop	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSSGGGSGGGGSGGGGSGGGGSGGGSLQI TCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSS LTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTV TTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQ LMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASH QPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKSR QTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHLSG VSKGAELFTGIVPILIELNGDVNGHKFSVSGEGEGDATYG KLTLKFICTTGKLPVPWPTLVTTLSYGVQCFSRYPDHMK QHDFFKSAMPEGYIQERTIFFEDDGNYKSRAEVKFEGDT LVNRIELTGTDFKEDGNILGNKMEYNYNAHNVYIMTDK AKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLP DNHYLSTQSALSKDPNEKRDHMIYFGFVTAAAITHGMDE LYKSGEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDL ETALCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYR KNVAYHNWRHAFNTAQCMFAALKAGKIQNKLTDLEILA LLIAALSHDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHH HFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAILATDL ALYIKRLGEFAELIRKNQFNLEDPHQKELFLAMLMTACD LSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEPTDL MNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLD GCRKNRQKWQALAEQQ*	8335	8353
OT-IL15-033 (OT-001470) IgE signal sequence; IL15 (Amino acid 49-162 of WT); linker (SG3-(SG4)3-SG3-SLQ); IL15Ra (Amino acid 31-267 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT, R732L, F736A); linker (SG); AcGFP (Amino acid 2-239 of WT); stop	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSSGGGSGGGGSGGGGSGGGGSGGGSLQI TCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSS LTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTV TTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQ LMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASH QPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKSR QTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHLSGE ETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYH NWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRL GEFAELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKP WPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNR QKWQALAEQQSGVSKGAELFTGIVPILIELNGDVNGHKF SVSGEGEGDATYGKLTLKFICTTGKLPVPWPTLVTTLSY GVQCFSRYPDHMKQHDFFKSAMPEGYIQERTIFFEDDGN YKSRAEVKFEGDTLVNRIELTGTDFKEDGNILGNKMEYN YNAHNVYIMTDKAKNGIKVNFKIRHNIEDGSVQLADHY QQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMIYF GFVTAAAITHGMDELYK*	8336	8354

OT-IL15-043 (OT-001315) IgE signal sequence; IL15 (Amino acid 49-162 of WT); Linker (SG3-(SG4)3-SG3-SLQ); IL15Ra (Amino acid 31-267 of WT); Linker (SG); Furin cleavage site (ESRRVRRNKRSK); hPDE5 (Amino acid 535-860 of WT, R732L); stop	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSSGGGSGGGGSGGGGSGGGGSGGGSLQI TCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSS LTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTV TTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQ LMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASH QPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKSR QTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHLSGE SRRVRRNKRSKEETRELQSLAAAVVPSAQTLKITDFSFSD FELSDLETALCTIRMFTDLNLVQNFQMKHEVLCRWILSV KKNYRKNVAYHNWRHAFNTAQCMFAALKAGKIQNKLT DLEILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLYCHS IMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIKQAIL ATDLALYIKRLGEFFELIRKNQFNLEDPHQKELFLAMLM TACDLSAITKPWPIQQRIAELVATEFFDQGDRERKELNIEP TDLMNREKKNKIPSMQVGFIDAICLQLYEALTHVSEDCFP LLDGCRKNRQKWQALAEQQ*	8337	8355
OT-IL15-044 (OT-001316) IgE signal sequence; IL15 (Amino acid 49-162 of WT); Linker (SG3-(SG4)3-SG3-SLQ); IL15Ra (Amino acid 31-267 of WT); Linker (SG); hPDE5 (Amino acid 535-860 of WT, R732L); stop	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSSGGGSGGGGSGGGGSGGGGSGGGSLQI TCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSS LTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTV TTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQ LMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASH QPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKSR QTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHLSGE ETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYH NWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRL GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKP WPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNR QKWQALAEQQ*	8338	8356
OT-IL15-048 (OT-001317) IgE signal sequence; IL15 (Amino acid 49-162 of WT); Linker (SG3-(SG4)3-SG3-SLQ); IL15Ra (Amino acid 31-267 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT); stop	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS FVHIVQMFINTSSGGGSGGGGSGGGGSGGGGSGGGSLQI TCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSS LTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTV TTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQ LMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASH QPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKSR QTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHLSGE ETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYH NWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKP WPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNR QKWQALAEQQ*	8339	8357
OT-IL15-194 (OT-001499) IgE signal	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMHI DATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQS	8340	8358

sequence; IL15 (Amino acid 49-162 of WT); Linker (SG3-(SG4)3-SG3-SLQ); IL15Ra (Amino acid 31-267 of WT); linker (SG); hPDE5 (Amino acid 535-860 of WT); stop	FVHIVQMFINTSSGGGSGGGGSGGGGSGGGGSGGGSLQI TCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSS LTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTV TTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQ LMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASH QPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKSR QTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHLSGE ETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLETALCTI RMFTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYH NWRHAFNTAQCMFAALKAGKIQNKLTDLEILALLIAALS HDLDHRGVNNSYIQRSEHPLAQLYCHSIMEHHHFDQCL MILNSPGNQILSGLSIEEYKTTLKIIKQAILATDLALYIKRR GEFFELIRKNQFNLEDPHQKELFLAMLMTACDLSAITKP WPIQQRIAELVATEFFDQGDRERKELNIEPTDLMNREKK NKIPSMQVGFIDAICLQLYEALTHVSEDCFPLLDGCRKNR QKWQALAEQQ*		
OT-IL15-111 (OT-001344) IgE signal sequence; Flag tag; IL15 (Amino acid 49-162 of WT); Linker (SG3-(SG4)3-SG3-SLQ); HA tag; IL15Ra (Amino acid 31-267 of WT); linker (GSGSGS); hPDE5 (Amino acid 535-860 of WT, R732L); stop TGA	MDWTWILFLVAAATRVHSDYKDDDDKNWVNVISDLKK IEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVIS LESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELE EKNIKEFLQSFVHIVQMFINTSSGGGSGGGGSGGGGSGG GGSGGGSLQYPYDVPDYAITCPPPMSVEHADIWVKSYSL YSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPS LKCIRDPALVHQRPAPPSTVTTAGVTPQPESLSPSGKEPA ASSPSSNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESS HGTPSQTTAKNWELTASASHQPPGVYPQGHSDTTVAIST STVLLCGLSAVSLLACYLKSRQTPPLASVEMEAMEALPV TWGTSSRDEDLENCSHHLGSGSGSEETRELQSLAAAVVP SAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNFQ MKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQCMF AALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNSYIQ RSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSGLSIE EYKTTLKIIKQAILATDLALYIKRLGEFFELIRKNQFNLED PHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATEFFD QGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQL YEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ*	8341	8359
OT-IL15-112 (OT-001345) IgE signal sequence; Flag tag; IL15 (Amino acid 49-162 of WT); Linker (SG3-(SG4)3-SG3-SLQ); HA tag; IL15Ra (Amino acid 31-267 of WT); linker (GSGSGSGS); hPDE5 (Amino acid 535-860 of WT, R732L); stop	MDWTWILFLVAAATRVHSDYKDDDDKNWVNVISDLKK IEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVIS LESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELE EKNIKEFLQSFVHIVQMFINTSSGGGSGGGGSGGGGSGG GGSGGGSLQYPYDVPDYAITCPPPMSVEHADIWVKSYSL YSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPS LKCIRDPALVHQRPAPPSTVTTAGVTPQPESLSPSGKEPA ASSPSSNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESS HGTPSQTTAKNWELTASASHQPPGVYPQGHSDTTVAIST STVLLCGLSAVSLLACYLKSRQTPPLASVEMEAMEALPV TWGTSSRDEDLENCSHHLGSGSGSGSEETRELQSLAAAV VPSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLVQNF QMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQC MFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVNNS YIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQILSG LSIEEYKTTLKIIKQAILATDLALYIKRLGEFFELIRKNQFN LEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELVATE FFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFIDAIC LQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ*	8342	8360
OT-IL15-113 (OT-001346) IgE signal sequence; Flag tag; IL15 (Amino acid	MDWTWILFLVAAATRVHSDYKDDDDKNWVNVISDLKK IEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVIS LESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELE EKNIKEFLQSFVHIVQMFINTSSGGGSGGGGSGGGGSGG GGSGGGSLQYPYDVPDYAITCPPPMSVEHADIWVKSYSL YSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPS	8343	8361

49-162 of WT); Linker (SG3-(SG4)3-SG3-SLQ); HA tag; IL15Ra (Amino acid 31-267 of WT); linker (GSGSGGGSGS); hPDE5 (Amino acid 535-860 of WT, R732L); stop	LKCIRDPALVHQRPAPPSTVTTAGVTPQPESLSPSGKEPA ASSPSSNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESS HGTPSQTTAKNWELTASASHQPPGVYPQGHSDTTVAIST STVLLCGLSAVSLLACYLKSRQTPPLASVEMEAMEALPV TWGTSSRDEDLENCSHHLGSGSGGGSGSEETRELQSLAA AVVPSAQTLKITDFSFSDFELSDLETALCTIRMFTDLNLV QNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTA QCMFAALKAGKIQNKLTDLEILALLIAALSHDLDHRGVN NSYIQRSEHPLAQLYCHSIMEHHHFDQCLMILNSPGNQIL SGLSIEEYKTTLKIIKQAILATDLALYIKRLGEFFELIRKNQ FNLEDPHQKELFLAMLMTACDLSAITKPWPIQQRIAELV ATEFFDQGDRERKELNIEPTDLMNREKKNKIPSMQVGFID AICLQLYEALTHVSEDCFPLLDGCRKNRQKWQALAEQQ*		

[0351] In some embodiments, the sequences described in Table 18, may contain an additional stop codon. For example, the construct "hPDE5 (Amino acid 535-860 of WT, R732L); stop" may be encoded by the nucleotide sequence of SEQ ID NO. 8362, and the construct "hPDE5 (Amino acid 535-860 of WT, R732L, F736A); stop" may be encoded by the nucleotide sequence of SEQ ID NO. 8363.

[0352] In one embodiment, the payload of the present invention may comprise IL18. IL18 is a proinflammatory and immune regulatory cytokine that promotes IFNγ production by T and NK cells. IL18 belongs to the IL1 family. Secreted IL18 binds to a heterodimer receptor complex, consisting of IL18Rα and β-chains and initiates signal transduction. IL18 acts in concert with other cytokines to modulate immune system functions, including induction of IFN γ production, Th1 responses, and NK cell activation in response to pathogen products. IL18 showed anti-cancer effects in several tumors. Administration of recombinant IL18 protein or IL18 transgene induces melanoma or sarcoma regression through the activation of $CD4^+$T and/or NK cell-mediated responses (reviewed by Srivastava et al., *Curr. Med. Chem.*, 2010,17: 3353–3357). The combination of IL18 with other cytokines, such as IL12 or co-stimulatory molecules (e.g., CD80) increases IL18 anti-tumor effects. For example, IL18 and IL12A/B or CD80 genes have been integrated successfully in the genome of oncolytic viruses, with the aim to trigger synergistically T cell-mediated anti-tumor immune responses (Choi et al., *Gene Ther.*, 2011, 18: 898-909). IL2/IL18 fusion proteins also display enhanced anti-tumor properties relative to either cytokine alone and low toxicity in preclinical models (Acres et al., *Cancer Res.*, 2005, 65:9536–9546).

[0353] IL18 alone, or in combination of IL12 and IL15, activates NK cells. Preclinical studies have demonstrated that adoptively transferred IL12, IL15 and IL18 pre-activated NK cells display enhanced effector function against established tumors *in vivo* (Ni et al., *J Exp Med.* 2012, 209: 2351–2365; and Romee et al., *Blood.* 2012,120:4751–4760). Human

IL12/IL15/IL18 activated NK cells also display memory-like features and secrete more IFN γ in response to cytokines (e.g., low concentration of IL2). In one embodiment, the effector module of the present invention may be a DD-IL18 fusion polypeptide.

[0354] In one embodiment, the payload of the present invention may comprise IL21. IL21 is another pleiotropic type I cytokine that is produced mainly by T cells and natural killer T (NKT) cells. IL21 has diverse effects on a variety of cell types including but not limited to $CD4^+$ and $CD8^+$ T cells, B cells, macrophages, monocytes, and dendritic cells (DCs). The functional receptor for IL21 is composed of IL21 receptor (IL21R) and the common cytokine receptor gamma chain, which is also a subunit of the receptors for IL2, IL4, IL7, IL9 and IL15. Studies provide compelling evidence that IL21 is a promising immunotherapeutic agent for cancer immunotherapy. IL21 promotes maturation, enhances cytotoxicity, and induces production of IFN γ and perforin by NK cells. These effector functions inhibit the growth of B16 melanoma (Kasaian et al., *Immunity.* 2002, 16(4):559–569; and Brady et al., *J Immunol.*2004, 172(4):2048–2058). IL21 together with IL15 expands antigen-specific $CD8^+$ T-cell numbers and their effector function, resulting in tumor regression (Zeng et al., *J Exp Med.*2005, 201(1):139–148). IL21 may also be used to rejuvenate multiple immune effector cells in the tumor microenvironment. IL21 may also directly induce apoptosis in certain types of lymphoma such as diffuse large B-cell lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia cells, via activation of STAT3 or STAT1 signal pathway. IL21, alone or in combination with anti-CD20 mAb (rituximab) can activate NK cell-dependent cytotoxic effects. Interestingly, discovery of the immunosuppressive actions of IL21 suggests that this cytokine is a "double-edged sword"- IL21 stimulation may lead to either the induction or suppression of immune responses. Both stimulatory and suppressive effects of IL21 must be considered when using IL21-related immunotherapeutic agents. The level of IL21 needs to be tightly controlled by regulatory elements. In one aspect, the effector module of the present invention may be a DD-IL21 fusion polypeptide.

[0355] In some embodiments, payloads of the present invention may comprise type I interferons. Type I interferons (IFNs-I) are soluble proteins important for fighting viral infection in humans. IFNs-I include IFN alpha subtypes (IFN α1, IFN α1b, IFN α1c), IFN beta, IFN delta subtypes (IFN delta 1, IFN delta 2, IFN delta 8), IFN gamma, IFN kappa, and IFN epsilon, IFN lambda, IFN omega, IFN tau and IFN zeta. IFN α and IFN β are the main IFN I subtypes in immune responses. All subtypes of IFN I signal through a unique heterodimeric receptor, interferon alpha receptor (IFNAR), composed of 2 subunits, IFNAR1 and IFNAR2. IFNR activation regulates the host response to viral infections and in adaptive

immunity. Several signaling cascades can be activated by IFNR, including the Janus activated kinase–signal transducer and activation of transcription (JAK-STAT) pathway, the mitogen activated protein kinase (MAPK) pathway, the phosphoinositide 3-kinase (PI3K) pathway, the v-crk sarcoma virus CT10 oncogene homolog (avian)-like (CRKL) pathway, and NF-κB cascade. It has long been established that type I IFNs directly inhibit the proliferation of tumor cells and virus-infected cells, and increase MHC class I expression, enhancing antigen recognition. IFNs-I have also proven to be involved in immune system regulation. IFNs can either directly, through interferon receptor (IFNR), or indirectly by the induction of chemokines and cytokines, regulate the immune system. Type I IFNs enhance NK cell functions and promote survival of NK cells. Type I IFNs also affect monocytes, supporting the differentiation of monocytes into DC with high capacity for antigen presentation, and stimulate macrophage function and differentiation. Several studies also demonstrate that IFNs-I promote $CD8^+$ T cell survival and functions. In some instances, it may be desirable to tune the expression of Type I IFNs using biocircuits of the present invention to avoid immunosuppression caused by long-term treatment with IFNs.

[0356] New anticancer immunotherapies are being developed that use recombinant type I IFN proteins, type I IFN transgene, type I IFN encoding vectors and type I IFN expressing cells. For example, IFN α has received approval for treatment of several neoplastic diseases, such as melanoma, RCC and multiple myeloma. Though type I IFNs are powerful tools to directly and indirectly modulate the functions of the immune system, side effects of systemic long-term treatments and lack of sufficiently high efficacy have dampened the interest of IFN α for clinical use in oncology. It is believed that if IFN levels are tightly regulated at the malignant tissues, type I IFNs are likely more efficacious. Approaches for intermittent delivery are proposed according to the observation that intermittency at an optimized pace may help to avoid signaling desensitizing mechanisms (negative feedback mechanisms) induced by IFNs-I (i.e., because of SOCS1 induction) in the responding immune cells. In accordance with the present invention, the effector module may comprise a DD-IFN fusion polypeptide. The DD and its ligand control the expression of IFN to induce an antiviral and antitumor immune responses and in the meantime, to minimize the side effects caused by long-term exposure of IFN.

[0357] In some embodiments, payloads of the present invention may comprise members of tumor necrosis factor (TNF) superfamily. The term "TNF superfamily" as used herein refers to a group of cytokines that can induce apoptosis. Members of TNF family include TNF-alpha, TNF-beta (also known as lymphotoxin-alpha (LT-α)), lymphotoxin-beta (LT-β),

CD40L(CD154), CD27L (CD70), CD30L(CD153), FASL(CD178), 4-1BBL (CD137L), OX40L, TRAIL (TNF-related apoptosis inducing ligand), APRIL (a proliferation-inducing ligand), TWEAK, TRANCE, TALL-1, GITRL, LIGHT and TNFSF1 to TNFSF20 (TNF ligand superfamily member 1 to 20). In one embodiment, the payload of the invention may be TNF-alpha. TNF-alpha can cause cytolysis of tumor cells, and induce cell proliferation differentiation as well. In one aspect, the effector module of the present invention may comprise a DD-TNF alpha fusion polypeptide.

[0358] In one embodiment, the payloads of the present invention may be cytokines fused to TNF alpha ectodomain. Such payloads are produced as membrane associated cytokines fused to the TNF ectodomain. In one embodiment, the cytokine may be shed from the cell surface by the action of membrane associated proteases, and/or proteases in the extracellular space e.g. MMP9. Any of the cytokines described herein may be useful in the present invention. Such cytokine-TNF scaffold constructs may be used to preserve the native sequence of the processed cytokine while preserving regulation.

[0359] In some embodiments, payloads of the present invention may comprise inhibitory molecules that block inhibitory cytokines. The inhibitors may be blocking antibodies specific to an inhibitory cytokine, and antagonists against an inhibitory cytokine, or the like.

[0360] In some aspects, payloads of the present invention may comprise an inhibitor of a secondary cytokine IL35. IL35 belongs to the interleukin-12 (IL12) cytokine family, and is a heterodimer composed of the IL27 β chain Ebi3 and the IL12 α chain p35. Secretion of bioactive IL35 has been described only in forkhead box protein 3 $(Foxp3)^+$ regulatory T cells (Tregs) (resting and activated Tregs). Unlike other membranes in the family, IL35 appears to function solely in an anti-inflammatory fashion by inhibiting effector T cell proliferation and perhaps other parameters (Collison et al., *Nature*, 2007, 450(7169): 566–569).

[0361] In some embodiments, payloads of the present invention may comprise inhibitors that block the transforming growth factor beta (TGF-β) subtypes (TGF-β1, TGF-β2 and TGF-β3). TGF-β is secreted by many cell types, including macrophages and is often complexed with two proteins LTBP and LAP. Serum proteinases such as plasmin catalyze the release of active TGF-β from the complex from the activated macrophages. It has been shown that an increase in expression of TGF-β correlates with the malignancy of many cancers. The immunosuppressive activity of TGF-β in the tumor microenvironment contributes to oncogenesis.

[0362] In some embodiments, payloads of the present invention may comprise inhibitors of IDO enzyme. In some embodiments, payloads fused to the DDs of the invention may be an inhibitor of an immunosuppressive molecule such as TGF-beta and IDO.

[0363] In some embodiments, payloads of the present invention may comprise chemokines and chemokine receptors. Chemokines are a family of secreted small cytokines, or signaling proteins that can induce directed chemotaxis in nearby responsive cells. The chemokine may be a SCY (small cytokine) selected from the group consisting of SCYA1-28 (CCL1-28), SCYB1-16 (CXCL1-16), SCYC1-2 (XCL1-2), SCYD-1 and SCYE-1; or a C chemokine selected from XCL1 and XCL2; or a CC chemokine selected from CCL1, CCL2, CCL3, CCL4, CCL5, CCL6, CCL7, CCL8, CCL9, CCL10, CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27 and CCL28; or a CXC chemokine selected from CXCL1, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16 and CXCL17; or a CX3C chemokine CX3CL1. In some aspects, the chemokine receptor may be a receptor for the C chemokines including XCR1; or a receptor for the CC chemokines including CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9 and CCR10; or a receptor for the CXC chemokines including CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5; or a CX3C chemokine receptor CX3CR1.

[0364] In some embodiments, payloads of the present invention may comprise other immunomodulators that play a critical role in immunotherapy, such as GM-CSF (Granulocyte-macrophage colony stimulating factor), erythropoietin (EPO), MIP3a, monocyte chemotactic protein (MCP)-1, intracellular adhesion molecule (ICAM), macrophage colony stimulating factor (M-CSF), Interleukin-1 receptor activating kinase (iRAK-1), lactotransferrin, and granulocyte colony stimulating factor (G-CSF).

[0365] In some embodiments, the payload of the present invention may comprise Amphiregulin. Amphiregulin (AREG) is an EGF-like growth factor which binds to the EGFR receptor and enhances CD4+ regulatory T cells (Tregs) function. AREG promotes immune suppression in the tumor environment. Thus, in some embodiment, the payloads of the present invention may comprise Amhiregulin to dampen immune response during immunotherapy.

[0366] In some embodiments, payloads of the present invention may comprise fusion proteins wherein a cytokine, chemokine and/or other soluble factor may be fused to other biological molecules such as antibodies and or ligands for a receptor. Such fusion molecules

may increase the half-life of the cytokines, reduce systemic toxicity, and increase local concentration of the cytokines at the tumor site. Fusion proteins containing two or more cytokines, chemokines and or other soluble factors may be utilized to obtain synergistic therapeutic benefits. In one embodiment, payload may be a GM-CSF/IL2 fusion protein.

[0367] In some embodiments, any of the hinge and transmembrane domains described herein may be used as a scaffold for soluble cytokine presentation. The cytokine may be operably linked to the CD8 hinge and transmembrane domain by a protease cleavage site. Cleavage at the cleavage site releases the cytokine from the cell surface membrane. In some aspects, the cytokine may be in a precursor form. Generation of the active form of the cytokine from the precursor form occurs via cleavage at the cleavage site. Any of the cytokines described herein may be engineered using the any of the hinge and transmembrane domains described herein as a scaffold.

7. Immune regulators

[0368] In some embodiments, payloads of the present invention may comprise inhibitors (antagonists) of co-inhibitory molecules (e.g., immune checkpoint), including without limitation, PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, VISTA, BTLA, TIGIT, LAIRA, CD160, 2B4 and TGFR. In some aspects, the inhibitor may be a blocking/antagonistic antibody or fragment thereof, as discussed previously, or a ligand of the co-inhibitory receptor.

[0369] In some embodiments, payloads of the present invention may comprise agonists of co-stimulatory molecules, including without limitation, CD27, CD28, CD30, CD40, OX40 (CD134), 4-1BB (CD137), CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), GITR, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 and CD83. As a non-limiting example, agonists of co-stimulatory molecule ICOS (CD278) may be an ICOS binding protein comprising an amino acid sequence of SEQ ID NOs: 1, 2, 3, 4, 5 and 6 disclosed in International Patent Publication NO: WO2016120789; the contents of which are incorporated by reference herein in their entirety.

[0370] In some aspects, the agonist of a co-stimulatory molecule may be an agonistic antibody or fragment thereof, as discussed previously; or a ligand of the co-stimulatory receptor; or any binding molecules that can enhance the biological activity of its target. For example, an agonistic ligand of OX40 may be OX40L (CD252). The OX40 ligand as used herein, includes the intact OX40 ligand, soluble OX40 ligand, fusion proteins including a functionally active portion of OX40 ligand covalently linked to a second moiety, e.g., a protein domain, and variants may be which vary in amino acid sequence from naturally

occurring OX4L but which retain the ability to specifically bind to the OX40 receptor or even enhance the biological activity of OX40L.

[0371] In general, an agonist of a co-stimulatory molecule substantially enhances the biological activity of its target molecule, such as T cell activation. Desirably, the biological activity is enhanced by 10, 20, 30, 50, 70, 80, 90, 95, or even 100.

[0372] In some embodiments, payloads of the present invention may comprise immunomodulators including stress proteins and heat shock proteins (HSPs) that can integrate both innate and adaptive immune responses. They may also be other chaperones and adaptors that stimulate immune responses. As a non-limiting example, the payload of the present invention may be a fusion protein comprising an NF-KB-activating domain of Flagellin fused with an ATP-binding domain truncated glucose regulated protein 170 (Grp170) (See. US patent publication NO.: US2015/0315255; the contents of which are incorporated herein by reference in their entirety). The fusion construct forms a secretable Grp170-Flagellin hybrid chaperone (Flagrp170) which can be used to stimulate anti-cancer immune responses.

[0373] In other embodiments, the payload of the present invention may comprise a STING (stimulator of interferon gene) protein, an adaptor molecule in the cytoplasm which, as a component of the host cytosolic surveillance pathway, activates the TANK binding kinase (TBK1)-IRF3 signaling axis, resulting in the induction of IFN β and other IRF-3 dependent gene products that strongly activate innate immunity, leading to the development of an adaptive immune response consisting of both antigen-specific $CD4^+$ and $CD8^+$ T cells as well as pathogen-specific antibodies.

[0374] Demaria et al. reported that enforced activation of a STING protein by intratumoral injection of cyclic dinucleotide GMP-AMP (cGAMP), an agonist of STING, can enhance antitumor $CD8^+$ T cell responses leading to growth control of injected and contralateral tumors in mouse models of melanoma and colon cancer. The STING-dependent antitumor immunity was dependent on type I IFNs produced by endothelial cells in the tumor microenvironment (Demaria et al., *Proc. Natl. Acad. Sci. USA*, 2015, 112(5): 15408-15413). These studies demonstrate that STING contributes to anti-tumor immune responses via enhancement of type I IFN signaling in the tumor microenvironment. Biocircuits, effector modules comprising STING may be applied to the tumor microenvironment to enhance anti-tumor responses either alone or in combination with other immunotherapeutic agents of the invention.

[0375] In addition to STING proteins, payloads of the present invention may comprise PRRs (pattern recognition receptors) that are involved in sensing the infection of cells by viruses and microorganisms to activate innate immune inflammatory responses. Such PRRs include Toll like receptors (TLRs), RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), and C-type lectin receptors (CLRs). The RLR family is a RNA sensing system that is comprised of retinoic acid inducible gene-like-I (RIG-1), melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2). RIG-1 recognizes relatively short dsRNA (up to 1 kb) whereas MDA5 detects long dsRNA (more than 2 kb) to activate synthesis of type I IFNs, including IFN α and IFN β (Wilkins et al., *Curr Opin Immunol.*, 2010, 22: 41–47). RLRs activate downstream signaling proteins evoking type I IFN production. TLRs recognize distinct structures in microbes; often referred to as "PAMPs" (pathogen associated molecular patterns). Ligand binding to TLRs invokes a cascade of intra-cellular signaling pathways that induce the production of factors involved in inflammation and immunity such as pro-inflammatory cytokines, and chemokines, as well as $CD4^+$ and $CD8^+$ T cell activation. Among ten TLRs identified in human, TLRs-1, 2, 4, 5 and 6 are expressed in the cell surface, while TLR-3, -7/8, and -9 are expressed with the ER compartment. In some embodiments, payloads of the invention may be one of the PRRs, or agonists of PRRs.

8. Metabolic factors/metabolic checkpoint

[0376] In some embodiments, immune cells such as T cells used for immunotherapy may be metabolically reprogrammed to enhance anti-tumor T cell responses. Metabolic activities are necessary to support immune cells, specifically T cells growth, expansion, differentiation and effector functions, upon activation through T cell receptor or CAR and co-stimulatory signals. Metabolic competition between cancer cells and infiltrating immune effector cells leads to T cell energy and dysfunction.

[0377] In some embodiments, payloads of the present invention may be modulators of glycolysis. The Warburg effect in cancer cells leads to the massive generation of lactic acid that can suppress T cell cytotoxic and effector functions. As a non-limiting example, immune cells for adoptive transfer may be modified to overexpress phosphoenolpyruvate carboxykinase 1 (PCK1), which increases PEP production in T cells. Increased production of the glycolytic metabolite phosphoenolpyruvate (PEP) can repress sarco/ER Ca (2+)-ATPase (SERCA) activity, therefore sustaining T cell receptor-mediated Ca (2+)-NFAT signaling and effector functions (Ho et al, *Cell*, 2015, 162(6): 1217-1228).

[0378] In some embodiments, the payloads of the present invention may comprise of proteins involved in the OXPHOS pathway. For example, LEM (lymphocyte expansion molecule), a protein that can promote cytotoxic $CD8^+$ T cell proliferation and effector function, and memory T cell generation in response to infection with lymphocyte choriomeningitis (CMV). LEM is part of a complex of CRIF1 (CR6 interacting factor 1) that mediates the translation and insertion of OXPHOS (Oxidative phosphorylation) proteins into mitochondrial inner membrane, thereby regulates OXPHOS activity. Thus, LEM is a positive modulator of T cell metabolism (mitochondria respiratory levels) and expansion (Okoye et al., *Science*, 2015, 348(6238): 995-1001).

[0379] In some embodiments, the payloads of the present invention may be inhibitors of metabolic enzymes involved in amino acid regulation. Metabolic competition for between immune cells and tumor cells can lead to establishing and maintaining an immunosuppressive tumor microenvironment due to T cell energy. Non-limiting examples include inhibitors of nitric oxide synthase and arginase I that can degrade extracellular arginine, or Indoleamine 2,3- dioxygense (IDO) that degrades tryptophan. Abrogation of these enzymes secreted by tumor cells and immune suppressive cells can promote antitumor immunity.

[0380] In other embodiments, payloads of the present invention may comprise proteins critical for *de novo* fatty acid and cholesterol biosynthesis. This may include proteins such as SREBP1 (also known as SREBF1), SREBP2 (SREBF2), HMGCR, HMGCS, FASN, ACACA and SQLE, and transport pathways, such as LDLR. Modulating cholesterol metabolism of cytotoxic $CD8^+$ T cells may potentiate their anti-tumor effector function and proliferation. Cholesterol is a key component of membrane lipids, and has been shown that the increase in the plasma membrane cholesterol level of $CD8^+$ T cells, enhances T-cell receptor clustering and signaling as well as more efficient formation of the immunological synapse (Molnár et al., *J Biol Chem*. 2012, 287:42664–42674). T cells used for adoptive transfer (e.g., anti-tumor CAR T cells) may be further engineered to express a protein that enhances cholesterol biosynthesis and/or transportation.

9. Safety switch

[0381] In some embodiments, payloads of the present invention may comprise SRE regulated safety switches that can eliminate adoptively transferred cells in the case of severe toxicity, thereby mitigating the adverse effects of T cell therapy. Adoptively transferred T cells in immunotherapy may attack normal cells in response to normal tissue expression of TAA. Even on-tumor target activity of adoptively transferred T cells can result in toxicities

such as tumor lysis syndrome, cytokine release syndrome and the related macrophage activation syndrome.

[0382] In one embodiment, the payloads of the present invention may eliminate the inappropriately activated cells by induction of apoptosis or by immunosurveillance have been developed in the art.

[0383] In some embodiments, payloads of the present invention may comprise inducible killer/suicide genes that acts as a safety switch. The killer/suicide gene when introduced into adoptively transferred immune cells, could control their alloreactivity. The killer/suicide gene may be an apoptotic gene (e.g., a caspase) which allows conditional apoptosis of the transduced cells by administration of a non-therapeutic ligand of the SRE (e.g., DD).

[0384] In some embodiments, the payload of the present invention may include Caspase 9. In some instances, Caspase 9 may be modified to have low basal expression and lacking the caspase recruitment domain (CARD) (SEQ ID NO.: 26 and SEQ ID NO.: 28 of US Patent No. US9434935B2; the contents of which are incorporated by reference in their entirety).

[0385] In one embodiment, the payload of the present invention is a suicide gene system, iCasp9/Chemical induced dimerization (CID) system which consists of a polypeptide derived from the Caspase9 gene fused to a drug binding domain derived from the human FK506 protein. Administration of bioinert, small molecule AP1903(rimiducid), induces cross linking of the drug binding domains and dimerization of the fusion protein and in turn the dimerization of Caspase 9. This results in the activation of downstream effector Caspase 3 and subsequent induction of cellular apoptosis (Straathof et al., *Blood*, 2005, 105: 4247–4254; incorporated herein by reference in its entirety). Preclinical trials using CART including an iCasp9 gene have shown effective elimination of CAR T cells *invivo* in mouse models and demonstrate the potential efficacy of this approach. (Budde et al, *Plos One*, 2013, 8: e82742.10.1371; Hoyos et al., *Leukemia*, 2010; 24(6):1160-1170). In one embodiment, the payload of the invention may comprise Caspase9. In one aspect, the effector module of the invention may be a DD-Caspase9 fusion polypeptide. In some embodiments, the payload of the invention may be full length Caspase 9 (SEQ ID NO. 8364, encoded by SEQ ID No. 8365, 8366) or caspase 9 delta CD (SEQ ID NO. 8367, encoded by SEQ ID No. 8368). The Caspases 9 sequences described herein may optionally include a stop codon at the C terminal of the sequence.

[0386] In some instances, the iCasp9/CID system has been shown to have a basal rate of dimerization even in the absence of rimiducid, resulting in unintended cell death. Regulating the expression levels of iCasp9/CID is critical for maximizing the efficacy of iCasp9/CID

system. Biocircuits of the present invention and/or any of their components may be utilized in regulating or tuning the iCasp9/CID system in order to optimize its utility. Other examples of proteins used in dimerization-induced apoptosis paradigm may include, but are not limited to Fas receptor, the death effector domain of Fas-associated protein, FADD, Caspase 1, Caspase 3, Caspase 7 and Caspase 8. (Belshaw P.J. et al, *Chem Biol.*, 996,3:731-738; MacCorkle R.A. et al, *Proc Natl Acad Sci*, 1998, 95:3655-3660; Spencer, D.M. et al., *Curr Biol.*1996; 6:839-847; the contents of each of which are incorporated herein by reference in their entirety).

[0387] In some embodiments, the safety switch of the present invention may comprise a metabolic enzyme, such as herpes simplex virus thymidine kinase (HSV-TK) and cytosine deaminase (CD). HSV-TK phosphorylates nucleoside analogs, including acyclovir and ganciclovir (GCV) to generate triphosphate form of nucleosides. When incorporated into DNA, it leads to chain termination and cell death. Unlike the mammalian thymidine kinase, HSV-TK is characterized by 1000-fold higher affinity to nucleoside analogs such as GCV, making it suitable for use as a suicide gene in mammalian cells. Cytosine deaminase (CD) can converts 5-fluorocytosine (5-FC) into the cytotoxic 5-fluorouracil (5-FU) (Tiraby et al., *FEMS* Lett., 1998, 167: 41–49).

[0388] In some embodiments, the safety switch of the present invention may comprise a CYP4B1 mutant (as suicide gene), which may be co-expressed in a CAR engineered T cells (Roellecker et al., *Gen Ther.*, 2016, May 19, doi: 10.1038/gt.2016.38.).

[0389] In some embodiments, the payload of the present invention may comprise a fusion construct that can induce cell death, for example, a polypeptide with the formula of St-R1-S1-Q-S2-R2, wherein the St is a stalk sequence, R1/2 and Q are different epitopes; and S1/2 are optional spacer sequences (See, International patent publication NO.: WO2013/153391; the content of which are incorporated herein by reference in their entirety).

[0390] In some embodiments, safety switch may be mediated by therapeutic antibodies which specifically bind to an antigen that is expressed in the plasma membrane of adoptively transferred cells. The antigen-antibody interaction allows cell removal after administration of a specific monoclonal antibody against the antigen. As non-limiting examples, payloads of the present invention may comprise the antigen and antibody pair used to mediate safety switch such as CD20 and anti-CD20 antibody (Griffioen et al., *Haematologica*, 2009, 94:1316–1320), a protein tag and anti-tag antibody (Kieback et al., *Natl. Acad. Sci. U.S.A.*, 2008, 105: 623–628), a compact suicide gene (RQR8) combining epitopes from CD34 (as a marker moiety) and CD20 (as a suicide moiety) which enables CD34 selection, cell tracking, as well as cell deletion after anti-CD20 monoclonal antibody administration (Philip et al.,

Blood, 2014, 124: 1277–1287); truncated human EGFR polypeptide and anti-EGFR monoclonal antibody (Wang et al., *Blood*, 2011, 118:1255–1263); and a compact polypeptide safety switch having a structural formula as discussed in U.S Patent Application Publication NO: 2015/0093401; the contents of each of which are incorporated herein by reference in their entirety.

10. Regulatory switch

[0391] The utility of adoptive cell therapy (ACT) has been limited by the high incidence of graft versus host disease (GVHD). GVHD occurs when adoptively transferred T cells elicit an immune response resulting in host tissue damage. Recognition of host antigens by the graft cells triggers a proinflammatory cytokine storm cascade that signifies acute GVHD. GVHD is characterized as an imbalance between the effector and the regulatory arms of the immune system. In some embodiments, the payloads of the present invention may be used as regulatory switches. As used herein "regulatory switch" refers proteins, which when expressed in target cells increase tolerance to the graft by enhancing the regulatory arm of the immune system.

[0392] In one embodiment, regulatory switches may include payloads that preferentially promote the expansion of regulatory T (Treg cells). Tregs are a distinct population of cells that are positively selected on high affinity ligands in the thymus and play an important role in the tolerance to self-antigens. In addition, T regs have also been shown to play a role in peripheral tolerance to foreign antigens. Since Tregs promote immune tolerance, expansion of Tregs with the compositions of the invention may be desirable to limit GVHD.

[0393] In some embodiments, the regulatory switch may include, but is not limited to T regs activation factors such NFκB, FOXO, nuclear receptor Nr4a, Retinoic acid receptor alpha, NFAT, AP-1 and SMAD. Such factors can result in the expression of Fork headbox P3 (FOXP3) in T cells resulting in the activation of the regulatory T cell program and the expansion of T cells.

[0394] In one embodiment, the regulatory switch may be FOXP3, a transcriptional regulator in T cells. A function of FOXP3 is to suppress the function of NFAT, which leads to the suppression of expression of many genes including IL2 and effector T-cell cytokines. FOXP3 acts also as a transcription activator for genes such as CD2S, Cytotoxic T-Lymphocyte Antigen Cytotoxic T-Lymphocyte Antigen 4 (CTLA4), glucocorticoid-induced TNF receptor family gene (GITR) and folate receptor 4. FOXP3 also inhibits the differentiation of IL17 producing helper T-cells (Th17) by antagonizing RORC (RAR related orphan receptor C). Isoforms of FOXP3 lacking exon2 (FOXP3 delta 2), or exon 7 (FOXP3

delta 7) may also be used as regulatory switches. In one aspect, the effector module of the invention may be a DD-FOXP3 fusion polypeptide. FOXP3 may be a full length FOXP3 (SEQ ID NO. 8369, encoded by SEQ ID NO. 8370); or FOXP3 (amino acid 2-431 of WT) (SEQ ID NO.8371, encoded by SEQ ID NO. 8372), delta 2 FOXP3 (SEQ ID NO. 8373, encoded by SEQ ID NO. 8374); or FOXP3 delta (amino acid 2-396 of WT) (SEQ ID NO. 8375, encoded by SEQ ID NO. 8376).

11. Homing receptors

[0395] In some embodiments, payloads of the present invention may comprise homing receptors that guide immunotherapeutic cells to different anatomical compartments, such as designated tumor sites. For example, T cells expressing a chimeric antigen receptor may be further modified to express a homing receptor that is not normally expressed by the T cell. As used herein, the term "homing receptor" is a receptor that guides a cell expressing the receptor to a designated organ, a particular tissue, or a particular type of cell. Such trafficking receptors favor T cell accumulation in certain target organs. In some embodiments, the homing receptors of the present invention may be adhesion molecules. In other embodiments, the homing receptors of the invention may be chemokine receptors which mediate chemotaxis to chemokines. As non-limiting examples, a homing receptor may be a B cell zone homing receptor such as CXCR5; T cell zone homing receptor such as CXCR7; a gastrointestinal homing receptor such as CCR9 and integrin $\alpha 4\beta 7$ (also known as lymphocyte Peyer patch adhesion molecule); a skin homing receptor such as CLA (cutaneous lymphocyte-associated antigen receptor), CCR4, CCR8 and CCR10 (See, e.g., International Patent Publication NO.: WO2016025454; the contents of which are incorporated herein by reference in their entirety). Other homing receptors include, without limitation, CXCR2 and CXCR1 which redirect chemokine receptor modified tumor-infiltrating lymphocytes to melanoma tumor (Idorn et al., *Methods Mol. Biol.*, 2016, 1428: 261-276; and Sapoznik et al., *Cancer Immunol Immunother.*, 2012, 61(10): 1833-1847); CCR2 which, when expressed by $CD8^+$ T cells, can home modified $CD8^+$ T cells to the site of prostate cancer in which the CCL2 (a CCR2 ligand) expression is increased (Garetto et al., *Oncotarget*, 2016, May 10. doi: 10.18632/oncotarget.9280); and CD103 as an intestinal homing receptor.

12. Immune signaling

[0396] Treatment with immunotherapeutic agents may induce immune cell signaling, leading to the activation of cell- type specific immune activities, ultimately resulting in an immune response. In some embodiments, payloads of the present invention may be immune signaling biomolecules used to achieve exogenous control of signaling pathways. Exemplary

immune signaling biomolecules include transcription factors such as Nuclear factor of activated T-cells (NFAT) (e.g., NFAT, NFAT2, NFAT3 and NFAT 4), Nuclear Factor Kappa B (NFκB), Signal transducer and activator of transcription (STAT), Activator protein-1 (AP-1), Rel, Fos, and Jun; kinases such as Janus Kinase (JAK), Extracellullar signal-regulated kinases (ERK), Mitogen- Activated Protein Kinases (MAPK), Mammalian target of rapamycin (mTOR), Phsophoinositide- dependent kinase (PDK), Protein kinase B (PKB), IkB kinase (IKK), Calcium/Calmodulin dependent kinase(CaMK); and other signaling molecules such as Ras, Cbl, Calmodulin (CaM), Calpain, and IkkB kinase.

[0397] In one embodiment, the payloads of the present invention may be administered in conjunction with inhibitors of SHP-1 and/or SHP-2. The tyrosine-protein phosphatase SHP1 (also known as PTPN6) and SHP2 (also known as PTPN11) are involved in the Programmed Cell Death (PD1) inhibitory signaling pathway. The intracellular domain of PD1 contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). ITSM has been shown to recruit SHP-1 and 2. This generates negative costimulatory micro clusters that induce the dephosphorylation of the proximal TCR signaling molecules, thereby resulting in suppression of T cell activation, which can lead to T cell exhaustion. In one embodiment, inhibitors of SHP-1 and 2 may include expressing dominant negative versions of the proteins in T cells, TILs or other cell types to relieve exhaustion. Such mutants can bind to the endogenous, catalytically active proteins, and inhibit their function. In one embodiment, the dominant negative mutant of SHP-1 and/ or SHP-2 lack the phosphatase domain required for catalytic activity. In some embodiments, any of the dominant negative SHP-1 mutants taught Bergeron S et al. (2011). Endocrinology. 2011 Dec;152(12):4581-8.; Dustin JB et al. (1999) J Immunol. Mar 1;162(5):2717-24.; Berchtold S (1998) Mol Endocrinol. Apr;12(4):556-67 and Schram et al. (2012) Am J Physiol Heart Circ Physiol. 1;302(1):H231-43.; may be useful in the invention (the contents of each of which are incorporated by reference in their entirety).

13. Oncolytic viruses

[0398] In some embodiments, payloads of the present invention may comprise oncolytic viruses or any components of oncolytic viruses. In some embodiments, the payload may be oncolytic viruses or components that have been genetically modified oncolytic viruses for use in oncolytic virotherapy. As used herein, the term "virotherapy" refers to a therapeutic use of oncolytic viruses (replication competent viruses) to attack and destroy cancer cells. Oncolytic viruses refer to those viruses that are able to eliminate malignancies by direct targeting and killing of cancer cells within the tumor, without causing harm to normal tissues. Exemplary

oncolytic viruses and genetically engineered oncolytic viruses with cancer specific tropism may include Arvoviruses, Adenoviruses, Coxsackie viruses, Herpes Simplex Viruses (HSVs), Measles, Mumps viruses, Moloney leukemia viruses, Myxovirus, Newcastle Disease Viruses, Reoviruses, Rhabdovirus, Vesticular Stomatic Viruses, and Vaccinia Viruses (VV). It may also be chimeric viruses with increased oncolytic potential such as an adeno-parvovirus chimera in US. Pat. NO.: 9,441,246. The oncolytic viruses may be modified to be less susceptible to immune suppression while more specifically targeting particular classes of cancer cells, or be modified to insert and express cancer-suppressing transgenes. Modifications to the oncolytic virus may also be made to improve replicative potential of the virus, increase viral titers, and/ or enhance the range cancer cells that can be infected by the virus. Examples of modified oncolytic viruses that may be used as payload include US Patent NO.: US8282917B2, International Patent Publication NO.: WO2011070440, WO2004078206A1, WO2016144564, WO2016119052, WO2009111892; the contents of each of which are incorporated herein by reference in their entirety.

[0399] In some embodiments, payloads of the present invention may be one or more coat proteins of the viruses, inserted transgenes, other factors that can increase intratumoral virus replication and the combinations.

[0400] In some instance, two or more oncolytic viruses may also be used as payload within the same SRE or in two or more SREs to achieve synergistic killing of target cancer cells as described in International Patent Publication NO.: WO2010020056 (the contents of which are incorporated herein by reference in their entirety).

14. Genomic editing systems

[0401] In some embodiments, payloads of the present invention may be components of gene editing systems including a CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), CRISPR enzyme (Cas9), CRISPR-Cas9 or CRISPR system and CRISPR-CAS9 complex. It may also be other genomic editing systems, such as Zinc finger nucleases, TALEN (Transcription activator-like effector-based nucleases) and meganucleases.

Additional features

[0402] The effector module of the present invention may further comprise a signal sequence which regulates the distribution of the payload, a cleavage and/or processing feature which facilitate cleavage of the payload from the effector module construct, a targeting and/or penetrating signal which can regulate the cellular localization of the effector module, and/or one or more linker sequences which link different components (e.g. a DD and a

payload) of the effector module. In some embodiments, the effector module may further comprise of one or more additional features such as linker sequences (with specific sequences and lengths), cleavage sites, regulatory elements (that regulate expression of the protein of interest such as microRNA targeting sites), signal sequences that lead the effector module to a specific cellular or subcellular location, penetrating sequences, or tags and biomarkers for tracking the effector module.

1. Signal sequences

[0403] In addition to the SRE (e.g., DD) and payload region, effector modules of the invention may further comprise one or more signal sequences. Signal sequences (sometimes referred to as signal peptides, targeting signals, target peptides, localization sequences, transit peptides, leader sequences or leader peptides) direct proteins (e.g., the effector module of the present invention) to their designated cellular and/or extracellular locations. Protein signal sequences play a central role in the targeting and translocation of nearly all secreted proteins and many integral membrane proteins.

[0404] A signal sequence is a short (5-30 amino acids long) peptide present at the N-terminus of the majority of newly synthesized proteins that are destined towards a particular location. Signal sequences can be recognized by signal recognition particles (SRPs) and cleaved using type I and type II signal peptide peptidases. Signal sequences derived from human proteins can be incorporated as a regulatory module of the effector module to direct the effector module to a particular cellular and/or extracellular location. These signal sequences are experimentally verified and can be cleaved (Zhang et al., *Protein Sci.* 2004, 13:2819-2824).

[0405] In some embodiments, a signal sequence may be, although not necessarily, located at the N-terminus or C-terminus of the effector module, and may be, although not necessarily, cleaved off the desired effector module to yield a "mature" payload, i.e., an immunotherapeutic agent as discussed herein.

[0406] In some examples, a signal sequence may be a secreted signal sequence derived from a naturally secreted protein, and its variant thereof. In some instances, the secreted signal sequences may be cytokine signal sequences such as, but not limited to, IL2 signal sequence comprising amino acid of SEQ ID NO. 261 (encoded by the nucleotide sequence of SEQ ID NO. 262-265), and/or p40 signal sequence comprising the amino acid sequence of SEQ ID NO. 266 (encoded by the nucleotide sequence of SEQ ID NO. 267-275).

[0407] In some instances, signal sequences directing the payload to the surface membrane of the target cell may be used. Expression of the payload on the surface of the target cell may

be useful to limit the diffusion of the payload to non-target *in vivo* environments, thereby potentially improving the safety profile of the payloads. Additionally, the membrane presentation of the payload may allow for physiologically and qualitative signaling as well as stabilization and recycling of the payload for a longer half-life. Membrane sequences may be the endogenous signal sequence of the N terminal component of the payload. Optionally, it may be desirable to exchange this sequence for a different signal sequence. Signal sequences may be selected based on their compatibility with the secretory pathway of the cell type of interest so that the payload is presented on the surface of the T cell. In some embodiments, the signal sequence may be IgE signal sequence comprising amino acid of SEQ ID NO. 276 (encoded by the nucleotide sequence of SEQ ID NO. 277) or CD8a signal sequence comprising amino acid SEQ ID NO. 278 (encoded by the nucleotide sequence of SEQ ID NO. 279-283).

[0408] Other examples of signal sequences include, a variant may be a modified signal sequence discussed in U.S. Pat. NOs. 8,148,494, 8,258,102, 9,133,265, 9,279,007, and U.S. patent application publication NO. 2007/0141666; and International patent application publication NO. WO1993/018181; the contents of each of which are incorporated herein by reference in their entirety. In other examples, a signal sequence may be a heterogeneous signal sequence from other organisms such as virus, yeast and bacteria, which can direct an effector module to a particular cellular site, such as a nucleus (e.g., EP 1209450). Other examples may include Aspartic Protease (NSP24) signal sequences from *Trichoderma* that can increase secretion of fused protein such as enzymes (e.g., U. S. Pat. NO. 8,093,016 to Cervin and Kim), bacterial lipoprotein signal sequences (e.g., PCT application publication NO. 1991/09952 to Lau and Rioux), *E.coli* enterotoxin II signal peptides (e.g., U.S. Pat. NO. 6,605,697 to Kwon et al.), *E.coli* secretion signal sequence (e.g., U.S. patent publication NO. 2016/090404 to Malley et al.), a lipase signal sequence from a methylotrophic yeast (e.g., U.S. Pat. NO. 8,975,041), and signal peptides for DNases derived from *Coryneform bacteria* (e.g., U.S. Pat. NO. 4,965,197); the contents of each of which are incorporated herein by reference in their entirety.

