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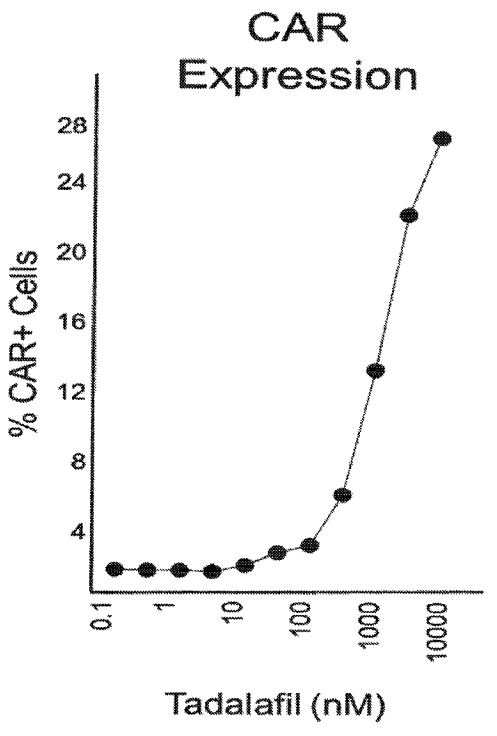
Figure 19H



(57) Abrégé/Abstract:
The present invention relates to compositions and methods for the regulated and controlled expression of proteins. Methods for inducing anti-cancer immune responses in a subject are also provided.

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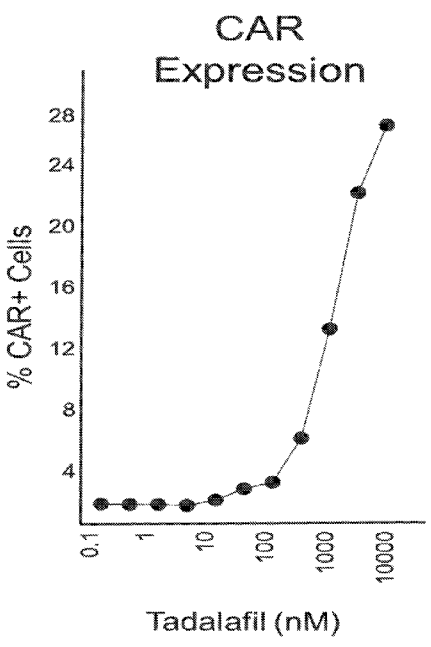
(54) Title: PDE5 COMPOSITIONS AND METHODS FOR IMMUNOTHERAPY

Figure 19H



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[Continued on next page]

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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 SAIRQSPSPPPEEESRGPGHPPLPDKFQFELTLEEEEEEEISM	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
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EGFRvIII	VH	2150	SEQ ID NO: 2 in US20160200819A1
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Endoglin	VH	2160	SEQ ID NO. 91 in US20160009811
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EphA2receptor	VH	2162	US20150274824 SEQ ID NO: 20
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EphA2receptor	VH	2166	US20150274824 SEQ ID NO: 34
EphA2receptor	VH	2167	US20150274824 SEQ ID NO: 36
EphA2receptor	VH	2168	US20150274824 SEQ ID NO: 37
EphA2receptor	VH	2169	US20150274824 SEQ ID NO: 38
EphA2receptor	VH	2170	US20150274824 SEQ ID NO: 40
EphA2receptor	VH	2171	US20150274824 SEQ ID NO: 42

EphA2receptor	VH	2172	US20150274824 SEQ ID NO: 43
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
ERBB2	VH	2177	US20110129464 SEQ ID NO: 4
ERBB2	VH	2178	US20130089544 SEQ ID NO: 10
ERBB2	VH	2179	US20130089544 SEQ ID NO: 2
ERBB2	VH	2180	US20130089544 SEQ ID NO: 26
ERBB2	VH	2181	US20130089544 SEQ ID NO: 30
ERBB2	VH	2182	US20130089544 SEQ ID NO: 38
ERBB2	VH	2183	US20130089544 SEQ ID NO: 4
ERBB2	VH	2184	US20130089544 SEQ ID NO: 40
ERBB2	VH	2185	US20130089544 SEQ ID NO: 42
ERBB2	VH	2186	US20130089544 SEQ ID NO: 52
ERBB2	VH	2187	US20130089544 SEQ ID NO: 54
ERBB2	VH	2188	US20130089544 SEQ ID NO: 56
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
FactorD	VH	2195	SEQ ID NO. 20 in US20160017052
FactorD	VH	2196	SEQ ID NO. 27 in US20160017052
FactorD	VH	2197	SEQ ID NO. 29 in US20160017052
FactorD	VH	2198	SEQ ID NO. 30 in US20160017052
FactorD	VH	2199	SEQ ID NO. 31 in US20160017052
FactorD	VH	2200	SEQ ID NO. 32 in US20160017052
FactorD	VH	2201	SEQ ID NO. 33 in US20160017052
FactorD	VH	2202	SEQ ID NO. 4 in US20160017052
FactorXII	VH	2203	SEQ ID NO.15 in WO2014089493
FAP	VH	2204	SEQ ID NO. 1 in WO2015118030
FAP	VH	2205	SEQ ID NO. 5 in WO2015118030
FAP	VH	2206	SEQ ID NO. 170 in WO2016120216
FAP	VH	2207	SEQ ID NO. 172 in WO2016120216
FcRL5(FcReceptorLike5)	VH	2208	SEQ ID NO: 12 WO2016090337
FcRL5(FcReceptorLike5)	VH	2209	SEQ ID NO: 16 WO2016090337
FcRL5(FcReceptorLike5)	VH	2210	SEQ ID NO: 20 WO2016090337
FcRL5(FcReceptorLike5)	VH	2211	SEQ ID NO: 24 WO2016090337
FcRL5(FcReceptorLike5)	VH	2212	SEQ ID NO: 28 WO2016090337
FcRL5(FcReceptorLike5)	VH	2213	SEQ ID NO: 32 WO2016090337
FcRL5(FcReceptorLike5)	VH	2214	SEQ ID NO: 36 WO2016090337
FcRL5(FcReceptorLike5)	VH	2215	SEQ ID NO: 4 WO2016090337
FcRL5(FcReceptorLike5)	VH	2216	SEQ ID NO: 40 WO2016090337
FcRL5(FcReceptorLike5)	VH	2217	SEQ ID NO: 44 WO2016090337
FcRL5(FcReceptorLike5)	VH	2218	SEQ ID NO: 48 WO2016090337
FcRL5(FcReceptorLike5)	VH	2219	SEQ ID NO: 8 WO2016090337
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
GM2	VH	2242	US20090028877 SEQ ID NO: 22
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
GPRC5D	VH	2260	SEQ ID NO. 17 in WO2016090312
GPRC5D	VH	2261	SEQ ID NO. 21 in WO2016090312
GPRC5D	VH	2262	SEQ ID NO. 25 in WO2016090312
GPRC5D	VH	2263	SEQ ID NO. 29 in WO2016090312
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
GPRC5D	VH	2278	SEQ ID NO. 57 in WO2016090312
GPRC5D	VH	2279	SEQ ID NO. 61 in WO2016090312
GPRC5D	VH	2280	SEQ ID NO. 65 in WO2016090312
GPRC5D	VH	2281	SEQ ID NO. 69 in WO2016090312
GPRC5D	VH	2282	SEQ ID NO. 73 in WO2016090312
GPRC5D	VH	2283	SEQ ID NO. 77 in WO2016090312
GPRC5D	VH	2284	SEQ ID NO. 81 in WO2016090312
GPRC5D	VH	2285	SEQ ID NO. 85 in WO2016090312

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
IL1RAP	VH	2329	SEQ ID NO. 10 in WO2016020502
IL1RAP	VH	2330	SEQ ID NO. 19 in WO2016020502
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
IL33	VH	2338	SEQ ID NO 134. in US20160168242
IL33	VH	2339	SEQ ID NO 136. in US20160168242
IL33	VH	2340	SEQ ID NO 138. in US20160168242

IL33	VH	2341	SEQ ID NO 183. in US20160168242
IL33	VH	2342	SEQ ID NO 185. in US20160168242
IL33	VH	2343	SEQ ID NO 187. in US20160168242
IL33	VH	2344	SEQ ID NO 189. in US20160168242
IL33	VH	2345	SEQ ID NO 216. in US20160168242
IL33	VH	2346	SEQ ID NO 218. in US20160168242
IL33	VH	2347	SEQ ID NO 220. in US20160168242
IL33	VH	2348	SEQ ID NO 221. in US20160168242
IL33	VH	2349	SEQ ID NO 236. in US20160168242
IL33	VH	2350	SEQ ID NO 246. in US20160168242
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IL33	VH	2353	SEQ ID NO 286. in US20160168242
IL33	VH	2354	SEQ ID NO 36. in US20160168242
IL33	VH	2355	SEQ ID NO 38. in US20160168242
IL33	VH	2356	SEQ ID NO 40. in US20160168242
IL33	VH	2357	SEQ ID NO 84. in US20160168242
IL33	VH	2358	SEQ ID NO 86. in US20160168242
IL33	VH	2359	SEQ ID NO 88. in US20160168242
IL3alpha	VH	2360	SEQ ID NO. 22 in WO2008127735
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
LAG3	VH	2376	SEQ ID NO. 104 in US20150259420
LAG3	VH	2377	SEQ ID NO. 108 in US20150259420
LAG3	VH	2378	SEQ ID NO. 28 in US20150259420
LAG3	VH	2379	SEQ ID NO. 64 in US20150259420
LAG3	VH	2380	SEQ ID NO. 68 in US20150259420
LAG3	VH	2381	SEQ ID NO. 72 in US20150259420
LAG3	VH	2382	SEQ ID NO. 76 in US20150259420
LAG3	VH	2383	SEQ ID NO. 8 in US20150259420
LAG3	VH	2384	SEQ ID NO. 80 in US20150259420
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
LGR4	VH	2388	SEQ ID NO. 12 in US20160046723
LGR4	VH	2389	SEQ ID NO. 13 in US20160046723
LGR4	VH	2390	SEQ ID NO. 5 in US20160046723
LGR4	VH	2391	SEQ ID NO. 9 in US20160046723
LGR5	VH	2392	SEQ ID NO. 10 in US20160102146
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LGR5	VH	2394	SEQ ID NO. 16 in US20160102146
LGR5	VH	2395	SEQ ID NO. 18 in US20160102146
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LGR5	VH	2397	SEQ ID NO. 22 in US20160102146
LGR5	VH	2398	SEQ ID NO. 24 in US20160102146

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LGR5	VH	2400	SEQ ID NO. 4 in US20160102146
LHR	VH	2401	SEQ ID NO: 1 in WO2016160618A3
LHR	VH	2402	SEQ ID NO: 2 in WO2016160618A3
LHR	VH	2403	SEQ ID NO: 3 in WO2016160618A3
LHR	VH	2404	SEQ ID NO: 4 in WO2016160618A3
LHR	VH	2405	SEQ ID NO: 5 in WO2016160618A3
LHR	VH	2406	SEQ ID NO: 6 in WO2016160618A3
LHR	VH	2407	SEQ ID NO: 7 in WO2016160618A3
LHR	VH	2408	SEQ ID NO: 8 in WO2016160618A3
lL4R	VH	2409	SEQ ID NO. 10 in WO2009121847
lL4R	VH	2410	SEQ ID NO. 11 in WO2009121847
lL4R	VH	2411	SEQ ID NO. 14 in WO2009121847
lL4R	VH	2412	SEQ ID NO. 15 in WO2009121847
lL4R	VH	2413	SEQ ID NO. 9 in WO2009121847
Lymphotoxin beta receptor	VH	2414	SEQ ID NO. 10 in WO2004002431
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
MCAM	VH	2422	SEQ ID NO. 115 in US20150259419
MCAM	VH	2423	SEQ ID NO. 116 in US20150259419
MCAM	VH	2424	SEQ ID NO. 117 in US20150259419
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MCAM	VH	2438	SEQ ID NO. 77 in US20150239980
MCAM	VH	2439	SEQ ID NO. 89 in US20150239980
MCSF	VH	2440	SEQ ID NO 102 in WO2005030124
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MCSF	VH	2442	SEQ ID NO 14 in WO2005030124
MCSF	VH	2443	SEQ ID NO 18 in WO2005030124
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MCSF	VH	2459	SEQ ID NO 82 in WO2005030124
MCSF	VH	2460	SEQ ID NO 86 in WO2005030124
MCSF	VH	2461	SEQ ID NO 90 in WO2005030124
MCSF	VH	2462	SEQ ID NO 94 in WO2005030124
MCSF	VH	2463	SEQ ID NO 98 in WO2005030124
Mesothelin	VH	2464	SEQ ID NO. 1 WO2015188141
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
MN	VH	2472	SEQ ID NO. 133 in WO2007070538
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MN	VH	2479	SEQ ID NO. 147 in WO2007070538
MN	VH	2480	SEQ ID NO. 149 in WO2007070538
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
MUC1	VH	2484	SEQ ID NO:2 in WO2013023162
MUC1	VH	2485	SEQ ID NO: 14 in WO2013023162
MUC1	VH	2486	SEQ ID NO. 15 in WO2015116753
MUC1	VH	2487	SEQ ID NO. 19 in WO2015116753
MUC1	VH	2488	SEQ ID NO. 23 in WO2015116753
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MUC1	VH	2490	SEQ ID NO. 64 in WO2015116753
MUC1	VH	2491	SEQ ID NO. 68 in WO2015116753
MUC16	VH	2492	SEQ ID NO. 1 in WO2016149368
MUC16	VH	2493	SEQ ID NO. 11 in US20130171152
MUC16	VH	2494	SEQ ID NO. 21 in WO2016149368
MUC16	VH	2495	SEQ ID NO. 41 in WO2016149368
MUC16	VH	2496	SEQ ID NO. 81 in WO2016149368
MUC16	VH	2497	SEQ ID NO.4 in US20130171152
MUC16	VH	2498	SEQ ID NO.6 in US20130171152
MUC16	VH	2499	SEQ ID NO.61 in WO2016149368
MUC16	VH	2500	SEQ ID NO.8 in US20130171152
MUCIN1	VH	2501	SEQ ID NO: 101 in EP3049812A2
MUCIN1	VH	2502	SEQ ID NO: 106 in EP3049812A2
MUCIN1	VH	2503	SEQ ID NO: 109 in EP3049812A2
MUCIN1	VH	2504	SEQ ID NO: 115 in EP3049812A2
MUCIN1	VH	2505	SEQ ID NO: 119 in EP3049812A2
MUCIN1	VH	2506	SEQ ID NO: 123 in EP3049812A2
MUCIN1	VH	2507	SEQ ID NO: 127 in EP3049812A2
MUCIN1	VH	2508	SEQ ID NO: 141 in EP3049812A2
MUCIN1	VH	2509	SEQ ID NO: 15 in EP3049812A2
MUCIN1	VH	2510	SEQ ID NO: 23 in EP3049812A2
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TIGIT	VH	2858	SEQ ID NO. 13 in US20160355589
TIGIT	VH	2859	SEQ ID NO. 136 in US20160355589
TIGIT	VH	2860	SEQ ID NO. 138 in US20160355589
TIGIT	VH	2861	SEQ ID NO. 14 in US20160355589

TIGIT	VH	2862	SEQ ID NO. 143 in US20160355589
TIGIT	VH	2863	SEQ ID NO. 144 in US20160355589
TIGIT	VH	2864	SEQ ID NO. 149 in US20160355589
TIGIT	VH	2865	SEQ ID NO. 15 in US20160355589
TIGIT	VH	2866	SEQ ID NO. 150 in US20160355589
TIGIT	VH	2867	SEQ ID NO. 16 in US20160355589
TIGIT	VH	2868	SEQ ID NO. 17 in US20160355589
TIGIT	VH	2869	SEQ ID NO. 18 in US20160355589
TIGIT	VH	2870	SEQ ID NO. 19 in US20160355589
TIGIT	VH	2871	SEQ ID NO. 20 in US20160355589
TIGIT	VH	2872	SEQ ID NO. 21 in US20160355589
TIGIT	VH	2873	SEQ ID NO. 22 in US20160355589
TIGIT	VH	2874	SEQ ID NO. 23 in US20160355589
TIGIT	VH	2875	SEQ ID NO. 24 in US20160355589
TIGIT	VH	2876	SEQ ID NO. 37 in US20160355589
TIGIT	VH	2877	SEQ ID NO. 38 in US20160355589
TIGIT	VH	2878	SEQ ID NO. 39 in US20160355589
TIGIT	VH	2879	SEQ ID NO. 40 in US20160355589
TIGIT	VH	2880	SEQ ID NO. 41 in US20160355589
TIGIT	VH	2881	SEQ ID NO. 42 in US20160355589
TIGIT	VH	2882	SEQ ID NO. 43 in US20160355589
TIGIT	VH	2883	SEQ ID NO. 44 in US20160355589
TIGIT	VH	2884	SEQ ID NO. 45 in US20160355589
TIGIT	VH	2885	SEQ ID NO. 46 in US20160355589
TIGIT	VH	2886	SEQ ID NO. 47 in US20160355589
TIGIT	VH	2887	SEQ ID NO. 63 in US20160355589
TIGIT	VH	2888	SEQ ID NO. 94 in US20160355589
TIGIT	VH	2889	SEQ ID NO.7 in US20160355589
TIGIT	VH	2890	SEQ ID NO.9 in US20160355589
TIM3	VH	2891	SEQ ID NO:82 in WO2013006490
TIM3	VH	2892	SEQ ID NO: 13 in WO2016179319A1
TIM3	VH	2893	SEQ ID NO: 21 in WO2016179319A1
TIM3	VH	2894	SEQ ID NO: 29 in WO2016179319A1
TIM3	VH	2895	SEQ ID NO: 37 in WO2016179319A1
TIM3	VH	2896	SEQ ID NO: 45 in WO2016179319A1
TIM3	VH	2897	SEQ ID NO: 5 in WO2016179319A1
TIM3	VH	2898	SEQ ID NO: 53 in WO2016179319A1
TIM3	VH	2899	SEQ ID NO: 61 in WO2016179319A1
TIM3	VH	2900	SEQ ID NO: 69 in WO2016179319A1
TIM3	VH	2901	SEQ ID NO: 77 in WO2016179319A1
TIM3	VH	2902	SEQ ID NO: 85 in WO2016179319A1
TIM3	VH	2903	SEQ ID NO: 93 in WO2016179319A1
Tissue factor	VH	2904	SEQ ID NO 10 in WO2004094475
Tissue factor	VH	2905	SEQ ID NO 19 in WO2004094475
Tissue factor	VH	2906	SEQ ID NO 23 in WO2004094475
Tissue factor	VH	2907	SEQ ID NO 27 in WO2004094475
Tissue factor	VH	2908	SEQ ID NO 29 in WO2004094475
Tissue factor	VH	2909	SEQ ID NO 6 in WO2004094475
Tissue factor	VH	2910	SEQ ID NO: 38 in US20160333114A1
Tn Glycopeptide	VH	2911	SEQ ID NO. 20 in WO2015120180
Tn Glycopeptide	VH	2912	SEQ ID NO. 19 in WO2015120180
TRBC1	VH	2913	SEQ ID NO. 1 in WO2015132598
Trophoblast Glycoprotein5T4	VH	2914	SEQ ID NO. 17 in WO2016034666A1
Trophoblast Glycoprotein5T4VH	VH	2915	SEQ ID NO. 13 in WO2016034666A1
Trophoblast Glycoprotein5T4VH	VH	2916	SEQ ID NO. 15 in WO2016034666A1

