# ANTI-TNF ANTIBODY FORMULATIONS

~~PROTEIN FORMULATIONS AND METHODS OF MAKING SAME~~

## RELATED APPLICATIONS

This application claims the benefit of priority to US Provisional Appln. No. 61/004992, filed on November 30, 2007. The contents of the priority application are hereby incorporated by reference.

## BACKGROUND OF THE INVENTION

A basic principle of pharmaceutical protein formulations is that certain instabilities must be overcome. Degradation pathways of proteins can be separated into two distinct classes, involving chemical instability and physical instability. Chemical instabilities lead to the modification of the protein through bond formation or cleavage. Examples of chemical instability problems include deamidation, racemization, hydrolysis, oxidation, beta elimination and disulfide exchange. Physical instabilities, on the other hand, do not lead to covalent changes in proteins. Rather, they involve changes in the higher order structure (secondary and above) of proteins. These include denaturation, adsorption to surfaces, aggregation and precipitation (Manning *et al.*, *Pharm. Res.* 6, 903 (1989)).

It is generally accepted that these instabilities, which can have great effect on the commercial viability and efficacy of pharmaceutical protein formulations, can be overcome by including additional molecules in the formulation. Protein stability can be improved by including excipients that interact with the protein in solution to keep the protein stable, soluble and unaggregated. For example, salt compounds and other ionic species are very common additives to protein formulations. They assist in fighting denaturation of proteins by binding to proteins in a non-specific fashion and increasing thermal stability. Salt compounds (e.g., NaCl, KCl) have been used successfully in commercial insulin preparations to fight aggregation and precipitation (*ibid.* at 911). Amino acids (e.g., histidine, arginine) have been shown to reduce alterations in proteins' secondary structures when used as formulation additives (Tian *et al.*, *Int'l J. Pharm.* 355, 20 (2007)). Other examples of commonly used additives include polyalcohol materials such as glycerol and sugars, and surfactants such as detergents, both nonionic (e.g., Tween, Pluronic) and anionic (sodium dodecyl sulfate). The near universal prevalence of additives in all liquid commercial protein formulations indicates that

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<130> 117813-26920

<140> PCT/US2008/085066
<141> 2008-11-28

<150> 61/004,992
<151> 2007-11-30

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What is claimed:

1. An aqueous formulation comprising a protein and water, wherein the formulation has a conductivity of less than about 2.5 mS/cm, the concentration of the protein is at least 20 mg/mL, and the protein has a molecular weight ($M_w$) greater than about 47 kDa.

2. The formulation of claim 1, wherein the protein has a $M_w$ greater than about 57 kDa.

3. The formulation of claim 1, wherein the protein has a $M_w$ greater than about 100 kDa.

4. The formulation of claim 1, wherein the protein has a $M_w$ greater than about 150 kDa.

5. The formulation of claim 1, wherein the protein has a $M_w$ greater than about 200 kDa.

6. The formulation of claim 1, wherein the protein has a $M_w$ greater than about 250 kDa.

7. The formulation of claim 1, wherein the formulation has a conductivity of less than about 2 mS/cm.

8. The formulation of claim 1, wherein the formulation has a conductivity of less than about 1.5 mS/cm.

9. The formulation of claim 1, wherein the formulation has a conductivity of less than about 1 mS/cm.

10. The formulation of claim 1, wherein the formulation has a conductivity of less than about 0.5 mS/cm.

11. An aqueous formulation comprising a protein at a concentration of at least about 20 μg/mL and water, wherein the formulation has a conductivity of less than about 2 mS/cm.

