

SUMMARY

[0006] Methods to produce antibodies useful as human therapeutics include generation of chimeric antibodies and humanized antibodies (see, for example, U.S. 6,949,245). See, for example, WO 94/02602 (Abgenix) and U.S. 6,596,541 (Regeneron Pharmaceuticals), which publications are herein specifically incorporated by reference, describing methods of generating nonhuman transgenic mice capable of producing human antibodies. U.S. Patent No. 9,718,881 discloses antibodies to human Activin A, and is incorporated in its entirety herein by reference.

[0007] Therapeutic antibodies must be formulated in a manner that not only makes the antibodies suitable for administration to patients, but also in a manner that maintains their stability during storage and subsequent use. For example, therapeutic antibodies in liquid solution are prone to fragmentation, precipitation, aggregation, and undesired chemical modifications unless the solution is formulated properly. The stability of an antibody in liquid formulation depends not only on the kinds of excipients used in the formulation, but also on the amounts and proportions of the excipients relative to one another. Furthermore, other considerations aside from stability must be taken into account when preparing a liquid antibody formulation. Examples of such additional considerations include the viscosity of the solution and the concentration of antibody that can be accommodated by a given formulation, and the visual quality or appeal of the formulation. Thus, when formulating a therapeutic antibody, great care must be taken to arrive at a formulation that remains stable, contains an adequate concentration of antibody, and possesses a suitable viscosity as well as other properties which enable the formulation to be conveniently administered to patients.

[0008] The present invention satisfies the aforementioned need by providing pharmaceutical formulations comprising a human antibody that specifically binds to human Activin A.

[0009] In one ~~aspect~~example, a liquid pharmaceutical formulation is provided, comprising: (i) an antibody that specifically binds to Activin A; (ii) a buffer; (iii) an organic cosolvent; and (iv) thermal stabilizers.

[0010] In ~~another one~~ aspect, the present ~~invention~~disclosure provides a pharmaceutical formulation comprising: (i) an anti-human Activin A antibody, or antigen-binding portion thereof; (ii) a buffer at pH of 6.3 ± 0.3 ; (iii) an organic cosolvent; and (iv) one or more thermal stabilizers.

[0011] In some embodimentexamples, the antibody, or the antigen-binding portion thereof, comprises the following six CDR sequences: (a) an HCDR1 having the sequence GGSFSSHF (SEQ ID NO.: 1); (b) an HCDR2 having the sequence ILYTGGT (SEQ ID NO.: 2); (c) an HCDR3 having the sequence ARARSGITFTGIIVPGSFDI (SEQ ID NO.: 3); (d) an LCDR1 having the sequence QSVSSSY (SEQ ID NO.: 4); (e) an LCDR2 having the sequence GAS (SEQ ID NO.: 5); and (f) an LCDR3 having the sequence QQYGSSPWT (SEQ ID NO.: 6).

[0012] In some embodimentexamples, the antibody has a molecular weight of about 145,235.3 Da.

[0013] In some embodimentexamples, the concentration of the antibody, or the antigen-binding portion thereof, is 60 mg/mL $\pm$ 6 mg/mL.

[0014] In some embodimentexamples, the buffer is a histidine buffer. In some embodimentexamples, the histidine concentration is 10 mM $\pm$ 2 mM .

[0015] In some embodimentexamples, the organic cosolvent is polysorbate 20. In some embodimentexamples, the polysorbate 20 concentration is 0.05% w/v $\pm$ 0.025 %.

[0016] In some embodimentexamples, the one or more thermal stabilizers comprise sucrose and arginine. In some embodimentexamples, the sucrose concentration is 5% $\pm$ 1% (w/v) and the Arginine concentration is 70 mM $\pm$ 14 mM .

[0017] In some embodimentexamples, the pharmaceutical formulation comprises 60 mg/mL $\pm$ 6 mg/mL antibody, 10 mM $\pm$ 2 mM histidine, pH 6.3 $\pm$ 0.3, 0.05% w/v $\pm$ 0.025% polysorbate 20, 5% w/v $\pm$ 1% sucrose, and 70 mM $\pm$ 14 mM Arginine.

[0018] In some embodimentexamples, after 56 days of storage at 40°C and 75% relative humidity (RH), at least 90% of the antibody, or the antigen-binding portion thereof, has native conformation , or at least 30% of the antibody, or the antigen-binding portion thereof, is the main charge form.

[0019] In some embodimentexamples, after 56 days of storage at 40°C and 75% RH, at least 93% of the antibody, or the antigen-binding portion thereof, has native conformation, or at least 34.5% of the antibody, or the antigen-binding portion thereof, is the main charge form.

