

BRIEF SUMMARY OF THE INVENTION

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 ~~invention-disclosure~~ satisfies this and other needs. Embodiments of the present ~~invention-disclosure~~ relate generally to synthetic peptides and more specifically to synthetic peptides that are stapled and/or include one or more D-enantiomeric forms of the amino acids.

In one ~~aspect~~example, the present ~~invention-provides-disclosure describes~~ synthetic peptides that regulate the complement system and methods of using these peptides. Specifically, in some ~~embodiments~~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 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 ~~embodiments~~examples, the peptides regulate classical pathway activation but not lectin pathway activation. The peptides are useful for various therapeutic indications.

In some ~~embodiments~~examples, the ~~invention-disclosure~~ is based on the identification and modification of peptides of 15 amino acids from Polar Assortant (PA) peptide (SEQ ID NO: 2), modifications of the peptides, and methods of their use. The PA peptide is a scrambled peptide derived from human astrovirus protein, called CP1 (SEQ ID NO: 1). The PA peptide is also known as PIC1 (Peptide Inhibitors of Complement C1), AstroFend, AF, or SEQ ID NO: 2. 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 (SEQ ID NO: 3), has 24 PEG moieties on the C-terminus of the peptide and was shown to have improved effects on complement inhibition. A form of the PIC1 peptide with the amino acid derivative sarcosine at position 8, called PA-I8Sar (SEQ ID NO: 4), also has improved effects on complement inhibition. A form of the PIC1 peptide with the amino acid derivative sarcosine at position 9, called PA-C9Sar (SEQ ID NO: 5), also has improved effects on complement inhibition. PA-dPEG24, PA-I8Sar, and PA-C9Sar are described in, e.g., U.S. Patent No. 10,005, 818, and U.S. Patent Publication No. US2019/0209660. As used herein, the term “PIC1 peptides” include SEQ ID NOs: 6-35 and 54-

55 which are stapled forms of SEQ ID NO: 4 and/or substitutions of SEQ ID NO: 4 that have one or more D-enantiomeric forms of amino acids in place of the usual L-enantiomers, and SEQ ID NOs: 36-53 which are stapled forms of SEQ ID NO: 5 and/or substitutions of SEQ ID NO: 5 that have one or more D-enantiomeric forms of amino acids in place of the usual L-enantiomers.

5 In some ~~aspect~~examples, the ~~invention~~disclosure is directed to~~describes~~ peptides that are stapled forms of PA-I8Sar and/or comprise one or more D-enantiomeric amino acid substitutions in the sequence of PA-I8Sar that are able to regulate the classical and lectin pathway activation by binding to C1q and MBL. In some ~~aspect~~examples, the ~~invention is directed to~~disclosure describes peptides that are stapled forms of PA-I9Sar and/or comprise one or more D-enantiomeric amino acid substitutions in the sequence of PA-I9Sar that are able to regulate the classical and lectin pathway activation by binding to C1q and MBL.

10 In some ~~embodiment~~examples, the peptide sequence has at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NOs: 6-55. In some ~~example~~embodiments, the peptide sequence has at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NOs: 6-35 and 54-55. In some ~~example~~embodiments, the peptide sequence has at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NOs: 36-53.

15 In one aspect, the ~~invention provides~~disclosure describes a synthetic peptide comprising at least about 95% sequence identity to an amino acid sequence selected from the group of SEQ ID NO: 6-55. In one example, ~~present disclosure describes~~ a synthetic peptide comprising at least about 95% sequence identity to an amino acid sequence of SEQ ID NO: 6-35 and 54-55. In some ~~embodiment~~examples, the ~~invention is~~there is described a synthetic peptide comprising the amino acid sequence and modifications of SEQ ID NO: 6-35 and 54-55. In one ~~example~~aspect, the ~~invention is~~ a synthetic peptide comprising at least about 95% sequence identity to an amino acid sequence of SEQ ID NO: 36-53 is disclosed. In some examples, there is disclosed ~~embodiments~~, the ~~invention is~~ a synthetic peptide comprising the amino acid sequence and modifications of SEQ ID NO: 36-53.

