

mitigate toxic side effects, particularly intestinal necrosis or damage, associated with checkpoint inhibitors.

BRIEF SUMMARY

As specified in the Background Section, there is a great need in the art to identify technologies for peptide-based inhibitors of the different pathways of the complement system and use this understanding to develop novel therapeutic peptides. The present disclosure satisfies this and other needs. Examples of the present disclosure relate generally to synthetic peptides and more specifically to synthetic peptides that are PEGylated or contain a sarcosine substitution and their use in methods of regulating the complement system and preventing, treating and/or mitigating toxic side effects associated with checkpoint therapeutics, particularly intestinal necrosis or damage.

In one aspect, the present disclosure refers to the use of a composition comprising a synthetic peptide comprising SEQ ID NO: 2 and/or 3 in the manufacture of a medicament for preventing, treating and/or mitigating toxic side effects of checkpoint inhibitors in a subject in need thereof. In another aspect, the present disclosure refers to the use of a composition comprising a synthetic peptide comprising SEQ ID NO: 2 and/or 3 in the manufacture of a medicament for preventing, treating and/or mitigating intestinal necrosis and/or damage in a subject in need thereof. In yet another aspect, the present disclosure refers to the use of a composition comprising a synthetic peptide comprising SEQ ID NO: 2 and/or 3 and at least one checkpoint inhibitor in the manufacture of a medicament for combination therapy to prevent, treat and/or mitigate intestinal necrosis and/or damage in a subject. Described herein are synthetic peptides that regulate the complement system and methods of using these peptides. Specifically, in some examples, the synthetic peptides can bind, regulate and inactivate C1 and MBL, and therefore can efficiently inhibit classical and lectin pathway activation at its earliest point of the complement cascade while leaving the alternative pathway intact. These peptides are of therapeutic value for selectively regulating and inhibiting C1 and MBL activation without affecting the alternative pathway and can be used for treating diseases mediated by dysregulated activation of the classical and lectin pathways. In other examples, the peptides regulate classical pathway activation but not lectin pathway activation.

The peptides are useful for various therapeutic indications.

In any example, the synthetic peptides are capable of preventing, treating and/or mitigating toxic side effects of checkpoint inhibitors.

5 In any example, the synthetic peptides are capable of preventing, treating and/or mitigating intestinal necrosis and/or damage, e.g., necrosis or damage resulting from severe inflammatory responses, intestinal infarction (i.e., ischemia reperfusion injury of intestinal tissue), autoimmune inflammatory bowel disease (IBD) and associated therapies, and chemotherapy-induced or toxin-induced intestinal necrosis.

10 In any example, the disclosure is based on the identification and modification of peptides of 15 amino acids from Polar Assortant (PA) peptide (SEQ ID NO: 1), derivatives of the

peptides, and methods of their use. The PA peptide is a scrambled peptide derived from human astrovirus protein, called CP1. The PA peptide is also known as PIC1 (Peptide Inhibitors of Complement C1), AstroFend, AF, or SEQ ID NO: 1. The PIC1 peptide was originally named as such because it was found to be associated with diseases mediated by the complement system. A PEGylated form of the PIC1 peptide, called PA-dPEG24 or RLS-0071 (SEQ ID NO: 2), has 24 PEG units on the C terminus of the peptide and was shown to have improved solubility in aqueous solution. A sarcosine substitution scan of SEQ ID NO: 2 revealed that replacement of isoleucine at position 8 with sarcosine resulted in a peptide, IALILEP(Sar)CCQERAA (PA-I8Sar; RLS-0088; SEQ ID NO: 3) that was water soluble without PEGylation (as described in U.S. Patent No. 10,005,818).

In an example, there is disclosed a method of preventing, treating and/or mitigating toxic side effects of checkpoint inhibitors comprising administering to the subject in need thereof a composition comprising a therapeutically effective amount of a synthetic peptide comprising SEQ ID NO: 2 and/or 3.