[0409] Signal sequences may also include nuclear localization signals (NLSs), nuclear export signals (NESs), polarized cell tubulo-vesicular structure localization signals (See, e.g., U.S. Pat. NO.: 8, 993,742; Cour et al., *Nucleic Acids Res.* 2003, 31(1): 393-396; the contents of each of which are incorporated herein by reference in their entirety), extracellular localization signals, signals to subcellular locations (e.g. lysosome, endoplasmic reticulum, golgi, mitochondria, plasma membrane and peroxisomes, etc.) (See, e.g., U.S. Pat. NO.

7,396,811; and Negi et al., *Database,* 2015, 1-7; the contents of each of which are incorporated herein by reference in their entirety).

2. Cleavage sites

[0410] In some embodiments, the effector module comprises a cleavage and/or processing feature. The effector module of the present invention may include at least one protein cleavage signal/site. The protein cleavage signal/site may be located at the N-terminus, the C-terminus, at any space between the N- and the C- termini such as, but not limited to, half-way between the N- and C-termini, between the N-terminus and the half-way point, between the half-way point and the C-terminus, and combinations thereof.

[0411] The effector module may include one or more cleavage signal(s)/site(s) of any proteinases. The proteinases may be a serine proteinase, a cysteine proteinase, an endopeptidase, a dipeptidase, a metalloproteinase, a glutamic proteinase, a threonine proteinase and an aspartic proteinase. In some aspects, the cleavage site may be a signal sequence of furin, actinidain, calpain-1, carboxypeptidase A, carboxypeptidase P, carboxypeptidase Y, caspase-1, caspase-2, caspase-3, caspase-4, caspase-5, caspase-6, caspase-7, caspase-8, caspase-9, caspase-10, cathepsin B, cathepsin C, cathepsin G, cathepsin H, cathepsin K, cathepsin L, cathepsin S, cathepsin V, clostripain, chymase, chymotrypsin, elastase, endoproteinase, enterokinase, factor Xa, formic acid, granzyme B, Matrix metallopeptidase-2, Matrix metallopeptidase-3, pepsin, proteinase K, SUMO protease, subtilisin, TEV protease, thermolysin, thrombin, trypsin and TAGZyme.

[0412] In one embodiment, the cleavage site is a furin cleavage site comprising the amino acid sequence SARNRQKRS (SEQ ID NO. 284, encoded by the nucleotide sequence of SEQ ID NO. 285), or a revised furin cleavage site comprising the amino acid sequence ARNRQKRS (SEQ ID NO. 286, encoded by the nucleotide sequence of SEQ ID NO. 287), or a modified furin site comprising the amino acid sequence ESRRVRRNKRSK (SEQ ID NO. 288, encoded by the nucleotide sequence of SEQ ID NO. 289-291).

3. Protein tags

[0413] In some embodiments, the effector module of the invention may comprise a protein tag. The protein tag may be used for detecting and monitoring the process of the effector module. The effector module may include one or more tags such as an epitope tag (e.g., a FLAG or hemagglutinin (HA) tag). A large number of protein tags may be used for the present effector modules. They include, but are not limited to, self-labeling polypeptide tags (e.g., haloalkane dehalogenase (halotag2 or halotag7), ACP tag, clip tag, MCP tag, snap tag), epitope tags (e.g., FLAG, HA, His, and Myc), fluorescent tags (e.g., green fluorescent protein

(GFP), red fluorescent protein (RFP), yellow fluorescent protein (YFP), and its variants), bioluminescent tags (e.g. luciferase and its variants), affinity tags (e.g., maltose-binding protein (MBP) tag, glutathione-S-transferase (GST) tag), immunogenic affinity tags (e.g., protein A/G, IRS, AU1, AU5, glu-glu, KT3, S-tag, HSV, VSV-G, Xpress and V5), and other tags (e.g., biotin (small molecule), StrepTag (StrepII), SBP, biotin carboxyl carrier protein (BCCP), eXact, CBP, CYD, HPC, CBD intein-chitin binding domain, Trx, NorpA, and NusA.

[0414] In other embodiments, a tag may also be selected from those disclosed in U.S. Pat. NOs.: 8,999,897; 8,357,511; 7,094,568; 5,011,912; 4,851,341; and 4,703,004; U.S patent application publication NOs.: 2013/115635 and 2013/012687; and International application publication NO.: WO2013/091661; the contents of each of which are incorporated herein by reference in their entirety.

[0415] In some aspects, a multiplicity of protein tags, either the same or different tags, may be used; each of the tags may be located at the same N- or C-terminus, whereas in other cases these tags may be located at each terminus.

4. Targeting peptides

[0416] In some embodiments, the effector module of the invention may further comprise a targeting and/or penetrating peptide. Small targeting and/or penetrating peptides that selectively recognize cell surface markers (e.g. receptors, trans-membrane proteins, and extra-cellular matrix molecules) can be employed to target the effector module to the desired organs, tissues or cells. Short peptides (5-50 amino acid residues) synthesized *in vitro* and naturally occurring peptides, or analogs, variants, derivatives thereof, may be incorporated into the effector module for homing the effector module to the desired organs, tissues and cells, and/or subcellular locations inside the cells.

[0417] In some embodiments, a targeting sequence and/or penetrating peptide may be included in the effector module to drive the effector module to a target organ, or a tissue, or a cell (e.g., a cancer cell). In other embodiments, a targeting and/or penetrating peptide may direct the effector module to a specific subcellular location inside a cell.

[0418] A targeting peptide has any number of amino acids from about 6 to about 30 inclusive. The peptide may have 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 amino acids. Generally, a targeting peptide may have 25 or fewer amino acids, for example, 20 or fewer, for example 15 or fewer.

[0419] Exemplary targeting peptides may include, but are not limited to, those disclosed in the art, e.g., U.S. Pat. NOs. 9,206,231, 9,110,059, 8,706,219; and 8,772,449, and U.S.

application publication NOs. 2016/089447. 2016/060296. 2016/060314. 2016/060312. 2016/060311. 2016/009772. 2016/002613. 2015/314011 and 2015/166621. and International application publication NOs. WO2015/179691 and WO2015/183044; the contents of each of which are incorporated herein by reference in their entirety.

5. Linkers

[0420] In some embodiments, the effector module of the invention may further comprise a linker sequence. The linker region serves primarily as a spacer between two or more polypeptides within the effector module. A "linker" or "spacer", as used herein, refers to a molecule or group of molecules that connects two molecules, or two parts of a molecule such as two domains of a recombinant protein.

[0421] In some embodiments, “Linker" (L) or "linker domain" or "linker region" or “linker module” or “peptide linker” as used herein refers to an oligo- or polypeptide region of from about 1 to 100 amino acids in length, which links together any of the domains/regions of the effector module (also called peptide linker). The peptide linker may be 1-40 amino acids in length, or 2-30 amino acids in length, or 20-80 amino acids in length, or 50-100 amino acids in length. Linker length may also be optimized depending on the type of payload utilized and based on the crystal structure of the payload. In some instances, a shorter linker length may be preferably selected. In some aspects, the peptide linker is made up of amino acids linked together by peptide bonds, preferably from 1 to 20 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally occurring amino acids: Glycine (G), Alanine (A), Valine (V), Leucine (L), Isoleucine (I), Serine (S), Cysteine (C), Threonine (T), Methionine (M), Proline (P), Phenylalanine (F), Tyrosine (Y), Tryptophan (W), Histidine (H), Lysine (K), Arginine (R), Aspartate (D), Glutamic acid (E), Asparagine (N), and Glutamine (Q). One or more of these amino acids may be glycosylated, as is understood by those in the art. In some aspects, amino acids of a peptide linker may be selected from Alanine (A), Glycine (G), Proline (P), Asparagine (R), Serine (S), Glutamine (Q) and Lysine (K).

[0422] In one example, an artificially designed peptide linker may preferably be composed of a polymer of flexible residues like Glycine (G) and Serine (S) so that the adjacent protein domains are free to move relative to one another. Longer linkers may be used when it is desirable to ensure that two adjacent domains do not interfere with one another. The choice of a particular linker sequence may concern if it affects biological activity, stability, folding, targeting and/or pharmacokinetic features of the fusion construct. Examples of peptide linkers include, but are not limited to: SG, MH, GGSG (SEQ ID NO.

292, encoded by the nucleotide sequence of SEQ ID NO. 293; GGSGG (SEQ ID NO. 294), encoded by the nucleotide sequence of SEQ ID NOs. 295-299; GGSGGG (SEQ ID NO. 78), encoded by the nucleotide sequence of SEQ ID NO. 93 and 300; SGGGS (SEQ ID NO. 301), encoded by the nucleotide sequence of SEQ ID NO. 302-303; GGSGGGSGG (SEQ ID NO. 77), encoded by the nucleotide sequence of SEQ ID NO. 92; GGGGG (SEQ ID NO. 304), GGGGS (SEQ ID NO. 305) or (GGGGS)n (n= 2 (SEQ ID NO. 306), 3 (SEQ ID NO. 307; encoded by SEQ ID NO. 308-313), 4 (SEQ ID NO. 314), 5 (SEQ ID NO. 315), or 6 (SEQ ID NO. 316)), SSSSG (SEQ ID NO. 317) or (SSSSG)n (n= 2 (SEQ ID NO. 318), 3 (SEQ ID NO. 319), 4 (SEQ ID NO. 320), 5 (SEQ ID NO. 321), or 6 (SEQ ID NO. 322)), SGGGSGGGGSGGGGSGGGGSGGGSLQ (SEQ ID NO. 323), encoded by the nucleotide sequence of SEQ ID NO. 324; EFSTEF (SEQ ID NO. 325), encoded by the nucleotide sequence of SEQ ID NOs. 326-327; GKSSGSGSESKS (SEQ ID NO. 328), GGSTSGSGKSSEGKG (SEQ ID NO. 329), GSTSGSGKSSSEGSGSTKG (SEQ ID NO. 330), GSTSGSGKPGSGEGSTKG (SEQ ID NO. 331), VDYPYDVPDYALD (SEQ ID NO. 332), encoded by the nucleotide sequence of SEQ ID NO. 333; or EGKSSGSGSESKEF (SEQ ID NO. 334) ; or GSGSGS (SEQ ID NO. 8330), encoded by the nucleotide sequence of SEQ ID NO. 8347; or GSGSGSGS (SEQ ID NO. 8331), encoded by the nucleotide sequence of SEQ ID NO. 8348; or GSGSGGGSGS (SEQ ID NO. 8332), encoded by the nucleotide sequence of SEQ ID NO. 8349; SGSGSGS linker (SEQ ID NO: 8382), or SG linker, encoded by AGTGGT; or an LD Linker comprising Lysine Aspartic acid, encoded by CTAGAT. Linkers may also be DNA restriction enzyme recognition sites or modifications thereof such as flexible GS or G/S rich linker; BamH1 Site encoded by GGATCC; flexible G/S rich linker or BamH1 Site; SR/Xba I site, encoded by TCTAGA; or a GSG linker (BamH1-Gly) linker, encoded by GGATCCGGA.

[0423] In other examples, a peptide linker may be made up of a majority of amino acids that are sterically unhindered, such as Glycine (G) and Alanine (A). Exemplary linkers are polyglycines (such as $(G)_4$ (SEQ ID NO: 8378), $(G)_5$ (SEQ ID NO: 8379), $(G)_8$ (SEQ ID NO: 8380)), poly(GA), and polyalanines. The linkers described herein are exemplary, and linkers that are much longer and which include other residues are contemplated by the present invention.

[0424] A linker sequence may be a natural linker derived from a multi-domain protein. A natural linker is a short peptide sequence that separates two different domains or motifs within a protein.

[0425] In some aspects, linkers may be flexible or rigid. In other aspects, linkers may be cleavable or non- cleavable. As used herein, the terms "cleavable linker domain or region" or "cleavable peptide linker" are used interchangeably. In some embodiments, the linker sequence may be cleaved enzymatically and/or chemically. Examples of enzymes (e.g., proteinase/peptidase) useful for cleaving the peptide linker include, but are not limited, to Arg-C proteinase, Asp-N endopeptidase, chymotrypsin, clostripain, enterokinase, Factor Xa, glutamyl endopeptidase, Granzyme B, Achromobacter proteinase I, pepsin, proline endopeptidase, proteinase K, Staphylococcal peptidase I, thermolysin, thrombin, trypsin, and members of the Caspase family of proteolytic enzymes (e.g. Caspases 1-10). Chemical sensitive cleavage sites may also be included in a linker sequence. Examples of chemical cleavage reagents include, but are not limited to, cyanogen bromide, which cleaves methionine residues; N-chloro succinimide, iodobenzoic acid or BNPS-skatole [2-(2-nitrophenylsulfenyl)-3-methylindole], which cleaves tryptophan residues; dilute acids, which cleave at aspartyl-prolyl bonds; and e aspartic acid-proline acid cleavable recognition sites (i.e., a cleavable peptide linker comprising one or more D-P dipeptide moieties). The fusion module may include multiple regions encoding peptides of interest separated by one or more cleavable peptide linkers.

[0426] In other embodiments, a cleavable linker may be a "self-cleaving" linker peptide, such as 2A linkers (for example T2A), 2A-like linkers or functional equivalents thereof and combinations thereof. In some embodiments, the linkers include the picornaviral 2A-like linker, CHYSEL sequences of porcine teschovirus (P2A), Thosea asigna virus (T2A) or combinations, variants and functional equivalents thereof. In some embodiments, the biocircuits of the present invention may include 2A peptides. The 2A peptide is a sequence of about 20 amino acid residues from a virus that is recognized by a protease (2A peptidases) endogenous to the cell. The 2A peptide was identified among picornaviruses, a typical example of which is the Foot-and Mouth disease virus (Robertson BH, et. al., J Virol 1985, 54:651-660). 2A-like sequences have also been found in Picornaviridae like equine rhinitis A virus, as well as unrelated viruses such as porcine teschovirus-1 and the insect Thosea asigna virus (TaV). In such viruses, multiple proteins are derived from a large polyprotein encoded by an open reading frame. The 2A peptide mediates the co-translational cleavage of this polyprotein at a single site that forms the junction between the virus capsid and replication polyprotein domains. The 2A sequences contain the consensus motif D-V/I-E-X-N-P-G-P (SEQ ID NO: 8381). These sequences are thought to act co-translationally, preventing the formation of a normal peptide bond between the glycine and last proline, resulting in the

ribosome skipping of the next codon (Donnelly ML et al. (2001). J Gen Virol, 82:1013-1025). After cleavage, the short peptide remains fused to the C -terminus of the protein upstream of the cleavage site, while the proline is added to the N-terminus of the protein downstream of the cleavage site. Of the 2A peptides identified, four have been widely used namely FMDV 2A (abbreviated herein as F2A); equine rhinitis A virus (ERAV) 2A (E2A); porcine teschovirus-1 2A (P2A) and Thoseaasigna virus 2A (T2A). In some embodiments, the 2A peptide sequences useful in the present invention are selected from SEQ ID NO.8-11 of International Patent Publication WO2010042490, the contents of which are incorporated by reference in its entirety. In some embodiments, the cleavage site may be a P2A cleavable peptide (SEQ ID NO. 8239), encoded by the nucleotide sequence of SEQ ID NO. 8269.

[0427] Other linkers will be apparent to those skilled in the art and may be used in connection with alternate embodiments of the invention.

[0428] The linkers of the present invention may also be non-peptide linkers. For example, alkyl linkers such as —NH—(CH_2) a-C(O)—, wherein a=2-20 can be used. These alkyl linkers may further be substituted by any non-sterically hindering group such as lower alkyl (e.g., C_1-C_6) lower acyl, halogen (e.g., Cl, Br), CN, NH_2, phenyl, etc.

[0429] In some aspects, the linker may be an artificial linker from U.S. Pat. NOs. 4,946,778, 5,525,491, 5,856,456, and International patent publication NO. WO2012/083424; the contents of each of which are incorporated herein by reference in their entirety.

6. Embedded stimulus, signals and other regulatory features

[0430] microRNAs (or miRNA) are 19-25 nucleotide long noncoding RNAs that bind to the 3′UTR of nucleic acid molecules and down-regulate gene expression either by reducing nucleic acid molecule stability or by inhibiting translation. The polynucleotides of the invention may comprise one or more microRNA target sequences, microRNA sequences, or microRNA seeds. Such sequences may correspond to any known microRNA such as those taught in US Publication No. US2005/0261218 and US Publication No. US2005/0059005, the contents of which are incorporated herein by reference in their entirety. As a non-limiting embodiment, known microRNAs, their sequences and their binding site sequences in the human genome are listed Table 14 of the co-owned U.S. Provisional Patent Application No. 62/320,864 filed April 11, 2016, 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587 (the contents of each of which are herein incorporated by reference in their entirety).

[0431] A microRNA sequence comprises a “seed” region, i.e., a sequence in the region of positions 2-8 of the mature microRNA, which sequence has perfect Watson-Crick

complementarity to the miRNA target sequence. A microRNA seed may comprise positions 2-8 or 2-7 of the mature microRNA. In some embodiments, a microRNA seed may comprise 7 nucleotides (e.g., nucleotides 2-8 of the mature microRNA), wherein the seed-complementary site in the corresponding miRNA target is flanked by an adenine (A) opposed to microRNA position 1. In some embodiments, a microRNA seed may comprise 6 nucleotides (e.g., nucleotides 2-7 of the mature microRNA), wherein the seed-complementary site in the corresponding miRNA target is flanked by an adenine (A) opposed to microRNA position 1. See for example, Grimson A, Farh KK, Johnston WK, Garrett-Engele P, Lim LP, Bartel DP; Mol Cell. 2007 Jul 6;27(1):91-105. The bases of the microRNA seed have complete complementarity with the target sequence. By engineering microRNA target sequences into the polynucleotides encoding the biocircuit components, effector modules, SREs or payloads of the invention one can target the molecule for degradation or reduced translation, provided the microRNA in question is available. This process will reduce the hazard of off target effects upon nucleic acid molecule delivery.

[0432] Identification of microRNA, microRNA target regions, and their expression patterns and role in biology have been reported (Bonauer et al., Curr Drug Targets 2010 11:943-949; Anand and Cheresh Curr Opin Hematol 2011 18:171-176; Contreras and Rao Leukemia 2012 26:404-413 (2011 Dec 20. doi: 10.1038/leu.2011.356); Bartel Cell 2009 136:215-233; Landgraf et al, Cell, 2007 129:1401-1414; Gentner and Naldini, Tissue Antigens. 2012 80:393-403 and all references therein; each of which is herein incorporated by reference in its entirety).

[0433] For example, if the polynucleotide is not intended to be delivered to the liver but ends up there, then miR-122, a microRNA abundant in liver, can inhibit the expression of the polynucleotide if one or multiple target sites of miR-122 are engineered into the polynucleotide. Introduction of one or multiple binding sites for different microRNA can be engineered to further decrease the longevity, stability, and protein translation of a polynucleotide hence providing an additional layer of tenability beyond the stimulus selection, SRE design and payload variation.

[0434] As used herein, the term “microRNA site” refers to a microRNA target site or a microRNA recognition site, or any nucleotide sequence to which a microRNA binds or associates. It should be understood that “binding” may follow traditional Watson-Crick hybridization rules or may reflect any stable association of the microRNA with the target sequence at or adjacent to the microRNA site.

[0435] Conversely, for the purposes of the polynucleotides of the present invention, microRNA binding sites can be engineered out of (i.e. removed from) sequences in which they naturally occur in order to increase protein expression in specific tissues. For example, miR-122 binding sites may be removed to improve protein expression in the liver.

[0436] Regulation of expression in multiple tissues can be accomplished through introduction or removal or one or several microRNA binding sites.

[0437] Specifically, microRNAs are known to be differentially expressed in immune cells (also called hematopoietic cells), such as antigen presenting cells (APCs) (e.g. dendritic cells and macrophages), macrophages, monocytes, B lymphocytes, T lymphocytes, granulocytes, natural killer cells, etc. Immune cell specific microRNAs are involved in immunogenicity, autoimmunity, the immune -response to infection, inflammation, as well as unwanted immune response after gene therapy and tissue/organ transplantation. Immune cells specific microRNAs also regulate many aspects of development, proliferation, differentiation and apoptosis of hematopoietic cells (immune cells). For example, miR-142 and miR-146 are exclusively expressed in the immune cells, particularly abundant in myeloid dendritic cells. Introducing the miR-142 binding site into the 3'-UTR of a polypeptide of the present invention can selectively suppress the gene expression in the antigen presenting cells through miR-142 mediated mRNA degradation, limiting antigen presentation in professional APCs (e.g. dendritic cells) and thereby preventing antigen-mediated immune response after gene delivery (see, Annoni A et al., blood, 2009, 114, 5152-5161, the content of which is herein incorporated by reference in its entirety.)

[0438] In one embodiment, microRNAs binding sites that are known to be expressed in immune cells, in particular, the antigen presenting cells, can be engineered into the polynucleotides to suppress the expression of the polynucleotide in APCs through microRNA mediated RNA degradation, subduing the antigen-mediated immune response, while the expression of the polynucleotide is maintained in non-immune cells where the immune cell specific microRNAs are not expressed.

[0439] Many microRNA expression studies have been conducted, and are described in the art, to profile the differential expression of microRNAs in various cancer cells /tissues and other diseases. Some microRNAs are abnormally over-expressed in certain cancer cells and others are under-expressed. For example, microRNAs are differentially expressed in cancer cells (WO2008/154098, US2013/0059015, US2013/0042333, WO2011/157294); cancer stem cells (US2012/0053224); pancreatic cancers and diseases (US2009/0131348, US2011/0171646, US2010/0286232, US8389210); asthma and inflammation (US8415096);

prostate cancer (US2013/0053264); hepatocellular carcinoma (WO2012/151212, US2012/0329672, WO2008/054828, US8252538); lung cancer cells (WO2011/076143, WO2013/033640, WO2009/070653, US2010/0323357); cutaneous T cell lymphoma (WO2013/011378); colorectal cancer cells (WO2011/0281756, WO2011/076142); cancer positive lymph nodes (WO2009/100430, US2009/0263803); nasopharyngeal carcinoma (EP2112235); chronic obstructive pulmonary disease (US2012/0264626, US2013/0053263); thyroid cancer (WO2013/066678); ovarian cancer cells (US2012/0309645, WO2011/095623); breast cancer cells (WO2008/154098, WO2007/081740, US2012/0214699), leukemia and lymphoma (WO2008/073915, US2009/0092974, US2012/0316081, US2012/0283310, WO2010/018563, the content of each of which is incorporated herein by reference in their entirety).

[0440] In one embodiment, microRNA may be used as described herein in support of the creation of tunable biocircuits.

[0441] In some embodiments, effector modules may be designed to encode (as a DNA or RNA or mRNA) one or more payloads, SREs and/or regulatory sequence such as a microRNA or microRNA binding site. In some embodiments, any of the encoded payloads or SREs may be stabilized or de-stabilized by mutation and then combined with one or more regulatory sequences to generate a dual or multi-tuned effector module or biocircuit system.

[0442] Each aspect or tuned modality may bring to the effector module or biocircuit a differentially tuned feature. For example, an SRE may represent a destabilizing domain, while mutations in the protein payload may alter its cleavage sites or dimerization properties or half-life and the inclusion of one or more microRNA or microRNA binding site may impart cellular detargeting or trafficking features. Consequently, the present invention embraces biocircuits which are multifactorial in their tenability.

[0443] In some embodiments, compositions of the invention may include optional proteasome adaptors. As used herein, the term "proteasome adaptor" refers to any nucleotide/ amino acid sequence that targets the appended payload for degradation. In some aspects, the adaptors target the payload for degradation directly thereby circumventing the need for ubiquitination reactions. Proteasome adaptors may be used in conjunction with destabilizing domains to reduce the basal expression of the payload. Exemplary proteasome adaptors include the UbL domain of Rad23 or hHR23b, HPV E7 which binds to both the target protein Rb and the S4 subunit of the proteasome with high affinity, which allows direct proteasome targeting, bypassing the ubiquitination machinery; the protein gankyrin which binds to Rb and the proteasome subunit S6.

[0444] Such biocircuits may be engineered to contain one, two, three, four or more tuned features.

Polynucleotides

[0445] The present invention provides polynucleotides encoding novel hPDE5 DDs, effector modules comprising payloads and associated DDs, biocircuit systems comprising DDs and effector modules, and other components of the present invention.

[0446] The invention provides isolated biocircuit polypeptides, effector modules, stimulus response elements (SREs) and payloads, as well as polynucleotides encoding any of the foregoing; vectors comprising polynucleotides of the invention; and cells expressing polypeptides, polynucleotides and vectors of the invention. The polypeptides, polynucleotides, viral vectors and cells are useful for inducing anti-tumor immune responses in a subject.

[0447] The term "polynucleotide" or "nucleic acid molecule" in its broadest sense, includes any compound and/or substance that comprise a polymer of nucleotides, e.g., linked nucleosides. These polymers are often referred to as polynucleotides. Exemplary nucleic acids or polynucleotides of the invention include, but are not limited to, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β- D-ribo configuration, α-LNA having an α-L-ribo configuration (a diastereomer of LNA), 2′-amino-LNA having a 2′-amino functionalization, and 2′-amino- α-LNA having a 2′-amino functionalization) or hybrids thereof.

[0448] In some embodiments, polynucleotides of the invention may be a messenger RNA (mRNA) or any nucleic acid molecule and may or may not be chemically modified. In one aspect, the nucleic acid molecule is a mRNA. As used herein, the term "messenger RNA (mRNA)" refers to any polynucleotide which encodes a polypeptide of interest and which is capable of being translated to produce the encoded polypeptide of interest *in vitro*, *in vivo*, *in situ* or *ex vivo*.

[0449] Traditionally, the basic components of an mRNA molecule include at least a coding region, a 5′UTR, a 3′UTR, a 5′ cap and a poly-A tail. Building on this wild type modular structure, the present invention expands the scope of functionality of traditional mRNA molecules by providing payload constructs which maintain a modular organization, but which comprise one or more structural and/or chemical modifications or alterations which impart useful properties to the polynucleotide, for example tenability of function. As used herein, a "structural" feature or modification is one in which two or more linked nucleosides

are inserted, deleted, duplicated, inverted or randomized in a polynucleotide without significant chemical modification to the nucleosides themselves. Because chemical bonds will necessarily be broken and reformed to effect a structural modification, structural modifications are of a chemical nature and hence are chemical modifications. However, structural modifications will result in a different sequence of nucleotides. For example, the polynucleotide "ATCG" may be chemically modified to "AT-5meC-G". The same polynucleotide may be structurally modified from "ATCG" to "ATCCCG". Here, the dinucleotide "CC" has been inserted, resulting in a structural modification to the polynucleotide.

[0450] In some embodiments, polynucleotides of the present invention may harbor 5'UTR sequences which play a role in translation initiation. 5'UTR sequences may include features such as Kozak sequences which are commonly known to be involved in the process by which the ribosome initiates translation of genes, Kozak sequences have the consensus XCCR(A/G) CCAUG, where R is a purine (adenine or guanine) three bases upstream of the start codon (AUG) and X is any nucleotide. In one embodiment, the Kozak sequence is ACCGCC. By engineering the features that are typically found in abundantly expressed genes of target cells or tissues, the stability and protein production of the polynucleotides of the invention can be enhanced.

[0451] Further provided are polynucleotides, which may contain an internal ribosome entry site (IRES) which play an important role in initiating protein synthesis in the absence of 5' cap structure in the polynucleotide. An IRES may act as the sole ribosome binding site, or may serve as one of the multiple binding sites. Polynucleotides of the invention containing more than one functional ribosome binding site may encode several peptides or polypeptides that are translated independently by the ribosomes giving rise to bicistronic and/or multicistronic nucleic acid molecules.

[0452] In some embodiments, polynucleotides encoding biocircuits, effector modules, DDs and payloads may include from about 30 to about 100,000 nucleotides (e.g., from 30 to 50, from 30 to 100, from 30 to 250, from 30 to 500, from 30 to 1,000, from 30 to 1,500, from 30 to 3,000, from 30 to 5,000, from 30 to 7,000, from 30 to 10,000, from 30 to 25,000, from 30 to 50,000, from 30 to 70,000, from 100 to 250, from 100 to 500, from 100 to 1,000, from 100 to 1,500, from 100 to 3,000, from 100 to 5,000, from 100 to 7,000, from 100 to 10,000, from 100 to 25,000, from 100 to 50,000, from 100 to 70,000, from 100 to 100,000, from 500 to 1,000, from 500 to 1,500, from 500 to 2,000, from 500 to 3,000, from 500 to 5,000, from 500 to 7,000, from 500 to 10,000, from 500 to 25,000, from 500 to 50,000, from 500 to

70,000, from 500 to 100,000, from 1,000 to 1,500, from 1,000 to 2,000, from 1,000 to 3,000, from 1,000 to 5,000, from 1,000 to 7,000, from 1,000 to 10,000, from 1,000 to 25,000, from 1,000 to 50,000, from 1,000 to 70,000, from 1,000 to 100,000, from 1,500 to 3,000, from 1,500 to 5,000, from 1,500 to 7,000, from 1,500 to 10,000, from 1,500 to 25,000, from 1,500 to 50,000, from 1,500 to 70,000, from 1,500 to 100,000, from 2,000 to 3,000, from 2,000 to 5,000, from 2,000 to 7,000, from 2,000 to 10,000, from 2,000 to 25,000, from 2,000 to 50,000, from 2,000 to 70,000, and from 2,000 to 100,000 nucleotides). In some aspects, polynucleotides of the invention may include more than 10,000 nucleotides.

[0453] Regions of the polynucleotides which encode certain features such as cleavage sites, linkers, trafficking signals, tags or other features may range independently from 10-1,000 nucleotides in length (e.g., greater than 20, 30, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, and 900 nucleotides or at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, and 1,000 nucleotides).

[0454] In some embodiments, polynucleotides of the present invention may further comprise embedded regulatory moieties such as microRNA binding sites within the 3′UTR of nucleic acid molecules which when bind to microRNA molecules, down-regulate gene expression either by reducing nucleic acid molecule stability or by inhibiting translation. Conversely, for the purposes of the polynucleotides of the present invention, microRNA binding sites can be engineered out of (i.e. removed from) sequences in which they naturally occur in order to increase protein expression in specific tissues. For example, miR-142 and miR-146 binding sites may be removed to improve protein expression in the immune cells. In some embodiments, any of the encoded payloads may be may be regulated by an SRE and then combined with one or more regulatory sequences to generate a dual or multi-tuned effector module or biocircuit system.

[0455] In some embodiments, polynucleotides of the present invention may encode fragments, variants, derivatives of polypeptides of the inventions. In some aspects, the variant sequence may keep the same or a similar activity. Alternatively, the variant may have an altered activity (e.g., increased or decreased) relative to the start sequence. Generally, variants of a particular polynucleotide or polypeptide of the invention will have at least about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% but less than 100% sequence identity to that particular reference polynucleotide or polypeptide as determined by sequence alignment programs and parameters described herein and known to those skilled in the art. Such tools for alignment include those

of the BLAST suite (Stephen et al., Gapped BLAST and PSI-BLAST: a new generation of protein database search programs, *Nucleic Acids Res.*, 1997, 25:3389-3402.)

[0456] In some embodiments, polynucleotides of the present invention may be modified. As used herein, the terms "modified", or as appropriate, "modification" refers to chemical modification with respect to A, G, U (T in DNA) or C nucleotides. Modifications may be on the nucleoside base and/or sugar portion of the nucleosides which comprise the polynucleotide. In some embodiments, multiple modifications are included in the modified nucleic acid or in one or more individual nucleoside or nucleotide. For example, modifications to a nucleoside may include one or more modifications to the nucleobase and the sugar. Modifications to the polynucleotides of the present invention may include any of those taught in, for example, International Publication NO. WO2013/052523, the contents of which are incorporated herein by reference in its entirety.

[0457] As described herein "nucleoside" is defined as a compound containing a sugar molecule (e.g., a pentose or ribose) or a derivative thereof in combination with an organic base (e.g., a purine or pyrimidine) or a derivative thereof (also referred to herein as "nucleobase"). As described herein, "nucleotide" is defined as a nucleoside including a phosphate group.

[0458] In some embodiments, the modification may be on the internucleoside linkage (e.g., phosphate backbone). Herein, in the context of the polynucleotide backbone, the phrases "phosphate" and "phosphodiester" are used interchangeably. Backbone phosphate groups can be modified by replacing one or more of the oxygen atoms with a different substituent. Further, the modified nucleosides and nucleotides can include the wholesale replacement of an unmodified phosphate moiety with another internucleoside linkage. Examples of modified phosphate groups include, but are not limited to, phosphorothioate, phosphoroselenates, boranophosphates, boranophosphate esters, hydrogen phosphonates, phosphoramidates, phosphorodiamidates, alkyl or aryl phosphonates, and phosphotriesters. Phosphorodithioates have both non-linking oxygens replaced by sulfur. The phosphate linker can also be modified by the replacement of a linking oxygen with nitrogen (bridged phosphoramidates), sulfur (bridged phosphorothioates), and carbon (bridged methylene-phosphonates). Other modifications which may be used are taught in, for example, International Application NO.: WO2013/052523, the contents of which are incorporated herein by reference in their entirety.

[0459] Chemical modifications and/or substitution of the nucleotides or nucleobases of the polynucleotides of the invention which are useful in the present invention include any

modified substitutes known in the art, for example, (±)1-(2-Hydroxypropyl)pseudouridine TP, (2R)-1-(2-Hydroxypropyl)pseudouridine TP, 1-(4-Methoxy-phenyl)pseudo-UTP, ,2′-O-dimethyladenosine, 1,2′-O-dimethylguanosine, 1,2′-O-dimethylinosine, 1-Hexyl-pseudo-UTP , 1-Homoallylpseudouridine TP, 1-Hydroxymethylpseudouridine TP, 1-iso-propyl-pseudo-UTP , 1-Me-2-thio-pseudo-UTP, 1-Me-4-thio-pseudo-UTP, 1-Me-alpha-thio-pseudo-UTP , 1-Me-GTP, 2'-Amino-2'-deoxy-ATP, 2'-Amino-2'-deoxy-CTP, 2'-Amino-2'-deoxy-GTP, 2'-Amino-2'-deoxy-UTP, 2'-Azido-2'-deoxy-ATP, tubercidine, undermodified hydroxywybutosine, uridine 5-oxyacetic acid, uridine 5-oxyacetic acid methyl ester, wybutosine, wyosine, xanthine, Xanthosine-5'-TP, xylo-adenosine, zebularine, α-thio-adenosine, α-thio-cytidine, α-thio-guanosine, and/or α-thio-uridine.

[0460] Polynucleotides of the present invention may comprise one or more of the modifications taught herein. Different sugar modifications, base modifications, nucleotide modifications, and/or internucleoside linkages (e.g., backbone structures) may exist at various positions in the polynucleotide of the invention. One of ordinary skill in the art will appreciate that the nucleotide analogs or other modification(s) may be located at any position(s) of a polynucleotide such that the function of the polynucleotide is not substantially decreased. A modification may also be a 5′ or 3′ terminal modification. The polynucleotide may contain from about 1% to about 100% modified nucleotides (either in relation to overall nucleotide content, or in relation to one or more types of nucleotide, i.e. any one or more of A, G, U or C) or any intervening percentage (e.g., from 1% to 20%, from 1% to 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from 10% to 90%, from 10% to 95%, from 10% to 100%, from 20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from 20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100%).

[0461] In some embodiments, one or more codons of the polynucleotides of the present invention may be replaced with other codons encoding the native amino acid sequence to tune the expression of the SREs, through a process referred to as codon selection. Since mRNA codon, and tRNA anticodon pools tend to vary among organisms, cell types, sub

cellular locations and over time, the codon selection described herein is a spatiotemporal (ST) codon selection.

[0462] In some embodiments of the invention, certain polynucleotide features may be codon optimized. Codon optimization refers to a process of modifying a nucleic acid sequence for enhanced expression in the host cell by replacing at least 1, 2, 3, 4, 5, 10, 15, 20, 25, 50 or more codons of the native sequence with codons that are most frequently used in the genes of that host cell while maintaining the native amino acid sequence. Codon usage may be measured using the Codon Adaptation Index (CAI) which measures the deviation of a coding polynucleotide sequence from a reference gene set. Codon usage tables are available at the Codon Usage Database (www.kazusa.or.jp/codon/) and the CAI can be calculated by EMBOSS CAI program (emboss.sourceforge.net/). Codon optimization methods are known in the art and may be useful in efforts to achieve one or more of several goals. These goals include to match codon frequencies in target and host organisms to ensure proper folding, bias nucleotide content to alter stability or reduce secondary structures, minimize tandem repeat codons or base runs that may impair gene construction or expression, customize transcriptional and translational control regions, insert or remove protein signaling sequences, remove/add post translation modification sites in encoded protein (e.g. glycosylation sites), add, remove or shuffle protein domains, insert or delete restriction sites, modify ribosome binding sites and degradation sites, to adjust translational rates to allow the various domains of the protein to fold properly, or to reduce or eliminate problem secondary structures within the polynucleotide. Codon optimization tools, algorithms and services are known in the art, and non-limiting examples include services from GeneArt (Life Technologies), DNA2.0 (Menlo Park CA), OptimumGene (GenScript, Piscataway, NJ), algorithms such as but not limited to, DNAWorks v3.2.3, and/or proprietary methods. In one embodiment, a polynucleotide sequence or portion thereof is codon optimized using optimization algorithms. Codon options for each amino acid are well-known in the art as are various species table for optimizing for expression in that particular species.

[0463] In some embodiments of the invention, certain polynucleotide features may be codon optimized. For example, a preferred region for codon optimization may be upstream (5') or downstream (3') to a region which encodes a polypeptide. These regions may be incorporated into the polynucleotide before and/or after codon optimization of the payload encoding region or open reading frame (ORF).

[0464] After optimization (if desired), the polynucleotide components are reconstituted and transformed into a vector such as, but not limited to, plasmids, viruses, cosmids, and artificial chromosomes.

[0465] Spatiotemporal codon selection may impact the expression of the polynucleotides of the invention, since codon composition determines the rate of translation of the mRNA species and its stability. For example, tRNA anticodons to optimized codons are abundant, and thus translation may be enhanced. In contrast, tRNA anticodons to less common codons are fewer and thus translation may proceed at a slower rate. Presnyak et al. have shown that the stability of an mRNA species is dependent on the codon content, and higher stability and thus higher protein expression may be achieved by utilizing optimized codons (Presnyak et al. (2015) Cell 160, 1111–1124; the contents of which are incorporated herein by reference in their entirety). Thus, in some embodiments, ST codon selection may include the selection of optimized codons to enhance the expression of the SRES, effector modules and biocircuits of the invention. In other embodiments, spatiotemporal codon selection may involve the selection of codons that are less commonly used in the genes of the host cell to decrease the expression of the compositions of the invention. The ratio of optimized codons to codons less commonly used in the genes of the host cell may also be varied to tune expression.

[0466] In some embodiments, certain regions of the polynucleotide may be modified using codon selection methods. For example, a preferred region for codon selection may be upstream (5') or downstream (3') to a region which encodes a polypeptide. These regions may be incorporated into the polynucleotide before and/or after codon selection of the payload encoding region or open reading frame (ORF).

[0467] The stop codon of the polynucleotides of the present invention may be modified to include sequences and motifs to alter the expression levels of the SREs, payloads and effector modules of the present invention. Such sequences may be incorporated to induce stop codon readthrough, wherein the stop codon may specify amino acids e.g. selenocysteine or pyrrolysine. In other instances, stop codons may be skipped altogether to resume translation through an alternate open reading frame. Stop codon read through may be utilized to tune the expression of components of the effector modules at a specific ratio (e.g.as dictated by the stop codon context). Examples of preferred stop codon motifs include UGAN, UAAN, and UAGN, where N is either C or U.

[0468] Polynucleotide modifications and manipulations can be accomplished by methods known in the art such as, but not limited to, site directed mutagenesis and recombinant technology. The resulting modified molecules may then be tested for activity using *in vitro* or

in vivo assays such as those described herein or any other suitable screening assay known in the art.

[0469] In some embodiments, polynucleotides of the invention may comprise two or more effector module sequences, or two or more payload sequences, which are in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than three times. In these patterns, each letter, A, B, or C represent a different effector module component.

[0470] In yet another embodiment, polynucleotides of the invention may comprise two or more effector module component sequences with each component having one or more SRE sequences (DD sequences), or two or more payload sequences. As a non-limiting example, the sequences may be in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than three times in each of the regions. As another non-limiting example, the sequences may be in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than three times across the entire polynucleotide. In these patterns, each letter, A, B, or C represent a different sequence or component.

[0471] According to the present invention, polynucleotides encoding distinct biocircuits, effector modules, SREs and payload constructs may be linked together through the 3′-end using nucleotides which are modified at the 3′-terminus. Chemical conjugation may be used to control the stoichiometry of delivery into cells. Polynucleotides can be designed to be conjugated to other polynucleotides, dyes, intercalating agents (e.g. acridines), cross-linkers (e.g. psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial endonucleases (e.g. EDTA), alkylating agents, phosphate, amino, mercapto, PEG (e.g., PEG-40K), MPEG, $[MPEG]_2$, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (e.g. biotin), transport/absorption facilitators (e.g., aspirin, vitamin E, folic acid), synthetic ribonucleases, proteins, e.g., glycoproteins, or peptides, e.g., molecules having a specific affinity for a co-ligand, or antibodies e.g., an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell, hormones and hormone receptors, non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, or a drug. As non-limiting examples, they may be conjugates with other immune conjugates.

[0472] In some embodiments, the compositions of the polynucleotides of the invention may generated by combining the various components of the effector modules using the Gibson assembly method. The Gibson assembly reaction consists of three isothermal

reactions, each relying on a different enzymatic activity including a 5' exonuclease which generates long overhangs, a polymerase which fills in the gaps of the annealed single strand regions and a DNA ligase which seals the nicks of the annealed and filled-in gaps. Polymerase chain reactions are performed prior to Gibson assembly which may be used to generate PCR products with overlapping sequence. These methods can be repeated sequentially, to assemble larger and larger molecules. For example, the method can comprise repeating a method as above to join a second set of two or more DNA molecules of interest to one another, and then repeating the method again to join the first and second set DNA molecules of interest, and so on. At any stage during these multiple rounds of assembly, the assembled DNA can be amplified by transforming it into a suitable microorganism, or it can be amplified in vitro (e.g., with PCR).

[0473] In some embodiments, polynucleotides of the invention may encode effector modules comprising a destabilizing domain (DD) and at least one payload taught herein. The DD domain may be a hPDE5 mutant comprising one, two, three, four, five or more mutations

[0474] In some embodiments, the effector module may be a PDE5-GFP fusion encoded by SEQ ID NO. 95-106; 205-222; 234-236; 256-260; 378-379; 469-503; and 526-533.In some embodiments, the effector module may be hPDE5-CAR constructs, encoded by SEQ ID NO. 8285-8298 or a hPDE5-IL15-IL15Ra constructs, encoded by SEQ ID NO. 8352- 8361.

Cells

[0475] In accordance with the present invention, cells genetically modified to express at least one biocircuit, SRE (e. g, DD), effector module and immunotherapeutic agent of the invention, are provided. Cells of the invention may include, without limitation, immune cells, stem cells and tumor cells. In some embodiments, immune cells are immune effector cells, including, but not limiting to, T cells such as $CD8^+$ T cells and $CD4^+$ T cells (e.g., Th1, Th2, Th17 , Foxp3+ cells), memory T cells such as T memory stem cells, central T memory cells, and effector memory T cells, terminally differentiated effector T cells, natural killer (NK) cells, NK T cells, tumor infiltrating lymphocytes (TILs), cytotoxic T lymphocytes (CTLs), regulatory T cells (Tregs), and dendritic cells (DCs), other immune cells that can elicit an effector function, or the mixture thereof. T cells may be Tαβ cells and Tγδ cells. In some embodiments, stem cells may be from human embryonic stem cells, mesenchymal stem cells, and neural stem cells. In some embodiments, T cells may be depleted endogenous T cell receptors (See US Pat. NOs.: 9,273,283; 9,181,527; and 9,028,812; the contents of each of which are incorporated herein by reference in their entirety).

[0476] In some embodiments, cells of the invention may be autologous, allogeneic, syngeneic, or xenogeneic in relation to a particular individual subject.

[0477] In some embodiments, cells of the invention may be mammalian cells, particularly human cells. Cells of the invention may be primary cells or immortalized cell lines.

[0478] In some embodiments, cells of the invention may include expansion factors as payload to trigger proliferation and expansion of the cells. Exemplary payloads include RAS such as KRAS, NRAS, RRAS, RRAS2, MRAS, ERAS, and HRAS, DIRAS such as DIRAS1, DIRAS2, and DIRAS3, NKIRAS such as NKIRAS1, and NKIRAS2, RAL such as RALA, and RALB, RAP such as RAP1A, RAP1B, RAP2A, RAP2B, and RAP2C, RASD such as RASD1, and RASD2, RASL such as RASL10A, RASL10B, RASL11A, RASL11B, and RASL12, REM such as REM1, and REM2, GEM, RERG, RERGL, and RRAD.

[0479] Engineered immune cells can be accomplished by transducing a cell compositions with a polypeptide of a biocircuit, an effector module, a SRE and/or a payload of interest (i.e., immunotherapeutic agent), or a polynucleotide encoding said polypeptide, or a vector comprising said polynucleotide. The vector may be a viral vector such as a lentiviral vector, a gamma-retroviral vector, a recombinant AAV, an adenoviral vector and an oncolytic viral vector. In other aspects, non-viral vectors for example, nanoparticles and liposomes may also be used. In some embodiments, immune cells of the invention are genetically modified to express at least one immunotherapeutic agent of the invention which is tunable using a stimulus. In some examples, two, three or more immunotherapeutic agents constructed in the same biocircuit and effector module are introduced into a cell. In other examples, two, three, or more biocircuits, effector modules, each of which comprises an immunotherapeutic agent, may be introduced into a cell.

[0480] In some embodiments, immune cells of the invention may be T cells modified to express an antigen-specific T cell receptor (TCR), or an antigen specific chimeric antigen receptor (CAR) taught herein (known as CAR T cells). Accordingly, at least one polynucleotide encoding a CAR system (or a TCR) described herein, or a vector comprising the polynucleotide is introduced into a T cell. The T cell expressing the CAR or TCR binds to a specific antigen via the extracellular targeting moiety of the CAR or TCR, thereby a signal via the intracellular signaling domain (s) is transmitted into the T cell, and as a result, the T cell is activated. The activated CAR T cell changes its behavior including release of a cytotoxic cytokine (e.g., a tumor necrosis factor, and lymphotoxin, etc.), improvement of a cell proliferation rate, change in a cell surface molecule, or the like. Such changes cause destruction of a target cell expressing the antigen recognized by the CAR or TCR. In

addition, release of a cytokine or change in a cell surface molecule stimulates other immune cells, for example, a B cell, a dendritic cell, a NK cell, and a macrophage.

[0481] The CAR introduced into a T cell may be a first-generation CAR including only the intracellular signaling domain from TCR CD3zeta, or a second-generation CAR including the intracellular signaling domain from TCR CD3zeta and a costimulatory signaling domain, or a third-generation CAR including the intracellular signaling domain from TCR CD3zeta and two or more costimulatory signaling domains, or a split CAR system, or an on/off switch CAR system. In one example, the expression of the CAR or TCR is controlled by a destabilizing domain (DD) such as a hDHFR mutant, in the effector module of the invention. The presence or absence of hDHFR binding ligand such as TMP is used to tune the CAR or TCR expression in transduced T cells or NK cells.

[0482] In some embodiments, CAR T cells of the invention may be further modified to express another one, two, three or more immunotherapeutic agents. The immunotherapeutic agents may be another CAR or TCR specific to a different target molecule; a cytokine such as IL2, IL12, IL15 and IL18, or a cytokine receptor such as IL15Ra; a chimeric switch receptor that converts an inhibitory signal to a stimulatory signal; a homing receptor that guides adoptively transferred cells to a target site such as the tumor tissue; an agent that optimizes the metabolism of the immune cell; or a safety switch gene (e.g., a suicide gene) that kills activated T cells when a severe event is observed after adoptive cell transfer or when the transferred immune cells are no-longer needed. These molecules may be included in the same effector module or in separate effector modules.

[0483] In one embodiment, the CAR T cell (including TCR T cell) of the invention may be an "armed" CAR T cell which is transformed with an effector module comprising a CAR and an effector module comprising a cytokine. The inducible or constitutively secrete active cytokines further armor CAR T cells to improve efficacy and persistence. In this context, such CAR T cell is also referred to as "armored CAR T cell". The "armor" molecule may be selected based on the tumor microenvironment and other elements of the innate and adaptive immune systems. In some embodiments, the molecule may be a stimulatory factor such as IL2, IL12, IL15, IL18, type I IFN, CD40L and 4-1BBL which have been shown to further enhance CAR T cell efficacy and persistence in the face of a hostile tumor microenvironment via different mechanisms (Yeku et al., *Biochem Soc Trans.*, 2016, 44(2): 412-418).

[0484] In some aspects, the armed CAR T cell of the invention is modified to express a CD19 CAR and IL12. Such T cells, after CAR mediated activation in the tumor, release

inducible IL12 which augments T-cell activation and attracts and activates innate immune cells to eliminate CD19-negative cancer cells.

[0485] In one embodiment, T cells of the invention may be modified to express an effector module comprising a CAR and an effector module comprising a suicide gene.

[0486] In one embodiment, the CAR T cell (including TCR T cell) of the invention may be transformed with effector modules comprising a cytokine and a safety switch gene (e.g., suicide gene). The suicide gene may be an inducible caspase such as caspase 9 which induces apoptosis, when activated by an extracellular stimulus of a biocircuit system. Such induced apoptosis eliminates transferred cell as required to decrease the risk of direct toxicity and uncontrolled cell proliferation.

[0487] In some embodiments, immune cells of the invention may be NK cells modified to express an antigen-specific T cell receptor (TCR), or an antigen specific chimeric antigen receptor (CAR) taught herein.

[0488] Natural killer (NK) cells are members of the innate lymphoid cell family and characterized in humans by expression of the phenotypic marker CD56 (neural cell adhesion molecule) in the absence of CD3 (T-cell co-receptor). NK cells are potent effector cells of the innate immune system which mediate cytotoxic attack without the requirement of prior antigen priming, forming the first line of defense against diseases including cancer malignancies and viral infection.