Trophoblast Glycoprotein5T4VH	VH	2917	SEQ ID NO.11 in WO2016034666A1
uPAR	VH	2918	SEQ ID NO: 72 in US20160333114A1
V2	VH	2919	SEQ ID NO: 11 in US20160194375A1
VEGF	VH	2920	SEQ ID NO 4 in WO2000034337
VEGF	VH	2921	SEQ ID NO 8 in WO2000034337
VEGF	VH	2922	SEQ ID NO 12 in WO2006012688A1
VEGF	VH	2923	SEQ ID NO 20 in WO2006012688A1
VEGF	VH	2924	SEQ ID NO 4 in WO2006012688A1
VEGF	VH	2925	SEQ ID NO 44 in WO2006012688A1
VEGF	VH	2926	SEQ ID NO.7 in US20030175276A1
VEGF	VH	2927	US20160090427 SEQ ID NO: 152
VEGF	VH	2928	US20160090427 SEQ ID NO: 153
VEGF	VH	2929	US20160090427 SEQ ID NO: 154
VEGF	VH	2930	US20160090427 SEQ ID NO: 155
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
AMC	VL	3112	SEQ ID NO. 28 in WO2016161390
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
APRIL	VL	3139	SEQ ID NO. 28 in US20160264674
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
B7H4	VL	3174	SEQ ID NO. 55 in US20160159910
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
BCMA	VL	3186	SEQ ID NO: 25 in WO2016168773A3
BCMA	VL	3187	SEQ ID NO: 42 in WO2016097231
BCMA	VL	3188	SEQ ID NO:143 in WO2016168595A1
BCMA	VL	3189	SEQ ID NO:149 in WO2016168595A1
BCMA	VL	3190	SEQ ID NO:155 in WO2016168595A1
BCMA	VL	3191	SEQ ID NO:161 in WO2016168595A1
BCMA	VL	3192	SEQ ID NO:167 in WO2016168595A1
BCMA	VL	3193	SEQ ID NO:173 in WO2016168595A1
BCMA	VL	3194	SEQ ID NO:179 in WO2016168595A1
BCMA	VL	3195	SEQ ID NO:185 in WO2016168595A1
BCMA	VL	3196	SEQ ID NO:191 in WO2016168595A1
BCMA	VL	3197	SEQ ID NO:197 in WO2016168595A1
BCMA	VL	3198	SEQ ID NO:203 in WO2016168595A1
BCMA	VL	3199	SEQ ID NO:209 in WO2016168595A1
BCMA	VL	3200	SEQ ID NO:215 in WO2016168595A1
BCMA	VL	3201	SEQ ID NO:221 in WO2016168595A1
BCMA	VL	3202	SEQ ID NO:227 in WO2016168595A1
BCMA	VL	3203	SEQ ID NO:233 in WO2016168595A1
BCMA	VL	3204	SEQ ID NO:239 in WO2016168595A1
BCMA	VL	3205	SEQ ID NO:245 in WO2016168595A1

BCMA	VL	3206	SEQ ID NO:251 in WO2016168595A1
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Endoglin	VL	4678	SEQ ID NO. 103 in US20160009811
Endoglin	VL	4679	SEQ ID NO. 3 in US20160009811
Endoglin	VL	4680	SEQ ID NO. 4 in US20160009811
Endoglin	VL	4681	SEQ ID NO. 5 in US20160009811
Endoglin	VL	4682	SEQ ID NO. 70 in US20160009811
Endoglin	VL	4683	SEQ ID NO. 72 in US20160009811
Endoglin	VL	4684	SEQ ID NO. 74 in US20160009811
Endoglin	VL	4685	SEQ ID NO. 93 in US20160009811
Endoglin	VL	4686	SEQ ID NO. 94 in US20160009811
Endoglin	VL	4687	SEQ ID NO. 95 in US20160009811
Endoglin	VL	4688	SEQ ID NO. 96 in US20160009811
Endoglin	VL	4689	SEQ ID NO. 97 in US20160009811
EphA2receptor	VL	4690	US20150274824 SEQ ID NO: 26
EphA2receptor	VL	4691	US20150274824 SEQ ID NO: 28
EphA2receptor	VL	4692	US20150274824 SEQ ID NO: 30
EphA2receptor	VL	4693	US20150274824 SEQ ID NO: 47
EphA2receptor	VL	4694	US20150274824 SEQ ID NO: 48
EphA2receptor	VL	4695	US20150274824 SEQ ID NO: 49
EphA2receptor	VL	4696	US20150274824 SEQ ID NO: 50
EphA2receptor	VL	4697	US20150274824 SEQ ID NO: 52
EphA2receptor	VL	4698	US20150274824 SEQ ID NO: 78
EphA2receptor	VL	4699	US20150274824 SEQ ID NO: 80
ERBB2	VL	4700	US20110129464 SEQ ID NO: 1
ERBB2	VL	4701	US20130089544 SEQ ID NO: 12
ERBB2	VL	4702	US20130089544 SEQ ID NO: 16
ERBB2	VL	4703	US20130089544 SEQ ID NO: 20
ERBB2	VL	4704	US20130089544 SEQ ID NO: 24
ERBB2	VL	4705	US20130089544 SEQ ID NO: 32
ERBB2	VL	4706	US20130089544 SEQ ID NO: 36
ERBB2	VL	4707	US20130089544 SEQ ID NO: 44
ERBB2	VL	4708	US20130089544 SEQ ID NO: 50
ERBB2	VL	4709	US20130089544 SEQ ID NO: 51
ERBB2	VL	4710	US20130089544 SEQ ID NO: 53
ERBB2	VL	4711	US20130089544 SEQ ID NO: 8
ERBB2	VL	4712	US20130266564 SEQ ID NO: 7
FactorD	VL	4713	SEQ ID NO. 16 in US20160017052

FactorD	VL	4714	SEQ ID NO. 18 in US20160017052
FactorD	VL	4715	SEQ ID NO. 19 in US20160017052
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
FAP	VL	4719	SEQ ID NO. 2 in WO2015118030
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
FcRL5(FcReceptorLike5)	VL	4724	SEQ ID NO: 11 WO2016090337
FcRL5(FcReceptorLike5)	VL	4725	SEQ ID NO: 15 WO2016090337
FcRL5(FcReceptorLike5)	VL	4726	SEQ ID NO: 19 WO2016090337
FcRL5(FcReceptorLike5)	VL	4727	SEQ ID NO: 23 WO2016090337
FcRL5(FcReceptorLike5)	VL	4728	SEQ ID NO: 27 WO2016090337
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FcRL5(FcReceptorLike5)	VL	4732	SEQ ID NO: 39 WO2016090337
FcRL5(FcReceptorLike5)	VL	4733	SEQ ID NO: 43 WO2016090337
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FcRL5(FcReceptorLike5)	VL	4735	SEQ ID NO: 7 WO2016090337
FcRL5(FcReceptorLike5)	VL	4736	SEQ ID NO: 917 WO2016090337
FcRL5(FcReceptorLike5)	VL	4737	SEQ ID NO: 921 WO2016090337
FGFR3	VL	4738	SEQ ID NO. 133 in US9499623
FGFR3	VL	4739	SEQ ID NO. 135 in US9499623
FGFR3	VL	4740	SEQ ID NO. 137 in US9499623
FGFR3	VL	4741	SEQ ID NO. 139 in US9499623
Frizzled Receptor	VL	4742	SEQ ID NO. 12 in WO2010037041
Frizzled Receptor	VL	4743	SEQ ID NO. 14 in WO2010037041
GAH	VL	4744	SEQ ID NO 8 in US20060057147A1
GCC1	VL	4745	SEQ ID NO. 4 in US20160030595A1
GCC1	VL	4746	SEQ ID NO. 2 in US20160030595A1
GD2	VL	4747	SEQ ID NO. 10 in US20130216528
GD2	VL	4748	SEQ ID NO. 11 in WO2015132604
GD2	VL	4749	SEQ ID NO. 12 in WO2015132604
GD2	VL	4750	SEQ ID NO. 18 in WO2016134284
GD2	VL	4751	SEQ ID NO. 2 in US20130216528
GD2	VL	4752	SEQ ID NO. 5 in US20130216528
GD2	VL	4753	SEQ ID NO. 7 in US20130216528
GD2	VL	4754	SEQ ID NO. 9 in US20130216528
GD3	VL	4755	SEQ ID NO: 12 in WO2016185035A1
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
GM2	VL	4760	US20090028877 SEQ ID NO: 21
GM2	VL	4761	US20090028877 SEQ ID NO: 24
GM2	VL	4762	US20090028877 SEQ ID NO: 25
GM2	VL	4763	US20090028877 SEQ ID NO: 31
GM2	VL	4764	US20090028877 SEQ ID NO: 32
GM2	VL	4765	US20090028877 SEQ ID NO: 33
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
GPC3	VL	4772	SEQ ID NO: 22 in US9409994B2
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	4779	SEQ ID NO. 2 in WO2016090312
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GPRC5D	VL	4805	SEQ ID NO. 86 in WO2016090312
GPRC5D	VL	4806	SEQ ID NO. 94 in WO2016090312
Her1/her3	VL	4807	SEQ ID NO: 4 of WO2016073629
Her2	VL	4808	SEQ ID NO: 140 in WO2016054555A2
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
Her2	VL	4813	SEQ ID NO: 269 in WO2016168773A3
HER2	VL	4814	SEQ ID NO. 10 in US9518118
HER2	VL	4815	SEQ ID NO. 18 in US9518118
HER2	VL	4816	SEQ ID NO. 23 in US9518118
HER2	VL	4817	SEQ ID NO: 3 in WO2016168769A1
HER2	VL	4818	SEQ ID NO: 59 in US20160333114A1
HER2	VL	4819	SEQ ID NO: 61 in US20160333114A1
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HLAG	VL	4821	SEQ ID NO. 20 in WO2016160622A2
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HSP70	VL	4823	SEQ ID NO. 17 in WO2016120217
humanCD79b	VL	4824	SEQ ID NO.28 in WO2016112870
humanCD79b	VL	4825	SEQ ID NO.30 in WO2016112870
Human collagen VII	VL	4826	SEQ ID NO.32 in WO2016112870
humanERBB3	VL	4827	SEQ ID NO: 10 in WO2013052745
humanERBB3	VL	4828	SEQ ID NO: 20 in WO2013052745

humanERBB3	VL	4829	SEQ ID NO: 30 in WO2013052745
humanERBB3	VL	4830	SEQ ID NO: 39 in WO2013052745
humanERBB3	VL	4831	SEQ ID NO: 46 in WO2013052745
humanERBB3	VL	4832	SEQ ID NO: 56 in WO2013052745
humanERBB3	VL	4833	SEQ ID NO: 62 in WO2013052745
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ICOS	VL	4835	SEQ ID NO. 18 in US20160215059
ICOS	VL	4836	SEQ ID NO. 20 in US20160215059
ICOS	VL	4837	SEQ ID NO. 24 in US20160215059
ICOS	VL	4838	SEQ ID NO. 8 in US20160215059
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IGFI	VL	4841	SEQ ID NO. 6 in WO2007118214
IGFI	VL	4842	SEQ ID NO. 8 in WO2007118214
IGFR1	VL	4843	SEQ ID NO:8 in WO2015073575A2
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IL1RAP	VL	4848	SEQ ID NO. 18 in WO2016020502
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IL1RAP	VL	4851	SEQ ID NO: 121 in WO2016179319A1
IL1RAP	VL	4852	SEQ ID NO: 123 in WO2016179319A1
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IL33	VL	4856	SEQ ID NO 139. in US20160168242
IL33	VL	4857	SEQ ID NO 184. in US20160168242
IL33	VL	4858	SEQ ID NO 188. in US20160168242
IL33	VL	4859	SEQ ID NO 217. in US20160168242
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IL3alpha	VL	4871	SEQ ID NO. 37 in WO2008127735
Integrin	VL	4872	SEQ ID NO. 10 in US 20140161794
Integrin	VL	4873	SEQ ID NO. 11 in US 20140161794
Integrin	VL	4874	SEQ ID NO. 8 in US 20140161794
Integrin	VL	4875	SEQ ID NO. 9 in US 20140161794
KDR	VL	4876	SEQ ID NO. 22 IN WO2003075840
KIR(Lirilumab)	VL	4877	SEQ ID NO. 5 in US20150290316
KIR(Lirilumab)	VL	4878	SEQ ID NO.2 in WO2014055648
KIR2DL1andKIR2DL2/3	VL	4879	SEQIDNO:37 in WO2016126213A1
Klon43	VL	4880	SEQ ID NO: 48 in WO2016097231
KMA	VL	4881	SEQ ID NO: 2 in WO2016172703A2
KMA	VL	4882	SEQ ID NO: 21 in WO2016172703A2
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LAG3	VL	4908	SEQ ID NO.2 in WO2015042246
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LGR5	VL	4913	SEQ ID NO. 15 in US20160102146
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Lymphotoxin beta receptor	VL	4926	SEQ ID NO. 8 in WO2004002431
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MUC1	VL	4989	SEQ ID NO. 66 in WO2015116753
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MUC16	VL	4993	SEQ ID NO. 42 in WO2016149368
MUC16	VL	4994	SEQ ID NO. 62 in WO2016149368
MUC16	VL	4995	SEQ ID NO. 82 in WO2016149368
MUC1C/ECD	VL	4996	SEQ ID NO: 17 in US20160340442A1
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MUC1C/ECD	VL	5000	SEQ ID NO: 66 in US20160340442A1
MUC1C/ECD	VL	5001	SEQ ID NO: 70 in US20160340442A1
MUC1C/ECD	VL	5002	SEQ ID NO: 75 in US20160340442A1

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NKG2A	VL	5041	SEQ ID NO. 7 in WO2016041947
NKG2D	VL	5042	SEQ ID NO. 134 in WO2016122701
NKG2D	VL	5043	SEQ ID NO. 136 in WO2016122701
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NOTCH1	VL	5045	SEQ ID NO:20 in WO2013074596
NOTCH2/3	VL	5046	SEQ ID NO:31 in WO2013074596
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Notch l	VL	5048	SEQ ID NO: 57 in US20160333114A1
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Notum	VL	5050	SEQ ID NO: 58 in WO2012027723
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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
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ERBB2	scFv	6165	SEQ ID NO. 2 in US7244826
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FcRL5(FcReceptorLike5)	scFv	6201	SEQ ID NO. 640 in WO2016090337
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FcRL5(FcReceptorLike5)	scFv	6276	SEQ ID NO. 794 in WO2016090337

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FcRL5(FcReceptorLike5)	scFv	6324	SEQ ID NO. 890 in WO2016090337
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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
GD2	scFv	6338	SEQ ID NO. 19 in WO2016134284
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
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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
humanCD79b1F10	scFv	6379	SEQ ID NO.33 in WO2016112870
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

Mesothelin	scFv	6393	SEQ ID NO. 49 in WO2016090034
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Mesothelin	scFv	6417	SEQ ID NO. 12 in WO2013142034
Mesothelin	scFv	6418	SEQ ID NO.11 in WO2013063419
MUC1	scFv	6419	SEQ ID NO.15 in US20160130357
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
O acetylated GD2 ganglioside	scFv	6429	SEQ ID NO. 29 in US20150140023
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
PD1	scFv	6440	SEQ ID NO.47 in US20160311917A1
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PD1	scFv	6450	SEQ ID NO.57 in US20160311917A1

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PD1	scFv	6453	SEQ ID NO.60 in US20160311917A1
PD1	scFv	6454	SEQ ID NO.61 in US20160311917A1
PDK1	scFv	6455	SEQ ID NO.15 in WO2016090365
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
PDL1	Nanobody	6459	SEQ ID NO.25 in US20110129458
PDL1	Nanobody	6460	SEQ ID NO.26 in US20110129458
PDL1	Nanobody	6461	SEQ ID NO.27 in US20110129458
PDL2	Nanobody	6462	SEQ ID NO.28 in US20110129458
PDL2	Nanobody	6463	SEQ ID NO.29 in US20110129458
PDL2	Nanobody	6464	SEQ ID NO.30 in US20110129458
PDL2	Nanobody	6465	SEQ ID NO.31 in US20110129458
PDL2	Nanobody	6466	SEQ ID NO.32 in US20110129458
PDL2	Nanobody	6467	SEQ ID NO.33 in US20110129458
PRAME	scFv	6468	SEQ ID NO. 63 in WO2016191246A2
PRAME	scFv	6469	SEQ ID NO. 64 in WO2016191246A2
PRAME	scFv	6470	SEQ ID NO. 65 in WO2016191246A2
PRAME	scFv	6471	SEQ ID NO. 66 in WO2016191246A2
PRAME	scFv	6472	SEQ ID NO. 67 in WO2016191246A2
PRAME	scFv	6473	SEQ ID NO. 68 in WO2016191246A2
PRAME	scFv	6474	SEQ ID NO. 69 in WO2016191246A2
PSMA	scFv	6475	SEQ ID NO. 19 in WO2012145714
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
RORI	scFv	6494	SEQ ID NO. 250 in US20160208018A1
RORI	scFv	6495	SEQ ID NO. 251 in US20160208018A1
RORI	scFv	6496	SEQ ID NO. 252 in US20160208018A1
RORI	scFv	6497	SEQ ID NO. 253 in US20160208018A1
RORI	scFv	6498	SEQ ID NO. 254 in US20160208018A1
RORI	scFv	6499	SEQ ID NO. 255 in US20160208018A1
RORI	scFv	6500	SEQ ID NO. 256 in US20160208018A1
RORI	scFv	6501	SEQ ID NO. 257 in US20160208018A1
RORI	scFv	6502	SEQ ID NO. 258 in US20160208018A1
RORI	scFv	6503	SEQ ID NO. 259 in US20160208018A1
RORI	scFv	6504	SEQ ID NO. 260 in US20160208018A1
RORI	scFv	6505	SEQ ID NO. 261 in US20160208018A1
RORI	scFv	6506	SEQ ID NO. 262 in US20160208018A1
RORI	scFv	6507	SEQ ID NO. 263 in US20160208018A1
RORI	scFv	6508	SEQ ID NO. 264 in US20160208018A1

RORI	scFv	6509	SEQ ID NO. 265 in US20160208018A1
RORI	scFv	6510	SEQ ID NO. 266 in US20160208018A1
RORI	scFv	6511	SEQ ID NO. 267 in US20160208018A1
RORI	scFv	6512	SEQ ID NO. 268 in US20160208018A1
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
Trastuzumab	scFv	6520	SEQ ID NO. 35 in US20160208021
Trastuzumab	scFv	6521	SEQ ID NO.35 in WO2016112870
TRBC1	scFv	6522	SEQ ID NO. 13 in WO2015132598
TRBC1	scFv	6523	SEQ ID NO. 14 in WO2015132598
TRBC1	scFv	6524	SEQ ID NO. 15 in WO2015132598
TRBC1	scFv	6525	SEQ ID NO. 16 in WO2015132598
TRBC1	scFv	6526	SEQ ID NO. 17 in WO2015132598
TRBC1	scFv	6527	SEQ ID NO. 18 in WO2015132598
TRBC1	scFv	6528	SEQ ID NO. 19 in WO2015132598
TRBC1	scFv	6529	SEQ ID NO. 20 in WO2015132598
TRBC1	scFv	6530	SEQ ID NO. 21 in WO2015132598
TRBC1	scFv	6531	SEQ ID NO. 22 in WO2015132598
TRBC1	scFv	6532	SEQ ID NO. 3 in WO2015132598
TRBC2	scFv	6533	SEQ ID NO. 23 in WO2015132598
TRBC2	scFv	6534	SEQ ID NO. 24 in WO2015132598
TRBC2	scFv	6535	SEQ ID NO. 25 in WO2015132598
TRBC2	scFv	6536	SEQ ID NO. 26 in WO2015132598
TRBC2	scFv	6537	SEQ ID NO. 27 in WO2015132598
TRBC2	scFv	6538	SEQ ID NO. 28 in WO2015132598
TRBC2	scFv	6539	SEQ ID NO. 29 in WO2015132598
TRBC2	scFv	6540	SEQ ID NO. 30 in WO2015132598
TRBC2	scFv	6541	SEQ ID NO. 31 in WO2015132598
TRBC2	scFv	6542	SEQ ID NO. 32 in WO2015132598
TSLPR	scFv	6543	SEQ ID NO. 1 in US20160311910A1
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 IgG_4 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

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 246

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 246

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

AMENDED CLAIMS
received by the International Bureau on 19 november 2018 (19.11.2018)

CLAIMS

1. A composition for inducing an immune response in a cell or a subject comprising an effector module, said effector module comprising:

(a) a stimulus response element (SRE); and

(b) at least one payload, which is attached, appended or associated with said SRE, wherein said SRE comprises a destabilizing domain (DD), said DD comprising, in whole or in part, the cGMP-specific 3',5'-cyclic phosphodiesterase (hPDE5; SEQ ID NO.1).