In an example, there is disclosed a method of preventing, treating and/or mitigating intestinal necrosis and/or damage, e.g., necrosis or damage resulting from severe inflammatory responses, intestinal infarction (i.e., ischemia reperfusion injury of intestinal tissue), autoimmune inflammatory bowel disease (IBD) and associated therapies, and chemotherapy-induced or toxin-induced intestinal necrosis, comprising administering to the subject in need thereof a composition comprising a therapeutically effective amount of a synthetic peptide comprising SEQ ID NO: 2 and/or 3.

In an example, there is disclosed a method of preventing, treating and/or mitigating intestinal necrosis and/or damage in a subject who is being treated, has been treated, and/or will be treated with at least one checkpoint inhibitor comprising administering to the subject in need thereof a composition comprising a therapeutically effective amount of a synthetic peptide comprising SEQ ID NO: 2 and/or 3.

In an example of any of the foregoing methods, the composition further comprises at least one pharmaceutically acceptable carrier, diluent, stabilizer, or excipient. In an example of any of the foregoing methods, the therapeutically effective amount of SEQ ID NO: 2 and/or 3 is about 10 mg/kg to about 160 mg/kg. In an example of any of the foregoing methods, the

therapeutically effective amount of SEQ ID NO: 2 and/or 3 is about 20 mg/kg to about 160 mg/kg. In an example of any of the foregoing methods, the therapeutically effective amount of SEQ ID NO: 2 and/or 3 is about 40 mg/kg to about 160 mg/kg. In any example, the therapeutically effective amount of SEQ ID NO: 2 and/or 3 is administered in at least one dose, the first dose comprising about 1 mg/kg to about 160 mg/kg SEQ ID NO: 2 and/or 3. In any example, a second dose comprising a therapeutically effective amount of SEQ ID NO: 2 and/or 3 is administered, the second dose comprising about 1 mg/kg to about 120 mg/kg SEQ ID NO: 2 and/or 3, including about 10 mg/kg to about 120 mg/kg SEQ ID NO: 2 and/or 3. In any example, the therapeutically effective amount of SEQ ID NO: 2 and/or 3 is administered in two doses, the first dose comprising about 1 mg/kg to about 160 mg/kg SEQ ID NO: 2, including about 10 mg/kg to about 120 mg/kg SEQ ID NO: 2 and/or 3, and the second dose comprising about 1 mg/kg to about 120 mg/kg SEQ ID NO: 2 and/or 3, including about 1 mg/kg to about 40 mg/kg SEQ ID NO: 2 and/or 3. In any example, a second dose is administered 30 seconds to 10 hours after a first dose is administered, including about eight hours after administration of the first dose. In any example, the therapeutically effective amount of SEQ ID NO: 2 and/or 3 is administered in multiple doses over a period of about one week to about two weeks, each dose comprising about 1 mg/kg to about 160 mg/kg SEQ ID NO: 2 and/or 3, including about 1 mg/kg to about 120 mg/kg SEQ ID NO: 2 and/or 3, being administered every 4 to 10 hours, including about every eight hours.

In any example, at least one loading dose of about 10 mg/kg to about 160 mg/kg SEQ ID NO: 2 and/or 3 is administered, including about 10 mg/kg to about 120 mg/kg SEQ ID NO: 2 and/or 3, followed by at least one maintenance dose of about 1 mg/kg to about 120 mg/kg SEQ ID NO: 2 and/or 3, including about 1 mg/kg to about 40 mg/kg SEQ ID NO: 2 and/or 3. In any example, the first maintenance dose is administered 4 to 10 hours after the last loading dose. In any example, the maintenance doses are administered every 4 to 10 hours for a period of about one week to about two weeks. In any example, the first maintenance dose is administered 8 hours after the last loading dose, and the maintenance doses are administered every 8 hours for a period of about one week to about two weeks.

In any example of any of the foregoing methods, the composition is formulated for subcutaneous, intravenous, intraperitoneal, or intramuscular administration. In an example, the composition further comprises a pharmaceutically acceptable carrier and/or excipient.

