There remains a need in the immunotherapy field for alternative compositions and methods that provide immunomodulatory signals to host cells for treating various diseases, such as cancer or infections. Presently disclosed embodiments address these needs and provide other related advantages.

~~BRIEF~~ SUMMARY

In certain aspects, the present disclosure is directed to a fusion protein, comprising an extracellular component that contains a binding domain that specifically binds a target, an intracellular component comprised of an intracellular signaling domain, and a hydrophobic component connecting the extracellular and intracellular components, provided that the length of a fusion protein::target complex spans a distance similar to a distance between membranes in an immunological synapse.

In some ~~embodiments~~examples, a length or spatial distance of a complex formed between the fusion protein and the target or a portion of such fusion protein::target complex (generally the extracellular portion of such complex) is or spans a particular distance, *e.g.*, in some examples~~embodiments~~, is a distance that is less than or less than about a certain distance. In some aspects, a distance of the fusion protein::target complex (or, typically, the extracellular portion thereof) is less than at or about 50 nm, less than at or about 40 nm, less than at or about 30 nm, or less than at or about 20 nm or equal to or less than at or about 15 nm. In some examples~~embodiments~~, it is at or about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nm, such as at or about 14 or 15 nm. In some aspects, the distance is one that is similar to a distance between membranes in an immunological synapse or is a distance that is the same, about the same, or substantially the same, as a distance between the membrane proximal-most portion, *e.g.*, residue, of the extracellular domain of a TCR and the membrane proximal-most portion, *e.g.*, residue, of an MHC (*e.g.*, HLA, such as an MHCI or MHCII) molecule, with respect to a TCR-peptide/MHC complex or the distance spanned by the extracellular portions of such a complex (or spatial distance spanned by the extracellular portion known to be contained within a synapse, such as a complex containing CD8, CD4, CD28, and the respective binding partner or ligand thereof).

In some examples~~embodiments~~, spatial distances of

complexes refer to a distance between membranes of two different cells, wherein a first cell and a second cell each express on their surface a binding partner that can form a complex between the membranes when the cells are in proximity to each other. In some aspects, the distance is a distance that is the same, about the same, or substantially the same, as a distance spanned by the extracellular portions of a complex formed between a TCR and cognate interaction with an MHC molecule. In some aspects, such as where a fusion protein comprises a binding domain from a molecule ordinarily capable of entering an immunological synapse or co-localizing with an antigen receptor, the distance is similar to or the same as that spanned by a complex formed between the molecule (having the binding domain used in the fusion protein), and a natural binding partner thereof. In some aspects, such as where the fusion protein comprises a binding domain from a molecule ordinarily not capable of entering an immunological synapse or ordinarily not capable of co-localizing with an antigen receptor, the distance is different than, *e.g.*, less than or substantially less than, that spanned by a complex formed between the molecule (having the binding domain or functional portion thereof used in the fusion protein), and a natural binding partner thereof.

In some examples~~embodiments~~, a binding domain within the extracellular component of a fusion protein of this disclosure contains a target-binding portion of a molecule capable of delivering an inhibitory signal, such as of an inhibitory molecule, *e.g.*, an immunoinhibitory molecule, such as an immunoinhibitory receptor or immune checkpoint molecule. In some aspects, such a molecule is a glycoprotein, checkpoint family member. In certain examples~~embodiments~~, the fusion protein comprising a binding domain from a glycoprotein, checkpoint family member or is not a B7 or B7-binding molecule or is not a CD28-B7-superfamily member (*e.g.*, is not a CD28, CTLA4, ICOS, or other B7 family binding molecule) Exemplary glycoprotein, checkpoint family members include CD200R, SIRPα, CD279 (PD-1), CD2, CD95 (Fas), CTLA4 (CD152), CD223 (LAG3), CD272 (BTLA), A2aR, KIR, TIM3, CD300, or LPA5, or a binding variant of any such molecule. In some examples~~embodiments~~, a binding domain within the extracellular component of a fusion protein of this disclosure comprises a binding partner of any of the foregoing, or a binding variant of any such molecule. In some

aspects of such examples~~embodiments~~, the intracellular portion of a fusion protein includes a signaling domain capable of delivering a stimulatory, such as a costimulatory, signal to a lymphocyte, such as a T cell, such as a costimulatory region of CD28, 41BB, ICOS, or other costimulatory molecule. In some aspects, the intracellular portion of the fusion protein does not include an intracellular signaling domain of the inhibitory molecule, such as of a checkpoint or immunoinhibitory molecule, when the extracellular binding portion is from a checkpoint or immunoinhibitory molecule. In some aspects, a fusion protein does not include a primary signaling domain such as a CD3ζ signaling domain or other domain capable of delivering a primary signal to a T cell.

In certain aspects, the extracellular component or the binding portion thereof contains or is a binding domain of a molecule or ectodomain capable of specifically binding to CD200, such as a binding portion of a CD200R or variant thereof. In some examples~~embodiments~~, the binding domain is or includes a binding region of a molecule or of an ectodomain that is capable of specifically binding to a CD47, such as a SIRP ectodomain or CD47-binding region thereof, such as a SIRPα ectodomain or CD47-binding region thereof. In some examples~~embodiments~~, the binding domain is capable of binding to a PD-L1 or a PD-L2 or a LAG3 molecule. Exemplary targets may be one or more proteins whose expression is increased or upregulated in certain cells or tissues associated with or of a disease or condition to be treated or ameliorated with the fusion proteins and compositions provided herein, such as a tumor cell or tumor microenvironment, or is bound by a receptor generally upregulated on immune cells such as lymphocytes infiltrating a diseased tissue, such as a tumor.