2. The composition of claim 1, wherein said payload is appended to the SRE.

3. The composition of claim 1, wherein the DD comprises the catalytic domain of hPDE5 (SEQ ID NO.3), said catalytic domain comprising amino acids 535 to 860 of hPDE5 (SEQ ID NO.1).

4. The composition of claim 3, wherein the DD comprises a mutation in the amino acid at position 732 (R732) of SEQ ID NO.1.

5. The composition of claim 4, 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.

6. The composition of claim 4 or claim 5, wherein the DD is selected from the group consisting of 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).

7. The composition of claim 4, wherein the mutation in the amino acid at position R732 is R732L and wherein the DD comprises the amino acid sequence of SEQ ID NO. 12.

8. The composition of claim 4, wherein the mutation in the amino acid at position R732 is R732A and wherein the DD comprises the amino acid sequence of SEQ ID NO. 384.

9. The composition of claim 4, wherein the mutation in the amino acid at position R732 is R732G and wherein the DD comprises SEQ ID NO. 383.

10. The composition of claim 5, wherein the DD further comprises 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.

11. The composition of claim 10, wherein the DD comprises the mutation H653A, and wherein the DD comprises the amino acid sequence of SEQ ID NO. 509.

12. The composition of claim 10, wherein the DD comprises the mutation F736A, and wherein the DD comprises the amino acid sequence of SEQ ID NO. 227.

13.The composition of claim 10, wherein the DD comprises the mutation D764A, and wherein the DD comprises the amino acid sequence of SEQ ID NO. 510.

14. The composition of claim 10, wherein the DD comprises the mutation Y612F, and wherein the DD comprises the amino acid sequence of SEQ ID NO. 506.

15. The composition of claim 10, wherein the DD comprises the mutation Y612W, and wherein the DD comprises the amino acid sequence of SEQ ID NO. 507.

16. The composition of claim 10, wherein the DD comprises the mutation Y612A, and wherein the DD comprises the amino acid sequence of SEQ ID NO. 508.

17. The composition of claim 10, wherein the DD comprises the mutation D764N, and wherein the DD comprises the amino acid sequence of SEQ ID NO. 505.

18. The composition of claim 2, wherein the payload is an immunotherapeutic agent.

19. The composition of claim 18, wherein the immunotherapeutic agent is selected from a chimeric antigen receptor (CAR) and a cytokine-cytokine receptor fusion polypeptide.

20. The composition of claim 19, wherein the immunotherapeutic agent is a chimeric antigen receptor, and said chimeric antigen receptor comprises

(a) an extracellular target moiety;

(b) a hinge and transmembrane domain;

(c) an intracellular signaling domain; and

(d) optionally, one or more co-stimulatory domains.

21. The composition of claim 20, wherein the CAR is 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.

22. The composition of claim 20, wherein the extracellular target of the CAR moiety has an affinity or binds to a target molecule on the surface of a cancer cell.

23. The composition of claim 22, wherein the extracellular target moiety of the CAR is an scFv.

24. The composition of claim 22, wherein the target molecule is CD19.

25. The composition of claim 23 or claim 24, wherein the extracellular target moiety of the CAR is a CD19 scFv (SEQ ID NO. 8233).

26. The composition of claim 20, wherein the hinge and transmembrane domain of the CAR are paired and wherein the paired hinge and transmembrane domain is derived from any of the members of the group consisting of:

(a) a molecule selected 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;

(b) the CD3 epsilon chain of a T-cell receptor;

(c) a transmembrane region of an alpha, beta or zeta chain of a T-cell receptor; and

(d) an immunoglobulin selected from IgG1, IgD, IgG4, and an IgG4 Fc region.

27. The composition of claim 26, wherein the paired hinge and transmembrane domain of the CAR is derived from CD8a and said paired hinge and transmembrane domain comprises the amino acid sequence of SEQ ID NO. 8235.

28. The composition of claim 20, wherein

(a) the intracellular signaling domain of the CAR is the signaling domain 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; and

(b) the co-stimulatory domain is present and is derived from the group consisting of 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.

29. The composition of claim 28, wherein the intracellular signaling domain of the CAR is derived from CD3 zeta and said intracellular signaling domain comprises the amino acid sequence of SEQ ID NO. 8236.

30. The composition of claim 28, wherein the co-stimulatory domain of the CAR is present, said co-stimulatory domain being derived from 4-1BB, wherein the costimulatory domain comprises the amino acid sequence of SEQ ID NO. 8237.

31. The composition of claim 20, wherein the chimeric antigen receptor further comprises a signal sequence.

32. The composition of claim 31, wherein the signal sequence is derived from CD8α and wherein the signal sequence comprises the amino acid sequence of SEQ ID NO. 278.

33. The composition of claim 19, wherein the immunotherapeutic agent is a cytokine-cytokine receptor fusion polypeptide.

34. The composition of claim 33, wherein the cytokine-cytokine receptor fusion polypeptide comprises the whole or a portion of IL15, fused to the whole or a portion of IL15Ra to produce a IL15-IL15Ra fusion polypeptide.

35. The composition of claim 34, wherein the cytokine-cytokine receptor fusion polypeptide comprises the amino acid sequence of SEQ ID NO. 8324 fused to the amino acid sequence of SEQ ID NO. 8329 to produce a fusion polypeptide.

36. The composition of any one of claims 1-32, wherein the effector module is a DD-CD19 CAR fusion polypeptide selected from the group consisting of SEQ ID NO. 8283; SEQ ID NO. 8271-8282; and SEQ ID NO. 8284.

37. The composition of claim 1-19 and claim 33- 35, wherein the effector module is a DD-IL15-IL15Ra fusion polypeptide selected from the group consisting of SEQ ID NO. 8338; SEQ ID NO. 8334-8337; and SEQ ID NO. 8339-8343.

38. The composition of claim 1-37, wherein the SRE is responsive to one or more stimuli.

39. The composition of claim 38, wherein the stimulus is a small molecule and wherein the small molecule is selected from Tadalafil, Vardenafil, Sildenafil, Avanafil, Lodenafil, Mirodenafil, Udenafil, Benzamidenafil, Dasantafil, and Beminafil.

40. The composition of claim 39, wherein the small molecule is Tadalafil.

41. A pharmaceutical composition comprising the composition of any one of claims 1-40 and a pharmaceutically acceptable excipient.

42. A polynucleotide encoding any of the compositions of claims 1-40 or the pharmaceutical composition of claim 41.

43. A vector comprising a polynucleotide of claim 42.

44. An immune cell for adoptive cell transfer (ACT) which expresses the compositions of any of claims 1-40, the pharmaceutical composition of claim 41, the polynucleotide of claim 42 and/or is transduced or transfected with the vector of claim 43.

45. A method of inducing an immune response in a cell comprising:

(a) administering to the cell, a therapeutically effective amount of any of the pharmaceutical composition of claim 41; and

(b) administering to the cell, a therapeutically effective amount of a stimulus to modulate the expression of the immunotherapeutic agent, wherein the stimulus is a ligand and wherein the immunotherapeutic agent is capable of inducing an immune response in the cell, in response to the stimulus.

46. A method of reducing a tumor burden in a subject, comprising:

(a) administering to the subject a therapeutically effective amount of the immune cells of claim 44; 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.

47. The method of claim 46, wherein the ligand is Tadalafil.

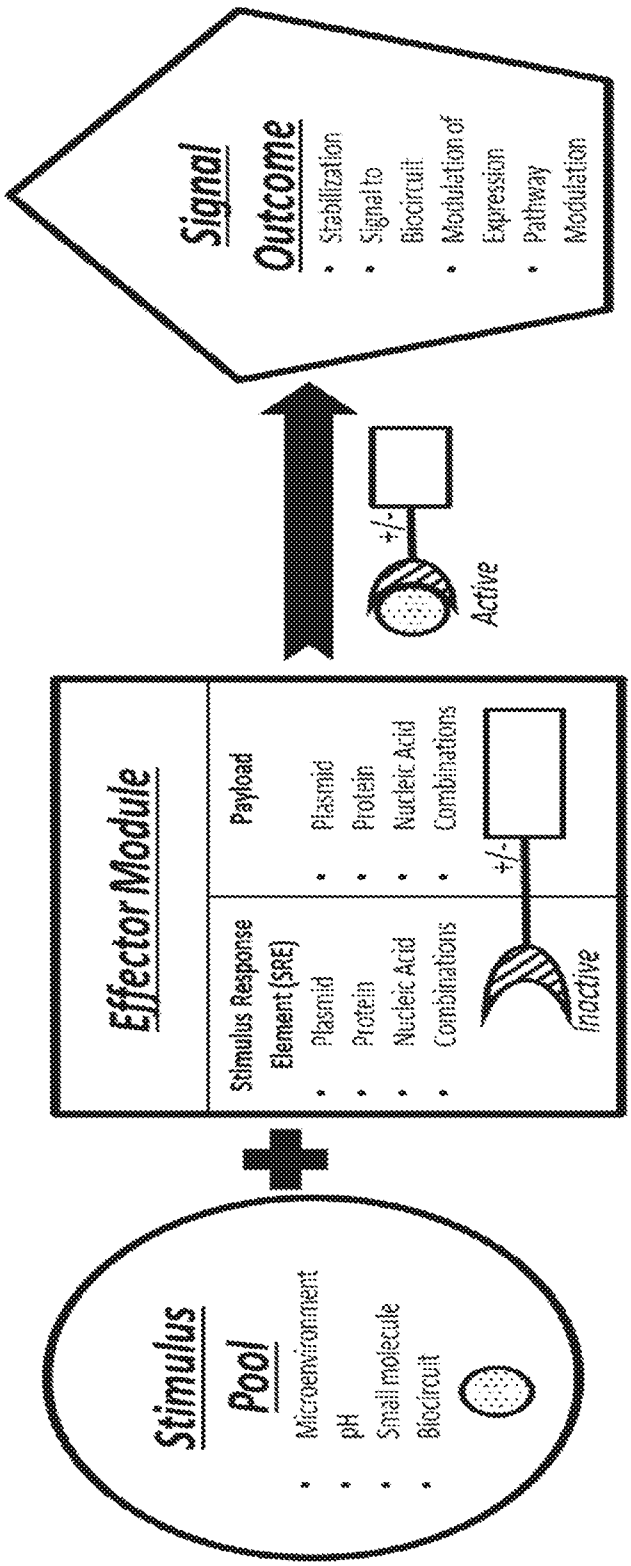
48. The method of claim 47, wherein Tadalafil is administered to the subject at a dose ranging from about 0.1 mg/kg to about 100 mg/kg body weight of the subject.

49. The method of claim 48, wherein the Tadalafil is administered to the subject at a dose of 10 mg/kg body weight of the subject.

50. The method of claim 48, wherein the Tadalafil is administered to the subject at a dose of 30 mg/kg body weight of the subject.

51. The method of claim 48, wherein the Tadalafil is administered to the subject at a dose of 100 mg/kg body weight of the subject.

Figure 1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Small molecule
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Effector Module
Stimulus Response Element (SRE)
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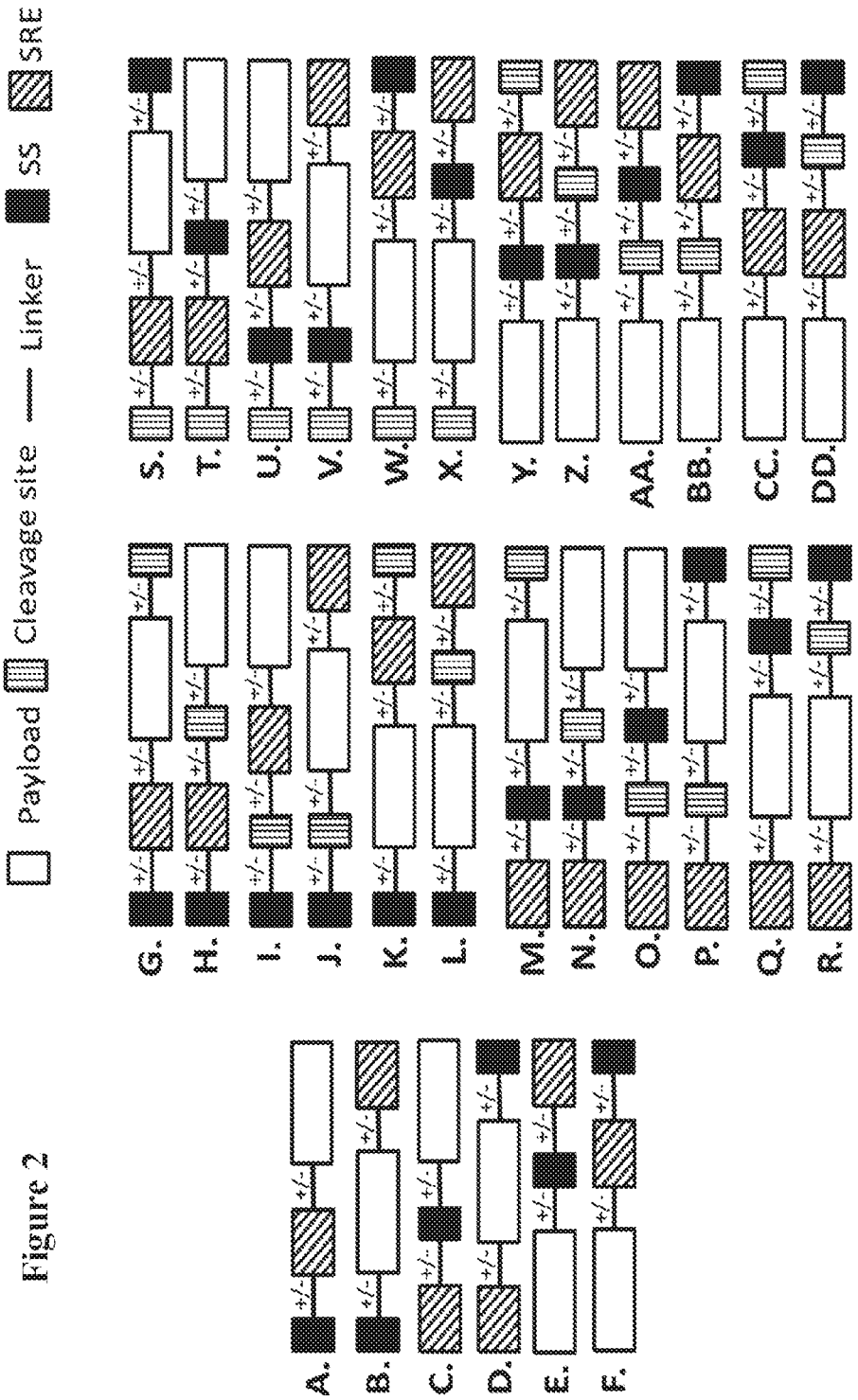
Payload
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Figure 2