12. The formulation of claim 11, wherein the concentration of the protein is at least about 50 mg/mL.

13. The formulation of claim 11, wherein the concentration of the protein is at least about 100 mg/mL.

14. The formulation of claim 11, wherein the concentration of the protein is at least about 150 mg/mL.

15. The formulation of claim 11, wherein the concentration of the protein is at least about 200 mg/mL.

16. The formulation of claim 11, wherein the concentration of the protein is greater than about 200 mg/mL.

17. The formulation of claim 11, wherein the formulation has a conductivity of less than about 1 mS/cm.

18. The formulation of claim 11, wherein the formulation has a conductivity of less than about 0.5 mS/cm.

19. An aqueous formulation comprising a protein at a concentration of at least about 50 mg/mL and water, wherein the formulation has an osmolality of no more than about 30 mOsmol/kg.

20. The formulation of claim 19, wherein the osmolality of the formulation is no more than about 15 mOsmol/kg.

21. The formulation of claim 19, wherein the concentration of the protein is at least about 100 mg/mL.

22. The formulation of claim 19, wherein the concentration of the protein is at least about 150 mg/mL.

23. The formulation of claim 19, wherein the concentration of the protein is at least about 200 mg/mL.

24. The formulation of claim 19, wherein the concentration of the protein is greater than about 200 mg/mL.

25. An aqueous formulation comprising water and a given concentration of a protein, wherein the protein has a hydrodynamic diameter ($D_h$) which is at least about 50% less than the $D_h$ of the protein in a buffered solution at the given concentration.

26. The formulation of claim 25, wherein the $D_h$ of the protein is at least about 50% less than the $D_h$ of the protein in phosphate buffered saline (PBS) at the given concentration.

27. The formulation of claim 26, wherein the $D_h$ of the protein is at least about 60% less than the $D_h$ of the protein in PBS at the given concentration.

28. The formulation of claim 26, wherein the $D_h$ of the protein is at least about 70% less than the $D_h$ of the protein in PBS at the given concentration.

29. The formulation of any one of claims 1-28, wherein the protein is an antibody, or an antigen-binding fragment thereof.

30. The formulation of claim 29, wherein the antibody, or antigen-binding fragment thereof, is selected from the group consisting of a chimeric antibody, a human antibody, a humanized antibody, and a domain antibody (dAb).

31. The formulation of claim 29, wherein the antibody, or antigen-binding fragment thereof, is an anti-TNFa or an anti-IL-12 antibody.

32. The formulation of claim 29, wherein the antibody, or antigen-binding fragment thereof, is selected from the group consisting of Humira (adalimumab), Campath (Alemtuzumab), CEA-Scan Arcitumomab (fab fragment), Erbitux (Cetuximab), Herceptin (Trastuzumab), Myoscint (Imciromab Pentetate), ProstaScint (Capromab Pendetide), Remicade (Infliximab), ReoPro (Abciximab), Rituxan (Rituximab), Simulect (Basiliximab), Synagis (Palivizumab), Verluma (Nofetumomab), Xolair (Omalizumab), Zenapax (Daclizumab), Zevalin (Ibritumomab Tiuxetan), Orthoclone OKT3 (Muromonab-CD3), Panorex (Edrecolomab), Mylotarg (Gemtuzumab ozogamicin), golimumab (Centocor), Cimzia (Certolizumab pegol), Soliris (Eculizumab), CNTO 1275 (ustekinumab), Vectibix (panitumumab), Bexxar (tositumomab and $I^{131}$ tositumomab), and Avastin (bevacizumab).

33. The formulation of any one of claims 1-28, wherein the protein is a therapeutic protein.

34. The formulation of claim 33, wherein the therapeutic protein is selected from the group consisting of Pulmozyme (Dornase alfa), Rebif, Regranex (Becaplermin), Activase (Alteplase), Aldurazyme (Laronidase), Amevive (Alefacept), Aranesp (Darbepoetin alfa), Becaplermin Concentrate, Betaseron (Interferon beta-lb), BOTOX