[0489] Several pre-clinical and clinical trials have demonstrated that adoptive transfer of NK cells is a promising treatment approach against cancers such as acute myeloid leukemia (Ruggeri et al., *Science*; 2002, 295: 2097–2100; and Geller et al., *Immunotherapy*, 2011, 3: 1445-1459). Adoptive transfer of NK cells expressing CAR such as DAP12-Based Activating CAR revealed improved eradication of tumor cells (Topfer et al., *J Immunol.* 2015; 194:3201–3212). NK cell engineered to express a CS-1 specific CAR also displayed enhanced cytolysis and interferon-γ (IFN γ) production in multiple myeloma (Chu et al., *Leukemia*, 2014, 28(4): 917-927).

[0490] NK cell activation is characterized by an array of receptors with activating and inhibitory functions. The important activation receptors on NK cells include CD94/NKG2C and NKG2D (the C-type lectin-like receptors), and the natural cytotoxicity receptors (NCR) NKp30, NKp44 and NKp46, which recognize ligands on tumor cells or virally infected cells. NK cell inhibition is essentially mediated by interactions of the polymorphic inhibitory killer cell immunoglobulin-like receptors (KIRs) with their cognate human–leukocyte–antigen (HLA) ligands via the alpha-1 helix of the HLA molecule. The balance between signals that

are generated from activating receptors and inhibitory receptors mainly determines the immediate cytotoxic activation.

[0491] NK cells may be isolated from peripheral blood mononuclear cells (PBMCs), or derived from human embryonic stem (ES) cells and induced pluripotent stem cells (iPSCs). The primary NK cells isolated from PBMCs may be further expanded for adoptive immunotherapy. Strategies and protocols useful for the expansion of NK cells may include interleukin 2 (IL2) stimulation and the use of autologous feeder cells, or the use of genetically modified allogeneic feeder cells. In some aspects, NK cells can be selectively expanded with a combination of stimulating ligands including IL15, IL21, IL2, 41BBL, IL12, IL18, MICA, 2B4, LFA-1, and BCM1/SLAMF2 (e.g., US patent publication NO: US20150190471).

[0492] Immune cells expressing effector modules comprising a CAR and/or other immunotherapeutic agents can be used as cancer immunotherapy. The immunotherapy comprises the cells expressing a CAR and/or other immunotherapeutic agents as an active ingredient, and may further comprise a suitable excipient. Examples of the excipient may include the pharmaceutically acceptable excipients, including various cell culture media, and isotonic sodium chloride.

[0493] In some embodiments, cells of the present invention may be dendritic cells that are genetically modified to express the compositions of the invention. Such cells may be used as cancer vaccines.

III. PHARMACEUTICAL COMPOSITIONS AND FORMULATIONS

[0494] The present invention further provides pharmaceutical compositions comprising one or more biocircuits, effector modules, SREs (e.g., DDs), stimuli and payloads of interest (i.e., immunotherapeutic agents), vectors, cells and other components of the invention, and optionally at least one pharmaceutically acceptable excipient or inert ingredient.

[0495] As used herein the term "pharmaceutical composition" refers to a preparation of biocircuits, SREs, stimuli and payloads of interest (i.e., immunotherapeutic agents), other components, vectors, cells and described herein, or pharmaceutically acceptable salts thereof, optionally with other chemical components such as physiologically suitable carriers and excipients. The pharmaceutical compositions of the invention comprise an effective amount of one or more active compositions of the invention. The preparation of a pharmaceutical composition that contains at least one composition of the present invention and/or an additional active ingredient will be known to those skilled in the art considering the present disclosure, as exemplified by Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, incorporated herein by reference.

[0496] The term "excipient" or "inert ingredient" refers to an inactive substance added to a pharmaceutical composition and formulation to further facilitate administration of an active ingredient. For the purposes of the present disclosure, the phrase "active ingredient" generally refers to any one or more biocircuits, effector modules, SREs, stimuli and payloads of interest (i.e., immunotherapeutic agents), other components, vectors, and cells to be delivered as described herein. The phrases "pharmaceutically acceptable" refers to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, such as, for example, a human, as appropriate.

[0497] In some embodiments, pharmaceutical compositions and formulations are administered to humans, human patients or subjects. Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to any other animal, e.g., to non-human animals, e.g. non-human mammals. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, non-human mammals, including agricultural animals such as cattle, horses, chickens and pigs, domestic animals such as cats, dogs, or research animals such as mice, rats, rabbits, dogs and non-human primates. It will be understood that, for human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA Office of Biological Standards.

[0498] A pharmaceutical composition and formulation in accordance with the invention may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[0499] The compositions of the present invention may be formulated in any manner suitable for delivery. The formulation may be, but is not limited to, nanoparticles, poly (lactic-co-glycolic acid) (PLGA) microspheres, lipidoids, lipoplex, liposome, polymers, carbohydrates (including simple sugars), cationic lipids and combinations thereof.

[0500] In one embodiment, the formulation is a nanoparticle which may comprise at least one lipid. The lipid may be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG

and PEGylated lipids. In another aspect, the lipid may be a cationic lipid such as, but not limited to, DLin-DMA, DLin-D-DMA, DLin-MC3-DMA, DLin-KC2-DMA and DODMA.

[0501] For polynucleotides of the invention, the formulation may be selected from any of those taught, for example, in International Application PCT/US2012/069610, the contents of which are incorporated herein by reference in its entirety.

[0502] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient or inert ingredient, and/or any additional ingredients in a pharmaceutical composition in accordance with the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1 and 100, e.g., between 0.5 and 50, between 1-30, between 5-80, at least 80 (w/w) active ingredient.

[0503] Efficacy of treatment or amelioration of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of compositions of the present invention, "effective against" for example a cancer, indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as an improvement of symptoms, a cure, a reduction in disease load, reduction in tumor mass or cell numbers, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating the particular type of cancer.

[0504] A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10 in a measurable parameter of disease, and preferably at least 20, 30, 40, 50 or more can be indicative of effective treatment. Efficacy for a given composition or formulation of the present invention can also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant change is observed.

IV. DELIVERY MODALITIES AND/OR VECTORS

Vectors

[0505] The present invention also provides vectors that package polynucleotides of the invention encoding biocircuits, effector modules, SREs (DDs) and payload constructs, and combinations thereof. In some embodiments, polynucleotides encoding destabilizing domains, effector modules and biocircuit systems, are provided. Vectors comprising polynucleotides of the invention are provided. In some aspects, the vector may be a non-viral vector, or a viral vector. In some embodiments, the vector of the invention is a viral vector. The viral vector may include, but is not limited to a retroviral vector, an adenoviral vector, an adeno-associated viral vector, or a lentiviral vector. In some embodiments, the vector of the invention may be a non-viral vector, such as a nanoparticles and liposomes.

[0506] Vectors of the present invention may also be used to deliver the packaged polynucleotides to a cell, a local tissue site or a subject. These vectors may be of any kind, including DNA vectors, RNA vectors, plasmids, viral vectors and particles. Viral vector technology is well known and described in Sambrook et al. (2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York). Viruses, which are useful as vectors include, but are not limited to lentiviral vectors, adenoviral vectors, adeno-associated viral (AAV) vectors, herpes simplex viral vectors, retroviral vectors, oncolytic viruses, and the like.

[0507] In general, vectors contain an origin of replication functional in at least one organism, a promoter sequence and convenient restriction endonuclease site, and one or more selectable markers e.g. a drug resistance gene.

[0508] As used herein a promoter is defined as a DNA sequence recognized by transcription machinery of the cell, required to initiate specific transcription of the polynucleotide sequence of the present invention. Vectors can comprise native or non-native promoters operably linked to the polynucleotides of the invention. The promoters selected may be strong, weak, constitutive, inducible, tissue specific, development stage-specific, and/or organism specific. One example of a suitable promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable of driving high levels of expression of polynucleotide sequence that is operatively linked to it. Another example of a preferred promoter is Elongation Growth Factor-1. Alpha (EF-1. alpha). Other constitutive promoters may also be used, including, but not limited to simian virus 40 (SV40), mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV), long terminal repeat (LTR), promoter, an avian

leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter as well as human gene promoters including, but not limited to the phosphoglycerate kinase (PGK) promoter , actin promoter, the myosin promoter, the hemoglobin promoter, the Ubiquitin C (Ubc) promoter, the human U6 small nuclear protein promoter and the creatine kinase promoter. In some instances, inducible promoters such as but not limited to metallothionine promoter, glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter may be used. In some embodiments, the promoter may be selected from the following a CMV promoter, comprising a nucleotide sequence of SEQ ID NO. 335, an EF1a promoter, comprising a nucleotide sequence of SEQ ID NOs. 336-337, and a PGK promoter, comprising a nucleotide sequence of SEQ ID NO. 338.

[0509] In some embodiments, the optimal promoter may be selected based on its ability to achieve minimal expression of the SREs and payloads of the invention in the absence of the ligand and detectable expression in the presence of the ligand.

[0510] Additional promoter elements e.g. enhancers may be used to regulate the frequency of transcriptional initiation. Such regions may be located 10-100 base pairs upstream or downstream of the start site. In some instances, two or more promoter elements may be used to cooperatively or independently activate transcription.

[0511] In some embodiments, the recombinant expression vector may comprise regulatory sequences, such as transcription and translation initiation and termination codons, which are specific to the type of host cell into which the vector is to be introduced.

1. Lentiviral vectors

[0512] In some embodiments, lentiviral vectors/particles may be used as vehicles and delivery modalities. Lentiviruses are subgroup of the *Retroviridae* family of viruses, named because reverse transcription of viral RNA genomes to DNA is required before integration into the host genome. As such, the most important features of lentiviral vehicles/particles are the integration of their genetic material into the genome of a target/host cell. Some examples of lentivirus include the Human Immunodeficiency Viruses: HIV-1 and HIV-2, the Simian Immunodeficiency Virus (SIV), feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV), Jembrana Disease Virus (JDV), equine infectious anemia virus (EIAV), equine infectious anemia virus, visna-maedi and caprine arthritis encephalitis virus (CAEV).

[0513] Typically, lentiviral particles making up the gene delivery vehicle are replication defective on their own (also referred to as “self-inactivating”). Lentiviruses can infect both dividing and non-dividing cells by virtue of the entry mechanism through the intact host

nuclear envelope (Naldini L et al., *Curr. Opin. Biotechnol*, 1998, 9: 457-463). Recombinant lentiviral vehicles/particles have been generated by multiply attenuating the HIV virulence genes, for example, the genes Env, Vif, Vpr, Vpu, Nef and Tat are deleted making the vector biologically safe. Correspondingly, lentiviral vehicles, for example, derived from HIV-1/HIV-2 can mediate the efficient delivery, integration and long-term expression of transgenes into non-dividing cells. As used herein, the term "recombinant" refers to a vector or other nucleic acid containing both lentiviral sequences and non-lentiviral retroviral sequences.

[0514] Lentiviral particles may be generated by co-expressing the virus packaging elements and the vector genome itself in a producer cell such as human HEK293T cells. These elements are usually provided in three (in second generation lentiviral systems) or four separate plasmids (in third generation lentiviral systems). The producer cells are co-transfected with plasmids that encode lentiviral components including the core (i.e. structural proteins) and enzymatic components of the virus, and the envelope protein(s) (referred to as the packaging systems), and a plasmid that encodes the genome including a foreign transgene, to be transferred to the target cell, the vehicle itself (also referred to as the transfer vector). In general, the plasmids or vectors are included in a producer cell line. The plasmids/vectors are introduced via transfection, transduction or infection into the producer cell line. Methods for transfection, transduction or infection are well known by those of skill in the art. As non-limiting example, the packaging and transfer constructs can be introduced into producer cell lines by calcium phosphate transfection, lipofection or electroporation, generally together with a dominant selectable marker, such as neo, DHFR, Gln synthetase or ADA, followed by selection in the presence of the appropriate drug and isolation of clones.

[0515] The producer cell produces recombinant viral particles that contain the foreign gene, for example, the effector module of the present invention. The recombinant viral particles are recovered from the culture media and titrated by standard methods used by those of skill in the art. The recombinant lentiviral vehicles can be used to infect target cells.

[0516] Cells that can be used to produce high-titer lentiviral particles may include, but are not limited to, HEK293T cells, 293G cells, STAR cells (Relander et al., *Mol. Ther.*, 2005, 11: 452-459), FreeStyle™ 293 Expression System (ThermoFisher, Waltham, MA), and other HEK293T-based producer cell lines (e.g., Stewart et al., *Hum Gene Ther.*_2011, 22(3):357-369; Lee et al., *Biotechnol Bioeng*, 2012, 10996): 1551-1560; Throm et al., *Blood.* 2009, 113(21): 5104-5110; the contents of each of which are incorporated herein by reference in their entirety).

[0517] In some aspects, the envelope proteins may be heterologous envelop proteins from other viruses, such as the G protein of vesicular stomatitis virus (VSV G) or baculoviral gp64 envelop proteins. The VSV-G glycoprotein may especially be chosen among species classified in the vesiculovirus genus: *Carajas virus* (CJSV), *Chandipura virus* (CHPV), *Cocal virus* (COCV), *Isfahan virus* (ISFV), *Maraba virus* (MARAV), *Piry virus* (PIRYV), *Vesicular stomatitis Alagoas virus* (VSAV), *Vesicular stomatitis Indiana virus* (VSIV) *and Vesicular stomatitis New Jersey virus* (VSNJV) and/or stains provisionally classified in the vesiculovirus genus as *Grass carp rhabdovirus*, *BeAn 157575 virus* (BeAn 157575), *Boteke virus* (BTKV), *Calchaqui virus* (CQIV), *Eel virus American* (EVA), *Gray Lodge virus* (GLOV), *Jurona virus* (JURY), *Klamath virus* (KLAV*), Kwatta virus* (KWAV), *La Joya virus* (LJV), *Malpais Spring virus* (MSPV), *Mount Elgon bat virus* (MEBV), *Perinet virus* (PERV), *Pike fry rhabdovirus* (PFRV), *Porton virus* (PORV), *Radi virus* (RADIV), *Spring viremia of carp virus* (SVCV), *Tupaia virus* (TUPV), *Ulcerative disease rhabdovirus* (UDRV) and *Yug Bogdanovac virus* (YBV). The gp64 or other baculoviral env protein can be derived from *Autographa californica* nucleopolyhedrovirus (AcMNPV), *Anagrapha falcifera* nuclear polyhedrosis virus, *Bombyx mori* nuclear polyhedrosis virus, *Choristoneura fumiferana* nucleopolyhedrovirus, *Orgyia pseudotsugata* single capsid nuclear polyhedrosis virus, *Epiphyas postvittana* nucleopolyhedrovirus, *Hyphantria cunea* nucleopolyhedrovirus, *Galleria mellonella* nuclear polyhedrosis virus, Dhori virus, Thogoto virus, *Antheraea pemyi* nucleopolyhedrovirus or Batken virus.

[0518] Additional elements provided in lentiviral particles may comprise retroviral LTR (long-terminal repeat) at either 5' or 3' terminus, a retroviral export element, optionally a lentiviral reverse response element (RRE), a promoter or active portion thereof, and a locus control region (LCR) or active portion thereof. Other elements include central polypurine tract (cPPT) sequence to improve transduction efficiency in non-dividing cells, Woodchuck Hepatitis Virus (WHP) Posttranscriptional Regulatory Element (WPRE) which enhances the expression of the transgene, and increases titer. The effector module is linked to the vector.

[0519] Methods for generating recombinant lentiviral particles are discussed in the art, for example, U.S. Pat. NOs.: 8, 846, 385; 7,745, 179; 7,629,153; 7,575,924; 7,179, 903; and 6, 808, 905; the contents of each of which are incorporated herein by reference in their entirety.

[0520] Lentivirus vectors used may be selected from, but are not limited to pLVX, pLenti, pLenti6, pLJM1, FUGW, pWPXL, pWPI, pLenti CMV puro DEST, pLJM1-EGFP, pULTRA, pInducer20, pHIV-EGFP, pCW57.1, pTRPE, pELPS, pRRL, and pLionII.

[0521] Lentiviral vehicles known in the art may also be used (See, U.S. Pat. NOs. 9, 260, 725; 9,068,199; 9,023,646; 8,900,858; 8,748,169; 8,709,799; 8,420,104; 8,329,462; 8,076,106; 6,013,516; and 5,994,136; International Patent Publication NO.: WO2012079000; the contents of each of which are incorporated herein by reference in their entirety).

2. Retroviral vectors (γ-retroviral vectors)

[0522] In some embodiments, retroviral vectors may be used to package and deliver the biocircuits, biocircuit components, effector modules, SREs or payload constructs of the present invention. Retroviral vectors (RVs) allow the permanent integration of a transgene in target cells. In addition to lentiviral vectors based on complex HIV-1/2, retroviral vectors based on simple gamma-retroviruses have been widely used to deliver therapeutic genes and demonstrated clinically as one of the most efficient and powerful gene delivery systems capable of transducing a broad range of cell types. Example species of Gamma retroviruses include the murine leukemia viruses (MLVs) and the feline leukemia viruses (FeLV).

[0523] In some embodiments, gamma-retroviral vectors derived from a mammalian gamma-retrovirus such as murine leukemia viruses (MLVs), are recombinant. The MLV families of gamma retroviruses include the ecotropic, amphotropic, xenotropic and polytropic subfamilies. Ecotropic viruses are able to infect only murine cells using mCAT-1 receptor. Examples of ecotropic viruses are Moloney MLV and AKV. Amphotropic viruses infect murine, human and other species through the Pit-2 receptor. One example of an amphotropic virus is the 4070A virus. Xenotropic and polytropic viruses utilize the same (Xpr1) receptor, but differ in their species tropism. Xenotropic viruses such as NZB-9-1 infect human and other species but not murine species, whereas polytropic viruses such as focus-forming viruses (MCF) infect murine, human and other species.

[0524] Gamma-retroviral vectors may be produced in packaging cells by co-transfecting the cells with several plasmids including one encoding the retroviral structural and enzymatic (gag-pol) polyprotein, one encoding the envelope (env) protein, and one encoding the vector mRNA comprising polynucleotide encoding the compositions of the present invention that is to be packaged in newly formed viral particles.

[0525] In some aspects, the recombinant gamma-retroviral vectors are pseudotyped with envelope proteins from other viruses. Envelope glycoproteins are incorporated in the outer lipid layer of the viral particles which can increase/alter the cell tropism. Exemplary envelop proteins include the gibbon ape leukemia virus envelope protein (GALV) or vesicular stomatitis virus G protein (VSV-G), or Simian endogenous retrovirus envelop protein, or Measles Virus H and F proteins, or Human immunodeficiency virus gp120 envelope protein,

or cocal vesiculovirus envelop protein (See, e.g., U.S. application publication NO.: 2012/164118; the contents of which are incorporated herein by reference in its entirety). In other aspects, envelope glycoproteins may be genetically modified to incorporate targeting/binding ligands into gamma-retroviral vectors, binding ligands including, but not limited to, peptide ligands, single chain antibodies and growth factors (Waehler et al., *Nat. Rev. Genet.* 2007, 8(8):573–587; the contents of which are incorporated herein by reference in its entirety). These engineered glycoproteins can retarget vectors to cells expressing their corresponding target moieties. In other aspects, a "molecular bridge" may be introduced to direct vectors to specific cells. The molecular bridge has dual specificities: one end can recognize viral glycoproteins, and the other end can bind to the molecular determinant on the target cell. Such molecular bridges, for example ligand-receptor, avidin-biotin, and chemical conjugations, monoclonal antibodies and engineered fusogenic proteins, can direct the attachment of viral vectors to target cells for transduction (Yang et al., *Biotechnol. Bioeng.*, 2008, 101(2): 357-368; and Maetzig et al., *Viruses*, 2011, 3, 677-713; the contents of each of which are incorporated herein by reference in their entirety).

[0526] In some embodiments, the recombinant gamma-retroviral vectors are self-inactivating (SIN) gammaretroviral vectors. The vectors are replication incompetent. SIN vectors may harbor a deletion within the 3' U3 region initially comprising enhancer/promoter activity. Furthermore, the 5' U3 region may be replaced with strong promoters (needed in the packaging cell line) derived from Cytomegalovirus or RSV, or an internal promoter of choice, and/or an enhancer element. The choice of the internal promoters may be made according to specific requirements of gene expression needed for a particular purpose of the invention.

[0527] In some embodiments, polynucleotides encoding the biocircuit, biocircuit components, effector module, SRE are inserted within the recombinant viral genome. The other components of the viral mRNA of a recombinant gamma-retroviral vector may be modified by insertion or removal of naturally occurring sequences (e.g., insertion of an IRES, insertion of a heterologous polynucleotide encoding a polypeptide or inhibitory nucleic acid of interest, shuffling of a more effective promoter from a different retrovirus or virus in place of the wild-type promoter and the like). In some examples, the recombinant gamma-retroviral vectors may comprise modified packaging signal, and/or primer binding site (PBS), and/or 5'-enhancer/promoter elements in the U3-region of the 5'- long terminal repeat (LTR), and/or 3'-SIN elements modified in the U3-region of the 3'-LTR. These modifications may increase the titers and the ability of infection.

[0528] Gamma retroviral vectors suitable for delivering biocircuit components, effector modules, SREs or payload constructs of the present invention may be selected from those disclosed in U.S. Pat. NOs.: 8,828,718; 7,585,676; 7,351,585; U.S. application publication NO.: 2007/048285; PCT application publication NOs.: WO2010/113037; WO2014/121005; WO2015/056014; and EP Pat. NOs.: EP1757702; EP1757703 (the contents of each of which are incorporated herein by reference in their entirety).

3. Adeno-associated viral vectors (AAV)

[0529] In some embodiments, polynucleotides of present invention may be packaged into recombinant adeno-associated viral (rAAV) vectors. Such vectors or viral particles may be designed to utilize any of the known serotype capsids or combinations of serotype capsids. The serotype capsids may include capsids from any identified AAV serotypes and variants thereof, for example, AAV1, AAV2, AAV2G9, AAV3, AAV4, AAV4-4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12 and AAVrh10.

[0530] In one embodiment, the AAV serotype may be or have a sequence as described in United States Publication No. US20030138772, herein incorporated by reference in its entirety, such as, but not limited to, AAV1 (SEQ ID NO: 6 and 64 of US20030138772), AAV2 (SEQ ID NO: 7 and 70 of US20030138772), AAV3 (SEQ ID NO: 8 and 71 of US20030138772), AAV4 (SEQ ID NO: 63 of US20030138772), AAV5 (SEQ ID NO: 114 of US20030138772), AAV6 (SEQ ID NO: 65 of US20030138772), AAV7 (SEQ ID NO: 1-3 of US20030138772), AAV8 (SEQ ID NO: 4 and 95 of US20030138772), AAV9 (SEQ ID NO: 5 and 100 of US20030138772), AAV10 (SEQ ID NO: 117 of US20030138772), AAV11 (SEQ ID NO: 118 of US20030138772), AAV12 (SEQ ID NO: 119 of US20030138772), AAVrh10 (amino acids 1 to 738 of SEQ ID NO: 81 of US20030138772) or variants thereof. Non-limiting examples of variants include SEQ ID NOs: 9, 27-45, 47-62, 66-69, 73-81, 84-94, 96, 97, 99, 101-113 of US20030138772, the contents of which are herein incorporated by reference in their entirety.

[0531] In one embodiment, the AAV serotype may have a sequence as described in Pulicherla et al. (*Molecular Therapy*, 2011, 19(6):1070-1078), U.S. Pat. NOs.: 6,156,303; 7,198,951; U.S. Patent Publication NOs.: US2015/0159173 and US2014/0359799; and International Patent Publication NOs.: WO1998/011244, WO2005/033321 and WO2014/14422; the contents of each of which are incorporated herein by reference in their entirety.

[0532] AAV vectors include not only single stranded vectors but self-complementary AAV vectors (scAAVs). scAAV vectors contain DNA which anneals together to form double

stranded vector genome. By skipping second strand synthesis, scAAVs allow for rapid expression in the cell.

[0533] The rAAV vectors may be manufactured by standard methods in the art such as by triple transfection, in sf9 insect cells or in suspension cell cultures of human cells such as HEK293 cells.

[0534] The biocircuits, biocircuit components, effector modules, SREs or payload constructs may be encoded in one or more viral genomes to be packaged in the AAV capsids taught herein.

[0535] Such vectors or viral genomes may also include, in addition to at least one or two ITRs (inverted terminal repeats), certain regulatory elements necessary for expression from the vector or viral genome. Such regulatory elements are well known in the art and include for example promoters, introns, spacers, stuffer sequences, and the like.

[0536] In some embodiments, more than one effector module or SRE (e.g. DD) may be encoded in a viral genome.

4. Oncolytic viral vector

[0537] In some embodiments, polynucleotides of present invention may be packaged into oncolytic viruses, such as vaccine viruses. Oncolytic vaccine viruses may include viral particles of a thymidine kinase (TK)-deficient, granulocyte macrophage (GM)-colony stimulating factor (CSF)-expressing, replication-competent vaccinia virus vector sufficient to induce oncolysis of cells in the tumor (e.g., US Pat. NO.: 9,226,977).

[0538] In some embodiments, the viral vector of the invention may comprise two or more immunotherapeutic agents taught herein, wherein the two or more immunotherapeutic agents may be included in one effector module under the regulation of the same DD. In this case, the two or more immunotherapeutic agents are tuned by the same stimulus simultaneously. In other embodiments, the viral vector of the invention may comprise two or more effector modules, wherein each effector module comprises a different immunotherapeutic agent. In this case, the two or more effector modules and immunotherapeutic agents are tuned by different stimuli, providing separately independent regulation of the two or more components.

5. Messenger RNA (mRNA)

[0539] In some embodiments, the effector modules of the invention may be designed as a messenger RNA (mRNA). As used herein, the term "messenger RNA" (mRNA) refers to any polynucleotide which encodes a polypeptide of interest and which is capable of being translated to produce the encoded polypeptide of interest *in vitro, in vivo, in situ* or *ex vivo*.

Such mRNA molecules may have the structural components or features of any of those taught in International Application number PCT/US2013/030062, the contents of which are incorporated herein by reference in its entirety.

[0540] Polynucleotides of the invention may also be designed as taught in, for example, Ribostem Limited in United Kingdom patent application serial number 0316089.2 filed on July 9, 2003 now abandoned, PCT application number PCT/GB2004/002981 filed on July 9, 2004 published as WO2005005622, United States patent application national phase entry serial number 10/563,897 filed on June 8, 2006 published as US20060247195 now abandoned, and European patent application national phase entry serial number EP2004743322 filed on July 9, 2004 published as EP1646714 now withdrawn; Novozymes, Inc. in PCT application number PCT/US2007/88060 filed on December 19, 2007 published as WO2008140615, United States patent application national phase entry serial number 12/520,072 filed on July 2, 2009 published as US20100028943 and European patent application national phase entry serial number EP2007874376 filed on July 7, 2009 published as EP2104739; University of Rochester in PCT application number PCT/US2006/46120 filed on December 4, 2006 published as WO2007064952 and United States patent application serial number 11/606,995 filed on December 1, 2006 published as US20070141030; BioNTech AG in European patent application serial number EP2007024312 filed December 14, 2007 now abandoned, PCT application number PCT/EP2008/01059 filed on December 12, 2008 published as WO2009077134, European patent application national phase entry serial number EP2008861423 filed on June 2, 2010 published as EP2240572, United States patent application national phase entry serial number 12/,735,060 filed November 24, 2010 published as US20110065103, German patent application serial number DE 10 2005 046 490 filed September 28, 2005, PCT application PCT/EP2006/0448 filed September 28, 2006 published as WO2007036366, national phase European patent EP1934345 published March, 21, 2012 and national phase US patent application serial number 11/992,638 filed August 14, 2009 published as 20100129877; Immune Disease Institute Inc. in United States patent application serial number 13/088,009 filed April 15, 2011 published as US20120046346 and PCT application PCT/US2011/32679 filed April 15, 2011 published as WO20110130624; Shire Human Genetic Therapeutics in United States patent application serial number 12/957,340 filed on November 20, 2010 published as US20110244026; Sequitur Inc. in PCT application PCT/US1998/019492 filed on September 18, 1998 published as WO1999014346; The Scripps Research Institute in PCT application number PCT/US2010/00567 filed on February 24, 2010 published as WO2010098861, and United States patent application

national phase entry serial number 13/203,229 filed November 3, 2011 published as US20120053333; Ludwig-Maximillians University in PCT application number PCT/EP2010/004681 filed on July 30, 2010 published as WO2011012316; Cellscript Inc. in United States patent number 8,039,214 filed June 30, 2008 and granted October 18, 2011, United States patent application serial numbers 12/962,498 filed on December 7, 2010 published as US20110143436, 12/962,468 filed on December 7, 2010 published as US20110143397, 13/237,451 filed on September 20, 2011 published as US20120009649, and PCT applications PCT/US2010/59305 filed December 7, 2010 published as WO2011071931 and PCT/US2010/59317 filed on December 7, 2010 published as WO2011071936; The Trustees of the University of Pennsylvania in PCT application number PCT/US2006/32372 filed on August 21, 2006 published as WO2007024708, and United States patent application national phase entry serial number 11/990,646 filed on March 27, 2009 published as US20090286852; Curevac GMBH in German patent application serial numbers DE10 2001 027 283.9 filed June 5, 2001, DE10 2001 062 480.8 filed December 19, 2001, and DE 20 2006 051 516 filed October 31, 2006 all abandoned, European patent numbers EP1392341 granted March 30, 2005 and EP1458410 granted January 2, 2008, PCT application numbers PCT/EP2002/06180 filed June 5, 2002 published as WO2002098443, PCT/EP2002/14577 filed on December 19, 2002 published as WO2003051401, PCT/EP2007/09469 filed on December 31, 2007 published as WO2008052770, PCT/EP2008/03033 filed on April 16, 2008 published as WO2009127230, PCT/EP2006/004784 filed on May 19, 2005 published as WO2006122828, PCT/EP2008/00081 filed on January 9, 2007 published as WO2008083949, and United States patent application serial numbers 10/729,830 filed on December 5, 2003 published as US20050032730, 10/870,110 filed on June 18, 2004 published as US20050059624, 11/914,945 filed on July 7, 2008 published as US20080267873, 12/446,912 filed on October 27, 2009 published as US2010047261 now abandoned, 12/522,214 filed on January 4, 2010 published as US20100189729, 12/787,566 filed on May 26, 2010 published as US20110077287, 12/787,755 filed on May 26, 2010 published as US20100239608, 13/185,119 filed on July 18, 2011 published as US20110269950, and 13/106,548 filed on May 12, 2011 published as US20110311472 all of which are herein incorporated by reference in their entirety.

[0541] In some embodiments, the effector modules may be designed as self-amplifying RNA. "Self-amplifying RNA" as used herein refers to RNA molecules that can replicate in the host resulting in the increase in the amount of the RNA and the protein encoded by the

RNA. Such self-amplifying RNA may have structural features or components of any of those taught in International Patent Application Publication No. WO2011005799 (the contents of which are incorporated herein by reference in their entirety.)

V. DOSING, DELIVERY AND ADMINISTRATIONS

[0542] The compositions of the invention may be delivered to a cell or a subject through one or more routes and modalities. The viral vectors containing one or more effector modules, SREs, immunotherapeutic agents and other components described herein may be used to deliver them to a cell and/or a subject. Other modalities may also be used such as mRNAs, plasmids, and as recombinant proteins.

1. Delivery to cells

[0543] In another aspect of the invention, polynucleotides encoding biocircuits, effector modules, SREs (e.g., DDs), payloads of interest (immunotherapeutic agents) and compositions of the invention and vectors comprising said polynucleotides may be introduced into cells such as immune effector cells.

[0544] In one aspect of the invention, polynucleotides encoding biocircuits, effector modules, SREs (e.g., DDs), payloads of interest (immunotherapeutic agents) and compositions of the invention, may be packaged into viral vectors or integrated into viral genomes allowing transient or stable expression of the polynucleotides. Preferable viral vectors are retroviral vectors including lentiviral vectors. In order to construct a retroviral vector, a polynucleotide molecule encoding a biocircuit, an effector module, a DD or a payload of interest (i.e. an immunotherapeutic agent) is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. The recombinant viral vector is then introduced into a packaging cell line containing the gag, pol, and env genes, but without the LTR and packaging components. The recombinant retroviral particles are secreted into the culture media, then collected, optionally concentrated, and used for gene transfer. Lentiviral vectors are especially preferred as they are capable of infecting both dividing and non-dividing cells.

[0545] Vectors may also be transferred to cells by non-viral methods by physical methods such as needles, electroporation, sonoporation, hyrdoporation; chemical carriers such as inorganic particles (e.g. calcium phosphate, silica, gold) and/or chemical methods. In some embodiments, synthetic or natural biodegradable agents may be used for delivery such as cationic lipids, lipid nano emulsions, nanoparticles, peptide based vectors, or polymer based vectors.

[0546] In some embodiments, the polypeptides of the invention may be delivered to the cell directly. In one embodiment, the polypeptides of the invention may be delivered using synthetic peptides comprising an endosomal leakage domain (ELD) fused to a cell penetration domain (CLD). The polypeptides of the invention are co introduced into the cell with the ELD-CLD-synthetic peptide. ELDs facilitate the escape of proteins that are trapped in the endosome, into the cytosol. Such domains are derived proteins of microbial and viral origin and have been described in the art. CPDs allow the transport of proteins across the plasma membrane and have also been described in the art. The ELD-CLD fusion proteins synergistically increase the transduction efficiency when compared to the co-transduction with either domain alone. In some embodiments, a histidine rich domain may optionally be added to the shuttle construct as an additional method of allowing the escape of the cargo from the endosome into the cytosol. The shuttle may also include a cysteine residue at the N or C terminus to generate multimers of the fusion peptide. Multimers of the ELD-CLD fusion peptides generated by the addition of cysteine residue to the terminus of the peptide show even greater transduction efficiency when compared to the single fusion peptide constructs. The polypeptides of the invention may also be appended to appropriate localization signals to direct the cargo to the appropriate sub-cellular location e.g. nucleus. In some embodiments any of the ELDs, CLDs or the fusion ELD-CLD synthetic peptides taught in the International Patent Publication, WO2016161516 and WO2017175072 may be useful in the present invention (the contents of each of which are herein incorporated by reference in their entirety).

2. Dosing

[0547] The present invention provides methods comprising administering any one or more compositions for immunotherapy to a subject in need thereof. These may be administered to a subject using any amount and any route of administration effective for preventing or treating a clinical condition such as cancer, infection diseases and other immunodeficient diseases.

[0548] Compositions in accordance with the invention are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective, or prophylactically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of

administration, previous or concurrent therapeutic interventions and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

[0549] Compositions of the invention may be used in varying doses to avoid T cell anergy, prevent cytokine release syndrome and minimize toxicity associated with immunotherapy. For example, low doses of the compositions of the present invention may be used to initially treat patients with high tumor burden, while patients with low tumor burden may be treated with high and repeated doses of the compositions of the invention to ensure recognition of a minimal tumor antigen load. In another instance, the compositions of the present invention may be delivered in a pulsatile fashion to reduce tonic T cell signaling and enhance persistence *in vivo*. In some aspects, toxicity may be minimized by initially using low doses of the compositions of the invention, prior to administering high doses. Dosing may be modified if serum markers such as ferritin, serum C-reactive protein, IL6, IFN γ, and TNF-α are elevated.

[0550] In one embodiment, polypeptides and/or polynucleotides expressing the compositions described herein e.g. effector modules, are administered to a subject in need thereof to treat cancer. In one embodiment, a population of cells comprising the biocircuits, effector modules and/or the SREs described herein is administered to a subject in need thereof to treat cancer.

[0551] In one embodiment, the cells expressing the compositions described herein is administered at a dose and/or dosing schedule described herein.

[0552] In one embodiment, compositions are introduced into immune cells (e.g., T cells, NK cells). The compositions may be introduced into the immune cells by methods including but not limited to viral transduction, transfection and/or in vitro transcription. In some embodiments, the immune cells are transduced with retroviruses. In one aspect, the retrovirus may be a lentivirus. In some aspects, the titer of the lentiviruses may be used to tune the expression of the payload. In some embodiments, the titer of the lentivirus may have a multiplicity of infection (MOI) ranging from 0.001- 0.01, 0.01- 0.1, 0.1-1, or 1-10. In some embodiments, the MOI may be 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[0553] In some embodiments, the subject (e.g., human) receives an initial administration of immune cells comprising the compositions described herein e.g. SREs, and one or more subsequent administrations of cells. In some embodiments, a therapeutically effective amount of the compositions and/or cells described herein may be administered to the subject. In some

embodiments, the therapeutically effective amount may indicate the precise amount required to tumor inhibition, tumor prevalence and/or tumor burden. The therapeutically effective amount may be determined with consideration of the subject's age, weight, tumor size, sex, extent of infection or metastasis. In some embodiments, the cells expressing the compositions described herein may be administered at a dosage of 10^4 to 10^9 cells/kg body weight of the subject. The cells can be administered by using infusion techniques that are commonly known in immunotherapy (see, e.g., Rosenberg et al., New Eng. J. of Med. 319: 1676, 1988; the contents of which are incorporated herein by reference in their entirety).

[0554] In some aspects, subjects may undergo leukapheresis, wherein leukocytes are collected, enriched, or depleted ex vivo to select and/or isolate the cells of interest, e.g., T cells. These T cell isolates may be expanded by methods known in the art and treated such that the compositions of the invention may be introduced into the cell. Subjects in need thereof may subsequently undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain aspects, following or concurrent with the transplant, subjects receive an infusion of the immune cells of the present invention. In an additional aspect, expanded cells are administered before or following surgery.

[0555] The dosage of the above treatments to be administered to a patient will vary with the precise nature of the condition being treated and the recipient of the treatment. The scaling of dosages for human administration can be performed according to art- accepted practices.

[0556] In one embodiment, the compositions are introduced into immune cells (e.g., T cells, NK cells), e.g., using in vitro transcription, and the subject (e.g., human) receives an initial administration of immune cells (e.g., T cells, NK cells) of the invention, and one or more subsequent administrations of the immune cells (e.g., T cells, NK cells) of the invention, wherein the one or more subsequent administrations are administered less than 15 days, e.g., 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 days after the previous administration. In one embodiment, more than one administration of the immune cells (e.g., T cells, NK cells) of the invention are administered to the subject (e.g., human) per week, e.g., 2, 3, or 4 administrations of the immune cells (e.g., T cells, NK cells) of the invention are administered per week. In one embodiment, the subject (e.g., human subject) receives more than one administration of the immune cells (e.g., T cells, NK cells) per week (e.g., 2, 3 or 4 administrations per week) (also referred to herein as a cycle), followed by a week of no immune cells (e.g., T cells, NK cells) administrations, and then one or more additional administration of the immune cells (e.g., T cells, NK cells) (e.g., more than one

administration of the immune cells (e.g., T cells, NK cells) per week) is administered to the subject. In another embodiment, the subject (e.g., human subject) receives more than one cycle of immune cells (e.g., T cells, NK cells), and the time between each cycle is less than 10, 9, 8, 7, 6, 5, 4, or 3 days. In one embodiment, the immune cells (e.g., T cells, NK cells) are administered every other day for 3 administrations per week. In one embodiment, the immune cells (e.g., T cells, NK cells) of the invention are administered for at least two, three, four, five, six, seven, eight or more weeks. In some embodiments, a dose of immune cells expressing compositions of the invention described herein comprises about 1 x 10^6, 1.1 x 10^6, 2 x 10^6, 3.6 x 10^6, 5 x 10^6, 1 x 10^7, 1.8 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10 ^{8}, 3 x 10^8, or 5 x 10^8 cells/kg. In some embodiments, a dose of immune cells comprises at least about 1 x 10^6, 1.1 x 10^6, 2 x 10^6, 3.6 x 10^6, 5 x 10^6, 1 x 10^7, 1.8 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 3 x 10^8, or 5 x 10^8 cells/kg. In some embodiments, a dose of immune cells comprises up to about 1 x 10^6, 1.1 x 10^6, 2 x 10^6, 3.6 x 10^6, 5 x 10^6, 1 x 10^7, 1.8 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 3 x 10^8, or 5 x 10^8 cells/kg. In some embodiments, a dose of immune cells comprises about 1.1 x 10^6- 1.8 x 10^7 cells/kg. In some embodiments, a dose of immune cells comprises about 1 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 3 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9cells. In some embodiments, a dose of the immune cells comprises at least about 1 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 3 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9cells. In some embodiments, a dose of immune cells comprises up to about 1 x $10^{7,}$ 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 3 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9 cells. In some embodiments, a dose of the immune cells comprises up to about 1 x 10^7, 1.5 x 10^7, 2 x 10^7, 2.5 x 10^7, 3 x 10^7, 3.5 x 10^7, 4 x 10^7, 5 x 10^7, 1 x 10^8, 1.5 x 10^8, 2 x 10^8, 2.5 x 10^8, 3 x 10^8, 3.5 x 10^8, 4 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9 cells. In some embodiments, a dose of immune cells comprises up to about 1-3 x 10^7 to 1-3 x 10 ^{8} cells.

[0557] In one embodiment, the cells expressing the compositions described herein, are administered as a first line treatment for the disease, e.g., the cancer, e.g., the cancer described herein. In another embodiment, the cells expressing the compositions described herein, are administered as a second, third, fourth line treatment for the disease, e.g., the cancer, e.g., the cancer described herein. In some embodiments, the subject may undergo preconditioning prior to the administration of the cells.

[0558] Also provided herein are methods of administering ligands in accordance with the invention to a subject in need thereof. The ligand may be administered to a subject or to cells, using any amount and any route of administration effective for tuning the biocircuits of the invention. The exact amount required will vary from subject to subject, depending on the

species, age, and general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like. The subject may be a human, a mammal, or an animal. Compositions in accordance with the invention are typically formulated in unit dosage form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention may be decided by the attending physician within the scope of sound medical judgment. In certain embodiments, the ligands in accordance with the present invention may be administered at dosage levels sufficient to deliver from about 0.0001 mg/kg to about 100 mg/kg, from about 0.001 mg/kg to about 0.05 mg/kg, from about 0.005 mg/kg to about 0.05 mg/kg, from about 0.001 mg/kg to about 0.005 mg/kg, from about 0.05 mg/kg to about 0.5 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, from about 10 mg/kg to about 100 mg/kg, from about 50 mg/kg to about 500 mg/kg, from about 100 mg/kg to about 1000 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired effect. In some embodiments, the dosage levels may be 1mg/kg, 5 mg/kg, 10mg/kg, 20mg/kg, 30 mg/kg, 40 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg, 90 mg/kg, 100 mg/kg, 100 mg/kg, 110 mg/kg, 120 mg/kg, 130 mg/kg,140 mg/kg, 150 mg/kg, 160 mg/kg, 170 mg/kg, 180 mg/kg, 190 mg/kg or mg/kg of subject body weight per day, or more times a day, to obtain the desired effect.

[0559] The present disclosure provides methods for delivering to a cell or tissue any of the ligands described herein, comprising contacting the cell or tissue with said ligand and can be accomplished in vitro, ex vivo, or in vivo. In certain embodiments, the ligands in accordance with the present invention may be administered to cells at dosage levels sufficient to deliver from about 1 nM to about 10 nM, from about 5 nM to about 50 nM, from about 10 nM to about 100 nM, from about 50 nM to about 500 nM, from about 100 nM to about 1000 nM, from about 1μM to about 10μM, from about 5μM to about 50μM, from about 10μM to about 100μM from about 25μM to about 250μM, from about 50μM to about 500μM. In some embodiments, the ligand may be administered to cells at doses selected from but not limited to 0.0064μM, 0.0032μM, 0.016μM, 0.08μM, 0.4μM, 1μM, 2μM, 5μM, 10μM,25μM, 50μM, 75μM, 100μM, 150μM, 200μM, 250μM.

[0560] The desired dosage of the ligands of the present invention may be delivered only once, three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the

desired dosage may be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. As used herein, a "split dose" is the division of "single unit dose" or total daily dose into two or more doses, e.g., two or more administrations of the "single unit dose". As used herein, a "single unit dose" is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event. The desired dosage of the ligand of the present invention may be administered as a "pulse dose" or as a "continuous flow". As used herein, a "pulse dose" is a series of single unit doses of any therapeutic administered with a set frequency over a period of time. As used herein, a "continuous flow" is a dose of therapeutic administered continuously for a period of time in a single route/single point of contact, i.e., continuous administration event. A total daily dose, an amount given or prescribed in 24-hour period, may be administered by any of these methods, or as a combination of these methods, or by any other methods suitable for a pharmaceutical administration.

3. Administration

[0561] In some embodiments, the compositions for immunotherapy may be administered to cells *ex vivo* and subsequently administered to the subject. Immune cells can be isolated and expanded *ex vivo* using a variety of methods known in the art. For example, methods of isolating cytotoxic T cells are described in U.S. Pat. NOs. 6,805,861 and 6,531, 451; the contents of each of which are incorporated herein by reference in their entirety. Isolation of NK cells is described in U.S. Pat. NOs.: 7,435, 596; the contents of which are incorporated by reference herein in its entirety.

[0562] In some embodiments, depending upon the nature of the cells, the cells may be introduced into a host organism e.g. a mammal, in a wide variety of ways including by injection, transfusion, infusion, local instillation or implantation. In some aspects, the cells of the invention may be introduced at the site of the tumor. The number of cells that are employed will depend upon a number of circumstances, the purpose for the introduction, the lifetime of the cells, the protocol to be used, for example, the number of administrations, the ability of the cells to multiply, or the like. The cells may be in a physiologically-acceptable medium.

[0563] In some embodiments, the cells of the invention may be administrated in multiple doses to subjects having a disease or condition. The administrations generally effect an

improvement in one or more symptoms of cancer or a clinical condition and/or treat or prevent cancer or clinical condition or symptom thereof.

[0564] In some embodiments, the compositions for immunotherapy may be administered *in vivo*. In some embodiments, polypeptides of the present invention comprising biocircuits, effector molecules, SREs, payloads of interest (immunotherapeutic agents) and compositions of the invention may be delivered in vivo to the subject. In vivo delivery of immunotherapeutic agents is well described in the art. For example, methods of delivery of cytokines are described in the E.P. Pat. No.: EP0930892 A1, the contents of which are incorporated herein by reference.

Routes of delivery

[0565] The pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs (e.g., DDs), payloads (i.e. immunotherapeutic agents), vectors and cells of the present invention may be administered by any route to achieve a therapeutically effective outcome.

[0566] These include, but are not limited to enteral (into the intestine), gastroenteral, epidural (into the dura matter), oral (by way of the mouth), transdermal, peridural, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), epicutaneous (application onto the skin), intradermal, (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intravenous bolus, intravenous drip, intra-arterial (into an artery), intramuscular (into a muscle), intracranial (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraperitoneal, (infusion or injection into the peritoneum), intrasinal infusion, intravitreal, (through the eye), intravenous injection (into a pathologic cavity) intracavitary (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), transvaginal, insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), in ear drops, auricular (in or by way of the ear), buccal (directed toward the cheek), conjunctival, cutaneous, dental (to a tooth or teeth), electro-osmosis, endocervical, endosinusial, endotracheal, extracorporeal, hemodialysis, infiltration, interstitial, intra-abdominal, intra-amniotic, intra-articular, intrabiliary, intrabronchial, intrabursal, intracartilaginous (within a cartilage), intracaudal (within the cauda equine), intracisternal (within the cisterna magna cerebellomedularis), intracorneal (within the cornea), dental intracornal, intracoronary (within the coronary arteries), intracorporus cavernosum (within the dilatable spaces of the

corporus cavernosa of the penis), intradiscal (within a disc), intraductal (within a duct of a gland), intraduodenal (within the duodenum), intradural (within or beneath the dura), intraepidermal (to the epidermis), intraesophageal (to the esophagus), intragastric (within the stomach), intragingival (within the gingivae), intraileal (within the distal portion of the small intestine), intralesional (within or introduced directly to a localized lesion), intraluminal (within a lumen of a tube), intralymphatic (within the lymph), intramedullary (within the marrow cavity of a bone), intrameningeal (within the meninges), intramyocardial (within the myocardium), intraocular (within the eye), intraovarian (within the ovary), intrapericardial (within the pericardium), intrapleural (within the pleura), intraprostatic (within the prostate gland), intrapulmonary (within the lungs or its bronchi), intrasinal (within the nasal or periorbital sinuses), intraspinal (within the vertebral column), intrasynovial (within the synovial cavity of a joint), intratendinous (within a tendon), intratesticular (within the testicle), intrathecal (within the cerebrospinal fluid at any level of the cerebrospinal axis), intrathoracic (within the thorax), intratubular (within the tubules of an organ), intratumor (within a tumor), intratympanic (within the aurus media), intravascular (within a vessel or vessels), intraventricular (within a ventricle), iontophoresis (by means of electric current where ions of soluble salts migrate into the tissues of the body), irrigation (to bathe or flush open wounds or body cavities), laryngeal (directly upon the larynx), nasogastric (through the nose and into the stomach), occlusive dressing technique (topical route administration which is then covered by a dressing which occludes the area), ophthalmic (to the external eye), oropharyngeal (directly to the mouth and pharynx), parenteral, percutaneous, periarticular, peridural, perineural, periodontal, rectal, respiratory (within the respiratory tract by inhaling orally or nasally for local or systemic effect), retrobulbar (behind the pons or behind the eyeball), intramyocardial (entering the myocardium), soft tissue, subarachnoid, subconjunctival, submucosal, topical, transplacental (through or across the placenta), transtracheal (through the wall of the trachea), transtympanic (across or through the tympanic cavity), ureteral (to the ureter), urethral (to the urethra), vaginal, caudal block, diagnostic, nerve block, biliary perfusion, cardiac perfusion, photopheresis or spinal.

Kits

[0567] The also provides a kit comprising any of the polynucleotides or expression vectors described herein.

[0568] The present invention includes a variety of kits for conveniently and/or effectively carrying out methods of the present invention. Typically, kits will comprise sufficient

amounts and/or numbers of components to allow a user to perform one or multiple treatments of a subject(s) and/or to perform one or multiple experiments.

[0569] In one embodiment, the present invention provides kits for inhibiting genes in vitro or in vivo, comprising a biocircuit of the present invention or a combination of biocircuits of the present invention, optionally in combination with any other suitable active agents.

[0570] The kit may further comprise packaging and instructions and/or a delivery agent to form a formulation composition. The delivery agent may comprise, for example, saline, a buffered solution.

[0571] In additional embodiments, assay screening kits are provided. The kit includes a container for the screening assay. An instruction for the use of the assay and the information about the screening method are to be included in the kit.

[0572] In some embodiments, the DDs, effector modules and biocircuit system and compositions of the invention may be used as research tools to investigate protein activity in a biological system such a cell and a subject. In other embodiments, the DDs, effector modules and biocircuit system and compositions of the invention may be used for treating a disease such as a cancer and a genetic disorder.

