

bind. That is, the antibodies described herein share a common, novel epitope that is distinct from that of other agonist anti-CD137 antibodies. And, as exemplified in the working examples, engagement of this epitope by the antibodies described herein gives rise to differentiated *in vitro* activity, such as effects on regulatory T cell proliferation, cytokine production by CD8⁺ T cells and macrophages, and intracellular signaling, as compared to agonist antibodies that bind to different epitopes of CD137. Furthermore, it has been demonstrated that an affinity range (a “sweet spot”) for antibodies is particularly optimal for anti-tumor activity. For example, antibodies of intermediate affinity were shown to be more efficacious against large tumors as compared to antibodies with higher or lower affinity.

The disclosure relates, at least in part, to stable anti-CD137 antibody formulations. Notably, the anti-CD137 antibody formulations of the disclosure maintain the stability of the antibody, or antigen binding fragment thereof, minimize the formation of antibody aggregates (high molecular weight species) and particulates, reduce the percentage of charge variants, and maintain the structural integrity of the antibody.

In one aspect, the disclosure provides a formulation comprising: (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively ~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~ and (b) a buffer comprising histidine.

In another aspect, the disclosure provides a formulation comprising: (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively ~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~ (b) a buffer comprising histidine; and (c) a disaccharide sugar.

In another aspect, the disclosure provides a formulation comprising: (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively ~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~ and (b) a buffer comprising histidine, wherein the formulation has a pH of ~~about~~ 5.0-7.0.

In another aspect, the disclosure provides a formulation comprising: (a) an anti-CD137 antibody at a concentration of 1 mg/ml to 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively, and (b) a buffer comprising histidine; wherein the formulation has a pH of 5.0-7.4.

5. In another aspect, the disclosure provides a formulation comprising: (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, ~~wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~ wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid, (b) a buffer comprising histidine, (c) a disaccharide sugar, (d) a non-ionic surfactant, and (e) a salt, wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.0.

~~———— In another aspect, the disclosure provides a formulation comprising: an anti-CD137 antibody at a concentration of about 1 mg/ml to about 100 mg/ml, wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid, (b) a buffer comprising histidine, (c) a disaccharide sugar, (d) a non-ionic surfactant, and (e) a salt, wherein the pH of the formulation is about 5.0 to about 7.4.~~

In another aspect, the disclosure provides a formulation comprising: (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~ (b) a buffer comprising histidine, (c) a disaccharide sugar at ~~about~~ 5%-~~about~~ 15% weight/volume, (d) a non-ionic surfactant at ~~about~~ 0.01%-~~about~~ 0.1% weight/volume (w/v), and (e) a salt at ~~about~~ 50 mM – 200 mM, wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.0.

In another aspect, the disclosure provides a formulation comprising: (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~ (b) a buffer comprising ~~about~~ 10 mM to ~~about~~ 100 mM histidine, (c) sucrose at ~~about~~ 5%-~~about~~ 15% weight/volume, (d) polysorbate-80 at ~~about~~ 0.01%-~~about~~ 0.1% weight/volume (w/v), and (e) NaCl at ~~about~~ 50 mM – 200 mM, wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.0.

In another aspect, the disclosure provides a formulation comprising: an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~ (b) a buffer comprising histidine, (c) a disaccharide sugar, (d) a non-ionic surfactant, and (e) a salt, wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.4.

In another aspect, the disclosure provides a formulation comprising: (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~ (b) a buffer comprising histidine, (c) a disaccharide sugar at ~~about~~ 5%-~~about~~ 15% weight/volume, (d) a non-ionic surfactant at ~~about~~ 0.01%-~~about~~ 0.1% weight/volume (w/v), and (e) a salt at ~~about~~ 50 mM – 200 mM, wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.4.

~~———— In another aspect, the disclosure provides a formulation comprising: (a) an anti-CD137 antibody at a concentration of about 1mg/ml to about 100 mg/ml, wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid, (b) a buffer comprising about 10 mM to about 100 mM histidine, (c) sucrose at about 5% about 15% weight/volume, (d) polysorbate 80 at about 0.01% about 0.1% weight/volume (w/v), and (e) NaCl at about 50 mM — 200 mM, wherein the pH of the formulation is about 5.0 to about 7.0.~~

In another aspect, the disclosure provides a formulation comprising: (a) an anti-CD137 antibody at a concentration of ~~about~~ 1mg/ml to ~~about~~ 100 mg/ml, ~~wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID Nos: 4 and 6, respectively~~ wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid, (b) a buffer comprising ~~about~~ 10 mM to ~~about~~ 100 mM histidine, (c) sucrose at ~~about~~ 5% ~~about~~ 15% weight/volume, (d) polysorbate-80 at ~~about~~ 0.01% ~~about~~ 0.1% weight/volume (w/v), and (e) NaCl at ~~about~~ 50 mM – 200 mM, wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.4.

