

stability of the antibodies, and inhibiting aggregation. However, the excipient used in one antibody formulation may not be suitable for another antibody due to differences in antibody sequence (Awwad *et al.*). Thus, there continues to be an unmet need for the development of stable antibody formulations, including stable formulations comprising novel agonistic antibodies that bind to human CD137.

SUMMARY

The present disclosure is based, at least in part, on the discovery of novel agonist anti-CD137 antibodies exhibiting protective anti-tumor immunity in animals, and formulations thereof. Notably, the antibodies described herein are efficacious against diverse tumor types, and over a wide dose range. Moreover, as exemplified in the working examples, the antibodies described herein are therapeutically effective against very large tumors. For example, treatment of tumor-bearing mice with agonist anti-CD137 antibodies described herein resulted in complete regression of tumors as large as 1,800 mm³. As set forth in FIG. 15, treatment of such mice also resulted in protective immunity. And coincident with the observed efficacy were positive immunophenotypic changes in the tumor microenvironment, such as increased immune cell infiltration with concomitant reductions in regulatory T cell and exhausted T cell populations (see, *e.g.*, FIGs. 22A-22D).

As described above, agonism of CD137 has been associated with certain adverse events, including hepatotoxicity-related deaths in humans (see, *e.g.*, Segal et al. (2017) *Clin Cancer Res* 23(8): 1929-1935). Similar toxicities resulting from treatment with agonist anti-CD137 antibodies (such as the 3H3 antibody) have also been observed in animal models (see, *e.g.*, Bartkowiak et al. (2018) *Clin Cancer Res* 24(5):1138-1151). Yet, the agonist anti-CD137 antibodies described herein have minimal effects on the liver, as determined by, *e.g.*, plasma levels of liver enzymes (*e.g.*, alanine aminotransferase (ALT)) and immune cell infiltration. For example, there was no evidence of increased intrahepatic or intrasplenic immune cell infiltration in mice treated with the antibodies. Thus, the antibodies described herein are not only highly efficacious, but also sparing of certain toxicities associated with CD137 agonism.

While the disclosure is not bound by any particular theory or mechanism of action, the superior therapeutic and toxicity-sparing properties of the antibodies described herein are believed to derive in part from one or both of their affinity and the novel epitope to which they

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 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, and a buffer comprising histidine.

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, a buffer comprising histidine; and a disaccharide sugar.

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, and 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 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, a buffer comprising histidine, a disaccharide sugar, a non-ionic surfactant, and 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 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, a buffer comprising histidine, a disaccharide sugar at about 5%-about 15% weight/volume, a non-ionic surfactant at about 0.01%-about 0.1% weight/volume (w/v), and 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 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, a buffer comprising about 10 mM to about 100 mM histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v), and 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 a heavy chain CDR3 of SEQ ID NO: 126, wherein X is any amino acid, a buffer comprising histidine, a disaccharide sugar, a non-ionic surfactant, and 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 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, a buffer comprising histidine, a disaccharide sugar at about 5%-about 15% weight/volume, a non-ionic surfactant at about 0.01%-about 0.1% weight/volume (w/v), and 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 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, a buffer comprising about 10 mM to about 100 mM histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v), and 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 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, a buffer comprising about 20 mM histidine, sucrose at about 10% weight/volume (w/v), polysorbate-80 at about 0.03% weight/volume (w/v), and 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.

In any of the foregoing or related aspects of the disclosure, the anti-CD137 antibody comprises a heavy chain CDR1 of SEQ ID NO: 51, a heavy chain CDR2 of SEQ ID NO: 108, 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.

In any of the foregoing or related aspects of the disclosure, 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. In some examples, the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 4 and 6, respectively.

In any of the foregoing or related aspects of the disclosure, 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. In some examples, the anti-CD137 antibody comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 101 and 6, respectively.

In any of the foregoing or related aspects of the disclosure, the antibody comprises an IgG1 heavy chain constant region. In some examples, the IgG1 heavy chain constant region is a wild-type human IgG1 heavy chain constant region. In some examples, the IgG1 heavy chain constant region comprises an amino acid substitution relative to a wild-type human IgG1 heavy chain constant region.

In any of the foregoing or related aspects of the disclosure, the antibody comprises an IgG4 heavy chain constant region. In some examples, the IgG4 heavy chain constant region is a wild-type human IgG4 heavy chain constant region. In some examples, the IgG4 heavy chain constant region comprises an amino acid substitution relative to a wild-type human IgG4 heavy chain constant region.

In some examples, 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 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, and a buffer comprising histidine.

In some examples, 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 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, and a buffer comprising histidine. [new paragraph]

In some examples, 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 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, 150, respectively, and a buffer comprising histidine.

In some examples, 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 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, a buffer comprising histidine, and a disaccharide sugar.

In some examples, 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 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, a buffer comprising histidine, and a disaccharide sugar.

In some examples, 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 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, a buffer comprising histidine, and a disaccharide sugar.

In some examples, 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 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, and a buffer comprising histidine, wherein the formulation has a pH of about 5.0-7.0.

In some examples, 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 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, and a buffer comprising histidine, wherein the formulation has a pH of about 5.0-7.0.

In some examples, 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 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 a buffer comprising histidine, wherein the formulation has a pH of about 5.0-7.0.

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In some examples, 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 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, a buffer comprising histidine, a disaccharide sugar, a non-ionic surfactant, and a salt, wherein the pH of the formulation is about 5.0 to about 7.0.

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sugar, a non-ionic surfactant, and a salt, wherein the pH of the formulation is about 5.0 to about 7.0.

In some examples, 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 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, a buffer comprising histidine, a disaccharide sugar at about 5%-about 15% weight/volume, a non-ionic surfactant at about 0.01%-about 0.1% weight/volume (w/v), and a salt at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.0.

In some examples, 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 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, a buffer comprising histidine, a disaccharide sugar at about 5%-about 15% weight/volume, a non-ionic surfactant at about 0.01%-about 0.1% weight/volume (w/v), and a salt at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.0.

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In some examples, the disclosure provides a formulation comprising an anti-CD137 antibody at a concentration of about 1mg/ml to about 100 mg/ml, wherein the anti-CD137 antibody comprises 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, a buffer comprising about 10 mM to about 100 mM

histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v), and NaCl at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.0.

In some examples, the disclosure provides a formulation comprising an anti-CD137 antibody at a concentration of about 1mg/ml to about 100 mg/ml, wherein the anti-CD137 antibody comprises 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, a buffer comprising about 10 mM to about 100 mM histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v), and NaCl at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.0.

In some examples, the disclosure provides a formulation comprising an anti-CD137 antibody at a concentration of about 1mg/ml to about 100 mg/ml, wherein the anti-CD137 antibody comprises 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, a buffer comprising about 10 mM to about 100 mM histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v), and NaCl at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.0.

In some examples, 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 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, and a buffer comprising histidine, wherein the formulation has a pH of about 5.0-7.4.

In some examples, 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 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, and a buffer comprising histidine, wherein the formulation has a pH of about 5.0-7.4.

In some examples, 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 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 a buffer comprising histidine, wherein the formulation has a pH of about 5.0-7.4.

In some examples, 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 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, a buffer comprising histidine, a disaccharide sugar, a non-ionic surfactant, and a salt, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, 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 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, a buffer comprising histidine, a disaccharide sugar, a non-ionic surfactant, and a salt, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, 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 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, a buffer comprising histidine, a disaccharide sugar, a non-ionic surfactant, and a salt, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, 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 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, a buffer comprising histidine, a disaccharide sugar at about

5%-about 15% weight/volume, a non-ionic surfactant at about 0.01%-about 0.1% weight/volume (w/v), and a salt at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, 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 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, a buffer comprising histidine, a disaccharide sugar at about 5%-about 15% weight/volume, a non-ionic surfactant at about 0.01%-about 0.1% weight/volume (w/v), and a salt at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, 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 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, a buffer comprising histidine, a disaccharide sugar at about 5%-about 15% weight/volume, a non-ionic surfactant at about 0.01%-about 0.1% weight/volume (w/v), and a salt at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, the disclosure provides a formulation comprising an anti-CD137 antibody at a concentration of about 1mg/ml to about 100 mg/ml, wherein the anti-CD137 antibody comprises 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, a buffer comprising about 10 mM to about 100 mM histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v), and NaCl at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, the disclosure provides a formulation comprising an anti-CD137 antibody at a concentration of about 1mg/ml to about 100 mg/ml, wherein the anti-CD137 antibody comprises 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, a buffer comprising about 10 mM to about 100 mM histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v), and NaCl at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, the disclosure provides a formulation comprising an anti-CD137 antibody at a concentration of about 1mg/ml to about 100 mg/ml, wherein the anti-CD137 antibody comprises 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, a buffer comprising about 10 mM to about 100 mM histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v), and NaCl at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, 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 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, a buffer comprising about 20 mM histidine, sucrose at about 10% weight/volume (w/v), polysorbate-80 at about 0.03% weight/volume (w/v), and NaCl at about 100mM, wherein the pH of the formulation is about 6.0.