25 In another aspect, the ~~invention provides~~disclosure describes a composition comprising at least one synthetic peptide disclosed herein, optionally in further combination with another D-enantiomeric and/or stapled peptide form of SEQ ID NO: 4 and/or SEQ ID NO: 5, and variants thereof, and/or one or more of SEQ ID NO: 2, 3, 4, and/or 5, and variants thereof. In one example, the present disclosure describes a combination of peptides disclosed herein. In some ~~embodiment~~examples, the ~~invention provides~~there is described a composition comprising at least one synthetic peptide selected from the group consisting of SEQ ID NO: 6-55, and variants thereof. In ~~another aspect~~, the ~~invention provides~~example, there is disclosed a composition comprising at least one synthetic peptide selected from the group consisting of SEQ ID NO: 6-35 and 54-55, and variants thereof. In another ~~aspect~~, the

~~invention provides example~~, a composition comprising at least one synthetic peptide selected from the group consisting of SEQ ID NO: 36-53, and variants thereof is disclosed. In another ~~aspect~~example, the composition further comprises another D-enantiomeric and/or stapled peptide form of SEQ ID NO: 4 and/or SEQ ID NO: 5, and variants thereof. In another ~~aspect~~example, the composition further comprises one or more of SEQ ID NO: 2, 3, 4, and/or 5, and variants thereof.

In another aspect, the ~~invention is~~disclosure describes a pharmaceutical composition comprising a therapeutically effective amount of at least one synthetic peptide disclosed herein or the composition disclosed herein, and optionally at least one pharmaceutically acceptable carrier, diluent, or excipient. In one example, there is disclosed a pharmaceutical composition comprising a therapeutically effective amount of at least one synthetic peptide selected from the group consisting of SEQ ID NO: 6-55, and variants thereof. In another ~~aspect, the invention is~~example, there is disclosed a pharmaceutical composition comprising a therapeutically effective amount of at least one synthetic peptide selected from the group consisting of SEQ ID NO: 6-35 and 54-55, and variants thereof. In another ~~aspect, the invention is~~example, there is disclosed a pharmaceutical composition comprising a therapeutically effective amount of at least one synthetic peptide selected from the group consisting of SEQ ID NO: 36-53, and variants thereof. In another ~~aspect~~example, the pharmaceutical composition further comprises another D-enantiomeric and/or stapled peptide form of SEQ ID NO: 4 and/or SEQ ID NO: 5, and variants thereof. In another ~~example~~aspect, the pharmaceutical composition further comprises one or more of SEQ ID NO: 2, 3, 4, and/or 5, and variants thereof.

In another ~~aspect, the invention provides~~example, there is described a pharmaceutical composition comprising a therapeutically effective amount of at least one synthetic peptide selected from the group consisting of SEQ ID NO: 6-55, and variants thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient. In another ~~aspect, the invention is~~example, there is disclosed a pharmaceutical composition comprising a therapeutically effective amount of at least one synthetic peptide selected from the group consisting of SEQ ID NO: 6-35 and 54-55, and variants thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient. In another ~~aspect, the invention is~~example, there is disclosed a pharmaceutical composition comprising a therapeutically effective amount of at least one synthetic peptide selected from the group consisting of SEQ ID NO: 36-53, and variants thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient. In another ~~aspect~~example, the pharmaceutical composition further comprises another D-enantiomeric and/or stapled peptide form of SEQ ID NO: 4 and/or SEQ ID NO: 5. In another ~~aspect~~example, the pharmaceutical composition further comprises one or more of SEQ ID NO: 2, 3, 4, and/or 5, and variants thereof.

In one ~~aspect, the invention provides~~example, there is disclosed a synthetic peptide comprising at least about 95% sequence identity to an amino acid sequence selected from the group of SEQ ID NO: 6-55.