In another aspect, the disclosure provides a formulation comprising: (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, ~~wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~ wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid, (b) a buffer comprising ~~about~~ 20 mM histidine, (c) sucrose at ~~about~~ 10% weight/volume (w/v), (d) polysorbate-80 at ~~about~~ 0.03% weight/volume (w/v), and (e) NaCl at ~~about~~ 100mM, wherein the pH of the formulation is ~~about~~ 6.0.

In any of the foregoing or related aspects of the disclosure, the anti-CD137 antibody comprises a heavy chain CDR3 of DXPFXLDDXXYYYYYX (SEQ ID NO: 127), wherein X is any amino acid. In any of the foregoing or related aspects of the disclosure, the anti-CD137 antibody comprises a heavy chain CDR3 of DX₁X₂X₃X₄LX₅X₆X₇X₈YX₉YYX₁₀ (SEQ ID NO: 128), wherein X₁ is any amino acid, wherein X₂ is a non-polar amino acid, wherein X₃ is a non-polar amino acid, wherein X₄ is any amino acid, wherein X₅ is a polar amino acid, wherein X₆ is any amino acid, wherein X₇ is any amino acid, wherein X₈ is a polar amino acid, wherein X₉ is a polar amino acid, and wherein X₁₀ is any amino acid. In any of the foregoing or related aspects of the disclosure, X₂ is proline, X₃ is phenylalanine or tryptophan, X₅ is aspartic acid or glutamic acid, X₈ is tyrosine, and X₉ is tyrosine.

In any of the foregoing or related aspects of the disclosure, the anti-CD137 antibody of the formulation of the disclosure comprises a heavy chain CDR3 of SEQ ID NO: 68.

In any of the foregoing or related aspects of the disclosure, the anti-CD137 antibody comprises a heavy chain CDR1 of SEQ ID NO: 48, a heavy chain CDR2 of SEQ ID NO: 56, and a heavy chain CDR3 of SEQ ID NO: 68, and a light chain CDR1 of SEQ ID NO: 69, a light chain CDR2 of SEQ ID NO: 78, and a light chain CDR3 of SEQ ID NO: 89.

antibody at a concentration of about 30 mg/ml to about 45 mg/ml. In some examples, the formulation of the disclosure comprises the anti-CD137 antibody at a concentration of about 45 mg/ml to about 60 mg/ml. In some examples, the formulation of the disclosure comprises the anti-CD137 antibody at a concentration of about 60 mg/ml to about 75 mg/ml. In some examples, the formulation of the disclosure comprises the anti-CD137 antibody at a concentration of about 75 mg/ml to about 90 mg/ml. In some examples, the formulation of the disclosure comprises the anti-CD137 antibody at a concentration of about 85 mg/ml to about 100 mg/ml. In some examples, the formulation of the disclosure comprises the anti-CD137 antibody at a concentration of about 5 mg/ml. In some examples, the formulation of the disclosure comprises the anti-CD137 antibody at a concentration of about 10 mg/ml. In some examples, the formulation of the disclosure comprises the anti-CD137 antibody at a concentration of about 15 mg/ml. In some examples, the formulation of the disclosure comprises the anti-CD137 antibody at a concentration of about 20 mg/ml.

In a further aspect, the disclosure provides use of the formulation as described herein in the manufacture of a medicament for inducing or enhancing dimerization of human CD137 trimers in a subject that has cancer or a tumor. In a further aspect, the disclosure provides use of the formulation as described herein in the manufacture of a medicament for inducing or enhancing multimerization of human CD137 trimers in a subject that has cancer or a tumor. In a further aspect, the disclosure provides use of the formulation as described herein in the manufacture of a medicament for inducing or enhancing T cell activation in a subject that has cancer or a tumor.