In some examples, 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 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, a buffer comprising about 20 mM histidine, sucrose at about 10% weight/volume (w/v), polysorbate-80 at about 0.03% weight/volume (w/v), and NaCl at about 100mM, wherein the pH of the formulation is about 6.0.

In some examples, 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 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, a buffer comprising about 20 mM histidine,

sucrose at about 10% weight/volume (w/v), polysorbate-80 at about 0.03% weight/volume (w/v), and NaCl at about 100mM, wherein the pH of the formulation is about 6.0.

In some examples, 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 the heavy and light chain variable sequences set forth in SEQ ID NOs: 4 and 6, respectively, and a buffer comprising histidine.

In some examples, 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 the heavy and light chain variable sequences set forth in SEQ ID NOs: 4 and 6, respectively, a buffer comprising histidine, and a disaccharide sugar.

In some examples, 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 the heavy and light chain variable sequences set forth in SEQ ID NOs: 4 and 6, respectively, and a buffer comprising histidine, wherein the formulation has a pH of about 5.0-7.0.

In some examples, 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 the heavy and light chain variable sequences set forth in SEQ ID NOs: 4 and 6, respectively, a buffer comprising histidine, a disaccharide sugar, a non-ionic surfactant, and a salt, wherein the pH of the formulation is about 5.0 to about 7.0.

In some examples, 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 the heavy and light chain variable sequences set forth in SEQ ID NOs: 4 and 6, respectively, a buffer comprising histidine, a disaccharide sugar at about 5%-about 15% weight/volume, a non-ionic surfactant at about 0.01%-about 0.1% weight/volume (w/v), and a salt at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.0.

In some examples, the disclosure provides a formulation comprising an anti-CD137 antibody at a concentration of about 1mg/ml to about 100 mg/ml, wherein the anti-CD137 antibody comprises the heavy and light chain variable sequences set forth in SEQ ID NOs: 4 and 6, respectively, a buffer comprising about 10 mM to about 100 mM histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v),

and NaCl at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.0.

In some examples, 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 the heavy and light chain variable sequences set forth in SEQ ID NOs: 4 and 6, respectively, and a buffer comprising histidine, wherein the formulation has a pH of about 5.0-7.4.

In some examples, 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 the heavy and light chain variable sequences set forth in SEQ ID NOs: 4 and 6, respectively, a buffer comprising histidine, a disaccharide sugar, a non-ionic surfactant, and a salt, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, 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 the heavy and light chain variable sequences set forth in SEQ ID NOs: 4 and 6, respectively, a buffer comprising histidine, a disaccharide sugar at about 5%-about 15% weight/volume, a non-ionic surfactant at about 0.01%-about 0.1% weight/volume (w/v), and a salt at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, the disclosure provides a formulation comprising an anti-CD137 antibody at a concentration of about 1mg/ml to about 100 mg/ml, wherein the anti-CD137 antibody comprises the heavy and light chain variable sequences set forth in SEQ ID NOs: 4 and 6, respectively, a buffer comprising about 10 mM to about 100 mM histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v), and NaCl at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.4. In some examples, 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 the heavy and light chain variable sequences set forth in SEQ ID NOs: 4 and 6, respectively, a buffer comprising about 20 mM histidine, sucrose at about 10% weight/volume (w/v), polysorbate-80 at about 0.03% weight/volume (w/v), and NaCl at about 100mM, wherein the pH of the formulation is about 6.0.

In some examples, 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 amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively, and a buffer comprising histidine.

In some examples, 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 amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively, a buffer comprising histidine, and a disaccharide sugar.

In some examples, 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 amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively, and a buffer comprising histidine, wherein the formulation has a pH of about 5.0-7.0.

In some examples, 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 amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively, a buffer comprising histidine, a disaccharide sugar, a non-ionic surfactant, and a salt, wherein the pH of the formulation is about 5.0 to about 7.0.

In some examples, 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 amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively, a buffer comprising histidine, a disaccharide sugar at about 5%-about 15% weight/volume, a non-ionic surfactant at about 0.01%-about 0.1% weight/volume (w/v), and a salt at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.0.

In some examples, the disclosure provides a formulation comprising 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 amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively, a buffer comprising about 10 mM to about 100 mM histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v), and NaCl at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.0.

In some examples, 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 amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively, and a buffer comprising histidine, wherein the formulation has a pH of about 5.0-7.4.

In some examples, 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 amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively, a buffer comprising histidine, a disaccharide sugar, a non-ionic surfactant, and a salt, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, 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 amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively, a buffer comprising histidine, a disaccharide sugar at about 5%-about 15% weight/volume, a non-ionic surfactant at about 0.01%-about 0.1% weight/volume (w/v), and a salt at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, the disclosure provides a formulation comprising 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 amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively, a buffer comprising about 10 mM to about 100 mM histidine, sucrose at about 5%-about 15% weight/volume, polysorbate-80 at about 0.01%-about 0.1% weight/volume (w/v), and NaCl at about 50 mM – 200 mM, wherein the pH of the formulation is about 5.0 to about 7.4.

In some examples, 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 amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively, a buffer comprising about 20 mM histidine, sucrose at about 10% weight/volume (w/v), polysorbate-80 at about 0.03% weight/volume (w/v), and NaCl at about 100mM, wherein the pH of the formulation is about 6.0.

In any of the foregoing or related examples of the disclosure, the formulation of the disclosure comprises histidine. In some examples, the formulation of the disclosure comprises

about 10 mM histidine to about 100 mM histidine. In some examples, the formulation comprises about 20 mM histidine.

In any of the foregoing or related examples of the disclosure, the formulation of the disclosure comprises a disaccharide sugar. In some examples, the disaccharide sugar is selected from sucrose, lactose, maltose, and trehalose. In some examples, the disaccharide sugar is sucrose. In some examples, the formulation of the disclosure comprises the disaccharide sugar at about 5%-about 15% weight/volume. In some examples, the formulation of the disclosure comprises the disaccharide sugar at about 10% weight/volume.

In any of the foregoing or related examples of the disclosure, the formulation of the disclosure comprises a salt. In some examples, the salt is NaCl. In some examples, the formulation of the disclosure comprises salt at a concentration of about 50 mM - 200 mM. In some examples, the formulation of the disclosure comprises salt at a concentration of about 100 mM.

In any of the foregoing or related examples of the disclosure, the formulation of the disclosure has a pH of about 5.0-7.0. In some examples, the formulation of the disclosure has a pH of about 6.0.

In any of the foregoing or related examples of the disclosure, the formulation of the disclosure has a pH of about 5.0-8.0. In some examples, the formulation of the disclosure has a pH of about 5.0-7.4.

In any of the foregoing or related examples of the disclosure, the formulation of the disclosure comprises a non-ionic surfactant. In some examples, the non-ionic surfactant is a polysorbate. In some examples, the polysorbate is polysorbate-80. In some examples, the formulation of the disclosure comprises the non-ionic surfactant is at about 0.01%-about 0.1% weight/volume (w/v). In some examples, the formulation of the disclosure comprises the non-ionic surfactant is at about 0.03% weight/volume (w/v).

In any of the foregoing or related examples of the disclosure, the formulation of the disclosure comprises an anti-CD137 antibody at a concentration of about 1mg/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 to about 15 mg/ml. In some examples, the formulation of the disclosure comprises the anti-CD137 antibody at a concentration of about 15 mg/ml to about 30 mg/ml. In some examples, the formulation of the disclosure comprises the anti-CD137

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. 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. 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.

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. 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. 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.

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. 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.

In yet another aspect, the disclosure provides use of the formulation as described herein in the manufacture of a medicament for inducing an anti-tumor memory immune response.