In some examples~~embodiments~~, the extracellular component further includes one or more additional regions or domains, for example, from a molecule other than that from which the binding domain is derived or other than the molecule with which the binding domain shares identity. The one or more additional extracellular domain(s) may include a spacer region, such as one from an immunoglobulin molecule, which may contain all or a portion of a hinge, or constant region domain such as CH2 or CH3 domain, or from another cell surface molecule such as a costimulatory receptor, such as CD28. The additional extracellular domain(s) may include, in some aspects, a

multimerization domain, *e.g.*, a dimerization domain or sequence that may promote homo- or heterodimerization with another molecule, such as multimerization of two or more of the fusion proteins. In some examples~~embodiments~~, such a domain includes a portion of an extracellular domain of a CD28 molecule including at least the transmembrane-proximal-most cysteine, and generally an extracellular portion between such cysteine and the membrane, or modified variant thereof. In some aspects, such a domain includes an amino acid sequence as set forth in SEQ ID NO: 32, or portion thereof, or variant thereof such as having at least 90%, 95%, or 99 % identity thereto. In some aspects, such a domain may be included in order to facilitate or promote multimerization. In some examples~~embodiments~~, a fusion protein contains an extracellular component including a CD200-binding domain, such as an extracellular portion (or portion thereof, such as a binding domain thereof) of a CD200R, such as an extracellular portion of CD200R having an amino acid sequence as set forth in SEQ ID NO: 25 or encoded by a nucleic acid molecule as set forth in SEQ ID NO: 2, or a CD200-binding portion thereof or variant thereof or binding portion thereof. In some aspects of such examples~~embodiments~~, the extracellular portion of the fusion protein further includes a portion of an extracellular region of CD28, such as up to about 9 to about 12 amino acids thereof (*e.g.*, 9 amino acids or 12 amino acids), and in some aspects including a membrane-proximal-most cysteine residue of a CD28 extracellular region. In some such examples~~embodiments~~, the length of the CD200R portion of the extracellular region is reduced in length corresponding to the number of additional residues in the CD28-derived portion, such as by about 9 to about 12 amino acids (*e.g.*, 9 amino acids or 12 amino acids), or by a sufficient number of amino acids that the distance spanned by the extracellular portion of a complex between the fusion protein and a CD200 molecule is similar to, substantially similar to, or the same as that spanned by the extracellular portion of a complex between a human CD200R, *e.g.*, a CD200R, and CD200; or that spanned by the extracellular portion of a complex between a TCR in cognate interaction with an MHC molecule (*e.g.*, MHC I or MHCII) in binding to a cognate peptide-MHC complex; or that of an immunological synapse. In some aspects, the fusion protein further includes a transmembrane domain, such as a CD28

transmembrane, such as a transmembrane domain encoded by the sequence set forth as SEQ ID NO: 4 or portion thereof, or a modified version thereof, such as a variant modified to contain additional charged regions or residues or hydrophilic residues to facilitate intermolecular interactions. In some examples~~embodiments~~, the protein further includes a CD28 intracellular signaling domain, such as a costimulatory domain of CD28, such as one that is capable of recruiting one or more adapter molecules to a CD28 in response to ligation. In some aspects, the CD28 intracellular domain includes or is a sequence encoded by the nucleotide sequence of SEQ ID NO: 5 or a portion or functional variant thereof.

In some examples~~embodiments~~, the present disclosure is directed to a fusion protein comprising an extracellular component comprised of a binding domain that specifically binds a target, an intracellular component comprised of an intracellular signaling domain, and a hydrophobic component connecting the extracellular and intracellular components, provided that the length of a fusion protein:target complex spans a distance similar to a distance between membranes in an immunological synapse, wherein (a) the extracellular component comprises an extracellular portion of a CD200R, (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28. In one aspect, the present disclosure refers to a fusion protein, comprising (a) an extracellular component comprised of a binding domain that specifically binds a target, (b) an intracellular component comprised of an intracellular signaling domain, and (c) a hydrophobic component connecting the extracellular and intracellular components, wherein the extracellular component comprises an extracellular portion of a CD200R and the intracellular signaling domain comprises an intracellular signaling domain of CD28.

In some examples~~embodiments~~, the present disclosure is directed to a fusion protein comprising an extracellular component comprised of a binding domain that specifically binds a target, an intracellular component comprised of an intracellular signaling domain, and a hydrophobic component connecting the extracellular and intracellular components, provided that the length of a fusion protein:target complex spans a distance similar to a distance between membranes in an immunological synapse, wherein (a) the extracellular component comprises an extracellular portion of a CD200R, (b) the hydrophobic component comprises a

transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28 and an intracellular signaling domain of a CD137 (4-1BB).

In some examples~~embodiments~~, the present disclosure is directed to a fusion protein comprising an extracellular component comprised of a binding domain that specifically binds a target, an intracellular component comprised of an intracellular signaling domain, and a hydrophobic component connecting the extracellular and intracellular components, provided that the length of a fusion protein::target complex spans a distance similar to a distance between membranes in an immunological synapse, wherein (a) the extracellular component comprises an extracellular portion of a CD200R, (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD137 (4-1BB).

In some examples~~embodiments~~, the present disclosure is directed to a fusion protein comprising an extracellular component comprised of a binding domain that specifically binds a target, an intracellular component comprised of an intracellular signaling domain, and a hydrophobic component connecting the extracellular and intracellular components, provided that the length of a fusion protein:target complex spans a distance similar to a distance between membranes in an immunological synapse, wherein (a) the extracellular component comprises an extracellular portion of a SIRPα, (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.

In some examples~~embodiments~~, the present disclosure is directed to a fusion protein comprising an extracellular component comprised of a binding domain that specifically binds a target, an intracellular component comprised of an intracellular signaling domain, and a hydrophobic component connecting the extracellular and intracellular components, provided that the length of a fusion protein::target complex spans a distance similar to a distance between membranes in an immunological synapse, wherein (a) the extracellular component comprises an extracellular portion of a CD279 (PD-1), (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.

In some examples~~embodiments~~, the present disclosure is directed to a fusion protein comprising an extracellular component comprised of a binding domain that specifically binds a target, an intracellular component comprised of an intracellular signaling domain, and a hydrophobic component connecting the extracellular and intracellular components, provided that the length of a fusion protein::target complex spans a distance similar to a distance between membranes in an immunological synapse, wherein (a) the extracellular component comprises an extracellular portion of a CD95 (Fas), (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.