In a further aspect, the disclosure provides use of the formulation as described herein in the manufacture of a medicament for inducing or enhancing a cytotoxic T cell response in a subject that has cancer or a tumor. In another aspect, the disclosure provides use of the formulation as described herein in the manufacture of a medicament for inducing or enhancing cytokine production of an immune cell in a subject that has cancer or a tumor. In another aspect, the disclosure provides use of the formulation as described herein in the manufacture of a medicament for inducing or enhancing T cell proliferation in a subject that has cancer or a tumor.

In another aspect, the disclosure provides use of the formulation as described herein in the manufacture of a medicament for reducing or inhibiting tumor growth. In another aspect, the disclosure provides use of the formulation as described herein in the manufacture of a medicament for treating a disorder mediated by human CD137 in a subject that has cancer or a tumor. In another

aspect, the disclosure provides use of the formulation as described herein in the manufacture of a medicament for treating cancer in a subject.

CLAIMS

1. A formulation comprising:

- (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~ and
- (b) a buffer comprising histidine.

2. A formulation comprising:

- (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~
- (b) a buffer comprising histidine; and
- (c) a disaccharide sugar.

3. A formulation comprising:

- (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~ and
- (b) a buffer comprising histidine;

wherein the formulation has a pH of ~~about~~ 5.0-7.0.

4. A formulation comprising:

- (a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~ and
- (b) a buffer comprising histidine;

wherein the formulation has a pH of ~~about~~ 5.0-7.4.

5. A formulation comprising:

(a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~

(b) a buffer comprising histidine,

(c) a disaccharide sugar,

(d) a non-ionic surfactant, and

(e) a salt,

wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.0.

6. A formulation comprising:

(a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~

(b) a buffer comprising histidine,

(c) a disaccharide sugar,

(d) a non-ionic surfactant, and

(e) a salt,

wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.4.

7. A formulation comprising:

(a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~

(b) a buffer comprising histidine,

(c) a disaccharide sugar at ~~about~~ 5%-~~about~~ 15% weight/volume,

(d) a non-ionic surfactant at ~~about~~ 0.01%-~~about~~ 0.1% weight/volume (w/v), and

(e) a salt at ~~about~~ 50 mM – 200 mM,

wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.0.

8. A formulation comprising:

(a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~

(b) a buffer comprising histidine,

(c) a disaccharide sugar at ~~about~~ 5%-~~about~~ 15% weight/volume,

(d) a non-ionic surfactant at ~~about~~ 0.01%-~~about~~ 0.1% weight/volume (w/v), and

(e) a salt at ~~about~~ 50 mM – 200 mM,

wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.4.

9. A formulation comprising:

(a) an anti-CD137 antibody at a concentration of ~~about~~ 1mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~

(b) a buffer comprising ~~about~~ 10 mM to ~~about~~ 100 mM histidine,

(c) sucrose at ~~about~~ 5%-~~about~~ 15% weight/volume,

(d) polysorbate-80 at ~~about~~ 0.01%-~~about~~ 0.1% weight/volume (w/v), and

(e) NaCl at ~~about~~ 50 mM – 200 mM,

wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.0.

10. A formulation comprising:

(a) an anti-CD137 antibody at a concentration of ~~about~~ 1mg/ml to ~~about~~ 100 mg/ml, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~

(b) a buffer comprising ~~about~~ 10 mM to ~~about~~ 100 mM histidine,

(c) sucrose at ~~about~~ 5%-~~about~~ 15% weight/volume,

(d) polysorbate-80 at ~~about~~ 0.01%–~~about~~ 0.1% weight/volume (w/v), and
(e) NaCl at ~~about~~ 50 mM – 200 mM,
wherein the pH of the formulation is ~~about~~ 5.0 to ~~about~~ 7.4.

11. A formulation comprising:

(a) an anti-CD137 antibody at a concentration of ~~about~~ 1 mg/ml to ~~about~~ 100 mg/ml,
wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively~~wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid,~~
(b) a buffer comprising ~~about~~ 20 mM histidine,
(c) sucrose at ~~about~~ 10% weight/volume (w/v),
(d) polysorbate-80 at ~~about~~ 0.03% weight/volume (w/v), and
(e) NaCl at ~~about~~ 100mM,
wherein the pH of the formulation is ~~about~~ 6.0.