[0020] In some embodimentexamples, after 56 days of storage at 40°C and 75% RH, at least 97% of the antibody, or the antigen-binding portion thereof, has native conformation, or at least 45% of the antibody, or the antigen-binding portion thereof, is the main charge form.

[0021] In some embodimentexamples, after six months of storage at 25°C and 60% RH, at least 90% of the antibody, or the antigen-binding portion thereof, has native conformation, or at least 40% of the antibody, or the antigen-binding portion thereof, is the main charge form.

[0022] In some ~~embodiment~~examples, after six months of storage at 25°C and 60% RH, at least 95% of the antibody, or the antigen-binding portion thereof, has native conformation, or at least 45% of the antibody, or the antigen-binding portion thereof, is the main charge form.

[0023] In some ~~embodiment~~examples, after six months of storage at 25°C and 60% RH, at least 98% of the antibody, or the antigen-binding portion thereof, has native conformation, or at least 50% of the antibody, or the antigen-binding portion thereof, is the main charge form.

[0024] In some ~~embodiment~~examples, after 12 months of storage at 2-8°C, at least 94% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 45% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 100% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

[0025] In some ~~embodiment~~examples, after 12 months of storage at 2-8°C, at least 96% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 50% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 100% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

[0026] In some ~~embodiment~~examples, after 12 months of storage at 2-8°C, at least 98% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 55% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 100% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

[0027] In some ~~embodiment~~examples, after 18 months of storage at 2-8°C, at least 94% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 45% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 95% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

[0028] In some ~~embodiment~~examples, after 18 months of storage at 2-8°C, at least 96% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 50% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 95% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

[0029] In some ~~embodiment~~examples, after 18 months of storage at 2-8°C, at least 98% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 55% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 95% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

[0030] In some ~~embodiment~~examples, after 24 months of storage at 2-8°C, at least 94% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 45% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 95% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

[0031] In some ~~embodiment~~examples, after 24 months of storage at 2-8°C, at least 96% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 50% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 95% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

[0032] In some ~~embodiment~~examples, after 24 months of storage at 2-8°C, at least 98% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 55% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 95% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

[0033] In another aspect, the present disclosure refers to a pharmaceutical formulation comprising (a) 60 mg/mL $\pm$ 10 mg/mL of an anti-human Activin A antibody, or antigen-binding portion thereof (b) 10 mM $\pm$ 2 mM histidine, pH 6.3 $\pm$ 0.3, (c) 0.05% $\pm$ 0.025% polysorbate 20, (d) 70 mM $\pm$ 14 mM Arginine, and (e) 5% $\pm$ 1% sucrose, wherein the antibody, or the antigen-binding portion thereof, comprises an heavy chain variable region comprising SEQ ID NO: 7 and a light chain variable region comprising SEQ ID NO: 8. In another ~~aspect~~example, the present ~~invention~~disclosure provides a pharmaceutical formulation comprising (a) 60 mg/mL $\pm$ 10 mg/mL of an anti-human Activin A antibody, or antigen-binding portion thereof (b) 10 mM $\pm$ 2 mM histidine, pH 6.3 $\pm$ 0.3, (c) 0.05% $\pm$ 0.025% polysorbate 20, (d) 70 mM $\pm$ 14 mM Arginine, and (e) 5% $\pm$ 1% sucrose, wherein the antibody, or the antigen-binding portion thereof, comprises a heavy chain variable region having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identity to, comprises, or consists of SEQ ID NO: 7 and a light chain variable region having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identity to, comprises, or consists of SEQ ID NO: 8. In one ~~embodiment~~example, the heavy chain comprises a sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identity to,

comprises, or consists of SEQ ID NO:9. In one ~~embodiment~~example, the heavy chain comprises a sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identity to, comprises, or consists of SEQ ID NO:10.

[0034] In some ~~embodiment~~examples, the formulation is contained in a container. In some ~~embodiment~~examples, the container is a vial. In some ~~embodiment~~examples, the vial is glass. In some ~~embodiment~~examples, the glass is Type 1 borosilicate glass with a FluroTec® coated 4432/50 butyl rubber stopper.

[0035] In some ~~embodiment~~examples, the formulation is suitable for intravenous administration to a human subject in need thereof. In some ~~embodiment~~examples, the formulation is suitable for subcutaneous administration to a human subject in need thereof.

[0036] In some ~~embodiment~~examples, the formulation is a liquid formulation. In some ~~embodiment~~examples, the formulation is a lyophilized formulation.

[0037] In another aspect, the present ~~invention~~disclosure provides a kit comprising a pharmaceutical formulation disclosed herein, a container, and instructions of use thereof.