In some examples, the disclosure provides a method for inducing or enhancing dimerization of human CD137 trimers in a subject, comprising administering to a subject in need thereof, an effective amount of the formulation of the disclosure.

In some examples, the disclosure provides a method for inducing or enhancing multimerization of human CD137 trimers in a subject, comprising administering to a subject in need thereof, an effective amount of the formulation of the disclosure.

In some examples, the disclosure provides a method for inducing or enhancing T cell activation in a subject, comprising administering to a subject in need thereof, an effective amount of the formulation of the disclosure. In some examples, the T cell activation occurs in a tumor microenvironment.

In some examples, the disclosure provides a method for inducing or enhancing a cytotoxic T cell response in a subject, comprising administering to a subject in need thereof, an effective amount of the formulation of the disclosure. In some examples, the cytotoxic T cell response occurs in a tumor microenvironment.

In some examples, the disclosure provides a method for inducing or enhancing cytokine production of an immune cell in a subject, comprising administering to a subject in need thereof, an effective amount of the formulation of the disclosure. In some examples, the cytokine produced is IL-2, TNF α , IL-13, IFN- γ , or combinations thereof. In some examples, the cytokine production occurs in a tumor microenvironment.

In some examples, the disclosure provides a method for inducing or enhancing T cell proliferation in a subject, comprising administering to a subject in need thereof, an effective amount of the formulation of the disclosure. In some examples, the T cell proliferation occurs in a tumor microenvironment.

In some examples, the disclosure provides a method for reducing or inhibiting tumor growth, comprising administering to a subject in need thereof, an effective amount of the formulation of the disclosure.

In some examples, the disclosure provides a method for treating a disorder mediated by human CD137 in a subject, comprising administering to a subject in need thereof, an effective amount of the formulation of the disclosure.

In some examples, the disclosure provides a method for treating cancer in a subject, comprising administering to a subject in need thereof, an effective amount of the formulation of the disclosure.

In any of the foregoing examples, infiltration of immune cells into a tumor microenvironment is increased after administration of the formulation. In some examples, the immune cells express CD45.

In any of the foregoing examples, the quantity of T regulatory (Treg) cells is reduced in a tumor microenvironment after administration of the formulation. In some examples, the Treg cells express CD4, FOXP-3 and CD25.

In any of the foregoing examples, the quantity of macrophages is reduced in a tumor microenvironment after administration of the isolated monoclonal antibody or antigen binding portion. In some examples, the macrophages express CD45 and CD11b.

In any of the foregoing examples, T cell exhaustion is reduced in a tumor microenvironment after administration of the isolated monoclonal antibody or antigen binding portion. In some examples, reduction of T cell exhaustion comprises a decrease in expression of TIGIT, PD-1, LAG-3, or combinations thereof.

In any of the foregoing examples, the cancer is selected from the group consisting of melanoma, glioma, renal, breast, hematological, and head and neck cancer. In some examples, the hematological cancer is a B cell lymphoma.

In some examples, the disclosure provides a method of inducing an anti-tumor memory immune response, comprising administering to a subject in need thereof, an effective amount of the formulation of the disclosure.

In any of the foregoing examples, the anti-CD137 antibody binds Fc gamma receptor.

In any of the foregoing examples, depletion of CD4⁺ T cells, CD8⁺ T cells, Natural Killer cells, or combinations thereof, reduces the efficacy of the formulation.

In another aspect, the disclosure provides a kit comprising a container comprising the formulation of the disclosure, 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.

In another aspect, the disclosure provides a kit comprising a container comprising the formulation of the disclosure, 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.

In another aspect, the disclosure provides for the use of the formulation of the disclosure, for the manufacture of a medicament for treating or delaying progression of cancer or reducing or inhibiting tumor growth in a subject in need thereof.

In some examples, the disclosure provides a formulation of the disclosure for use 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.

In another aspect, the disclosure provides a formulation of the disclosure for use as a medicament.

In view of the foregoing, in some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of between about 40 nM to about 100 nM. In some examples, the disclosure provides an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 110 nM). In some examples, the affinity of the anti-CD137 antibody to human CD137 is at least two (*e.g.*, at least three, four, five, six, seven, eight, nine, or 10) fold higher than the affinity of mAb10 for mouse CD137. In some examples, the affinity of the anti-CD137 antibody is no greater than 500, 450, 400, 350, 300, 250, 200, 250, 200, 175, 150, 125, 110, or 100 nM. In some examples, the affinity of the anti-CD137 antibody to human CD137 is at least two (*e.g.*, at least three, four, five, six, seven, eight, nine, or 10) fold higher than the affinity of mAb10 for mouse CD137, but no greater than 500, 450, 400, 350, 300, 250, 200, 250, 200, 175, 150, 125, 110, or 100 nM.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein the antibody or antigen binding portion binds to an epitope on human CD137 comprising one or more (*e.g.*, one, two, three, four, five, six, seven, eight, nine, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or all 25) of amino acids 111-132 of SEQ ID NO:3. In some examples, the disclosure provides an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein the antibody or antigen binding portion binds to an

epitope within amino acids 111-132 of SEQ ID NO:3. In some examples, the disclosure provides an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein the antibody or antigen binding portion binds to all or a portion of amino acids 111-132 of SEQ ID NO:3. In some examples, the epitope comprises K114 of SEQ ID NO: 3. In some examples, the epitope comprises residues E111, T113, and K114 of SEQ ID NO: 3. In some examples, the epitope comprises residues E111, T113, K114, N126 and I132 of SEQ ID NO: 3. In some examples, the epitope comprises residues E111, T113, K114 and P135 of SEQ ID NO: 3. In some examples, the epitope comprises residues E111, T113, K114, N126, I132 and P135 of SEQ ID NO: 3. In some examples, the antibody or antigen binding portion thereof binds to human CD137 with an affinity of between about 30 nM and about 100 nM (*e.g.*, between about 30 nM and about 110 nM).

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 40-100 nM (*e.g.*, between about 40 nM and about 100 nM) and binds to an epitope on human CD137 comprising K114 of SEQ ID NO: 3. In some examples, the disclosure provides an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM) and binds to an epitope on human CD137 comprising K114 of SEQ ID NO: 3. In some examples, the epitope comprises residues E111, T113, and K114 of SEQ ID NO: 3. In some examples, the epitope comprises residues E111, T113, K114, N126 and I132 of SEQ ID NO: 3. In some examples, the epitope comprises residues E111, T113, K114 and P135 of SEQ ID NO: 3. In some examples, the epitope comprises residues E111, T113, K114, N126, I132 and P135 of SEQ ID NO: 3.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, about 30 nM to about 100 nM) and binds to an epitope on human CD137 comprising a sequence of one or more amino acid residues corresponding to amino acid positions 111 to 135 of SEQ ID NO: 3. In some examples, the epitope comprises 2, 3, 4, 5, 6, 7, 8, 9, 10,

11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid residues corresponding to amino acid positions 111 to 135 of SEQ ID NO: 3.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM) and binds to an epitope on human CD137 located within amino acid residues 111-135 of SEQ ID NO: 3. In some examples, the epitope is at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids. In some examples, the epitope is fewer than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6 or 5 amino acids.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM) and binds to an epitope on human CD137 comprising ELTK (corresponding to amino acid residues 111-114 of SEQ ID NO: 3). In some examples, the epitope further comprises one or more residues N126, I132 and P135 of SEQ ID NO: 3.

In any of the foregoing examples, the epitope is a non-linear epitope. In any of the foregoing examples, mutation of residue K114 of SEQ ID NO: 3 abrogates binding of the antibody or antigen binding portion thereof to human CD137.