VI. APPLICATIONS

[0573] In one aspect of the present invention, methods for reducing a tumor volume or burden are provided. The methods comprise administering a pharmaceutically effective amount of a pharmaceutical composition comprising at least one biocircuit system, effector module, DD, and/or payload of interest (i.e., an immunotherapeutic agent), at least one vector, or cells to a subject having a tumor. The biocircuit system and effector module having any immunotherapeutic agent as described herein may be in forms of a polypeptide, or a polynucleotide such as mRNA, or a viral vector comprising the polynucleotide, or a cell modified to express the biocircuit, effector module, DD, and payload of interest (i.e., immunotherapeutic agent).

[0574] In another aspect of the present invention, methods for inducing an anti-tumor immune response in a subject are provided. The methods comprise administering a pharmaceutically effective amount of a pharmaceutical composition comprising at least one biocircuit system, effector module, DD, and/or payload of interest (i.e., an immunotherapeutic agent), at least one vector, or cells to a subject having a tumor. The biocircuit and effector module having any immunotherapeutic agent as described herein may be in forms of a polypeptide, or a polynucleotide such as mRNA, or a viral vector comprising

the polynucleotide, or a cell modified to express the biocircuit, effector module, DD, and payload of interest (i.e., immunotherapeutic agent).

[0575] The methods, per the present invention, may be adoptive cell transfer (ACT) using genetically engineered cells such as immune effector cells of the invention, cancer vaccines comprising biocircuit systems, effector modules, DDs, payloads of interest (i.e., immunotherapeutic agents) of the invention, or compositions that manipulate the tumor immunosuppressive microenvironment, or the combination thereof. These treatments may be further employed with other cancer treatment such as chemotherapy and radiotherapy.

1. Adoptive cell transfer (adoptive immunotherapy)

[0576] Recent progress in the field of cancer immunology has allowed the development of several approaches to help the immune system keep the cancer at bay. Such immunotherapy approaches include the targeting of cancer antigens through monoclonal antibodies or through adoptive transfer of ex vivo engineered T cells (e.g., which contain chimeric antigen receptors or engineered T cell receptors). The present invention also provides methods for inducing immune responses in a subject using the compositions of the invention. Also provided are methods for reducing a tumor burden in a subject using the compositions of the invention. The present invention also provides immune cells engineered to include one or more polypeptides, polynucleotides, or vectors of the present invention. The cells may be immune effector cells, including T cells such as cytotoxic T cells, helper T cells, memory T cells, regulatory T cells, natural killer (NK) cells, NK T cells, cytokine-induced killer (CIK) cells, cytotoxic T lymphocytes (CTLs), and tumor infiltrating lymphocytes (TILs). The engineered cell may be used for adoptive cell transfer for treating a disease (e.g., a cancer).

[0577] In some embodiments, pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention may be used in the modulation or alteration or exploitation of the immune system to target one or more cancers. This approach may also be considered with other such biological approaches, e.g., immune response modifying therapies such as the administration of interferons, interleukins, colony-stimulating factors, other monoclonal antibodies, vaccines, gene therapy, and nonspecific immunomodulating agents are also envisioned as anti-cancer therapies to be combined with the pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention.

[0578] Cancer immunotherapy refers to a diverse set of therapeutic strategies designed to induce the patient's own immune system to fight the cancer. In some embodiments, pharmaceutical compositions, biocircuits, biocircuit components, effector modules including

their SREs or payloads of the present invention are designed as immune-oncology therapeutics.

[0579] In some embodiments, cells which are genetically modified to express at least one biocircuit system, effector module, DD, and/or payload of interest (immunotherapeutic agent) may be used for adoptive cell therapy (ACT). As used herein, Adoptive cell transfer refers to the administration of immune cells (from autologous, allogenic or genetically modified hosts) with direct anticancer activity. ACT has shown promise in clinical application against malignant and infectious disease. For example, T cells genetically engineered to recognize CD19 have been used to treat follicular B cell lymphoma (Kochenderfer et al., *Blood*, 2010, 116:4099-4102; and Kochenderfer and Rosenberg, *Nat Rev Clin Oncol.*, 2013, 10(5): 267-276) and ACT using autologous lymphocytes genetically-modified to express anti-tumor T cell receptors has been used to treat metastatic melanoma (Rosenberg and Dudley, *Curr. Opin. Immunol.* 2009, 21: 233-240).

[0580] Immune cells for adoptive cell therapy may be selected from but not limited to selected from a CD8+ T cell, a CD4+ T cell, a helper T cell, a natural killer (NK) cell, a NKT cell, a cytotoxic T lymphocyte (CTL), a tumor infiltrating lymphocyte (TIL), a memory T cell, a regulatory T (Treg) cell, a cytokine-induced killer (CIK) cell, a dendritic cell, a human embryonic stem cell, a mesenchymal stem cell, a hematopoietic stem cell, or a mixture thereof.

[0581] There are several types of cellular immunotherapies, including tumor infiltrating lymphocyte (TIL) therapy, genetically engineered T cells bearing chimeric antigen receptors (CARs), and recombinant TCR technology. In some embodiments, the compositions of the present invention may be utilized to alter TIL (tumor infiltrating lymphocyte) populations in a subject. In one embodiment, any of the payloads described herein may be utilized to change the ratio of CD4 positive cells to CD8 positive populations. In some embodiments, TILs may be sorted ex vivo and engineered to express any of the cytokines described herein. Payloads of the invention may be used to expand CD4 and/or CD8 populations of TILs to enhance TIL mediated immune response.

[0582] In one embodiment, the chimeric antigen receptor (CAR) of the present invention may be a conditionally active CAR. A wild type protein or domain thereof, such as those described herein may be used to generate a conditionally active biologic protein which are reversibly or irreversibly inactivated at the wild type normal physiological conditions as well as to such conditionally active biologic proteins and domains and uses of such conditional active biologic proteins and domains are provided. Such methods and conditionally active

proteins are taught in, for example, International Publication No. WO2016033331, the contents of which are incorporated herein by reference in their entirety. As a non-limiting example, the CAR comprises at least one antigen specific targeting region evolved from a wild type protein or a domain thereof and one or more of a decrease in activity in the assay at the normal physiological condition compared to the antigen specific targeting region of the wild-type protein or a domain thereof, and an increase in activity in the assay under the aberrant condition compared to the antigen specific targeting region of the wild-type protein or a domain thereof.

[0583] According to the present invention, the biocircuits and systems may be used in the development and implementation of cell therapies such as adoptive cell therapy. Certain effector modules useful in cell therapy are given in Figures 7-12. The biocircuits, their components, effector modules and their SREs and payloads may be used in cell therapies to effect TCR removal -TCR gene disruption, TCR engineering, to regulate epitope tagged receptors, in APC platforms for stimulating T cells, as a tool to enhance *ex vivo* APC stimulation, to improve methods of T cell expansion, in *ex vivo* stimulation with antigen, in TCR/CAR combinations, in the manipulation or regulation of TILs, in allogeneic cell therapy, in combination T cell therapy with other treatment lines (e.g. radiation, cytokines), to encode engineered TCRs, or modified TCRs, or to enhance T cells other than TCRs (e.g. by introducing cytokine genes, genes for the checkpoint inhibitors PD1, CTLA4).

[0584] In some embodiments, improved response rates are obtained in support of cell therapies.

[0585] Expansion and persistence of cell populations may be achieved through regulation or fine tuning of the payloads, e.g., the receptors or pathway components in T cells, NK cells or other immune-related cells. In some embodiments, biocircuits, their components, SREs or effector modules are designed to spatially and/or temporally control the expression of proteins which enhance T-cell or NK cell response. In some embodiments, biocircuits, their components, SREs or effector modules are designed to spatially and/or temporally control the expression of proteins which inhibit T-cell or NK cell response.

[0586] Provided herein are methods for use in adoptive cell therapy. The methods involve preconditioning a subject in need thereof, modulating immune cells with SRE, biocircuits and compositions of the present invention, administering to a subject, engineered immune cells expressing compositions of the invention and the successful engraftment of engineered cells within the subject.

[0587] In some embodiments, SREs, biocircuits and compositions of the present invention may be used to minimize preconditioning regimens associated with adoptive cell therapy. As used herein "preconditioning" refers to any therapeutic regimen administered to a subject in order to improve the outcome of adoptive cell therapy. Preconditioning strategies include, but are not limited to total body irradiation and/or lymphodepleting chemotherapy. Adoptive therapy clinical trials without preconditioning have failed to demonstrate any clinical benefit, indicating its importance in ACT. Yet, preconditioning is associated with significant toxicity and limits the subject cohort that is suitable for ACT. In some instances, immune cells for ACT may be engineered to express cytokines such as IL12 and IL15 as payload using SREs of the present invention to reduce the need for preconditioning (Pengram et al. (2012) Blood 119 (18): 4133-41; the contents of which are incorporated by reference in their entirety).

[0588] In some embodiments, the neurotoxicity may be associated with CAR or TIL therapy. Such neurotoxicity may be associated CD19-CARs. Toxicity may be due to excessive T cell infiltration into the brain. In some embodiments, neurotoxicity may be alleviated by preventing the passage of T cells through the blood brain barrier. This can be achieved by the targeted gene deletion of the endogenous alpha-4 integrin inhibitors such as tysabri/natalizumab may also be useful in the present invention.

[0589] In some embodiments, the effector modules may encode one or more cytokines. In some embodiments, the cytokine is IL15. Effector modules encoding IL15 may be designed to induce proliferation in cytotoxic populations and avoid stimulation of T regs. In other cases, the effector modules which induce proliferation in cytotoxic populations may also stimulate NK and NKT cells.

[0590] In some embodiments, effector modules may encode, or be tuned or induced to produce, one or more cytokines for expansion of cells in the biocircuits of the invention. In such cases the cells may be tested for actual expansion. Expansion may be at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more.

[0591] In some embodiments, the tumor microenvironment may be remodeled using a biocircuit containing an effector module encoding IL17.

[0592] In some embodiments, biocircuits, their components, SREs or effector modules are designed to modulate Tregs to attenuate autoimmune disorders. In such a case, IL2 may be regulated using a singly tuned module or one having multiple tuned features as described herein.

[0593] In some embodiments, immune cells for ACT may be dendritic cells, T cells such as $CD8^+$ T cells and $CD4^+$ T cells, natural killer (NK) cells, NK T cells, Cytotoxic T

lymphocytes (CTLs), tumor infiltrating lymphocytes (TILs), lymphokine activated killer (LAK) cells, memory T cells, regulatory T cells (Tregs), helper T cells, cytokine-induced killer (CIK) cells, and any combination thereof. In other embodiments, immune stimulatory cells for ACT may be generated from embryonic stem cell (ESC) and induced pluripotent stem cell (iPSC). In some embodiments, autologous or allogeneic immune cells are used for ACT.

[0594] In some embodiments, cells used for ACT may be T cells engineered to express T cell receptors (TCRs) with new specificities or CARs comprising an antigen-binding domain specific to an antigen on tumor cells of interest. In other embodiments, cells used for ACT may be NK cells engineered to express CARs comprising an antigen-binding domain specific to an antigen on tumor cells of interest. In addition to adoptive transfer of genetically modified T cells (e.g., CAR T cells) for immunotherapy, alternate types of CAR-expressing leukocytes, either alone, or in combination with CAR T cells may be used for adoptive immunotherapy. In one example, a mixture of T cells and NK cells may be used for ACT. The expression level of CARs in T cells and NK cells, according to the present invention, is tuned and controlled by a small molecule that binds to the DD(s) operably linked to the CAR in the effector module.

[0595] In some embodiments, NK cells engineered to express the present compositions may be used for ACT. NK cell activation induces perforin/granzyme-dependent apoptosis in target cells. NK cell activation also induces cytokine secretion such as IFN γ, TNF-α and GM-CSF. These cytokines enhance the phagocytic function of macrophages and their antimicrobial activity, and augment the adaptive immune response via up-regulation of antigen presentation by antigen presenting cells such as dendritic cells (DCs) (Reviewed by Vivier et al., *Nat. Immunol.*, 2008, 9(5): 503-510).

[0596] Other examples of genetic modification may include the introduction of chimeric antigen receptors (CARs) and the down-regulation of inhibitory NK cell receptors such as NKG2A. Examples of CARs include, but are not limited to, CD19 and CD20 specific CARs against B cell malignancies, CARs targeting CD33 on leukemia cells, CS1 CAR and CD138 CAR on myeloma cells, GD2 CAR on neuroblastoma cells, Her2/Neu and erbB2 on breast cancer cells, carcinoembryonic antigen (CEA) on colon cancers, EpCAM on epithelial tumors, GPA7 on melanoma, NKG2D ligand on leukemia and solid tumors, and TRAIL R1 on various tumor targets. The CARs may be POIs of the effector modules and regulated by the binding of the DD with its corresponding ligand.

[0597] In another example, NK cells for ACT may be modified to express an effector module comprising the high-affinity CD16-158V polymorphism (HA-CD16) which augments NK cell mediated antibody dependent cell cytotoxicity (ADCC) against tumors. Infusion of NK cells genetically modified to express HA-CD16 could be used as a strategy to improve the efficacy of antibody-based therapies for cancer patients.

[0598] NK cells may also be genetically reprogrammed to circumvent NK cell inhibitory signals upon interaction with tumor cells. For example, using CRISPR, ZFN, or TALEN to genetically modify NK cells to silence their inhibitory receptors may enhance the anti-tumor capacity of NK cells.

[0599] Immune cells can be isolated and expanded *ex vivo* using a variety of methods known in the art. For example, methods of isolating and expanding cytotoxic T cells are described in U.S. Pat. NOs. 6,805,861 and 6,531, 451; US Patent Publication No.: US20160348072A1 and International Patent Publication NO: WO2016168595A1; the contents of each of which are incorporated herein by reference in their entirety. Isolation and expansion of NK cells is described in US Patent Publication NO.: US20150152387A1, U.S. Patent NO.: 7,435, 596; and Oyer, J.L. (2016). Cytotherapy.18(5):653-63; the contents of each of which are incorporated by reference herein in its entirety. Specifically, human primary NK cells may be expanded in the presence of feeder cells e.g. a myeloid cell line that has been genetically modified to express membrane bound IL15, IL21, IL12 and 4-1BBL.

[0600] In some instances, sub populations of immune cells may be enriched for ACT. Methods for immune cell enrichment are taught in International Patent Publication NO.: WO2015039100A1. In another example, T cells positive for B and T lymphocyte attenuator marker BTLA) may be used to enrich for T cells that are anti-cancer reactive as described in U.S. Pat. NO.: 9,512,401 (the content of each of which are incorporated herein by reference in their entirety).

[0601] In some embodiments, immune cells for ACT may be depleted of select sub populations to enhance T cell expansion. For example, immune cells may be depleted of Foxp3+ T lymphocytes to minimize the ant-tumor immune response using methods taught in US Patent Publication NO.: US 20160298081A1; the contents of which are incoporated by reference herein in their entirety.

[0602] In some embodiments, activation and expansion of T cells for ACT is achieved antigenic stimulation of a transiently expressed Chimeric Antigen Receptor (CAR) on the cell surface. Such activation methods are taught in International Patent NO.: WO2017015427, the content of which are incorporated herein by reference in their entirety.

[0603] In some embodiments, immune cells may be activated by antigens associated with antigen presenting cells (APCs). In some embodiments, the APCs may be dendritic cells, macrophages or B cells that antigen specific or nonspecific. The APCs may autologous or homologous in their organ. In some embodiments the APCs may be artificial antigen presenting cells (aAPCs) such as cell based aAPCs or acellular aAPCs. Cell based aAPCs are may be selected from either genetically modified allogeneic cells such as human erythroleukemia cells or xenogeneic cells such as murine fibroblasts and Drosophila cells. Alternatively, the APCs maybe be acellular wherein the antigens or costimulatory domains are presented on synthetic surfaces such as latex beads, polystyrene beads, lipid vesicles or exosomes.

[0604] In some embodiments, adoptive cell therapy is carried out by autologous transfer, wherein the cells are derived from a subject in need of a treatment and the cells, following isolation and processing are administered to the same subject. In other instances, ACT may involve allogenic transfer wherein the cells are isolated and/or prepared from a donor subject other than the recipient subject who ultimately receives cell therapy. The donor and recipient subject may be genetically identical, or similar or may express the same HLA class or subtype.

[0605] In some embodiments, the multiple immunotherapeutic agents introduced into the immune cells for ACT (e.g., T cells and NK cells) may be controlled by the same biocircuit system. In one example, a cytokine such as IL12 and a CAR construct such as CD19 CAR are linked to the same hDHFR destabilizing domain. The expression of IL12 and CD19 CAR is tuned using TMP simultaneously. In other embodiments, the multiple immunotherapeutic agents introduced into the immune cells for ACT (e.g., T cells and NK cells) may be controlled by different biocircuit systems. In one example, a cytokine such as IL12 and a CAR construct such as CD19 CAR are linked to different DDs in two separate effector modules, thereby can be tuned separately using different stimuli. In another example, a suicide gene and a CAR construct may be linked to two separate effector modules.

[0606] Following genetic modulation using SREs, biocircuits and compositions of the invention, cells are administered to the subject in need thereof. Methods for administration of cells for adoptive cell therapy are known and may be used in connection with the provided methods and compositions. For example, adoptive T cell therapy methods are described, e.g., in US Patent Application Publication No. 2003/0170238 to Gruenberg et al; US Patent No. 4,690,915 to Rosenberg; Rosenberg (2011) Nat Rev Clin Oncol. 8(10):577-85). See, e.g., Themeli et al. (2013) Nat Biotechnol. 31(10): 928-933; Tsukahara et al. (2013) Biochem

Biophys Res Commun 438(1): 84-9; Davila et al. (2013) PLoS ONE 8(4): e61338; the contents of each of which are incorporated herein by reference in their entirety.

[0607] In some embodiments, immune cells for ACT may be modified to express one or more immunotherapeutic agents which facilitate immune cells activation, infiltration, expansion, survival and anti-tumor functions. The immunotherapeutic agents may be a second CAR or TCR specific to a different target molecule; a cytokine or a cytokine receptor; a chimeric switch receptor that converts an inhibitory signal to a stimulatory signal; a homing receptor that guides adoptively transferred cells to a target site such as the tumor tissue; an agent that optimizes the metabolism of the immune cell; or a safety switch gene (e.g., a suicide gene) that kills activated T cells when a severe event is observed after adoptive cell transfer or when the transferred immune cells are no-longer needed.

[0608] In some embodiments, immune cells used for adoptive cell transfer can be genetically manipulated to improve their persistence, cytotoxicity, tumor targeting capacity, and ability to home to disease sites *in vivo*, with the overall aim of further improving upon their capacity to kill tumors in cancer patients. One example is to introduce effector modules of the invention comprising cytokines such as gamma-cytokines (IL2 and IL15) into immune cells to promote immune cell proliferation and survival. Transduction of cytokine genes (e.g., gamma-cytokines IL2 and IL15) into cells will be able to propagate immune cells without addition of exogenous cytokines and cytokine expressing NK cells have enhanced tumor cytotoxicity.

[0609] Another example includes the use of genetic modification for directing the infused NK cells to proper tumor tissues. NK cells may be genetically engineered with an effector module that encodes the CCR7 receptor to improve their migration toward one of its ligands CCL19. Other strategies may involve utilizing chemokine receptors, such as CXCR3 to improve NK cell migration to inflamed tissues, such as those infiltrated with metastatic tumors.

[0610] NK cells may be modified to become insensitive to suppressive cytokines such as TGF-β, thereby preserving their cytotoxicity. For example, NK cells can be genetically modified to express the dominant negative mutant form of TGF-β type II receptor (DNTβRII) on their surface that render NK cells resistant to the suppressive effects of TGF-β.

[0611] In some embodiments, biocircuits, their components, SREs or effector modules are designed to be significantly less immunogenic than other biocircuits or switches in the art.

[0612] As used herein, "significantly less immunogenic" refers to a detectable decrease in immunogenicity. In another embodiment, the term refers to a fold decrease in

immunogenicity. In another embodiment, the term refers to a decrease such that an effective amount of the biocircuits, their components, SREs or effector modules which can be administered without triggering a detectable immune response. In another embodiment, the term refers to a decrease such that the biocircuits, their components, SREs or effector modules can be repeatedly administered without eliciting an immune response. In another embodiment, the decrease is such that the biocircuits, their components, SREs or effector modules can be repeatedly administered without eliciting an immune response.

[0613] In another embodiment, the biocircuits, their components, SREs or effector modules is 2-fold less immunogenic than its unmodified counterpart or reference compound. In another embodiment, immunogenicity is reduced by a 3-fold factor. In another embodiment, immunogenicity is reduced by a 5-fold factor. In another embodiment, immunogenicity is reduced by a 7-fold factor. In another embodiment, immunogenicity is reduced by a 10-fold factor. In another embodiment, immunogenicity is reduced by a 15-fold factor. In another embodiment, immunogenicity is reduced by a fold factor. In another embodiment, immunogenicity is reduced by a 50-fold factor. In another embodiment, immunogenicity is reduced by a 100-fold factor. In another embodiment, immunogenicity is reduced by a 200-fold factor. In another embodiment, immunogenicity is reduced by a 500-fold factor. In another embodiment, immunogenicity is reduced by a 1000-fold factor. In another embodiment, immunogenicity is reduced by a 2000-fold factor. In another embodiment, immunogenicity is reduced by another fold difference.

[0614] Methods of determining immunogenicity are well known in the art, and include, e.g. measuring secretion of cytokines (e.g. IL12, IFNalpha, TNF-alpha, RANTES, MIP-1alpha or beta, IL6, IFN beta, or IL8), measuring expression of DC activation markers (e.g. CD83, HLA-DR, CD80 and CD86), or measuring ability to act as an adjuvant for an adaptive immune response.

[0615] The present invention provides method of inducing an immune response in a cell. As used herein the term “immune response” refers to the activity of the cells of the immune system in response to stimulus, or an antigen. In some embodiments, the antigen may be a cancer antigen. In some aspects, the methods of inducing an immune response may involve administering to the cell, a therapeutically effective amount of any of the compositions described herein. In one aspect, the method may involve administering the pharmaceutical compositions described herein. In one aspect, the method may involve administering the polynucleotides, vectors. In some embodiments, induction of the immune response occurs due to the expression and or function of the immunotherapeutic agents described herein.

Methods of inducing immune response further may involve administering to the cell, an effective amount of the stimulus to tune the expression of the immunotherapeutic agent. In some embodiments, the immunotherapeutic agent is capable of inducing an immune response in response to the stimulus. The induction of the immune response may occur in a cell within a subject i.e. *in vivo*, *ex vivo* or *in vitro*. The induction of an immune response may be evaluated by measuring the release of cytokine such as IL2 and IFNγ from the cells. In some embodiments, the induction of an immune response may be measured by evaluating the cell surface markers such as but not limited to CD3, CD4, CD8, CD 14, CD20, CD11b, CD16, CD45 and HLA-DR, CD 69, CD28, CD44, IFNgamma. Examples of cell surface markers for antigen presenting cells include, but are not limited to, MHC class I, MHC Class II, CD40, CD45, B7-1, B7-2, IFN γ receptor and IL2 receptor, ICAM-1 and/or Fcγ receptor. Examples of cell surface markers for dendritic cells include, but are not limited to, MHC class I, MHC Class II, B7-2, CD18, CD29, CD31, CD43, CD44, CD45, CD54, CD58, CD83, CD86, CMRF-44, CMRF-56, DCIR and/or Dectin-1 and the like; while in some cases also having the absence of CD2, CD3, CD4, CD8, CD14, CD15, CD16, CD 19, CD20, CD56, and/or CD57. Examples of cell surface markers for NK cells include, but are not limited to, CCL3, CCL4, CCL5, Granulysin, Granzyme B, Granzyme K, IL10, IL22, IFNg, LAP, Perforin, and TNFa.

2. Cancer vaccines

[0616] In some embodiments, biocircuits, effector modules, payloads of interest (immunotherapeutic agents), vectors, cells and compositions of the present invention may be used for cancer vaccines. In one aspect, dendritic cells are modified to express the compositions of the invention and used as cancer vaccines.

[0617] In some embodiments, cancer vaccine may comprise peptides and/or proteins derived from tumor associated antigen (TAA). Such strategies may be utilized to evoke an immune response in a subject, which in some instances may be a cytotoxic T lymphocyte (CTL) response. Peptides used for cancer vaccines may also modified to match the mutation profile of a subject. For example, EGFR derived peptides with mutations matched to the mutations found in the subject in need of therapy have been successfully used in patients with lung cancer (Li F et al. (2016) Oncoimmunology. Oct 7;5(12): e1238539; the contents of which are incoporated herein by reference in their entirety).

[0618] In one embodiment, cancer vaccines of the present invention may superagonist altered peptide ligands (APL) derived from TAAs. These are mutant peptide ligands deviate from the native peptide sequence by one or more amino acids, which activate specific CTL

clones more effectively than native epitopes. These alterations may allow the peptide to bind better to the restricting Class I MHC molecule or interact more favorably with the TCR of a given tumor-specific CTL subset. APLs may be selected using methods taught in US Patent Publication NO.: US20160317633A1, the contents of which are incorporated herein by reference in their entirety.

3. Tumor microenvironment (TME)

[0619] In some embodiments, biocircuits, their components, SREs or effector modules are designed to reshape the tumor microenvironment in order to extend utility of the biocircuit or a pharmaceutical composition beyond direct cell killing.

[0620] In some embodiments, biocircuits, their components, SREs or effector modules are designed to reduce, mitigate or eliminate the CAR cytokine storm. In some embodiments, such reduction, mitigation and/or elimination occurs in solid tumors or tumor microenvironments.

[0621] In some embodiments, biocircuits, effector modules, payloads of interest (immunotherapeutic agents), vectors, cells and pharmaceutical compositions of the present invention may be used to convert the immunosuppressive microenvironment to increase immune responses.

[0622] In some embodiments, the invention provides methods for converting the inhibitory immunoregulatory signals from immunosuppressive cytokines secreted by cancer cells or the surrounding tumor stroma into stimulatory signals using compositions of the invention. Immunosuppressive cytokines include without limitation, IL13, IL4, TGF-beta, IL6, IL8, and IL10. In one aspect, the genetically modified tumor-specific T cells (e.g., CAR T cells) or T cells with native tumor specificity may be further engineered to express an effector module comprising a chimeric switch receptor that binds to inhibitory/suppressive cytokines and converts their intracellular consequences to an immunostimulatory/activating signal, thus improving the efficacy of tumor-specific T cells. The chimeric switch receptor is composed of the extracellular domains of an inhibitory cytokine receptor (e.g., IL13R, IL4R, IL10R, TGFβR1/ALK5, TGFβR2, and TGFβR3/β-glycan) fused with the intracellular signal transducing domains derived from stimulatory cytokine receptors such as IL2R (i.e., IL2Rα/CD25, IL2Rβ/CD122, and common γ chain receptor/CD132 which is shared by various cytokine receptors) and/or IL7R (IL7Rα/CD127, common γ chain receptor/CD132). These manipulations render tumor specific T cells or CAR T cells resistant to the suppressive tumor microenvironment.

[0623] In some embodiments, the present invention provides methods to abrogate the immunosuppressive effects produced by myeloid derived suppressor cells (MDSCs). Tumor cells secrete indoleamine 2,3-dioxygenase (IDO) which promotes immunosuppression through the recruitment of MDSCs. The immunosuppressive environment is further promoted by the MDSCs through nitric oxide synthase (NOS) and arginase 1 (ARG1) which can degrade extracellular arginine. Amino acid deprivation within the tumor microenvironment suppresses T cell anti-tumor activity. In some embodiments, payloads of the present invention may comprise inhibitors of NOS, ARG1 and tryptophan metabolism pathway such as IDO. In one embodiment, the payload may include inhibitors of colony stimulating factor receptor 1 (CSFR1) which required for the proliferation and function of MDSCs.

[0624] In some embodiments, dominant negative mutants of inhibitory co receptor such as PD-1, CTLA-4, LAG-3, TIM-3, KIRs, or BTLA may be utilized as payloads of the invention to overcome inhibitory signals in the tumor microenvironment.

4. Combination treatments

[0625] In some embodiments, it is desirable to combine compositions, vectors and cells of the invention for administration to a subject. Compositions of the invention comprising different immunotherapeutic agents may be used in combination for enhancement of immunotherapy.

Immunotherapeutic Agents

[0626] In some embodiments, it is desirable to combine compositions of the invention with adjuvants, that can enhance the potency and longevity of antigen-specific immune responses. Adjuvants used as immunostimulants in combination therapy include biological molecules or delivery carriers that deliver antigens. As non-limiting examples, the compositions of the invention may be combined with biological adjuvants such as cytokines, Toll Like Receptors, bacterial toxins, and/or saponins. In other embodiments, the compositions of the present invention may be combined with delivery carriers. Exemplary delivery carriers include, polymer microspheres, immune stimulating complexes, emulsions (oil-in-water or water-in-oil), aluminum salts, liposomes or virosomes.

[0627] In some embodiments, immune effector cells modified to express biocircuits, effector modules, DDs and payloads of the invention may be combined with the biological adjuvants described herein. Dual regulation of CAR and cytokines and ligands to segregate the kinetic control of target-mediated activation from intrinsic cell T cell expansion. Such dual regulation also minimizes the need for pre-conditioning regimens in patients. As a non-limiting example, DD regulated CAR e.g. CD19 CAR may be combined with cytokines e.g.

IL12 to enhance the anti-tumor efficacy of the CAR (Pegram H.J., et al. Tumor-targeted T cells modified to secrete IL12 eradicate systemic tumors without need for prior conditioning. Blood.2012;119:4133–41; the contents of each of which are incorporated herein by reference in their entirety). As another non-limiting example, Merchant et al. combined dendritic cell- based vaccinations with recombinant human IL7 to improve outcome in high-risk pediatric sarcomas patients (Merchant, M.S. et. al. Adjuvant immunotherapy to Improve Outcome in High-Risk Pediatric Sarcomas. Clin Cancer Res. 2016. 22(13):3182-91; the contents of each of which are incorporated herein by reference in their entirety).

[0628] In some embodiments, immune effector cells modified to express one or more antigen-specific TCRs or CARs may be combined with compositions of the invention comprising immunotherapeutic agents that convert the immunosuppressive tumor microenvironment.

[0629] In one aspect, effector immune cells modified to express CARs specific to different target molecules on the same cell may be combined. In another aspect, different immune cells modified to express the same CAR construct such as NK cells and T cells may be used in combination for a tumor treatment, for instance, a T cell modified to express a CD19 CAR may be combined with a NK cell modified to express the same CD19 CAR to treat B cell malignancy.

[0630] In other embodiments, immune cells modified to express CARs may be combined with checkpoint blockade agents.

[0631] In some embodiments, immune effector cells modified to expressed biocircuits, effector modules, DDs and payloads of the invention may be combined with cancer vaccines of the invention.

[0632] In some embodiments, an effector module comprising a CAR may be used in combination with an effector module comprising a cytokine, or an effector module comprising a safety switch, or an effector module comprising a metabolic factor, or an effector module comprising a homing receptor.

[0633] In one embodiment, an effector module comprising a CD19 CAR may be used in combination with amino pyrimidine derivatives such as the Burkit's tyrosine receptor kinase (BTK) inhibitor using methods taught in International Patent Application NO.: WO2016164580, the contents of which are incorporated herein by reference in their entirety.

Cancer

[0634] In some embodiments, methods of the invention may include combination of the compositions of the invention with other agents effective in the treatment of cancers,

infection diseases and other immunodeficient disorders, such as anti-cancer agents. As used herein, the term "anti-cancer agent" refers to any agent which is capable of negatively affecting cancer in a subject, for example, by killing cancer cells, inducing apoptosis in cancer cells, reducing the growth rate of cancer cells, reducing the incidence or number of metastases, reducing tumor size, inhibiting tumor growth, reducing the blood supply to a tumor or cancer cells, promoting an immune response against cancer cells or a tumor, preventing or inhibiting the progression of cancer, or increasing the lifespan of a subject with cancer.

[0635] In some embodiments, anti-cancer agent or therapy may be a chemotherapeutic agent, or radiotherapy, immunotherapeutic agent, surgery, or any other therapeutic agent which, in combination with the present invention, improves the therapeutic efficacy of treatment.

[0636] In some embodiments, compositions of the present invention may be used in combination with immunotherapeutics other than the inventive therapy described herein, such as antibodies specific to some target molecules on the surface of a tumor cell.

[0637] Exemplary chemotherapies include, without limitation, Acivicin; Aclarubicin; Acodazole hydrochloride; Acronine; Adozelesin; Aldesleukin; Altretamine; Ambomycin; Ametantrone acetate; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperrin, Sulindac, Curcumin, alkylating agents including: Nitrogen mustards such as mechlor-ethamine, cyclophosphamide, ifosfamide, melphalan and chlorambucil; nitrosoureas such as carmustine (BC U), lomustine (CCNU), and semustine (methyl-CC U); thylenimines/methylmelamine such as thriethylenemelamine (TEM), triethylene, thiophosphoramide (thiotepa), hexamethylmelamine (HMM, altretamine); alkyl sulfonates such as busulfan; triazines such as dacarbazine (DTIC); antimetabolites including folic acid analogs such as methotrexate and trimetrexate, pyrrolidine analogs such as 5- fluorouracil, fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, 2,2'- difluorodeoxycytidine, purine analogs such as 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin (pentostatin), erythrohydroxynonyladenine (EHNA), fludarabine phosphate, and 2-chlorodeoxyadenosine (cladribine, 2- CdA); natural products including antimitotic drugs such as paclitaxel, vinca alkaloids including vinblastine (VLB), vincristine, and vinorelbine, taxotere, estramustine, and estramustine phosphate; epipodophylotoxins such as etoposide and teniposide; antibiotics, such as actimomycin D, daunomycin (rubidomycin), doxorubicin, mitoxantrone, idarubicin, bleomycins, plicamycin (mithramycin), mitomycinC, and actinomycin; enzymes such as L-asparaginase, cytokines

such as interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, TNF-beta and GM-CSF, anti-angiogenic factors, such as angiostatin and endostatin, inhibitors of FGF or VEGF such as soluble forms of receptors for angiogenic factors, including soluble VGF/VEGF receptors, platinum coordination complexes such as cisplatin and carboplatin, anthracenediones such as mitoxantrone, substituted urea such as hydroxyurea, methylhydrazine derivatives including N- methylhydrazine (MIFf) and procarbazine, adrenocortical suppressants such as mitotane (o,ρ'-DDD) and aminoglutethimide; hormones and antagonists including adrenocorticosteroid antagonists such as prednisone and equivalents, dexamethasone and aminoglutethimide; progestin such as hydroxyprogesterone caproate, medroxyprogesterone acetate and megestrol acetate; estrogen such as diethylstilbestrol and ethinyl estradiol equivalents; antiestrogen such as tamoxifen; androgens including testosterone propionate and fluoxymesterone/equivalents; antiandrogens such as flutamide, gonadotropin-releasing hormone analogs and leuprolide; non-steroidal antiandrogens such as flutamide; kinase inhibitors, histone deacetylase inhibitors, methylation inhibitors, proteasome inhibitors, monoclonal antibodies, oxidants, anti-oxidants, telomerase inhibitors, BH3 mimetics, ubiquitin ligase inhibitors, stat inhibitors and receptor tyrosin kinase inhibitors such as imatinib mesylate (marketed as Gleevac or Glivac) and erlotinib (an EGF receptor inhibitor) now marketed as Tarveca; anti-virals such as oseltamivir phosphate, Amphotericin B, and palivizumab; Sdi 1 mimetics; Semustine; Senescence derived inhibitor 1; Sparfosic acid; Spicamycin D; Spiromustine; Splenopentin; Spongistatin 1; Squalamine; Stipiamide; Stromelysin inhibitors; Sulfinosine; Superactive vasoactive intestinal peptide antagonist; Velaresol; Veramine; Verdins; Verteporfin; Vinorelbine; Vinxaltine; Vitaxin; Vorozole; Zanoterone; Zeniplatin; Zilascorb; and Zinostatin stimalamer; PI3Kβ small-molecule inhibitor, GSK2636771; pan-PI3K inhibitor (BKM120); BRAF inhibitors. Vemurafenib (Zelboraf) and dabrafenib (Tafinlar); or any analog or derivative and variant of the foregoing.

[0638] In one embodiment, the invention further relates to the use of pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention for treating one or more forms of cancer, in combination with other pharmaceuticals and/or other therapeutic methods, e.g., with known pharmaceuticals and/or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders. For example, the pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention can also be administered in conjunction with one or more additional anti-cancer treatments, such as biological, chemotherapy and radiotherapy.

Accordingly, a treatment can include, for example, imatinib (Gleevac), all-trans-retinoic acid, a monoclonal antibody treatment (gemtuzumab, ozogamicin), chemotherapy (for example, chlorambucil, prednisone, prednisolone, vincristine, cytarabine, clofarabine, farnesyl transferase inhibitors, decitabine, inhibitors of MDR1), rituximab, interferon-α, anthracycline drugs (such as daunorubicin or idarubicin), L-asparaginase, doxorubicin, cyclophosphamide, doxorubicin, bleomycin, fludarabine, etoposide, pentostatin, or cladribine), bone marrow transplant, stem cell transplant, radiation therapy, anti-metabolite drugs (methotrexate and 6-mercaptopurine), or any of the antibodies taught herein such as those in Table 6 of the co-owned U.S. Provisional Patent Application No. 62/320,864 filed April 11, 2016, 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587 (the contents of each of which are herein incorporated by reference in their entirety), or combinations thereof.

[0639] Radiotherapeutic agents and factors include radiation and waves that induce DNA damage for example, γ-irradiation, X-rays, UV-irradiation, microwaves, electronic emissions, radioisotopes, and the like. Therapy may be achieved by irradiating the localized tumor site with the above described forms of radiations. It is most likely that all of these factors effect a broad range of damage DNA, on the precursors of DNA, the replication and repair of DNA, and the assembly and maintenance of chromosomes. Dosage ranges for X-rays range from daily doses of 50 to 200 roentgens for prolonged periods of time (3 to 4 weeks), to single doses of 2000 to 6000 roentgens. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by the neoplastic cells.

[0640] Radiation therapy (also called radiotherapy, X-ray therapy, or irradiation) is the use of ionizing radiation to kill cancer cells and shrink tumors. Radiation therapy can be administered externally via external beam radiotherapy (EBRT) or internally via brachytherapy. The effects of radiation therapy are localized and confined to the region being treated. Radiation therapy may be used to treat almost every type of solid tumor, including cancers of the brain, breast, cervix, larynx, lung, pancreas, prostate, skin, stomach, uterus, or soft tissue sarcomas. Radiation is also used to treat leukemia and lymphoma.

[0641] In some embodiments, the chemotherapeutic agent may be an immunomodulatory agent such as lenalidomide (LEN). Recent studies have demonstrated that lenalidomide can enhance antitumor functions of CAR modified T cells (Otahal et al., *Oncoimmunology*, 2015, 5(4): e1115940). Some examples of anti-tumor antibodies include tocilizumab, siltuximab.

[0642] Chemotherapy is the treatment of cancer with drugs that can destroy cancer cells. In current usage, the term "chemotherapy" usually refers to cytotoxic drugs which affect

rapidly dividing cells in general, in contrast with targeted therapy. Chemotherapy drugs interfere with cell division in various possible ways, e.g. with the duplication of DNA or the separation of newly formed chromosomes. Most forms of chemotherapy target all rapidly dividing cells and are not specific to cancer cells, although some degree of specificity may come from the inability of many cancer cells to repair DNA damage, while normal cells generally can.

[0643] Most chemotherapy regimens are given in combination. Exemplary chemotherapeutic agents include , but are not limited to, 5-FU Enhancer, 9-AC, AG2037, AG3340, Aggrecanase Inhibitor, Aminoglutethimide, Amsacrine (m-AMSA), Asparaginase, Azacitidine, Batimastat (BB94), BAY 12-9566, BCH-4556, Bis-Naphthalimide, Busulfan, Capecitabine, Carboplatin, Carmustaine+Polifepr Osan, cdk4/cdk2 inhibitors, Chlorambucil, CI-994, Cisplatin, Cladribine, CS-682, Cytarabine HCl, D2163, Dactinomycin, Daunorubicin HCl, DepoCyt, Dexifosamide, Docetaxel, Dolastain, Doxifluridine, Doxorubicin, DX8951f, E 7070, EGFR, Epirubicin, Erythropoietin, Estramustine phosphate sodium, Etoposide (VP16-213), Farnesyl Transferase Inhibitor, FK 317, Flavopiridol, Floxuridine, Fludarabine, Fluorouracil (5-FU), Flutamide, Fragyline, Gemcitabine, Hexamethylmelamine (HMM), Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alfa-2a, Interferon Alfa-2b, Interleukin-2, Irinotecan, ISI 641, Krestin, Lemonal DP 2202, Leuprolide acetate (LHRH-releasing factor analogue), Levamisole, LiGLA (lithium-gamma linolenate), Lodine Seeds, Lometexol, Lomustine (CCNU), Marimistat, Mechlorethamine HCl (nitrogen mustard), Megestrol acetate, Meglamine GLA, Mercaptopurine, Mesna, Mitoguazone (methyl-GAG; methyl glyoxal bis-guanylhydrazone; MGBG), Mitotane (o.p'-DDD), Mitoxantrone, Mitoxantrone HCl, MMI 270, MMP, MTA/LY 231514, Octreotide, ODN 698, OK-432, Oral Platinum, Oral Taxoid, Paclitaxel (TAXOL.RTM.), PARP Inhibitors, PD 183805, Pentostatin (2' deoxycoformycin), PKC 412, Plicamycin, Procarbazine HCl, PSC 833, Ralitrexed, RAS Farnesyl Transferase Inhibitor, RAS Oncogene Inhibitor, Semustine (methyl-CCNU), Streptozocin, Suramin, Tamoxifen citrate, Taxane Analog, Temozolomide, Teniposide (VM-26), Thioguanine, Thiotepa, Topotecan, Tyrosine Kinase, UFT (Tegafur/Uracil), Valrubicin, Vinblastine sulfate, Vindesine sulfate, VX-710, VX-853, YM 116, ZD 0101, ZD 0473/Anormed, ZD 1839, ZD 9331.

[0644] Other agents may be used in combination with compositions of the invention may also include, but not limited to, agents that affect the upregulation of cell surface receptors and their ligands such as Fas/Fas ligand, DR4 or DR5/TRAIL and GAP junctions, cytostatic and differentiation agents, inhibitors of cell adhesion such as focal adhesion kinase (FAKs)

inhibitors and Lovastatin, or agents that increase the sensitivity of the hyper proliferative cells to apoptotic inducers such as the antibody C225.

[0645] The combinations may include administering the compositions of the invention and other agents at the same time or separately. Alternatively, the present immunotherapy may precede or follow the other agent/therapy by intervals ranging from minutes, days, weeks to months.

5. Therapeutic Uses

[0646] Provided in the present invention is a method of reducing a tumor volume or burden in a subject in need, the method comprising introducing into the subject a composition of the invention.

[0647] The present invention also provides methods for treating a cancer in a subject, comprising administering to the subject an effective amount of an immune effector cell genetically modified to express at least one effector module of the invention.

Cancer

[0648] Various cancers may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As used herein, the term "cancer" refers to any of various malignant neoplasms characterized by the proliferation of anaplastic cells that tend to invade surrounding tissue and metastasize to new body sites and refers to the pathological condition characterized by such malignant neoplastic growths. Cancers may be tumors or hematological malignancies, and include but are not limited to, all types of lymphomas/leukemias, carcinomas and sarcomas, such as those cancers or tumors found in the anus, bladder, bile duct, bone, brain, breast, cervix, colon/rectum, endometrium, esophagus, eye, gallbladder, head and neck, liver, kidney, larynx, lung, mediastinum (chest), mouth, ovaries, pancreas, penis, prostate, skin, small intestine, stomach, spinal marrow, tailbone, testicles, thyroid and uterus.

[0649] Types of carcinomas which may be treated with the compositions of the present invention include, but are not limited to, papilloma/carcinoma, choriocarcinoma, endodermal sinus tumor, teratoma, adenoma/adenocarcinoma, melanoma, fibroma, lipoma, leiomyoma, rhabdomyoma, mesothelioma, angioma, osteoma, chondroma, glioma, lymphoma/leukemia, squamous cell carcinoma, small cell carcinoma, large cell undifferentiated carcinomas, basal cell carcinoma and sinonasal undifferentiated carcinoma.

[0650] Types of carcinomas which may be treated with the compositions of the present invention include, but are not limited to, soft tissue sarcoma such as alveolar soft part sarcoma, angiosarcoma, dermatofibrosarcoma, desmoid tumor, desmoplastic small round cell

tumor, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, hemangiopericytoma, hemangiosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphosarcoma, malignant fibrous histiocytoma, neurofibrosarcoma, rhabdomyosarcoma, synovial sarcoma, and Askin's tumor, Ewing's sarcoma (primitive neuroectodermal tumor), malignant hemangioendothelioma, malignant schwannoma, osteosarcoma, and chondrosarcoma.

[0651] As a non-limiting example, the carcinoma which may be treated may be Acute granulocytic leukemia, Acute lymphocytic leukemia, Acute myelogenous leukemia, Adenocarcinoma, Adenosarcoma, Adrenal cancer, Adrenocortical carcinoma, Anal cancer, Anaplastic astrocytoma, Angiosarcoma, Appendix cancer, Astrocytoma, Basal cell carcinoma, B-Cell lymphoma), Bile duct cancer, Bladder cancer, Bone cancer, Bowel cancer, Brain cancer, Brain stem glioma, Brain tumor, Breast cancer, Carcinoid tumors, Cervical cancer, Cholangiocarcinoma, Chondrosarcoma, Chronic lymphocytic leukemia, Chronic myelogenous leukemia, Colon cancer, Colorectal cancer, Craniopharyngioma, Cutaneous lymphoma, Cutaneous melanoma, Diffuse astrocytoma, Ductal carcinoma in situ, Endometrial cancer, Ependymoma, Epithelioid sarcoma, Esophageal cancer, Ewing sarcoma, Extrahepatic bile duct cancer, Eye cancer, Fallopian tube cancer, Fibrosarcoma, Gallbladder cancer, Gastric cancer, Gastrointestinal cancer, Gastrointestinal carcinoid cancer, Gastrointestinal stromal tumors, General, Germ cell tumor, Glioblastoma multiforme, Glioma, Hairy cell leukemia, Head and neck cancer, Hemangioendothelioma, Hodgkin lymphoma, Hodgkin's disease, Hodgkin's lymphoma, Hypopharyngeal cancer, Infiltrating ductal carcinoma, Infiltrating lobular carcinoma, Inflammatory breast cancer, Intestinal Cancer, Intrahepatic bile duct cancer, Invasive / infiltrating breast cancer, Islet cell cancer, Jaw cancer, Kaposi sarcoma, Kidney cancer, Laryngeal cancer, Leiomyosarcoma, Leptomeningeal metastases, Leukemia, Lip cancer, Liposarcoma, Liver cancer, Lobular carcinoma in situ, Low-grade astrocytoma, Lung cancer, Lymph node cancer, Lymphoma, Male breast cancer, Medullary carcinoma, Medulloblastoma, Melanoma, Meningioma, Merkel cell carcinoma, Mesenchymal chondrosarcoma, Mesenchymous, Mesothelioma, Metastatic breast cancer, Metastatic melanoma, Metastatic squamous neck cancer, Mixed gliomas, Mouth cancer, Mucinous carcinoma, Mucosal melanoma, Multiple myeloma, Nasal cavity cancer, Nasopharyngeal cancer, Neck cancer, Neuroblastoma, Neuroendocrine tumors, Non-Hodgkin lymphoma, Non-Hodgkin's lymphoma, Non-small cell lung cancer, Oat cell cancer, Ocular cancer, Ocular melanoma, Oligodendroglioma, Oral cancer, Oral cavity cancer, Oropharyngeal cancer, Osteogenic sarcoma, Osteosarcoma, Ovarian cancer, Ovarian

epithelial cancer, Ovarian germ cell tumor, Ovarian primary peritoneal carcinoma, Ovarian sex cord stromal tumor, Paget's disease, Pancreatic cancer, Papillary carcinoma, Paranasal sinus cancer, Parathyroid cancer, Pelvic cancer, Penile cancer, Peripheral nerve cancer, Peritoneal cancer, Pharyngeal cancer, Pheochromocytoma, Pilocytic astrocytoma, Pineal region tumor, Pineoblastoma, Pituitary gland cancer, Primary central nervous system lymphoma, Prostate cancer, Rectal cancer, Renal cell cancer, Renal pelvis cancer, Rhabdomyosarcoma, Salivary gland cancer, Sarcoma, Sarcoma, bone, Sarcoma, soft tissue, Sarcoma, uterine, Sinus cancer, Skin cancer, Small cell lung cancer, Small intestine cancer, Soft tissue sarcoma, Spinal cancer, Spinal column cancer, Spinal cord cancer, Spinal tumor, Squamous cell carcinoma, Stomach cancer, Synovial sarcoma, T-cell lymphoma), Testicular cancer, Throat cancer, Thymoma / thymic carcinoma, Thyroid cancer, Tongue cancer, Tonsil cancer, Transitional cell cancer, Transitional cell cancer, Transitional cell cancer, Triple-negative breast cancer, Tubal cancer, Tubular carcinoma, Ureteral cancer, Ureteral cancer, Urethral cancer, Uterine adenocarcinoma, Uterine cancer, Uterine sarcoma, Vaginal cancer, and Vulvar cancer.

[0652] In some embodiments, the CARs of the present invention may be a CAR useful in the treatment of multiple myeloma such as a CS1 CAR, a CD38 CAR, a CD138 CAR, and a BCMA CAR. In some embodiments, the CARs of the present invention may be a CAR useful in the treatment of acute myeloid leukemia such as a CD33 CAR, a CD123 CAR, and a CLL1 CAR. In some embodiments, the CARs of the present invention may be a CAR useful in the treatment of T cell leukemia such as a CD5 CAR, and a CD7 CAR. In some embodiments, the CARs of the present invention may be a CAR useful in the treatment of solid tumors such a mesothelin CAR, a GD2 CAR, a GPC3 CAR, a Her2 CAR, an EGFR CAR, a Muc1 CAR, an EpCAM CAR, a PD-L1 CAR, a CEA CAR, a Muc16 CAR, a CD133 CAR, a CD171 CAR, a CD70 CAR, a CLD18 CAR, a cMET CAR, a EphA2 CAR, a FAP CAR, a Folate Receptor CAR, an IL13Ra2 CAR, an MG7 CAR, a PSMA CAR, a ROR1 CAR, and a VEGFR2 CAR.