~~12. The formulation of any one of claims 1-11, wherein the anti-CD137 antibody comprises a heavy chain CDR3 of DXPFXLDDXYYYYYX (SEQ ID NO: 127), wherein X is any amino acid.~~

~~13. The formulation of any one of claims 1-11, wherein the anti-CD137 antibody comprises a heavy chain CDR3 of DX₁X₂X₃X₄LX₅X₆X₇X₈YX₉YYX₁₀ (SEQ ID NO: 128), wherein X₁ is any amino acid, wherein X₂ is a non-polar amino acid, wherein X₃ is a non-polar amino acid, wherein X₄ is any amino acid, wherein X₅ is a polar amino acid, wherein X₆ is any amino acid, wherein X₇ is any amino acid, wherein X₈ is a polar amino acid, wherein X₉ is a polar amino acid, and wherein X₁₀ is any amino acid.~~

~~14. The formulation of claim 13, wherein X₂ is proline, X₃ is phenylalanine or tryptophan, X₅ is aspartic acid or glutamic acid, X₈ is tyrosine, and X₉ is tyrosine.~~

~~15~~12. The formulation of any one of claims 1-~~14~~11, wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 68.

~~1613.~~ The formulation of any one of claims 1-~~1512~~, wherein the anti-CD137 antibody comprises a heavy chain CDR1 of SEQ ID NO: 48, a heavy chain CDR2 of SEQ ID NO: 56, and a heavy chain CDR3 of SEQ ID NO: 68, and a light chain CDR1 of SEQ ID NO: 69, a light chain CDR2 of SEQ ID NO: 78, and a light chain CDR3 of SEQ ID NO: 89.

~~17. The formulation of any one of claims 1-15, wherein the anti-CD137 antibody comprises heavy and light chain CDRs selected from the group consisting of:~~

~~(a) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 48, 56 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;~~

~~(b) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 51, 108 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;~~

~~(c) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 135, 139 and 143, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 144, 147 and 150, respectively;~~

~~(d) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 137, 141 and 143, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 144, 147 and 150, respectively;~~

~~(e) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 48, 154 and 159, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 144, 147 and 150, respectively; and~~

~~(f) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 51, 156-159 respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 144, 147 and 150, respectively.~~

~~18. The formulation of any one of claims 1-16, wherein the anti-CD137 antibody comprises heavy and light chain sequences comprising amino acid sequences having at least 90% identity to SEQ ID NOs: 4 and 6, respectively.~~

~~19. The formulation of claim 18, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively.~~

~~20. The formulation of any one of claims 1-15 and 17, wherein the anti-CD137 antibody comprises heavy and light chain sequences comprising amino acid sequences having at least 90% identity to SEQ ID NOs: 101 and 6, respectively.~~

~~21. The formulation of claim 20, wherein the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 101 and 6, respectively.~~

~~22~~14. The formulation of any one of claims 1-~~19~~13, wherein the antibody comprises an IgG1 heavy chain constant region.

~~23~~15. The formulation of claim ~~22~~14, wherein the IgG1 heavy chain constant region is a wild-type human IgG1 heavy chain constant region.

~~24~~16. The formulation of claim ~~22~~14, wherein the IgG1 heavy chain constant region comprises an amino acid substitution relative to a wild-type human IgG1 heavy chain constant region.

~~25~~17. The formulation of any one of claim 1-~~19~~13, wherein the antibody comprises an IgG4 heavy chain constant region.

~~26~~18. The formulation of claim ~~25~~17, wherein the IgG4 heavy chain constant region is a wild-type human IgG4 heavy chain constant region.

~~27~~19. The formulation of claim ~~25~~17, wherein the IgG4 heavy chain constant region comprises an amino acid substitution relative to a wild-type human IgG4 heavy chain constant region.

~~28~~20. The formulation of any one of claims 1-~~10- and 12-~~2719, comprising ~~about~~ 10 mM histidine to ~~about~~ 100 mM histidine.

2921. The formulation of any one of claims 1-~~2820~~, comprising ~~about~~ 20 mM histidine.

3022. The formulation of any one of claims 1, 3-4, 9-10, and 12-~~2820~~, further comprising a disaccharide sugar.

3123. The formulation of any one of claims 2, 5-8, and 3022, wherein the disaccharide sugar is selected from sucrose, lactose, maltose, and trehalose.

3224. The formulation of claim 3123, wherein the disaccharide sugar is sucrose.

3325. The formulation of any one of claims 2, 5-6, and ~~3022-3224~~, wherein the disaccharide sugar is at ~~about~~ 5%-~~about~~ 15% weight/volume.

