potent and selective inhibitor of matrix metalloproteinase 8, (MMP-8) which lost its selectivity over other MMPs when its ring was opened (Cherney *et al*. (1998), J Med Chem 41 (11), 1749-51). The favorable binding properties achieved through macrocyclization are even more pronounced in multicyclic peptides having more than one peptide ring as for example in vancomycin, nisin and actinomycin.

[0005] Different research teams have previously tethered polypeptides with cysteine residues to a synthetic molecular structure (Kemp and McNamara (1985), J. Org. Chem; Timmerman *et al*. (2005), ChemBioChem). Meloen and co-workers had used tris(bromomethyl)benzene and related molecules for rapid and quantitative cyclisation of multiple peptide loops onto synthetic scaffolds for structural mimicry of protein surfaces (Timmerman *et al*. (2005), ChemBioChem). Methods for the generation of candidate drug compounds wherein said compounds are generated by linking cysteine containing polypeptides to a molecular scaffold as for example TATA (1,1',1''-(1,3,5-triazinane-1,3,5-triyl)triprop-2-en-1-one, Heinis *et al.* Angew Chem, Int Ed. 2014; 53:1602–1606).

[0006] Phage display-based combinatorial approaches have been developed to generate and screen large libraries of bicyclic peptides to targets of interest (Heinis *et al*. (2009), Nat Chem Biol *5* (7), 502-7 and WO 2009/098450). Briefly, combinatorial libraries of linear peptides containing three cysteine residues and two regions of six random amino acids (Cys-$(Xaa)_6$-Cys-$(Xaa)_6$-Cys) were displayed on phage and cyclised by covalently linking the cysteine side chains to a small molecule scaffold.

SUMMARY

[0006a] In an aspect of the present disclosure, there is provided a pharmaceutical composition comprising BT5528, or a pharmaceutically acceptable salt thereof, histidine hydrochloride, and about 0.01-0.15 mg Polysorbate 20 per mg of BT5528 or the pharmaceutically acceptable salt thereof.

[0006c] In a further aspect of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating an advanced solid tumor malignancy associated with EphA2-expression in a patient, wherein the pharmaceutical composition is to be intravenously administered to the patient.

[0006d] In another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein for use in therapy.

[0006e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein and Nivolumab for use in therapy.

[0007] According to one example, the disclosure provides a pharmaceutical composition comprising BT5528, or a pharmaceutically acceptable salt thereof, histidine hydrochloride, sucrose, and Polysorbate 20. In some examples, a pharmaceutical composition comprising BT5528, or a pharmaceutically acceptable salt thereof, histidine hydrochloride, sucrose, and Polysorbate 20 is a lyophilized powder.

[0008] In another example, the disclosure provides a pharmaceutical composition comprising BT5528, or a pharmaceutically acceptable salt thereof, histidine hydrochloride, sucrose, Polysorbate 20, and dextrose. In some examples, a pharmaceutical composition comprising BT5528, or a pharmaceutically acceptable salt thereof, histidine hydrochloride, sucrose, Polysorbate 20, and dextrose is a pharmaceutical formulation in water.

CLAIMS

1. A pharmaceutical composition comprising BT5528, or a pharmaceutically acceptable salt thereof, histidine hydrochloride, and about 0.01-0.15 mg Polysorbate 20 per mg of BT5528 or the pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition of claim 1, which is a solid pharmaceutical composition in lyophilized powder form.

3. The pharmaceutical composition of claim 1, which is a liquid pharmaceutical composition further comprising water.

4. The pharmaceutical composition of any one of claims 1-3, comprising about 0.05 mg Polysorbate 20 per mg BT5528 or the pharmaceutically acceptable salt thereof.

5. The pharmaceutical composition of any one of claims 1-4, comprising about 1-3 mg histidine hydrochloride per mg BT5528 or the pharmaceutically acceptable salt thereof.

6. The pharmaceutical composition of any one of claims 1 or 3-5, comprising between about 2 mg/ml and about 4 mg/ml BT5528.

7. The pharmaceutical composition of any one of claims 1 or 3-6, comprising about 4 mg/ml BT5528.

8. The pharmaceutical composition of any one of claims 1-7, comprising:

BT5528, or a pharmaceutically acceptable salt thereof;

about 1.31-2.62 mg histidine hydrochloride per mg of BT5528, or a pharmaceutically acceptable salt thereof;

about 15-30 mg sucrose per mg of BT5528, or a pharmaceutically acceptable salt thereof; and

about 0.05-0.1 mg Polysorbate 20 per mg of BT5528, or a pharmaceutically acceptable salt thereof.

9. The pharmaceutical composition of claim 8, comprising:

about 21.2 mg BT5528, or a pharmaceutically acceptable salt thereof;

about 55.5 mg histidine hydrochloride per mg of BT5528, or a pharmaceutically acceptable salt thereof;

about 636 mg sucrose per mg of BT5528, or a pharmaceutically acceptable salt thereof; and

about 1.06-2.12 mg Polysorbate 20 per mg of BT5528, or a pharmaceutically acceptable salt thereof.

10. The pharmaceutical composition of claim 9, comprising:

about 2-4 mg/mL BT5528, or a pharmaceutically acceptable salt thereof;

about 5.25 mg/mL histidine hydrochloride;

about 60 mg/mL sucrose; and

about 0.1-0.2 mg/mL Polysorbate 20.

11. Use of the pharmaceutical composition of any one of claims 1-10 in the manufacture of a medicament for treating an advanced solid tumor malignancy associated with EphA2-expression in a patient, wherein the pharmaceutical composition is to be intravenously administered to the patient.

12. The use of claim 11, wherein the advanced solid tumor malignancy associated with EphA2-expression is selected from non-small-cell lung cancer (NSCLC), ovarian cancer, triple-negative breast cancer (TNBC), gastric/upper gastrointestinal (GI) cancer, pancreatic and urothelial cancers.

13. The use of claim 11 or 12, wherein the pharmaceutical composition is to be administered once every 7 days.

14. The use of any one of claims 11-13, wherein the pharmaceutical composition is to be administered at a dose of about 2.2, 4.4, 7.3, 11, 14.6, or 19.4 mg/m^2.

15. The use of any one of claims 11-14, wherein the pharmaceutical composition is to be administered via an IV infusion of about 60 minutes.

16. The use of any one of claims 11-14, wherein Nivolumab is to be further administered to the patient.

17. The pharmaceutical composition of any one of claims 1-10 for use in therapy.

18. The pharmaceutical composition of any one of claims 1-10 and Nivolumab for use in therapy.