Figure 3

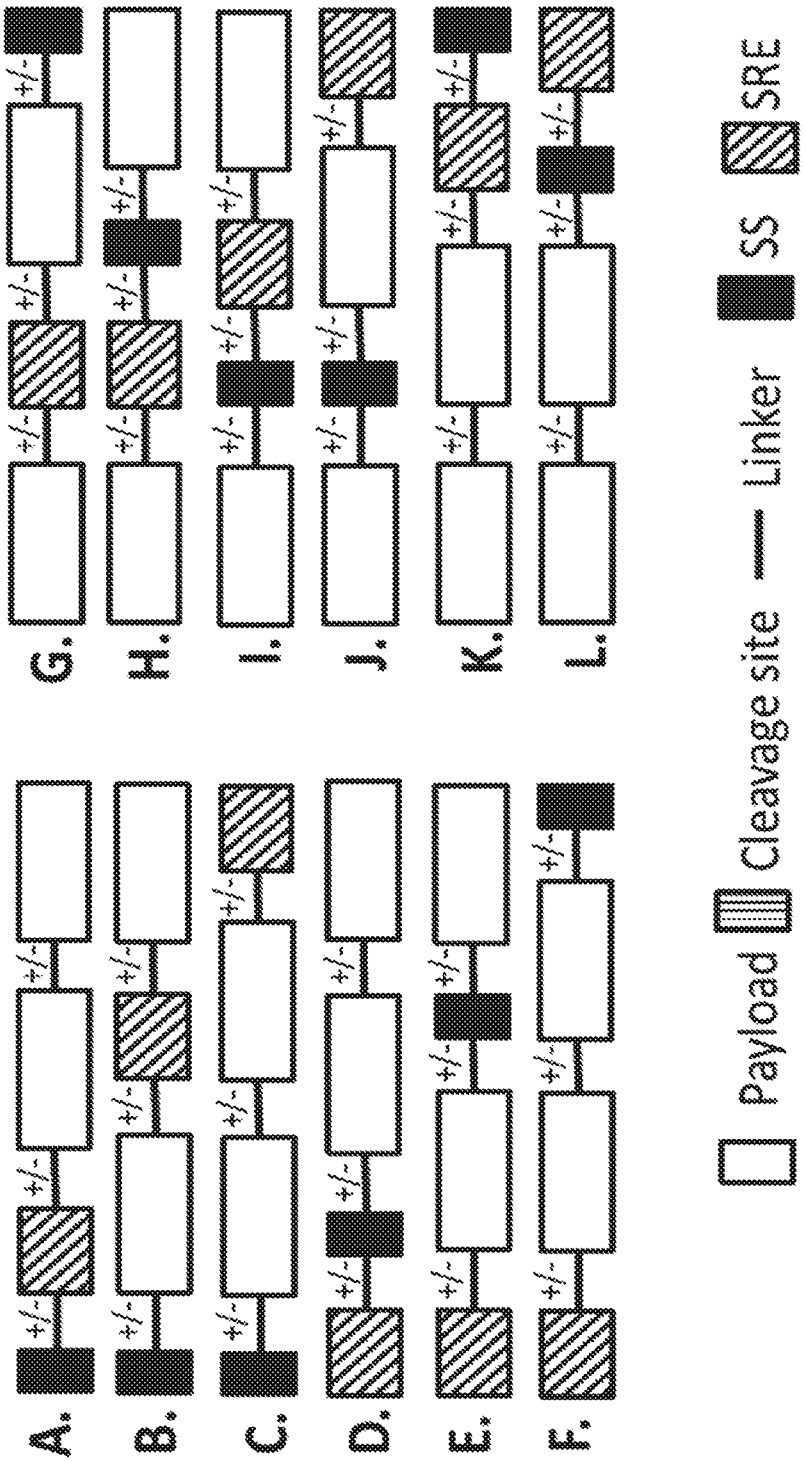
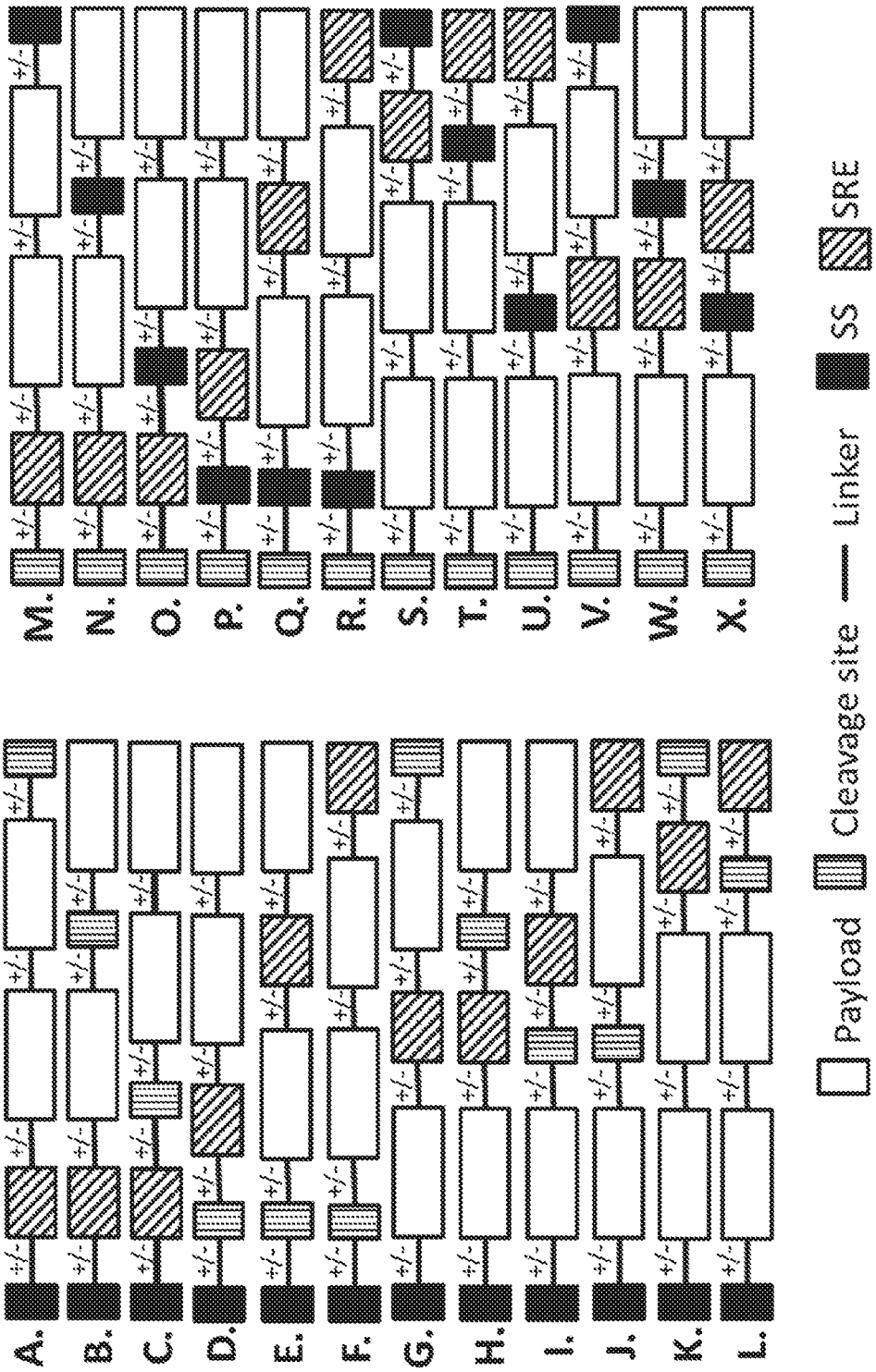


Figure 4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Payload
Cleavage site
Linker
SS
SRE

Figure 5

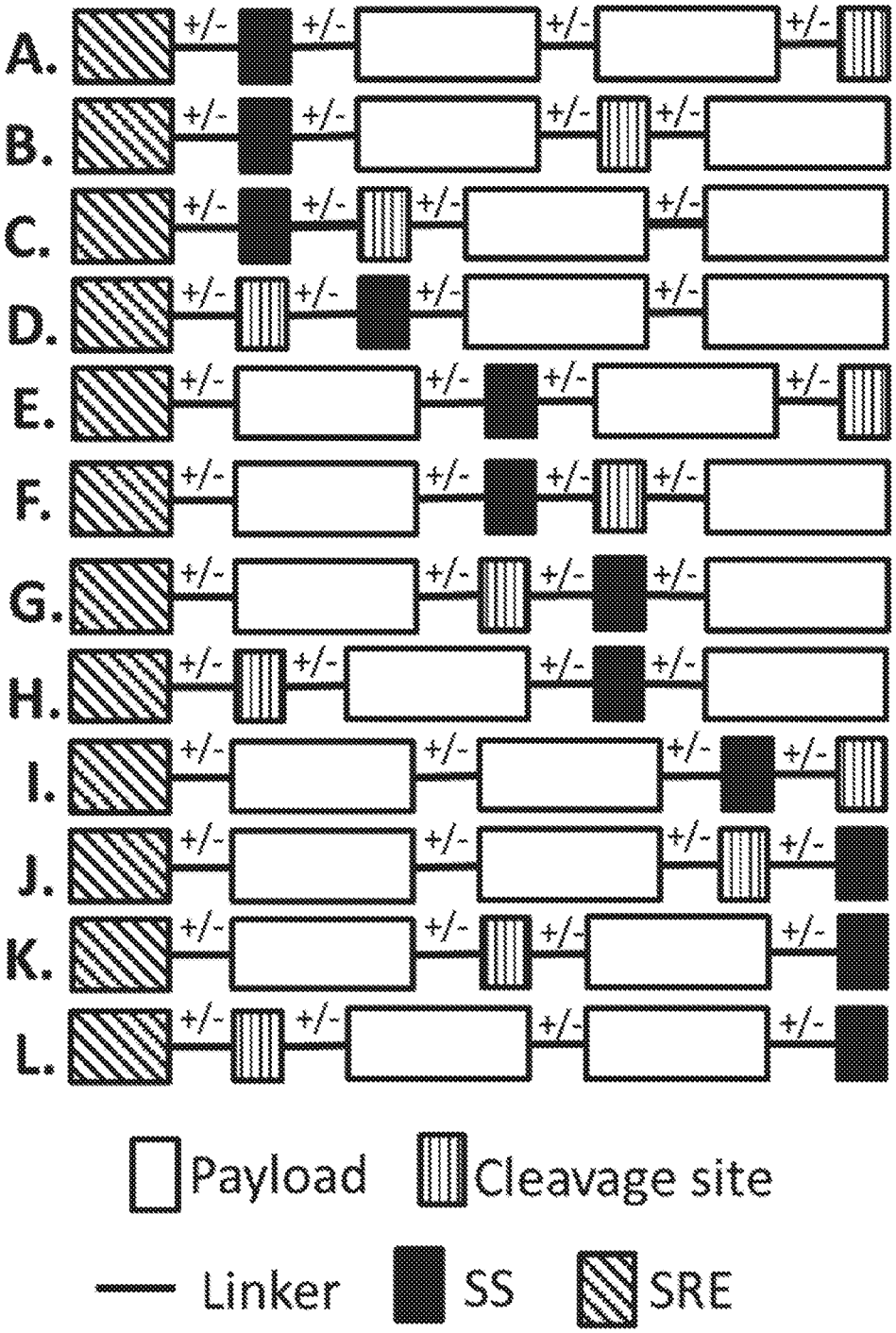
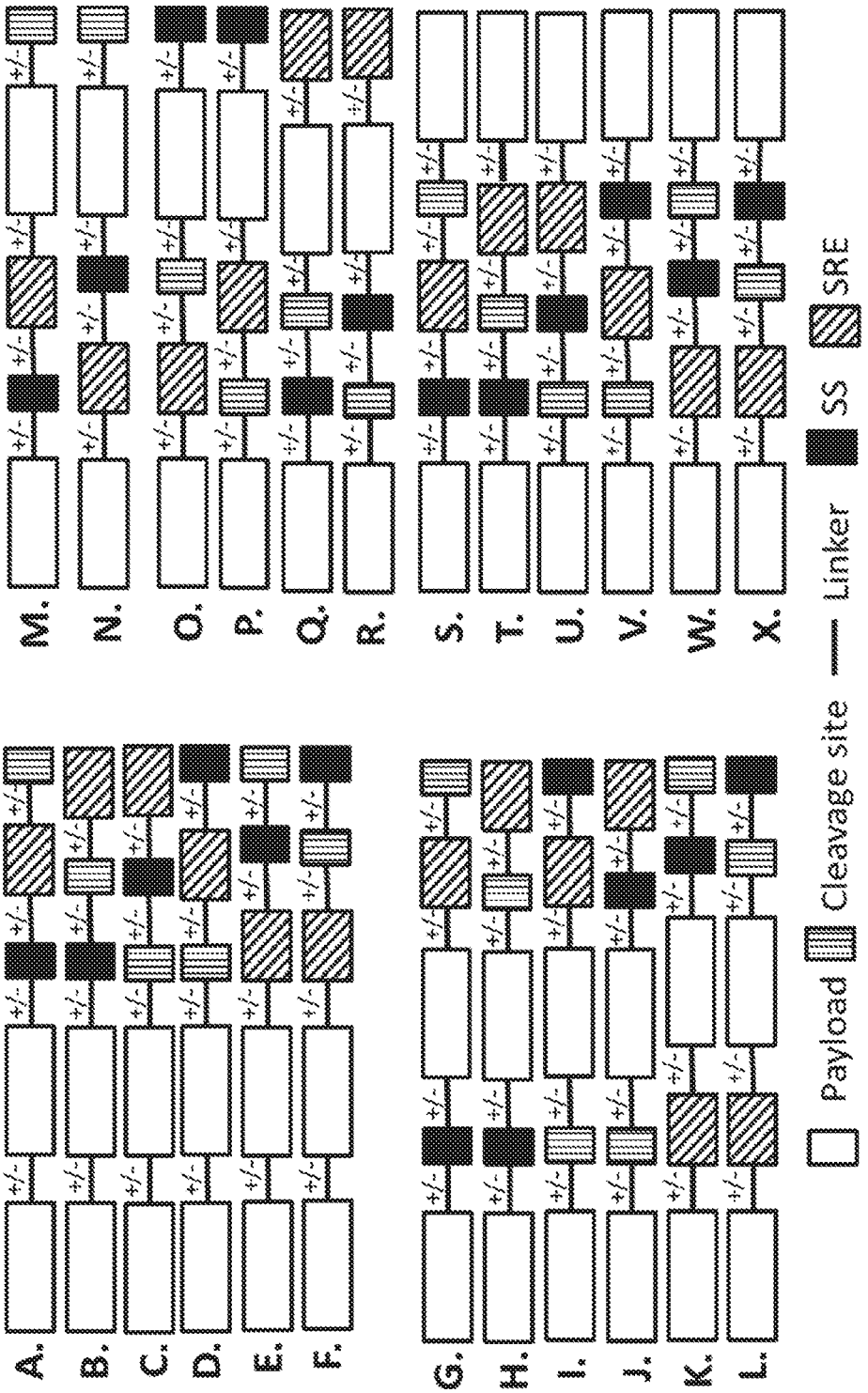


Figure 6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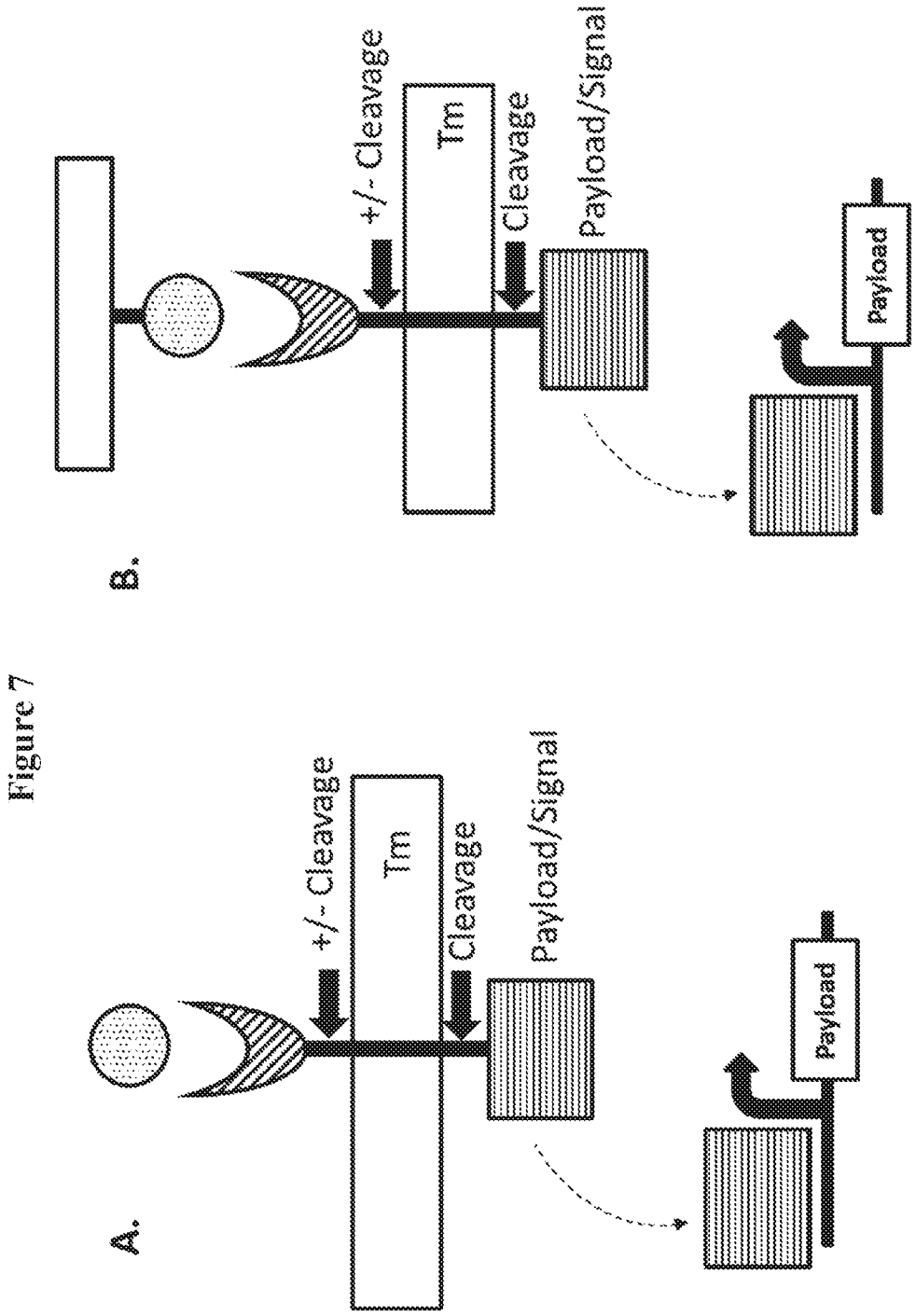
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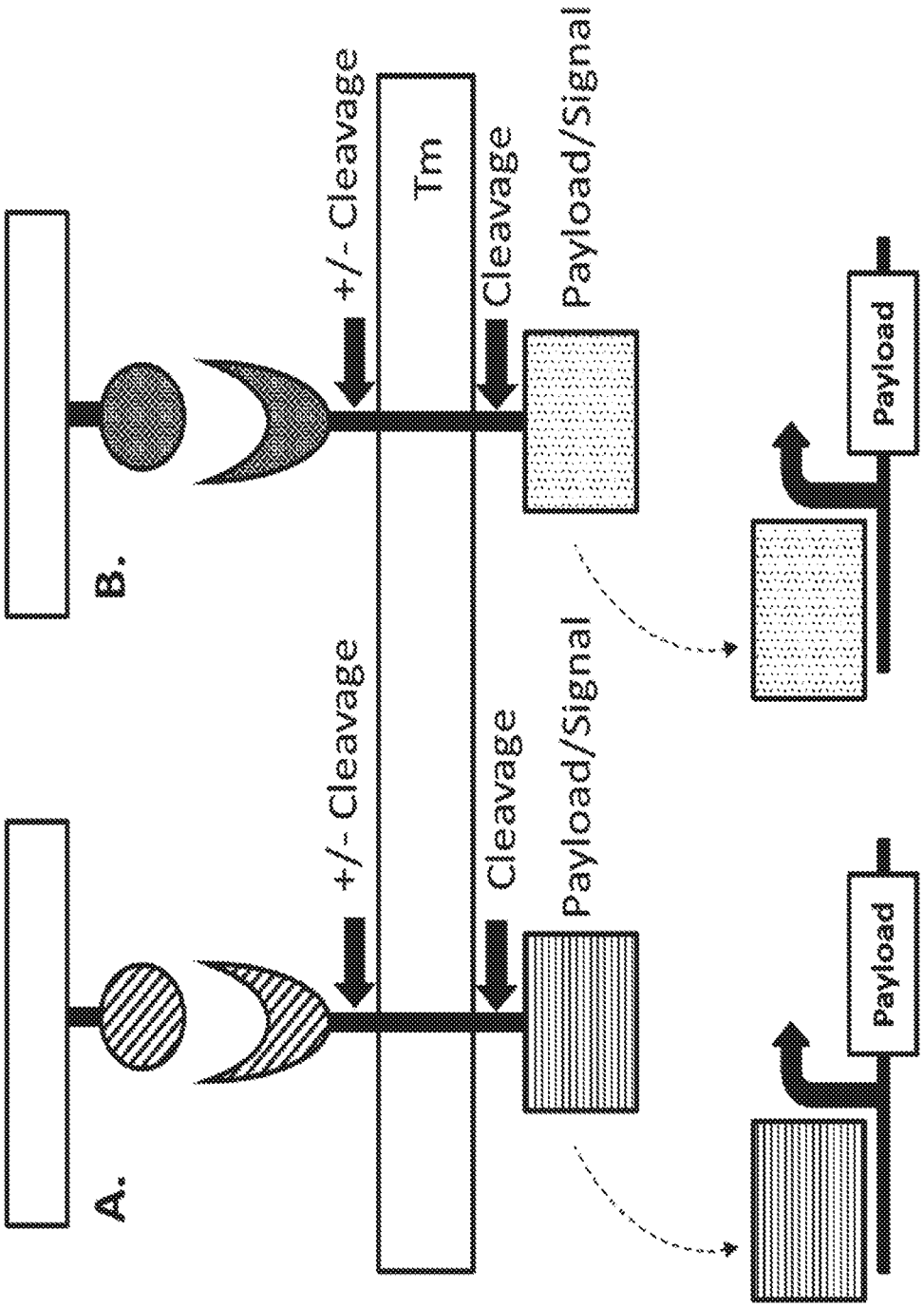
Payload/Signal
Payload
A.
+/- Cleavage
Tm
Cleavage
Payload/Signal
Payload