3426. The formulation of any one of claims 2, 5-8, and ~~30-3222-24~~, wherein the disaccharide sugar is at ~~about~~ 10% weight/volume.

3527. The formulation of any one of claims 1-4 and 12-~~2820~~, further comprising a salt.

3628. The formulation of any one of claims 5-8, and 3527, wherein the salt is NaCl.

3729. The formulation of any one of claims 5 and ~~3527-3628~~, wherein the salt is at a concentration of ~~about~~ 50 mM - 200 mM.

3830. The formulation of any one of claims 5-10 and ~~3527-3628~~, wherein the salt is at a concentration of ~~about~~ 100 mM.

3931. The formulation of any one of claims 1, 2, and 12-~~2820~~, wherein the formulation has a pH of ~~about~~ 5.0-7.0.

4032. The formulation of any one of claims 1, 2, and 12-~~2820~~, wherein the formulation has a pH of ~~about~~ 5.0-7.4.

4133. The formulation of any one of claims 3-4, 7-10, and ~~39-40~~31-32 wherein the pH is ~~about~~ 6.0.

4234. The formulation of any one of claims 1-4 and 12-~~41~~33, further comprising a non-ionic surfactant.

4335. The formulation of any one of claims 5-8, and ~~42~~34, wherein the non-ionic surfactant is a polysorbate.

4436. The formulation of claim ~~43~~35, wherein the polysorbate is polysorbate-80.

4537. The formulation of any one of claims 5-6 and ~~4234-43~~35, wherein the non-ionic surfactant is at ~~about~~ 0.01%-~~about~~ 0.1% weight/volume (w/v).

4638. The formulation of any one of claims 5-8, and ~~4234-43~~35, wherein the non-ionic surfactant is at ~~about~~ 0.03% weight/volume (w/v).

4739. The formulation of any one of claims 1-~~46~~38, comprising the anti-CD137 antibody at a concentration of ~~about~~ 5 mg/ml to ~~about~~ 15 mg/ml.

4840. The formulation of any one of claims 1-~~46~~38, comprising the anti-CD137 antibody at a concentration of ~~about~~ 15 mg/ml to ~~about~~ 30 mg/ml.

4941. The formulation of any one of claims 1-~~46~~38, comprising the anti-CD137 antibody at a concentration of ~~about~~ 30 mg/ml to ~~about~~ 45 mg/ml.

5042. The formulation of any one of claims 1-~~38~~46, comprising the anti-CD137 antibody at a concentration of ~~about~~ 45 mg/ml to ~~about~~ 60 mg/ml.

5143. The formulation of any one of claims 1-~~38~~46, comprising the anti-CD137 antibody at a concentration of ~~about~~ 60 mg/ml to ~~about~~ 75 mg/ml.

~~5244~~. The formulation of any one of claims 1-~~3846~~, comprising the anti-CD137 antibody at a concentration of ~~about~~-75 mg/ml to ~~about~~-90 mg/ml.

~~5345~~. The formulation of any one of claims 1-~~3846~~, comprising the anti-CD137 antibody at a concentration of ~~about~~-85 mg/ml to ~~about~~-100 mg/ml.

~~5446~~. The formulation of any one of claims 1-~~3846~~, comprising the anti-CD137 antibody at a concentration of ~~about~~-5 mg/ml.

~~5547~~. The formulation of any one of claims 1-~~3846~~, comprising the anti-CD137 antibody at a concentration of ~~about~~-10 mg/ml.

~~5648~~. The formulation of any one of claims 1-~~3846~~, comprising the anti-CD137 antibody at a concentration of ~~about~~-15 mg/ml.

~~5749~~. The formulation of any one of claims 1-~~3846~~, comprising the anti-CD137 antibody at a concentration of ~~about~~-20 mg/ml.

~~5850~~. Use of the formulation of any one of claims 1-~~57-49~~ in the manufacture of a medicament for inducing or enhancing dimerization of human CD137 trimers in a subject that has cancer or a tumor.

~~5951~~. Use of the formulation of any one of claims 1-~~49-57~~ in the manufacture of a medicament for inducing or enhancing multimerization of human CD137 trimers in a subject that has cancer or a tumor.

~~6052~~. Use of the formulation of any one of claims 1-~~49-57~~ in the manufacture of a medicament for inducing or enhancing T cell activation in a subject that has cancer or a tumor.

