

SUMMARY

[0007] The present disclosure provides a method comprising (a) reconstituting a lyophilized formulation comprising a polypeptide, a saccharide, a surfactant, and a buffer, with a diluent comprising an aromatic alcohol, a phenolic compound, or an amino acid with aromatic side chain, and (b) administering the reconstituted formulation to a subject in need thereof within 12 hours of reconstitution. In various examples, the polypeptide is a bispecific antibody construct. In various examples, the polypeptide binds human DLL3 and human CD3, such as a polypeptide comprising the amino acid sequence of SEQ ID NO: 75 and SEQ ID NO: 9. Optionally, the diluent comprises benzyl alcohol, phenol, m-Cresol, or phenylalanine. Also optionally, the pH of the reconstituted formulation is from about 4 to about 7 and/or the reconstituted formulation comprises about 1 mg/mL to about 20 mg/mL of the polypeptide. In various examples, the buffer is a glutamate buffer, the saccharide is sucrose, and/or the surfactant is polysorbate 80. For example, the formulation, prior to lyophilization, comprises 15 mM glutamate, 9% (w/V) sucrose and 0.01% (w/V) polysorbate 80, wherein the formulation has a pH of 4.2. In various examples, the subject is suffering from cancer, such as small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), glioma, glioblastoma, melanoma, neuroendocrine prostate cancer, neuroendocrine pancreatic cancer, hepatoblastoma, or hepatocellular carcinoma.

[0007a] Thus, in an aspect, there is provided a method comprising reconstituting a lyophilized formulation comprising a polypeptide, a saccharide selected from a monosaccharide or a disaccharide, a surfactant selected from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, poloxamer 188, poloxamer 407, Triton® X-100, polyoxyethylene, PEG 3350, PEG 4000, or a combination thereof, and a buffer selected from an acetate buffer, a glutamate buffer, a citrate buffer, a lactic buffer, a succinate buffer, a tartrate buffer, a fumarate buffer, a maleate buffer, a histidine buffer, or a phosphate buffer, with a diluent comprising an aromatic alcohol, a phenolic compound, or an amino acid with aromatic side chain, wherein the reconstituted formulation is to be administered to a subject in need thereof within 12 hours of reconstitution, and wherein the polypeptide is a bispecific antibody construct.

[0008] It should be understood that while various embodiments in the specification are presented using “comprising” language, under various circumstances, a related embodiment may also be described using “consisting of” or “consisting essentially of” language. The disclosure contemplates embodiments described as “comprising” a feature to include embodiments which “consist of” or “consists essentially of” the feature. The term “a” or “an” refers to one or more; for example, “an immunoglobulin molecule,” is understood to represent one or more immunoglobulin molecules. As such, the terms “a” (or “an”), “one or more,” and “at least one” can be used interchangeably herein.

[0009] It should also be understood that when describing a range of values, the characteristic being described could be an individual value found within the range. For example, “a pH from about pH 4 to about pH 6,” could be, but is not limited to, pH 4, 4.2, 4.6, 5.1, 5.5 etc. and any value in between such values. Additionally, “a pH from about pH 4 to about pH 6,” should not be construed to mean that the pH of a formulation in question varies 2 pH units in the

range from pH 4 to pH 6 during storage, but rather a value may be picked in that range for the pH of the solution, and the pH remains buffered at about that pH. In any of the ranges described herein, the endpoints of the range are included in the range. However, the description also contemplates the same ranges in which the lower and/or the higher endpoint is excluded.

[0010] When the term “about” is used, it means the recited number plus or minus 5%, 10%, 15% or more of that recited number. The actual variation intended is determinable from the context.