In some ~~embodiments, the invention provides~~examples, there is described a synthetic peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 6-55. In some ~~embodiments, the invention provides~~examples, a synthetic peptide comprising at least about 95% sequence identity to amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 19, 22, 25 is disclosed. In some examples, there is disclosed ~~embodiments, the invention provides~~ a synthetic peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 19, 22, and 25. In some ~~embodiments, the invention provides~~examples, there is disclosed a synthetic peptide comprising at least about 95% sequence identity to SEQ ID NO: 9. In some ~~embodiments, the invention provides~~examples, there is disclosed a synthetic peptide comprising at least about 95% sequence identity to SEQ ID NO: 19. In some ~~embodiments, the invention provides~~examples, there is disclosed a synthetic peptide comprising at least about 95% sequence identity to SEQ ID NO: 22. In some ~~embodiments, the invention provides~~example, there is disclosed a synthetic peptide comprising at least about 95% sequence identity to SEQ ID NO: 25. In another ~~aspect, the invention provides~~example, a combination of peptides is disclosed herein. In some ~~embodiments, the invention provides~~examples, a composition comprising at least one synthetic peptide selected from the group consisting of SEQ ID Nos: 9, 19, 22, and 25, and variants thereof is disclosed. In another ~~aspect~~example, the composition further comprises another D-enantiomeric and/or stapled peptide form of SEQ ID NO: 4 and/or SEQ ID NO: 5, and variants thereof. In another ~~aspect~~example, the composition further comprises one or more of SEQ ID NO: 2, 3, 4, and/or 5, and variants thereof.

In another ~~aspect, the invention is~~example, there is disclosed a pharmaceutical composition comprising a therapeutically effective amount of at least one synthetic peptide selected from the group consisting of SEQ ID NOs: 9, 19, 22, and 25, and variants thereof. In another ~~aspect~~example, the pharmaceutical composition further comprises another D-enantiomeric and/or stapled peptide form of SEQ ID NO: 4 and/or SEQ ID NO: 5, and variants thereof. In another ~~aspect~~example, the pharmaceutical composition further comprises one or more of SEQ ID NO: 2, 3, 4, and/or 5, and variants thereof. In another aspect, the present disclosure refers to the synthetic peptide disclosed herein, or the composition disclosed herein, or the pharmaceutical composition disclosed herein, for use in therapy.

In a related ~~aspect~~example, the invention provides a pharmaceutical composition is disclosed comprising a therapeutically effective amount of any of the synthetic peptides disclosed herein and at least one pharmaceutically acceptable carrier, diluent, or excipient.

In one aspect, the present disclosure refers to use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for regulating the complement system. In a related aspect, ~~the invention provides~~example, there is disclosed a method of regulating the complement system comprising administering a pharmaceutical composition as described herein to a subject in need thereof.

In one aspect, the present disclosure refers to use of the pharmaceutical composition as described herein in the manufacture of a medicament for inhibiting myeloperoxidase activity. In a related aspect, ~~the invention provides~~example, there is disclosed a method of inhibiting myeloperoxidase activity comprising administering a pharmaceutical composition as described herein to a subject in need thereof.

In one aspect, the present disclosure refers to use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting NETosis. In a related aspect, ~~the invention provides~~example, there is disclosed a method of inhibiting NETosis comprising administering a pharmaceutical composition as described herein to a subject in need thereof.

In one aspect, the present disclosure refers to use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting oxidant activity. In a related aspect, ~~the invention provides~~example, there is disclosed a method of inhibiting oxidant activity comprising administering a pharmaceutical composition as described herein to a subject in need thereof.

In one aspect, the present disclosure refers to use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting PD-1 binding to PD-L1. In a related aspect, ~~the invention provides~~example, there is disclosed a method of inhibiting PD-1 binding to PD-L1 comprising administering a pharmaceutical composition as described herein to a subject in need thereof.

