SUMMARY

[0004] The present invention is based on the discovery that a bifunctional protein containing at least portion of TGFβ Receptor II (TGFβRII) that is capable of binding TGFβ and antibody or antigen-binding fragment that binds to an immune checkpoint protein such as human protein Programmed Death Ligand 1 (PD-L1) can be an effective anti-tumor and anti-cancer therapeutic. The protein can exhibit a synergistic effect in cancer treatment, as compared to the effect of administering the two agents separately.

[0004a] In one aspect, the present invention refers to a protein comprising a first polypeptide comprising: a) at least a variable domain of a heavy chain of an antibody that binds human protein Programmed Death Ligand 1 (PD-L1); and b) human TGFβRII, or a fragment thereof capable of binding TGFβ; and a second polypeptide comprising at least a variable region of a light chain of an antibody that binds PD-L1, wherein the first polypeptide comprises an HVR-H1 sequence, an HVR-H2 sequence, and an HVR-H3 sequence of SYIMM, SIYPSGGITFYADTVKG, and IKLGTVTTVDY, respectively; and wherein the second polypeptide comprises an HVR-L1 sequence, an HVR-L2 sequence, and an HVR-L3 sequence of TGTSSDVGGYNYVS, DVSNRPS, and SSYTSSSTRV, respectively; and wherein the heavy chain of the first polypeptide and the light chain of the second polypeptide when combined, form an antigen binding site that binds PD-L1.

[0004b] In another aspect, the present invention refers to a nucleic acid comprising a first nucleotide sequence encoding the first polypeptide and a second nucleotide sequence encoding the second polypeptide according to the present invention.

[0004c] In yet another aspect, the present invention refers to a cell comprising the nucleic acid of the present invention.

[0004d] In yet another aspect, the present invention refers to a method of producing a protein comprising a) TGFβRII, or a fragment thereof capable of binding TGFβ, and b) an antibody, or an antigen-binding fragment thereof, that binds human protein Programmed Death Ligand 1 (PD-L1), the method comprising maintaining a cell according to the present invention under conditions permitting expression of the protein, and optionally further comprising harvesting the protein.

[0004e] In yet another aspect, the present invention refers to a protein according to the present invention for use in therapy.

[0004f] In yet another aspect, the present invention refers to the use of a protein according to the present invention in the manufacture of a medicament for inhibiting tumor growth or treating cancer in a patient.

WHAT IS CLAIMED IS:

1. A protein comprising a first polypeptide comprising:

a) at least a variable domain of a heavy chain of an antibody that binds human protein Programmed Death Ligand 1 (PD-L1); and

b) human TGFβRII, or a fragment thereof capable of binding TGFβ; and a second polypeptide comprising at least a variable region of a light chain of an antibody that binds PD-L1, wherein the first polypeptide comprises an HVR-H1 sequence, an HVR-H2 sequence, and an HVR-H3 sequence of SYIMM, SIYPSGGITFYADTVKG, and IKLGTVTTVDY, respectively; and wherein the second polypeptide comprises an HVR-L1 sequence, an HVR-L2 sequence, and an HVR-L3 sequence of TGTSSDVGGYNYVS, DVSNRPS, and SSYTSSSTRV, respectively; and wherein the heavy chain of the first polypeptide and the light chain of the second polypeptide when combined, form an antigen binding site that binds PD-L1.

2. The protein of claim 1, wherein the first polypeptide further comprises an amino acid linker connecting the C-terminus of the heavy chain to the N-terminus of the human TGFβRII or fragment thereof.

3. The protein of claim 1 or claim 2, wherein the human TGFβRII comprises an amino acid sequence of SEQ ID NO: 10.

4. The protein of any one of claims 1 to 3, wherein the second polypeptide comprises the amino acid sequence of SEQ ID NO: 1.

5. The protein of any one of claims 1 to 3, wherein the first polypeptide comprises the amino acid sequence of SEQ ID NO: 3.

6. The protein of any one of claims 1 to 3, wherein the first polypeptide comprises the amino acid sequence of SEQ ID NO: 3, and the second polypeptide comprises the amino acid sequence of SEQ ID NO: 1.

7. The protein of any one of claims 1 to 3, wherein the first polypeptide comprises the amino acid sequence of SEQ ID NO: 2.

8. A nucleic acid comprising a first nucleotide sequence encoding the first polypeptide and a second nucleotide sequence encoding the second polypeptide according to a claim1 or claim 6.

9. A cell comprising the nucleic acid of claim 8.

10. A method of producing a protein comprising a) TGFβRII, or a fragment thereof capable of binding TGFβ, and b) an antibody, or an antigen-binding fragment thereof, that binds human protein Programmed Death Ligand 1 (PD-L1), the method comprising maintaining a cell according to claim 9 under conditions permitting expression of the protein, and optionally further comprising harvesting the protein.

11. The protein of claim 1, comprising two polypeptides each having an amino acid sequence consisting of the amino acid sequence of SEQ ID NO: 3, and two additional polypeptides each having an amino acid sequence consisting of the amino acid sequence of SEQ ID NO: 1.

12. A protein according to claim 1, 6 or 11, for use in therapy.

13. Use of a protein according to claim 1, 6 or 11 in the manufacture of a medicament for inhibiting tumor growth or treating cancer in a patient

14. The use according to claim 13, wherein the use further comprises that the patient is to be exposed to radiation and/or is to be administered a chemotherapeutic.

15. The use according to claim 13 or 14, wherein the cancer or tumor is selected from the group consisting of colorectal, breast, ovarian, pancreatic, gastric, prostate, renal, cervical, myeloma, lymphoma, leukemia, thyroid, endometrial, uterine, bladder, neuroendocrine, head and neck, liver, nasopharyngeal, testicular, small cell lung cancer, non-small cell lung cancer, melanoma, basal cell skin cancer, squamous cell skin cancer, dermatofibrosarcoma protuberans, Merkel cell carcinoma, glioblastoma, glioma, sarcoma, mesothelioma, and myelodisplastic syndromes.