[0653] The present invention also provides methods of reducing tumor burden in a subject. In some embodiments. As used herein, “tumor burden” refers to the number of cancer cells, or the amount of cancer in a subject. In some aspects tumor burden also refers to tumor load. In some embodiments, the tumor may be disseminated throughout the body of the subject. In one aspect, the tumor may be a liquid tumor such as leukemia or a lymphoma. The methods of reducing tumor burden may involve administering to the subject, a therapeutically effective amount of the immune cells. Immune cells may be engineered to express the

compositions described herein. In some embodiments, the immune cells expressing the compositions of the invention may be administered to the subject via any of the routes of delivery described herein. Also provided herein are dosing regimens for administering the immune cells. In some embodiments, the subject may also be administered a therapeutically effective amount of the stimulus to tune the expression of the immunotherapeutic agent. In some aspects, the immunotherapeutic agents may be capable of reducing the tumor burden. Regimens for ligand/ stimulus dosing are also provided. Reduction in tumor burden may be measured by any of the methods known in the art including tumor imaging, and measurement of marker proteins. In some aspects, bioluminescent imaging may be used to measure tumor burden. Bioluminescence imaging utilizes native light emission from bioluminescent proteins such as luciferase. Such bioluminescent proteins can participate in chemical reactions that release photons by the addition of suitable substrates. The release of photons can be captured by sensitive detection methods and quantified. Tumor cells may be engineered to express luciferase and the efficacy of the compositions described herein to reduce tumor burden may quantified by imaging. In some aspects, the tumor burden may be measured by the flux of photons (photons per sec). In some embodiments, photon flux positively correlates with tumor burden.

Diseases and Toxins

[0654] Various infectious diseases may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As used herein, the term “infectious disease” refers to any disorders caused by organisms such as bacteria, viruses, fungi or parasites. As a non-limiting example, the infectious disease may be Acute bacterial rhinosinusitis, 14-day measles, Acne, Acrodermatitis chronica atrophicans (ACA)-(late skin manifestation of latent Lyme disease), Acute hemorrhagic conjunctivitis, Acute hemorrhagic cystitis, Acute rhinosinusitis, Adult T-cell Leukemia-Lymphoma (ATLL), African Sleeping Sickness, AIDS (Acquired Immunodeficiency Syndrome), Alveolar hydatid, Amebiasis, Amebic meningoencephalitis, Anaplasmosis, Anthrax, Arboviral or parainfectious, Ascariasis -(Roundworm infections), Aseptic meningitis, Athlete's foot (Tinea pedis), Australian tick typhus, Avian Influenza, Babesiosis, Bacillary angiomatosis, Bacterial meningitis, Bacterial vaginosis, Balanitis, Balantidiasis, Bang's disease, Barmah Forest virus infection, Bartonellosis (Verruga peruana; Carrion's disease; Oroya fever), Bat Lyssavirus Infection, Bay sore (Chiclero's ulcer), Baylisascaris infection (Racoon roundworm infection), Beaver fever, Beef tapeworm, Bejel (endemic syphilis), Biphasic meningoencephalitis, Black Bane, Black death, Black piedra,

Blackwater Fever, Blastomycosis, Blennorrhea of the newborn, Blepharitis, Boils, Bornholm disease (pleurodynia), Borrelia miyamotoi Disease, Botulism, Boutonneuse fever, Brazilian purpuric fever, Break Bone fever, Brill, Bronchiolitis, Bronchitis, Brucellosis (Bang's disease), Bubonic plague, Bullous impetigo, Burkholderia mallei (Glanders), Burkholderia pseudomallei (Melioidosis), Buruli ulcers (also Mycoburuli ulcers), Busse, Busse-Buschke disease (Cryptococcosis), California group encephalitis, Campylobacteriosis, Candidiasis, Canefield fever (Canicola fever; 7-day fever; Weil's disease; leptospirosis; canefield fever), Canicola fever, Capillariasis, Carate, Carbapenem-resistant Enterobacteriaceae (CRE), Carbuncle, Carrion's disease, Cat Scratch fever, Cave disease, Central Asian hemorrhagic fever, Central European tick, Cervical cancer, Chagas disease, Chancroid (Soft chancre), Chicago disease, Chickenpox (Varicella), Chiclero's ulcer, Chikungunya fever, Chlamydial infection, Cholera, Chromoblastomycosis, Ciguatera, Clap, Clonorchiasis (Liver fluke infection), Clostridium Difficile Infection, Clostridium Perfringens (Epsilon Toxin), Coccidioidomycosis fungal infection (Valley fever; desert rheumatism), Coenurosis, Colorado tick fever, Condyloma accuminata, Condyloma accuminata(Warts), Condyloma lata, Congo fever, Congo hemorrhagic fever virus, Conjunctivitis, cowpox, Crabs, Crimean, Croup, Cryptococcosis, Cryptosporidiosis (Crypto), Cutaneous Larval Migrans, Cyclosporiasis, Cystic hydatid, Cysticercosis, Cystitis, Czechoslovak tick, D68 (EV-D68), Dacryocytitis, Dandy fever, Darling's Disease, Deer fly fever, Dengue fever (1, 2, 3 and 4), Desert rheumatism, Devil's grip, Diphasic milk fever, Diphtheria, Disseminated Intravascular Coagulation, Dog tapeworm, Donovanosis, Donovanosis (Granuloma inguinale), Dracontiasis, Dracunculosis, Duke's disease, Dum Dum Disease, Durand-Nicholas-Favre disease, Dwarf tapeworm, E. Coli infection (*E.coli*), Eastern equine encephalitis, Ebola Hemorrhagic Fever (Ebola virus disease EVD), Ectothrix, Ehrlichiosis (Sennetsu fever), Encephalitis, Endemic Relapsing fever, Endemic syphilis, Endophthalmitis, Endothrix, Enterobiasis (Pinworm infection), Enterotoxin - B Poisoning (Staph Food Poisoning), Enterovirus Infection, Epidemic Keratoconjunctivitis, Epidemic Relapsing fever, Epidemic typhus, Epiglottitis, Erysipelis, Erysipeloid (Erysipelothricosis), Erythema chronicum migrans, Erythema infectiosum, Erythema marginatum, Erythema multiforme, Erythema nodosum, Erythema nodosum leprosum, Erythrasma, Espundia, Eumycotic mycetoma, European blastomycosis, Exanthem subitum (Sixth disease), Eyeworm, Far Eastern tick, Fascioliasis, Fievre boutonneuse(Tick typhus), Fifth Disease (erythema infectiosum), Filatow-Dukes' Disease (Scalded Skin Syndrome; Ritter's Disease), Fish tapeworm, Fitz-Hugh-Curtis syndrome - Perihepatitis, Flinders Island Spotted Fever, Flu (Influenza),

Folliculitis, Four Corners Disease, Four Corners Disease (Human Pulmonary Syndrome (HPS)), Frambesia, Francis disease, Furunculosis, Gas gangrene, Gastroenteritis, Genital Herpes, Genital Warts, German measles, Gerstmann-Straussler-Scheinker (GSS), Giardiasis, Gilchrist's disease, Gingivitis, Gingivostomatitis, Glanders, Glandular fever (infectious mononucleosis), Gnathostomiasis, Gonococcal Infection (Gonorrhea), Gonorrhea, Granuloma inguinale (Donovanosis), Guinea Worm, Haemophilus Influenza disease, Hamburger disease, Hansen's disease - leprosy, Hantaan disease, Hantaan-Korean hemorrhagic fever, Hantavirus Pulmonary Syndrome, Hantavirus Pulmonary Syndrome (HPS), Hard chancre, Hard measles, Haverhill fever - Rat bite fever, Head and Body Lice, Heartland fever, Helicobacterosis, Hemolytic Uremic Syndrome (HUS), Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Herpangina, Herpes- genital, Herpes labialis, Herpes- neonatal, Hidradenitis, Histoplasmosis, Histoplasmosis infection (Histoplasmosis), His-Werner disease, HIV infection, Hookworm infections, Hordeola, Hordeola (Stye), HTLV, HTLV- associated myelopathy (HAM), Human granulocytic ehrlichiosis, Human monocytic ehrlichiosis, Human Papillomavirus (HPV), Human Pulmonary Syndrome, Hydatid cyst, Hydrophobia, Impetigo, Including congenital (German Measles), Inclusion conjunctivitis, Inclusion conjunctivitis - Swimming Pool conjunctivitis- Pannus, Infantile diarrhea, Infectious Mononucleosis, Infectious myocarditis, Infectious pericarditis, Influenza, Isosporiasis, Israeli spotted fever, Japanese Encephalitis, Jock itch, Jorge Lobo disease - lobomycosis, Jungle yellow fever, Junin Argentinian hemorrhagic fever, Kala Azar, Kaposi's sarcoma, Keloidal blastomycosis, Keratoconjunctivitis, Kuru, Kyasanur forest disease, LaCrosse encephalitis, Lassa hemorrhagic fever, Legionellosis (Legionnaires Disease), Legionnaire's pneumonia, Lemierre's Syndrome (Postanginal septicemia), Lemming fever, Leprosy, Leptospirosis (Nanukayami fever; Weil's disease), Listeriosis (Listeria), Liver fluke infection, Lobo's mycosis, Lockjaw, Loiasis, Louping Ill, Ludwig's angina, Lung fluke infection, Lung fluke infection (Paragonimiasis), Lyme disease, Lymphogranuloma venereum infection (LGV), Machupo Bolivian hemorrhagic fever, Madura foot, Mal del pinto, Malaria, Malignant pustule, Malta fever, Marburg hemorrhagic fever, Masters disease, Maternal Sepsis (Puerperal fever), Measles, Mediterranean spotted fever, Melioidosis (Whitmore's disease), Meningitis, Meningococcal Disease, MERS, Milker's nodule, Molluscum contagiosum, Moniliasis, monkeypox, Mononucleosis, Mononucleosis-like syndrome, Montezuma's Revenge, Morbilli, MRSA (methicillin-resistant *Staphylococcus aureus*) infection, Mucormycosis- Zygomycosis, Multiple Organ Dysfunction Syndrome or MODS, Multiple-system atrophy (MSA), Mumps, Murine typhus, Murray Valley Encephalitis(MVE),

Mycoburuli ulcers, Mycoburuli ulcers- Buruli ulcers, Mycotic vulvovaginitis, Myositis, Nanukayami fever, Necrotizing fasciitis, Necrotizing fasciitis- Type 1, Necrotizing fasciitis- Type 2, Negishi, New world spotted fever, Nocardiosis, Nongonococcal urethritis, Non-Polio (Non-Polio Enterovirus), Norovirus infection, North American blastomycosis, North Asian tick typhus, Norwalk virus infection, Norwegian itch, O'Hara disease, Omsk hemorrhagic fever, Onchoceriasis, Onychomycosis, Opisthorchiasis, Opthalmia neonatorium, Oral hairy leukoplakia, Orf, Oriental Sore, Oriental Spotted Fever, Ornithosis (Parrot fever; Psittacosis), Oroya fever, Otitis externa, Otitis media, Pannus, Paracoccidioidomycosis, Paragonimiasis, Paralytic Shellfish Poisoning (Paralytic Shellfish Poisoning), Paronychia (Whitlow), Parotitis, PCP pneumonia, Pediculosis, Peliosis hepatica, Pelvic Inflammatory Disease , Pertussis (also called Whooping cough), Phaeohyphomycosis, Pharyngoconjunctival fever, Piedra (White Piedra), Piedra(Black Piedra), Pigbel, Pink eye conjunctivitis, Pinta, Pinworm infection, Pitted Keratolysis, Pityriasis versicolor (Tinea versicolor), Plague; Bubonic, Pleurodynia, Pneumococcal Disease, Pneumocystosis, Pneumonia, Pneumonic (Plague), Polio or Poliomyelitis, Polycystic hydatid, Pontiac fever, Pork tapeworm, Posada-Wernicke disease, Postanginal septicemia, Powassan, Progressive multifocal leukoencephalopathy, Progressive Rubella Panencephalitis, Prostatitis, Pseudomembranous colitis, Psittacosis, Puerperal fever, Pustular Rash diseases (Small pox), Pyelonephritis, Pylephlebitis, Q-Fever, Quinsy, Quintana fever (5-day fever), Rabbit fever, Rabies, Racoon roundworm infection, Rat bite fever, Rat tapeworm, Reiter Syndrome, Relapsing fever, Respiratory syncytial virus (RSV) infection, Rheumatic fever, Rhodotorulosis, Ricin Poisoning, Rickettsialpox, Rickettsiosis , Rift Valley Fever, Ringworm, Ritter's Disease, River Blindness, Rocky Mountain spotted fever, Rose Handler's disease (Sporotrichosis), Rose rash of infants, Roseola, Ross River fever, Rotavirus infection, Roundworm infections, Rubella, Rubeola, Russian spring, Salmonellosis gastroenteritis, San Joaquin Valley fever, Sao Paulo Encephalitis, Sao Paulo fever, SARS, Scabies Infestation (Scabies) (Norwegian itch), Scalded Skin Syndrome, Scarlet fever (Scarlatina), Schistosomiasis, Scombroid, Scrub typhus, Sennetsu fever, Sepsis (Septic shock), Severe Acute Respiratory Syndrome, Severe Acute Respiratory Syndrome (SARS), Shiga Toxigenic Escherichia coli (STEC/VTEC), Shigellosis gastroenteritis (Shigella), Shinbone fever, Shingles, Shipping fever, Siberian tick typhus, Sinusitis, Sixth disease, Slapped cheek disease, Sleeping sickness, Smallpox (Variola), Snail Fever, Soft chancre, Southern tick associated rash illness, Sparganosis, Spelunker's disease, Sporadic typhus, Sporotrichosis, Spotted fever, Spring, St. Louis encephalitis, Staphylococcal Food Poisoning, Staphylococcal Infection, Strep. throat,

Streptococcal Disease, Streptococcal Toxic-Shock Syndrome, Strongyloiciasis, Stye, Subacute Sclerosing Panencephalitis, Subacute Sclerosing Panencephalitis (SSPE), Sudden Acute Respiratory Syndrome, Sudden Rash, Swimmer's ear, Swimmer's Itch, Swimming Pool conjunctivitis, Sylvatic yellow fever, Syphilis, Systemic Inflammatory Response Syndrome (SIRS), Tabes dorsalis (tertiary syphilis), Taeniasis, Taiga encephalitis, Tanner's disease, Tapeworm infections, Temporal lobe encephalitis, Temporal lobe encephalitis, tetani (Lock Jaw), Tetanus Infection, Threadworm infections, Thrush, Tick, Tick typhus, *Tinea barbae, Tinea capitis, Tinea corporis, Tinea cruris, Tinea manuum, Tinea nigra, Tinea pedis, Tinea unguium, Tinea versicolor,* Torulopsosis, Torulosis, Toxic Shock Syndrome, Toxoplasmosis, transmissible spongioform (CJD), Traveler's diarrhea, Trench fever 5, Trichinellosis, Trichomoniasis, Trichomycosis axillaris, Trichuriasis, Tropical Spastic Paraparesis (TSP), Trypanosomiasis, Tuberculosis (TB), Tuberculosis, Tularemia, Typhoid Fever, Typhus fever, Ulcus molle, Undulant fever, Urban yellow fever, Urethritis, Vaginitis, Vaginosis, Vancomycin Intermediate (VISA), Vancomycin Resistant (VRSA), Varicella, Venezuelan Equine encephalitis, *Verruga peruana, Vibrio cholerae* (Cholera), Vibriosis (Vibrio), Vincent's disease or Trench mouth, Viral conjunctivitis, Viral Meningitis, Viral meningoencephalitis, Viral rash, Visceral Larval Migrans, Vomito negro, Vulvovaginitis, Warts, Waterhouse, Weil's disease, West Nile Fever, Western equine encephalitis, Whipple's disease, Whipworm infection, White Piedra, Whitlow, Whitmore's disease, Winter diarrhea, Wolhynia fever, Wool sorters' disease, Yaws, Yellow Fever, Yersinosis, Yersinosis (Yersinia), Zahorsky's disease, Zika virus disease, Zoster, Zygomycosis, John Cunningham Virus (JCV), Human immunodeficiency virus (HIV), Influenza virus, Hepatitis B, Hepatitis C, Hepatitis D, Respiratory syncytial virus (RSV), Herpes simplex virus 1 and 2, Human Cytomegalovirus, Epstein-Barr virus , Varicella zoster virus, Coronaviruses , Poxviruses, Enterovirus 71, Rubella virus, Human papilloma virus, *Streptococcus pneumoniae*, *Streptococcus viridans*, *Staphylococcus aureus (S. aureus)*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-intermediate *Staphylococcus aureus* (VISA) , Vancomycin-resistant *Staphylococcus aureus* (VRSA), *Staphylococcus epidermidis (S. epidermidis*), *Clostridium Tetani*, *Bordetella pertussis, Bordetella paratussis*, *Mycobacterium, Francisella tularensis, Toxoplasma gondii,* Candida (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei and C. lusitaniae*) and/or any other infectious diseases, disorders or syndromes.

[0655] Various toxins may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present

invention. Non-limited examples of toxins include Ricin, Bacillus anthracis, Shiga toxin and Shiga-like toxin, Botulinum toxins.

[0656] Various tropical diseases may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. Non-limited examples of tropical diseases include Chikungunya fever, Dengue fever, Chagas disease, Rabies, Malaria, Ebola virus, Marburg virus, West Nile Virus, Yellow Fever, Japanese encephalitis virus, St. Louis encephalitis virus.

[0657] Various foodborne illnesses and gastroenteritis may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. Non-limited examples of foodborne illnesses and gastroenteritis include Rotavirus, Norwalk virus (Norovirus), *Campylobacter jejuni, Clostridium difficile, Entamoeba histolytica, Helicobacter pylori*, Enterotoxin B of Staphylococcus aureus, Hepatitis A virus (HAV), Hepatitis E, Listeria monocytogenes, Salmonella, Clostridium perfringens, and Salmonella.

[0658] Various infectious agents may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. Non-limited examples of infectious agents include adenoviruses, *Anaplasma phagocytophilium*, *Ascaris lumbricoides*, *Bacillus anthracis*, *Bacillus cereus*, *Bacteriodes* sp, Barmah Forest virus, *Bartonella bacilliformis*, *Bartonella henselae*, *Bartonella quintana*, beta-toxin of *Clostridium perfringens*, *Bordetella pertussis, Bordetella parapertussis, Borrelia burgdorferi, Borrelia miyamotoi, Borrelia recurrentis*, *Borrelia* sp., *Botulinum* toxin, *Brucella* sp., *Burkholderia pseudomallei*, California encephalitis virus, *Campylobacter, Candida albicans*, chikungunya virus, *Chlamydia psittaci, Chlamydia trachomatis, Clonorchis sinensis, Clostridium difficile bacteria, Clostridium tetani,* Colorado tick fever virus, *Corynebacterium diphtheriae, Corynebacterium minutissimum, Coxiella burnetii*, coxsackie A, coxsackie B, Crimean-Congo hemorrhagic fever virus, cytomegalovirus, dengue virus, Eastern Equine encephalitis virus, Ebola viruses, echovirus, *Ehrlichia chaffeensis*, *Ehrlichia equi, Ehrlichia* sp., *Entamoeba histolytica, Enterobacter sp.*, *Enterococcus faecalis*, Enterovirus 71, Epstein-Barr virus (EBV), *Erysipelothrix rhusiopathiae, Escherichia coli,* Flavivirus, *Fusobacterium necrophorum, Gardnerella vaginalis*, Group B *streptococcus*, *Haemophilus aegyptius, Haemophilus ducreyi, Haemophilus influenzae*, hantavirus, *Helicobacter pylori,* Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, herpes simplex virus 1 and 2,, human herpes virus 6, human herpes Virus 8, human immunodeficiency virus 1 and 2, human T-cell leukemia viruses I and

II, influenza viruses (A, B, C), Jamestown Canyon virus, Japanese encephalitis antigenic, Japanese encephalitis virus, John Cunninham virus, juninvirus, Kaposi's Sarcoma-associated Herpes Virus (KSHV), *Klebsiella granulomatis, Klebsiella sp.*, Kyasanur Forest Disease virus, La Crosse virus, Lassavirus, *Legionella pneumophila*, *Leptospira interrogans, Listeria monocytogenes*, lymphocytic choriomeningitis virus, lyssavirus, Machupovirus, Marburg virus, measles virus, MERS coronavirus (MERS-CoV), *Micrococcus sedentarius, Mobiluncus sp.,* Molluscipoxvirus, *Moraxella catarrhalis,* Morbilli- Rubeola virus, Mumps virus, *Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium ulcerans, Mycoplasma genitalium, Mycoplasma* sp, Nairovirus, *Neisseria gonorrhoeae, Neisseria meningitidis*, Nocardia, Norwalk virus, norovirus, Omsk hemorrhagic fever virus, papilloma virus, parainfluenza viruses 1-3, parapoxvirus, parvovirus B19, *Peptostreptococccus* sp., *Plasmodium* sp., polioviruses types I, II, and III, *Proteus* sp., *Pseudomonas aeruginosa*, *Pseudomonas pseudomallei, Pseudomonas* sp., rabies virus, respiratory syncytial virus, ricin toxin, *Rickettsia australis, Rickettsia conori, Rickettsia honei, Rickettsia prowazekii*, Ross River Virus, rotavirus, rubellavirus, Saint Louis encephalitis, *Salmonella typhi, Sarcoptes scabiei*, SARS-associated coronavirus (SARS-CoV), *Serratia sp.*, Shiga toxin and Shiga-like toxin, *Shigella* sp., Sin Nombre Virus, Snowshoe hare virus, *Staphylococcus aureus, Staphylococcus epidermidis, Streptobacillus moniliformis, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus agalactiae, Streptococcus* group A-H, *Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum subsp. Pallidum, Treponema pallidum var. carateum, Treponema pallidum var. endemicum, Tropheryma whippelii, Ureaplasma urealyticum,* Varicella-Zoster virus, variola virus, *Vibrio cholerae*, West Nile virus, yellow fever virus, *Yersinia enterocolitica, Yersinia pestis*, and Zika virus.

[0659] Various rare diseases may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As used herein, the term “rare disease” refers to any disease that affects a small percentage of the population. As a non-limiting example, the rare disease may be Acrocephalosyndactylia, Acrodermatitis, Addison Disease, Adie Syndrome, Alagille Syndrome, Amylose, Amyotrophic Lateral Sclerosis, Angelman Syndrome, Angiolymphoid Hyperplasia with Eosinophilia, Arnold-Chiari Malformation, Arthritis, Juvenile Rheumatoid, Asperger Syndrome, Bardet-Biedl Syndrome, Barrett Esophagus, Beckwith-Wiedemann Syndrome, Behcet Syndrome, Bloom Syndrome, Bowen's Disease, Brachial Plexus Neuropathies, Brown-Sequard Syndrome, Budd-Chiari Syndrome, Burkitt Lymphoma, Carcinoma 256, Walker, Caroli Disease, Charcot-Marie-Tooth Disease, Chediak-Higashi

Syndrome, Chiari-Frommel Syndrome, Chondrodysplasia Punctata, Colonic Pseudo-Obstruction, Colorectal Neoplasms, Hereditary Nonpolyposis, Craniofacial Dysostosis, Creutzfeldt-Jakob Syndrome, Crohn Disease, Cushing Syndrome, Cystic Fibrosis, Dandy-Walker Syndrome, De Lange Syndrome, Dementia, Vascular, Dermatitis Herpetiformis, DiGeorge Syndrome, Diffuse Cerebral Sclerosis of Schilder, Duane Retraction Syndrome, Dupuytren Contracture, Ebstein Anomaly, Eisenmenger Complex, Ellis-Van Creveld Syndrome, Encephalitis, Enchondromatosis, Epidermal Necrolysis, Toxic, Facial Hemiatrophy, Factor XII Deficiency, Fanconi Anemia, Felty's Syndrome, Fibrous Dysplasia, Polyostotic, Fox-Fordyce Disease, Friedreich Ataxia, Fusobacterium, Gardner Syndrome, Gaucher Disease, Gerstmann Syndrome, Giant Lymph Node Hyperplasia, Glycogen Storage Disease Type I, Glycogen Storage Disease Type II, Glycogen Storage Disease Type IV, Glycogen Storage Disease Type V, Glycogen Storage Disease Type VII, Goldenhar Syndrome, Guillain-Barre Syndrome, Hallermann's Syndrome, Hamartoma Syndrome, Multiple, Hartnup Disease, Hepatolenticular Degeneration, Hepatolenticular Degeneration, Hereditary Sensory and Motor Neuropathy, Hirschsprung Disease, Histiocytic Necrotizing Lymphadenitis, Histiocytosis, Langerhans-Cell, Hodgkin Disease, Horner Syndrome, Huntington Disease, Hyperaldosteronism, Hyperhidrosis, Hyperostosis, Diffuse Idiopathic Skeletal, Hypopituitarism, Inappropriate ADH Syndrome, Intestinal Polyps, Isaacs Syndrome, Kartagener Syndrome, Kearns-Sayre Syndrome, Klippel-Feil Syndrome, Klippel-Trenaunay-Weber Syndrome, Kluver-Bucy Syndrome, Korsakoff Syndrome, Lafora Disease, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Langer-Giedion Syndrome, Leigh Disease, Lesch-Nyhan Syndrome, Leukodystrophy, Globoid Cell, Li-Fraumeni Syndrome, Long QT Syndrome, Machado-Joseph Disease, Mallory-Weiss Syndrome, Marek Disease, Marfan Syndrome, Meckel Diverticulum, Meige Syndrome, Melkersson-Rosenthal Syndrome, Meniere Disease, Mikulicz's Disease, Miller Fisher Syndrome, Mobius Syndrome, Moyamoya Disease, Mucocutaneous Lymph Node Syndrome, Mucopolysaccharidosis I, Mucopolysaccharidosis II, Mucopolysaccharidosis III, Mucopolysaccharidosis IV, Mucopolysaccharidosis VI, Multiple Endocrine Neoplasia Type 1, Munchausen Syndrome by Proxy, Muscular Atrophy, Spinal, Narcolepsy, Neuroaxonal Dystrophies, Neuromyelitis Optica, Neuronal Ceroid-Lipofuscinoses, Niemann-Pick Diseases, Noonan Syndrome, Optic Atrophies, Hereditary, Osteitis Deformans, Osteochondritis, Osteochondrodysplasias, Osteolysis, Essential, Paget Disease Extramammary, Paget's Disease, Mammary, Panniculitis, Nodular Nonsuppurative, Papillon-Lefevre Disease, Paralysis, Pelizaeus-Merzbacher Disease, Pemphigus, Benign Familial,

Penile Induration, Pericarditis, Constrictive, Peroxisomal Disorders, Peutz-Jeghers Syndrome, Pick Disease of the Brain, Pierre Robin Syndrome, Pigmentation Disorders, Pityriasis Lichenoides, Polycystic Ovary Syndrome, Polyendocrinopathies, Autoimmune, Prader-Willi Syndrome, Pupil Disorders, Rett Syndrome, Reye Syndrome, Rubinstein-Taybi Syndrome, Sandhoff Disease, Sarcoma, Ewing's, Schnitzler Syndrome, Sjogren's Syndrome, Sjogren-Larsson Syndrome, Smith-Lemli-Opitz Syndrome, Spinal Muscular Atrophies of Childhood, Sturge-Weber Syndrome, Sweating, Gustatory, Takayasu Arteritis, Tangier Disease, Tay-Sachs Disease, Thromboangiitis Obliterans, Thyroiditis, Autoimmune, Tietze's Syndrome, Togaviridae Infections, Tolosa-Hunt Syndrome, Tourette Syndrome, Uveomeningoencephalitic Syndrome, Waardenburg's Syndrome, Wegener Granulomatosis, Weil Disease, Werner Syndrome, Williams Syndrome, Wilms Tumor, Wolff-Parkinson-White Syndrome, Wolfram Syndrome, Wolman Disease, Zellweger Syndrome, Zollinger-Ellison Syndrome, and von Willebrand Diseases.

[0660] Various autoimmune diseases and autoimmune-related diseases may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As used herein, the term "autoimmune disease" refers to a disease in which the body produces antibodies that attack its own tissues. As a non-limiting example, the autoimmune disease may be Acute Disseminated Encephalomyelitis (ADEM), Acute necrotizing hemorrhagic leukoencephalitis, Addison's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome (APS), Autoimmune angioedema, Autoimmune aplastic anemia, Autoimmune dysautonomia, Autoimmune hepatitis, Autoimmune hyperlipidemia, Autoimmune immunodeficiency, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune thrombocytopenic purpura (ATP), Autoimmune thyroid disease, Autoimmune urticaria, Axonal & neuronal neuropathies, Balo disease, Behcet's disease, Bullous pemphigoid, Cardiomyopathy, Castleman disease, Celiac disease, Chagas disease, Chronic fatigue syndrome, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal ostomyelitis (CRMO), Churg-Strauss syndrome, Cicatricial pemphigoid/benign mucosal pemphigoid, Crohn's disease, Cogans syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST disease, Essential mixed cryoglobulinemia, Demyelinating neuropathies, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic

esophagitis, Eosinophilic fasciitis, Erythema nodosum, Experimental allergic encephalomyelitis, Evans syndrome, Fibromyalgia**, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis (GPA) (formerly called Wegener's Granulomatosis), Graves' disease, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura, Herpes gestationis, Hypogammaglobulinemia, Idiopathic thrombocytopenic purpura (ITP), IgA nephropathy, IgG4-related sclerosing disease, Immunoregulatory lipoproteins, Inclusion body myositis, Interstitial cystitis, Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis, Kawasaki syndrome, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosis, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus (SLE), Lyme disease, chronic, Meniere's disease, Microscopic polyangiitis, Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neuromyelitis optica (Devic's), Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism, PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus), Paraneoplastic cerebellar degeneration, Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Parsonnage-Turner syndrome, Pars planitis (peripheral uveitis), Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia, POEMS syndrome, Polyarteritis nodosa, Type I, II, & III autoimmune polyglandular syndromes, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Progesterone dermatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Psoriasis, Psoriatic arthritis, Idiopathic pulmonary fibrosis, Pyoderma gangrenosum, Pure red cell aplasia, Raynauds phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Reiter's syndrome, Relapsing polychondritis, Restless legs syndrome, Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome, Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia, Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome, Transverse myelitis, Ulcerative colitis, Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vesiculobullous dermatosis, Vitiligo, and Wegener's granulomatosis (now termed Granulomatosis with Polyangiitis (GPA).

[0661] Various kidney diseases may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the

present invention. As a non-limiting example, the kidney disease Abderhalden–Kaufmann–Lignac syndrome (Nephropathic Cystinosis), Abdominal Compartment Syndrome, Acute Kidney Failure/Acute Kidney Injury, Acute Lobar Nephronia, Acute Phosphate Nephropathy, Acute Tubular Necrosis, Adenine Phosphoribosyltransferase Deficiency, Adenovirus Nephritis, Alport Syndrome, Amyloidosis, ANCA Vasculitis Related to Endocarditis and Other Infections, Angiomyolipoma, Analgesic Nephropathy, Anorexia Nervosa and Kidney Disease, Angiotensin Antibodies and Focal Segmental Glomerulosclerosis, Antiphospholipid Syndrome, Anti-TNF-α Therapy-related Glomerulonephritis, APOL1 Mutations, Apparent Mineralocorticoid Excess Syndrome, Aristolochic Acid Nephropathy, Chinese Herbal Nephropathy, Balkan Endemic Nephropathy, Bartter Syndrome, Beeturia, β-Thalassemia Renal Disease, Bile Cast Nephropathy, BK Polyoma Virus Nephropathy in the Native Kidney, Bladder Rupture, Bladder Sphincter Dyssynergia, Bladder Tamponade, Border-Crossers' Nephropathy, Bourbon Virus and Acute Kidney Injury, Burnt Sugarcane Harvesting and Acute Renal Dysfunction, Byetta and Renal Failure, C1q Nephropathy, Cannabinoid Hyperemesis Acute Renal Failure, Cardiorenal syndrome, Carfilzomib-Indiced Renal Injury, CFHR5 nephropathy, Charcot–Marie–Tooth Disease with Glomerulopathy, Cherry Concentrate and Acute Kidney Injury, Cholesterol Emboli, Churg–Strauss syndrome, Chyluria, Colistin Nephrotoxicity, Collagenofibrotic Glomerulopathy, Collapsing Glomerulopathy, Collapsing Glomerulopathy Related to CMV, Congenital Nephrotic Syndrome, Conorenal syndrome (Mainzer-Saldino Syndrome or Saldino-Mainzer Disease), Contrast Nephropathy, Copper Sulfate Intoxication, Cortical Necrosis, Crizotinib-related Acute Kidney Injury, Cryoglobuinemia, Crystalglobulin-Induced Nephropathy, Crystal-Induced Acute Kidney injury, Cystic Kidney Disease, Acquired, Cystinuria, Dasatinib-Induced Nephrotic-Range Proteinuria, Dense Deposit Disease (MPGN Type 2), Dent Disease (X-linked Recessive Nephrolithiasis), Dialysis Disequilibrium Syndrome, Diabetes and Diabetic Kidney Disease, Diabetes Insipidus, Dietary Supplements and Renal Failure, Drugs of Abuse and Kidney Disease, Duplicated Ureter, EAST syndrome, Ebola and the Kidney, Ectopic Kidney, Ectopic Ureter, Edema, Swelling, Erdheim-Chester Disease, Fabry's Disease, Familial Hypocalciuric Hypercalcemia, Fanconi Syndrome, Fraser syndrome, Fibronectin Glomerulopathy, Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy, Fraley syndrome, Focal Segmental Glomerulosclerosis, Focal Sclerosis, Focal Glomerulosclerosis, Galloway Mowat syndrome, Giant Cell (Temporal) Arteritis with Kidney Involvement, Gestational Hypertension, Gitelman Syndrome, Glomerular Diseases, Glomerular Tubular Reflux, Glycosuria, Goodpasture Syndrome, Hair Dye Ingestion and

Acute Kidney Injury, Hantavirus Infection Podocytopathy, Hematuria (Blood in Urine), Hemolytic Uremic Syndrome (HUS), Atypical Hemolytic Uremic Syndrome (aHUS), Hemophagocytic Syndrome, Hemorrhagic Cystitis, Hemorrhagic Fever with Renal Syndrome (HFRS, Hantavirus Renal Disease, Korean Hemorrhagic Fever, Epidemic Hemorrhagic Fever, Nephropathis Epidemica), Hemosiderosis related to Paroxysmal Nocturnal Hemoglobinuria and Hemolytic Anemia, Hepatic Glomerulopathy, Hepatic Veno-Occlusive Disease, Sinusoidal Obstruction Syndrome, Hepatitis C-Associated Renal Disease, Hepatorenal Syndrome, Herbal Supplements and Kidney Disease, High Blood Pressure and Kidney Disease, HIV-Associated Nephropathy (HIVAN), Horseshoe Kidney (Renal Fusion), Hunner's Ulcer, Hyperaldosteronism, Hypercalcemia, Hyperkalemia, Hypermagnesemia, Hypernatremia, Hyperoxaluria, Hyperphosphatemia, Hypocalcemia, Hypokalemia, Hypokalemia-induced renal dysfunction, Hypokalemic Periodic Paralysis, Hypomagnesemia, Hyponatremia, Hypophosphatemia, IgA Nephropathy, IgG4 Nephropathy, Interstitial Cystitis, Painful Bladder Syndrome (Questionnaire), Interstitial Nephritis, Ivemark's syndrome, Ketamine-Associated Bladder Dysfunction, Kidney Stones, Nephrolithiasis, Kombucha Tea Toxicity, Lead Nephropathy and Lead-Related Nephrotoxicity, Leptospirosis Renal Disease, Light Chain Deposition Disease, Monoclonal Immunoglobulin Deposition Disease, Liddle Syndrome, Lightwood-Albright Syndrome, Lipoprotein Glomerulopathy, Lithium Nephrotoxicity, LMX1B Mutations Cause Hereditary FSGS, Loin Pain Hematuria, Lupus, Systemic Lupus Erythematosis, Lupus Kidney Disease, Lupus Nephritis, Lupus Nephritis with Antineutrophil Cytoplasmic Antibody Seropositivity, Lyme Disease-Associated Glomerulonephritis, Malarial Nephropathy, Malignancy-Associated Renal Disease, Malignant Hypertension, Malakoplakia, Meatal Stenosis, Medullary Cystic Kidney Disease, Medullary Sponge Kidney, Megaureter, Melamine Toxicity and the Kidney, Membranoproliferative Glomerulonephritis, Membranous Nephropathy, MesoAmerican Nephropathy, Metabolic Acidosis, Metabolic Alkalosis, Methotrexate-related Renal Failure, Microscopic Polyangiitis, Milk-alkalai syndrome, Minimal Change Disease, MDMA (Molly; Ecstacy; 3,4-Methylenedioxymethamphetamine) and Kidney Failure, Multicystic dysplastic kidney, Multiple Myeloma, Myeloproliferative Neoplasms and Glomerulopathy, Nail-patella Syndrome, Nephrocalcinosis, Nephrogenic Systemic Fibrosis, Nephroptosis (Floating Kidney, Renal Ptosis), Nephrotic Syndrome, Neurogenic Bladder, Nodular Glomerulosclerosis, Non-Gonococcal Urethritis, Nutcracker syndrome, Orofaciodigital Syndrome, Orotic Aciduria, Orthostatic Hypotension, Orthostatic Proteinuria, Osmotic Diuresis, Ovarian Hyperstimulation Syndrome, Page Kidney, Papillary Necrosis, Papillorenal

Syndrome (Renal-Coloboma Syndrome, Isolated Renal Hypoplasia), Parvovirus B19 and the Kidney, The Peritoneal-Renal Syndrome, Posterior Urethral Valve, Post-infectious Glomerulonephritis, Post-streptococcal Glomerulonephritis, Polyarteritis Nodosa, Polycystic Kidney Disease, Posterior Urethral Valves, Preeclampsia, Propofol infusion syndrome, Proliferative Glomerulonephritis with Monoclonal IgG Deposits (Nasr Disease), Propolis (Honeybee Resin) Related Renal Failure, Proteinuria (Protein in Urine), Pseudohyperaldosteronism, Pseudohypobicarbonatemia, Pseudohypoparathyroidism, Pulmonary-Renal Syndrome, Pyelonephritis (Kidney Infection), Pyonephrosis, Radiation Nephropathy, Ranolazine and the Kidney, Refeeding syndrome, Reflux Nephropathy, Rapidly Progressive Glomerulonephritis, Renal Abscess, Perinephric Abscess, Renal Agenesis, Renal Arcuate Vein Microthrombi-Associated Acute Kidney Injury, Renal Artery Aneurysm, Renal Artery Stenosis, Renal Cell Cancer, Renal Cyst, Renal Hypouricemia with Exercise-induced Acute Renal Failure, Renal Infarction, Renal Osteodystrophy, Renal Tubular Acidosis, Renin Secreting Tumors (Juxtaglomerular Cell Tumor), Reset Osmostat, Retrocaval Ureter, Retroperitoneal Fibrosis, Rhabdomyolysis, Rhabdomyolysis related to Bariatric Surgery, Rheumatoid Arthritis-Associated Renal Disease, Sarcoidosis Renal Disease, Salt Wasting, Renal and Cerebral, Schistosomiasis and Glomerular Disease, Schimke immuno-osseous dysplasia, Scleroderma Renal Crisis, Serpentine Fibula-Polycystic Kidney Syndrome, Exner Syndrome, Sickle Cell Nephropathy, Silica Exposure and Chronic Kidney Disease, Sri Lankan Farmers' Kidney Disease, Sjögren's Syndrome and Renal Disease, Synthetic Cannabinoid Use and Acute Kidney Injury, Kidney Disease Following Hematopoietic Cell Transplantation, Kidney Disease Related to Stem Cell Transplantation, Thin Basement Membrane Disease, Benign Familial Hematuria, Trigonitis, Tuberculosis, Genitourinary, Tuberous Sclerosis, Tubular Dysgenesis, Immune Complex Tubulointerstitial Nephritis Due to Autoantibodies to the Proximal Tubule Brush Border, Tumor Lysis Syndrome, Uremia, Uremic Optic Neuropathy, Ureteritis Cystica, Ureterocele, Urethral Caruncle, Urethral Stricture, Urinary Incontinence, Urinary Tract Infection, Urinary Tract Obstruction, Vesicointestinal Fistula, Vesicoureteral Reflux, Volatile Anesthetics and Acute Kidney Injury, Von Hippel-Lindau Disease, Waldenstrom's Macroglobulinemic Glomerulonephritis, Warfarin-Related Nephropathy, Wasp Stings and Acute Kidney Injury, Wegener's Granulomatosis, Granulomatosis with Polyangiitis, West Nile Virus and Chronic Kidney Disease, and Wunderlich syndrome.

[0662] Various cardiovascular diseases may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the

present invention. As a non-limiting example, the cardiovascular disease may be Ischemic heart disease also known as coronary artery disease, Cerebrovascular disease (Stroke), Peripheral vascular disease, Heart failure, Rheumatic heart disease, and Congenital heart disease.

[0663] Various antibody deficiencies may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As a non-limiting example, the antibody deficiencies may be X-Linked Agammaglobulinemia (XLA), Autosomal Recessive Agammaglobulinemia (ARA), Common Variable Immune Deficiency (CVID), IgG (IgG1, IgG2, IgG3 and IgG4) Subclass Deficiency, Selective IgA Deficiency, Specific Antibody Deficiency (SAD), Transient Hypogammaglobulinemia of Infancy, Antibody Deficiency with Normal or Elevated Immunoglobulins, Selective IgM Deficiency, Immunodeficiency with Thymoma (Good's Syndrome), Transcobalamin II Deficiency, Warts, Hypogammaglobulinemia, Infection, Myelokathexis (WHIM) Syndrome, Drug-Induced Antibody Deficiency, Kappa Chain Deficiency, Heavy Chain Deficiencies, Post-Meiotic Segregation (PMS2) Disorder, and Unspecified Hypogammaglobulinemia.

[0664] Various ocular diseases may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As a non-limiting example, the ocular disease may be thyroid eye disease (TED), Graves' disease (GD) and orbitopathy, Retina Degeneration, Cataract, optic atrophy, macular degeneration, Leber congenital amaurosis, retinal degeneration, cone-rod dystrophy, Usher syndrome, leopard syndrome, photophobia, and photoaversion.

[0665] Various neurological diseases may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As a non-limiting example, the neurological disease may be Absence of the Septum Pellucidum, Acid Lipase Disease, Acid Maltase Deficiency, Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, Attention Deficit-Hyperactivity Disorder (ADHD), Adie's Pupil, Adie's Syndrome, Adrenoleukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, Aicardi-Goutieres Syndrome Disorder, AIDS - Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis (ALS), Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Antiphospholipid Syndrome, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia Telangiectasia, Ataxias

and Cerebellar or Spinocerebellar Degeneration, Atrial Fibrillation and Stroke, Attention Deficit-Hyperactivity Disorder, Autism Spectrum Disorder, Autonomic Dysfunction, Back Pain, Barth Syndrome, Batten Disease, Becker's Myotonia, Behcet's Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbospinal Muscular Atrophy, Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy (CADASIL), Canavan Disease, Carpal Tunnel Syndrome, Causalgia, Cavernomas, Cavernous Angioma, Cavernous Malformation, Central Cervical Cord Syndrome, Central Cord Syndrome, Central Pain Syndrome, Central Pontine Myelinolysis, Cephalic Disorders, Ceramidase Deficiency, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysms, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Cavernous Malformation, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Palsy, Cerebro-Oculo-Facio-Skeletal Syndrome (COFS), Charcot-Marie-Tooth Disease, Chiari Malformation, Cholesterol Ester Storage Disease, Chorea, Choreoacanthocytosis, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Chronic Orthostatic Intolerance, Chronic Pain, Cockayne Syndrome Type II, Coffin Lowry Syndrome, Colpocephaly, Coma, Complex Regional Pain Syndrome, Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Cree encephalitis, Creutzfeldt-Jakob Disease, Cumulative Trauma Disorders, Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morsier's Syndrome, Dejerine-Klumpke Palsy, Dementia, Dementia -Multi-Infarct, Dementia - Semantic, Dementia -Subcortical, Dementia With Lewy Bodies, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Dravet Syndrome, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile Epileptic Encephalopathy, Empty Sella Syndrome, Encephalitis, Encephalitis Lethargica, Encephaloceles, Encephalopathy, Encephalopathy (familial infantile), Encephalotrigeminal Angiomatosis, Epilepsy, Epileptic Hemiplegia, Erb's Palsy, Erb-Duchenne and Dejerine-Klumpke Palsies, Essential Tremor, Extrapontine Myelinolysis, Fabry Disease, Fahr's

Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia Calcification, Familial Periodic Paralyses, Familial Spastic Paralysis, Farber's Disease, Febrile Seizures, Fibromuscular Dysplasia, Fisher Syndrome, Floppy Infant Syndrome, Foot Drop, Friedreich's Ataxia, Frontotemporal Dementia, Gaucher Disease, Generalized Gangliosidoses, Gerstmann's Syndrome, Gerstmann-Straussler-Scheinker Disease, Giant Axonal Neuropathy, Giant Cell Arteritis, Giant Cell Inclusion Disease, Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Glycogen Storage Disease, Guillain-Barré Syndrome, Hallervorden-Spatz Disease, Head Injury, Headache, Hemicrania Continua, Hemifacial Spasm, Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Heredopathia Atactica Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, Holoprosencephaly, HTLV-1 Associated Myelopathy, Hughes Syndrome, Huntington's Disease, Hydranencephaly, Hydrocephalus, Hydrocephalus - Normal Pressure, Hydromyelia, Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia, Hypoxia, Immune-Mediated Encephalomyelitis, Inclusion Body Myositis, Incontinentia Pigmenti, Infantile Hypotonia, Infantile Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease, Infantile Spasms, Inflammatory Myopathies, Iniencephaly, Intestinal Lipodystrophy, Intracranial Cysts, Intracranial Hypertension, Isaacs' Syndrome, Joubert Syndrome, Kearns-Sayre Syndrome, Kennedy's Disease, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Feil Syndrome, Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy Syndrome, Korsakoff's Amnesic Syndrome, Krabbe Disease, Kugelberg-Welander Disease, Kuru, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Lateral Femoral Cutaneous Nerve Entrapment, Lateral Medullary Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lesch-Nyhan Syndrome, Leukodystrophy, Levine-Critchley Syndrome, Lewy Body Dementia, Lipid Storage Diseases, Lipoid Proteinosis, Lissencephaly, Locked-In Syndrome, Lou Gehrig's Disease, Lupus - Neurological Sequelae, Lyme Disease - Neurological Complications, Machado-Joseph Disease, Macrocephaly, Megalocephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and Encephalitis, Menkes Disease, Meralgia Paresthetica, Metachromatic Leukodystrophy, Microcephaly, Migraine, Miller Fisher Syndrome, Mini Stroke, Mitochondrial Myopathy, Moebius Syndrome, Monomelic Amyotrophy, Motor Neuron Diseases, Moyamoya Disease, Mucolipidoses, Mucopolysaccharidosis, Multi-Infarct Dementia, Multifocal Motor Neuropathy, Multiple Sclerosis, Multiple System Atrophy, Multiple System Atrophy with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia - Congenital, Myasthenia Gravis, Myelinoclastic Diffuse

Sclerosis, Myoclonic Encephalopathy of Infants, Myoclonus, Myopathy, Myopathy-Congenital, Myopathy -Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy, Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurofibromatosis, Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological Complications of Lyme Disease, Neurological Consequences of Cytomegalovirus Infection, Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis Optica, Neuromyotonia, Neuronal Ceroid Lipofuscinosis, Neuronal Migration Disorders, Neuropathy- Hereditary, Neurosarcoidosis, Neurosyphilis, Neurotoxicity, Nevus Cavernosus, Niemann-Pick Disease, O'Sullivan-McLeod Syndrome, Occipital Neuralgia, Ohtahara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, Overuse Syndrome, Pain -Chronic, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Periodic Paralyses, Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytanic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Post-Polio Syndrome, Postherpetic Neuralgia, Post infectious Encephalomyelitis, Postural Hypotension, Postural Orthostatic Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal Leukoencephalopathy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear Palsy, Prosopagnosia, Pseudo-Torch syndrome, Pseudotoxoplasmosis syndrome, Pseudotumor Cerebri, Psychogenic Movement, Ramsay Hunt Syndrome I, Ramsay Hunt Syndrome II, Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease - Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Rett Syndrome, Reye's Syndrome, Rheumatic Encephalitis, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Sandhoff Disease, Schilder's Disease, Schizencephaly, Seitelberger Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Severe Myoclonic Epilepsy of Infancy (SMEI), Shaken Baby Syndrome, Shingles, Shy-Drager Syndrome, Sjögren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinal Muscular Atrophy, Spinocerebellar Atrophy, Spinocerebellar Degeneration, Steele-

Richardson-Olszewski Syndrome, Stiff-Person Syndrome, Striatonigral Degeneration, Stroke, Sturge-Weber Syndrome, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, Short-lasting, Unilateral, Neuralgiform (SUNCT) Headache, Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Systemic Lupus Erythematosus, Tabes Dorsalis, Tardive Dyskinesia, Tarlov Cysts, Tay-Sachs Disease, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's Paralysis, Tourette Syndrome, Transient Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia, Tropical Spastic Paraparesis, Troyer Syndrome, Tuberous Sclerosis, Vascular Erectile Tumor, Vasculitis Syndromes of the Central and Peripheral Nervous Systems, Von Economo's Disease, Von Hippel-Lindau Disease (VHL), Von Recklinghausen's Disease, Wallenberg's Syndrome, Werdnig-Hoffman Disease, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, Williams Syndrome, Wilson Disease, Wolman's Disease, X-Linked Spinal and Bulbar Muscular Atrophy.