In some examples~~embodiments~~, the present disclosure is directed to a fusion protein comprising an extracellular component comprised of a binding domain that specifically binds a target, an intracellular component comprised of an intracellular signaling domain, and a hydrophobic component connecting the extracellular and intracellular components, provided that the length of a fusion protein:target complex spans a distance similar to a distance between membranes in an immunological synapse, wherein (a) the extracellular component comprises an extracellular portion of a TIM3, (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.

In some examples~~embodiments~~, the present disclosure is directed to a fusion protein comprising an extracellular component comprised of a binding domain that specifically binds a target, an intracellular component comprised of an intracellular signaling domain, and a hydrophobic component connecting the extracellular and intracellular components, provided that the length of a fusion protein:target complex spans a distance similar to a distance between membranes in an immunological synapse, wherein (a) the extracellular component comprises an extracellular portion of a LAG3, (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.

In some examples~~embodiments~~, the present disclosure is directed to a fusion protein comprising an extracellular component comprised of a binding domain that specifically

binds a target, an intracellular component comprised of an intracellular signaling domain, and a hydrophobic component connecting the extracellular and intracellular components, provided that the length of a fusion protein::target complex spans a distance similar to a distance between membranes in an immunological synapse, wherein (a) the extracellular component comprises an extracellular portion of a CD2, (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.

In certain aspects, the present disclosure is directed to a nucleic acid molecule encoding a fusion protein as described herein. In another aspect, the present disclosure refers to a nucleic acid molecule encoding a fusion protein as described herein.

In certain aspects, the present disclosure is directed to a vector comprising a nucleic molecule that encodes a fusion protein as described herein. In another aspect, the present disclosure refers to a vector comprising a nucleic acid molecule as described herein.

In certain other aspects, the present disclosure is directed to a host cell comprising a fusion protein, nucleic acid, or vector as described herein. In another aspect, the present disclosure refers to a host cell, comprising a fusion protein as described herein.

In certain other aspects, a method of increasing the activity of an immune cell is provided, comprising administering to a subject in need of increased immune cell activity an effective amount of a host cell as described herein.

In other aspects, the present disclosure is directed to a method of enhancing or prolonging an immune response, comprising administering to a subject in need of enhanced or prolonged immune cell activity an effective amount of a host cell as described herein.

In still other aspects, the present disclosure provides a method of stimulating an antigen-specific T cell response, comprising administering to a subject in need of increased immune cell activity an effective amount of a host cell as described herein.

In other aspects, the present disclosure is directed to a method of inhibiting an immunosuppressive signaling pathway, comprising administering to a subject in need thereof an effective amount of a host cell as described herein.

In other aspects, the present disclosure is directed to a method of treating cancer, comprising administering to a subject having cancer a therapeutically effective amount of a host cell as described herein. In another aspect, the present disclosure refers to the use of a fusion protein as defined herein, a vector as defined herein, or a host cell as defined herein in the manufacture of a medicament for treating cancer in a subject.

In other aspects, the present disclosure is directed to a method of inhibiting immune resistance of cancer cells, comprising administering to a subject in need thereof an effective amount of a host cell as described herein.

In still other aspects, the present disclosure provides a method for treating a tumor, comprising administering to a subject having a tumor a therapeutically effective amount of a host cell as described herein, wherein the administered host cell is capable of proliferating in an immunosuppressive tumor microenvironment.

A method of treating an infection, comprising administering to a subject having the infection a therapeutically effective amount of a host cell as described herein, is also provided by the present disclosure.

These and other aspects of the present ~~invention~~disclosure will become apparent upon reference to the following detailed description and attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B show CD200R-CD28 constructs expressed at high levels on primary murine $CD8^+$ T cells. (A) Schematic representation of exemplary CD200R-CD28 constructs. Construct “I” contains CD200R extracellular ("EC") and transmembrane ("TM") domains and a CD28 intracellular ("IC") signaling domain (CD200Rtm-CD28). Construct "II" contains the extracellular domain of CD200R and the transmembrane and intracellular domains of CD28 (CD200R-CD28tm). Constructs "III-V" also incorporate a portion of the extracellular domain of CD28 to the transmembrane-proximal cysteine to promote multimerization and enhance CD28 signaling. To account for any extra extracellular amino acids (*e.g.*, from one to about 50 amino acids; such as exemplary murine constructs disclosed here contain an extra nine (9) amino acids and exemplary human constructs disclosed here contain twelve (12) amino acids), some constructs have a truncated portion of an extracellular or intracellular domain (*e.g.*, a CD200R that preserves an N linked glycosylation site). For example, construct IV has a truncated portion of CD200R that is truncated by 3 amino acids. Construct V has a truncated portion of

CD200R that is truncated 9 amino acids. Constructs "I", "II", and "V" maintain the short spatial distance between the cells (*e.g.*,

CLAIMS

1. A fusion protein, comprising (a) an extracellular component comprised of a binding domain that specifically binds a target, (b) an intracellular component comprised of an intracellular signaling domain, and (c) a hydrophobic component connecting the extracellular and intracellular components, wherein the extracellular component comprises an extracellular portion of a CD200R and the intracellular signaling domain comprises an intracellular signaling domain of CD28.