CLAIMS

1. A method comprising
reconstituting a lyophilized formulation comprising a polypeptide, a saccharide selected from a monosaccharide or a disaccharide, a surfactant selected from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, poloxamer 188, poloxamer 407, Triton® X-100, polyoxyethylene, PEG 3350, PEG 4000, or a combination thereof, and a buffer selected from an acetate buffer, a glutamate buffer, a citrate buffer, a lactic buffer, a succinate buffer, a tartrate buffer, a fumarate buffer, a maleate buffer, a histidine buffer, or a phosphate buffer, with a diluent comprising an aromatic alcohol, a phenolic compound, or an amino acid with aromatic side chain, wherein the reconstituted formulation is to be administered to a subject in need thereof within 12 hours of reconstitution, and
wherein the polypeptide is a bispecific antibody construct.
2. The method of claim 1, wherein the diluent comprises benzyl alcohol, phenol, m-Cresol, or phenylalanine.
3. The method of claim 1 or claim 2, wherein the pH of the reconstituted formulation is from 4 to 7.
4. The method of any one of claims 1-3, wherein the formulation has a pH of 4.2.
5. The method of any one of claims 1-4, wherein the reconstituted formulation comprises 1 mg/mL to 20 mg/mL of the polypeptide.
6. The method of any one of claims 1-5, wherein the reconstituted formulation comprises 15 mg/mL of the polypeptide.
7. The method of any one of claims 1 to 6, wherein the buffer is a glutamate buffer.
8. The method of any one of claims 1-7, wherein the buffer is present in at a concentration ranging from 5 to 200 mM prior to lyophilization.
9. The method of claim 8, wherein the buffer is present at a concentration ranging from 10 to 50 mM prior to lyophilization.
10. The method of any one of claims 1-8, wherein the saccharide is glucose, galactose, fructose, xylose, sucrose, lactose, maltose, trehalose, sorbitol, mannitol or xylitol.
11. The method of claim 10, wherein the saccharide is sucrose.
12. The method of any one of claims 1-11, wherein the saccharide is present in a concentration ranging from 1 to 15% (w/v) prior to lyophilization.
13. The method of any one of claims 1 to 12, wherein the surfactant is polysorbate 80.

14. The method of any one of claims 1-13, wherein the surfactant is present in a concentration ranging from 0.001% to 0.5% (w/v) prior to lyophilization.
15. The method of any one of claims 1-14, wherein, prior to lyophilization, the formulation comprises 15 mM glutamate, 9% (w/v) sucrose and 0.01% (w/v) polysorbate 80, and wherein the formulation has a pH of 4.2.
16. The method of any one of claims 1-15, wherein the diluent comprises 0.9% benzyl alcohol.
17. The method of any one of claims 1-15, wherein the diluent comprises phenol.
18. The method of any one of claims 1-15, wherein the diluent comprises m-Cresol.
19. The method of any one of claims 1-15, wherein the diluent comprises phenylalanine.
20. The method of any one of claims 1-19, wherein the reconstituted formulation is to be administered to a subject in need thereof within six hours of reconstitution.
21. The method of any one of claims 1-19, wherein the reconstituted formulation is to be administered to a subject in need thereof within four hours of reconstitution.
22. The method of any one of claims 1-19, wherein the reconstituted formulation is to be administered to a subject in need thereof within two hours of reconstitution.
23. The method of any one of claims 1-19, wherein the reconstituted formulation is to be administered to a subject in need thereof within one hour of reconstitution.
24. The method of any one of claims 1-19, wherein the subject is suffering from cancer.
25. The method of any one of claims 1-24, wherein polypeptide binds DLL3 and CD3.
26. The method of any one of claims 1-25, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 75 and SEQ ID NO: 9
27. The method of any one of claims 1-26, wherein the polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 76 or SEQ ID NO: 77.
28. The method of any one of claims claim 24-27, wherein the cancer is small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), glioma, glioblastoma, melanoma, neuroendocrine prostate cancer, neuroendocrine pancreatic cancer, hepatoblastoma, or hepatocellular carcinoma.
29. The method of claim 28, wherein the cancer is SCLC, NSCLC, glioma, glioblastoma, or neuroendocrine prostate cancer.
30. The method of any one of claims 1-24, wherein the polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 33, SEQ ID

NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 55, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 87, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 131, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 156, SEQ ID NO: 165, SEQ ID NO: 174, SEQ ID NO: 183, SEQ ID NO: 184, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 187, or SEQ ID NO: 188.

31. The method of claim 30, wherein the polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 156, SEQ ID NO: 165, SEQ ID NO: 174, or SEQ ID NO: 183.