(Botulinum Toxin Type A), Elitek (Rasburicase), Elspar (Asparaginase), Epogen (Epoetin alfa), Enbrel (Etanercept), Fabrazyme (Agalsidase beta), Infergen (Interferon alfacon-1), Intron A (Interferon alfa-2a), Kineret (Anakinra), MYOBLOC (Botulinum Toxin Type B), Neulasta (Pegfilgrastim), Neumega (Oprelvekin), Neupogen (Filgrastim), Ontak (Denileukin diftitox), PEGASYS (Peginterferon alfa-2a), Proleukin (Aldesleukin), Pulmozyme (Dornase alfa), Rebif (Interferon beta-la), Regranex (Becaplermin), Retavase (Reteplase), Roferon-A (Interferon alfa-2), TNKase (Tenecteplase), Xigris (Drotrecogin alfa), Arcalyst (Rilonacept), NPlate (Romiplostim), Mircera (methoxypolyethylene glycol-epoetin beta), Cinryze (Cl esterase inhibitor), Elaprase (idursulfase), Myozyme (alglucosidase alfa), Orencia (abatacept), Naglazyme (galsulfase), Kepivance (palifermin) and Actimmune (interferon gamma-Ib).

35. An aqueous formulation comprising an antibody, or an antigen-binding fragment, at a concentration of at least about 10 mg/mL and water, wherein the antibody, or antigen-binding fragment, has a hydrodynamic diameter ($D_h$) of less than about 5 μm.

36. The formulation of claim 35, wherein the antibody has a $D_h$ of less than about 3 μm.

37. The formulation of claim 35 or 36, wherein the antibody, or antigen-binding fragment thereof, is selected from the group consisting of a chimeric antibody, a human antibody, a humanized antibody, and a domain antibody (dAb).

38. The formulation of claim 35 or 36, wherein the antibody, or antigen-binding fragment thereof, is an anti-TNFa or an anti-IL-12 antibody.

39. The formulation of claim 35 or 36 , wherein the antibody, or antigen -binding fragment thereof, is selected from the group consisting of Humira (adalimumab), Campath (Alemtuzumab), CEA-Scan Arcitumomab (fab fragment), Erbitux (Cetuximab), Herceptin (Trastuzumab), Myoscint (Imciromab Pentetate), ProstaScint (Capromab Pendetide), Remicade (Infliximab), ReoPro (Abciximab), Rituxan (Rituximab), Simulect (Basiliximab), Synagis (Palivizumab), Verluma (Nofetumomab), Xolair (Omalizumab), Zenapax (Daclizumab), Zevalin (Ibritumomab Tiuxetan), Orthoclone OKT3 (Muromonab-CD3), Panorex (Edrecolomab), and Mylotarg (Gemtuzumab ozogamicin), golimumab (Centocor), Cimzia (Certolizumab pegol), Soliris (Eculizumab), CNTO 1275 (ustekinumab), Vectibix (panitumumab), Bexxar (tositumomab and $I^{131}$ tositumomab) and Avastin (bevacizumab).

40. The formulation of any one of claims 1-28 or 35, further comprising a non-ionizable excipient.

41. The formulation of claim 40, wherein the non-ionizable excipient is selected from the group consisting of sugar alcohols and polyols such as mannitol or sorbitol, a non-ionic surfactant, sucrose, trehalose, raffinose, and maltose.

42. The formulation of claim 41, wherein the non-ionic surfactant is polysorbate 20, polysorbate 40, polysorbate 60 or polysorbate 80.

43. The formulation of any one of claims 1-28 or 35, wherein the formulation is stable in a liquid form for at least about 3 months.

44. The formulation of any one of claims 1-28 or 35, wherein the formulation is stable in a liquid form for at least about 12 months.

45. The formulation of any one of claims 1-28 or 35, wherein the formulation is stable for at least about 3 months in a form selected from the group consisting of frozen, lyophilized, or spray-dried.

46. The formulation of any one of claims 1-28 or 35, wherein the formulation does not comprise an agent selected from the group consisting of a tonicity modifier, a stabilizing agent, a surfactant, an anti-oxidant, a cryoprotectant, a bulking agent, a lyroprotectant, a basic component, and an acidic component.