~~wherein the extracellular portion of a complex formed by specific binding of the fusion protein to the target (fusion protein::target complex) is of a size, or spans a distance, of (i) up to about a distance between two cell membranes of an immunological synapse, (ii) up to about or substantially the same as a distance spanned by the extracellular portion of a complex between a T cell receptor (TCR) and an MHC-peptide complex specifically bound by the TCR, (iii) up to about or substantially the same as a distance spanned by the extracellular portion of a complex between a natural molecule comprising the binding domain and its cognate binding partner; (iii) less than or up to about 40 nm, 25 nm, 20 nm, 15 nm, or 14 nm; or (iv) any combination thereof.~~

~~2. The fusion protein according to claim 1, wherein the fusion protein::target complex localizes to a supramolecular activation cluster (SMAC).~~

~~3. The fusion protein according to claim 1 or 2, wherein the fusion protein::target complex localizes to a central region supramolecular activation cluster (cSMAC).~~

~~4. The fusion protein according to claim 2 or claim 3, wherein the SMAC has a width of a T cell receptor (TCR) associated with an antigen::human leukocyte antigen (HLA) complex.~~

~~5. The fusion protein according to any one of claims 1-4, wherein the extracellular component is associated with a negative signal and the intracellular component is associated with a positive signal.~~

~~6. A fusion protein, comprising (a) an extracellular component comprised of a binding domain that specifically binds a target, (b) an intracellular component comprised of an intracellular signaling domain, and (c) a hydrophobic component connecting the extracellular and intracellular components,~~

~~wherein the binding domain is, or has at least 95 % identity to, an inhibitory molecule binding domain and the intracellular signaling domain is, or contains at least 95 % identity to, a costimulatory or stimulatory molecule binding domain, and~~

~~wherein the inhibitory molecule is not a B7-CD28 superfamily member, is not CTLA4, is not PD1, does not bind to B7, is a glycoprotein, or any combination thereof.~~

2~~7~~. The fusion protein according to ~~any of~~ claim~~s~~ 1~~-6~~, wherein the expression of the fusion protein in a T cell comprising a TCR or chimeric antigen receptor specific for an antigen results in at least about a 1.5-fold, 2-fold, or 3-fold increase in survival, expansion, cytotoxicity, cytokine secretion, and/or response to multiple rounds of stimulation, by the T cell, in response to binding of the antigen and/or following administration to a subject, and/or results in at least about a 1.5-fold, 2-fold, or 3-fold increase in time of survival, disease-free survival, or amelioration of one or more disease symptom, of a subject to which the cell is administered, as compared to a cell substantially the same as the T cell but not containing the fusion protein.

~~8. The fusion protein according to any of claims 1-7, wherein the fusion protein is capable, when expressed in a T cell, of co-localizing with a TCR or CAR expressed by the T cell.~~

~~9. The fusion protein according to any of claims 6-8, wherein the binding domain and/or the inhibitory molecule specifically binds to a CD200 or a CD47.~~

~~10. The fusion protein according to any of claims 6-9, wherein the binding domain is derived from, and/or the inhibitory molecule is, a CD200R, a SIRPα, a TIM3, a CD2, a CD95 (Fas), a CD223 (LAG3), an A2aR, a KIR, TIM3, a CD300, or a LPA5.~~

~~11. The fusion protein according to any of claims 6-9, wherein the inhibitory molecule is or comprises a CD200R.~~

~~12. The fusion protein according to any of claims 6-9, wherein the inhibitory molecule is or comprises a SIRPα.~~

~~13. The fusion protein according to any one of claims 1-12, wherein the binding domain is an antibody binding fragment, a receptor ectodomain, a cytokine, or a ligand.~~

~~14. The fusion protein according to any one of claims 1-13, wherein the extracellular component comprises an extracellular portion of a CD200R, SIRPα, CD279 (PD-1), CD2, CD95 (Fas), CD152 (CTLA4), CD223 (LAG3), CD272 (BTLA), A2aR, KIR, TIM3, CD300, or LPA5.~~

3~~15~~. The fusion protein according to any of claims 1~~-14~~ to 2, wherein the extracellular component further comprises an additional extracellular portion~~, wherein the additional extracellular portion optionally is from or shares identity with an extracellular portion of a molecule that is distinct from the binding domain source molecule or does not contain the binding domain~~.

~~16. The fusion protein according to any one of claims 1-15, wherein the extracellular component further comprises an extracellular portion from a the hydrophobic component, or that contains the hydrophobic component or a portion thereof.~~

417. The fusion protein according to claim 315 or 16, wherein the extracellular component or the additional extracellular portion comprises a multimerization domain and/or a spacer.

~~18. The fusion protein according to any one of claims 1-17, wherein the extracellular component comprises an extracellular portion of a CD200R or wherein the binding domain comprises a CD200-binding portion of a CD200R or binding variant thereof.~~

~~19. The fusion protein according to any one of claims 1-17, wherein the extracellular component comprises an extracellular portion of a SIRPα or wherein the binding domain comprises a CD47 binding portion of a SIRPα or binding variant thereof.~~

~~20. The fusion protein according to any one of claims 1-19, wherein the extracellular component or the additional extracellular portion comprises a multimerization domain.~~

~~21. The fusion protein according to claim 20, wherein the multimerization domain comprises a cysteine residue.~~

522. The fusion protein according to claim 204, wherein the multimerization domain comprises an extracellular component modified to contain a cysteine residue within about 2 to about 15 amino acids from the hydrophobic component.

623. The fusion protein according to any one of claims 1-22 to 5, wherein the hydrophobic component comprises a transmembrane domain of a CD2, CD3ε, CD3δ, CD3ζ, CD25, CD27, CD28, CD40, CD79A, CD79B, CD80, CD86, CD95 (Fas), CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD152 (CTLA4), CD200R, CD223 (LAG3), CD270 (HVEM), CD272 (BTLA), CD273 (PD-L2), CD274 (PD-L1), CD278 (ICOS), CD279 (PD-1), CD300, CD357 (GITR), A2aR, DAP10, FcRα, FcRβ, FcRγ, Fyn, GAL9, KIR, Lck, LAT, LRP, NKG2D, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PTCH2, ROR2, Ryk, Slp76, SIRPα, pTα, TCRα, TCRβ, TIM3, TRIM, LPA5, or Zap70.