In any of the foregoing examples, the antibody or antigen binding portion described herein binds human CD137 with an affinity (K_D) of about 30-100 nM, 30-95 nM, 45-95 nM, 50-90 nM, 55-85 nM, 60-80 nM, 65-75 nM, 55-75 nM, 40-70 nM, 50-80 nM, or 60-90 nM. In some examples, the antibody or antigen binding portion binds to a non-ligand binding region of the extracellular domain of human CD137. In some examples, the antibody or antigen binding portion does not inhibit the interaction between CD137 and CD137L. In some examples, the non-ligand binding region spans cysteine rich domain (CRD) III and CRD IV. In any of the foregoing examples, the antibody or antigen binding portion does not inhibit the formation of a trimer of CD137:CD137L monomers.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion:

(i) binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) binds to a non-ligand binding region of the extracellular domain of human CD137; and

(iii) binds to an epitope on human CD137 comprising K114 of SEQ ID NO: 3.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion:

(i) binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) does not inhibit the interaction between human CD137 and human CD137 ligand; and

(iii) binds to an epitope on human CD137 comprising K114 of SEQ ID NO: 3.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion: (i) binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM) and (ii) does not inhibit the formation of a trimer of CD137:CD137L monomers (that is, a CD137:CD137L trimer:trimer complex). In some examples, the disclosure features an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion: (i) binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM) and (ii) binds to a non-ligand binding region of the extracellular domain of human CD137. In some examples, the disclosure features an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion: (i) binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM) and (ii) does not inhibit the interaction between human CD137 and CD137 ligand.

In any of the foregoing examples, the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence DXXXXLXXXXYXYXX (SEQ ID

NO: 126), wherein X is any amino acid. In some examples, the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence DXPFXLDDXXYYYYYX (SEQ ID NO: 127), wherein X is any amino acid. In any of the foregoing examples, mutation of residues D95, L100, Y100E, Y100G, Y100H, or combinations thereof, of the heavy chain CDR3, to alanine results in loss of binding to human CD137. In any of the foregoing examples, mutation of residues P97, F98, D100A, Y100D, Y100F, or combinations thereof, to alanine results in reduction of binding to human CD137. In any of the foregoing examples, the antibody or antigen binding portion comprises heavy and light chain CDRs, wherein heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 68.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

- (i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM); and
- (ii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence DXXXXLXXXXYXYX (SEQ ID NO: 126), wherein X is any amino acid. In some examples, X is any amino acid except alanine.

In another example, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

- (i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM); and
- (ii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence $DX_1X_2X_3X_4LX_5X_6X_7X_8YX_9YYX_{10}$ (SEQ ID NO: 128), wherein X_1 is any amino acid, wherein X_2 is a non-polar amino acid, wherein X_3 is a non-polar amino acid, wherein X_4 is any amino acid, wherein X_5 is a polar amino acid, wherein X_6 is any amino acid, wherein X_7 is any amino acid, wherein X_8 is a polar amino acid, wherein X_9 is a polar amino acid, and wherein X_{10} is any amino acid. In some examples, X_2 is proline, X_3 is phenylalanine or tryptophan, X_5 is aspartic acid or glutamic acid, X_8 is tyrosine, and X_9 is tyrosine.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM); and

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope on human CD137 comprising one or more residues E111, T113, K114, N126, I132 and P135 of SEQ ID NO: 3.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope on human CD137 comprising one or more residues E111, T113, K114, N126, I132 and P135 of SEQ ID NO: 3;

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence DXXXXLXXXXYXYX (SEQ ID NO: 126), wherein X is any amino acid; or

(iv) combinations thereof. In some examples, X is any amino acid except alanine.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope on human CD137 comprising one or more residues E111, T113, K114, N126, I132 and P135 of SEQ ID NO: 3;

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence 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; or

(iv) combinations thereof. In some examples, X₂ is proline, X₃ is phenylalanine or tryptophan, X₅ is aspartic acid or glutamic acid, X₈ is tyrosine, and X₉ is tyrosine.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope on human CD137 comprising one or more residues E111, T113, K114, N126, I132 and P135 of SEQ ID NO: 3; and

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence DXXXXLXXXXYXYX (SEQ ID NO: 126), wherein X is any amino acid. In some examples, X is any amino acid except alanine.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope on human CD137 comprising one or more residues E111, T113, K114, N126, I132 and P135 of SEQ ID NO: 3; and

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence 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 some examples, 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 examples, the epitope comprises K114. In any of the foregoing examples, the epitope comprises E111, T113 and K114. In any of the foregoing examples, the epitope comprises E11, T113, K114, N126 and I132. In any of the foregoing examples, the epitope comprises residues E111, T113, K114, N126, I132 and P135 of SEQ ID NO: 3.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM); and

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope comprising a sequence of one or more amino acid residues corresponding to amino acid positions 111 to 135 of SEQ ID NO: 3.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope comprising a sequence of one or more amino acid residues corresponding to amino acid positions 111 to 135 of SEQ ID NO: 3;

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence DXXXXLXXXXYXYX (SEQ ID NO: 126), wherein X is any amino acid; or

(iv) combinations thereof. In some examples, X is any amino acid except alanine.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope comprising a sequence of one or more amino acid residues corresponding to amino acid positions 111 to 135 of SEQ ID NO: 3;

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence 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; or

(iv) combinations thereof. In some examples, X₂ is proline, X₃ is phenylalanine or tryptophan, X₅ is aspartic acid or glutamic acid, X₈ is tyrosine, and X₉ is tyrosine.

In another examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope comprising a sequence of one or more amino acid residues corresponding to amino acid positions 111 to 135 of SEQ ID NO: 3; and

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence DXXXXLXXXXYXYX (SEQ ID NO: 126), wherein X is any amino acid. In some examples, X is any amino acid except alanine.

In another examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope comprising a sequence of one or more amino acid residues corresponding to amino acid positions 111 to 135 of SEQ ID NO: 3; and

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence 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 some examples, 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 examples, the epitope comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid residues corresponding to amino acid positions 111 to 135 of SEQ ID NO: 3.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM); and

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope comprising ELTK (corresponding to amino acid residues 111-114 of SEQ ID NO: 3).

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope comprising ELTK (corresponding to amino acid residues 111-114 of SEQ ID NO: 3);

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence DXXXXLXXXXYXYX (SEQ ID NO: 126), wherein X is any amino acid; or

(iv) combinations thereof. In some examples, X is any amino acid except alanine.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope comprising ELTK (corresponding to amino acid residues 111-114 of SEQ ID NO: 3);

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence 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; or

(iv) combinations thereof. In some examples, X₂ is proline, X₃ is phenylalanine or tryptophan, X₅ is aspartic acid or glutamic acid, X₈ is tyrosine, and X₉ is tyrosine.

In some examples, the disclosure provides an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope comprising ELTK (corresponding to amino acid residues 111-114 of SEQ ID NO: 3); and

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence DXXXXLXXXXYXYX (SEQ ID NO: 126), wherein X is any amino acid. In some examples, X is any amino acid except alanine.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to human CD137, wherein

(i) the antibody or antigen binding portion binds human CD137 with an affinity (K_D) of about 30-100 nM (*e.g.*, between about 30 nM and about 100 nM);

(ii) the antibody or antigen binding portion thereof specifically binds to an epitope comprising ELTK (corresponding to amino acid residues 111-114 of SEQ ID NO: 3); and

(iii) the antibody or antigen binding portion comprises a heavy chain CDR3 comprising the amino acid sequence 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 some examples, 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 examples, the epitope comprises the residues ELTK of SEQ ID NO: 3 (corresponding to amino acid residues 111-114 of SEQ ID NO: 3). In some examples, the epitope comprises ELTK of SEQ ID NO: 3 (corresponding to amino acid residues 111-114 of SEQ ID NO: 3) and residues N126, I132 and P135 of SEQ ID NO: 3.

In any of the foregoing examples, the epitope is a non-linear epitope. In some examples, mutation of residue K114 of human CD137 (SEQ ID NO: 3) abrogates binding of the antibody or antigen binding portion thereof to human CD137.

In any of the foregoing examples, the antibody or antigen binding portion thereof comprises a heavy chain CDR3 comprising the amino acid sequence DXPFXLDDXXYYYYYX (SEQ ID NO: 128), wherein X is any amino acid. In some examples, mutation of residues D95, L100, Y100E, Y100G, Y100H, or combinations thereof, of the heavy chain CDR3 of the antibody or antigen binding portion described herein, results in loss of binding to human CD137. In some examples, mutation of residues P97, F98, D100A, Y100D, Y100F, or combinations

thereof, of the heavy chain CDR3 of the antibody or antigen binding portion described herein, to alanine results in reduction of binding to human CD137. In other examples, mutation of residues P97, F98, D100A, Y100D, Y100F, or combinations thereof, of the heavy chain CDR3 of the antibody or antigen binding portion described herein, to any residue except alanine, results in an increase in binding to human CD137.