[0666] Various psychological disorders may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As a non-limiting example, the psychological disorders may be Aboulia, Absence epilepsy, Acute stress Disorder, Adjustment Disorders, Adverse effects of medication NOS, Age related cognitive decline, Agoraphobia, Alcohol Addiction, Alzheimer's Disease, Amnesia (also known as Amnestic Disorder), Amphetamine Addiction, Anorexia Nervosa, Anterograde amnesia, Antisocial personality disorder (also known as Sociopathy), Anxiety Disorder (Also known as Generalized Anxiety Disorder), Anxiolytic related disorders, Asperger's Syndrome (now part of Autism Spectrum Disorder), Attention Deficit Disorder (Also known as ADD), Attention Deficit Hyperactivity Disorder (Also known as ADHD), Autism Spectrum Disorder (also known as Autism), Autophagia, Avoidant Personality Disorder, Barbiturate related disorders, Benzodiazepine related disorders, Bereavement, Bibliomania, Binge Eating Disorder, Bipolar disorder (also known as Manic Depression, includes Bipolar I and Bipolar II), Body Dysmorphic Disorder, Borderline intellectual functioning, Borderline Personality Disorder, Breathing-Related Sleep Disorder, Brief Psychotic Disorder, Bruxism, Bulimia Nervosa, Caffeine Addiction, Cannabis Addiction, Catatonic disorder, Catatonic schizophrenia, Childhood amnesia, Childhood Disintegrative Disorder (now part of Autism Spectrum Disorder), Childhood Onset Fluency Disorder (formerly known as Stuttering), Circadian Rhythm Disorders, Claustrophobia,

Cocaine related disorders, Communication disorder, Conduct Disorder, Conversion Disorder, Cotard delusion, Cyclothymia (also known as Cyclothymic Disorder), Delerium, Delusional Disorder, dementia , Dependent Personality Disorder (also known as Asthenic Personality Disorder), Depersonalization disorder (now known as Depersonalization / Derealization Disorder), Depression (also known as Major Depressive Disorder), Depressive personality disorder, Derealization disorder (now known as Depersonalization / Derealization Disorder), Dermotillomania, Desynchronosis, Developmental coordination disorder, Diogenes Syndrome, Disorder of written expression, Dispareunia, Dissocial Personality Disorder, Dissociative Amnesia, Dissociative Fugue, Dissociative Identity Disorder (formerly known as Multiple Personality Disorder), Down syndrome, Dyslexia, Dyspareunia, Dysthymia (now known as Persistent Depressive Disorder), Eating disorder NOS, Ekbom's Syndrome (Delusional Parasitosis), Emotionally unstable personality disorder, Encopresis, Enuresis (bedwetting), Erotomania, Exhibitionistic Disorder, Expressive language disorder, Factitious Disorder, Female Sexual Disorders, Fetishistic Disorder, Folie à deux, Fregoli delusion, Frotteuristic Disorder, Fugue State, Ganser syndrome, Gambling Addiction, Gender Dysphoria (formerly known as Gender Identity Disorder), Generalized Anxiety Disorder, General adaptation syndrome, Grandiose delusions, Hallucinogen Addiction, Haltlose personality disorder, Histrionic Personality Disorder, Primary hypersomnia, Huntington's Disease, Hypoactive sexual desire disorder, Hypochondriasis, Hypomania, Hyperkinetic syndrome, Hypersomnia, Hysteria, Impulse control disorder, Impulse control disorder NOS, Inhalant Addiction, Insomnia, Intellectual Development Disorder, Intermittent Explosive Disorder, Joubert syndrome, Kleptomania, Korsakoff's syndrome, Lacunar amnesia, Language Disorder, Learning Disorders, Major Depression (also known as Major Depressive Disorder), major depressive disorder, Male Sexual Disorders, Malingering, Mathematics disorder, Medication-related disorder, Melancholia, Mental Retardation (now known as Intellectual Development Disorder), Misophonia, Morbid jealousy, Multiple Personality Disorder (now known as Dissociative Identity Disorder), Munchausen Syndrome, Munchausen by Proxy, Narcissistic Personality Disorder, Narcolepsy, Neglect of child, Neurocognitive Disorder (formerly known as Dementia), Neuroleptic-related disorder, Nightmare Disorder, Non Rapid Eye Movement, Obsessive-Compulsive Disorder, Obsessive-Compulsive Personality Disorder (also known as Anankastic Personality Disorder), Oneirophrenia, Onychophagia, Opioid Addiction, Oppositional Defiant Disorder, Orthorexia (ON), Pain disorder, Panic attacks, Panic Disorder, Paranoid Personality Disorder, Parkinson's Disease, Partner relational problem, Passive-aggressive personality disorder,

Pathological gambling, Pedophilic Disorder, Perfectionism, Persecutory delusion, Persistent Depressive Disorder (also known as Dysthymia), Personality change due to a general medical condition, Personality disorder, Pervasive developmental disorder (PDD), Phencyclidine related disorder, Phobic disorder, Phonological disorder, Physical abuse, Pica, Polysubstance related disorder, Postpartum Depression, Post-traumatic embitterment disorder (PTED), Post-Traumatic Stress Disorder, Premature ejaculation, Premenstrual Dysphoric Disorder, Psychogenic amnesia, Psychological factor affecting medical condition, Psychoneurotic personality disorder, Psychotic disorder, not otherwise specified, Pyromania, Reactive Attachment Disorder, Reading disorder, Recurrent brief depression, Relational disorder, REM Sleep Behavior Disorder, Restless Leg Syndrome, Retrograde amnesia, Retts Disorder (now part of Autism Spectrum Disorder), Rumination syndrome, Sadistic personality disorder, Schizoaffective Disorder, Schizoid Personality Disorder, Schizophrenia, Schizophreniform disorder, Schizotypal Personality Disorder, Seasonal Affective Disorder, Sedative, Hypnotic, or Anxiolytic Addiction, Selective Mutism, Self-defeating personality disorder, Separation Anxiety Disorder, Sexual Disorders Female, Sexual Disorders Male, Sexual Addiction, Sexual Masochism Disorder, Sexual Sadism Disorder, Shared Psychotic Disorder, Sleep Arousal Disorders, Sleep Paralysis, Sleep Terror Disorder (now part of Nightmare Disorder, Social Anxiety Disorder, Somatization Disorder, Specific Phobias, Stendhal syndrome, Stereotypic movement disorder, Stimulant Addiction, Stuttering (now known as Childhood Onset Fluency Disorder), Substance related disorder, Tardive dyskinesia, Tobacco Addiction, Tourettes Syndrome, Transient tic disorder, Transient global amnesia, Transvestic Disorder, Trichotillomania, Undifferentiated Somatoform Disorder, Vaginismus, and Voyeuristic Disorder.

[0667] Various lung diseases may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As a non-limiting example, the lung diseases may be Asbestosis, Asthma, Bronchiectasis, Bronchitis, Chronic Cough, Chronic Obstructive Pulmonary Disease (COPD), Croup, Cystic Fibrosis, Hantavirus, Idiopathic Pulmonary Fibrosis, Pertussis, Pleurisy, Pneumonia, Pulmonary Embolism, Pulmonary Hypertension, Sarcoidosis, Sleep Apnea, Spirometry, Sudden Infant Death Syndrome (SIDS), Tuberculosis, Alagille Syndrome, Autoimmune Hepatitis, Biliary Atresia, Cirrhosis, ERCP (Endoscopic Retrograde Cholangiopancreatography), and Hemochromatosis. Nonalcoholic Steatohepatitis, Porphyria, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis.

[0668] Various bone diseases may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As a non-limiting example, the bone diseases may be osteoporosis, neurofibromatosis, osteogenesis imperfecta (OI), rickets, osteosarcoma, achondroplasia, fracture, osteomyelitis, Ewing tumor of bone, osteomalacia, hip dysplasia, Paget disease of bone, marble bone disease, osteochondroma, bone cancer, bone disease, osteochondrosis, osteoma, fibrous dysplasia, cleidocranial dysostosis, osteoclastoma, bone cyst, metabolic bone disease, melorheostosis, callus, Caffey syndrome, and mandibulofacial dysostosis.

[0669] Various blood diseases may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As a non-limiting example, the blood diseases may be Anemia and CKD (for health care professionals), Aplastic Anemia and Myelodysplastic Syndromes, Deep Vein Thrombosis, Hemochromatosis, Hemophilia, Henoch-Schönlein Purpura, Idiopathic Thrombocytopenic Purpura, Iron-Deficiency Anemia, Pernicious Anemia, Pulmonary Embolism, Sickle Cell Anemia, Sickle Cell Trait and Other Hemoglobinopathies, Thalassemia, Thrombotic Thrombocytopenic Purpura, and Von Willebrand Disease.

[0670] In some embodiment, biocircuits of the invention may be used for the treatment of infectious diseases. Biocircuits of the invention may be introduced in cells suitable for adoptive cell transfer such as macrophages, dendritic cells, natural killer cells, and or T cells. Infectious diseases treated by the biocircuits of the invention may be diseases caused by viruses, bacteria, fungi, and/or parasites. IL15-IL15Ra payloads of the invention may be used to increase immune cell proliferation and/or persistence of the immune cells useful in treating infectious diseases.

6. Microbiome

[0671] Alterations in the composition of the microbiome may impact the action of anti-cancer therapies. A diverse community of symbiotic, commensal and pathogenic microorganisms exist in all environmentally exposed sites in the body and is herein referred to as the "Microbiome." Environmentally exposed sites of the body that may be inhabited by a microbiome include the skin, nasopharynx, the oral cavity, respiratory tract, gastrointestinal tract, and the reproductive tract.

[0672] In some embodiments, microbiome engineered with the biocircuits of the present invention may be used to improve the efficacy of the anti-cancer immunotherapies. Sivan et al., found that mice with *Bifidobacterium* in their gut microbiome were more responsive to immune check point blockage e.g. anti PD-L1 immunotherapy in subcutaneous melanoma

tumor model (Sivan A., et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 2015; 350:1084–9; the contents of which are incorporated herein by reference in their entirety). In one embodiment, protein, RNA and/or other biomolecules derived from the microbiome may be used as a payload to influence the efficacy of the anti-cancer immunotherapies. In other embodiments, the microorganisms may be delivered along with immunotherapeutic compositions of the present invention to improve the efficacy of immunotherapy.

7. Tools and agents for making therapeutics

[0673] Provided in the present invention are tools and agents that may be used in generating immunotherapeutics for reducing a tumor volume or burden in a subject in need. A considerable number of variables are involved in producing a therapeutic agent, such as structure of the payload, type of cells, method of gene transfers, method and time of ex vivo expansion, pre- conditioning and the amount and type of tumor burden in the subject. Such parameters may be optimized using tools and agents described herein.

Cell lines

[0674] The present disclosure provides a mammalian cell that has been genetically modified with the compositions of the invention. Suitable mammalian cells include primary cells and immortalized cell lines. Suitable mammalian cell lines include, but are not limited to Human embryonic kidney cell line 293, fibroblast cell line NIH 3T3, human colorectal carcinoma cell line HCT116, ovarian carcinoma cell line SKOV-3, immortalized T cell lines Jurkat cells, lymphoma cell line Raji cells, NALM-6 cells, K562 cells, HeLa cells, PC12 cells, HL-60 cells, NK cell lines (e.g. NKL. NK962, and YTS), and the like. In some instances, the cell is not an immortalized cell line, but instead a cell obtained from an individual and is herein referred to as a primary cell. For example, the cell is a T lymphocyte obtained from an individual. Other examples include, but are not limited to cytotoxic cells, stem cells, peripheral blood mononuclear cells or progenitor cells obtained from an individual.

Tracking SREs, biocircuits and cell lines

[0675] In some embodiments, it may be desirable to track the compositions of the invention or the cells modified by the compositions of the invention. Tracking may be achieved by using payloads such as reporter moieties, which, as used herein, refers to any protein capable of creating a detectable signal, in response to an input. Examples include alkaline phosphatase, β-galactosidase, chloramphenicol acetyltransferase, β-glucuronidase,

peroxidase, β-lactamase, catalytic antibodies, bioluminescent proteins e.g. luciferase, and fluorescent proteins such as Green fluorescent protein (GFP).

[0676] Reporter moieties may be used to monitor the response of the DD upon addition of the ligand corresponding to the DD. In other instances, reporter moieties may be used to track cell survival, persistence, cell growth, and/or localization *in vitro, in vivo, or ex vivo.*

[0677] In some embodiments, the preferred reporter moiety may be luciferase proteins. In one embodiment, the reporter moiety is the Renilla luciferase, or a firefly luciferase.

Animal models

[0678] The utility and efficacy of the compositions of the present invention may be tested *in vivo* animal models, preferably mouse models. Mouse models used to may be syngeneic mouse models wherein mouse cells are modified with compositions of the invention and tested in mice of the same genetic background. Examples include pMEL-1 and 4T1 mouse models. Alternatively, xenograft models where human cells such as tumor cells and immune cells are introduced into immunodeficient mice may also be utilized in such studies. Immunodeficient mice used may be CByJ.Cg-Foxn1^{nu}/J, B6;129S7-*Rag1*^{tm1Mom}/J, B6.129S7-*Rag1*^{tm1Mom}/J, B6. CB17-*Prkdc*^{scid}/SzJ, NOD.129S7(B6)-*Rag1*^{tm1Mom}/J, NOD.Cg-*Rag1*^{tm1Mom}*Prf1*^{tm1Sd}z/Sz, NOD.CB17-*Prkdc*^{scid}/SzJ, NOD.Cg-*Prkdc*^{scid}*B2m*^{tm1Unc}/J, NOD-*scid* IL2Rg^{null}, Nude (nu) mice, SCID mice, NOD mice, RAG1/RAG2 mice, NOD-Scid mice, IL2rg*null* mice, b2m*null* mice, NOD-*scid* IL2rγnull mice, NOD-*scid*-B2m*null* mice, and HLA transgenic mice.

Cellular assays

[0679] In some embodiments, the effectiveness of the compositions of the inventions as immunotherapeutic agents may be evaluated using cellular assays. Levels of expression and/or identity of the compositions of the invention may be determined according to any methods known in the art for identifying proteins and/or quantitating proteins levels. In some embodiments, such methods may include Western Blotting, flow cytometry, and immunoprecipitation.

[0680] Provided herein are methods for functionally characterizing cells expressing SRE, biocircuits and compositions of the invention. In some embodiments, functional characterization is carried out in primary immune cells or immortalized immune cell lines and may be determined by expression of cell surface markers. Examples of cell surface markers for T cells include, but are not limited to, CD3, CD4, CD8, CD 14, CD20, CD11b, CD16, CD45 and HLA-DR, CD 69, CD28, CD44, IFNgamma. Examples of cell surface

markers for antigen presenting cells include, but are not limited to, MHC class I, MHC Class II, CD40, CD45, B7-1, B7-2, IFN γ receptor and IL2 receptor, ICAM-1 and/or Fcγ receptor. Examples of cell surface markers for dendritic cells include, but are not limited to, MHC class I, MHC Class II, B7-2, CD18, CD29, CD31, CD43, CD44, CD45, CD54, CD58, CD83, CD86, CMRF-44, CMRF-56, DCIR and/or Dectin-1 and the like; while in some cases also having the absence of CD2, CD3, CD4, CD8, CD14, CD15, CD16, CD 19, CD20, CD56, and/or CD57. Examples of cell surface markers for NK cells include, but are not limited to, CCL3, CCL4, CCL5, Granulysin, Granzyme B, Granzyme K, IL10, IL22, IFNg, LAP, Perforin, and TNFa.

8. Gene editing

[0681] The CRISPR-Cas9 system is a novel genome editing system which has been rapidly developed and implemented in a multitude of model organisms and cell types, and supplants other genome editing technologies, such as TALENs and ZFNs. CRISPRs are sequence motifs are present in bacterial and archaeal genomes, and are composed of short (about 24-48 nucleotide) direct repeats separated by similarly sized, unique spacers (Grissa et al.*BMC Bioinformatics* 8, 172 (2007). They are generally flanked by a set of CRISPR-associated (Cas) protein-coding genes that are required for CRISPR maintenance and function (Barrangou et al., *Science* 315, 1709 (2007), Brouns et al., *Science* 321, 960 (2008), Haft et al. *PLoS Comput Biol* 1, e60 (2005)). CRISPR-Cas systems provide adaptive immunity against invasive genetic elements (e.g., viruses, phages and plasmids) (Horvath and Barrangou, *Science*, 2010, 327: 167-170; Bhaya et al., *Annu. Rev. Genet.*, 2011, 45: 273-297; and Brrangou R, *RNA*, 2013, 4: 267-278). Three different types of CRISPR-Cas systems have been classified in bacteria and the type II CRISPR-Cas system is most studied. In the bacterial Type II CRISPR-Cas system, small CRISPR RNAs (crRNAs) processed from the pre-repeat-spacer transcript (pre-crRNA) in the presence of a trans-activating RNA (tracrRNA)/ Cas9 can form a duplex with the tracrRNA/Cas9 complex. The mature complex is recruited to a target double strand DNA sequence that is complementary to the spacer sequence in the tracrRNA: crRNA duplex to cleave the target DNA by Cas9 endonuclease (Garneau et al., *Nature*, 2010, 468: 67-71; Jinek et al., *Science*, 2012, 337: 816-821; Gasiunas et al., *Proc. Natl Acad. Sci. USA.*, 109: E2579-2586; and Haurwitz et al., *Science*, 2010, 329: 1355-1358). Target recognition and cleavage by the crRNA: tracrRNA/Cas9 complex in the type II CRISPR-CAS system not only requires a sequence in the tracrRNA: crRNA duplex that is a complementary to the target sequence (also called "protospacer" sequence) but also requires a protospacer adjacent motif (PAM) sequence located 3'end of the protospacer

sequence of a target polynucleotide. The PAM motif can vary between different CRISPR-Cas systems.

[0682] CRISPR-Cas9 systems have been developed and modified for use in genetic editing and prove to be a high effective and specific technology for editing a nucleic acid sequence even in eukaryotic cells. Many researchers disclosed various modifications to the bacterial CRISPR-Cas systems and demonstrated that CRISPR-Cas systems can be used to manipulate a nucleic acid in a cell, such as in a mammalian cell and in a plant cell. Representative references include US Pat. NOs.: 8,993,233; 8,999,641; 8,945,839; 8, 932,814; 8,906, 616; 8,895,308; 8,889,418; 8,889,356; 8,871,445; 8,865,406; 8,771,945; and 8,697,359; US patent publication NOs.: 20150031134; 20150203872; 20150218253; 20150176013; 20150191744; 20150071889; 20150067922; and 20150167000; each of which is incorporated herein by reference in their entirety.

[0683] However, controlling the effects and activity of the CRISPR-Cas system (e.g., guide RNA and nuclease) has been challenging and often can be problematic.

[0684] The biocircuits of the present invention and/or any of their components may be utilized in regulating or tuning the CRISPR/Cas9 system to optimize its utility.

[0685] In some embodiments, the payloads of the effector modules of the invention may include alternative isoforms or orthologs of the Cas9 enzyme.

[0686] The most commonly used Cas9 is derived from *Streptococcus pyogenes* and the RuvC domain can be inactivated by a D10A mutation and the HNH domain can be inactivated by an H840A mutation.

[0687] In addition to Cas9 derived from *S. pyogenes*, other RNA guided endonucleases (RGEN) may also be used for programmable genome editing. Cas9 sequences have been identified in more than 600 bacterial strains. Though Cas9 family shows high diversity of amino acid sequences and protein sizes, All Cas9 proteins share a common architecture with a central HNH nuclease domain and a split RuvC/RHase H domain. Examples of Cas9 orthologs from other bacterial strains including but not limited to, Cas proteins identified in *Acaryochloris marina* MBIC11017; *Acetohalobium arabaticum* DSM 5501; *Acidithiobacillus caldus*; *Acidithiobacillus ferrooxidans* ATCC 23270; *Alicyclobacillus acidocaldarius* LAA1; *Alicyclobacillus acidocaldarius subsp. acidocaldarius* DSM 446; *Allochromatium vinosum* DSM 180; *Ammonifex degensii* KC4; *Anabaena variabilis* ATCC 29413; *Arthrospira maxima* CS-328; *Arthrospira platensis str. Paraca*; *Arthrospira sp.* PCC 8005; *Bacillus pseudomycoides* DSM 12442; *Bacillus selenitireducens* MLS10; *Burkholderiales bacterium* 1_1_47; *Caldicelulosiruptor becscii* DSM 6725; *Candidatus Desulforudis audaxviator*

MP104C; *Caldicellulosiruptor hydrothermalis*_108; *Clostridium phage* c-st; *Clostridium botulinum A3 str. Loch Maree*; *Clostridium botulinum* Ba4 str. 657; *Clostridium difficile* QCD-63q42; *Crocosphaera watsonii* WH 8501; *Cyanothece sp.* ATCC 51142; *Cyanothece sp.* CCY0110; *Cyanothece sp.* PCC 7424; *Cyanothece sp.* PCC 7822; *Exiguobacterium sibiricum* 255-15; *Finegoldia magna* ATCC 29328; *Ktedonobacter racemifer* DSM 44963; *Lactobacillus delbrueckii subsp. bulgaricus* PB2003/044-T3-4; *Lactobacillus salivarius* ATCC 11741; *Listeria innocua*; *Lyngbya sp.* PCC 8106; *Marinobacter sp.* ELB17; *Methanohalobium evestigatum* Z-7303; *Microcystis phage* Ma-LMM01; *Microcystis aeruginosa* NIES-843; *Microscilla marina* ATCC 23134; *Microcoleus chthonoplastes* PCC 7420; *Neisseria meningitidis*; *Nitrosococcus halophilus* Nc4; *Nocardiopsis dassonvillei subsp. dassonvillei* DSM 43111; *Nodularia spumigena* CCY9414; *Nostoc sp.* PCC 7120; *Oscillatoria sp.* PCC 6506; *Pelotomaculum thermopropionicum* SI; *Petrotoga mobilis* SJ95; *Polaromonas naphthalenivorans* CJ2; *Polaromonas sp.* JS666; *Pseudoalteromonas haloplanktis* TAC125; *Streptomyces pristinaespiralis* ATCC 25486; *Streptomyces pristinaespiralis* ATCC 25486; *Streptococcus thermophilus; Streptomyces viridochromogenes* DSM 40736; *Streptosporangium roseum* DSM 43021; *Synechococcus sp.* PCC 7335; and *Thermosipho africanus* TCF52B (Chylinski et al., *RNA Biol.*, 2013; 10(5): 726-737).

[0688] In addition to Cas9 orthologs, other Cas9 variants such as fusion proteins of inactive dCas9 and effector domains with different functions may be served as a platform for genetic modulation. Any of the foregoing enzymes may be useful in the present invention.

9. Stem cell applications

[0689] The biocircuits of the present invention and/or any of their components may be utilized in the regulated reprogramming of cells, stem cell engraftment or other application where controlled or tunable expression of such reprogramming factors are useful.

[0690] The biocircuits of the present invention may be used in reprogramming cells including stem cells or induced stem cells. Induction of induced pluripotent stem cells (iPSC) was first achieved by Takahashi and Yamanaka (*Cell*, 2006. 126(4):663-76; herein incorporated by reference in its entirety) using viral vectors to express KLF4, c-MYC, OCT4 and SOX2 otherwise collectively known as KMOS.

[0691] Excisable lentiviral and transposon vectors, repeated application of transient plasmid, episomal and adenovirus vectors have also been used to try to derive iPSC (Chang, C.-W., et al., *Stem Cells*, 2009. 27(5):1042-1049; Kaji, K., et al., *Nature*, 2009. 458(7239):771-5; Okita, K., et al., *Science*, 2008. 322(5903):949-53; Stadtfeld, M., et al.,

Science, 2008. 322(5903):945-9; Woltjen, K., et al., *Nature*, 2009; Yu, J., et al., *Science*, 2009:1172482; Fusaki, N., et al., *Proc Jpn Acad Ser B Phys Biol Sci*, 2009. 85(8):348-62; each of which is herein incorporated by reference in its entirety).

[0692] DNA-free methods to generate human iPSC has also been derived using serial protein transduction with recombinant proteins incorporating cell-penetrating peptide moieties (Kim, D., et al., *Cell Stem Cell*, 2009. 4(6): 472-476; Zhou, H., et al., *Cell Stem Cell*, 2009. 4(5):381-4; each of which is herein incorporated by reference in its entirety), and infectious transgene delivery using the Sendai virus (Fusaki, N., et al., *Proc Jpn Acad Ser B Phys Biol Sci*, 2009. 85(8): p. 348-62; herein incorporated by reference in its entirety).

[0693] The effector modules of the present invention may include a payload comprising any of the genes including, but not limited to, OCT such as OCT4, SOX such as SOX1, SOX2, SOX3, SOX15 and SOX18, NANOG, KLF such as KLF1, KLF2, KLF4 and KLF5, MYC such as c-MYC and n-MYC, REM2, TERT and LIN28 and variants thereof in support of reprogramming cells. Sequences of such reprogramming factors are taught in for example International Application PCT/US2013/074560, the contents of which are incorporated herein by reference in their entirety.

[0694] In some embodiments, the payload of the present invention may be cardiac lineage specification factors such as eomesodermin (EOMES), a T-box transcription factor; WNT signaling pathway components such as WNT3 and WNT 3A. EOMES is crucially required for the development of the heart. Cardiomyocyte programming by EOMES involves autocrine activation of the canonical WNT signaling pathway and vice versa. Under conditions that are conducive to promoting cardiac lineage, WNT signaling activates EOMES and EOMES in turn promotes WNT signaling creating a self-sustaining loop that promotes the cardiac lineage. An activation loop that is too weak or too strong promotes non-cardiac fates such as endodermal and other mesodermal fates respectively. The DDs of the present invention may be used to tune EOMES and WNT payload levels to generate an activation loop that initiate and/or sustain cardiac specification during gastrulation.

VII. DEFINITIONS

[0695] At various places in the present specification, features or functions of the compositions of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual sub-combination of the members of such groups and ranges. The following is a non-limiting list of term definitions.

[0696] *Activity*: As used herein, the term "activity" refers to the condition in which things are happening or being done. Compositions of the invention may have activity and this

activity may involve one or more biological events. In some embodiments, biological events may include cell signaling events. In some embodiments, biological events may include cell signaling events associated protein interactions with one or more corresponding proteins, receptors, small molecules or any of the biocircuit components described herein.

[0697] *Adoptive cell therapy (ACT)*: The terms "Adoptive cell therapy" or "Adoptive cell transfer", as used herein, refer to a cell therapy involving in the transfer of cells into a patient, wherein cells may have originated from the patient, or from another individual, and are engineered (altered) before being transferred back into the patient. The therapeutic cells may be derived from the immune system, such as Immune effector cells: CD4+ T cell; CD8+ T cell, Natural Killer cell (NK cell); and B cells and tumor infiltrating lymphocytes (TILs) derived from the resected tumors. Most commonly transferred cells are autologous anti-tumor T cells after ex vivo expansion or manipulation. For example, autologous peripheral blood lymphocytes can be genetically engineered to recognize specific tumor antigens by expressing T-cell receptors (TCR) or chimeric antigen receptor (CAR).

[0698] *Agent*: As used herein, the term "agent" refers to a biological, pharmaceutical, or chemical compound. Non-limiting examples include simple or complex organic or inorganic molecule, a peptide, a protein, an oligonucleotide, an antibody, an antibody derivative, antibody fragment, a receptor, and soluble factor.

[0699] *Agonist*: the term "agonist" as used herein, refers to a compound that, in combination with a receptor, can produce a cellular response. An agonist may be a ligand that directly binds to the receptor. Alternatively, an agonist may combine with a receptor indirectly by, for example, (a) forming a complex with another molecule that directly binds to the receptor, or (b) otherwise resulting in the modification of another compound so that the other compound directly binds to the receptor. An agonist may be referred to as an agonist of a particular receptor or family of receptors, e.g., agonist of a co-stimulatory receptor.

[0700] *Antagonist*: the term "antagonist" as used herein refers to any agent that inhibits or reduces the biological activity of the target(s) it binds.

[0701] *Antigen*: the term "antigen" as used herein is defined as a molecule that provokes an immune response when it is introduced into a subject or produced by a subject such as tumor antigens which arise by the cancer development itself. This immune response may involve either antibody production, or the activation of specific immunologically-competent cells such as cytotoxic T lymphocytes and T helper cells, or both. An antigen can be derived from organisms, subunits of proteins/antigens, killed or inactivated whole cells or lysates. In the context of the invention, the terms "antigens of interest" or "desired antigens" refers to

those proteins and/or other biomolecules provided herein that are immunospecifically bound or interact with antibodies of the present invention and/or fragments, mutants, variants, and/or alterations thereof described herein. In some embodiments, antigens of interest may comprise any of the polypeptides or payloads or proteins described herein, or fragments or portions thereof.

[0702] *Approximately*: As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0703] *Alkyl:* The terms "alkyl", "alkoxy", "hydroxyalkyl", "alkoxy alkyl", and "alkoxy carbonyl", as used herein, include both straight and branched chains containing one to twelve carbon atoms, and/or which may or may not be substituted.

[0704] *Alkenyl:* The terms "alkenyl" and "alkynyl" as used herein alone or as part of a larger moiety shall include both straight and branched chains containing two to twelve carbon atoms.

[0705] *Aryl:* The term "aryl" as used herein alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic and tricyclic carbocyclic ring systems having a total of five to fourteen ring members, wherein at least one ring is aromatic and wherein each ring in the system contains 3 to 8 ring members. The term "aryl" may be used interchangeably with the term "aryl ring."

[0706] *Aromatic:* The term "aromatic" as used herein, refers to an unsaturated hydrocarbon ring structure with delocalized pi electrons. As used herein "aromatic" may refer to monocyclic, bicyclic or polycyclic aromatic compounds.

[0707] *Aliphatic:* The term "aliphatic" or "aliphatic group" as used herein, refers to a straight or branched C1-C8 hydrocarbon chain or a monocyclic C3-C8hydrocarbon or bicyclic C8- C12 hydrocarbon which are fully saturated or that contains one or more units of unsaturation, that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" or "cycloalkyl"), and that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members.

[0708] *Associated with*: As used herein, the terms "associated with," "conjugated," "linked," "attached," and "tethered," when used with respect to two or more moieties, mean that the moieties are physically associated or connected with one another, either directly or via one or more additional moieties that serve as linking agents, to form a structure that is sufficiently stable so that the moieties remain physically associated under the conditions in which the structure is used, e.g., physiological conditions. An "association" need not be strictly through direct covalent chemical bonding. It may also suggest ionic or hydrogen bonding or a hybridization based connectivity sufficiently stable such that the "associated" entities remain physically associated.

[0709] *Autologous*: the term "autologous" as used herein is meant to refer to any material derived from the same individual to which it is later to be re-introduced into the individual.

[0710] *Barcode*: the term "barcode" as used herein refers to polynucleotide or amino acid sequence that distinguishes one polynucleotide or amino acid from another.

[0711] *Biocircuit system*: As used herein, a "biocircuit" or "biocircuit system" is defined as a circuit within or useful in biologic systems comprising a stimulus and at least one effector module responsive to a stimulus, where the response to the stimulus produces at least one signal or outcome within, between, as an indicator of, or on a biologic system. Biologic systems are generally understood to be any cell, tissue, organ, organ system or organism, whether animal, plant, fungi, bacterial, or viral. It is also understood that biocircuits may be artificial circuits which employ the stimuli or effector modules taught by the present invention and effect signals or outcomes in acellular environments such as with diagnostic, reporter systems, devices, assays or kits. The artificial circuits may be associated with one or more electronic, magnetic, or radioactive components or parts. In the context of the present invention, a biocircuit includes a destabilizing domain (DD) biocircuit system.

[0712] *Checkpoint factor*: As used herein, a checkpoint factor is any moiety or molecule whose function acts at the junction of a process. For example, a checkpoint protein, ligand or receptor may function to stall or accelerate the cell cycle.

[0713] *Co-stimulatory molecule*: As used herein, in accordance with its meaning in immune T cell activation, refers to a group of immune cell surface receptor/ligands which engage between T cells and APCs and generate a stimulatory signal in T cells which combines with the stimulatory signal in T cells that results from T cell receptor (TCR) recognition of antigen/MHC complex (pMHC) on APCs

[0714] *Cytokines*: the term "cytokines", as used herein, refers to a family of small soluble factors with pleiotropic functions that are produced by many cell types that can influence and regulate the function of the immune system.

[0715] *Delivery*: the term "delivery" as used herein refers to the act or manner of delivering a compound, substance, entity, moiety, cargo or payload. A "delivery agent" refers to any agent which facilitates, at least in part, the in vivo delivery of one or more substances (including, but not limited to compounds and/or compositions of the present invention) to a cell, subject or other biological system cells.

[0716] *Destabilized*: As used herein, the term "destable," "destabilize," "destabilizing region" or "destabilizing domain" means a region or molecule that is less stable than a starting, reference, wild-type or native form of the same region or molecule.

[0717] *Engineered*: As used herein, embodiments of the invention are "engineered" when they are designed to have a feature or property, whether structural or chemical, that varies from a starting point, wild type or native molecule.

[0718] *Expression*: As used herein, "expression" of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (e.g., by transcription); (2) processing of an RNA transcript (e.g., by splicing, editing, 5′ cap formation, and/or 3′ end processing); (3) translation of an RNA into a polypeptide or protein; (4) folding of a polypeptide or protein; and (5) post-translational modification of a polypeptide or protein.

[0719] *Feature*: As used herein, a "feature" refers to a characteristic, a property, or a distinctive element.

[0720] *Formulation*: As used herein, a "formulation" includes at least a compound and/or composition of the present invention and a delivery agent.

[0721] *Fragment*: A "fragment," as used herein, refers to a portion. For example, fragments of proteins may comprise polypeptides obtained by digesting full-length protein. In some embodiments, a fragment of a protein includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 150, 200, 250 or more amino acids. In some embodiments, fragments of an antibody include portions of an antibody.

[0722] *Functional*: As used herein, a "functional" biological molecule is a biological entity with a structure and in a form in which it exhibits a property and/or activity by which it is characterized.

[0723] *Heterocycle:* The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein refers to monocyclic, bicyclic or tricyclic ring systems having three to fourteen ring members in which one or more ring members is a heteroatom, wherein each ring in the system contains 3 to 7 ring members and is non-aromatic.

[0724] *Hotspot:* As used herein, a "hotspot" or a "mutational hotspot" refers to an amino acid position in a protein coding gene that is mutated (by substitutions) more frequently relative to elsewhere within the same gene.

[0725] *Hydrophilic*: As used herein, "hydrophilic" refers to a molecule that interacts with or has affinity for water.

[0726] *Hydrophobic:* As used herein, "hydrophobic" refers to a molecule that does not interact or have affinity for water.

[0727] *Immune cells*: the term “an immune cell”, as used herein, refers to any cell of the immune system that originates from a hematopoietic stem cell in the bone marrow, which gives rise to two major lineages, a myeloid progenitor cell (which give rise to myeloid cells such as monocytes, macrophages, dendritic cells, megakaryocytes and granulocytes) and a lymphoid progenitor cell (which give rise to lymphoid cells such as T cells, B cells and natural killer (NK) cells). Exemplary immune system cells include a CD4+ T cell, a CD8+ T cell, a CD4− CD8− double negative T cell, a T γδ cell, a Tαβ cell, a regulatory T cell, a natural killer cell, and a dendritic cell. Macrophages and dendritic cells may be referred to as “antigen presenting cells” or “APCs,” which are specialized cells that can activate T cells when a major histocompatibility complex (MHC) receptor on the surface of the APC complexed with a peptide interacts with a TCR on the surface of a T cell.

[0728] *Immunotherapy*: the term “immunotherapy” as used herein, refers to a type of treatment of a disease that uses immunological tools, such as monoclonal antibodies, receptor-immunoglobulin fusion proteins, vaccines and/or immune cells.

[0729] *In vitro*: As used herein, the term “in vitro” refers to events that occur in an artificial environment, e.g., in a test tube or reaction vessel, in cell culture, in a Petri dish, etc., rather than within an organism (e.g., animal, plant, or microbe).

[0730] *In vivo*: As used herein, the term “in vivo” refers to events that occur within an organism (e.g., animal, plant, or microbe or cell or tissue thereof).

[0731] *Linker*: As used herein, a linker refers to a moiety that connects two or more domains, moieties or entities. In one embodiment, a linker may comprise 10 or more atoms. In a further embodiment, a linker may comprise a group of atoms, e.g., 10-1,000 atoms, and

can be comprised of the atoms or groups such as, but not limited to, carbon, amino, alkylamino, oxygen, sulfur, sulfoxide, sulfonyl, carbonyl, and imine. In some embodiments, a linker may comprise one or more nucleic acids comprising one or more nucleotides. In some embodiments, the linker may comprise an amino acid, peptide, polypeptide or protein. In some embodiments, a moiety bound by a linker may include, but is not limited to an atom, a chemical group, a nucleoside, a nucleotide, a nucleobase, a sugar, a nucleic acid, an amino acid, a peptide, a polypeptide, a protein, a protein complex, a payload (e.g., a therapeutic agent), or a marker (including, but not limited to a chemical, fluorescent, radioactive or bioluminescent marker). The linker can be used for any useful purpose, such as to form multimers or conjugates, as well as to administer a payload, as described herein. Examples of chemical groups that can be incorporated into the linker include, but are not limited to, alkyl, alkenyl, alkynyl, amido, amino, ether, thioether, ester, alkylene, heteroalkylene, aryl, or heterocyclyl, each of which can be optionally substituted, as described herein. Examples of linkers include, but are not limited to, unsaturated alkanes, polyethylene glycols (e.g., ethylene or propylene glycol monomeric units, e.g., diethylene glycol, dipropylene glycol, triethylene glycol, tripropylene glycol, tetraethylene glycol, or tetraethylene glycol), and dextran polymers, Other examples include, but are not limited to, cleavable moieties within the linker, such as, for example, a disulfide bond (-S-S-) or an azo bond (-N=N-), which can be cleaved using a reducing agent or photolysis. Non-limiting examples of a selectively cleavable bonds include an amido bond which may be cleaved for example by the use of tris(2-carboxyethyl) phosphine (TCEP), or other reducing agents, and/or photolysis, as well as an ester bond which may be cleaved for example by acidic or basic hydrolysis.

[0732] *Lipophilic*: As used herein, the term "lipophilic" refers to an affinity for lipids or fats.

[0733] *Metabolite*: Metabolites are the intermediate products of metabolic reactions catalyzed by enzymes that naturally occur within cells. This term is usually used to describe small molecules, fragments of larger biomolecules or processed products.

[0734] *Modified*: As used herein, the term “modified” refers to a changed state or structure of a molecule or entity as compared with a parent or reference molecule or entity. Molecules may be modified in many ways including chemically, structurally, and functionally. In some embodiments, compounds and/or compositions of the present invention are modified by the introduction of non-natural amino acids.

[0735] *Mutation*: As used herein, the term “mutation” refers to a change and/or alteration. In some embodiments, mutations may be changes and/or alterations to proteins (including

peptides and polypeptides) and/or nucleic acids (including polynucleic acids). In some embodiments, mutations comprise changes and/or alterations to a protein and/or nucleic acid sequence. Such changes and/or alterations may comprise the addition, substitution and or deletion of one or more amino acids (in the case of proteins and/or peptides) and/or nucleotides (in the case of nucleic acids and or polynucleic acids). In some embodiments, wherein mutations comprise the addition and/or substitution of amino acids and/or nucleotides, such additions and/or substitutions may comprise 1 or more amino acid and/or nucleotide residues and may include modified amino acids and/or nucleotides. The resulting construct, molecule or sequence of a mutation, change or alteration may be referred to herein as a mutant.

[0736] *Neoantigen*: the term "neoantigen", as used herein, refers to a tumor antigen that is present in tumor cells but not normal cells and do not induce deletion of their cognate antigen specific T cells in thymus (i.e., central tolerance). These tumor neoantigens may provide a "foreign" signal, similar to pathogens, to induce an effective immune response needed for cancer immunotherapy. A neoantigen may be restricted to a specific tumor. A neoantigen be a peptide/protein with a missense mutation (missense neoantigen), or a new peptide with long, completely novel stretches of amino acids from novel open reading frames (neoORFs). The neoORFs can be generated in some tumors by out-of-frame insertions or deletions (due to defects in DNA mismatch repair causing microsatellite instability), gene-fusion, read-through mutations in stop codons, or translation of improperly spliced RNA (e.g., Saeterdal et al., Proc Natl Acad Sci USA, 2001, 98: 13255-13260).

[0737] *Off-target*: As used herein, "off target" refers to any unintended effect on any one or more target, gene, cellular transcript, cell, and/or tissue.

[0738] *Operably linked*: As used herein, the phrase "operably linked" refers to a functional connection between two or more molecules, constructs, transcripts, entities, moieties or the like.

[0739] *Phenyl:* As used herein, " phenyl" refers to a cyclic group of atoms with a formula C_6H_5.

[0740] *Payload or payload of interest (POI)*: the terms "payload" and "payload of interest (POI)", as used herein, are used interchangeable. A payload of interest (POI) refers to any protein or compound whose function is to be altered. In the context of the present invention, the POI is a component in the immune system, including both innate and adaptive immune systems. Payloads of interest may be a protein, a fusion construct encoding a fusion protein,

or non-coding gene, or variant and fragment thereof. Payload of interest may, when amino acid based, may be referred to as a protein of interest.

[0741] *Pharmaceutically acceptable excipients*: the term "pharmaceutically acceptable excipient," as used herein, refers to any ingredient other than active agents (e.g., as described herein) present in pharmaceutical compositions and having the properties of being substantially nontoxic and non-inflammatory in subjects. In some embodiments, pharmaceutically acceptable excipients are vehicles capable of suspending and/or dissolving active agents. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspending or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[0742] *Pharmaceutically acceptable salts*: Pharmaceutically acceptable salts of the compounds described herein are forms of the disclosed compounds wherein the acid or base moiety is in its salt form (e.g., as generated by reacting a free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like.

Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Pharmaceutically acceptable salts include the conventional non-toxic salts, for example, from non-toxic inorganic or organic acids. In some embodiments, a pharmaceutically acceptable salt is prepared from a parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, Pharmaceutical Salts: Properties, Selection, and Use, P.H. Stahl and C.G. Wermuth (eds.), Wiley-VCH, 2008, and Berge et al., Journal of Pharmaceutical Science, 66, 1-19 (1977), each of which is incorporated herein by reference in its entirety. Pharmaceutically acceptable solvate: The term "pharmaceutically acceptable solvate," as used herein, refers to a crystalline form of a compound wherein molecules of a suitable solvent are incorporated in the crystal lattice. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), N-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), N, N'-dimethylformamide (DMF), N, N'-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the solvate is referred to as a "hydrate." In some embodiments, the solvent incorporated into a solvate is of a type or at a level that is physiologically tolerable to an organism to which the solvate is administered (e.g., in a unit dosage form of a pharmaceutical composition).

[0743] *Piperazine:* As used herein, " piperazine" refers to a six membered ring containing two nitrogen atoms at opposite positions in the ring.

[0744] *Protein of interest*: As used herein, the terms "proteins of interest" or "desired proteins" include those provided herein and fragments, mutants, variants, and alterations thereof.

[0745] *Purine:* As used herein, "purine" refers to an aromatic heterocyclic structure, wherein one of the heterocycles is an imidazole ring and one of the heterocycles is a pyrimidine ring.

[0746] *Pyrimidine:* As used herein, "pyrimidine" refers to an aromatic heterocyclic structure similar to benzene, but wherein two of the carbon atoms are replaced by nitrogen atoms.

[0747] *Pyridopyrimidine:* As used herein, "Pyridopyrimidine" refers to an aromatic heterocyclic structure, wherein one of the heterocycles is a purine ring and one of the heterocycles is a pyrimidine ring.

[0748] *Quinazoline:* As used herein, the term, "Quinazoline" refers to an aromatic heterocyclic structure, wherein one of the heterocycles is a benzene ring and one of the heterocycles is a pyrimidine ring.

[0749] *Stable*: As used herein "stable" refers to a compound or entity that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent.

[0750] *Stabilized*: As used herein, the term "stabilize", "stabilized," "stabilized region" means to make or become stable. In some embodiments, stability is measured relative to an absolute value. In some embodiments, stability is measured relative to a secondary status or state or to a reference compound or entity.

[0751] *Standard CAR*: As used herein, the term "standard CAR" refers to the standard design of a chimeric antigen receptor. The components of a CAR fusion protein including the extracellular scFv fragment, transmembrane domain and one or more intracellular domains are linearly constructed as a single fusion protein.

[0752] *Stimulus response element (SRE)*: the term "stimulus response element (SRE), as used herein, is a component of an effector module which is joined, attached, linked to or associated with one or more payloads of the effector module and in some instances, is responsible for the responsive nature of the effector module to one or more stimuli. As used herein, the "responsive" nature of an SRE to a stimulus may be characterized by a covalent or non-covalent interaction, a direct or indirect association or a structural or chemical reaction to the stimulus. Further, the response of any SRE to a stimulus may be a matter of degree or kind. The response may be a partial response. The response may be a reversible response. The response may ultimately lead to a regulated signal or output. Such output signal may be of a relative nature to the stimulus, e.g., producing a modulatory effect of between 1 and 100

or a factored increase or decrease such as 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more. One non-limiting example of an SRE is a destabilizing domain (DD).

[0753] *Subject*: As used herein, the term "subject" or "patient" refers to any organism to which a composition in accordance with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans) and/or plants.

[0754] *T cell*: A T cell is an immune cell that produces T cell receptors (TCRs). T cells can be naïve (not exposed to antigen; increased expression of CD62L, CCR7, CD28, CD3, CD127, and CD45RA, and decreased expression of CD45RO as compared to TCM), memory T cells (TM) (antigen-experienced and long-lived), and effector cells (antigen-experienced, cytotoxic). TM can be further divided into subsets of central memory T cells (TCM, increased expression of CD62L, CCR7, CD28, CD127, CD45RO, and CD95, and decreased expression of CD54RA as compared to naïve T cell and effector memory T cells (TEM, decreased expression of CD62L, CCR7, CD28, CD45RA, and increased expression of CD127 as compared to naïve T cells or TCM). Effector T cells (TE) refers to antigen-experienced CD8+ cytotoxic T lymphocytes that have decreased expression of CD62L, CCR7, CD28, and are positive for granzyme and perforin as compared to TCM. Other exemplary T cells include regulatory T cells, such as CD4+ CD25+ (Foxp3+) regulatory T cells and Treg17 cells, as well as Tr1, Th3, CD8+CD28−, and Qa-1 restricted T cells.

[0755] *T cell receptor*: T cell receptor (TCR) refers to an immunoglobulin superfamily member having a variable antigen binding domain, a constant domain, a transmembrane region, and a short cytoplasmic tail, which is capable of specifically binding to an antigen peptide bound to a MHC receptor. A TCR can be found on the surface of a cell or in soluble form and generally is comprised of a heterodimer having α and β chains (also known as TCRα and TCRβ, respectively), or γ and δ chains (also known as TCRγ and TCRδ, respectively). The extracellular portion of TCR chains (e.g., α-chain, β-chain) contains two immunoglobulin domains, a variable domain (e.g., α-chain variable domain or Vα, β-chain variable domain or Vβ) at the N-terminus, and one constant domain (e.g., α-chain constant domain or Cα and β-chain constant domain or Cβ,) adjacent to the cell membrane. Similar to immunoglobulin, the variable domains contain complementary determining regions (CDRs) separated by framework regions (FRs). A TCR is usually associated with the CD3 complex to form a TCR complex. As used herein, the term "TCR complex" refers to a complex formed by the association of CD3 with TCR. For example, a TCR complex can be composed of a

CD3γ chain, a CD3δ chain, two CD3ε chains, a homodimer of CD3ζ chains, a TCRα chain, and a TCRβ chain. Alternatively, a TCR complex can be composed of a CD3γ chain, a CD3δ chain, two CD3ε chains, a homodimer of CD3ζ chains, a TCRγ chain, and a TCRδ chain. A "component of a TCR complex," as used herein, refers to a TCR chain (i.e., TCRα, TCRβ, TCRγ or TCRδ), a CD3 chain (i.e., CD3γ, CD3δ, CD3ε or CD3ζ), or a complex formed by two or more TCR chains or CD3 chains (e.g., a complex of TCRα and TCRβ, a complex of TCRγ and TCRδ, a complex of CD3ε and CD3δ, a complex of CD3γ and CD3ε, or a sub-TCR complex of TCRα, TCRβ, CD3γ, CD3δ, and two CD3ε chains.

[0756] *Therapeutic Agent*: The term "therapeutic agent" refers to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect. Therapeutic agents of the present invention include any of the biocircuit components taught herein either alone or in combination with other therapeutic agents.

[0757] *Therapeutically effective amount*: As used herein, the term "therapeutically effective amount" means an amount of an agent to be delivered (e.g., nucleic acid, drug, therapeutic agent, diagnostic agent, prophylactic agent, etc.) that is sufficient, when administered to a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is provided in a single dose. In some embodiments, a therapeutically effective amount is administered in a dosage regimen comprising a plurality of doses. Those skilled in the art will appreciate that in some embodiments, a unit dosage form may be considered to comprise a therapeutically effective amount of a particular agent or entity if it comprises an amount that is effective when administered as part of such a dosage regimen.

[0758] *Triazine*: As used herein, "triazine" is a class of nitrogen containing heterocycles with a structure similar to benzene, but wherein three carbon atoms are replaced by nitrogen atoms.

[0759] *Treatment or treating:* As used herein, the terms "treatment" or "treating" denote an approach for obtaining a beneficial or desired result including and preferably a beneficial or desired clinical result. Such beneficial or desired clinical results include, but are not limited to, one or more of the following: reducing the proliferation of (or destroying) cancerous cells or other diseased, reducing metastasis of cancerous cells found in cancers, shrinking the size of the tumor, decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other

medications required to treat the disease, delaying the progression of the disease, and/or prolonging survival of individuals.

[0760] *Tune:* As used herein, the term "tune" means to adjust, balance or adapt one thing in response to a stimulus or toward a particular outcome. In one non-limiting example, the SREs and/or DDs of the present invention adjust, balance or adapt the function or structure of compositions to which they are appended, attached or associated with in response to particular stimuli and/or environments.

[0761] *Variant:* As used herein, the term "variant" refers to a first composition (e.g., a first DD or payload), that is related to a second composition (e.g., a second DD or payload, also termed a "parent" molecule). The variant molecule can be derived from, isolated from, based on or homologous to the parent molecule. The term variant can be used to describe either polynucleotides or polypeptides.

VIII. EQUIVALENTS AND SCOPE

[0762] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[0763] In the claims, articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process.

[0764] It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term "comprising" is used herein, the term "consisting of" is thus also encompassed and disclosed.

[0765] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0766] In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention (e.g., any antibiotic, therapeutic or active ingredient; any method of production; any method of use; etc.) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[0767] It is to be understood that the words which have been used are words of description rather than limitation, and that changes may be made within the purview of the appended claims without departing from the true scope and spirit of the invention in its broader aspects.

[0768] While the present invention has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the invention. The present invention is further illustrated by the following nonlimiting examples.

EXAMPLES

Example 1. Generation of novel ligand responsive DDs by mutagenesis screening

Study design

[0769] To engineer constructs that display ligand dependent stability, a candidate ligand binding domain (LBD) is selected and a cell-based screen using yellow fluorescent protein (YFP) as a reporter for protein stability is designed to identify mutants of the candidate LBD possessing the desired characteristics of a destabilizing domain: low protein levels in the absence of a ligand of the LBD, (i.e., low basal stability), large dynamic range, robust and predictable dose-response behavior, and rapid kinetics of degradation (Banaszynski, *et al.*, (2006) *Cell*; 126(5): 995–1004). The candidate LBD binds to a desired ligand but not endogenous signaling molecules.

[0770] The candidate LBD sequence (as a template) is first mutated using a combination of nucleotide analog mutagenesis and error-prone PCR, to generate libraries of mutants based on the template candidate domain sequence. The libraries generated are cloned in-frame at either the 5′- or 3′-ends of the YFP gene, and a retroviral expression system is used to stably transduce the libraries of YFP fusions into NIH3T3 fibroblasts.