~~24. The fusion protein according to any one of claims 1-23, wherein the hydrophobic component comprises a transmembrane domain of a CD28.~~

~~25. The fusion protein according to any one of claims 1-23, wherein the hydrophobic component comprises a transmembrane domain of a 4-1BB.~~

~~26. The fusion protein according to any one of claims 1-25, wherein the intracellular signaling domain comprises an intracellular signaling domain of a costimulatory molecule.~~

~~27. The fusion protein of claim 26, wherein the costimulatory molecule comprises CD28, CD137 (4-1BB), or ICOS.~~

7~~28~~. The fusion protein of any of claims 1~~-27~~ to 6, wherein the intracellular signaling domain further comprises an intracellular signaling domain of a CD3ε, CD3δ, CD3ζ, CD25, CD27~~, CD28~~, CD40, CD47, CD79A, CD79B, CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD278 (ICOS), CD357 (GITR), CARD11, DAP10, DAP12, FcRα, FcRβ, FcRγ, Fyn, Lck, LAT, LRP, NKG2D, NOTCH1, NOTCH2, NOTCH3, NOTCH4, ROR2, Ryk, Slp76, pTα, TCRα, TCRβ, TRIM, Zap70, PTCH2, or any combination thereof.

~~29. The fusion protein according to any one of claims 1-28, wherein the intracellular signaling domain comprises a costimulatory domain of a CD137 (4-1BB), CD27, CD28, ICOS, OX40 (CD134), or any combination thereof.~~

~~30. The fusion protein according to any one of claims 1-29, wherein the intracellular signaling domain comprises a costimulatory domain of a CD137 (4-1BB) or CD28, or any combination thereof.~~

~~31. The fusion protein according to any one of claims 1-30, wherein the intracellular signaling domain comprises a costimulatory domain of a CD28.~~

~~32. The fusion protein according to any one of claims 1-31, wherein the intracellular signaling domain comprises a costimulatory domain of a CD137 (4-1BB).~~

~~33. The fusion protein according to any one of claims 1-32, wherein the target is an immunosupressive ligand.~~

~~34. The fusion protein according to any one of claims 1-32, wherein the target is selected from a CD47, a CD58, a CD95L (FasL), a CD200, a CD270 (HVEM), a CD274 (PD-L1), and a GAL9.~~

8~~35~~. The fusion protein according to any of claims 1~~-34~~ to 7, wherein ~~(a) the extracellular component comprises an extracellular portion of a CD200R, (b)~~ the hydrophobic component comprises a transmembrane domain of a CD28~~, and (c) the intracellular component comprises an intracellular signaling domain of a CD28~~ or a CD137 (4-1BB).

~~36. The fusion protein according to claim 35, wherein the extracellular portion of the CD200R comprises the entire extracellular domain of CD200R.~~

~~37. The fusion protein according to claim 35, wherein the extracellular portion of the CD200R comprises at least 200 amino acids from the N-terminus of CD200R.~~

~~38. The fusion protein according to claim 35, wherein the extracellular portion of the CD200R comprises at least about 225 amino acids to at least about 235 amino acids from the N-terminus of CD200R.~~

~~39. The fusion protein according to claim 35, wherein the extracellular portion of the CD200R comprises at least about 234 amino acids from the N-terminus of CD200R.~~

~~40. The fusion protein according to any of claims 35-39, wherein the CD200R is a human CD200R.~~

941. The fusion protein according to ~~any one of~~ claim~~s~~ 8~~35-40~~, wherein the intracellular component comprises a second intracellular signaling domain.

~~42. The fusion protein according to claim 41, wherein the second intracellular signaling domain comprises an intracellular signaling domain of a CD137 (4-1BB).~~

1043. The fusion protein according to ~~any one of~~ claim~~s 35-42~~8 or 9, wherein the extracellular component comprises an extracellular portion of a CD28 extending from the CD28 transmembrane domain.

~~44. The fusion protein according to claim 43, wherein the extracellular portion of the CD28 comprises a cysteine residue.~~

~~45. The fusion protein according to any of claims 1-44, wherein the intracellular signaling component does not contain a CD3ζ signaling domain and/or does not contain a signaling domain capable of delivering a primary signal to a T cell and/or does not contain a signaling domain from a molecule naturally capable of delivering a primary signal to a T cell.~~

1146. The fusion protein according to claim 1, wherein ~~(a)~~ the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NOs.:2, 8, or 11, ~~(b)~~ the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NOs.:3 or 4, and ~~(c)~~ the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.

~~47. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:2, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component~~

~~comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.~~

~~48. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:8, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises the amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.~~

12~~49~~. The fusion protein according to claim ~~41~~11, wherein the extracellular component further comprises a multimerization domain having an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:9.

~~50. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:11, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.~~

~~51. The fusion protein according to claim 50, wherein the extracellular component further comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:9.~~

13~~52~~. The fusion protein according to claim ~~51~~12, wherein the intracellular component further comprises a second intracellular signaling domain having an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:13.

~~53. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an extracellular portion of a CD200R, (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD137 (4-1BB).~~

~~54. The fusion protein according to claim 53, wherein the extracellular portion of the CD200R comprises the entire extracellular domain of CD200R.~~

~~55. The fusion protein according to claim 53, wherein the extracellular portion of the CD200R comprises at least 200 amino acids from the N-terminus of CD200R.~~

~~56. The fusion protein according to claim 53, wherein the extracellular portion of the CD200R comprises at least about 225 amino acids to at least about 235 amino acids from the N-terminus of CD200R.~~

~~57. The fusion protein according to any one of claims 53-56, wherein the extracellular component comprises an extracellular portion of a CD28 extending from the CD28 transmembrane domain.~~

~~58. The fusion protein according to claim 57, wherein the extracellular portion of the CD28 comprises a cysteine residue.~~

~~59. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an extracellular portion of a CD200R, (b) the hydrophobic component comprises a transmembrane domain of a CD137 (4-1BB), and (c) the intracellular component comprises an intracellular signaling domain of a CD137 (4-1BB).~~

~~60. The fusion protein according to claim 59, wherein the extracellular portion of the CD200R comprises the entire extracellular domain of CD200R.~~

~~61. The fusion protein according to claim 59, wherein the extracellular portion of the CD200R comprises at least a portion of the extracellular domain at least 230 amino acids from the N-terminus of CD200R.~~