[0038] In some ~~embodiment~~examples, the container is a glass vial fitted with a FluroTec® coated chlorobutyl stopper.

[0039] In another aspect, the present disclosure provides the use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a disease or disorder associated with Activin A activity. In another ~~aspect~~example, the present ~~invention~~disclosure provides a method of treating a disease or disorder associated with Activin A activity, the method comprising administration of a therapeutically effective amount of one or more of the pharmaceutical compositions disclosed herein, to a subject in need thereof.

[0040] In some ~~embodiment~~examples, the disease or disorder associated with Activin A activity is Fibrodysplasia ossificans progressiva (FOP).

[0041] Other ~~embodiment~~examples of the present ~~invention~~disclosure will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF DRAWINGS

[0042] **FIG. 1** shows the heavy and light chain amino acid sequences (SEQ ID NO:9 and SEQ ID NO:10, respectively) of an exemplary anti-activin A monoclonal antibody.

[0043] **FIG. 2** shows the effect of varying the formulation on the rate of an anti-activin A antibody degradation when it is incubated at 40°C/75%RH for 2 months. For particle levels by HIAC and MFI the results shown are the final particle levels after 2 months of incubation

CLAIMS

What is claimed is:

1. A pharmaceutical formulation comprising: (i) an anti-human Activin A antibody, or antigen-binding portion thereof; (ii) a buffer at pH of 6.3 ± 0.3 ; (iii) an organic cosolvent; and (iv) one or more thermal stabilizers.
2. The pharmaceutical formulation of claim 1, wherein the antibody, or the antigen-binding portion thereof, comprises the following six CDR sequences:
 - (a) an HCDR1 having the sequence GGSFSSH (SEQ ID NO.: 1);
 - (b) an HCDR2 having the sequence ILYTGGT (SEQ ID NO.: 2);
 - (c) an HCDR3 having the sequence ARARSGITFTGIIVPGSFDI (SEQ ID NO.: 3);
 - (d) an LCDR1 having the sequence QSVSSSY (SEQ ID NO.: 4);
 - (e) an LCDR2 having the sequence GAS (SEQ ID NO.: 5); and
 - (f) an LCDR3 having the sequence QQYGSSPWT (SEQ ID NO.: 6).
3. The pharmaceutical formulation of claim 1 or claim 2, wherein the antibody has a molecular weight of about 145,235.3 Da.
4. The pharmaceutical formulation of any one of claims 1-3, wherein the antibody, or the antigen-binding portion thereof, concentration is $60 \text{ mg/mL} \pm 6 \text{ mg/mL}$.
5. The pharmaceutical formulation of any one of claims 1-4, wherein the buffer is a histidine buffer.
6. The pharmaceutical formulation of claim 5, wherein the histidine concentration is $10 \text{ mM} \pm 2 \text{ mM}$.
7. The pharmaceutical formulation of any one of the previous claims, wherein the organic cosolvent is polysorbate 20.
8. The pharmaceutical formulation of claim 7, wherein the polysorbate 20 concentration is $0.05\% \text{ w/v} \pm 0.025\%$.
9. The pharmaceutical formulation of any one of the previous claims, wherein the one or more thermal stabilizers comprise sucrose and arginine.

10. The pharmaceutical formulation of claim 9, wherein the sucrose concentration is $5\% \pm 1\%$ (w/v) and the Arginine concentration is $70 \text{ mM} \pm 14 \text{ mM}$.
11. The pharmaceutical formulation of any one of the previous claims, comprising $60 \text{ mg/mL} \pm 6 \text{ mg/mL}$ antibody, $10 \text{ mM} \pm 2 \text{ mM}$ histidine, $\text{pH } 6.3 \pm 0.3$, $0.05\% \text{ w/v} \pm 0.025\%$ polysorbate 20, $5\% \text{ w/v} \pm 1\%$ sucrose, and $70 \text{ mM} \pm 14 \text{ mM}$ Arginine.
12. The pharmaceutical formulation of any one of the previous claims, wherein after 56 days of storage at 40°C and 75% relative humidity (RH), at least 90% of the antibody, or the antigen-binding portion thereof, has native conformation, or at least 30% of the antibody, or the antigen-binding portion thereof, is the main charge form.
13. The pharmaceutical formulation of any one of the previous claims, wherein after 56 days of storage at 40°C and 75% RH, at least 93% of the antibody, or the antigen-binding portion thereof, has native conformation, or at least 34.5% of the antibody, or the antigen-binding portion thereof, is the main charge form.
14. The pharmaceutical formulation of any one of the previous claims, wherein after 56 days of storage at 40°C and 75% RH, at least 97% of the antibody, or the antigen-binding portion thereof, has native conformation, or at least 45% of the antibody, or the antigen-binding portion thereof, is the main charge form.
15. The pharmaceutical formulation of any one of claims 1-11, wherein after six months of storage at 25°C and 60% RH, at least 90% of the antibody, or the antigen-binding portion thereof, has native conformation, or at least 40% of the antibody, or the antigen-binding portion thereof, is the main charge form.
16. The pharmaceutical formulation of any one of claims 1-11, wherein after six months of storage at 25°C and 60% RH, at least 95% of the antibody, or the antigen-binding portion thereof, has native conformation, or at least 45% of the antibody, or the antigen-binding portion thereof, is the main charge form.
17. The pharmaceutical formulation of any one of claims 1-11, wherein after six months of storage at 25°C and 60% RH, at least 98% of the antibody, or the antigen-binding portion thereof, has native conformation, or at least 50% of the antibody, or the antigen-binding portion thereof, is the main charge form.

