

CLAIMS

1. A fusion protein that is capable of binding both CD137 and GPC3, wherein the fusion protein comprises at least two subunits, wherein a first subunit comprises a full-length immunoglobulin and is specific for GPC3, and wherein a second subunit comprises a lipocalin mutein and is specific for CD137, wherein the second subunit is linked at the N-terminus to the C-terminus of the first subunit via a peptide linker, and wherein the fusion protein comprises two chains of SEQ ID NOs: 87 and 82.
2. The fusion protein of claim 1,
 - (a) wherein the fusion protein is capable of binding GPC3 with a K_D value of at most about 1 nM or comparable to or lower than the K_D value of the immunoglobulin that is included in the first subunit alone;
 - (b) wherein the fusion protein is capable of binding CD137 with an EC_{50} value of at most about 3 nM or comparable to or lower than the EC_{50} value of the lipocalin mutein specific for CD137 that is included in the second subunit alone;
 - (c) wherein the fusion protein is cross-reactive with cynomolgus GPC3;
 - (d) wherein the fusion protein is capable of simultaneously binding CD137 and GPC3 with an EC_{50} values of at most about 10 nM, when said fusion protein is measured in an ELISA assay;
 - (e) wherein the fusion protein is capable of binding GPC3 expressing tumor cells;
 - (f) wherein the fusion protein is capable of inducing increased secretion of IL-2;
 - (g) wherein the fusion protein is capable of inducing increased IL-2 secretion to a higher level than SEQ ID NO: 83 and/or with a better efficiency as compared to SEQ ID NO: 83;
 - (h) wherein the fusion protein is capable of inducing lymphocyte-mediated cytotoxicity;
 - (i) wherein the fusion protein is capable of inducing enhanced killing of GPC3 expressing tumor cells mediated by T cells than SEQ ID NO: 83 and/or inducing cytotoxic T cell-activation with a better efficacy as compared to SEQ ID NO: 83;
 - (j) wherein the fusion protein is capable of co-stimulating T-cell responses in a GPC3-dependent manner; or
 - (k) wherein the fusion protein is capable of co-stimulating T-cell responses in a tumor microenvironment.
3. The fusion protein of claim 1 or 2, wherein the fusion protein has a half-life in mice of at least 50 hours, at least 75 hours, at least 100 hours, at least 125 hours, at least

150 hours, at least 175 hours, at least 200 hours, at least 250 hours, or even longer, and/or wherein the fusion protein has a half-life in mice that is longer than that of SEQ ID NO: 83, and/or wherein the fusion protein has an isoelectric point of at least 6.5, at least 6.8, at least 7.1, at least 7.4, at least 7.5, at least 7.7, or even higher, and/or wherein the fusion protein has an isoelectric point higher than that of SEQ ID NO: 83.

4. The fusion protein of any one of claims 1-3, wherein the second subunit is linked at the N-terminus via a linker to the C-terminus of the heavy chain constant region (CH) of the first subunit.
5. The fusion protein of any one of claims 1-4, wherein the first subunit comprises the set of CDR sequences: GYTFTDYE (HCDR1, SEQ ID NO: 72), LDPKTGDT (HCDR2, SEQ ID NO: 73), TRFYSTY (HCDR3, SEQ ID NO: 74), and the set of CDR sequences: QSLVHSNRNTY (LCDR1, SEQ ID NO: 75), KVS (LCDR2), SQNTHVPPT (LCDR3, SEQ ID NO: 77).
6. The fusion protein of any one of claims 1-5 wherein the immunoglobulin has an IgG4 backbone.
7. A nucleic acid molecule comprising a nucleotide sequence encoding the fusion protein of any one of claims 1-6.
8. A method of producing the fusion protein according to any one of claims 1-6, wherein the fusion protein is produced starting from the nucleic acid coding for the fusion protein.
9. A pharmaceutical composition comprising one or more fusion proteins of any one of claims 1-6.
10. Use of one or more fusion proteins of any one of claims 1-6 or a composition of claim 9 comprising such fusion protein(s) in the manufacture of a medicament for the treatment of GPC3-positive cancers for simultaneously activating downstream signaling pathways of CD137 and engaging GPC3-positive tumor cells, wherein the medicament is to be administered to a tissue comprising a tumor.
11. Use of one or more fusion proteins of any one of claims 1-6 or a composition of claim 9 comprising such fusion protein(s) in the manufacture of a medicament for the

treatment of GPC3-positive cancers for simultaneously co-stimulating T-cells and engaging GPC3-positive tumor cells, wherein the medicament is to be administered to a tissue comprising a tumor.

12. Use of one or more fusion proteins of any one of claims 1-6 or a composition of claim 9 comprising such fusion protein(s) in the manufacture of a medicament for the treatment of GPC3-positive cancers for inducing a localized lymphocyte response in the vicinity of GPC3-positive tumor cells, wherein the medicament is to be administered to a tissue comprising a tumor.
13. Use of one or more fusion proteins of any one of claims 1-6 or a composition of claim 9 comprising such fusion protein(s) in the manufacture of a medicament for the treatment of GPC3-positive cancers for inducing increased lymphocyte-mediated cytotoxicity of GPC3-positive tumor cells, wherein the medicament is to be administered to a tissue comprising a tumor.
14. Use of the fusion protein of any one claims 1-6 or a composition of claim 9 comprising such fusion protein(s) in the manufacture of a medicament for ameliorating, or treating GPC3-positive cancers.