In any of the foregoing examples, the antibody or antigen binding portion thereof, binds human CD137 with an (K_D) of about 45-95 nM, 50-90 nM, 55-85 nM, 60-80 nM, 65-75 nM, 55-75 nM, 40-70 nM, 50-80 nM, or 60-90 nM. In any of the foregoing examples, the antibody or antigen binding portion thereof, binds human CD137 with an (K_D) of about 45 nM to about 95 nM, about 50 to about 90 nM, about 55 to about 85 nM, about 60 to about 80 nM, about 65 to about 75 nM, about 55 to about 75 nM, about 40 to about 70 nM, about 50 to about 80 nM, or about 60 to about 90 nM.

In any of the foregoing examples, the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 68.

In any of the foregoing examples, the antibody or antigen binding portion thereof 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; and

(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.

In some examples, the agonistic isolated monoclonal antibody or antigen-binding portion thereof 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: 135, 139 and 143, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 144, 147 and 150, respectively; and

(b) 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.

In some examples, the agonistic isolated monoclonal antibody or antigen-binding portion thereof 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, 154 and 159, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 144, 147 and 150, respectively; and

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

In any of the foregoing examples, the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 4 and 101; and wherein the light chain variable region comprises an amino acid sequence of SEQ ID NO: 6.

In any of the foregoing examples, the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, comprising amino acid sequences selected from the group consisting of:

(a) SEQ ID NO: 4 and 6, respectively; and

(b) SEQ ID NO: 101 and 6, respectively.

In any of the foregoing examples, the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 4 and 101; and wherein the light chain variable region comprises an amino acid sequence which is at least 90% identical to the amino acid sequence of SEQ ID NO: 6.

In any of the foregoing examples, the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences at least 90% identical to the amino acid sequences selected from the group consisting of:

(a) SEQ ID NO: 4 and 6, respectively; and

(b) SEQ ID NO: 101 and 6, respectively.

In any of the foregoing examples, the antibody or antigen binding portion comprises heavy and light chains comprising amino acid sequences selected from the group consisting of:

(a) SEQ ID NOs: 129 and 133, respectively; and

(b) SEQ ID NOs: 131 and 133, respectively.

In any of the foregoing examples, the isolated monoclonal antibody, or antigen binding portion thereof described herein, is an agonist of human CD137 activity.

In any of the foregoing examples, the isolated monoclonal antibody, or antigen binding portion thereof described herein, competes with mAb1 or an antigen binding fragment of mAb1, for binding to the epitope of human CD137.

In some examples, the formulations described herein comprise an isolated monoclonal antibody that specifically binds CD137, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof 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: 48, 56 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 70, 79 and 90, respectively;

(c) 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: 71, 80 and 91, respectively;

(d) 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: 72, 81 and 92, respectively;

(e) 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: 73, 82 and 91, respectively;

(f) 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: 74, 83 and 93, respectively;

(g) 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: 75, 84 and 91, respectively;

(h) 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: 74, 85 and 94, respectively;

(i) 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: 76, 86 and 95, respectively;

(j) 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: 77, 87 and 93, respectively;

(k) 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, 88 and 90, respectively;

(l) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 49, 57 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;

(m) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 49, 58 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;

(n) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 49, 59 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;

(o) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 49, 60 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;

(p) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 50, 61 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;

(q) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 50, 58 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;

(r) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 51, 62 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;

(s) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 52, 63 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;

(t) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 50, 64 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;

(u) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 50, 65 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively;

(v) 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;

(w) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 107, 56 and 68, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 69, 78 and 89, respectively; and

(x) 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: 109, 110 and 92, respectively.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 101 and 103; and wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 105.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the

antibody or antigen binding portion comprises heavy and light chain variable regions encoded by nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 5 and 7, respectively; and
- (b) SEQ ID NOs: 102 and 7, respectively.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions encoded by nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NO: 5 and 7, respectively;
- (b) SEQ ID NO: 5 and 29, respectively;
- (c) SEQ ID NO: 5 and 31, respectively;
- (d) SEQ ID NO: 5 and 33, respectively;
- (e) SEQ ID NO: 5 and 35, respectively;
- (f) SEQ ID NO: 5 and 37, respectively;
- (g) SEQ ID NO: 5 and 39, respectively;
- (h) SEQ ID NO: 5 and 41, respectively;
- (i) SEQ ID NO: 5 and 43, respectively;
- (j) SEQ ID NO: 5 and 45, respectively;
- (k) SEQ ID NO: 5 and 47, respectively;
- (l) SEQ ID NO: 9 and 7, respectively;
- (m) SEQ ID NO: 11 and 7, respectively;
- (n) SEQ ID NO: 13 and 7, respectively;
- (o) SEQ ID NO: 15 and 7, respectively;
- (p) SEQ ID NO: 17 and 7, respectively;
- (q) SEQ ID NO: 19 and 7, respectively;
- (r) SEQ ID NO: 21 and 7, respectively;
- (s) SEQ ID NO: 23 and 7, respectively;
- (t) SEQ ID NO: 25 and 7, respectively;
- (u) SEQ ID NO: 27 and 7, respectively;
- (v) SEQ ID NO: 102 and 7, respectively;
- (w) SEQ ID NO: 104 and 7, respectively; and

(x) SEQ ID NO: 5 and 106, respectively.

In yet other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 68.

In another example, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein heavy chain CDR3 comprises the amino acid sequence DXXXXLXXXXYXYXX (SEQ ID NO: 126), wherein X is any amino acid. In some examples, X is any amino acid except for alanine.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein heavy chain CDR3 comprises the amino acid sequence DXPFXLDDYXYXYXX (SEQ ID NO: 127), wherein X is any amino acid. In some examples, X is any amino acid except for alanine.

In yet other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein heavy chain CDR3 comprises the amino acid sequence DXXXXLXXXXYXYXX (SEQ ID NO: 126), wherein X is any amino acid, and wherein mutation of residues D95, L100, Y100E, Y100G, Y100H, or combinations thereof, results in loss of binding to human CD137.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein heavy chain CDR3 comprises the amino acid sequence DXPFXLDDYXYXYXX (SEQ ID NO: 127), wherein X is any amino acid, and wherein mutation of residues P97, F98, D100A, Y100D, Y100F, or combinations thereof to alanine results in reduction of binding to human CD137.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein heavy chain CDR3 comprises the amino acid sequence DXPFXLDDYXYXYXX (SEQ ID NO: 127),

wherein X is any amino acid, and wherein mutation of residues P97, F98, D100A, Y100D, Y100F, or combinations thereof to any residue except alanine, results in an increase in binding to human CD137.

In yet other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein heavy chain CDR3 comprises the amino acid sequence 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 some examples, wherein X2 is proline, wherein X3 is phenylalanine or tryptophan, wherein X5 is aspartic acid or glutamic acid wherein X8 is tyrosine, and wherein X9 is tyrosine.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences selected from the group consisting of:

- (a) SEQ ID NO: 4 and 6, respectively;
- (b) SEQ ID NO: 4 and 28, respectively;
- (c) SEQ ID NO: 4 and 30, respectively;
- (d) SEQ ID NO: 4 and 32, respectively;
- (e) SEQ ID NO: 4 and 34, respectively;
- (f) SEQ ID NO: 4 and 36, respectively;
- (g) SEQ ID NO: 4 and 38, respectively;
- (h) SEQ ID NO: 4 and 40, respectively;
- (i) SEQ ID NO: 4 and 42, respectively;
- (j) SEQ ID NO: 4 and 44, respectively;
- (k) SEQ ID NO: 4 and 46, respectively;
- (l) SEQ ID NO: 8 and 6, respectively;
- (m) SEQ ID NO: 10 and 6, respectively;
- (n) SEQ ID NO: 12 and 6, respectively;

- (o) SEQ ID NO: 14 and 6, respectively;
- (p) SEQ ID NO: 16 and 6, respectively;
- (q) SEQ ID NO: 18 and 6, respectively;
- (r) SEQ ID NO: 20 and 6, respectively;
- (s) SEQ ID NO: 22 and 6, respectively;
- (t) SEQ ID NO: 24 and 6, respectively;
- (u) SEQ ID NO: 26 and 6, respectively;
- (v) SEQ ID NO: 101 and 6, respectively;
- (w) SEQ ID NO: 103 and 6, respectively; and
- (x) SEQ ID NO: 4 and 105, respectively.