47. The formulation of any one of claims 1-28 or 35, further comprising at least about one additional, distinct protein.

48. The formulation of any one of claims 1-28 or 35, wherein the formulation is suitable for in vitro use.

49. The formulation of any one of claims 1-28 or 35, wherein the formulation is suitable for in vivo use.

50. The formulation of claim 49, wherein the formulation is suitable for administration to a subject via a mode of administration selected from the group consisting of subcutaneous, intravenous, inhalation, intradermal, transdermal, intraperitoneal, and intramuscular.

51. Use of the formulation of claim 49 in the treatment of a disorder in a subject.

52. A device comprising the formulation of any one claims 1-28 or 35.

53. The device of claim 52, wherein the device is selected from the group consisting of a syringe, a pen, an implant, a needle-free injection device, an inhalation device, and a patch.

54. An article of manufacure comprising the formulation of any one of claims 1-28 or 35.

55. A method of preparing an aqueous formulation comprising a protein and water, the method comprising:

a) providing the protein in a first solution; and

b) subjecting the first solution to diafiltration using water as a diafiltration medium until at least a five fold volume exchange with the water has been achieved to thereby prepare the aqueous formulation.

56. A method of preparing an aqueous formulation of a protein, the method comprising:

a) providing the protein in a first solution;

b) subjecting the first solution to diafiltration using water as a diafiltration medium until at least a five-fold volume exchange with the water has been achieved to thereby prepare a diafiltered protein solution; and

c) concentrating the diafiltered protein solution to thereby prepare the aqueous formulation of the protein.

57. The method of claim 56, wherein the concentration of the diafiltered protein solution is achieved via centrifugation.

58. The method of any one of claims 55-57, wherein the diafiltration medium consists of water.

59. The method of any one of claims 55-57, wherein the first solution is subjected to diafiltration with water until at least about a six-fold volume exchange is achieved.

60. The method of any one of claims 55-57, wherein the first solution is subjected to diafiltration with water until at least about a seven-fold volume exchange is achieved.

61. The method of any one of claims 5-57, wherein the aqueous formulation has a final concentration of excipients which is at least about 95% less than the first solution.

62. The method of any one of claims 55-57, wherein the aqueous formulation has a final concentration of excipients which is at least about 99% less than the first solution.

63. The method of any one of claims 55-57, wherein the first protein solution is obtained from a mammalian cell expression system and has been purified to remove host cell proteins (HCPs).

64. The method of any one of claims 55-57, wherein the protein has a $M_w$ greater than about 1 kDa.

65. The method of any one of claims 55-57, wherein the protein has a $M_w$ greater than about 10 kDa.

66. The method of any one of claims 55-57, wherein the protein has a $M_w$ greater than about 47 kDa.

67. The method of any one of claims 55-57, wherein the protein has a $M_w$ greater than about 57 kDa.

68. The method of any one of claims 55-57, wherein the protein has a $M_w$ greater than about 100 kDa.

69. The method of any one of claims 55-57, wherein the protein has a $M_w$ greater than about 15O kDa.

70. The method of any one of claims 55-57, wherein the protein has a $M_w$ greater than about 200 kDa.

71. The method of any one of claims 55-57, wherein the protein has a $M_w$ greater than about 250 kDa.

72. The method of any one of claims 55-57, further comprising adding an excipient to the aqueous formulation.

73. The method of claim 72, wherein the aqueous formulation is a pharmaceutical formulation.

74. The method of any one of claims 55-57, wherein the aqueous formulation is a pharmaceutical formulation.

75. The method of claim 74, further comprising loading the aqueous formulation into a device suitable for administering the aqueous formulation to a subject.

76. The method of claim 75, wherein the device is selected from the group consisting of a syringe, a pen, an implant, and a dermal patch.

77. The method of any one of claims 55-57, wherein the protein is an antibody, or an antigen-binding fragment thereof.

78. The method of claim 77, wherein the antibody, or antigen-binding fragment thereof, is selected from the group consisting of a chimeric antibody, a human antibody, a humanized antibody, and a domain antibody (dAb).