Figure 7

Figure 8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B.
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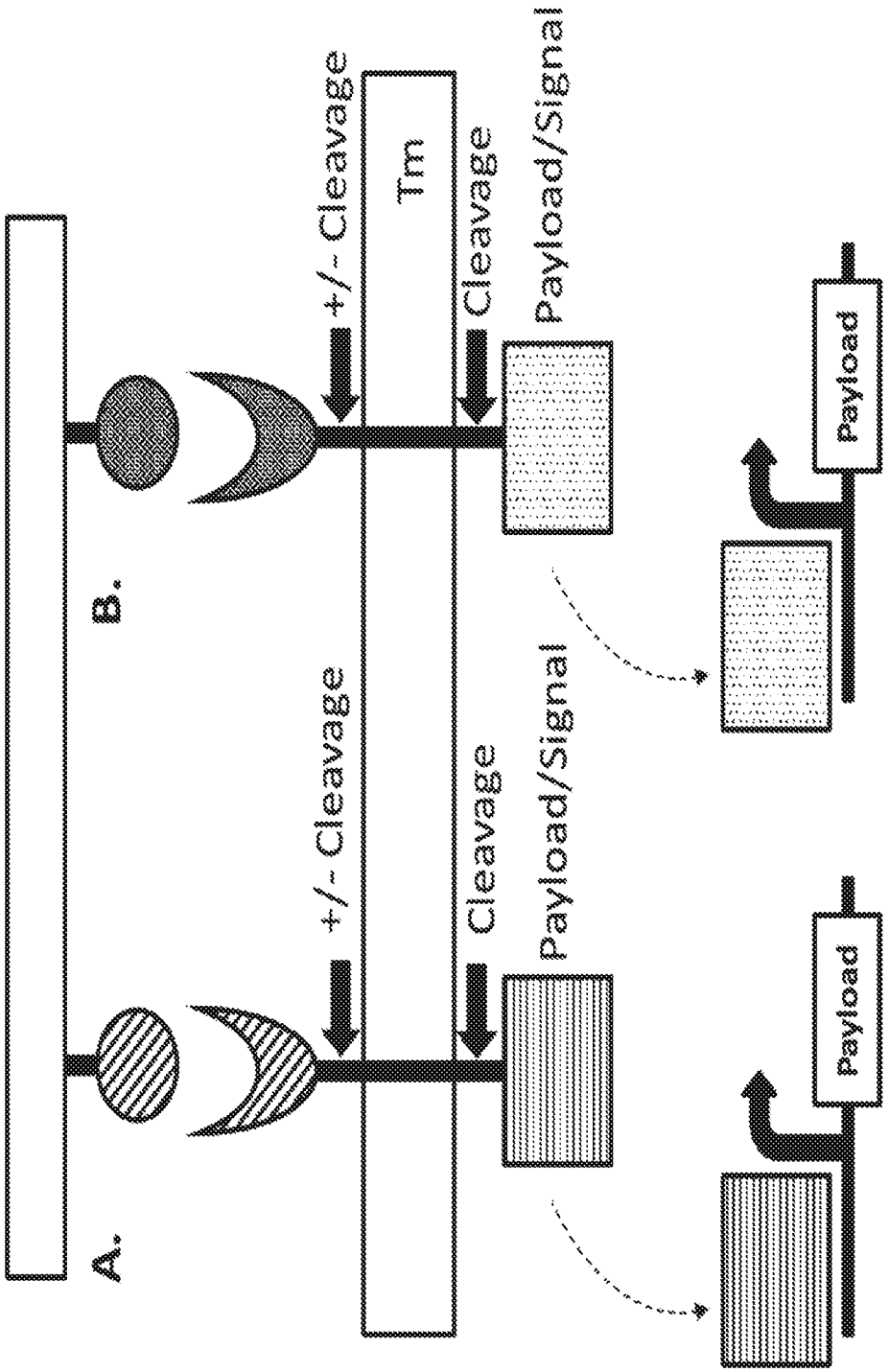
+/- Cleavage
Cleavage
Payload/Signal
Payload

Figure 9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B.
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Tm
Cleavage
Payload/Signal
+/- Cleavage
Cleavage
Payload/Signal
Payload
Payload

Figure 10

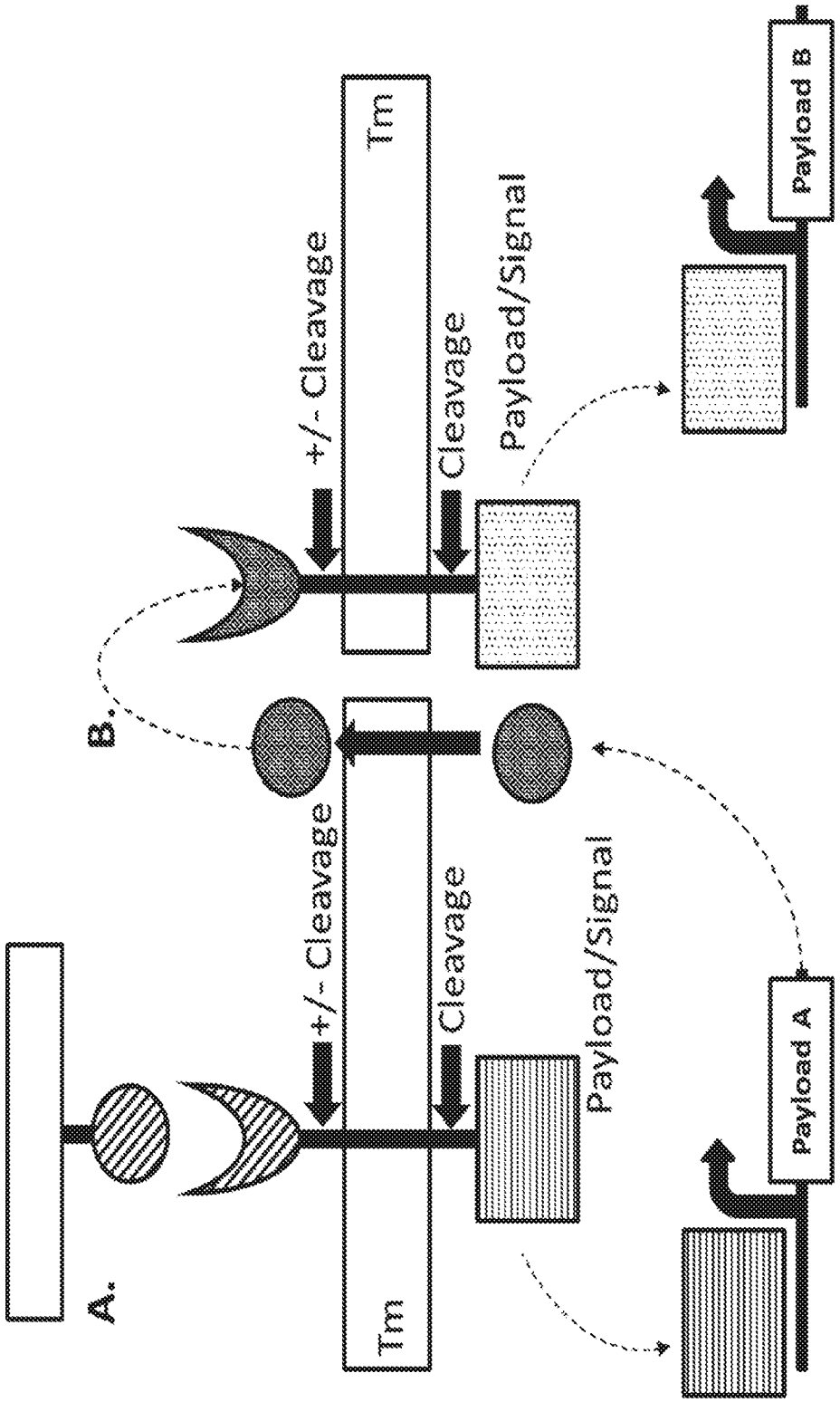

Figure 11

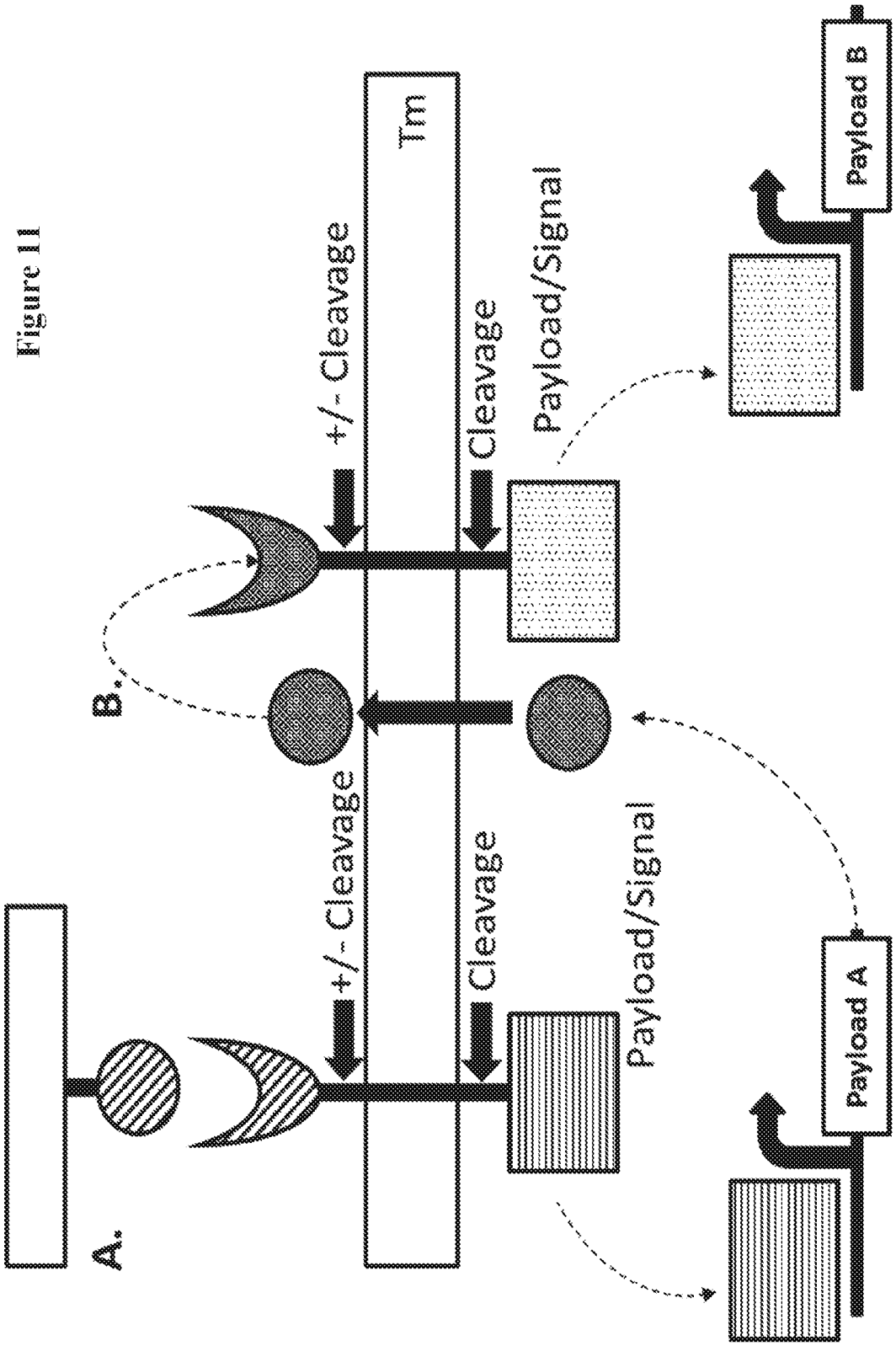

Figure 12

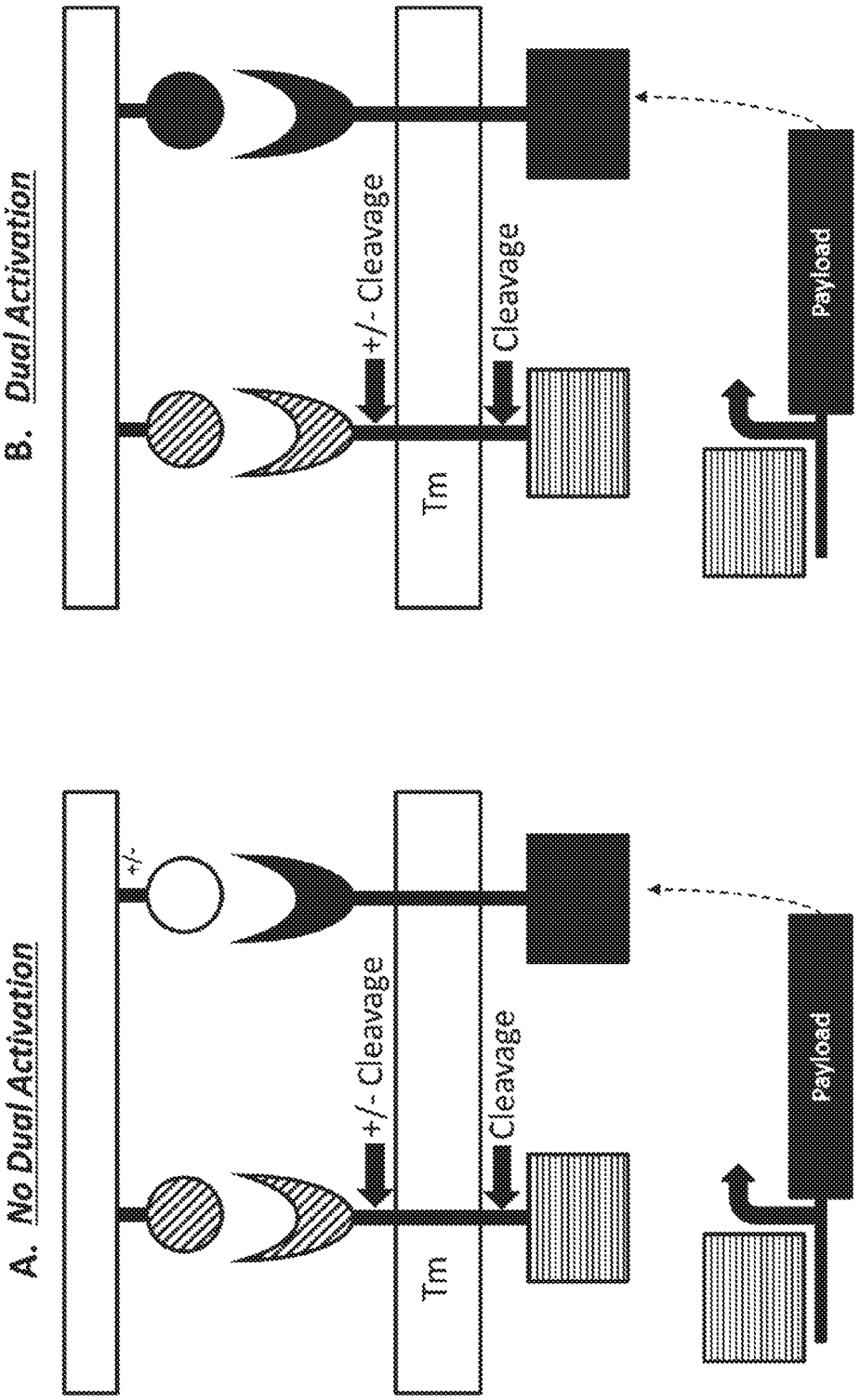
A. No Dual Activation
+/-
+/- Cleavage
Cleavage
Tm
Payload
B. Dual Activation
+/- Cleavage
Cleavage
Tm
Payload