~~6153~~. The use of claim ~~6052~~, wherein the T cell activation occurs in a tumor microenvironment.

~~6254~~. Use of the formulation of any one of claims 1-~~49 57~~ in the manufacture of a medicament for inducing or enhancing a cytotoxic T cell response in a subject that has cancer or a tumor.

~~6355~~. The use of claim ~~6254~~, wherein the cytotoxic T cell response occurs in a tumor microenvironment.

~~6456~~. Use of the formulation of any one of claims 1-~~49 57~~ in the manufacture of a medicament for inducing or enhancing cytokine production of an immune cell in a subject that has cancer or a tumor.

~~6557~~. The use of claim ~~6456~~, wherein the cytokine produced is IL-2, TNF α , IL-13, IFN- γ , or combinations thereof.

~~6658~~. The use of claim ~~6456~~ or claim ~~6557~~, wherein the cytokine production occurs in a tumor microenvironment.

~~6759~~. Use of any one of claims 1-~~49 57~~ in the manufacture of a medicament for inducing or enhancing T cell proliferation in a subject that has cancer or a tumor.

~~6860~~. The use of claim ~~6759~~, wherein the T cell proliferation occurs in a tumor microenvironment.

~~6961~~. Use of the formulation of any one of claims 1-~~49 57~~ in the manufacture of a medicament for reducing or inhibiting tumor growth.

~~7062~~. Use of the formulation of any one of claims 1-~~49 57~~ in the manufacture of a medicament for treating a disorder mediated by human CD137 in a subject that has cancer or a tumor.

~~7163~~. Use of the formulation of any one of claims 1-~~49 57~~ in the manufacture of a medicament for treating cancer in a subject.

~~7264~~. The use of any one of claims ~~6961-7163~~, wherein infiltration of immune cells into a tumor microenvironment is increased after administration of the formulation.

~~7365~~. The use of claim ~~7264~~, wherein the immune cells express CD45.

~~7466~~. The use of any one of claims ~~6961-7365~~, wherein the quantity of T regulatory (Treg) cells is reduced in a tumor microenvironment after administration of the formulation.

~~7567~~. The use of claim ~~7466~~, wherein the Treg cells express CD4, FOXP-3 and CD25.

~~7668~~. The use of any one of claims ~~6961-7567~~, wherein the quantity of macrophages is reduced in a tumor microenvironment after administration of ~~the-an~~ isolated monoclonal antibody or antigen binding portion.

~~7769~~. The use of claim ~~7668~~, wherein the macrophages express CD45 and CD11b.

~~7870~~. The use of any one of claims ~~6961-7769~~, wherein T cell exhaustion is reduced in a tumor microenvironment after administration of ~~the-an~~ isolated monoclonal antibody or antigen binding portion, optionally wherein reduction of T cell exhaustion comprises a decrease in expression of TIGIT, PD-1, LAG-3, or combinations thereof.

~~7971~~. The use of any one of claims ~~7163-7870~~, wherein the cancer is selected from the group consisting of melanoma, glioma, renal, breast, hematological, and head and neck cancer.

~~8072~~. The use of claim ~~7971~~, wherein the hematological cancer is a B cell lymphoma.

~~8173~~. Use of the formulation of claims 1-~~49 57~~ in the manufacture of a medicament for inducing an anti-tumor memory immune response.

~~8274~~. The use of any one of claims ~~5850-8173~~, wherein the anti-CD137 antibody binds Fc gamma receptor.

8375. The use of any one of claims ~~5850-8274~~, wherein depletion of CD4+ T cells, CD8+ T cells, Natural Killer cells, or combinations thereof, reduces the efficacy of the formulation.

8476. A kit comprising a container comprising the formulation of any one of claims 1-~~4957~~, and a package insert comprising instructions for administration of the formulation, for treating or delaying progression of cancer or reducing or inhibiting tumor growth in a subject in need thereof.

8577. A kit comprising a container comprising the formulation of any one of claims 1-~~4957~~, and a package insert comprising instructions for administration of the formulation alone or in combination with another agent, for treating or delaying progression of cancer or reducing or inhibiting tumor growth in a subject in need thereof.

8678. Use of the formulation of any one of claims 1-~~49 57~~ in the manufacture of a medicament for treating or delaying progression of cancer or reducing or inhibiting tumor growth in a subject in need thereof.

8779. A formulation according to any one of claims 1-~~4957~~, for use as a medicament.