In other examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137 wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 101 and 103; and wherein the light chain variable region comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 105.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences at least 90% identical to the amino acid sequences selected from the group consisting of:

- (a) SEQ ID NO: 4 and 6, respectively;
- (b) SEQ ID NO: 4 and 28, respectively;
- (c) SEQ ID NO: 4 and 30, respectively;
- (d) SEQ ID NO: 4 and 32, respectively;
- (e) SEQ ID NO: 4 and 34, respectively;
- (f) SEQ ID NO: 4 and 36, respectively;
- (g) SEQ ID NO: 4 and 38, respectively;
- (h) SEQ ID NO: 4 and 40, respectively;

- (i) SEQ ID NO: 4 and 42, respectively;
- (j) SEQ ID NO: 4 and 44, respectively;
- (k) SEQ ID NO: 4 and 46, respectively;
- (l) SEQ ID NO: 8 and 6, respectively;
- (m) SEQ ID NO: 10 and 6, respectively;
- (n) SEQ ID NO: 12 and 6, respectively;
- (o) SEQ ID NO: 14 and 6, respectively;
- (p) SEQ ID NO: 16 and 6, respectively;
- (q) SEQ ID NO: 18 and 6, respectively;
- (r) SEQ ID NO: 20 and 6, respectively;
- (s) SEQ ID NO: 22 and 6, respectively;
- (t) SEQ ID NO: 24 and 6, respectively;
- (u) SEQ ID NO: 26 and 6, respectively;
- (v) SEQ ID NO: 101 and 6, respectively;
- (w) SEQ ID NO: 103 and 6, respectively; and
- (x) SEQ ID NO: 4 and 105, respectively.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain sequences comprising amino acid sequences selected from the group consisting of:

- (a) SEQ ID NOs: 129 and 133, respectively; and
- (b) SEQ ID NOs: 131 and 133, respectively.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 129 and 133, respectively.

In some examples, the formulations described herein comprise an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, wherein the antibody or antigen binding portion thereof comprises heavy and light chain sequences having amino acid sequences set forth in SEQ ID NOs: 131 and 133, respectively.

In any of the foregoing examples, the antibody or antigen binding portion specifically binds to and agonizes human CD137.

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof, exhibits at least one or more of the following properties selected from the group consisting of:

- (a) induces or enhances dimerization of CD137 trimers;
- (b) induces or enhances multimerization of CD137 trimers;
- (c) induces or enhances T cell activation;
- (d) induces or enhances a cytotoxic T cell response;
- (e) induces or enhances T cell proliferation;
- (f) induces or enhances cytokine production; and
- (g) any combination of properties (a)-(f).

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof, exhibits at least one or more of the following properties relative to a reference antibody that binds human CD137, selected from the group consisting of:

- (a) does not induce or enhance intrahepatic T cell activation;
- (b) does not induce or enhance intrahepatic T cell proliferation;
- (c) does not induce or enhance intrasplenic T cell activation;
- (d) does not induce or enhance intrasplenic T cell proliferation;
- (e) does not induce or enhance macrophage activation;
- (f) does not induce or enhance macrophage differentiation;
- (g) does not induce or enhance alanine aminotransferase (ALT) activity; and
- (h) any combination of properties (a) – (g). In some examples, the reference antibody is urelumab.

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof, induces or enhances human CD137-mediated T cell activation in the tumor microenvironment, but does not significantly induce or enhance human CD137-mediated T cell activation in the spleen and/or liver.

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof, induces or enhances T cell activation in the tumor microenvironment, but does not significantly induce or enhance T cell activation in the spleen and/or liver.

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof, induces or enhances human CD137-mediated cytotoxic T cell response in the tumor microenvironment, but does not significantly induce or enhance human CD137-mediated cytotoxic T cell response in the spleen and/or liver.

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof, induces or enhances a cytotoxic T cell response in the tumor microenvironment, but does not significantly induce or enhance a T cell response in the spleen and/or liver.

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof, induces human CD137-mediated T cell proliferation in the tumor microenvironment, but does not significantly induce human CD137-mediated T cell proliferation in the spleen and/or liver.

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof, induces T cell proliferation in the tumor microenvironment, but does not significantly induce T cell proliferation in the spleen and/or liver.

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof, induces human CD137-mediated T cell infiltration in the tumor microenvironment, but does not significantly induce human CD137-mediated T cell infiltration in the spleen and/or liver.

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof, induces T cell infiltration in the tumor microenvironment, but does not significantly induce T cell infiltration in the spleen and/or liver.

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding fragment thereof, induces or enhances human CD137-mediated cytokine production in the tumor microenvironment, but does not significantly induce or enhance human CD137-mediated cytokine production in the spleen and/or liver.

In any of the foregoing examples, the properties of the antibody or antigen binding portion described herein, are not Fc gamma receptor binding dependent. In some examples, the properties of the antibody or antigen binding portion described herein, are enhanced by Fc gamma receptor binding.

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof cross competes with mAb1 (*i.e.*, an antibody comprising the heavy and light chain

variable sequences of SEQ ID NOs: 4 and 6, respectively). In some examples, the isolated monoclonal antibody or antigen binding portion thereof cross competes with mAb1 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 4 and 6, respectively), mab8 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 101 and 6, respectively) or mAb10 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 26 and 6, respectively). In some examples, the isolated monoclonal antibody or antigen binding portion thereof cross competes with mab8 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 101 and 6, respectively). In some examples, the isolated monoclonal antibody or antigen binding portion thereof cross competes with mAb10 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 26 and 6, respectively).

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof comprises at least the functional properties of mAb1 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 4 and 6, respectively). In some examples, the isolated monoclonal antibody or antigen binding portion thereof comprises at least the functional properties of mAb1 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 4 and 6, respectively), mab8 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 101 and 6, respectively) or mAb10 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 26 and 6, respectively). In some examples, the isolated monoclonal antibody or antigen binding portion thereof comprises at least the functional properties of mab8 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 101 and 6, respectively). In some examples, the isolated monoclonal antibody or antigen binding portion thereof comprises at least the functional properties of mAb10 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 26 and 6, respectively).

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof has a K_D value at least equivalent to mAb1 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 4 and 6, respectively). In some examples, the isolated monoclonal antibody or antigen binding portion thereof has a K_D value at least equivalent to mAb1 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 4 and 6, respectively), mab8 (*i.e.*, an antibody comprising the heavy and light chain variable

sequences of SEQ ID NOs: 101 and 6, respectively) or mAb10 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 26 and 6, respectively). In some examples, the isolated monoclonal antibody or antigen binding portion thereof has a K_D value at least equivalent to mAb8 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 101 and 6, respectively). In some examples, the isolated monoclonal antibody or antigen binding portion thereof has a K_D value at least equivalent to mAb10 (*i.e.*, an antibody comprising the heavy and light chain variable sequences of SEQ ID NOs: 26 and 6, respectively).

In any of the foregoing examples, the isolated monoclonal antibody or antigen binding portion thereof, cross-reacts with cynomolgus CD137 and/or mouse CD137.

In any of the foregoing examples, the isolated monoclonal antibody, or antigen binding portion thereof, is selected from the group consisting of an IgG1, an IgG2, and IgG3, an IgG4, and IgM, and IgA1, and IgA2, and IgD, and an IgE antibody. In some examples, the isolated monoclonal antibody, or antigen binding portion thereof, is an IgG1 antibody or IgG4 antibody.

In any of the foregoing examples, the isolated monoclonal antibody comprises a wild-type IgG1 or wild-type IgG4 heavy chain constant region. In some examples, the isolated monoclonal antibody comprises a mutant IgG1 heavy chain constant region. In some examples, the isolated monoclonal antibody comprises a mutant IgG4 heavy chain constant region. In some examples, the mutant IgG4 heavy chain constant region comprises a substitution at Ser228. In some examples, the mutant IgG4 heavy chain constant region comprises substitution S228P.

In any of the foregoing examples, the isolated monoclonal antibody, or antigen binding portion thereof, binds to an epitope of CD137, wherein the amino acid residues comprising the epitope bound by the antibody are located within 4 angstroms of the amino acid residues comprising the paratope of the mAb1 antibody, described herein.