18. The pharmaceutical formulation of any one of claims 1-11, wherein after 12 months of storage at 2-8°C, at least 94% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 45% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 100% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

19. The pharmaceutical formulation of any one of claims 1-11, wherein after 12 months of storage at 2-8°C, at least 96% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 50% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 100% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

20. The pharmaceutical formulation of any one of claims 1-11, wherein after 12 months of storage at 2-8°C, at least 98% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 55% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 100% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

21. The pharmaceutical formulation of any one of claims 1-11, wherein after 18 months of storage at 2-8°C, at least 94% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 45% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 95% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

22. The pharmaceutical formulation of any one of claims 1-11, wherein after 18 months of storage at 2-8°C, at least 96% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 50% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 95% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

23. The pharmaceutical formulation of any one of claims 1-11, wherein after 18 months of storage at 2-8°C, at least 98% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 55% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 95% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.

24. The pharmaceutical formulation of any one of claims 1-11, wherein after 24 months of storage at 2-8°C, at least 94% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 45% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 99% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.
25. The pharmaceutical formulation of any one of claims 1-11, wherein after 24 months of storage at 2-8°C, at least 96% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 50% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 99% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.
26. The pharmaceutical formulation of any one of claims 1-11, wherein after 24 months of storage at 2-8°C, at least 98% of the antibody, or the antigen-binding portion thereof, has native conformation, at least 55% of the antibody, or the antigen-binding portion thereof, is the main charge variant, and/or the antibody retains at least 99% of the potency of the antibody, or the antigen-binding portion thereof, prior to storage.
27. A pharmaceutical formulation comprising (a) 60 mg/mL $\pm$ 10 mg/mL of an anti-human Activin A antibody, or antigen-binding portion thereof (b) 10 mM $\pm$ 2 mM histidine, pH 6.3 $\pm$ 0.3, (c) 0.05% $\pm$ 0.025% polysorbate 20, (d) 70 mM $\pm$ 14 mM Arginine, and (e) 5% $\pm$ 1% sucrose, wherein the antibody, or the antigen-binding portion thereof, comprises an heavy chain variable region comprising SEQ ID NO: 7 and a light chain variable region comprising SEQ ID NO: 8.
28. The pharmaceutical formulation of any one of the previous claims, wherein the formulation is contained in a container.
29. The pharmaceutical formulation of claim 28, wherein the container is a vial.
30. The pharmaceutical formulation of claim 29, wherein the vial is glass.
31. The pharmaceutical formulation of claim 30, wherein the glass is Type 1 borosilicate glass with a FluroTec® coated 4432/50 butyl rubber stopper.

32. The pharmaceutical formulation of any one of the previous claims, wherein the formulation is suitable for intravenous administration to a human subject in need thereof.
33. The pharmaceutical formulation of any one of claims 1-31, wherein the formulation is suitable for subcutaneous administration to a human subject in need thereof.
34. The pharmaceutical formulation of any one of the previous claims, wherein the formulation is a liquid formulation.
35. The pharmaceutical formulation of any one of claims 1-33, wherein the formulation is a lyophilized formulation.
36. A kit comprising a pharmaceutical formulation of any one of the previous claims, a container, and instructions of use thereof.
37. The kit of claim 36, wherein the container is a glass vial fitted with a FluroTec® coated chlorobutyl stopper.
38. Use of the pharmaceutical composition of any one of claims 1-35 in the manufacture of a medicament for ~~A method of treating a disease or disorder associated with Activin A activity; the method comprising administration of a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-35 to a subject in need thereof.~~
39. ~~The method use~~ of claim 38, wherein the disease or disorder associated with Activin A activity is Fibrodysplasia ossificans progressiva (FOP).