~~62. The fusion protein according to any one of claims 59-61, wherein the extracellular component comprises an extracellular portion of a CD137 (4-1BB) extending from the CD137 (4-1BB) transmembrane domain.~~

~~63. The fusion protein according to claim 62, wherein the extracellular portion of the CD137 (4-1BB) comprises a cysteine residue.~~

14~~64~~. The fusion protein according to claim 1, wherein ~~(a)~~ the extracellular component is associated with a negative signal and the intracellular component is associated with a positive signal and wherein the extracellular component comprises a binding domain with an amino acid sequence ~~encoded by a nucleic acid molecule~~ as set forth in SEQ ID NOs.:31 or 34,~~NO.:8~~ and a multimerization domain with an amino acid sequence ~~encoded by a nucleic acid molecule~~ as set forth in SEQ ID NO.:32~~9~~, ~~(b)~~ the hydrophobic component comprises an amino acid sequence ~~encoded by a nucleic acid molecule~~ as set forth in SEQ ID NO.:427, and ~~(c)~~ the intracellular component comprises an amino acid ~~sequence encoded by a nucleic acid molecule~~ as set forth in SEQ ID NO.:~~13~~28.

15~~65~~. The fusion protein according to claim 14~~64~~, wherein the intracellular component further comprises a second intracellular signaling domain having an amino acid sequence ~~encoded by a nucleic acid molecule~~ as set forth in SEQ ID NO.:365.

~~66. The fusion protein according to claim 1, wherein (a) the extracellular component comprises a binding domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:11 and a multimerization domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:9, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth~~

~~in SEQ ID NO.:4, and (c) the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:13.~~

~~67. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an extracellular portion of a SIRPα, (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.~~

~~68. The fusion protein according to claim 67, wherein the extracellular portion of the SIRPα comprises the entire extracellular domain of SIRPα.~~

~~69. The fusion protein according to claim 67, wherein the extracellular portion of the SIRPα comprises at least 361 amino acids from the N-terminus of SIRPα.~~

~~70. The fusion protein according to any one of claims 67-69, wherein the intracellular component comprises a second intracellular signaling domain.~~

~~71. The fusion protein according to claim 70, wherein the second intracellular signaling domain comprises an intracellular signaling domain of a CD137 (4-1BB).~~

~~72. The fusion protein according to any one of claims 67-71, wherein the extracellular component comprises an extracellular portion of a CD28 extending from the CD28 transmembrane domain.~~

~~73. The fusion protein according to claim 72, wherein the extracellular portion of the CD28 comprises a cysteine residue.~~

~~74. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:17, (b) the hydrophobic component comprises an amino acid sequence encoded~~

by a nucleic acid molecule as set forth in SEQ ID NO.:18, and (c) the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.

75. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:17, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.

76. The fusion protein according to claim 1, wherein (a) the extracellular component comprises a binding domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:21 and a multimerization domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:9, (b) the hydrophobic component comprises the amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises the amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.

77. The fusion protein according to claim 1, wherein (a) the extracellular component comprises a binding domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:21 and a multimerization domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:9, (b) the hydrophobic component comprises the amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises the amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:13.

78. The fusion protein according to claim 70, wherein the intracellular component further comprises the amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ. ID. NO:5.

~~79. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an extracellular portion of a CD279 (PD-1), (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.~~

~~80. The fusion protein according to claim 79, wherein the extracellular portion of the CD279 (PD-1) comprises the entire extracellular domain of CD279 (PD-1).~~

~~81. The fusion protein according to claim 79, wherein the extracellular portion of the CD279 (PD-1) comprises a portion of the extracellular domain at least 100 amino acids from the N-terminus of CD279 (PD-1).~~

~~82. The fusion protein according to claim 79, wherein the extracellular portion of the CD279 (PD-1) comprises a portion of the extracellular domain at least 149 amino acids from the N-terminus of CD279 (PD-1).~~

~~83. The fusion protein according to any one of claims 79-82, wherein the extracellular component comprises an extracellular portion of a CD28 extending from the CD28 transmembrane domain.~~

~~84. The fusion protein according to claim 83, wherein the extracellular portion of the CD28 comprises a cysteine residue.~~

~~85. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:89 and a multimerization domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:9, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.~~

~~86. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:91 and a multimerization domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:9, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.~~

~~87. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:95 and a multimerization domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:9, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.~~

~~88. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an extracellular portion of a CD95 (Fas), (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.~~

~~89. The fusion protein according to claim 88, wherein the extracellular portion of the CD95 (Fas) comprises the entire extracellular domain of CD95 (Fas).~~

~~90. The fusion protein according to claim 88, wherein the extracellular portion of the CD95 (Fas) comprises at least a portion of the extracellular domain of at least 175 amino acids from the N-terminus of CD95 (Fas).~~

~~91. The fusion protein according to claim 88, wherein the extracellular portion of the CD95 (Fas) comprises at least a portion of the extracellular domain of at least 173 amino acids from the N-terminus of CD95 (Fas).~~

~~92. The fusion protein according to claim 88, wherein the extracellular portion of the CD95 (Fas) comprises at least a portion of the extracellular domain of at least 166 amino acids from the N-terminus of CD95 (Fas).~~

~~93. The fusion protein according to claim 88, wherein the extracellular portion of the CD95 (Fas) comprises at least a portion of the extracellular domain of at least 161 amino acids from the N-terminus of CD95 (Fas).~~

~~94. The fusion protein according to any one of claims 88-93, wherein the extracellular component comprises an extracellular portion of a CD28 extending from the CD28 transmembrane domain.~~

~~95. The fusion protein according to claim 94, wherein the extracellular portion of the CD28 comprises a cysteine residue.~~

~~96. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:71 and a multimerization domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:9, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.~~

~~97. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:73 and a multimerization domain with an amino acid sequence encoded by a~~

~~nucleic acid molecule as set forth in SEQ ID NO.:9, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.~~

~~98. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:75 and a multimerization domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:9, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.~~

~~99. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an extracellular portion of a CD2, (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.~~

