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Summary of Invention

Technical Problem

[0005] Effective receptor signaling is a key requirement for the effectiveness of agonistic ligands. Well-known examples are cytokines, which are key immune mediators residing in many lesion sites whose effects, when harnessed, can significantly improve immune responses. This also applies to interleukin-2 (IL-2). While many therapies with agonistic ligands have been developed, the issue of high toxicity and low efficacy remains of concern.

Solution to Problem

[0005a] In one aspect, the present disclosure relates to a protein complex comprising a first binding domain, a second binding domain, a third binding domain and a fourth binding domain, wherein the first binding domain is capable of binding to a scaffold protein, the second binding domain is capable of binding to a first receptor protein, the third binding domain is capable of binding to the scaffold protein, and the fourth binding domain is capable of binding to a second receptor protein, wherein the first binding domain and the second binding domain are capable of non-competitively binding to the scaffold protein, wherein the first receptor protein and the second receptor protein are each receptor subunits that can associate to form a receptor complex, and wherein the protein complex is capable of inducing receptor signaling of the receptor complex.
[0005b] In another aspect, the present disclosure relates to a nucleic acid molecule or a plurality of nucleic acid molecules encoding the protein complex as disclosed herein.
[0005c] In another aspect, the present disclosure relates to a vector or a plurality of vectors comprising the nucleic acid molecule or plurality of nucleic acid molecules as disclosed herein.
[0005d] In another aspect, the present disclosure relates to a host cell or a plurality of host cells comprising the vector or the plurality of vectors as disclosed herein.
[0005e] In another aspect, the present disclosure relates to a method for producing the protein complex as disclosed herein comprising the steps of: (i) culturing the host cell of or plurality of host cells as disclosed herein under conditions suitable for protein expression; (ii) optionally lysing the host cell; and (iii) isolating the protein complex.
[0005f] In another aspect, the present disclosure relates to a pharmaceutical composition comprising the protein complex as disclosed herein.

[0005f] In another aspect, the present disclosure relates to the pharmaceutical composition of as disclosed herein for use in therapy.
[0005g] In another aspect, the present disclosure relates to use of the protein complex as disclosed herein in the manufacture of a medicament for treating cancer or autoimmune disease. [0006] The present inventors have thought that the ability to deliver an agonist capable of site-specifically activating receptor signaling would overcome systemic toxicity and low efficacy issue. To achieve such site-specific activation of receptor signaling, the present inventors have inter alia developed combinations of target-binding molecules or protein complexes, which, in the presence of a scaffold protein, are capable of inducing receptor signaling of a receptor complex. The combination of target-binding molecules or the protein complex of the present invention comprises a first binding domain, and a third binding domain, which are each capable of non-competitively binding to a scaffold protein. The combination of target-binding molecules or the protein complex of the present invention comprises a second binding domain, which is capable of binding to a first receptor protein, and a fourth binding domain, which is capable of binding to a second receptor protein. The first receptor protein and the second receptor protein are each receptor subunits that can associate to form a receptor complex. Upon binding of all four binding domains, the receptor complex is activated

Claims

[Claim 1]
A protein complex comprising a first binding domain, a second binding domain, a third binding domain and a fourth binding domain, wherein
the first binding domain is capable of binding to a scaffold protein,
the second binding domain is capable of binding to a first receptor protein,
the third binding domain is capable of binding to the scaffold protein, and
the fourth binding domain is capable of binding to a second receptor protein,
wherein the first binding domain and the third binding domain are capable of non-competitively binding to the scaffold protein,
wherein the first receptor protein and the second receptor protein are each receptor subunits that can associate to form a receptor complex, and
wherein the protein complex is capable of inducing receptor signaling of the receptor complex.

[Claim 2]
The protein complex of claim 1, wherein the first binding domain and the third binding domain are capable of binding the scaffold protein biparatopically.

[Claim 3]
The protein complex of any one of claims 1 to 2, wherein the first binding domain is connected to the second binding domain, optionally via a linker, and/or the third binding domain is connected to the fourth binding domain, optionally via a linker.

[Claim 4]
The protein complex of claim 3, wherein the first binding domain is connected to the second binding domain via a linker, and the third binding domain is connected to the fourth binding domain via a linker, wherein the linker is 20, 15, 10 amino acids or less.

[Claim 5]
The protein complex of any one of claims 1 to 4, wherein the first binding domain and the third binding domain are each selected from the group consisting of a neutralizing binding domain and a non-neutralizing binding domain, wherein the first binding domain is a neutralizing binding domain and the third binding domain is a non-neutralizing binding domain or vice versa.

[Claim 6]
The protein complex of any one of claim 1 to claim 5, wherein the first binding domain and the third binding domain each are capable of binding subunits of the scaffold protein which can associate to form the scaffold protein.

[Claim 7]
The protein complex of any one of claim 1 to claim 6, wherein the scaffold protein is a membrane-bound protein, a soluble protein, an insoluble protein deposition, a cell surface marker, an immune cell surface marker, a T cell exhaustion marker, tumor-specific marker, tumor-associated marker, or a protein whose expression is characteristic of a disease or disorder.