[0771] The transduced NIH3T3 cells are subjected to three to four rounds of sorting using fluorescence-activated cell sorting (FACS) to screen the libraries of candidate DDs. Transduced NIH3T3 cells are cultured in the absence of the high affinity ligand of the ligand binding domain (LBD), and cells that exhibit low levels of YFP expression are selected through FACS.

Screening Strategy I

[0772] The selected cell population is cultured in the presence of the high affinity ligand of the ligand binding domain for a period of time (e.g., 24 hours), at which point cells are sorted again by FACS. Cells that exhibit high levels of YFP expression are selected through FACS and the selected cell population is split into two groups and treated again with the high affinity ligand of the ligand binding domain at different concentrations; one group is treated with the lower concentration of the ligand and the other is treated with a high concentration of the ligand, for a period of time (e.g., 24 hours), at which point cells are sorted again by FACS. Cells expressing mutants that are responsive to lower concentrations of the ligand are isolated.

[0773] The isolated cells responsive to the lower concentration of the ligand are treated with the ligand again and cells exhibiting low fluorescence levels are collected 4 hours following removal of the ligand from the media. This fourth sorting is designed to enrich cells that exhibit fast kinetics of degradation (Iwamoto *et al.*, *Chem Biol.* 2010 Sep 24; 17(9): 981–988).

Screening Strategy II

[0774] The selected cell population is subject to additional one or more sorts by FACS in the absence of high affinity ligand of LBD and cells that exhibit low levels of YFP expression are selected for further analysis. Cells are treated with high affinity ligand of the ligand binding domain, for a period of time (e.g. 24 hours), and sorted again by FACS. Cells expressing high levels of YFP are selected for through FACS. Cells with high expression of YFP are treated with ligand again and cells exhibiting low fluorescence levels are collected 4 hours following removal of the ligand from the media to enrich cells that exhibit fast kinetics of degradation. Any of the sorting steps may be repeated to identify DDs with ligand dependent stability.

[0775] The cells are recovered after sorting. The identified candidate cells are harvested and the genomic DNA is extracted. The candidate DDs are amplified by PCR and isolated. The candidate DDs are sequenced and compared to the LBD template to identify the mutations in candidate DDs.

Example 2. Novel DDs derived from human PDE5 by site directed mutagenesis

[0776] To identify novel destabilizing domain mutations, mutagenic PCR was performed on the open reading frame of human PDE5 catalytic domain (SEQ ID NO. 3) using non-natural nucleotides. The mutant library was ligated in frame with an AcGFP reporter at C-terminus and cloned into pLVX-IRES- Puro vectors. The lentivirus library was then used to infect HEK 293T cells. Cells were selected with puromycin and the library was screened using screening strategies described in Example 1. DNA was extracted from the cell pool, cloned into vectors, and transformed into *E. coli*. Individual clones were sequenced and cloned in frame with a linker GGSGGGSGG (SEQ ID NO. 77) and AcGFP at C terminus into pLVX.IRES puro. The catalytic domain of wildtype hPDE5 was also cloned into pLVX.IRES. Puro and used as a control. HEK293 cells were transduced with individual clones and selected with puromycin.

[0777] HEK293 cells expressing OT-hPDE5N constructs were incubated with 10μM Sildenafil or vehicle control, DMSO for 48 hours and the stability of hPDE5 mutants was evaluated at the protein level. Cell lysates obtained from hPDE5N construct expressing cells were immunoblotted using the AcGFP antibody (Clonetech, Mountain View, CA). Samples were also immunoblotted with the GAPDH antibody to ensure uniform protein loading. The immunoblot demonstrated that OT-hPDE5N-002, OT-hPDE5N-003, OT-hPDE5N-006, OT-hPDE5N-008, OT-hPDE5N-009, OT-hPDE5N-010 showed an increase in PDE5-GFP protein levels with Sildenafil treatment when compared to DMSO treatment suggesting a Sildenafil dependent stabilization of the construct. Further, the hPDE5-GFP levels with DMSO treatment in OT-hPDE5N-002, OT-hPDE5N-003, and OT-hPDE5N-006 was lower than in the wildtype hPDE5 construct, OT-hPDE5N-001, indicating that these constructs are destabilized in the absence of ligand.

[0778] The GFP expression in cells expressing hPDE5 constructs was measured by FACS. HEK293 cells expressing OT-hPDE5N-001 to OT-hPDE5N-010 were incubated with 10μM Sildenafil or vehicle control, DMSO for 48 hours and the mean fluorescence intensity (MFI) was calculated. The stabilization ratio was calculated as the fold change in GFP intensity in Sildenafil treated samples compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. The destabilizing mutation co-efficient was calculated as the fold change in GFP intensity in the hPDE5 mutant constructs (OT-hPDE5N-002 to OT-hPDE5N-010) compared to the hPDE5 wildtype construct (OT-hPDE5N-001) in the absence of the ligand. Destabilizing mutation co-efficient less than 1 and stabilization ratios greater than 1 are desired in DDs. The results and ratios are presented in Table 19.

Table 19: GFP expression in hPDE5 derived DDs

Constructs	MFI		Stabilization ratio	Destabilizing mutation co-efficient
	DMSO	Sildenafil		
OT-hPDE5N-001	11064	25789	2.33	
OT-hPDE5N-002	1649	12285	7.45	0.15
OT-hPDE5N-003	1184	7303	6.17	0.11
OT-hPDE5N-004	795	1065	1.34	0.07
OT-hPDE5N-005	6924	29491	4.26	0.63
OT-hPDE5N-006	1542	19211	12.46	0.14
OT-hPDE5N-007	3038	7078	2.33	0.27
OT-hPDE5N-008	1134	13189	11.63	0.10
OT-hPDE5N-009	744	15587	20.95	0.07
OT-hPDE5N-010	5053	21755	4.31	0.46

[0779] As shown in Table 19, all constructs demonstrated a stabilization ratio greater than one, indicating that all constructs show ligand (Sildenafil) dependent stabilization. The stabilization ratios of OT-hPDE5N-006, OT-hPDE5N-008, and OT-hPDE5N-009 was greater than 10 indicating strong ligand dependent stabilization. Constructs OT-hPDE5N-002, OT-hPDE5N-003, OT-hPDE5N-005, and OT-hPDE5N-010 showed stabilization ratio in the range of 2 to 10 indicating modest ligand dependent stabilization. The destabilizing mutation coefficient observed with all constructs was less than 1 indicating that all hPDE5 mutants are destabilized as compared to the wildtype hPDE5. Notably, constructs OT-hPDE5N-002, OT-hPDE5N-003, OT-hPDE5N-004, 0T-hPDE5N-006, OT-hPDE5N-008, and OT-hPDE5N-009 demonstrated destabilizing mutation coefficients less than 0.2 indicating strong destabilizing in the absence of ligand. OT-hPDE5N-006, OT-hPDE5N-008, and OT-hPDE5N-009 were identified as mutants with desirable characteristics of a DD i.e., low basal expression in the absence of ligand and high expression in the presence of ligand.

Example 3. Sildenafil dependent stabilization of hPDE5 mutants

[0780] HEK293 cells expressing OT-hPDE5N-006, OT-hPDE5N-008, or OT-hPDE5N-009 constructs were incubated with varying concentrations of Sildenafil ranging from 0.005 μM to 10μM, or vehicle control (DMSO) for 48 hours. The stability of hPDE5 mutants was measured using FACS and mean fluorescence intensity (MFI) of GFP was calculated. The stabilization ratio was calculated as the fold change in GFP intensity in Sildenafil treated samples compared to treatment with DMSO (i.e. absence of ligand) with the same construct. Stabilization ratio greater than 1 is desired in DDs. The MFI and stabilization ratios are presented in Table 20.

Table 20: Sildenafil Dose titration

Sildenafil dose (μM)	OT-hPDE5N-006		OT-hPDE5N-008		OT-hPDE5N-009	
	MFI	Stabilization ratio	MFI	Stabilization ratio	MFI	Stabilization ratio
Untreated	7036		4388		3506	
0.0005	6848	0.97	4422	1.01	3513	1.00
0.0015	7239	1.03	4557	1.04	3473	0.99
0.0046	7218	1.03	4397	1.00	3539	1.01
0.0137	7127	1.01	4274	0.97	3683	1.05
0.041	8097	1.15	4395	1.00	4171	1.19
0.123	12248	1.74	4875	1.11	6463	1.84
0.37	22018	3.13	6753	1.54	13076	3.73
1.11	34171	4.86	10495	2.39	23468	6.69
3.33	49220	7.00	17960	4.09	34615	9.87
10	67084	9.53	32480	7.40	47793	13.63

[0781] As shown in Table 20, all three constructs showed an increase in stabilization ratio with increasing doses of Sildenafil indicating a ligand dose-dependent stabilization of hPDE5 mutants. The half maximal effective concentration or EC_{50} was approximately 1μM.

[0782] Sildenafil dependent stabilization of hPDE5 mutants was also measured over a period of time. HEK293 cells expressing OT-hPDE5N-006, OT-hPDE5N-008, and OT-hPDE5N-009 were treated with 10μM of Sildenafil for 2, 4, 6, 16, 24, and 48 hours. The stability of hPDE5 mutants was measured using FACS and mean fluorescence intensity (MFI) of GFP was calculated. The stabilization ratio was calculated as the fold change in GFP intensity in Sildenafil treated samples compared to treatment with DMSO (i.e. absence of ligand) with the same construct. Stabilization ratio greater than 1 is desired in DDs. The MFI and stabilization ratios are presented in Table 21.

Table 21: Time course of Sildenafil treatment

Time (h)	OT-hPDE5N-006		OT-hPDE5N-008		OT-hPDE5N-009	
	MFI	Stabilization ratio	MFI	Stabilization ratio	MFI	Stabilization ratio
Parental	675	-	667	-	673	-
0	7921	-	5304	-	4195	-
2	12088	1.54	7290	1.37	6337	1.51
4	14046	1.77	8675	1.64	8159	1.95
6	16710	2.11	10929	2.06	10203	2.43
16	39029	4.93	19034	3.59	26279	6.26
24	51534	6.51	27246	5.14	36516	8.71
48	70811	8.94	34796	6.56	47407	11.30

[0783] As shown in Table 21, all three constructs showed an increase in stabilization ratio with increasing duration of treatment with Sildenafil indicating a time-dependent increase in stabilization of hPDE5 mutants.

Example 4. Vardenafil dependent stabilization of hPDE5 DDs

[0784] Vardenafil has an IC_{50} of 0.7 nM and is a more potent inhibitor of hPDE5 than Sildenafil which has an IC_{50} of 3.9 nM (Doggrell S, et al. (2007) Int J Impot. Res 19(3):281-95). To test if Vardenafil is capable of stabilizing hPDE5 DDs, HEK293 cells expressing OT-hPDE5-006, OT-hPDE5-008, and OT-hPDE5-009 were treated with Vardenafil at concentrations ranging from 0.0005μM to 10μM for 48 hours. The stability of hPDE5 mutants was measured using FACS and mean fluorescence intensity (MFI) of GFP was calculated. The stabilization ratio was calculated as the fold change in GFP intensity in Vardenafil treated samples compared to treatment with DMSO (i.e. absence of ligand) with the same construct. Stabilization ratio greater than 1 is desired in DDs. The MFI and stabilization ratios are presented in Table 22.

Table 22: Vardenafil Dose Titration

Vardenafil dose (μM)	OT-hPDE5N-006		OT-hPDE5N-008		OT-hPDE5N-009	
	MFI	Stabilization ratio	MFI	Stabilization ratio	MFI	Stabilization ratio
Parental	988	-	999	-	980	-
0	11287	-	7971	-	5841	-
0.0005	11770	1.04	7894	0.99	5954	1.02
0.0015	12965	1.15	8099	1.02	6601	1.13
0.0046	18739	1.66	8897	1.12	9946	1.70
0.0137	36940	3.27	12440	1.56	21894	3.75
0.041	58755	5.21	18527	2.32	39580	6.78
0.123	91994	8.15	33614	4.22	63622	10.89
0.37	125140	11.09	61010	7.65	86481	14.81
1.11	144927	12.84	95149	11.94	105930	18.14
3.33	172990	15.33	134306	16.85	123757	21.19
10	188068	16.66	166236	20.86	139165	23.83

[0785] As shown in Table 22, all three constructs showed an increase in stabilization ratio with increasing doses of Vardenafil indicating a Vardenafil dose-dependent stabilization of hPDE5 DDs. The half maximal effective concentration or EC_{50} was approximately 0.1-0.3μM which was less than the EC_{50} observed with sildenafil (~1μM) indicating that Vardenafil may stabilize hPDE5 DDs more potently than sildenafil.

[0786] The ability of Vardenafil to stabilize hPDE5 derived DDs was measured in cell lines stably transduced with hPDE5 DDs e.g. HEK293 cells, HCT-116 cells, and SKOV-3 cells. Cells were transduced with OT-hPDE5N-006, 008, and 009 constructs and incubated with 1μM or 10 μM Vardenafil or with DMSO for 48 hours. The stability of hPDE5 mutants was measured using FACS and mean fluorescence intensity (MFI) of GFP was calculated. The stabilization ratio was calculated as the fold change in GFP intensity in Vardenafil treated samples compared to treatment with DMSO (i.e. absence of ligand) with the same

construct. Stabilization ratio greater than 1 is desired in DDs. The MFI and stabilization ratios are presented in Table 23.

Table 23: Vardenafil Dose Titration

Dose	OT-hPDE5N-006 (hPDE5- F736A)		OT-hPDE5N-008 (hPDE5- Y728L)		OT-hPDE5N-009 (hPDE5- R732L)	
	MFI	Stabilization ratio	MFI	Stabilization ratio	MFI	Stabilization ratio
DMSO	9604	-	5191	-	3605	-
Vardenafil (1μM)	110603	11.52	68816	13.26	81484	22.60
Vardenafil (10μM)	143351	14.93	123150	23.72	106403	29.52

[0787] As shown in Table 23, all three constructs showed an increase in stabilization ratio with both doses of Vardenafil indicating a ligand dose-dependent stabilization of hPDE5 DDs. These data are consistent with the results observed with the dose response of Vardenafil observed in Table 22.

Example 5. hPDE5 C terminus fusion proteins

[0788] DDs may be positioned upstream or downstream of the payload within an SRE. hPDE5 mutants generated by site mutagenesis as discussed in example 2 are fused at the C - terminus of GFP to test if the hPDE5 mutants can destabilize proteins of interest when fused to the C-terminus of the protein of interest. A linker is placed between GFP and hPDE5 and cloned into pLVX.IRES. Puro. HEK 293T cells stably expressing GFP-hPDE5 (wildtype and mutant) constructs are incubated with 10μM Sildenafil or 10μM Vardenafil or DMSO (control) for 48 hours. Following the incubation, mean fluorescence intensity (MFI) is measured using FACS. All hPDE5 (mutant)-GFP constructs are expected to stabilize GFP in the presence of ligand while they are expected to destabilize GFP in the absence of ligand when fused to C terminus.

Example 6. Novel DDs derived from human hPDEs by site directed mutagenesis

[0789] Known mutations in phosphodiesterases that affect protein stability are identified and utilized to identify novel hPDE derived DDs. Mutations previously identified include, but are not limited to, hPDE5 (I778T), or hPDE6C (H602L), hPDE6C (E790K), hPDE6C(R104W), hPDE6C (Y323N), and hPDE6C (P391L) or hPDE4D (S752A), hPDE4D (S754A), hPDE4D (S752A, S754A), and hPDE4D (E757A, E758A, D759A) (Zhu et al. (2010) Mol Cell Biol. 4379-4390; Alexandre et al. (2015). Endocr. Relat. Cancer 22(4):519-30; Cheguru P. et al. (2015) Mol Cell Neurosci; 64: 1–8.; the contents of each of which are incorporated herein by reference in their entirety). Human PDE mutants are fused to a linker, and a reporter gene e.g. GFP. The reporter constructs are transfected into cells such as NIH 3T3 cells and 293T cells.

Transfected cells are incubated with appropriate ligand e.g. Sildenafil and Vardenafil for hPDE5 or Apremilast and Roflumilast for hPDE4. Fluorescence signal is measured by FACS and mean fluorescence signal intensity is calculated.

Example 7. Characterization of hPDE5 mutants using thermal shift assays

[0790] Thermal shift assays can be used to measure the thermal denaturation temperature of a protein as an indicator of its stability in response to different conditions such as pH, ions, salts, additives, drugs, and/or mutations. Additionally, thermal shift assays can be used to understand the correlation between ligand binding, enzymatic activity and stabilization potencies. Human PDE5 mutants are mixed with a thermal assay dye, thermal assay buffer, and ligand (or DMSO control). Samples are also treated with varying concentrations of factors such as drugs, salts, ions, or other parameters. The samples are loaded into an instrument such as a real-time PCR instrument and the temperature ramp rates is set within a range of approximately 0.1-10 degrees Celsius per minute. The fluorescence in each condition is measured at regular intervals, over a temperature range spanning the typical protein unfolding temperatures of 25-95 degrees Celsius.

Example 8. Characterization of hPDE5 truncation mutants

[0791] The data shown in the previous examples show that the catalytic domain of hPDE5 was a suitable template for the identification of destabilizing domains. Several truncation mutants of the full length hPDE5 were generated to identify regions beyond the catalytic within the catalytic domain that may serve as a template for identifying DDs. The truncation mutants tested included amino acids 535- 860 of hPDE5 WT (E535-Q860), amino acids 535 to 836 of hPDE5 WT (E535-S836), amino acids 590 to 860 of hPDE5 WT (M590-Q860), amino acids 590 to 836 of hPDE5 WT (M590-S836), wherein the amino acids positions are with respect to SEQ ID NO.1. The DD mutation R732L was incorporated into all truncation mutants and its destabilizing potential was compared to E535-Q860 wildtype by fusing the mutants to an SG linker and reporter, AcGFP. HCT-116 cells were stably transduced with the constructs described above and treated with 10μM stabilizing ligands, Sildenafil, or Vardenafil or DMSO for 48 hours. As a control, parental untransduced cells and cells expressing OT-hPDE5N-001, or OT-hPDE5N-028 were also included in the analysis. The mean fluorescence intensity (MFI) of GFP was analyzed by FACS. The stabilization ratio was calculated as the fold change in GFP intensity in Sildenafil treated samples compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. The destabilizing mutation coefficient was calculated as the fold change in GFP intensity in the hPDE5 mutant constructs compared to the hPDE5 wildtype construct (OT-hPDE5N-019)

in the absence of the ligand. Destabilizing mutation coefficients less than 1 are desirable. Stabilization ratios greater than 1 are desired in DDs. The results and ratios are presented in Table 24.

Table 24: Expression of hPDE5 truncation mutants

Construct	MFI			Sildenafil Stabilization ratio	Vardenafil Stabilization ratio	Destabilizing mutation coefficient
	DMSO	Sildenafil	Vardenafil			
Parental	2093	3735	3200	1.78	1.53	-
OT-hPDE5N-001	42973	53736	49344	1.25	1.15	-
OT-hPDE5N-028	150356	187845	170129	1.25	1.13	-
OT-hPDE5N-019	64942	66860	67388	1.03	1.04	-
OT-hPDE5N-020	9248	55636	93216	6.02	10.08	0.14
OT-hPDE5N-021	4542	4608	5188	1.01	1.14	0.07
OT-hPDE5N-022	3395	3434	3523	1.01	1.04	0.05
OT-hPDE5N-023	2689	2686	2660	1.00	0.99	0.04
OT-hPDE5N-024	2809	2663	2770	0.95	0.99	0.04

[0792] As shown in Table 24, OT-hPDE5N-020 construct consisting of E535-Q860 amino acids of hPDE5 with the R732L mutant displayed the strongest ligand dependent stabilization with both ligands with the highest stabilization ratio. The destabilizing mutation coefficient was also calculated for constructs 020-024 and this analysis showed that the constructs were all effective in destabilizing the payload. This suggests that the removal of residues from the catalytic domain does not appear to enhance the ligand dependent stabilization potential of hPDE5.

[0793] Protein expression analysis of the truncation mutants was performed in parallel via western blot. HCT 116 cells expressing OT-hPDE5N-019 to OT-hPDE5N-024 were treated with 10μM Vardenafil for 24 hours and immunoblotted for AcGFP using anti AcGFP antibodies (catalog no. 63277, Clonetech, Mountain View, California). GAPDH levels were also analyzed to ensure even protein loading. OT-hPDE5N-020 construct consisting of E535-Q860 i.e. amino acids 535 to 860 of hPDE5 WT (SEQ ID NO.1) with the R732L mutant showed vardenafil dependent stabilization. This result is consistent with the FACS analysis. Stabilization was not observed with OT-hPDE5N-021, while constructs OT-hPDE5N-022, OT-hPDE5N-023, and OT-hPDE5N-024 showed no AcGFP expression, both in the presence and absence of vardenafil, indicating that the expression of the construct in these mutants is below the detection levels of the western blot method.

Example 9. Characterization of hPDE5 combination mutants

[0794] Single destabilizing mutants identified were combined to test if the combining two or more mutations generates domains with greater destabilizing potential either additively or synergistically. Desirable qualities of a DD include, low expression of the SRE in the absence of ligand and ligand dependent stabilization of the SRE. Constructs were generated using DDs linked to GFP using an SG linker. HCT-116 cells were stably transduced with the constructs described above and treated with 10μM stabilizing ligands, Sildenafil, or Vardenafil or DMSO for 48 hours. As a control, parental untransduced cells and cells expressing OT-hPDE5N-001, or OT-hPDE5N-028 were also included in the analysis. The mean fluorescence intensity (MFI) of GFP was analyzed by FACS. The stabilization ratio was calculated as the fold change in GFP intensity in Sildenafil treated samples compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. The destabilizing mutation coefficient was calculated as the fold change in GFP intensity in the hPDE5 mutant constructs compared to the hPDE5 wildtype construct (OT-hPDE5N-019) in the absence of the ligand. Destabilizing mutation coefficient less than 1 are desirable. Stabilization ratios greater than 1 are desired in DDs. The results and ratios are presented in Table 25.

Table 25: Expression of hPDE5 combination mutants

Construct	MFI			Sildenafil Stabilization ratio	Vardenafil Stabilization ratio	Destabilizing mutation coefficient
	DMSO	Sildenafil	Vardenafil			
Parental	2093	3735	3200	1.78	1.53	-
OT-hPDE5N-001	42973	53736	49344	1.25	1.15	-
OT-hPDE5N-028	150356	187845	170129	1.25	1.13	-
OT-hPDE5N-019	64942	66860	67388	1.03	1.04	-
OT-hPDE5N-025	12633	13862	53848	1.10	4.26	0.19
OT-hPDE5N-026	8625	48592	109667	5.63	12.72	0.13

[0795] As shown in Table 25, only the OT-hPDE5N-026 construct with R732L and D764N mutations showed Sildenafil dependent stabilization with a ratio of 5.63. Similar results were obtained with OT-hPDE5N-026 upon treatment with Vardenafil. OT-hPDE5N-025 however only showed Vardenafil dependent stabilization with a ratio of 4.26. Both constructs were destabilized in the absence of ligand. As expected, hPDE5 wildtype constructs did not show any significant ligand dependent stabilization. These data suggest that the strategy of combining mutations may be used to identify improved DDs as well as DDs that are stabilized by specific ligands.

[0796] Protein expression analysis of the combination mutants was performed in parallel via western blot. HCT 116 cells expressing OT-hPDE5N-025, and 26 were treated with 10μM Vardenafil for 24 hours and immunoblotted for AcGFP using anti AcGFP antibodies (catalog no. 63277, Clonetech, Mountain View, California). GAPDH levels were also analyzed to ensure even protein loading. OT-hPDE5N-025 with hPDE5 (F736A, D764N) and OT-hPDE5N-026 with hPDE5 (R732L, D764N) constructs consisting showed Vardenafil dependent stabilization of AcGFP protein levels as measured via western blotting. This result is consistent with the FACS analysis.

[0797] The response of hPDE5 combination mutants to increasing doses of sildenafil was tested. HCT116 cells transduced with hPDE5 constructs were treated with Sildenafil for 24 hours at doses ranging from 0.04μM to 30 μM. Mean fluorescence intensity (MFI) was measured by FACS. Parental HCT116 and cells expressing OT-hPDE5N-019 wildtype construct were also included as controls. The response of the combination mutants to Sildenafil was compared to the response of the single mutant construct OT-hPDE5N-020. The stabilization ratio indicated as SR in Table 26 was calculated as the fold change in GFP intensity in Sildenafil treated samples compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. The destabilizing mutation coefficient ratio was calculated as the fold change in GFP intensity in the hPDE5 mutant constructs compared to the hPDE5 wildtype construct (OT-hPDE5N-019) in the absence of the ligand. Destabilizing mutation coefficient ratios less than 1 are desirable. Stabilization ratios greater than 1 are desired in DDs. The results and stabilization ratios are presented in Table 26.

Table 26: Sildenafil dose response of combination mutants

Dose (μM Sildenafil)	**OT-hPDE5N-019**		**OT-hPDE5N-020**		**OT-hPDE5N-025**		**OT-hPDE5N-026**	
	MFI	SR	MFI	SR	MFI	SR	MFI	SR
DMSO	62116	-	6172	-	10736	-	7093	-
30	75478	1.22	47992	7.78	26837	2.50	69864	9.85
10	-	-	27693	4.49	13263	1.24	34587	4.88
3.33	-	-	23549	3.82	10384	0.97	22392	3.16
1.11	-	-	15952	2.58	9636	0.90	10353	1.46
0.37	-	-	12739	2.06	9802	0.91	6961	0.98
0.12	-	-	6441	1.04	8619	0.80	6603	0.93
0.04	-	-	5299	0.86	8688	0.81	5948	0.84

[0798] As shown in Table 26, the stabilization ratios for OT-hPDE5N-026 construct obtained across multiple doses of sildenafil were higher than the single mutant OT-hPDE5N-020 construct. The combination mutant 025, achieved stabilization ratios much lower than the

026 construct for any given ligand dose. The destabilizing mutation co-efficient ratios obtained for the OT-hPDE5N-020 (ratio= 0.1), OT-hPDE5N-025 (ratio= 0.17), and OT-hPDE5N-026 (ratio =0.1) indicate that all constructs are destabilized in the absence of the ligand. These data indicate that the combination mutant OT-hPDE5N-026 is strong DD candidate when the stabilizing ligand is Sildenafil.

[0799] The response of hPDE5 combination mutants to increasing doses of Vardenafil was tested. HCT116 cells transduced with hPDE5 constructs were treated with Vardenafil for 24 hours at doses ranging from 0.04 μM to 30 μM. Mean fluorescence intensity (MFI) was measured by FACS. Parental HCT116 and cells expressing OT-hPDE5N-019 comprising hPDE5 wildtype construct were also included as controls. The response of the combination mutants to Vardenafil was compared to the response of the single mutant construct OT-hPDE5N-020. The stabilization ratio (SR) was calculated as the fold change in GFP intensity in Vardenafil treated samples compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. The destabilizing mutation coefficient ratio was calculated as the fold change in GFP intensity in the hPDE5 mutant constructs compared to the hPDE5 wildtype construct (OT-hPDE5N-019) in the absence of the ligand. Destabilizing mutation co-efficient ratios less than 1 are desirable. Stabilization ratios greater than 1 are desired in DDs. The results and stabilization ratios are presented in Table 27.

Table 27: Vardenafil dose response of combination mutants

Dose (μM Vardenafil)	OT-hPDE5N-019		OT-hPDE5N-020		OT-hPDE5N-025		OT-hPDE5N-026	
	MFI	SR	MFI	SR	MFI	SR	MFI	SE
DMSO	62116	-	7829	-	7694	-	5156	
30	70898	1.14	75323	9.62	46109	5.99	55843	10.83
10	-	-	39089	4.99	29971	3.90	35191	6.83
3.33	-	-	35564	4.54	29520	3.84	40408	7.84
1.11	-	-	30879	3.94	12634	1.64	32868	6.37
0.37	-	-	24847	3.17	6667	0.87	14543	2.82
0.12	-	-	16866	2.15	7314	0.95	10676	2.07
0.04	-	-	14745	1.88	6174	0.80	5497	1.07

[0800] As shown in Table 27, the stabilization ratios for OT-hPDE5N-026 construct obtained across multiple doses of Vardenafil were higher than the single mutant OT-hPDE5N-020 construct. The combination mutant 025, achieved stabilization ratios much lower than the 026 construct for any given ligand dose. The destabilizing mutation coefficient obtained for the OT-hPDE5N-020 (ratio= 0.13), OT-hPDE5N-025 (ratio= 0.12), and OT-hPDE5N-026 (ratio =0.08) indicate that all constructs are destabilized in the absence of the

ligand. These data indicate that the combination mutant OT-hPDE5N-026 is strong DD candidate when the stabilizing ligand is Vardenafil.

[0801] The response of hPDE5 combination mutants to increasing doses of Tadalafil was tested. HCT116 cells transduced with hPDE5 constructs were treated with Tadalafil for 24 hours at doses ranging from 0.14 to 100 μM. Mean fluorescence intensity (MFI) was measured by FACS. Parental HCT116 and cells expressing OT-hPDE5N-019 comprising hPDE5 wildtype construct were also included as controls. The response of the combination mutants to Tadalafil was compared to the response of the single mutant construct OT-hPDE5N-020. The stabilization ratio (SR) was calculated as the fold change in GFP intensity in Tadalafil treated samples compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. The destabilizing mutation coefficient was calculated as the fold change in GFP intensity in the hPDE5 mutant constructs compared to the hPDE5 wildtype construct (OT-hPDE5N-0019) in the absence of the ligand. Destabilizing mutation coefficient less than 1 are desirable. Stabilization ratios greater than 1 are desired in DDs. The results and stabilization ratios are presented in Table 28.

Table 28: Tadalafil dose response of combination mutants

Dose (μM Vardenafil)	OT-hPDE5N-019		OT-hPDE5N-020		OT-hPDE5N-025		OT-hPDE5N-026	
	MFI	SR	MFI	SR	MFI	SR	MFI	SR
DMSO	36453	-	3806	-	6043	-	3746	-
100	58468	1.60	34041	8.94	23542	3.90	30029	8.02
33.33	-	-	44713	11.75	20464	3.39	30028	8.02
11.11	-	-	30641	8.05	13789	2.28	24499	6.54
3.7	-	-	26480	6.96	9515	1.57	17317	4.62
1.23	-	-	20458	5.38	8634	1.43	9283	2.48
0.41	-	-	13206	3.47	6141	1.02	6044	1.61
0.14	-	-	8512	2.24	5768	0.95	4682	1.25

[0802] As shown in Table 28, the stabilization ratios for OT-hPDE5N-026 construct obtained across multiple doses of Tadalafil were higher than the single mutant OT-hPDE5N-020 construct, except at the 100 μM concentration of the drug. The combination mutant OT-hPDE5-025, achieved stabilization ratios much lower than the OT-hPDE5-026 construct for any given ligand dose. The destabilizing mutation coefficient obtained for the OT-hPDE5N-020 (ratio= 0.1), OT-hPDE5N-025 (ratio= 0.17), and OT-hPDE5N-026 (ratio =0.1) indicate that all constructs are destabilized in the absence of the ligand. These data indicate that the combination mutant OT-hPDE5N-026 is strong DD candidate when the stabilizing ligand is Tadalafil.

[0803] The stabilization ratios obtained for the highest concentrations of all three ligands, Sildenafil, Vardenafil and Tadalafil for each of the constructs were compared and are shown Table 29.

Table 29: Comparative analysis of hPDE5 ligands

Ligand	Stabilization ratio			
	OT-hPDE5N-019	OT-hPDE5N-020	OT-hPDE5N-025	OT-hPDE5N-026
Sildenafil (30 μM)	1.22	7.78	2.5	9.85
Vardenafil (30 μM)	1.14	9.62	5.99	10.83
Tadalafil (100 μM)	1.60	8.94	3.9	8.02

[0804] As shown in Table 29, based on the stabilization ratios it was evident that OT-hPDE5N-026 was effectively stabilized by all three ligands, in comparison to both the single mutant construct as well as the other combination mutant construct (OT-hPDE5N-025). Both combination mutants were most effectively stabilized by Vardenafil, which is the most potent inhibitor of hPDE5. Construct OT-hPDE5N-025 was stabilized more effectively by Tadalafil than Sildenafil, although only by a small margin-this observation is noteworthy as Sildenafil is a much stronger inhibitor of hPDE5 than Tadalafil

[0805] The response of hPDE5 combination mutants to increasing duration treatment with sildenafil was tested. HCT116 cells transduced with hPDE5 constructs were treated with Sildenafil at 0.5 or 5 μM for 0-72 hours. Mean fluorescence intensity (MFI) was measured by FACS. The response of the combination mutants to Sildenafil was compared to the response of the single mutant construct OT-hPDE5-020. The stabilization ratio was calculated as the fold change in GFP intensity in Sildenafil treated samples compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. The destabilizing mutation coefficient was calculated as the fold change in GFP intensity in the hPDE5 mutant constructs compared to the hPDE5 wildtype construct (OT-hPDE5N-019) in the absence of the ligand. Destabilizing mutation coefficient less than 1 are desirable. Stabilization ratios greater than 1 are desired in DDs. The results and stabilization ratios for time course experiments with 5 or 0.5 μM are presented in Table 30 and Table 31 respectively.

Table 30: Response to Sildenafil (5 μM) over time

Time (hours)	OT-hPDE5N-020		OT-hPDE5N-025		OT-hPDE5N-026	
	MFI	Stabilization ratio	MFI	Stabilization ratio	MFI	Stabilization ratio
0	2668	-	3364	-	2769	-
72	58479	21.92	26995	8.02	90413	32.65
48	46604	17.47	22061	6.56	65233	23.56

24	20955	7.85	16705	4.97	27962	10.10
20	15529	5.82	13280	3.95	21603	7.80
16	14855	5.57	12280	3.65	17600	6.36
12	9097	3.41	9199	2.73	10451	3.77
8	5672	2.13	7021	2.09	6179	2.23
4	4236	1.59	6314	1.88	4266	1.54

Table 31: Response to Sildenafil (0.5 µM) over time

Time (hours)	OT-hPDE5N-020		OT-hPDE5N-025		OT-hPDE5N-026	
	MFI	Stabilization ratio	MFI	Stabilization ratio	MFI	Stabilization ratio
0	2727	-	3245	-	2611	-
72	58786	21.56	6906	2.13	31835	12.19
48	45754	16.78	6682	2.06	27231	10.43
24	20524	7.53	6144	1.89	17848	6.84
20	16142	5.92	6003	1.85	13318	5.10
16	14469	5.31	5600	1.73	11390	4.36
12	9058	3.32	5122	1.58	8126	3.11
8	5461	2.00	5083	1.57	5742	2.20
4	4127	1.51	5322	1.64	3870	1.48

[0806] As shown in Table 30 and Table 31, the stabilization ratios for OT-hPDE5N-026 construct obtained over time at 5 µM dose of Sildenafil were higher than the single mutant OT-hPDE5N-020 construct. However, this pattern was reversed at lower dose of 0.5 µM where the single mutant construct showed greater stabilization. The combination mutant OT-hPDE5-025, achieved stabilization ratios much lower than the OT-hPDE5-026 construct for both ligand doses at any given time. These data indicate that the choice of a suitable DD may sometime depend on the duration of the ligand treatment desired as well as the concentration of the ligand that is available for use in a system.

Example 10. Mutagenesis of DD hotspots

[0807] The analysis of mutants identified by site directed mutagenesis identified amino acid hotspots whose mutation confers destabilization and ligand dependent stabilization properties to hPDE5. To improve the DD characteristics of these constructs, the amino acid at the hotspot position is mutated to any of the known amino acids, including, but not limited to lysine, aspartic acid, glutamic acid, glutamine, asparagine, histidine, serine, threonine, tyrosine, cysteine, methionine, tryptophan, alanine, isoleucine, leucine, phenylalanine, valine, proline, and glycine. The library of hotspot mutations is generated by site directed mutagenesis and each of the mutants in the library is fused to a reporter protein e.g. AcGFP via a linker. The properties of the DDs are analyzed in the presence and absence of ligands

via western blot and FACS as previously described. Ligands that are evaluated include, but not limited Sildenafil, Vardenafil and Tadalafil.

Example 11. Optimizing biocircuit behavior

[0808] The biocircuits of the invention comprises multiple modules which can be optimized. Libraries of each of the components is generated to allow for the rapid generation of new constructs with desired behaviors. Ligand pharmacokinetics is a powerful tool for payload specific tuning *in vivo,* which can be used to shift the ligand response curve of the effector module to the left or right depending on the modulating factors. Several modulating factors are tested, including, but not limited to the ligand dose, concentrations, magnitude, duration, and route of administration. Destabilizing domains can also be modified to improve biocircuit behavior. The destabilizing domain is the core determinant of the dynamic range of the biocircuit. Depending on the DD selected, the ligand response curve of the effector module can be shifted up or down. The nature, position of the DD within the effector module as well as the number of DDs within an effector module are modified. DD selection is also altered depending on its degradation kinetics desired. Promoters that transcriptionally control the expression of the SREs are optimized. Choice of promoter impacts the basal-off state and affects the dynamic range of stabilization. Further, promoter choice contributes to the extent of stabilized payload produced. Other optimizable elements of the biocircuits include vector, translational elements, leader sequence, placement of the components within the SRE, codon selection, protease sites, linkers, and mRNA stability.

Example 12. Vardenafil dose response curve in hPDE5 mutants

[0809] Combination mutants were generated as described in Example 9. The response of hPDE5 combination mutants to increasing doses of Vardenafil was tested in HCT116 cells transduced with hPDE5 constructs were treated with Vardenafil for 48 hours at doses ranging from 0.1 to 10 μM or vehicle control (DMSO). Mean fluorescence intensity (MFI) of GFP was measured by FACS. The response of the combination mutants to Vardenafil was compared to the response of the single mutant construct OT-hPDE5N-020. The fold change in MFI over DMSO is presented in Table 32.

Table 32: Vardenafil dose response

Sildenafil (μM)	OT-hPDE5-020	OT-hPDE5-025	OT-hPDE5-026
0.01	4026	4444	3815
0.04	6970	4934	3839
0.12	14832	5133	4870
0.37	26429	5007	8107
1.11	34932	5751	21857

3.33	49739	10516	49105
10.00	51306	24927	64734

[0810] As shown in Table 32, the ligand dependent stabilization obtained for OT-hPDE5N-020 construct was observed at lower doses i.e. 0.1 and 0.3 micro molar concentrations of Vardenafil compared to the other two constructs, indicating that very low doses of the ligand are sufficient to stabilize this hPDE5 mutant. The OT-hPDE5N-026 construct did not show ligand dependent stabilization at similar doses. However, at the highest dose of Vardenafil the GFP expression obtained was much higher than OT-hPDE5N-020. In contrast, OT-hPDE5N-025 showed very little expression of GFP at lower doses and only modest GFP expression compared to the other two constructs at the higher doses. These experiments indicate that combination of single hPDE5 DD mutations produces synergistic effects not predicted by the properties of the single mutants. Thus, based on the properties of the payload of interest and the expression levels desired, suitable hPDE5 DDs may be selected.

Example 13. DD regulated immunotherapeutic agent expression in vitro

[0811] Immunotherapeutic payloads of the invention such as cytokines (e.g. IL2, IL12, IL15, IL15-IL15Ra), chimeric antigen receptors (CD19 CAR), regulatory proteins (e.g. FOXP3), safety switch (e.g. Caspase 9) are fused to any of the DDs described herein and cloned into expression vectors. Optional linkers and cleavage sites are added to optimize the confirmation of the effector module.

[0812] To test ligand dependent immunotherapeutic payload production, cells are plated in a growth media e.g. DMEM with 10% FBS and incubated overnight at 37°C, 5% CO2. Cells are transiently transfected or transduced with the constructs using Lipofectamine 2000 and incubated for 48 hrs. Following the incubation, growth media is exchanged for media containing ligands (e.g. Sildenafil, Vardenafil, and Tadalafil). Following 24-hour incubation with ligand, cells are lysed and immunoblotted using antibodies specific to the payload. For secreted payloads, such as cytokines, the growth media is harvested from the cultures expressing the effector modules of the present invention. Similar to the immunoblot, the media is assayed for the expression of the payload using methods known in the art such as ELISA and MSD assay. For cell surface expressed payloads, the expression of the payload is also assayed using methods of cell surface expression analysis that are known in the art such as flow cytometry. Expression of the payload obtained in the presence of ligand is compared to expression in the absence of ligand. Increase in the levels of the payload with increase in

ligand concentrations and/or duration of treatment is indicative of DD mediated regulation of the payload. Expression is also compared to parental untransduced cells as well as cells expressing immunotherapeutic payloads that are not appended to DD (i.e. expressed constitutively).

Example 14. DD regulated immunotherapeutic agent function *in vitro*

[0813] To test if DD regulated IL12's expression is capable of activating IL12 signaling. Human T-cells are isolated from PBMCs and activated with phytohemagglutinin (PHA, 2 μg/ml) for 3 days, followed by treatment with 50 IU/ml of Interleukin-2 (IL2) for 24 hrs. Cells are washed, resuspended in fresh media and rested for 4 hrs. T cells are transduced with DD-regulated IL12 constructs and treated with the ligand (e.g. Sildenafil, Vardenafil, and Tadalafil) based on the DD utilized or the vehicle control. Activation via IL12 results in STAT4 phosphorylation. Additionally, IL12 promotes the differentiation of naïve T cells into Th1 cells, which results in the secretion of IFN gamma from T cells. Cells are harvested and STAT4 phosphorylation is measured using STAT4 antibody (Cell Signaling Technology, Danvers, MA). Cell supernatants and cell lysates are analyzed for IFNgamma. In the presence of ligand, cells expressing DD regulated IL12 are expected to have increased STAT4 phosphorylation and increased expression of IFNgamma.

[0814] IL15 and IL15/IL15Ra fusion molecule can confer the memory phenotype on T cells and increase proliferation of NK cells (Hurton L et al. (2016), PNAS, 113: E7788-7797). This dependence of NK cell proliferation on cytokines can be used to test the functionality of DD regulated or constitutively expressed cytokines and cytokine fusion proteins. NK-92 cell activation in response to ligand treatment is evaluated by FACS using a panel of markers whose increased expression is associated with NK activation. These include NKG2D, CD71, CD69; chemokine receptors such as CCR5, CXCR4, and CXCR3, Perforin, Granzyme B and Interferon gamma (IFNg). Expression of DD regulated IL15 or IL15-IL15Ra fusion molecules is expected to increase NK cell activation. To evaluate the effect by ligand-dependent stabilization of IL15 and IL15-IL15Ra on primary T cells, T cells are transduced with DD-IL15Ra constructs. T cell proliferation and memory phenotype markers (e.g. CD62L) are measured either in the presence or absence of ligand by using flow cytometry.

[0815] To test the ability of DD regulated CD19 CAR cells to kill target cells *in vitro*, primary T cell populations are transduced with DD regulated CD19 CAR constructs are co cultured with K562 cells expressing CD19 (target cells) in the presence or absence of the ligand specific to the DD. Multiple combinations of T cells and target cells are set up. These

include DD regulated CAR expressing T cells co cultured with K562 cells (in the presence or absence of the ligand), T cells co cultured with K562 cells expressing CD19 and K562 cells expressing CD19 without T cell co culture. Additional controls include target cells only; untransduced T cells; T cells transduced with empty vector. Target cells are treated with Mitomycin C to prevent their proliferation. The K562 cells are fluorescently labelled with NucLight Red and co cultured with T cells for 300 hours. Cell death is monitored by labelling cells with Annexin V and the cell death in target K562 cells is monitored by evaluating cells that are positive for both Annexin V and NucLight Red using the IncuCyte® Live Cell Analysis System (Essen Biosciences, Ann Arbor, MI). Target cell killing is expected with the DD regulated CAR constructs only in the presence of ligand and when K562 target cells ectopically expressing CD19 are utilized. No cell killing is expected in untreated controls of the same co-culture set up and when T cells are co cultured with parental K562 cells that do not express CD19 in the presence or absence of ligand. Constitutive constructs are predicted to show cell killing both in the presence of ligand.

Example 15. DD regulated immunotherapeutic agent function *in vivo*

[0816] The ligand-dependent in vivo function of DD-regulated immunotherapeutic payloads is characterized by evaluating the ability of T cells expressing DD regulated constructs to inhibit the growth of established tumors upon treatment with the ligands of the invention. Tumor cells such as HCT116 cells are subcutaneously xenografted into mice. T cells stably transduced with a DD regulated constructs described herein are injected intravenously into mice. Approximately, two weeks after injection when the tumors reach a size of approximately 300 cubic mm, mice are dosed with the ligand (e.g. Sildenafil, Vardenafil, and Tadalafil) or vehicle control at varying concentrations every two days. Tumor volume and body weight are monitored twice a week. Plasma and tumor samples are also collected after the last dosing of the ligand and the payload levels as well as the ligand levels are measured. Tumor volume is expected to be significantly smaller in mice treated the ligand compared to vehicle treated animals. Tumor payload levels are expected to positively correlate with tumor volume.

[0817] To measure if compositions of the invention promote immune cell persistence, T cells transduced with DD-IL15/IL15Ra constructs are injected into mice. Mice are treated with the ligand (e.g. Sildenafil, Vardenafil, and Tadalafil) and monitored over a period of 40-50 days. T cells transduced with a constitutive OT-IL15-008 construct and untransduced parental T cells are injected into separate mice as controls. Blood is routinely withdrawn from the mice and tested for the presence of T cells. Mice treated with the ligand are expected to

retain T cells expressing hPDE5 DD-IL15-IL15Ra while T cells in vehicle treated mice are not expected to persist.

Example 16. Co-expression of DD regulated payloads

[0818] Toxicity related to systemic administration of interleukins can be circumvented by using CAR-T cells to deliver interleukins to the target tissue. This combinatorial approach also has greater anti-tumor activity than interleukin and CAR therapy alone. Cells are co-transfected with CD19 CAR (constitutive or DD regulated) and DD-Interleukin e.g. DD-IL2, DD- IL12, DD-IL15 and DD-IL15/IL15Ra constructs. Transfected cells are treated with stabilizing ligands depending on the DD utilized. CD19 CAR expression is evaluated by immunoblotting for CD3 zeta. DD-IL2, DD-IL12, DD-IL15 and DD-IL15/IL15Ra expression in the media is measured by ELISA.

[0819] A DD-regulated caspase 9 has the potential improve safety and minimize the toxicity associated with CD19 CAR therapy. Cells are co-transfected with CD19 CAR (constitutive or DD regulated) and DD-caspase 9 constructs. Transfected cells are treated with stabilizing ligands depending on the DD utilized. CD19 CAR and caspase 9 expression are evaluated by immunoblotting for CD3 zeta and caspase 9 respectively.

Example 17. Sildenafil and Tadalafil dose response curve in hPDE5 mutants

[0820] Combination mutations were generated as previously described in Example 9. The response of HCT 116 cells expressing hPDE5 combination mutants to increasing doses ranging from 0.1 μM to 100 μM of Tadalafil and Sildenafil for 48 hours or vehicle control (DMSO) was tested. Mean fluorescence intensity (MFI) was measured by FACS. The response of the combination mutants to ligand treatment was compared to the single mutant construct, OT-hPDE5N-020. The MFI with ligand treatment is shown in Table 33 and Table 34.

Table 33: Tadalafil dose response

Tadalafil (μM)	OT-hPDE5-020	OT-hPDE5-025	OT-hPDE5-026
0.14	3616	4328	3720
0.41	5811	5002	3804
1.23	11694	5503	4810
3.70	24185	5744	7893
11.11	40380	8299	24617
33.33	57233	15831	52927
100.00	72587	31020	84334

Table 34: Sildenafil dose response

Sildenafil (μM)	OT-hPDE5-020	OT-hPDE5-025	OT-hPDE5-026
0.14	3771	4398	3401
0.41	5463	4832	3681
1.23	10479	5031	4477
3.70	22441	4974	7625
11.11	35561	5675	24104
33.33	52029	9677	51416
100.00	101226	37494	136010

[0821] As shown in Table 33 and Table 34, ligand dose dependent stabilization was obtained with all three constructs. The dose dependent stabilization at lower doses (e.g., up to 11 μM of Sildenafil and Tadalafil) is more evident in the single mutant construct, OT-hPDE5- 020, compared to the other two constructs. At higher concentrations of ligand, both OT-hPDE5-025 and OT-hPDE5- 026 showed ligand dependent stabilization. In fact, OT-hPDE5-026 construct demonstrated much higher MFI values at 33 and 100 μM, compared to both OT-hPDE5-020 and OT-hPDE5-025. These experiments indicate that combination of single hPDE5 DD mutations produces synergistic effects not predicted by the properties of the single mutants. Thus, suitable hPDE5 DDs may be selected based on the properties of the payload of interest and the expression levels desired,

Example 18. Kinetics of hPDE5 mutants

[0822] The off kinetics of hPDE5 mutants, OT-hPDE5-020 and OT-hPDE5-026 was tested by treating HCT 116 cells expressing these constructs or the wild type control construct OT-hPDE5-019. Cells were treated with ligand for 48 hours. The media containing the ligand was removed and fresh media without the ligand was added. MFI was analyzed by FACS at 0 hours (i.e., prior to the beginning of the experiment), 48 hours after ligand treatment, as well as at several time points after the ligand washout, up until 96 hours. The stabilization ratio was calculated as the fold change in GFP intensity in ligand treated samples compared to the GFP intensity in the absence of ligand with the same construct. The results are shown in Table 35.

Table 35: Off-Kinetics

Time (hrs)	OT-hPDE5-020		OT-hPDE5-026		OT-hPDE5-019 (WT)	
	MFI	Stabilization Ratio	MFI	Stabilization Ratio	MFI	Stabilization Ratio
0	3675	-	3648	-	45512	-
48	71538	19.47	57105	15.65	102137	2.24
50	63832	17.37	41074	11.26	97225	2.14
52	51544	14.03	26926	7.38	96264	2.12
54	41800	11.37	16391	4.49	95410	2.10
56	25521	6.94	7700	2.11	81733	1.80

60	19598	5.33	5635	1.54	84323	1.85
72	8062	2.19	4062	1.11	70151	1.54
80	6427	1.75	3587	0.98	63208	1.39
96	4319	1.18	3443	0.94	55918	1.23

[0823] As shown in Table 35, the stabilization ratio of hPDE5 mutants decreased following removal of the ligand. The stabilization ratio values decreased more quickly in the combination mutant OT-hPDE5-026 compared to OT-hPDE5-020 construct suggesting the destabilization of the DD is achieved more quickly in the OT-hPDE5-026 construct. The ligand dependent stabilization as indicated by the stabilization ratio, achieved with OT-hPDE5-026 construct is lower than OT-hPDE5-020 construct, which may also contribute to the superior off kinetics seen with the OT-hPDE5-026 construct.