Figure 13

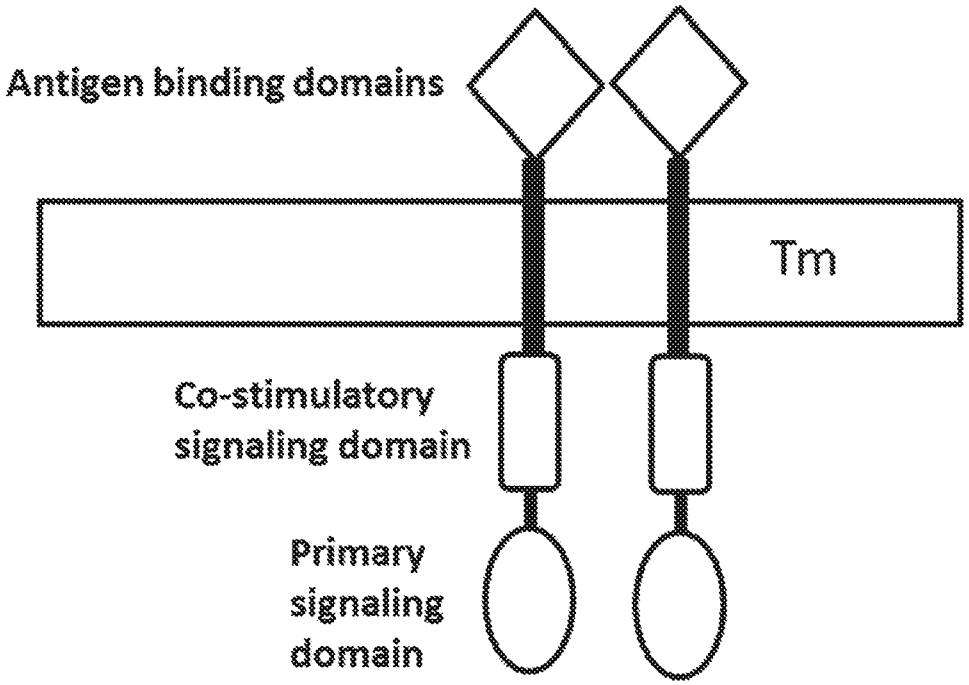

Figure 14

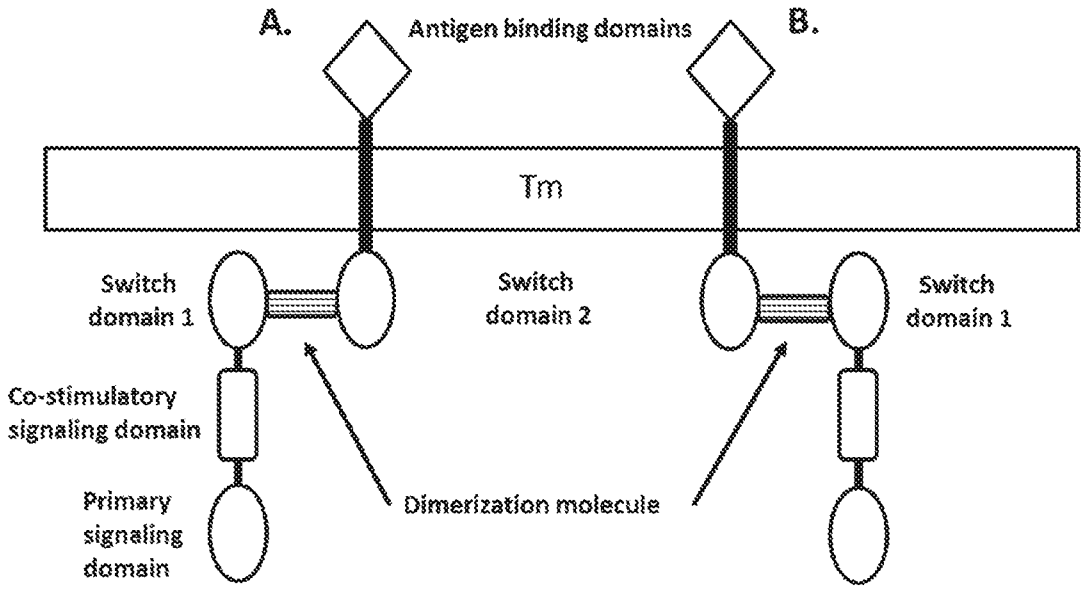

Figure 15

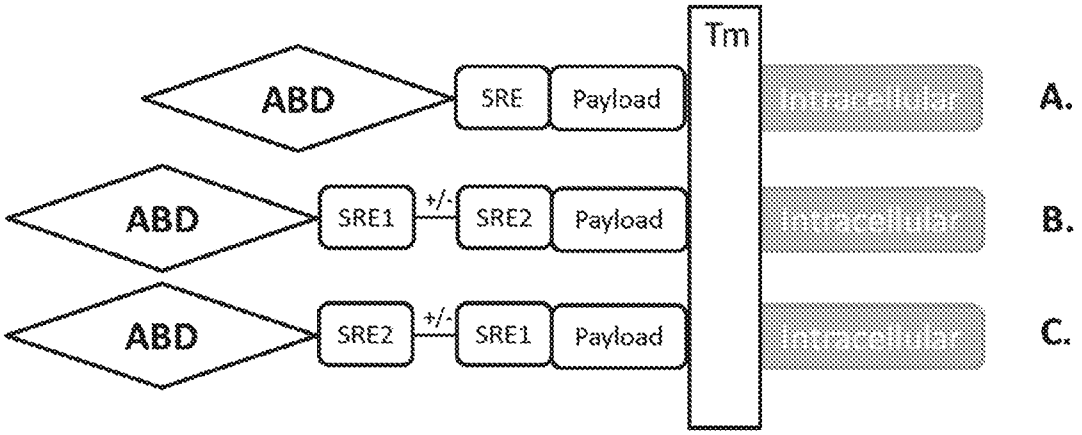
Tm
ABD
SRE
Payload
A.
ABD
SRE1
+/-
SRE2
Payload
B.
ABD
SRE2
+/-
SRE1
Payload
C.

Figure 16

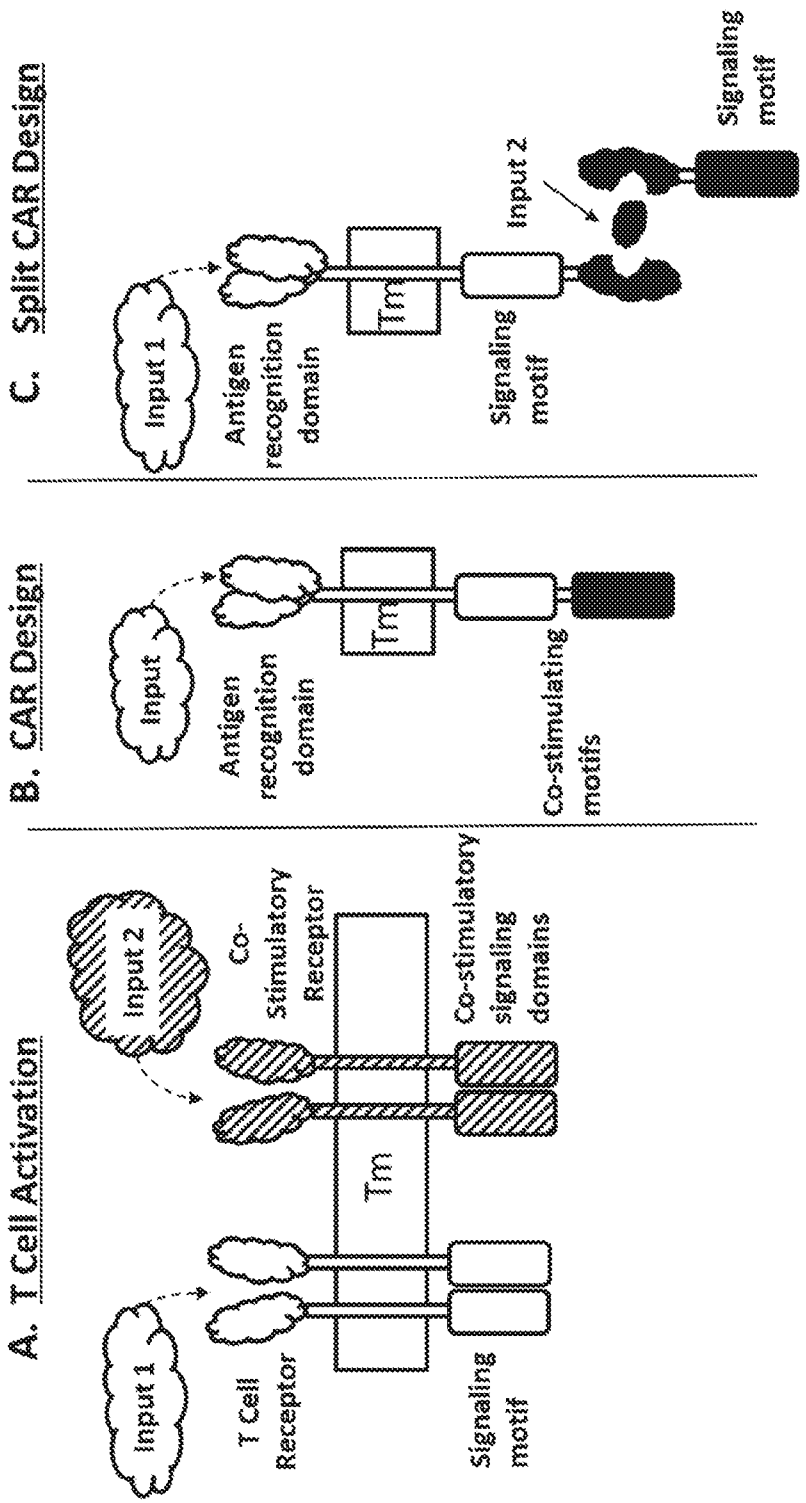
A. T Cell Activation
Input 1
T Cell Receptor
Input 2
Co-Stimulatory Receptor
Tm
Signaling motif
Co-stimulatory signaling domains
B. CAR Design
Input
Antigen recognition domain
Tm
Co-stimulating motifs
C. Split CAR Design
Input 1
Antigen recognition domain
Tm
Signaling motif
Input 2
Signaling motif

Figure 17

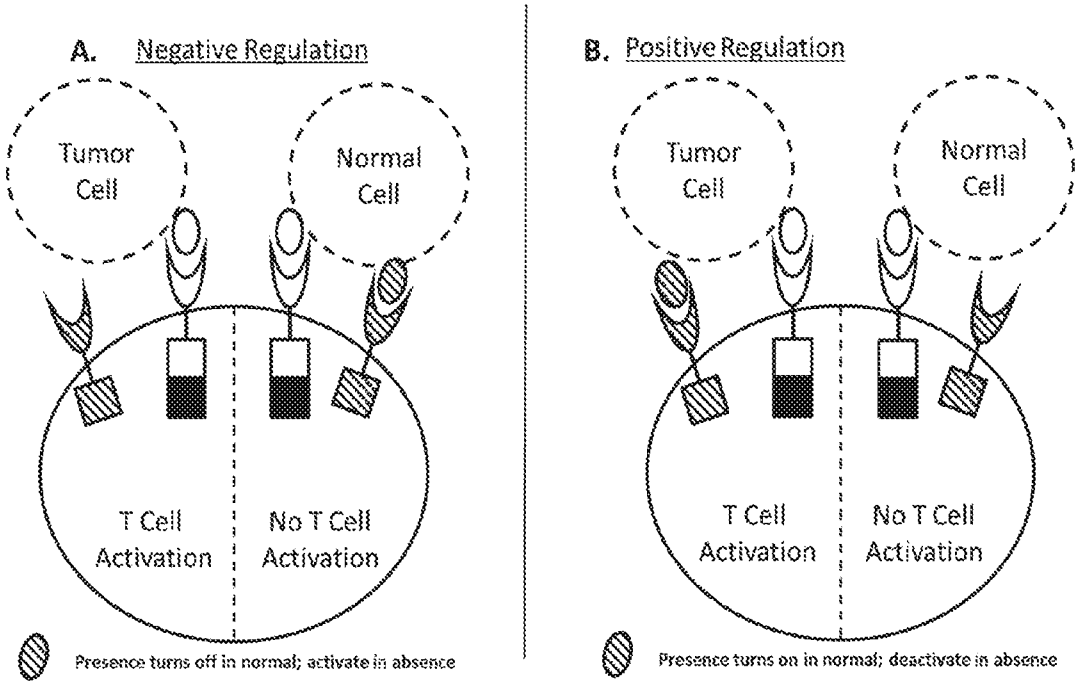

Figure 18

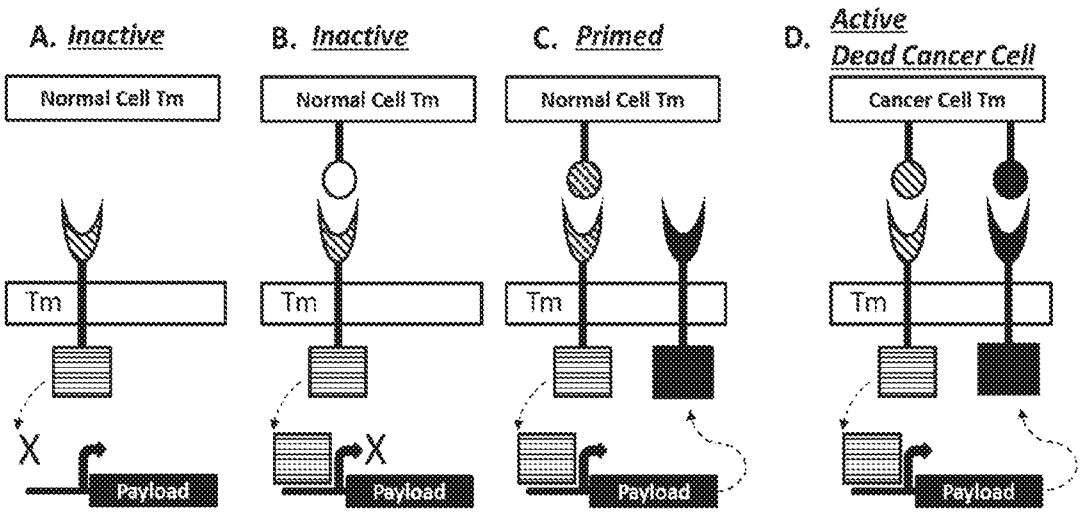

Figure 19A

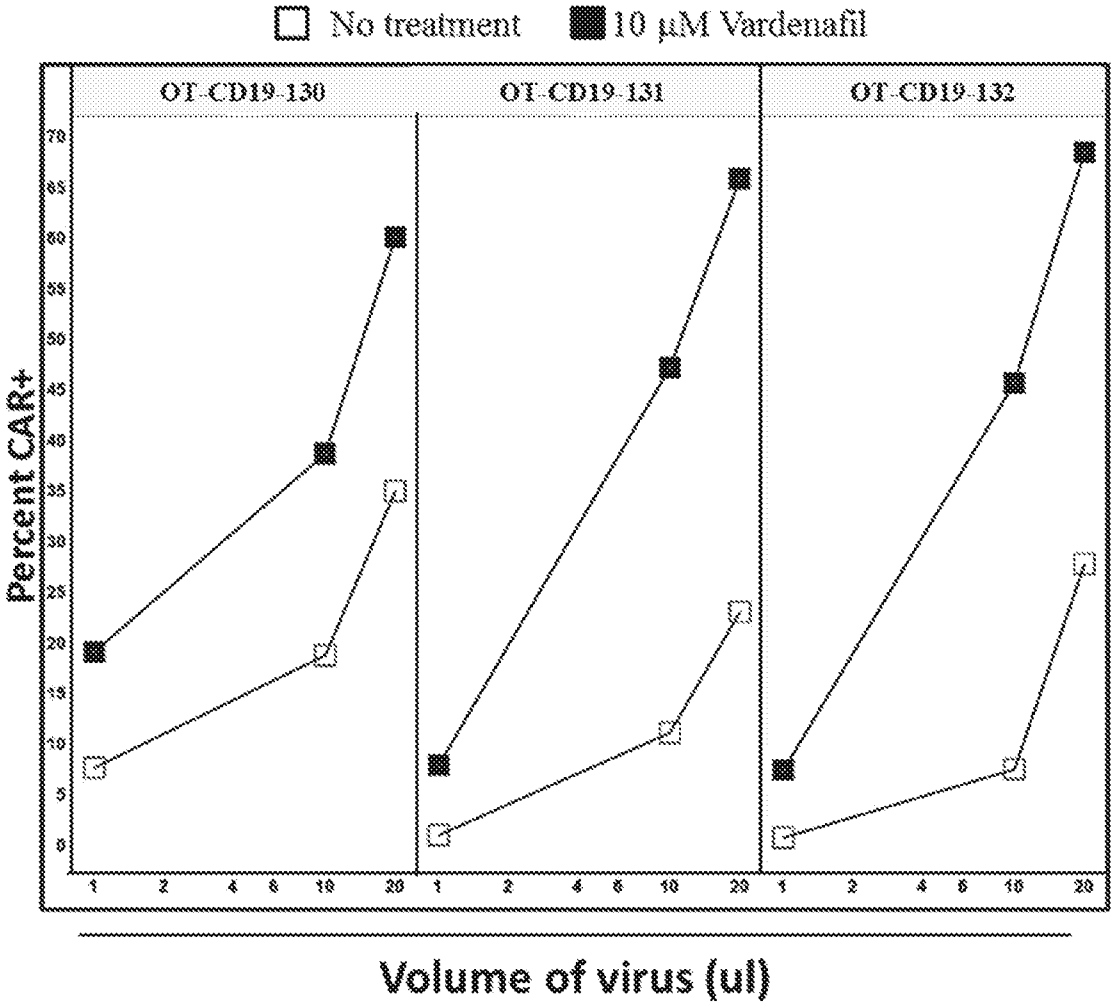
No treatment
10 µM Vardenafil
OT-CD19-130
OT-CD19-131
OT-CD19-132
Percent CAR+
Volume of virus (ul)

Figure 19B

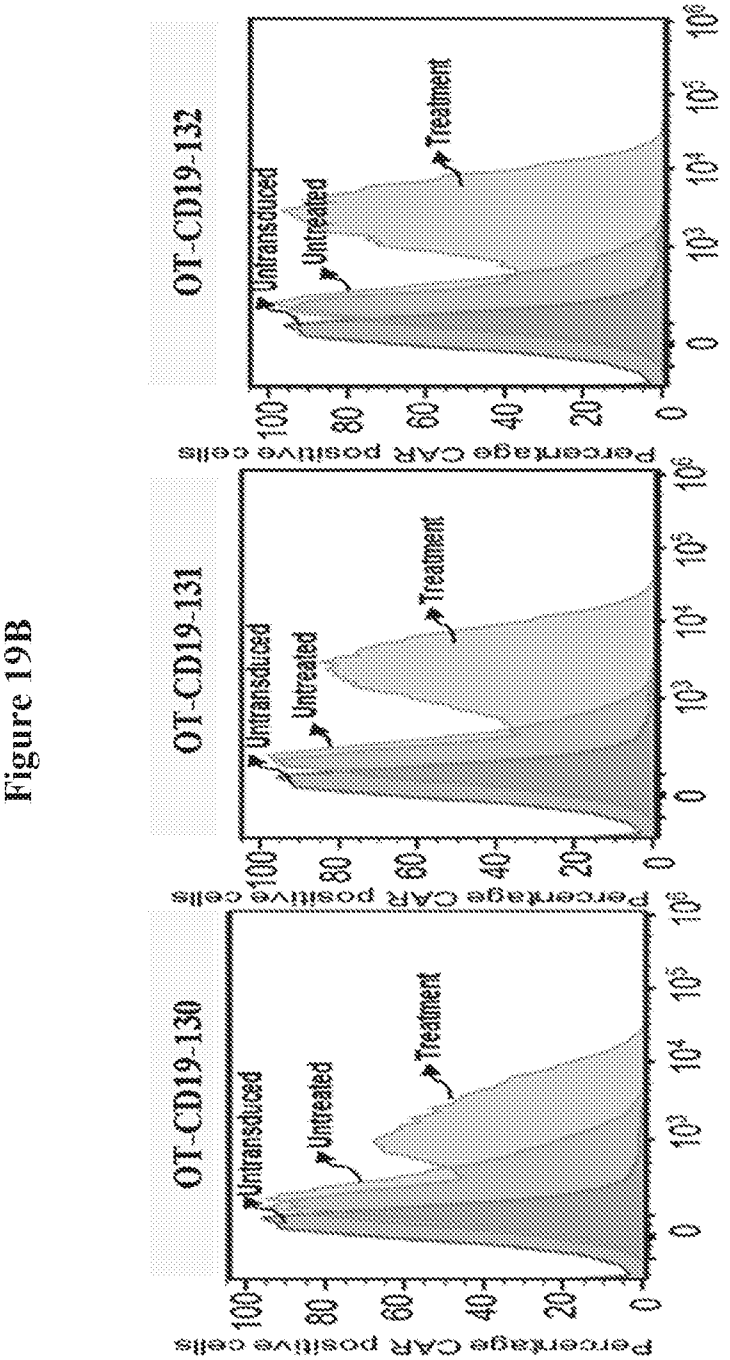
OT-CD19-130
OT-CD19-131
OT-CD19-132
Percentage CAR positive cells
Untransduced
Untreated
Treatment
0
20
40
60
80
100
0
10³
10⁴
10⁵
10⁶