[Claim 8]
The protein complex of any one of claim 1 to claim 7, wherein the scaffold protein is selected from the group consisting of PD1, PDL1, CSF2RB, CD4, CD5, CD6, CD7, CD8, CD9, CCR4, CD8, CD25, CD27, CD38, CD39, CD45, CD62L, CCR6, CD69, CD103, CD73, CD127, GITR, LRRC32, ICOS, TIGIT, RBD, MUC1, CEA, CTLA4, IL2R alpha, CXCR5, Neuropilin-1, TIM3, LAG3, TNF alpha, CD19, CD20, CD22, CD30, CD33, Glycoprotein NMB, CD56, CD70, CD79A, CD79B, CD138, PSCA, PSMA, BCMA, FcRH5, GPRC5D, FAP, LRRC15, E-selectin, EphB2, Melanotransferrin, HER2, TROP2, Nectine-4, EGFRvIII, IL13RA2, TMEFF2, Muc16, EpCAM, FcRH2, AFP, PSA, Amyloid beta, MBP and ASGPR.

[Claim 9]
The protein complex of any one of claim 1 to claim 8, wherein the first and second receptor proteins are each independently selected from the group consisting of IL2R beta, IL2R gamma, IL4R, IL13RA1, IL7R, IL9R, IL21R, TSLPR, IL3RA, CSF2RB, IL5RA, CSF2RA, IL6R, gp130, IL11RA, IL12RB1, IL12RB2, IL27RA, IL31RA, OSMR, CNTFR, LIFR, IL10RA, IL10RB, IL20RA, IL20RB, IL22RA1, IL28RA, IFNAR1, IFNAR2, IFNGR1, IFNGR2, IL1R1, IL1RAP, IL18R1, IL18RAP, ST2, IL17RA, IL17RC, TLR3, TLR4, TLR7, TLR9, CSF1R, TNFR1, TNFR2, LTBR, HVEM, FAS, CD28, cMET, DR3, DR4, DR5, NGFR, RANK, FN14, CD40, 4-1BB, OX40, GITR, TGFBR1, TGFBR2, ACVRL1, ACVR2A, BMPR2, ACVR2B, ACVR1B, ACVR1C, ACVR1, AMHR2, BMPR1A, BMPR1B, BMPR2, TRA, TRB, CD3E, CD16, TREM2, FGFR1, FGFR2, FGFR3, FGFR4, Fzd1, Fzd2, Fzd3, Fzd4, Fzd5, Fzd6, Fzd7, Fzd8 Fzd9, Fzd10, LRP5, LRP6 and LGR5.

[Claim 10]
The protein complex of any one of claim 1 to claim 7, wherein the receptor complex is IL-2R.

[Claim 11]
The protein complex of any one of claim 1 to claim 7, wherein the scaffold protein is PD1, the first receptor protein is IL2R beta, and the second receptor protein is IL2R gamma.

[Claim 12]
The protein complex of any one of claim 1 to claim 7, wherein the scaffold protein, the first receptor protein, and the second receptor protein is a combination chosen from any of (i) to (vi) below:
(i) the scaffold protein is PDL1, the first receptor protein is IL2R beta, and the second receptor protein is IL2R gamma;
(ii) the scaffold protein is TNFa, the first receptor protein is IL2R beta, and the second receptor protein is IL2R gamma;
(iii) the scaffold protein is CD25, the first receptor protein is IL2R beta, and the second receptor protein is IL2R gamma;
(iv) the scaffold protein is PDL1, the first receptor protein is CSF2RA, and the second receptor protein is CSF2RB;
(v) the scaffold protein is MUC1 or CEA, the first receptor protein is a Fzd receptor, and the second receptor protein is a Lrp; or
(vi) the scaffold protein is CD8, the first receptor protein is IL2R beta, and the second receptor protein is IL2R gamma.

[Claim 13]
The protein complex of any one of claim 1 to claim 12, wherein each binding domain is an antigen binding domain comprising VH and VL, sdAb, VHH, scFv, Fab, scFab, Fab', Fab'-SH, F(ab')2, diabody, triabody, Fv, aptamer, Affibody, a cytokine, a ligand, or a split cytokine.

[Claim 14]
The protein complex of any one of claim 1 to claim 13, the protein complex further comprises a half-life extending domain comprising an Fc domain, FcRn-binding domain, an albumin-binding domain, an albumin or variant thereof, or polyethylene glycol.

[Claim 15]
A nucleic acid molecule or a plurality of nucleic acid molecules encoding the or protein complex of any one of claim 1 to claim 14.

[Claim 16]
A vector or a plurality of vectors comprising the nucleic acid molecule or plurality of nucleic acid molecules of claim 15.

[Claim 17]
A host cell or a plurality of host cells comprising the vector or the plurality of vectors of claim 16.

[Claim 18]
A method for producing the protein complex of any of claim 1 to claim 14, comprising the steps of:
(i) culturing the host cell of or plurality of host cells of claim 17 under conditions suitable for protein expression;
(ii) optionally lysing the host cell; and
(iii) isolating the protein complex.

[Claim 19]
A pharmaceutical composition comprising the protein complex of any of claim 1 to claim 14.

[Claim 20]
The pharmaceutical composition of claim 19 for use in therapy.

[Claim 21]
Use of the protein complex of any one of claim 1 to claim 14 in the manufacture of a medicament for treating cancer or autoimmune disease.