79. The method of claim 77, wherein the antibody, or antigen -binding fragment thereof, is an anti-TNFα or an anti-IL-12 antibody.

80. The method of claim 77, wherein the antibody, or antigen-binding fragment thereof, is selected from the group consisting of Humira (adalimumab), Campath (Alemtuzumab), CEA-Scan Arcitumomab (fab fragment), Erbitux (Cetuximab), Herceptin (Trastuzumab), Myoscint (Imciromab Pentetate), ProstaScint (Capromab Pendetide), Remicade (Infliximab), ReoPro (Abciximab), Rituxan (Rituximab), Simulect (Basiliximab), Synagis (Palivizumab), Verluma (Nofetumomab), Xolair (Omalizumab), Zenapax (Daclizumab), Zevalin (Ibritumomab Tiuxetan), Orthoclone OKT3 (Muromonab-CD3), Panorex (Edrecolomab), Mylotarg (Gemtuzumab ozogamicin), golimumab (Centocor), Cimzia (Certolizumab pegol), Soliris (Eculizumab), CNTO 1275 (ustekinumab), Vectibix (panitumumab), Bexxar (tositumomab and $I^{131}$ tositumomab), and Avastin (bevacizumab).

81. The method of any one of claims 55-57, wherein the protein is a therapeutic protein.

82. The method of claim 81, wherein the therapeutic protein is selected from the group consisting of Pulmozyme (Dornase alfa), Rebif, Regranex (Becaplermin), Activase (Alteplase), Aldurazyme (Laronidase), Amevive (Alefacept), Aranesp (Darbepoetin alfa), Becaplermin Concentrate, Betaseron (Interferon beta-lb), BOTOX (Botulinum Toxin Type A), Elitek (Rasburicase), Elspar (Asparaginase), Epogen (Epoetin alfa), Enbrel (Etanercept), Fabrazyme (Agalsidase beta), Infergen (Interferon alfacon-1), Intron A (Interferon alfa-2a), Kineret (Anakinra), MYOBLOC (Botulinum

Toxin Type B), Neulasta (Pegfilgrastim), Neumega (Oprelvekin), Neupogen (Filgrastim), Ontak (Denileukin diftitox), PEGASYS (Peginterferon alfa-2a), Proleukin (Aldesleukin), Pulmozyme (Dornase alfa), Rebif (Interferon beta-la), Regranex (Becaplermin), Retavase (Reteplase), Roferon-A (Interferon alfa-2), TNKase (Tenecteplase), and Xigris (Drotrecogin alfa), Arcalyst (Rilonacept), NPlate (Romiplostim), Mircera (methoxypolyethylene glycol-epoetin beta), Cinryze (Cl esterase inhibitor), Elaprase (idursulfase), Myozyme (alglucosidase alfa), Orencia (abatacept), Naglazyme (galsulfase), Kepivance (palifermin) and Actimmune (interferon gamma- Ib).

83. The method of any one of claims 55-57, wherein the aqueous formulation comprises at least about two distinct proteins.

84. An aqueous formulation prepared according to the methods of any one of claims 55-57.

85. The formulation of claim 84, wherein the protein has a concentration of at least about 10 μg/mL.

86. The formulation of claim 84, wherein the protein has a concentration of at least about 1 mg/mL.

87. The formulation of claim 84, wherein the protein has a concentration of at least about 10 mg/mL.

88. The formulation of claim 84, wherein the protein has a concentration of at least about 50 mg/mL.

89. The formulation of claim 84, wherein the protein has a concentration of at least about 100 mg/mL.

90. The formulation of claim 84, wherein the protein has a concentration of at least about 150 mg/mL.

91. The formulation of claim 84, wherein the protein has a concentration of at least about 200 mg/mL.

92. The formulation of claim 84, wherein the protein has a concentration greater than about 200 mg/mL.

93. The formulation of claim 84, having a conductivity of less than about 2 mS/cm.

94. The formulation of claim 84, having a conductivity of less than about 1 mS/cm.

95. The formulation of claim 84, having a conductivity of less than about 0.5 mS/cm.

96. The formulation of claim 84, further comprising an excipient.

97. The formulation of claim 96, wherein the excipient is a non-ionic excipient or an ionic excipient.

98. The formulation of claim 84, wherein the protein retains its biological activity.

99. The formulation of claim 33, which is a pharmaceutical formulation.

What is claimed:

1. An aqueous pharmaceutical formulation consisting essentially of:

(a) an anti-tumor necrosis factor alpha antibody comprising a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO:5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO:8, wherein the concentration of the antibody is 50 to 200 mg/ml; and

(b) water.

2. The formulation of claim 1, wherein the antibody comprises a LCVR comprising the amino acid sequence set forth in SEQ ID NO: 1, and a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 2.

3. The formulation of claim 2, wherein the antibody is adalimumab.

4. The formulation of claim 1, wherein the pH of the formulation is from 4 to 8.

5. The formulation of claim 3, wherein the pH of the formulation is from 4 to 8.

6. An aqueous pharmaceutical formulation comprising:

(a) an anti-tumor necrosis factor alpha antibody comprising a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO:5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1

domain comprising the amino acid sequence of SEQ ID NO:8, wherein the concentration of the antibody is 50 to 200 mg/ml; and

(b) water;

wherein the formulation does not comprise a tonicity modifier.

7. The formulation of claim 6, wherein the antibody comprises a LCVR comprising the amino acid sequence set forth in SEQ ID NO: 1, and a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 2.

8. The formulation of claim 7, wherein the antibody is adalimumab.

9. The formulation of claim 6, wherein the pH of the formulation is from 4 to 8.

10. The formulation of claim 6, wherein the pH of the formulation is from 4 to 6.

11. The formulation of claim 6, wherein the pH of the formulation is from 5 to 6.

12. The formulation of claim 8, wherein the pH of the formulation is from 4 to 8.

13. The formulation of claim 8, wherein the pH of the formulation is from 4 to 6.

14. The formulation of claim 8, wherein the pH of the formulation is from 5 to 6.

15. The formulation of claim 8, wherein the pH of the formulation is 5.2.

16. An aqueous pharmaceutical formulation comprising:

(a) an anti-tumor necrosis factor alpha antibody comprising a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO:5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1

domain comprising the amino acid sequence of SEQ ID NO:8, wherein the concentration of the antibody is 50 to 200 mg/ml; and

(b) water;

wherein the formulation does not comprise a buffering system.

17. The formulation of claim 16, wherein the antibody comprises a LCVR comprising the amino acid sequence set forth in SEQ ID NO: 1, and a HCVR comprising the amino acid sequence set forth in SEQ ID NO: 2.

18. The formulation of claim 17, wherein the antibody is adalimumab.

19. The formulation of claim 16, wherein the formulation further comprises a non-ionizable excipient.

20. The formulation of claim 16, wherein the formulation further comprises a polyol.

21. The formulation of claim 20, wherein the polyol is selected from the group consisting of mannitol, sorbitol, and sucrose.

22. The formulation of claim 16, wherein the formulation further comprises a surfactant.

23. The formulation of claim 22, wherein the surfactant is selected from the group consisting of polysorbate 80 and polysorbate 20.

24. The formulation of claim 16, wherein the pH of the formulation is from 4 to 8.

25. The formulation of claim 16, wherein the pH of the formulation is from 4 to 6.

26. The formulation of claim 16, wherein the pH of the formulation is from 5 to 6.

27. The formulation of claim 18, wherein the pH of the formulation is from 4 to 8.

28. The formulation of claim 18, wherein the pH of the formulation is from 4 to 6.

29. The formulation of claim 18, wherein the pH of the formulation is from 5 to 6.

30. The formulation of claim 18, wherein the pH of the formulation is 5.2.