Figure 19C

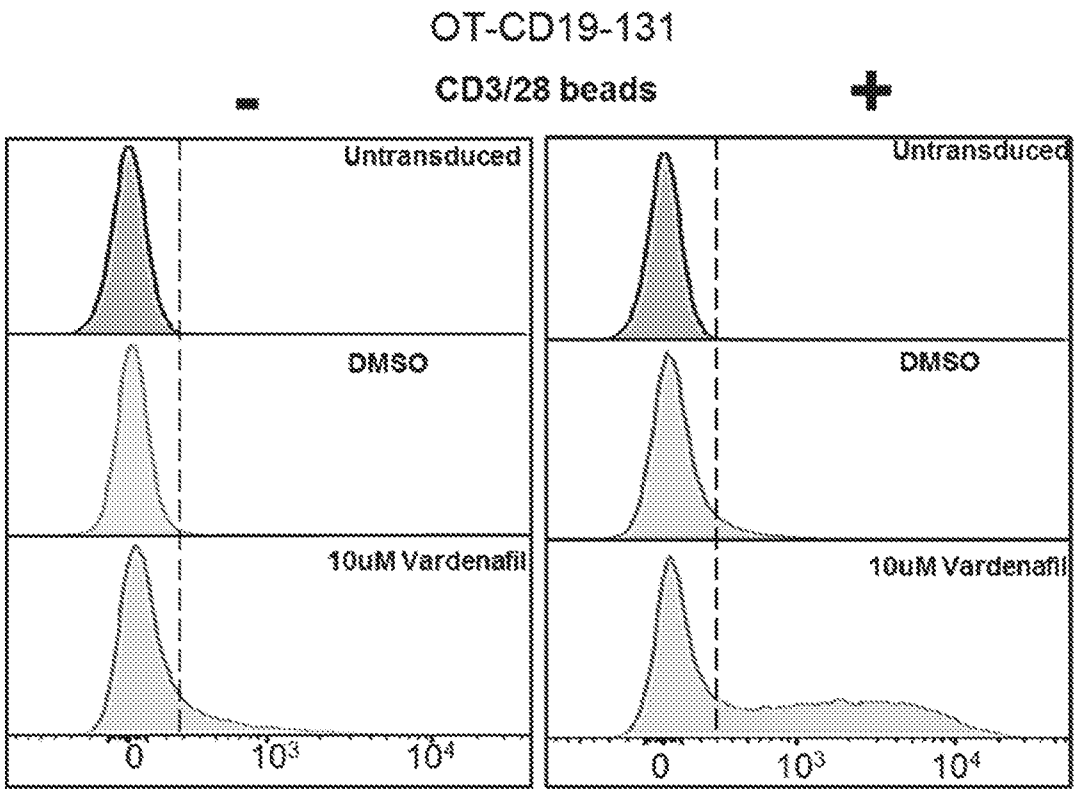
OT-CD19-131
CD3/28 beads
-
+
Untransduced
DMSO
10uM Vardenafil
Untransduced
DMSO
10uM Vardenafil
0
10^3
10^4
0
10^3
10^4

Figure 19D

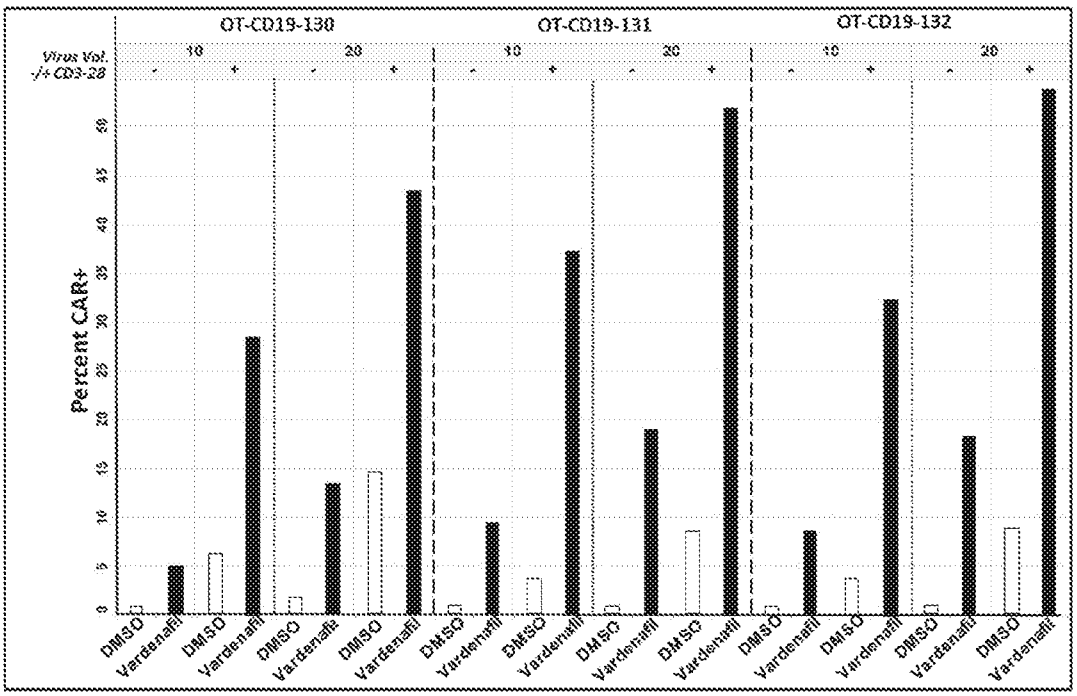
OT-CD19-130
OT-CD19-131
OT-CD19-132
Virus Vol.
-/+ CD3-28
10
20
Percent CAR+
0
5
10
15
20
25
30
35
40
45
50
DMSO
Vardenafil

Figure 19E

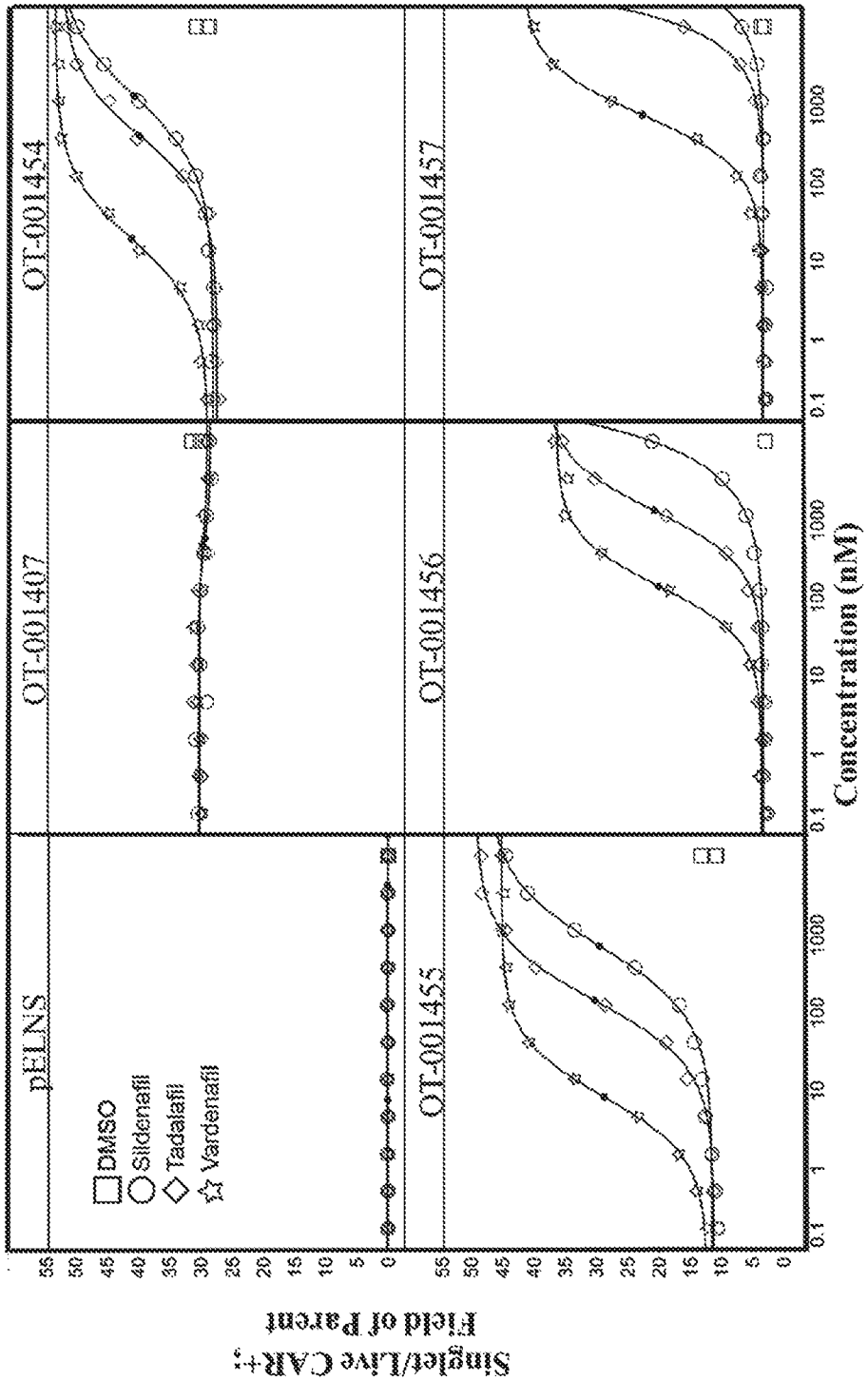
pELNS
OT-001407
OT-001454
OT-001455
OT-001456
OT-001457
DMSO
Sildenafil
Tadalafil
Vardenafil
Singlet/Live CAR+;
Field of Parent
Concentration (nM)
0
5
10
15
20
25
30
35
40
45
50
55
0.1
1
10
100
1000

Figure 19F

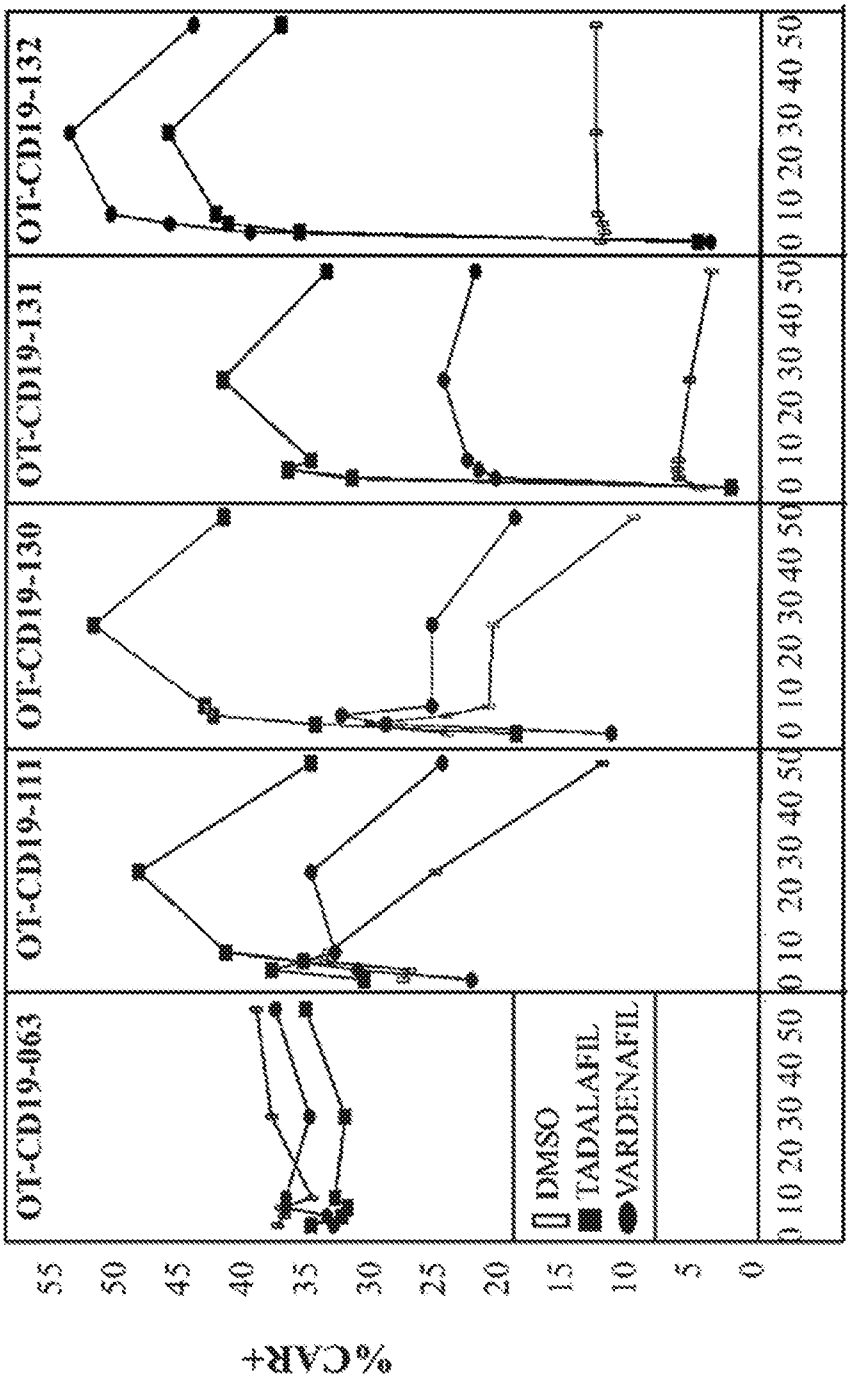
OT-CD19-063
OT-CD19-111
OT-CD19-130
OT-CD19-131
OT-CD19-132
DMSO
TADALAFIL
VARDENAFIL
%CAR+
Time of Ligand Treatment (hr)

Figure 19G

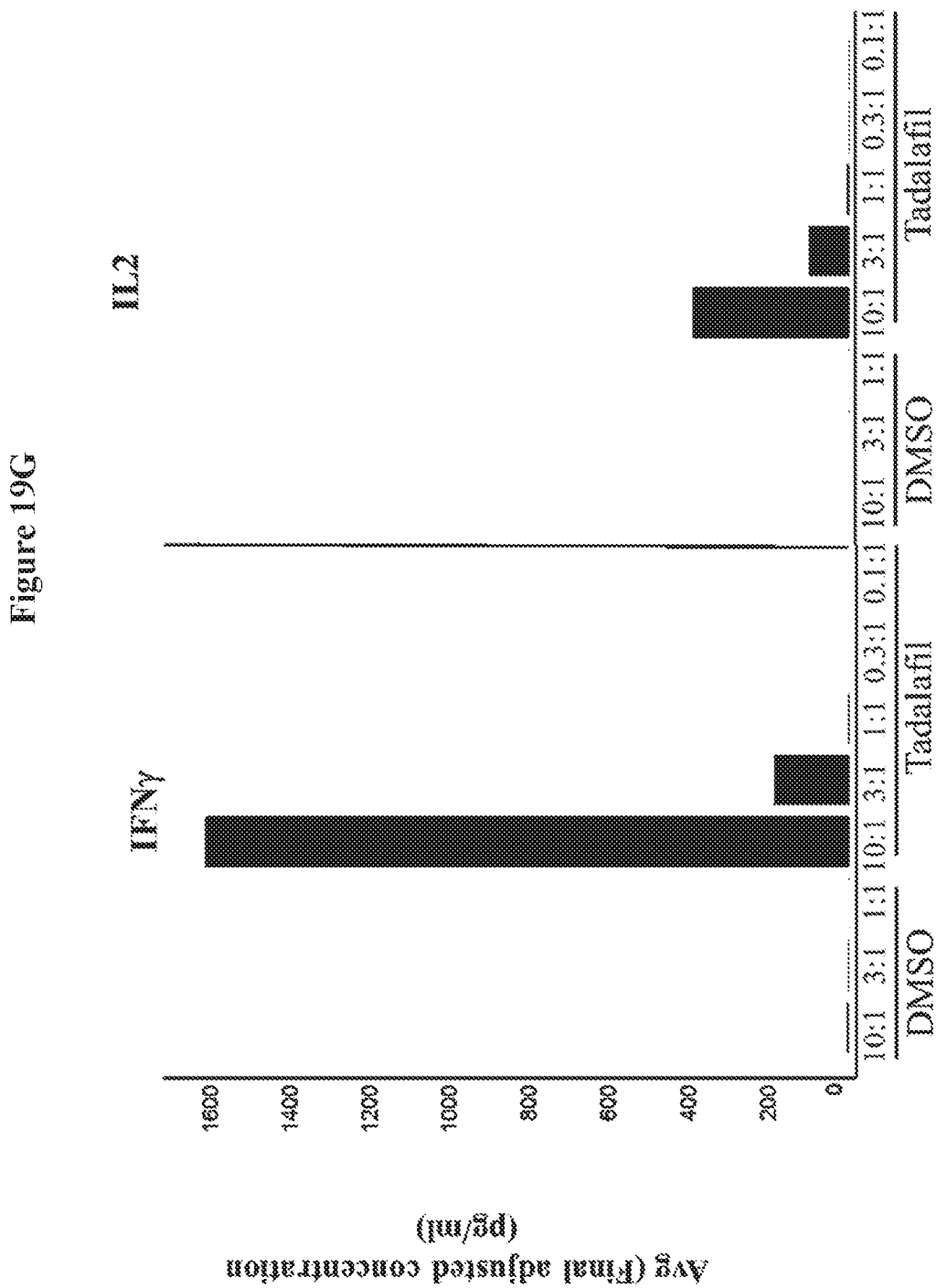
IFNγ
IL2
Avg (Final adjusted concentration (pg/ml)
0
200
400
600
800
1000
1200
1400
1600
10:1 3:1 1:1 10:1 3:1 1:1 0.3:1 0.1:1 10:1 3:1 1:1 10:1 3:1 1:1 0.3:1 0.1:1
DMSO
Tadalafil
DMSO
Tadalafil