~~100. The fusion protein according to claim 99, wherein the extracellular portion of the CD2 comprises the entire extracellular domain of CD2.~~

~~101. The fusion protein according to claim 99, wherein the extracellular portion of the CD2 comprises at least a portion of the extracellular domain of at least 175 amino acids from the N-terminus of CD2.~~

~~102. The fusion protein according to any one of claims 99-101, wherein the extracellular component comprises an extracellular portion of a CD28 extending from the CD28 transmembrane domain.~~

~~103. The fusion protein according to claim 102, wherein the extracellular portion of the CD28 comprises a cysteine residue.~~

~~104. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:61 and a multimerization domain with an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:9, (b) the hydrophobic component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:4, and (c) the intracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:5.~~

~~105. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an extracellular portion of a TIM3, (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.~~

~~106. The fusion protein according to claim 105, wherein the extracellular portion of the TIM3 comprises the entire extracellular domain of TIM3.~~

~~107. The fusion protein according to claim 105, wherein the extracellular portion of the TIM3 comprises at least a portion of the extracellular domain of at least 180 amino acids from the N-terminus of TIM3.~~

~~108. The fusion protein according to any one of claims 105-107, wherein the extracellular component comprises an extracellular portion of a CD28 extending from the CD28 transmembrane domain.~~

~~109. The fusion protein according to claim 108, wherein the extracellular portion of the CD28 comprises a cysteine residue.~~

~~110. The fusion protein according to claim 1, wherein (a) the extracellular component comprises an extracellular portion of a LAG3, (b) the hydrophobic component comprises a transmembrane domain of a CD28, and (c) the intracellular component comprises an intracellular signaling domain of a CD28.~~

~~111. The fusion protein according to claim 110, wherein the extracellular portion of the LAG3 comprises the entire extracellular domain of LAG3.~~

~~112. The fusion protein according to claim 110, wherein the extracellular portion of the LAG3 comprises at least a portion of the extracellular domain of at least 410 amino acids from the N-terminus of LAG3.~~

~~113. The fusion protein according to any one of claims 110-112, wherein the extracellular component comprises an extracellular portion of a LAG3 extending from the CD28 transmembrane domain.~~

~~114. The fusion protein according to claim 113, wherein the extracellular portion of the CD28 comprises a cysteine residue.~~

~~115. A fusion protein according to claim 5, wherein the extracellular component comprises a binding domain with an amino acid sequence as set forth in SEQ ID NO.:31 and a multimerization domain with an amino acid sequence as set forth in SEQ ID NO.:32, (b) the hydrophobic component comprises an amino acid sequence as set forth in SEQ ID NO.:27, and (c) the intracellular component comprises an amino acid as set forth in SEQ ID NO.:36.~~

~~116. The fusion protein according to claim 115, wherein the intracellular component further comprises a second intracellular signaling domain having an amino acid sequence as set forth in SEQ ID NO.:28.~~

~~117. The fusion protein according to claim 5, wherein (a) the extracellular component comprises a binding domain with an amino acid sequence as set forth in SEQ ID NO.:34 and a multimerization domain with an amino acid sequence as set forth in SEQ ID NO.:32, (b) the hydrophobic component comprises an amino acid sequence as set forth in SEQ ID NO.:27, and (c) the intracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:36.~~

~~118. The fusion protein according to claim 5, wherein (a) the extracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:40, (b) the hydrophobic component comprises an amino acid sequence as set forth in SEQ ID NO.:41, and (c) the intracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:28.~~

~~119. The fusion protein according to claim 5, wherein (a) the extracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:40, (b) the hydrophobic component comprises an amino acid sequence as set forth in SEQ ID NO.:27, and (c) the intracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:28.~~

~~120. The fusion protein according to claim 5, wherein (a) the extracellular component comprises a binding domain with an amino acid sequence as set forth in SEQ ID NO.:44 and a multimerization domain with an amino acid sequence as set forth in SEQ ID NO.:32, (b) the hydrophobic component comprises the amino acid sequence as set forth in SEQ ID NO.:27, and (c) the intracellular component comprises the amino acid sequence as set forth in SEQ ID NO.:28.~~

~~121. The fusion protein according to claim 5, wherein (a) the extracellular component comprises a binding domain with an amino acid sequence as set forth in SEQ ID NO.:44 and a multimerization domain with an amino acid sequence as set forth in SEQ ID NO.:32, (b) the hydrophobic component comprises the amino acid sequence as set forth in SEQ~~

~~ID NO.:27, and (c) the intracellular component comprises the amino acid sequence as set forth in SEQ ID NO.:36.~~

~~122. The fusion protein according to claim 121, wherein the intracellular component further comprises the amino acid sequence as set forth in SEQ. ID. NO:28.~~

~~123. The fusion protein according to claim 5, wherein (a) the extracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:90 and a multimerization domain with an amino acid sequence as set forth in SEQ ID NO.:32, (b) the hydrophobic component comprises an amino acid sequence as set forth in SEQ ID NO.:27, and (c) the intracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:28.~~

~~124. The fusion protein according to claim 5, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:92 and a multimerization domain with an amino acid sequence as set forth in SEQ ID NO.:32, (b) the hydrophobic component comprises an amino acid sequence as set forth in SEQ ID NO.:27, and (c) the intracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:28.~~

~~125. The fusion protein according to claim 5, wherein (a) the extracellular component comprises an amino acid sequence encoded by a nucleic acid molecule as set forth in SEQ ID NO.:96 and a multimerization domain with an amino acid sequence as set forth in SEQ ID NO.:32, (b) the hydrophobic component comprises an amino acid sequence as set forth in SEQ ID NO.:27, and (c) the intracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:28.~~

~~126. The fusion protein according to claim 5, wherein (a) the extracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:72 and a multimerization domain with an amino acid sequence as set forth in SEQ ID NO.:32, (b) the~~

~~hydrophobic component comprises an amino acid sequence as set forth in SEQ ID NO.:27, and (c) the intracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:28.~~