In any of the foregoing examples, the isolated monoclonal antibody, or antigen binding portion thereof, binds to an epitope of CD137, wherein a mutation of the epitope bound by the antibody inhibits, reduces, or blocks binding to both the antibody and to antibody mAb1.

In any of the foregoing examples, the isolated antibody, or antigen binding portion thereof, is fully human or humanized (*i.e.*, a fully human or humanized antibody or antigen binding portion thereof).

In some examples, the disclosure provides a pharmaceutical composition comprising an isolated monoclonal antibody or antigen binding portion thereof, as described herein, and a pharmaceutically acceptable carrier.

In other examples, the disclosure provides a nucleic acid comprising a nucleotide sequence encoding the light chain, heavy chain, or both light and heavy chains of an isolated monoclonal antibody, or antigen binding portion thereof, described herein. In some examples, the nucleic acid comprises SEQ ID NOs: 5 and 7. In some examples, the nucleic acid comprises SEQ ID NOs: 102 and 7. In some examples, the disclosure provides an expression vector comprising the nucleic acid described herein. In other examples, the disclosure provides a cell transformed with an expression vector described herein.

In another example, the disclosure provides a method for producing an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds human CD137, the method comprising maintaining a cell described herein under conditions permitting expression of the monoclonal antibody or antigen binding portion thereof. In some examples, the method for producing the monoclonal antibody that specifically binds human CD137, or antigen binding portion thereof, further comprises obtaining the monoclonal antibody or antigen binding portion thereof.

In yet another example, the disclosure provides a method for inducing or enhancing dimerization of human CD137 trimers in a subject, comprising administering to a subject in need thereof, an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, or a pharmaceutical composition described herein.

In another example, the disclosure provides a method for inducing or enhancing multimerization of human CD137 trimers in a subject, comprising administering to a subject in need thereof, an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, or a pharmaceutical composition described herein.

In other examples, the disclosure provides a method for inducing or enhancing T cell activation mediated by human CD137 in a subject, comprising administering to a subject in need thereof, an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, or a pharmaceutical composition described herein. In some examples, T cell activation occurs in a tumor microenvironment. In other examples, T cell activation does not significantly occur in the spleen and/or liver of the subject.

In another example, the disclosure provides a method for inducing or enhancing a cytotoxic T cell response mediated by human CD137 in a subject, comprising administering to a subject in need thereof, an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, or a pharmaceutical composition described herein. In some examples, the cytotoxic T cell response occurs in a tumor microenvironment. In other examples, the cytotoxic T cell response does not significantly occur in the spleen and/or liver of the subject.

In some examples, the disclosure provides a method for inducing or enhancing cytokine production mediated by human CD137 in a subject, comprising administering to a subject in need thereof, an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, or a pharmaceutical composition described herein. In some examples, the cytokine produced is IL-2, TNF α , IL-13, IFN- γ , or combinations thereof. In some examples, the cytokine produced is IL-2. In some examples, the cytokine produced is TNF α . In some examples, the cytokine produced is IL-13. In some examples, the cytokine produced is IFN- γ . In some examples, the cytokine produced is IL-2 and TNF α . In some examples, the cytokine produced is IL-2 and IL-13. In some examples, the cytokine produced is IL-2 and IFN- γ . In some examples, the cytokine produced is TNF α and IL-13. In some examples, the cytokine produced is TNF α and IFN- γ . In some examples, the cytokine produced is IL-13 and IFN- γ . In some examples, the cytokine produced is IL-2, TNF α and IL-13. In some examples, the cytokine produced is IL-2, TNF α and IFN- γ . In some examples, the cytokine produced is IFN- γ TNF α and IL-13. In other examples, cytokine production occurs in a tumor microenvironment. In yet other examples, cytokine production does not significantly occur in the spleen and/or liver of the subject.

In another example, the disclosure provides a method for inducing or enhancing T cell proliferation mediated by human CD137 in a subject, comprising administering to a subject in need thereof, an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, or a pharmaceutical composition described herein. In some examples, T cell proliferation occurs in a tumor microenvironment. In other examples, T cell proliferation does not significantly occur in the spleen and/or liver of the subject.

In another example, the disclosure provides a method for reducing or inhibiting tumor growth, comprising administering to a subject in need thereof, an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, or a pharmaceutical composition described herein.

In yet another example, the disclosure provides a method for treating a disorder mediated by human CD137 in a subject, comprising administering to a subject in need thereof, an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, or a pharmaceutical composition described herein.

In some examples, the disclosure provides a method for treating cancer in a subject, comprising administering to a subject in need thereof, an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, or a pharmaceutical composition described herein. In some examples, the cancer is selected from the group consisting of melanoma, glioma, renal, breast, hematological and head and neck cancer. In some examples, the hematological cancer is a B cell lymphoma.

In some examples, the disclosure provides a method of inducing an anti-tumor memory immune response, comprising administering to a subject in need thereof, an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, or a pharmaceutical composition described herein.

In any of the foregoing examples, infiltration of immune cells into a tumor microenvironment is increased after administration of an antibody or antigen binding portion. In some examples, immune cells express CD45.

In any of the foregoing examples, quantity of T regulatory (Treg) cells is reduced in a tumor microenvironment after administration of an antibody or antigen binding portion. In some examples, Treg cells express CD4, FOXP-3 and CD24.

In any of the foregoing examples, quantity of macrophages cells is reduced in a tumor microenvironment after administration of a monoclonal antibody or antigen binding portion. In some examples, macrophages express CD45 and CD11b.

In any of the foregoing examples, T cell exhaustion is reduced after administration of an antibody or antigen binding portion. In some examples, reduction of T cell exhaustion comprises a decrease in expression of TIGIT, PD-1, LAG-3 or a combination thereof. In some examples, reduction of T cell exhaustion comprises a decrease in expression of TIGIT and PD-1.

In any of the foregoing examples, depletion of CD4⁺ T cells, CD8⁺ T cells, Natural Killer cells, or combinations thereof, reduces the efficacy of the antibody or antigen binding portion thereof.

In another example, the disclosure provides a method for detecting the presence or absence of human CD137 in a biological sample, comprising:

(a) contacting a biological sample with an antibody or antigen-binding portion described herein, wherein the antibody or antigen-binding portion is labeled with a detectable substance; and

(b) detecting the antibody or antigen-binding portion bound to human CD137 to thereby detect the presence or absence of human CD137 in the biological sample.

In another example, the disclosure provides a kit comprising a container comprising an antibody or antigen-binding portion described herein, and an optional pharmaceutically acceptable carrier, or a pharmaceutical composition described herein, and a package insert comprising instructions for administration of the antibody or pharmaceutical composition, for treating or delaying progression of cancer or reducing or inhibiting tumor growth in a subject in need thereof.

In another example, the disclosure provides a kit comprising a container comprising an antibody or antigen-binding portion described herein, and an optional pharmaceutically acceptable carrier, or a pharmaceutical composition described herein, and a package insert comprising instructions for administration of the antibody or pharmaceutical composition 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.

In another example, the disclosure provides use of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, to induce or enhance T cell activation mediated by human CD137 in a subject. In other examples, the disclosure provides use of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, to induce or enhance multimerization of human CD137 trimers in a subject. In another example, the disclosure provides use of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, to induce or enhance a cytotoxic T cell response mediated by human CD137 in a subject. In other examples, the disclosure provides use of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, to induce or enhance cytokine production mediated by human CD137 in a subject. In another example, the disclosure provides use of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, to induce or enhance T cell proliferation mediated by human CD137 in a subject.

In another example, the disclosure provides use of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, to reduce or inhibit tumor growth in a subject in need thereof. In other examples, the disclosure provides use of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, to treat a disorder mediated by human CD137 in a subject in need thereof. In another example, the disclosure provides use of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, to treat cancer in a subject in need thereof.

In another example, the disclosure provides use of an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, for the manufacture of a medicament for treating or delaying progression of cancer or reducing or inhibiting tumor growth in a subject in need thereof. In other examples, the disclosure provides an isolated monoclonal antibody, or antigen binding portion thereof, as described herein, 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. In another example, the disclosure provides an isolated monoclonal antibody or antigen binding portion thereof, as described herein, for use as a medicament.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

FIG. 1 provides graphs depicting the distribution of binding affinities of affinity matured clones of the parental anti-CD137 antibody mAb1.

FIG. 2 provides a schematic showing the results of mAb1 CDRH3 alanine scanning, as measured by binding affinity (K_D) to human or mouse CD137.