Figure 19H

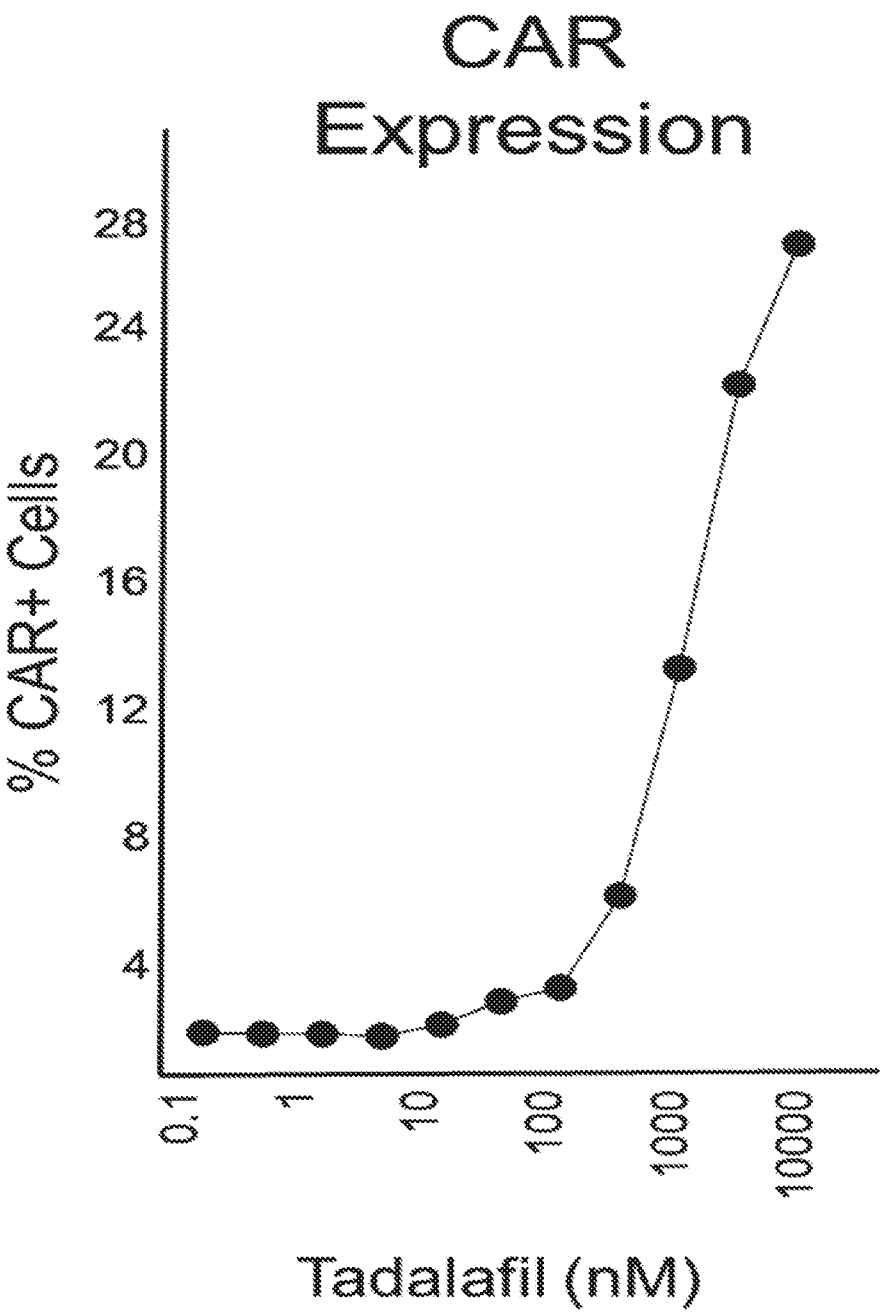
CAR
Expression
% CAR+ Cells
28
24
20
16
12
8
4
0.1
1
10
100
1000
10000
Tadalafil (nM)

Figure 19I

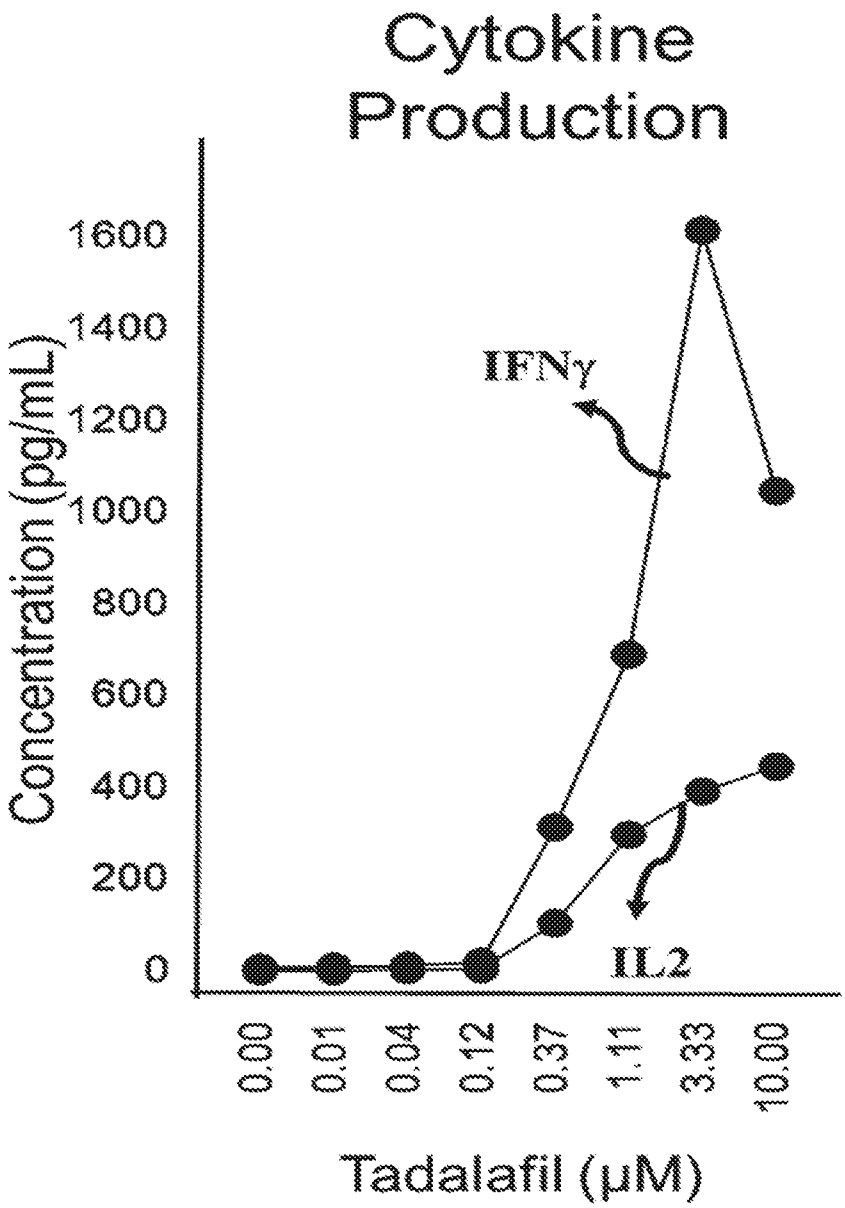
Cytokine Production
Concentration (pg/mL)
1600
1400
1200
1000
800
600
400
200
0
IFNγ
IL2
0,00
0,01
0,04
0,12
0,37
1,11
3,33
10,00
Tadalafil (μM)

Figure 19J

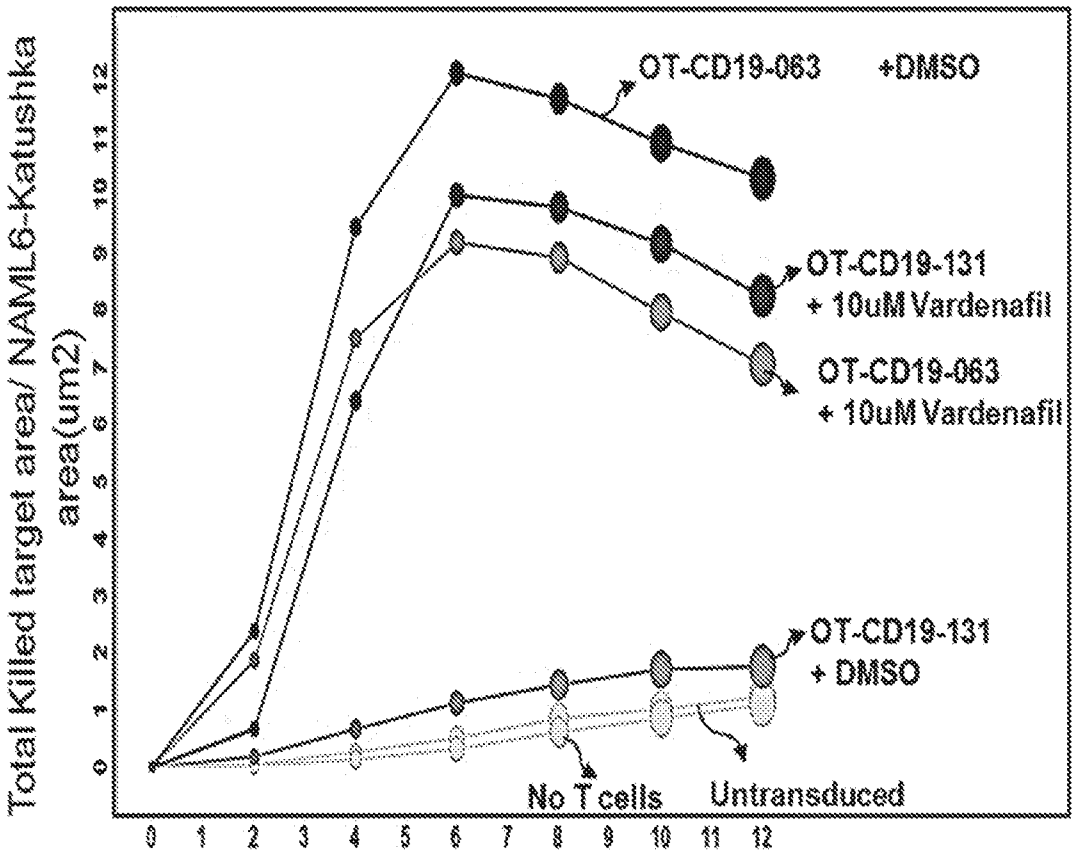
Total Killed target area/ NAML6-Katushka area(um2)
0 1 2 3 4 5 6 7 8 9 10 11 12
0 1 2 3 4 5 6 7 8 9 10 11 12
OT-CD19-063 +DMSO
OT-CD19-131 + 10uM Vardenafil
OT-CD19-063 + 10uM Vardenafil
OT-CD19-131 + DMSO
No T cells
Untransduced

Figure 19K

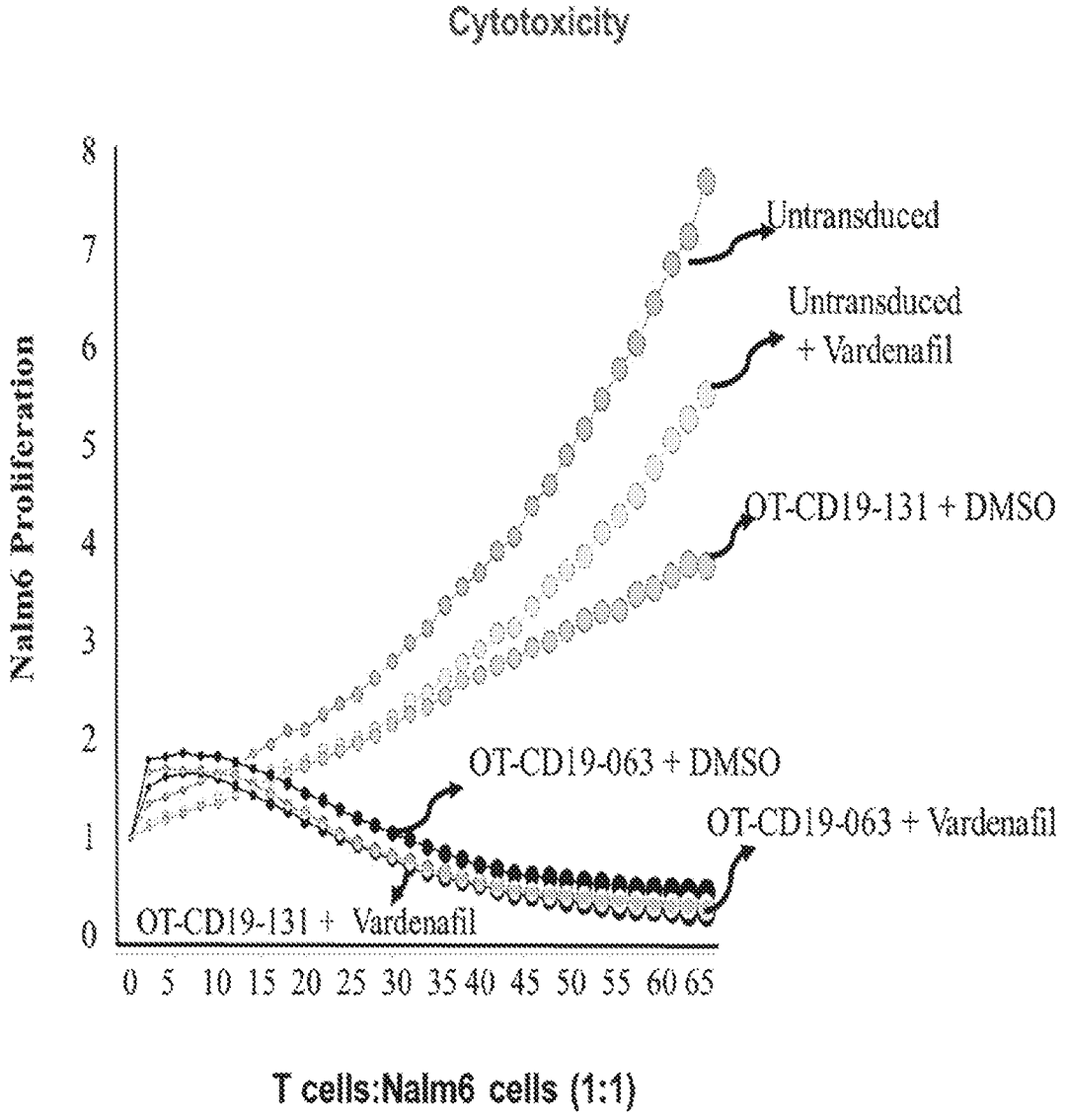
Cytotoxicity
Nalm6 Proliferation
0
1
2
3
4
5
6
7
8
0 5 10 15 20 25 30 35 40 45 50 55 60 65
T cells:Nalm6 cells (1:1)
Untransduced
Untransduced + Vardenafil
OT-CD19-131 + DMSO
OT-CD19-063 + DMSO
OT-CD19-063 + Vardenafil
OT-CD19-131 + Vardenafil

Figure 20A

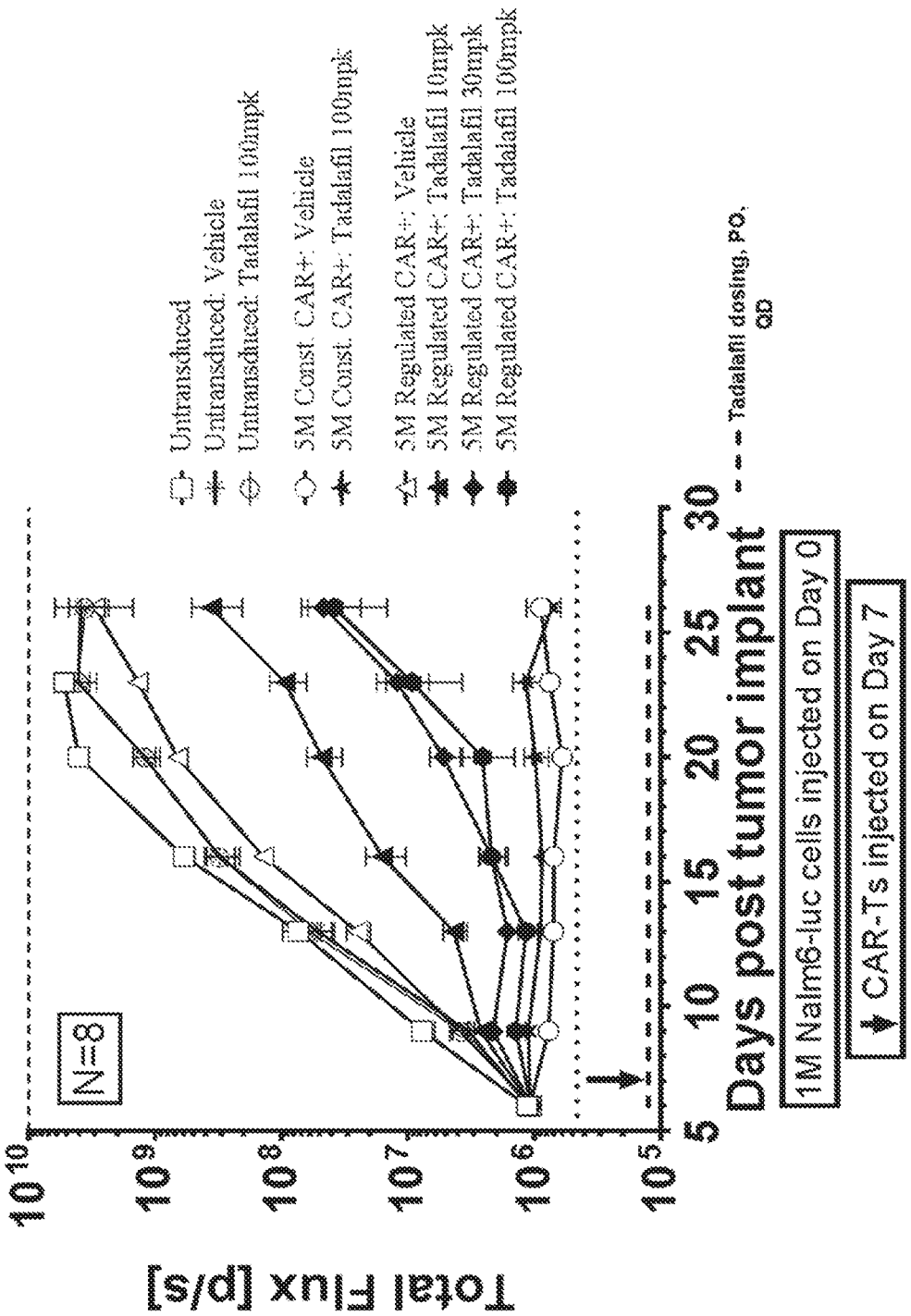
Untransduced
Untransduced: Vehicle
Untransduced: Tadalafil 100mpk
5M Const. CAR+: Vehicle
5M Const. CAR+: Tadalafil 100mpk
5M Regulated CAR+: Vehicle
5M Regulated CAR+: Tadalafil 10mpk
5M Regulated CAR+: Tadalafil 30mpk
5M Regulated CAR+: Tadalafil 100mpk
- - - Tadalafil dosing, P.O., QD
N=8
Total Flux [p/s]
Days post tumor implant
1M Nalm6-luc cells injected on Day 0
CAR-Ts injected on Day 7

Figure 20B

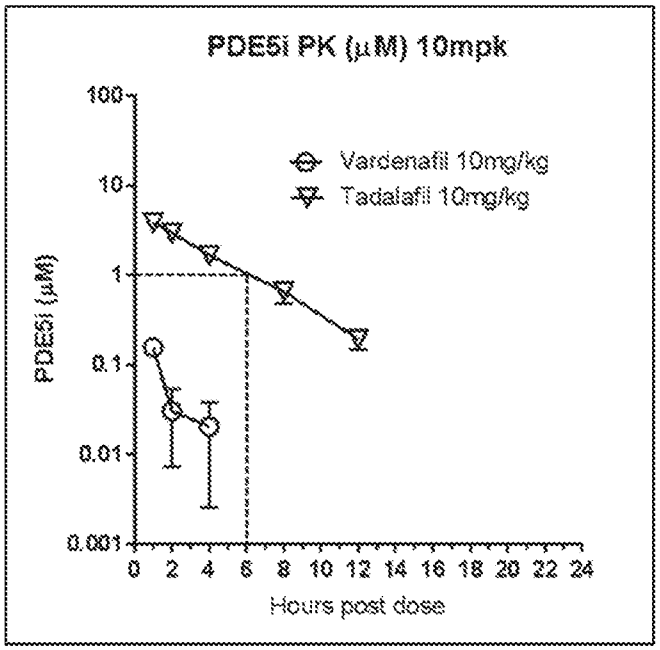

Figure 20C