To date, the majority of approved therapeutic proteins are antibodies. The development of commercially viable antibody pharmaceutical formulations has not, however, been straightforward despite the fact that antibodies generally have the same structure (see Wang *et al.* (2007) J. Pharm. Sci. 96:1). Concentration dependent aggregation is considered one of the greatest challenges in formulating antibodies (see Shire *et al.* (2004) J. Pharm. Sci. 93:1390).

Dual Variable Domain Immunoglobulin (DVD-Ig™) proteins are multivalent binding proteins that are engineered to combine the function and specificity of two monoclonal antibodies into one molecular entity (See Wu *et al.*, US Patent No. 7,612,181). Given the multivalent nature of DVD-Ig proteins, these molecules hold tremendous promise as therapeutics. However, DVD-Ig proteins present a new formulation challenge given their much larger size (approximately 200 kDa) and complexity, compared to antibodies.

SUMMARY OF THE INVENTION

While the majority of Dual Variable Domain Immunoglobulin (DVD-Ig™) proteins are prone to destabilization (*e.g.*, aggregation) in aqueous formulations, a subset of DVD-Ig proteins can be stably formulated. Some DVD-Ig proteins in the aqueous state suffer from certain problems, such as aggregation and/or fragmentation of the DVD-Ig protein monomer. Unpredictably, a subset of DVD-Ig proteins can be stably formulated in the aqueous state even at high concentrations. Such stable DVD-Ig proteins are referred to herein as Aqueous Stable Dual Variable Domain Immunoglobulin proteins or "AS-DVD-Ig" proteins.

In one aspect, there is provided an aqueous formulation comprising an Aqueous Stable DVD-Ig (AS-DVD-Ig) protein and a buffer having a molarity of about 5 to about 50 mM, wherein the formulation has a pH of about 4.5 to about 7.5.

In one aspect, there is provided an an aqueous formulation comprising a Aqueous Stable DVD-Ig (AS-DVD-Ig) protein, a buffer having a molarity of about 5 to about 50 mM, a surfactant, and a polyol, wherein the formulation has a pH of about 4.5 to about 7.5.

In one aspect, there is provided an aqueous formulation comprising an AS-DVD-Ig protein, a polyol, buffer, and a surfactant, wherein said formulation has a pH of about 5 to about 7, and wherein the AS-DVD-Ig protein is characterized as a DVD-Ig protein having less than about 15% loss in relative percentage monomers as determined by SEC when formulated in a histidine or citrate phosphate buffer at a concentration of about 60 mg/ml following 14 days storage at about 40 degrees C.

In one aspect, there is provided an aqueous formulation comprising an AS-DVD-Ig protein, a polyol, histidine buffer, and a polysorbate, wherein said formulation has a pH of about 5 to about 7, and wherein the AS-DVD-Ig protein is characterized as a DVD-Ig protein having less than about 15% aggregation as determined by SEC when formulated in a histidine or citrate phosphate buffer at a concentration of about60 mg/ml following 14 days storage at about 40 degrees C.

In one aspect, there is provided a pharmaceutical composition comprising an Aqueous Stable DVD-Ig (AS-DVD-Ig) protein and a buffer having a molarity of about 5 to about 50 mM, wherein the AS-DVD-Ig protein is characterized as a DVD-Ig protein having less than about 10% loss in relative percentage monomers as determined by SEC when formulated in a histidine or citrate phosphate buffer at a concentration of about 60 mg/ml, following 14 days storage at about 40 degrees C, and the formulation has a pH of 4.5 to 7.5.

In one aspect, there is provided the use of the pharmaceutical composition as described herein, in the manufacture of a medicament for treating a disorder.

In one aspect, there is provided a lyophilized formulation comprising a Lyophilized-Stable DVD-Ig (LS-DVD-Ig) protein, wherein when said formulation is reconstituted, it comprises about 1 to about 100 mg/ml of the LS-DVD-Ig protein, about 10 to about 50 mM of a buffer, a polyol, about 0.01 to about 0.2 mg/ml of a polysorbate, and has a pH of about 5 to about 7.

In one aspect, there is provided a lyophilized formulation prepared by lyophilizing an aqueous formulation comprising a LS-DVD-Ig protein, a buffer have a molarity of about 5 to about 50 mM, a surfactant, and a polyol, wherein the formulation has a pH of about 4.5 to about 7.5.

In one aspect, there is provided a formulation comprising an anti-TNF/IL-17 DVD-IG protein and a buffer, wherein the DVD-Ig protein comprises a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 62 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 63.

In one aspect, there is provided a formulation comprising an anti-TNF/IL-17 DVD-IG protein and a surfactant, wherein the DVD-Ig protein comprises a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 62 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 63.

In one aspect, there is provided a formulation comprising an anti-TNF/IL-17 DVD-IG protein and a polyol, wherein the DVD-Ig protein comprises a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 62 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 63.