FIG. 3A shows the amino acid sequence of human CD137 wherein residues comprising an epitope bound by mAb1, mAb4 or mAb5 are indicated in bold.

FIG. 3B is a graph depicting kinetic binding data of mAb1 to the extracellular domain of mouse and rat CD137 as determined by surface plasmon resonance.

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 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 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 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 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 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 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 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 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 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 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 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 DXPFXLDXXYYYYYX (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. The formulation of any one of claims 1-14, wherein the anti-CD137 antibody comprises a heavy chain CDR3 of SEQ ID NO: 68.
16. The formulation of any one of claims 1-15, 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 and 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. The formulation of any one of claims 1-19, wherein the antibody comprises an IgG1 heavy chain constant region.
23. The formulation of claim 22, wherein the IgG1 heavy chain constant region is a wild-type human IgG1 heavy chain constant region
24. The formulation of claim 22, wherein the IgG1 heavy chain constant region comprises an amino acid substitution relative to a wild-type human IgG1 heavy chain constant region.
25. The formulation of any one of claim 1-19, wherein the antibody comprises an IgG4 heavy chain constant region.
26. The formulation of claim 25, wherein the IgG4 heavy chain constant region is a wild-type human IgG4 heavy chain constant region
27. The formulation of claim 25, wherein the IgG4 heavy chain constant region comprises an amino acid substitution relative to a wild-type human IgG4 heavy chain constant region.
28. The formulation of any one of claims 1-27, comprising about 10 mM histidine to about 100 mM histidine.
29. The formulation of any one of claims 1-28, comprising about 20 mM histidine.
30. The formulation of any one of claims 1, 3-4, 9-10, and 12-28, further comprising a disaccharide sugar.
31. The formulation of any one of claims 2, 5-8, and 30, wherein the disaccharide sugar is selected from sucrose, lactose, maltose, and trehalose.

32. The formulation of claim 31, wherein the disaccharide sugar is sucrose.
33. The formulation of any one of claims 2, 5-6, and 30-32, wherein the disaccharide sugar is at about 5%-about 15% weight/volume.
34. The formulation of any one of claims 2, 5-8, and 30-32, wherein the disaccharide sugar is at about 10% weight/volume.
35. The formulation of any one of claims 1-4 and 12-28, further comprising a salt.
36. The formulation of any one of claims 5-8, and 35, wherein the salt is NaCl.
37. The formulation of any one of claims 5 and 35-36, wherein the salt is at a concentration of about 50 mM - 200 mM.
38. The formulation of any one of claims 5-10 and 35-36, wherein the salt is at a concentration of about 100 mM.
39. The formulation of any one of claims 1, 2, and 12-28, wherein the formulation has a pH of about 5.0-7.0.
40. The formulation of any one of claims 1, 2, and 12-28, wherein the formulation has a pH of about 5.0-7.4.
41. The formulation of any one of claims 3-4, 7-10, and 39-40 wherein the pH is about 6.0.
42. The formulation of any one of claims 1-4 and 12-41, further comprising a non-ionic surfactant.
43. The formulation of any one of claims 5-8, and 42, wherein the non-ionic surfactant is a polysorbate.

44. The formulation of claim 43, wherein the polysorbate is polysorbate-80.
45. The formulation of any one of claims 5-6 and 42-43, wherein the non-ionic surfactant is at about 0.01%-about 0.1% weight/volume (w/v).
46. The formulation of any one of claims 5-8, and 42-43, wherein the non-ionic surfactant is at about 0.03% weight/volume (w/v).
47. The formulation of any one of claims 1-46, comprising the anti-CD137 antibody at a concentration of about 5 mg/ml to about 15 mg/ml.
48. The formulation of any one of claims 1-46, comprising the anti-CD137 antibody at a concentration of about 15 mg/ml to about 30 mg/ml.
49. The formulation of any one of claims 1-46, comprising the anti-CD137 antibody at a concentration of about 30 mg/ml to about 45 mg/ml.
50. The formulation of any one of claims 1-46, comprising the anti-CD137 antibody at a concentration of about 45 mg/ml to about 60 mg/ml.
51. The formulation of any one of claims 1-46, comprising the anti-CD137 antibody at a concentration of about 60 mg/ml to about 75 mg/ml.
52. The formulation of any one of claims 1-46, comprising the anti-CD137 antibody at a concentration of about 75 mg/ml to about 90 mg/ml.
53. The formulation of any one of claims 1-46, comprising the anti-CD137 antibody at a concentration of about 85 mg/ml to about 100 mg/ml.
54. The formulation of any one of claims 1-46, comprising the anti-CD137 antibody at a concentration of about 5 mg/ml.

55. The formulation of any one of claims 1-46, comprising the anti-CD137 antibody at a concentration of about 10 mg/ml.
56. The formulation of any one of claims 1-46, comprising the anti-CD137 antibody at a concentration of about 15 mg/ml.
57. The formulation of any one of claims 1-46, comprising the anti-CD137 antibody at a concentration of about 20 mg/ml.
58. Use of the formulation of any one of claims 1-57 in the manufacture of a medicament for inducing or enhancing dimerization of human CD137 trimers in a subject.
59. Use of the formulation of any one of claims 1-57 in the manufacture of a medicament for inducing or enhancing multimerization of human CD137 trimers in a subject.
60. Use of the formulation of any one of claims 1-57 in the manufacture of a medicament for inducing or enhancing T cell activation in a subject.
61. The use of claim 60, wherein the T cell activation occurs in a tumor microenvironment.
62. Use of the formulation of any one of claims 1-57 in the manufacture of a medicament for inducing or enhancing a cytotoxic T cell response in a subject.
63. The use of claim 62, wherein the cytotoxic T cell response occurs in a tumor microenvironment.
64. Use of the formulation of any one of claims 1-57 in the manufacture of a medicament for inducing or enhancing cytokine production of an immune cell in a subject.
65. The use of claim 64, wherein the cytokine produced is IL-2, TNF α , IL-13, IFN- γ , or combinations thereof.

66. The use of claim 64 or claim 65, wherein the cytokine production occurs in a tumor microenvironment.
67. Use of any one of claims 1-57 in the manufacture of a medicament for inducing or enhancing T cell proliferation in a subject.
68. The use of claim 67, wherein the T cell proliferation occurs in a tumor microenvironment.
69. Use of the formulation of any one of claims 1-57 in the manufacture of a medicament for reducing or inhibiting tumor growth.
70. Use of the formulation of any one of claims 1-57 in the manufacture of a medicament for treating a disorder mediated by human CD137 in a subject.
71. Use of the formulation of any one of claims 1-57 in the manufacture of a medicament for treating cancer in a subject.
72. The use of any one of claims 69-71, wherein infiltration of immune cells into a tumor microenvironment is increased after administration of the formulation.
73. The use of claim 72, wherein the immune cells express CD45.
74. The use of any one of claims 69-73, wherein the quantity of T regulatory (Treg) cells is reduced in a tumor microenvironment after administration of the formulation.
75. The use of claim 74, wherein the Treg cells express CD4, FOXP-3 and CD25.
76. The use of any one of claims 69-75, wherein the quantity of macrophages is reduced in a tumor microenvironment after administration of the isolated monoclonal antibody or antigen binding portion.

77. The use of claim 76, wherein the macrophages express CD45 and CD11b.
78. The use of any one of claims 69-77, wherein T cell exhaustion is reduced in a tumor microenvironment after administration of the 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.
79. The use of any one of claims 71-78, wherein the cancer is selected from the group consisting of melanoma, glioma, renal, breast, hematological, and head and neck cancer.
80. The use of claim 79, wherein the hematological cancer is a B cell lymphoma.
81. Use of the formulation of claims 1-57 in the manufacture of a medicament for inducing an anti-tumor memory immune response.
82. The use of any one of claims 58-81, wherein the anti-CD137 antibody binds Fc gamma receptor.
83. The use of any one of claims 58-82, wherein depletion of CD4⁺ T cells, CD8⁺ T cells, Natural Killer cells, or combinations thereof, reduces the efficacy of the formulation.
84. A kit comprising a container comprising the formulation of any one of claims 1-57, 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.
85. A kit comprising a container comprising the formulation of any one of claims 1-57, 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.

86. Use of the formulation of any one of claims 1-57 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.

87. A formulation according to any one of claims 1-57, for use as a medicament.