Example 19. Behavior of hPDE5 C terminal mutants

[0824] The ability of hPDE5 mutants to tune the expression of payloads when appended to the C terminal of the payload was tested. OT-hPDE5C-030 was compared to OT-hPDE5C-036. NIH 3T3 cells were incubated with varying doses of Sildenafil or Vardenafil for 48 hours and MFIs were analyzed by FACS. The stabilization ratio (SR) was calculated as the fold change in GFP intensity in ligand treated samples compared to the GFP intensity in the absence of ligand with the same construct. The results are shown in Table 36.

Table 36: hPDE5 C-terminal mutant's response to Sildenafil and Vardenafil

Ligand concentration (nM)	OT-hPDE5C-030				OT-hPDE5C-036			
	Sildenafil		Vardenafil		Sildenafil		Vardenafil	
	MFI	SR	MFI	SR	MFI	SR	MFI	SR
0	102	-	104	-	1476	-	1410	-
100	278	2.73	971	9.34	1639	1.11	1614	1.14
300	562	5.51	1165	11.20	1648	1.12	1656	1.03
1000	1039	10.19	1235	11.88	1780	1.21	1686	1.02
3000	1276	12.51	1299	12.49	1784	1.21	1721	1.02
10000	1442	14.14	1309	12.59	1888	1.28	1721	1.00

[0825] As shown in Table 36, OT-hPDE5C-030 construct showed stabilization ratios greater than one, indicating that both Vardenafil and Tadalafil ligand could stabilize GFP expression. As expected, the wildtype construct, OT-hPDE5C-036 did not stabilization much greater than one, indicating that virtually no stabilization was achieved with the wildtype construct.

[0826] GFP expression was also measured at 24 and 48 hours to monitor the dependence of hPDE5-DD GFP constructs on the duration of ligand exposure. The results are shown in Table 37 and Table 38A, where SR indicates stabilization ratio.

Table 37: Dose response of hPDE5 C-terminal mutants with Sildenafil treatment

Sildenafil concentration (nM)	OT-hPDE5C-030				OT-hPDE5C-036			
	24 hours		48 hours		24 hours		48 hours	
	MFI	SR	MFI	SR	MFI	SR	MFI	SR
0	108		102	-	1385	-	1476	-
100	243	2.25	278	2.73	1495	1.08	1639	1.11
300	380	3.52	562	5.51	1565	1.13	1648	1.12
1000	575	5.32	1039	10.19	1669	1.21	1780	1.21
3000	666	6.17	1276	12.51	1831	1.32	1784	1.21
10000	-	-	1442	14.14	-	-	1888	1.28

Table 38A: Dose response of hPDE5 C-terminal mutants with Vardenafil treatment

Vardenafil concentration (nM)	OT-hPDE5C-030				OT-hPDE5C-036			
	24 hours		48 hours		24 hours		48 hours	
	MFI	SR	MFI	SR	MFI	SR	MFI	SR
0	108		104	-	1360	-	1410	-
100	684	6.33	971	9.34	1439	1.06	1614	1.14
300	761	7.05	1165	11.20	1730	1.27	1656	1.17
1000	863	7.99	1235	11.88	1721	1.27	1666	1.18
3000	856	7.93	1299	12.49	1606	1.18	1721	1.22
10000	889	8.23	1309	12.59	1678	1.23	1721	1.22

[0827] Consistent with the responses measured at 48 hours, the responses measured at 24 hours showed that the hPDE5 mutant construct stabilized GFP expression as evidenced by the stabilization ratios greater than one, while the wildtype construct, OT-hPDE5C-036 showed stabilization ratios around 1, indicating no ligand dependent stabilization. Results were consistent between Sildenafil and Vardenafil treatment. It was noted that the stabilization ratios obtained at 48 hours was much greater than the values obtained at 24 hours suggesting, a time dependent stabilization of GFP expression. Similar results were obtained by western blot analysis using a GFP antibody. At 0.1μM sildenafil, modest stabilization of GFP protein levels was observed via western blot. The stabilization of GFP increased when the cells were treated with 1μM sildenafil Both 0.1μM and 1μM dose of vardenafil showed stabilization of GFP levels. These trends were observed both at 24 hours and 48 hours. All comparisons were made against cells that were not treated with either ligand.

[0828] The response of hPDE5C terminal mutants to lower doses of Vardenafil was also tested and is shown in Table 38B.

Table 38B: Dose response of hPDE5 C-terminal mutants with Vardenafil treatment

Vardenafil (nM)	MFI	Stabilization ratio
0	137	-

1	163	1.19
3	230	1.68
10	477	3.48
30	909	6.64
100	1417	10.34
1000	1789	13.06

[0829] As shown in Table 38B, the hPDE5C terminal mutant showed a dose dependent stabilization even at lower doses of Vardenafil as indicated by the increase in the stabilization ratio. Thus, even low nano molar doses of Vardenafil are sufficient to induce ligand dependent stabilization of hPDE5 DD.

Example 20. Behavior hPDE5 luciferase constructs

[0830] PDE5 derived DDs were appended to reporter payload such as luciferase to generate constructs OT-hPDE5-031, OT-hPDE5-032, OT-hPDE5-033, and OT-hPDE5-035 constructs. Such constructs may be useful to study in the dynamics of destabilization and stabilization of DDs *in vivo*. These constructs were transduced into HCT116 cells. Cells were seeded into 96 well plates at 2000 cells per well and incubated with 1 μM or DMSO Vardenafil for 48 hours. The luciferase activity was then measured using a plate reader assay. Parental untransduced cells were used as a control to measure the background fluorescence levels. The results are shown in Table 39. In Table 39, the stabilization ratio was calculated as the fold change in luciferase signal in Vardenafil treated samples compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. The destabilizing mutation coefficient was calculated as the fold change in GFP intensity in the hPDE5 mutant constructs compared to the hPDE5 wildtype construct (OT-hPDE5-031) in the absence of the ligand. Destabilizing mutation coefficients less than 1 are desirable. Stabilization ratios greater than 1 are desired in DDs.

Table 39: Stability of Luciferase constructs

Construct	Control (DMSO)	Vardenafil	Destabilizing mutation co-efficient	Stabilization ratio
Parental cells	1367.47	3824.04	-	-
OT-hPDE5-031	85429.26	127499.78	-	1.49
OT-hPDE5-032	88881.46	174814.64	1.04	1.97
OT-hPDE5-033	53239.88	88918.04	0.62	1.67
OT-hPDE5-035	96460.45	269718.66	1.13	2.80

[0831] The luciferase signal intensity observed in parental cells that did not express the construct indicated that some of the signal was likely background noise. Construct, OT-

hPDE5-033 showed the lowest destabilizing mutation coefficient indicating the construct is destabilized. Increase in stabilization ratios was observed with all constructs including the wildtype hPDE5 construct, OT-hPDE5-031. Construct OT-hPDE5-035 showed the highest stabilization ratio indicating the strongest ligand dependent stabilization. Among the constructs tested, OT-hPDE5-033 showed destabilization in the absence of ligand and stabilization in the presence of ligand.

Example 21. Mutagenesis of the amino acid 732 of hPDE5

[0832] The analysis of mutants identified by site directed mutagenesis identified amino acid hotspots whose mutation confers destabilization and ligand dependent stabilization properties to hPDE5. The amino acid at position 735 was chosen for the further analysis since the hPDE5 (R732L) mutation possessed the properties described above. To improve the DD characteristics of this DD, the amino acid at the position 732 was mutated to any of the known amino acids, including, but not limited to, aspartic acid, glutamic acid, glutamine, asparagine, histidine, serine, threonine, tyrosine, cysteine, methionine, tryptophan, alanine, isoleucine, leucine, phenylalanine, valine, proline, and glycine. The library of mutations was generated by site directed mutagenesis and each of the mutants in the library was fused to a reporter protein e.g. AcGFP via a linker and transduced into HCT116 cells. The properties of the DDs were analyzed in the presence and absence of ligands via FACS as previously described. Ligands that were evaluated included, but not limited Sildenafil, and Vardenafil. The results are shown in Table 40A and Table 40B.

Table 40A: Ligand responsive behavior of hotspot constructs

Construct	Mutation	Vardenafil		Sildenafil	
		0 µM (DMSO)	1 µM	0 µM (DMSO)	10 µM
OT-hPDE5-001	-	161	294	989	219
OT-hPDE5-009	R732L	182	173	143	122
OT-hPDE5-064	R732G	176	854	298	288
OT-hPDE5-065	R732A	175	853	288	348
OT-hPDE5-066	R732V	150	507	189	113
OT-hPDE5-067	R732I	151	587	201	170
OT-hPDE5-068	R732P	355	310	379	361
OT-hPDE5-069	R732F	189	943	233	351
OT-hPDE5-070	R732W	301	179	248	158
OT-hPDE5-071	R732Y	302	345	397	648
OT-hPDE5-072	R732H	308	328	352	710
OT-hPDE5-073	R732S	566	399	760	746
OT-hPDE5-074	R732T	235	270	276	546
OT-hPDE5-075	R732D	294	422	298	394
OT-hPDE5-076	R732E	276	212	295	316

OT-hPDE5-077	R732Q	305	289	353	553
OT-hPDE5-078	R732N	313	290	315	516
OT-hPDE5-079	R732M	316	337	285	503
OT-hPDE5-080	R732C	526	349	499	707
OT-hPDE5-081	R732K	113	423	165	765

Table 40B: Stabilization ratio and Destabilizing mutation coefficient of hotspot constructs

Construct	Mutation	Vardenafil		Sildenafil	
		Destabilizing mutation coefficient	Stabilization ratio	Destabilizing mutation coefficient	Stabilization ratio
OT-hPDE5-001	-	-	1.83	-	0.22
OT-hPDE5-009	R732L	1.13	0.95	0.14	0.85
OT-hPDE5-064	R732G	1.09	4.85	0.3	0.97
OT-hPDE5-065	R732A	1.09	4.87	0.29	1.21
OT-hPDE5-066	R732V	0.93	3.38	0.19	0.6
OT-hPDE5-067	R732I	0.94	3.89	0.2	0.85
OT-hPDE5-068	R732P	2.2	0.87	0.38	0.95
OT-hPDE5-069	R732F	1.17	4.99	0.24	1.51
OT-hPDE5-070	R732W	1.87	0.59	0.25	0.64
OT-hPDE5-071	R732Y	1.88	1.14	0.4	1.63
OT-hPDE5-072	R732H	1.91	1.06	0.36	2.02
OT-hPDE5-073	R732S	3.52	0.7	0.77	0.98
OT-hPDE5-074	R732T	1.46	1.15	0.28	1.98
OT-hPDE5-075	R732D	1.83	1.44	0.3	1.32
OT-hPDE5-076	R732E	1.71	0.77	0.3	1.07
OT-hPDE5-077	R732Q	1.89	0.95	0.36	1.57
OT-hPDE5-078	R732N	1.94	0.93	0.32	1.64
OT-hPDE5-079	R732M	1.96	1.07	0.29	1.76
OT-hPDE5-080	R732C	3.27	0.66	0.5	1.42
OT-hPDE5-081	R732K	0.7	3.74	0.17	4.64

[0833] The destabilizing mutation coefficients and stabilization ratios obtained for each construct with the indicated ligands were analyzed to identify constructs which possessed the lowest destabilizing mutation coefficient ratio and a second sort of the data was then performed to identify constructs with the highest stabilization ratio. This analysis allowed the identification of constructs with both the lowest destabilizing mutation coefficient that also possessed the highest stabilization ratios. Based on this analysis, it was identified that virtually all mutants tested showed destabilizing mutation coefficients less than one for the DMSO control of Sildenafil treatment, indicating that all constructs are destabilized in the absence of sildenafil. In the presence of Sildenafil, OT- hPDE5-081 construct with arginine to lysine substitution showed high sildenafil dependent stabilization ratio. Similar analysis of

the constructs with Vardenafil identified OT-hPDE5-081, OT-hPDE5-066, OT-hPDE5-067, and OT-hPDE5-065 as having a low destabilizing mutation coefficient and high-ligand dependent stabilization ratios. Other constructs with low destabilizing mutation coefficients and high stabilization ratios include OT-hPDE5-067, OT-hPDE5-065, OT-hPDE5-069, OT-hPDE5-074, and OT-hPDE5-075.

[0834] The response of select mutants to increasing doses of Sildenafil, Vardenafil and Tadalafil was also tested in HCT 116 cells treated with the ligand for 48 hours. The MFI values obtained with each ligand treatment are shown in Table 41A, Table 41B and Table 41C.

Table 41A: Vardenafil Dose Response

Vardenafil (μM)	OT-hPDE5-065	OT-hPDE5-067	OT-hPDE5-069	OT-hPDE5-074	OT-hPDE5-075
0	2551	1810	2188	2854	4336
0.01	2551	1810	2188	2854	4336
0.04	8345	3356	8468	6862	7350
0.12	10946	4874	10941	13187	15637
0.37	13850	7855	12987	28895	25047
1.11	15202	11777	13754	33075	37828
3.33	16783	14531	14705	41788	44499
10	18945	17645	17021	48946	50822
30	22548	24322	20693	67364	70645
1000	22548	24322	20693	67364	70645

Table 41B: Sildenafil Dose Response

Sildenafil (μM)	OT-hPDE5-065	OT-hPDE5-067	OT-hPDE5-069	OT-hPDE5-074	OT-hPDE5-075
0.01	808	579	688	856	1192
0.04	1025	612	916	1041	1270
0.12	1270	592	1205	1113	1337
0.37	1931	771	2002	1835	1867
1.11	2655	1040	2711	3355	3108
3.33	3769	1709	3555	6896	6171
10	4716	2733	4427	12407	13971
30	5694	4197	5449	21258	21120
1000	5694	4197	5449	21258	21120

Table 41C: Tadalafil Dose Response

Tadalafil (μM)	OT-hPDE5-065	OT-hPDE5-067	OT-hPDE5-069	OT-hPDE5-074	OT-hPDE5-075
0.01	752	498	631	825	1163

0.14	1259	540	1193	1068	1361
0.41	2066	712	2075	1655	1548
1.23	3412	1041	3134	3433	2504
3.7	4690	1745	4294	6697	4821
11.11	5126	2746	4734	12843	10583
33.33	6264	3970	5293	17164	16956
100	6301	5487	5867	21113	22630
1000	6301	5487	5867	21113	22630

[0835] OT- hPDE5-074 with an arginine to threonine substitution showed the strongest increase in GFP expression at the highest dose, with all three ligands tested. At doses lower than 1 μM of Vardenafil, all constructs showed ligand dependent stabilization. At doses of Sildenafil lower than 1 μM, OT-hPDE5-069, OT-hPDE5-074 and OT-hPDE5-075 showed ligand dependent stabilization. With doses of Tadalafil lower than 1 μM, OT-hPDE5-065, OT-hPDE5-069 and OT-hPDE5-074 showed ligand dependent stabilization. By mutagenesis of the R732 locus, DDs with a variety of properties were obtained. The selection of a particular DD may be made based on the payload utilized and the extent of expression desired with the payload. The EC50 values for each of the constructs with each of the ligands is shown in Table 41D.

Table 41D: EC_{50} for Hotspot Mutants

Ligand	OT-hPDE5-065	OT-hPDE5-067	OT-hPDE5-069	OT-hPDE5-074	OT-hPDE5-075
Vardenafil	0.30	2.20	0.28	1.47	1.44
Sildenafil	2.08	6.90	1.76	7.50	7.04
Tadalafil	1.45	14.28	1.33	8.64	14.54

[0836] These results are consistent with the western blot analysis of GFP protein levels in HCT 116 cells stably transduced with these mutants. The following constructs showed a strong stabilization of GFP levels in the presence of vardenafil and when compared to DMSO controls: OT-hPDE5-009, OT-hPDE5-064, OT-hPDE5-065, OT-hPDE5-068, OT-hPDE5-070, OT-hPDE5-071, OT-hPDE5-072, OT-hPDE5-073, OT-hPDE5-074, OT-hPDE5-075, OT-hPDE5-076, OT-hPDE5-077, OT-hPDE5-078, OT-hPDE5-079, and OT-hPDE5-080. Modest ligand dependent stabilization of GFP levels was observed with OT-hPDE5-066, OT-hPDE5-067, OT-hPDE5-069, and OT-hPDE5-081. All samples showed equal protein loading as measured by GAPDH protein levels.

Example 22: Dynamic range of hPDE5 regulation

[0837] HCT116 cells were transduced with hPDE5-GFP constructs, OT-hPDE5-083, OT-hPDE5-084, OT-hPDE5-085, and OT-hPDE5-094 and incubated with the indicated

concentrations of ligand for 48 hours. GFP fluorescence was measured by FACS. The fold change in GFP expression over untreated DMSO control is shown in Table 42A, Table 42B and Table 42C for vardenafil, sildenafil and tadalafil respectively.

Table 42A: Vardenafil dose response

Vardenafil (log)	OT-hPDE5-83	OT-hPDE5-84	OT-hPDE5-85	OT-hPDE5-94
1.477	20.664	13.612	4.507	16.171
1.000	18.207	12.030	2.178	13.462
0.523	18.327	10.260	1.277	13.230
0.046	17.229	7.465	1.078	12.550
-0.431	16.143	4.374	1.022	11.992
-0.908	13.764	2.258	1.025	9.770
-1.386	10.108	1.323	1.015	5.477
-1.863	4.673	0.834	1.030	2.303
-2.340	2.575	0.741	1.034	1.412
-2.817	1.744	0.725	1.047	1.105

Table 42B: Sildenafil dose response

Sildenafil (log)	OT-hPDE5-83	OT-hPDE5-84	OT-hPDE5-85	OT-hPDE5-94
2.000	11.370	14.212	1.909	11.290
1.523	12.925	15.247	1.509	13.091
1.046	12.066	10.028	1.212	12.344
0.569	10.587	5.408	1.091	10.615
0.092	9.190	2.822	0.995	8.165
-0.386	6.849	1.640	1.040	5.536
-0.863	4.225	1.249	0.993	2.540
-1.340	2.295	1.106	1.007	1.397
-1.817	1.434	1.025	1.013	1.134
-2.294	1.136	1.024	0.966	0.997

Table 42C: Tadalafil dose response

Tadalafil (log)	OT-hPDE5-83	OT-hPDE5-84	OT-hPDE5-85	OT-hPDE5-94
2.000	12.074	14.919	1.498	12.606
1.523	11.481	13.740	1.224	11.910
1.046	9.897	8.083	1.011	11.144
0.569	8.403	4.360	0.945	9.902
0.092	5.445	2.312	0.973	7.992
-0.386	2.725	1.472	0.907	5.049
-0.863	1.563	1.225	0.946	2.887
-1.340	1.121	1.034	0.938	1.402
-1.817	1.095	1.013	0.976	1.077
-2.294	1.045	0.985	0.942	1.064

[0838] As shown in Table 42A, Table 42B and Table 42C, dynamic regulation of hPDE5 DDs was observed with OT-hPDE5-083, OT-hPDE5-084, and OT-hPDE5-085. The hPDE5 wildtype construct shown little to no ligand dependent stabilization with all three ligands. The stabilization concentration 50 or (SC_{50}), which is the concentration of ligand required to achieve 50% stabilization, was also calculated for all four constructs with each of the ligands and the results are shown Table 42D.

Table 42D: Stabilization Concentration 50 (SC_{50}) of hPDE5 DDs

Ligand	OT-hPDE5-83	OT-hPDE5-84	OT-hPDE5-85	OT-hPDE5-94
Vardenafil	0.04	1.15	>30	0.07
Sildenafil	0.38	6.82	>30	0.67
Tadalafil	1.97	9.54	>100	0.77

[0839] Taken together these results indicate that structure-guided mutagenesis of ligand-binding site in PDE5 generates 23 nM ligand-DD interaction. OT-hPDE5-083 with Y612F, R732L, was able to bind to Vardenafil with SC_{50}, of 23 nM suggesting potent DD-ligand interaction.

Example 23. DD regulated IL15-IL15-Ra expression in vitro

[0840] Immunotherapeutic payloads of the invention such as, IL15-IL15Ra fusion proteins, were fused to any of the DDs described herein and cloned into expression vectors, such as pLVX and pELNS vectors. To test ligand dependent IL15-IL15Ra production, HEK293T cells were transiently transfected with the constructs. Cells were then plated in DMEM with 10% FBS and incubated overnight at 37°C, 5% CO2. The growth media was exchanged for media containing ligand, e.g. Vardenafil at 10 µM. Following 48-hour incubation with ligand, cells were lysed and immunoblotted using antibodies specific to IL15Ra. hPDE5-DDs were able to regulate IL15Ra levels in the presence of Vardenafil with all three constructs tested OT-IL15-043, OT-IL15-044 and OT-IL15-045. In contrast, the IL15Ra levels remained unchanged both in the presence and absence of ligand with the constitutive construct, OT-IL15-008. It was noted that the ligand dependent stabilization was accompanied by an upward shift in the mobility of IL15Ra only in the presence of Vardenafil, indicating that the stabilization is likely accompanied by a post translation protein modification. Uniform loading of samples was demonstrated using actin as a loading control.

[0841] The effects of vector backbone on the expression of the payload were examined by cloning the OT-IL15-031 construct into the pELPS vector backbone to generate the OT-IL15-079 construct. The constructs were transduced into HEK293T cells and IL15Ra expression was assayed as described above. Only OT-IL15-031 showed vardenafil dependent stabilization of IL15Ra protein levels. Only modest ligand dependent stabilization was observed with the OT-IL15-079 construct in the presence of vardenafil.

[0842] The IL15 levels were also examined using the MSD assay. The growth media was harvested from the cells expressing IL15-IL15Ra and that were exposed to 10 μM Vardenafil or vehicle control for 48 hours. The results are shown in Table 43, where the stabilization ratio was defined as the ratio of expression, function or level of a protein of interest, i.e. IL15-IL15Ra in response to the stimulus, i.e. Vardenafil; to the expression, of the IL15-IL15Ra in the absence of the stimulus, i.e. DMSO control. The destabilization ratio was calculated as the ratio of expression, of IL15Ra in the absence of the stimulus specific to the effector module i.e. Vardenafil to the expression, function or level of the protein of interest, that is expressed constitutively (OT-IL15-008) and in the absence of the stimulus specific to the SRE. Stabilization ratios greater than one and destabilization ratios less than one are desired.

Table 43: IL15 levels (pg/ml)

Construct	Control	Vardenafil	Destabilization ratio	Stabilization ratio
OT-IL15-008	710.73	799.39	-	1.12
OT-IL15-043	63.37	93.63	0.09	1.48
OT-IL15-044	193.09	203.21	0.27	1.05
OT-IL15-045	255.05	320.39	0.36	1.26

[0843] As shown in Table 43, all three hPDE5 regulated constructs showed destabilization ratios less than one indicating destabilization in the absence of ligand. OT-IL15-043 appeared to be the most destabilized construct. It was also the most ligand-stabilized construct, with the highest stabilization ratio.

[0844] Expression of OT-IL15-031 construct was also analyzed in HCT-116 cells via western blot. The cells were exposed to 10 μM Vardenafil for 48 hours and IL15 and IL15Ra levels were analyzed by western blot. Similar to the HEK293T cells, HCT 116 cells also displayed a Vardenafil dependent stabilization with a concomitant upward shift in mobility of IL15Ra protein indicating protein modifications.

Example 24. Effect of linker on DD regulation of IL15-IL15Ra

[0845] The effect of the type of linker used and the length of the linker on the regulation of the expression of the payload was tested. IL15-IL15Ra fusion constructs were linked to the hPDE5 (R732L) DD using GSGSGS (SEQ ID NO. 8330) as the linker (as in OT-IL15-111), or GSGSGSGS (SEQ ID NO. 8331) as the linker (as in OT-IL15-112) or using GSGSGGGSGS (SEQ ID NO. 8332) as the linker (as in OT-IL15-113). The IL15 portion of the construct was tagged with a Flag tag while the IL15Ra portion was tagged with a HA tag. These tags allow both the components of the construct to be tracked individually in experiments. The constructs were transiently transfected into HEK293T cells and then incubated with 1 μM Vardenafil for 24 hours. The properties of the DDs regulated IL15-IL15Ra payloads were analyzed in the presence and absence of ligands via FACS using the HA antibody as previously described. The results are shown in Table 44, where the stabilization ratio was defined as the ratio of expression, function or level of a protein of interest, i.e. IL15-IL15Ra in response to the stimulus, i.e. Vardenafil; to the expression, of the IL15-IL15Ra in the absence of the stimulus, i.e. DMSO control treated samples.

Table 44: % HA positive cells with different linkers

Construct Name	Control	Vardenafil	Stabilization ratio
OT-IL15-111	37.5	63.2	1.69
OT-IL15-112	41.6	74.6	1.79
OT-IL15-113	42	69.1	1.65

[0846] As shown in Table 44, all three constructs each with a different linker resulted in a somewhat similar stabilization ratio, indicating that linker length and identity did not impact regulation of the payload by the DD. All three constructs also had a stabilization ratio greater than one suggesting that the payload expression was stabilized in the presence of the ligand. Among the three constructs tested OT-IL15-112 showed a slightly higher stabilization ratio than the other two constructs indicating that the use of the GSGSGSGS linker may result in a slightly improved ligand dependent stabilization.

Example 25. DD regulated CD19 CAR expression and function

[0847] Immunotherapeutic payloads of the invention such as CD19 CAR were fused to any of the DDs described herein and cloned into expression vectors pLVX and pELNS vectors. In this manner, OT-CD19-052 (hPDE5 (WT)) and OT-CD19-053 (hPDE5(R732L)). The HA tag was added to enable the easy detection of the chimeric proteins.

[0848] To test ligand dependent CD19 CAR production, NIH 3T3 cells were transiently transfected with the constructs. Cells were then plated in a growth media e.g. DMEM with 10% FBS and incubated overnight at 37°C, 5% CO2. The growth media was exchanged for media containing ligand, at various concentrations of Vardenafil ranging from 30 nM to 10,000 nM. Following 48-hour incubation with ligand, cells were analyzed by FACS using the HA antibody and the mean fluorescence intensity (MFI) was calculated. The results are shown in Table 45A, where the stabilization ratio was defined as the ratio of expression, function or level of a protein of interest, i.e. CD19 CAR in response to the stimulus, i.e. Vardenafil; to the expression, of the CD19 CAR in the absence of the stimulus, i.e. DMSO control. Stabilization ratios greater than one are desired.

Table 45A: CD19 CAR expression

Vardenafil (nM)	OT-CD19-052 (WT)	OT-CD19-053 (R732L)	
	MFI	MFI	Stabilization ratio
0	0	1336	-
30	9125	3066	2.29
100	9592	4674	3.50
300	10509	5732	4.29
1000	10328	6738	5.04
10000	9285	3931	2.94

[0849] As shown in Table 45A, a stabilization ration greater than 1 was observed with all doses of Vardenafil, and even with the lowest concentration of Vardenafil (30nM) suggesting that low doses of ligand may be sufficient to achieve ligand dependent stabilization. It was also noted that the stabilization ratio obtained at the highest concentration of ligand i.e. 10,000 nM was lower than the ratio obtained with 1000nM ligand suggesting a bimodal pattern of stabilization.

[0850] The dose dependent regulation of OT-CD19-052 and OT-CD19-053 was measured in HEK 293 cells transfected with 2ug DNA and stably selected using 2ug/ml puromycin. CAR surface expression was detected using Protein L staining following 24 hours of ligand treatment at the indicated concentrations. The median Protein L fluorescence is shown in Table 45B.

Table 45B: Ligand dose dependent CAR expression

Ligand (nM)	Tadalafil			Sildenafil			Vardenafil		
	OT-CD19-052	OT-CD19-053	Empty Vector (pLVX)	OT-CD19-052	OT-CD19-053	Empty Vector (pLVX)	OT-CD19-052	OT-CD19-053	Empty Vector (pLVX)
0.15	21122	4064	77	14703	2848	89.8	17946	4202	87.9

0.46	15335	3501	75.8	15335	3304	87	17746	4064	92
1.39	14662	3501	78.8	13143	3250	83.9	16175	4604	89.8
4.22	14377	3341	77	13901	2810	85.7	16450	5977	93.9
12.79	10773	3599	78.8	9419	2976	81.8	17646	9210	92
38.74	14098	4042	80	12083	3268	84.8	16175	13329	94.8
117.41	18354	6302	77	15037	3589	83	19856	20594	93.9
355.78	13785	11235	72.9	13901	5274	83.9	22406	23175	95.8
1078.11	18200	15640	80	13708	8054	88.8	22343	31138	97.7
3267.00	15950	21301	75.8	14337	13291	84.8	24933	31226	100
9900.00	21421	24654	75.8	17746	23371	84.8	26824	36249	110
30000.00	27902	33691	77	25003	25215	84.8	30617	35945	140

[0851] As shown in Table 45B, only OT-CD19-053 responded to increasing doses of ligand with increase surface CAR expression, but not the WT construct OT-CD19-052. This was observed with all three ligands. However, the highest levels of CAR expression were observed with increasing doses of vardenafil. The EC50 for vardenafil, tadalafil and sildenafil were determined to 25 nM, 380 nM, and 1500 nM respectively.

[0852] Cells were also treated with ligand for varying durations of time with ligand concentrations shown in Table 45C and Protein L expression was measured using FACS. The results are shown in Table 45C and Table 45D. Stabilization ratios are shown in Table 45E.

Table 45C: Time dependent increase in CAR expression with Vardenafil

Hours	Vardenafil 10 µM			Vardenafil 1 uM	DMSO		
	Empty Vector (pLVX)	OT-CD19-052	OT-CD19-053	OT-CD19-053	OT-CD19-052	OT-CD19-053	Empty Vector (pLVX)
0	1412	5188	1486	65.9	5060	1386	71.9
2	2863	11643	2918	78.7	5545	1270	71
4	3654	11258	3526	76.8	5408	1274	71.9
24	6624	10439	8005	83.7	5845	1241	71
48	7764	8118	8489	93.8	6128	1287	71
72	9282	7961	9788	92.8	6442	1329	65.9

Table 45D: Time dependent increase in CAR expression with Tadalafil and Sildenafil

Hours	Tadalafil 10 µM			Tadalafil 1 µM	Sildenafil 10 µM			Sildenafil 1 µM
	Empty Vector (pLVX)	OT-CD19-052	OT-CD19-053	OT-CD19-053	Empty Vector (pLVX)	OT-CD19-052	OT-CD19-053	OT-CD19-053
0	65	4909	1336	1368	62.8	5469	1534	1372
2	65	5911	2778	2451	65	8536	2801	2278
4	65	6196	3032	2950	63.7	8560	3256	2617
24	65	8608	6606	4346	62.8	8118	5499	3159
48	62.8	8827	7384	4683	62.8	7404	5927	3283
72	58.7	8118	8050	6027	58.7	6111	5188	3506

Table 45E: Time dependent increase in CAR expression

Time (hrs)	Tadalafil 10 µM		Tadalafil 1 µM	Sildenafil 10 µM		Sildenafil 1 µM	Vardenafil 10 µM	Vardenafil 1 µM	
	OT-CD19-052	OT-CD19-053	OT-CD19-053	OT-CD19-052	OT-CD19-053	OT-CD19-053	OT-CD19-052	OT-CD19-053	OT-CD19-053
0	0.97	0.96	0.99	1.08	1.11	0.99	1.03	1.07	0.05
2	1.07	2.19	1.93	1.54	2.21	1.79	2.10	2.30	0.06
4	1.15	2.38	2.32	1.58	2.56	2.05	2.08	2.77	0.06
24	1.47	5.32	3.50	1.39	4.43	2.55	1.79	6.45	0.07
48	1.44	5.74	3.64	1.21	4.61	2.55	1.32	6.60	0.07
72	1.26	6.06	4.53	0.95	3.90	2.64	1.24	7.36	0.07

[0853] The analysis of the stabilization ratios indicated that OT-CD19-053 is stabilized by all three ligands with increased duration of incubation time with ligand. As expected, 10 µM dose of ligand showed much greater expression of CAR than the 1 µM dose. Regulation was evident even at the lower doses.

[0854] Constructs OT-CD19-130, OT-CD19-131 and OT-CD19-132 were cloned into pELNS vectors and transduced into T cells. Three different volumes of lentiviral supernatant were tested on cells i.e. 1 µl, 10 µl and 20 µl. Following transduction, cells were treated with 10 µM Vardenafil or left untreated for 24 hours beginning on day 4. Untransduced cells were also included as negative control. On day 5, the percentage CAR positive cells were measured by FACS using 1 µg /ml CD19 Fc. The results are shown in Figure 19A.

[0855] As shown in Figure 19A, all three constructs showed a viral dose dependent increase in the percentage of CAR positive cells, in the presence of Vardenafil. Although similar trends were observed in untreated controls, the percentage of CAR positive cells observed with no vardenafil treatment was substantially lesser than the vardenafil treated controls. Among the three constructs, OT-CD19-132 showed lowest basal expression of the CAR in the absence of ligand and the highest percentage of CAR positive cells in the presence of vardenafil. Similar observations were made when comparing the percentage CAR positive cells obtained with different constructs using 20 µl of virus as shown in Figure 19B, where a shift in the number of cells that are CAR positive was observed in vardenafil treated cells (labelled treatment) compared to untransduced as well as untreated cells.

[0856] T cells maintained in culture for over 10 days reach quiescence and accordingly T cells transduced with OT-CD19-131 did not show vardenafil dependent CAR expression at day 11. However, restimulation of the same T cells on day 11 with CD3/CD28 beads (at 3:1 bead: cell ratio, for 24 hours concomitant with ligand treatment) restored vardenafil dependent CAR expression in T cells transduced with 20 µl of virus (Figure 19C). The effect of restimulation on the expression of the CAR was evident at all concentrations of the virus

tested Figure 19D. Taken together, these data show that CD19 CARs operably linked to hPDE5 DDs demonstrate ligand dependent CAR expression. Further, ligand responsiveness and subsequent CAR expression may be restored in quiescent T cells by restimulation with CD3/CD28 beads.

[0857] To test the effect on different ligands on hPDE5-CAR constructs, the constructs were packaged into plasmids and transduced into T cells using 10 µl of virus. On day 9, T cells expressing either OT-CD19-111, OT-CD19-130, OT-CD19-131 or OT-CD19-132 were treated with varying doses of ligand ranging from 0.1 nM to 10 µM for 24 hours. The constitutive construct OT-CD19-063 was included as the positive control, and the cells transduced with the empty vector (pELNS) served as the negative control. Three different ligands for hPDE5 were tested including, Sildenafil, Tadalafil and Vardenafil. Cells were analyzed by FACS and sorted for singlets/live CAR positive cells. The results are shown in Figure 19E. Among the three ligands tested, all constructs were most responsive to Vardenafil, followed by Tadalafil and Sildenafil. As seen previously, the OT-CD19-131 and OT-CD19-132 showed lower basal expression, and had the higher EC50 values than the other constructs. The experiments were repeated with the OT-CD19-131 construct by transducing T cells with different volumes of virus transduced into T cells using 10µL, 2µL, 0.4µL, or 0.08µL of virus and the CAR expression was measured by FACS, both in the presence of all three ligands and in the absence of the ligands. The results are shown in Table 45F, where "basal % CAR+" indicates the percentage of CAR positive cells in the absence of ligand, and the "Max % CAR+," indicates the maximum expression of the CAR in the presence of ligand. The EC50 is defined as the concentration of a drug/ligand that gives half-maximal response. The response herein refers to the expression of the chimeric antigen receptor.

Table 45F. hPDE5 regulation of CD19-CAR

Construct	Virus Volume (uL)	Basal % CAR+	Max % CAR+	Vardenafil EC50 (nM)	Tadalafil EC50 (nM)	Sildenafil EC50 (nM)
Empty vector (pELNS)	1	0.2	0.2	-	-	-
OT-CD19-063	1	30.0	30.0	-	-	-
OT-CD19-131	10	3.6	37.5	140.0	1312.2	>10000.0
OT-CD19-131	2	2.0	29	157.0	1402.8	>10000.0
OT-CD19-131	0.4	0.9	16.1	197.7	2511.9	>10000.0
OT-CD19-131	0.08	0.4	5.0	220.8	1857.8	>10000.0

[0858] Among the three ligands tested, higher transduction volume increased the maximum CAR expression level achieved, but did not alter ligand EC50 values.

[0859] To test how rapidly hPDE5-CAR can be stabilized with ligand, the indicated constructs were tested in T cells. T cells from donor were thawed and activated overnight in the presence of CD3/CD28 Dynabeads at a 3:1 bead: cell ratio. The following day, cells were transduced with 10µL lentivirus prepared from OT-CD19-063, OT-CD19-111, OT-CD19-130, OT-CD19-131, and OT-CD19-132 constructs. Cells were expanded by addition of fresh media over the course of 10 days, maintaining cells around 0.5x10^6 cells/mL, then frozen. Expanded T cells were thawed and restimulated with CD3/CD28 beads for 48 hours. Cells were treated with 10µM Tadalafil or Vardenafil at various times such that all conditions received 48 hr of bead stimulation with either 0, 2, 4, 6, 24, or 48 hours of ligand treatment. CAR surface expression was measured with 1µg/mL CD19-Fc. The results are shown in Figure 19F. In activated T cells, CAR surface expression occurred at nearly maximum levels by 2 hours after ligand addition.

[0860] To test whether CD19-CARs showing regulated expression also show regulated cytotoxicity, transduced T cells were tested in a cytotoxicity assay against the CD19-expressing Nalm6 tumor cell line, T cells from a human donor were thawed and activated overnight in the presence of CD3/CD28 Dynabeads at a 3:1 bead: cell ratio. The following day, cells were transduced with 10µL lentivirus from OT-CD19-063, OT-CD19-111, OT-CD19-130, OT-CD19-131, and OT-CD19-132. Cells were expanded by addition of fresh media over the course of 10 days, maintaining cells around 0.5x10^6 cells/mL, then frozen. Expanded T cells were thawed and cocultured with CD19 expressing target cells, Nalm6-Katushka, at effector: target cell ratio of 10:1 for 6 days, in the absence or presence of Tadalafil. Images captured on the Incucyte Zoom were analyzed for proliferation of target cells by measuring red fluorescence over time (Total NucRed Area). In the absence of ligand, i.e. DMSO, OT-CD19-131 and OT-CD19-132 showed target cell proliferation as measured by the increase in total NucRed area (red fluorescence). Constructs, OT-CD19-130, OT-CD19-111 showed very low levels of red fluorescence indicating basal activity that was comparable to the constitutively expressed CAR construct OT-CD19-063. All constructs tested showed a reduction in red fluorescence when treated with either 3µM Tadalafil or 10µM Tadalafil that was comparable to the red fluorescence levels observed with the constitutively expressed CAR. As expected, the untransduced cells showed high levels of red fluorescence both in the presence and absence of ligand.

[0861] Constructs showing higher basal CAR expression in T cells, OT-CD19-111 and OT-CD19-130, inhibited target cell growth in the absence of tadalafil. T cells transduced with OT-CD19-132, which had the highest Tadalafil EC50 in terms of CAR expression, required higher concentrations of ligand to generate an *in vitro* functional response.

[0862] To measure cytokine levels in T cells, supernatants from the previous coculture assay were harvested at 48 hours and analyzed for IFNγ and IL2 levels by MSD assay (Meso Scale Discovery's ELISA). The results are shown in Figure 19G. The cytokine levels at the following effector to target cell rations: 10:1, 3:1,1:1, 0.3:1, and 0.1:1. High levels of both IFNγ and IL2 are produced by OT-CD19-131 transduced T cells when co-cultured with Nalm6 targets only in the presence of 3μM Tadalafil, correlating with the cytotoxicity observed.

[0863] To confirm the cytotoxicity and cytokine secretion is directly related to CAR expression, OT-CD19-131 transduced T cells were cocultured with Nalm6-Katushka target cells at 10:1 effector: target cell ratio for 6 days in the presence of a dose titration of Tadalafil from 10 μM to 10 nM. The fluorescence of Nalm6 cells was measured over a period of 6 days in response to the following doses of tadalafil: 0.01μM, 0.04μM, 0.12 μM, 0.37μM, 1.11μM, 3.33 μM, 10 μM. Tadalafil doses at 0.37μM, 1.11μM, 3.33 μM, 10 μM showed a reduction in Nalm6 proliferation over 6 days. Lower concentrations (<0.37μM) tadalafil did not cause a reduction in Nalm6 fluorescence, in fact, Nalm6 cells continue to proliferate over the span of 6 days. Significant CAR expression was detected by FACS using CD19-Fc at Tadalafil concentrations at or above 300nM. This CAR expression corresponded to Tadalafil dose-dependent cytotoxicity (Figure 19H) and cytokine secretion of IFNγ and IL2 (Figure 19I).

[0864] The functionality of the CAR transduced T cells was also tested *in vitro.* T cells were transduced with OT-CD19-131 or the constitutive construct OT-CD19-063. Cells were then frozen. Prior to the experiment, T cells were thawed overnight, and cocultured with Nalm6 target cells stably expressing Katushka RFP. Nalm6 cells express high levels of CD19 antigen and are hence ideal target cells in cell killing assay that test CD19 CAR constructs. T cells were mixed with Nalm6 cells at an effector cell to target cell (E: T) ratio of 5:1 for 12 hours in the presence of 10 μM vardenafil or DMSO. Target cell apoptosis was determined by measuring Annexin V fluorescence over time using the Incucyte instrument. Cell killing is measured as the ratio of the total killed target area and to the NALM6-Katushka area (μM^2). As shown in Figure 19J, the total killed target cell area increased when Nalm6 cells were co-

cultured with OT-CD19-131 expressing T cells in the presence of vardenafil. Similar trend was observed in the proliferation of Nalm6 cells (Figure 19K). The same cells did not result in significant cell killing in presence of DMSO, showing that the target cell killing by the T cells is specifically in response to the presence of the ligand. As expected, the constitutive construct, OT-CD19-063 showed increased total killed target cell area both in the presence and absence of ligand, with a trend towards more killing in the presence of the ligand. Nalm6 cells co-cultured with untransduced T cells and Nalm6 cells that were not co-cultured with T cells did not show an increase in the total killed target area. Taken together, these data show that the regulated CAR construct, OT-CD19-131 is active on antigen positive cells only in response to ligand.

[0865] The cell supernatants were also collected from the T cell/Nalm6 cytotoxicity co-culture assays at 66 hours and Interferon gamma levels were measured by MSD assays. The results are shown in Table 45G.

Table 45G: Interferon gamma production (pg/mL)

Construct	DMSO	Vardenafil 10 µM
OT-CD19-131	443.99	2282.98
OT-CD19-063	3268.72	1980.48
Untransduced	16.57	18.48

[0866] As shown in Table 45G, the interferon gamma levels showed a five-fold induction in OT-CD19-131 transduced T cells with the addition of vardenafil. Vardenafil treatment did not induce interferon gamma production in OT-CD19-063 transduced T cells or untransduced T cells, indicating that the ligand specific induction of interferon gamma is related to the increased CAR expression and cell killing observed under similar conditions. The interferon gamma levels in DMSO treated OT-CD19-131 was lower than the levels observed with the constitutive construct indicating that the OT-CD19-131 cells have low basal expression of the CD19 CAR.

Example 26. *In vivo* assessment of hPDE5-regulated CD19 CAR

[0867] To test the efficacy of ligand regulated CAR efficacy in a tumor rejection model, 5 million CAR positive T cells (25 million total T cells) were injected in Nalm6 tumor bearing female NSG mice. The Nalm6-Luc is a B-cell precursor leukemia cell line used to generate an intravenous disseminated tumor model for studying blood tumors. Mice were treated daily with vehicle or Tadalafil at the following mg/kg body weight or mpk: 10mpk, 30mpk, or 100mpk. Constitutive OT-CD19-063 transduced T cells served as a positive control and untransduced T cells as a negative control. T cells were injected 7 days after the Nalm6 cells

were implanted. Animals in the Tadalafil groups received 2 doses of ligand prior to T cells being injected. The objective of the study was to test the ligand dose response regulation of a hPDE5 DD CD19 CAR-T and its impact on efficacy. Further, the study was also used to address if the presence of antigen was necessary for detection and expression of the CAR. Dose groups included (a) untransduced T cells (b) untransduced vehicle treated cells (c) Untransduced cells dosed with Tadalafil 100mg/kg (d) 5.0 Million CD19+ OT-CD19-063 CAR T cells (e) 5.0 Million CD19 positive Nalm6 cells with OT-CD19-063 CAR T cells (Vehicle) (f) 5.0 Million CD19 positive Nalm6 cells with OT-CD19-063 CAR T cells (Tadalafil 100mg) (g) 5.0 Million CD19 positive Nalm6 cells with OT-CD19-131 CAR T cells (Vehicle) (h) 5.0 Million CD19 positive Nalm6 cells with OT-CD19-131(Tadalafil 10mg/kg) (i) 5.0 Million CD19 positive Nalm6 cells with OT-CD19-131 CAR T cells (Tadalafil 30mg/kg (j) 5.0 Million CD19 positive Nalm6 cells with OT-CD19-131 CAR T cells (Tadalafil 100mg/kg). All animals were dosed once a day, orally for 25 days. Tumor burden assessments were made biweekly using bio luminescent imaging and the fluorescence intensity of Nalm6 Luc cells was observed over time. Two terminal collections were made to assess bone marrow, blood and spleen cell populations. Reduction in tumor burden/ prevalence was measured by decreased luminescence from Nalm6-Luciferase cells, and was observed in Tadalafil treated CD19-131 animals (Figure 20A). In Figure 20A, “const” refers to OT-CD19-063 and “regulated” refers to OT-CD19-131. Taken together these data show that daily oral dosing of tadalafil resulted in dose-dependent suppression of tumor growth and/or reduction in tumor burden. Maximal tumor suppression was comparable to constitutive CAR with very low activity in the absence of drug. Plasma PK was also established in non-tumor-bearing mice of the hPDE5 inhibitors Tadalafil and Vardenafil after a single dose at the indicated dose levels and is shown in Figure 20B and Figure 20C.

CLAIMS

1. A composition comprising an effector module, said effector module comprising a stimulus response element (SRE) and at least one payload which is operably linked to said SRE, wherein the SRE comprises a destabilizing domain (DD), said DD comprising, in whole or in part, a cGMP-specific 3',5'-cyclic phosphodiesterase (hPDE5; SEQ ID NO.1) which is capable of ligand binding, and further comprising a mutation in the amino acid at position 732 (R732) of SEQ ID NO: 1.

2. A composition comprising an effector module, said effector module comprising a stimulus response element (SRE) and at least one payload which is operably linked to said SRE, wherein the SRE comprises a destabilizing domain (DD), wherein the DD comprises the catalytic domain of hPDE5 (SEQ ID NO: 3) which is capable of ligand binding, and comprises a mutation in the amino acid at the position corresponding to amino acid 732 (R732) of SEQ ID NO: 1.

3. The composition of claim 2, wherein the mutation in the amino acid at position 732 (R732) is selected from the group consisting of R732L, R732A, R732G, R732V, R732I, R732P, R732F, R732W, R732Y, R732H, R732S, R732T, R732D, R732E, R732Q, R732N, R732M, R732C, and R732K.

4. The composition of claim 3, wherein the mutation in the amino acid at position R732 is R732L.

5.The composition of claim 2, wherein the DD further comprises a mutation in the amino acid at the position corresponding to amino acid 764 (D764) of SEQ ID NO: 1, wherein the mutation at D764 is selected from the group consisting of D764N and D764A.

6. The composition of claim 2, wherein the DD further comprises a mutation in the amino acid at the position corresponding to amino acid 612 (Y612) of SEQ ID NO: 1, wherein the mutation at Y612 is selected from the group consisting of Y612A, Y612F, and Y612W.

7. The composition of claim 2, wherein the DD further comprises an F736A mutation in the amino acid at the position corresponding to amino acid 736 (F736) of SEQ ID NO: 1.

8. The composition of claim 2, wherein the DD further comprises an H653A mutation in the amino acid at the position corresponding to amino acid 653 (H653) of SEQ ID NO: 1.

9. The composition of claim 2, wherein the at least one payload is an immunotherapeutic agent.

10. The composition of claim 9, wherein the immunotherapeutic agent is selected from a chimeric antigen receptor (CAR) and a cytokine-cytokine receptor fusion polypeptide.

11. The composition of claim 10, wherein the immunotherapeutic agent is a chimeric antigen receptor (CAR) that comprises

(a) an extracellular target moiety;

(b) a transmembrane domain;

(c) an intracellular signaling domain; and

(d) optionally, one or more co-stimulatory domains.

12. The composition of claim 11, wherein the extracellular target moiety is a scFv derived from an antibody that specifically recognizes a CD 19 target molecule.

13. The composition of claim 10, wherein the immunotherapeutic agent is a cytokine-cytokine receptor fusion polypeptide that comprises the whole or a portion of IL15, fused to the whole or a portion of IL15Ra to produce a IL15-IL15Ra fusion polypeptide.

14. The composition of claim 2, wherein the SRE is responsive to one or more stimuli, and wherein said one or more stimuli is selected from Tadalafil, Vardenafil, Sildenafil, Avanafil, Lodenafil, Mirodenafil, Udenafil, Benzamidenafil, Dasantafil, and Beminafil.

15. A pharmaceutical composition comprising the composition of claim 2 and a pharmaceutically acceptable excipient.

16. A polynucleotide encoding the composition of claim 2.

17. A pharmaceutical composition comprising the polynucleotide of claim 16 and a pharmaceutically acceptable excipient.

18. A vector comprising a polynucleotide of claim 16.

19. A cell comprising the polynucleotide of claim 16.

20. The cell of claim 19, wherein said cell is an immune cell for adoptive cell transfer (ACT), and optionally wherein the immune cell is a $CD8^+$ T cell, a $CD4^+$ T cell, a memory T cell, a terminally differentiated effector T cell, a natural killer (NK) cell, a NK T cell, a tumor infiltrating lymphocyte (TIL), a cytotoxic T lymphocyte (CTL), a regulatory T cell (Treg), or a dendritic cell (DC).

21. A pharmaceutical composition comprising the cell of claim 19 and a pharmaceutically acceptable excipient.

22. A method of producing a modified cell, said method comprising introducing into a cell a nucleic acid molecule comprising the polynucleotide of claim 16.

23. A cell of claim 20 for use in a method of reducing a tumor burden in a subject, comprising:

(a) administering to the subject a therapeutically effective amount of the cells; and

(b) administering to the subject, a therapeutically effective amount of a stimulus, wherein the stimulus is a ligand, to modulate the expression of the immunotherapeutic agent, thereby reducing the tumor burden.

24. A cell of claim 19 for use in a method of treating a disease in a subject in need thereof, said method comprising:

(a) administering to the subject a therapeutically effective amount of the cell, wherein the cell comprises a payload that treats the disease; and

(b) administering to the subject a therapeutically effective amount of a stimulus, wherein the SRE is responsive to the stimulus and wherein expression of the payload is modulated in response to the stimulus to thereby treat the disease.