In one aspect, there is provided a formulation comprising an anti-TNF/IL-17 DVD-IG protein and two or more components selected from a buffer, a surfactant, and a polyol, wherein the DVD-Ig protein comprises a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 62 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 63.

In one aspect, there is provided an aqueous formulation comprising an anti-TNF/IL-17 DVD-IG protein a buffer, a surfactant, and a polyol, wherein the DVD-Ig protein comprises a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 62 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 63.

In one aspect, there is provided a lyophilized formulation comprising an anti-TNF/IL-17 DVD-Ig protein and two or more component selected from a buffer, a surfactant, and a polyol, wherein the DVD-Ig protein comprises a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 62 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 63.

In one aspect, there is provided a formulation comprising an anti-IL1α/IL1β DVD-Ig protein and a buffer, wherein the DVD-Ig protein comprises a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 66 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 67.

In one aspect, there is provided a formulation comprising an anti-IL1α/IL1β DVD-Ig protein and a surfactant, wherein the DVD-Ig protein comprises a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 66 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 67.

In one aspect, there is provided a formulation comprising an anti-IL1α/IL1β DVD-Ig protein and a polyol, wherein the DVD-Ig protein comprises a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 66 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 67.

In one aspect, there is provided a formulation comprising an anti-IL1α/IL1β DVD-Ig protein and two or more components selected from a buffer, a surfactant, and a polyol, wherein the DVD-Ig protein comprises a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 66 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 67.

In one aspect, there is provided an aqueous formulation comprising an anti-IL1α/IL1β DVD-Ig protein, a buffer, a surfactant, and a polyol, wherein the DVD-Ig protein comprises a heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 66 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 67.

In one aspect, there is provided a lyophilized formulation comprising an anti-IL1α/IL1β DVD-Ig protein a buffer, a surfactant, and a polyol, wherein the DVD-Ig protein comprises a

heavy chain comprising the amino acid sequence set forth as SEQ ID NO: 66 and a light chain comprising the amino acid sequence set forth as SEQ ID NO: 67.

In certain embodiments, the disclosure provides stable aqueous formulations comprising AS-DVD-Ig proteins, including high concentration AS-DVD-Ig formulations. AS-DVD-Ig proteins are a subpopulation of DVD-Ig proteins characterized by their ability to remain stable, *e.g.*, in concentrations 50 mg/ml or greater, during storage (*e.g.*, exhibit an aggregation increase of less than 3 % (determined by size exclusion chromatography (SEC)) following accelerated storage (40°C) in an aqueous formulation at a concentration of at least 50 mg/ml). In certain embodiments, the AS-DVD-Ig protein is characterized as a DVD-Ig protein having less than about 15% loss in relative percentage monomers as determined by size exclusion chromatography (SEC) when formulated in a histidine or citrate phosphate buffer at a concentration of at least about 50 mg/ml, following 14 days storage at about 40 °C. In certain embodiments, the AS-DVD-Ig protein is characterized as a DVD-Ig protein having less than about

56. A pharmaceutical composition comprising an Aqueous Stable DVD-Ig (AS-DVD-Ig) protein and a buffer having a molarity of about 5 to about 50 mM, wherein the AS-DVD-Ig protein is characterized as a DVD-Ig protein having less than about 10% loss in relative percentage monomers as determined by SEC when formulated in a histidine or citrate phosphate buffer at a concentration of about 60 mg/ml, following 14 days storage at about 40 degrees C, and the formulation has a pH of 4.5 to 7.5.

57. The pharmaceutical composition of claim 56, further comprising at least one component selected from a surfactant, a polyol, and combinations thereof.

58. ~~A method of treating a disorder, comprising administering~~ Use of the pharmaceutical composition of claim 56 or 57, in the manufacture of a medicament for treating a disorder~~such that the disorder is treated~~.

59. A lyophilized formulation comprising a Lyophilized-Stable DVD-Ig (LS-DVD-Ig) protein, wherein when said formulation is reconstituted, it comprises about 1 to about 100 mg/ml of the LS-DVD-Ig protein, about 10 to about 50 mM of a buffer, a polyol, about 0.01 to about 0.2 mg/ml of a polysorbate, and has a pH of about 5 to about 7

60. The lyophilized formulation of claim 59, wherein the formulation has a pH of about 5.5 to about 6.5.

61. The lyophilized formulation of claim 59 or 60, wherein the LS-DVD-Ig protein has more than 10% rel. peak area change in monomers observed, following accelerated storage at a pH between about 5.5 and about 6.5 in an aqueous formulation for 21 days at about 40°C, when formulated at a concentration over about 100 mg/ml.

62. The lyophilized formulation of claim 64, wherein the first polypeptide chain comprises a first VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

X1 is a linker with the proviso that it is not CH1;

X2 is an Fc region;

n is 0 or 1, and

wherein the second polypeptide chain comprises a second VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

X1 is a linker with the proviso that it is not CH1;

X2 does not comprise an Fc region;