~~127. The fusion protein according to claim 5, wherein (a) the extracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:74 and a multimerization domain with an amino acid sequence as set forth in SEQ ID NO.:32, (b) the hydrophobic component comprises an amino acid sequence as set forth in SEQ ID NO.:27, and (c) the intracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:28.~~

~~128. The fusion protein according to claim 5, wherein (a) the extracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:76 and a multimerization domain with an amino acid sequence as set forth in SEQ ID NO.:32, (b) the hydrophobic component comprises an amino acid sequence as set forth in SEQ ID NO.:27, and (c) the intracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:28.~~

~~129. The fusion protein according to claim 5, wherein (a) the extracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:62 and a multimerization domain with an amino acid sequence as set forth in SEQ ID NO.:32, (b) the hydrophobic component comprises an amino acid sequence as set forth in SEQ ID NO.:27, and (c) the intracellular component comprises an amino acid sequence as set forth in SEQ ID NO.:28.~~

16~~130~~. A nucleic acid molecule encoding a fusion protein according to any one of claims 1~~-129~~ to 15.

17~~131~~. A vector comprising a nucleic acid molecule according to claim 16~~130~~.

18~~132~~. The vector according to claim 17~~131~~, wherein the vector is a viral vector~~.~~

~~133. The vector according to claim 132~~, optionally wherein the viral vector is a lentiviral or retroviral vector.

~~134. The vector according to claim 133, wherein the viral vector is a lentiviral vector.~~

19~~135~~. The vector according to ~~any one of~~ claim~~s 131-134~~17 or claim 18, further encoding an antigen-specific TCR.

~~136. The vector according to claim 135, wherein the TCR is exogenous to a host cell.~~

~~137. The vector according to claim 135 or claim 136, wherein the TCR is specific to a HLA class I restricted antigen.~~

~~138. The vector according to any one of claims 135-137, wherein the antigen is a cancer-specific antigen.~~

~~139. The vector according to claim 138, wherein the cancer-specific antigen comprises WT-1, mesothelin, or cyclin-A1.~~

~~140. The vector according to any one of claims 131-139, further encoding a ligand.~~

~~141. The vector according to claim 140, wherein the ligand is CD200, CD47, PD-L1, or CD58.~~

~~142. The vector according to any one of claims 131-141, further encoding an siRNA for reducing the expression of an endogenous receptor.~~

~~143. The vector according to claim 142, wherein the endogenous receptor comprises CD200R, SIRPα, CD279 (PD-1), CD95 (Fas), or CD2 or is a TCR or portion thereof.~~

20144. A host cell, comprising a fusion protein according to any one of claims 1 to 15.

~~145. A host cell, comprising at least two different fusion proteins according to any one of claims 1-129.~~

~~146. A host cell according to claim 145, comprising:~~

~~a fusion protein according to claim 79; and~~

~~a fusion protein according to claim 105.~~

~~147. A host cell, comprising a nucleic acid molecule according to claim 130.~~

~~148. A host cell, comprising a vector according to any one of claims 131-143.~~

~~149. The host cell according to any one of claims 144-148, wherein the host cell is an immune system cell.~~

~~150. The host cell according to claim 149, wherein the immune system cell is a T cell.~~

~~151. The host cell according to claim 150, wherein the T cell is a CD4+ T cell.~~

~~152. The host cell according to claim 150, wherein the T cell is a CD8+ T cell.~~

~~153. The host cell according to any one of claims 144-152, further comprising an antigen receptor, which optionally is an antigen-specific TCR.~~

~~154. The host cell according to any one of claims 153, wherein the antigen-specific TCR is exogenous to the cell or the host.~~

~~155. The host cell according to claim 153 or claim 154, wherein the TCR binds to an antigen::HLA complex with high affinity.~~

~~156. The host cell according to claim 155, wherein the high affinity binding has a K_a equal to or greater than 10^7 M^{-1}.~~

~~157. The host cell according to any one of claims 153-156, wherein the TCR is specific to a HLA class I restricted antigen.~~

~~158. The host cell according to any one of claims 153-156, wherein the antigen is a cancer-specific antigen.~~

~~159. The host cell according to claim 158, wherein the cancer-specific antigen comprises WT-1, mesothelin, or cyclin-A1.~~

~~160. The host cell according to any one of claims 153-156, wherein the antigen is a viral antigen.~~

~~161. The host cell according to claim 153, wherein the antigen receptor is a chimeric antigen receptor.~~

~~162. The host cell according to claim 161, wherein the chimeric antigen receptor comprises an extracellular antigen binding domain and an intracellular signaling domain capable of delivering a primary signal to a T cell and optionally a costimulatory domain.~~

~~163. The host cell according to any one of claims 144-162, further encoding a ligand.~~

~~164. The host cell according to claim 163, wherein the ligand is CD200, CD47, PD-L1, or CD58.~~

~~165. The host cell according to any one of claims 144-164, further encoding an siRNA for reducing the expression of an endogenous receptor.~~

~~166. The host cell according to claim 165, wherein the endogenous receptor comprises CD200R, SIRPα, CD279 (PD-1), CD95 (Fas) or CD2.~~

21~~167~~. Use of~~A method of treating a disease in a subject comprising administering~~ a fusion protein according to any one of claims 1~~-129~~ to 15, ~~to the subject.~~

~~168. A method of treating a disease in a subject comprising administering~~ a vector according to any one of claims ~~131-143~~17 to 19, ~~to the subject.~~

~~169. A method of treating a disease in a subject comprising administering~~or a host cell according to ~~any one of~~ claim~~s~~ ~~144-166~~20 in the manufacture of a medicament for treating cancer ~~to the~~in a subject.

~~170. The method according to any one of claims 167-169, wherein the disease is selected from the group consisting of viral infection, bacterial infection, cancer, and autoimmune disease.~~

~~171. The method according to any one of claims 167-170, wherein the subject is human.~~

~~172. A fusion protein according to any one of claims 1-129, for use in treating cancer.~~