CLAIMS

What is claimed is:

1. Use of a composition comprising a synthetic peptide comprising SEQ ID NO: 2 and/or 3 in the manufacture of a medicament for preventing, treating and/or mitigating toxic side effects of checkpoint inhibitors in a subject in need thereof.
2. Use of a composition comprising a synthetic peptide comprising SEQ ID NO: 2 and/or 3 in the manufacture of a medicament for preventing, treating and/or mitigating intestinal necrosis and/or damage in a subject in need thereof.
3. Use of a composition comprising a synthetic peptide comprising SEQ ID NO: 2 and/or 3 and at least one checkpoint inhibitor in the manufacture of a medicament for combination therapy to prevent, treat and/or mitigate intestinal necrosis and/or damage in a subject.
4. The use of any of claims 1 to 2, wherein the composition and at least one checkpoint inhibitor, or the use of claim 3, wherein the composition and the at least one checkpoint inhibitor, is to be administered sequentially, simultaneously, separately, and/or concurrently.
5. The use of any of claims 1-4, wherein the composition further comprises at least one pharmaceutically acceptable carrier, diluent, stabilizer, or excipient.
6. The use of any of claims 1-5, wherein the SEQ ID NO: 2 and/or 3 is present in an amount of 10 mg/kg to 160 mg/kg.
7. The use of any of claims 1-5, wherein the SEQ ID NO: 2 and/or 3 is present in an amount of 20 mg/kg to 160 mg/kg.
8. The use of any of claims 1-5, wherein the SEQ ID NO: 2 and/or 3 is present in an amount of 40 mg/kg to 160 mg/kg.
9. The use of any of claims 1-5, wherein the SEQ ID NO: 2 and/or 3 is to be administered in at least one dose, the first dose comprising 1 mg/kg to 160 mg/kg of SEQ ID NO: 2 and/or 3.
10. The use of claim 9, wherein a second dose comprising SEQ ID NO: 2 and/or 3 is to be administered, the second dose comprising 1 mg/kg to 120 mg/kg of SEQ ID NO: 2 and/or 3.

11. The use of any of claims 1-5, wherein the SEQ ID NO: 2 and/or 3 is to be administered in two doses, the first dose comprising 1 mg/kg to 160 mg/kg of SEQ ID NO: 2 and/or 3 and the second dose comprising 1 mg/kg to 120 mg/kg of SEQ ID NO: 2 and/or 3.
12. The use of claim 11, wherein the second dose is to be administered 30 seconds to 10 hours after the first dose had been administered.
13. The use of any of claims 1-5, wherein the SEQ ID NO: 2 and/or 3 is to be administered in multiple doses over a period of about one week to about two weeks, each dose comprising 1 mg/kg to 160 mg/kg of SEQ ID NO: 2 and/or 3 and are to be administered every 4 to 10 hours.
14. The use of claim 13, wherein each dose is to be administered every 8 hours.
15. The use of any of claims 1-5, wherein the SEQ ID NO: 2 and/or 3 is to be administered in at least one loading dose of 10 mg/kg to 160 mg/kg of SEQ ID NO: 2 and/or 3, followed by at least one maintenance dose of 1 mg/kg to 120 mg/kg of SEQ ID NO: 2 and/or 3,
wherein the first maintenance dose is to be administered 4 to 10 hours after the last loading dose,
and
wherein the maintenance doses are to be administered every 4 to 10 hours for a period of one week to two weeks.
16. The use of claim 15, wherein the first maintenance dose is to be administered 8 hours after the last loading dose, and wherein the maintenance doses are to be administered every 8 hours for a period of one week to two weeks.
17. The use of any of claims 3-16, wherein the checkpoint inhibitor is selected from the group consisting of CTLA-4 inhibitors, PD-1 inhibitors and PD-L1 inhibitors, such as pembrolizumab (Keytruda), ipilimumab (Yervoy), nivolumab (Opdivo) and atezolizumab (Tecentriq).