In one aspect, the present disclosure refers to use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting T cell exhaustion. In a related aspect, ~~the invention provides~~example, there is disclosed a method of inhibiting T cell exhaustion comprising administering a pharmaceutical composition as described herein to a subject in need thereof.

In one aspect, the present disclosure refers to use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting angiogenesis. In a related aspect, ~~the invention provides~~ example, there is disclosed a method of inhibiting angiogenesis comprising administering a pharmaceutical composition as described herein to a subject in need thereof.

These and other objects, features and advantages of the present invention will become more apparent upon reading the following specification in conjunction with the accompanying description, claims and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying Figures, which are incorporated in and constitute a part of this specification, illustrate several aspects described below.

Figure 1A-1B show PIC1 peptides' inhibition of complement activation in an ABO incompatibility assay. Figure 1A shows modifications of PA-I8Sar and Figure 1B shows modifications of PA-C9Sar. Inhibition of ABO incompatibility hemolysis in a CH50-type assay.

CLAIMS

What is claimed is:

1. A synthetic peptide comprising at least ~~about~~ 95% sequence identity to an amino acid sequence selected from the group of SEQ ID NO: 6-55.
2. The synthetic peptide of claim 1 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 6-55.
3. The synthetic peptide of claim 1 comprising at least ~~about~~ 95% sequence identity to amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 19, 22, 25.
4. The synthetic peptide of claim 1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 19, 22, and 25.
5. The synthetic peptide of claim 1 consisting of an amino acid sequence comprising at least ~~about~~ 95% sequence identity to SEQ ID NO: 9.
6. The synthetic peptide of claim 1 consisting of an amino acid sequence comprising at least ~~about~~ 95% sequence identity to SEQ ID NO: 19.
7. The synthetic peptide of claim 1 consisting of an amino acid sequence comprising at least ~~about~~ 95% sequence identity to SEQ ID NO: 22.
8. The synthetic peptide of claim 1 consisting of an amino acid sequence comprising at least ~~about~~ 95% sequence identity to SEQ ID NO: 25.
9. A composition comprising at least one synthetic peptide of any of claims 1-8, optionally in further combination with another D-enantiomeric and/or stapled peptide form of SEQ ID NO: 4 and/or SEQ ID NO: 5, and variants thereof, and/or one or more of SEQ ID NO: 2, 3, 4, and/or 5, and variants thereof.

10. A pharmaceutical composition comprising a therapeutically effective amount of at least one synthetic peptide of any of claims 1-8 or the composition of claim 9, and optionally at least one pharmaceutically acceptable carrier, diluent, or excipient.

11. The synthetic peptide of any one of claims 1 to 8, or the composition of claim 9, or the pharmaceutical composition of claim 10, for use in therapy.

~~1112. A method of regulating the complement system comprising administering~~ Use of the pharmaceutical composition of claim 10 in the manufacture of a medicament for regulating the complement system ~~to a subject in need thereof.~~

~~1213. A method of inhibiting myeloperoxidase activity comprising administering~~ Use of the pharmaceutical composition of claim 10 in the manufacture of a medicament for inhibiting myeloperoxidase activity ~~to a subject in need thereof.~~

~~1314. A method of inhibiting NETosis comprising administering~~ Use of the pharmaceutical composition of claim 10 in the manufacture of a medicament for inhibiting NETosis ~~to a subject in need thereof.~~

~~1415. A method of inhibiting oxidant activity comprising administering~~ Use of the pharmaceutical composition of claim 10 in the manufacture of a medicament for inhibiting oxidant activity ~~to a subject in need thereof.~~

~~1516. A method of inhibiting PD-1 binding to PD-L1 comprising administering~~ Use of the pharmaceutical composition of claim 10 in the manufacture of a medicament for inhibiting PD-1 binding to PD-L1 ~~to a subject in need thereof.~~

~~1617. A method of inhibiting T cell exhaustion comprising administering the~~ Use of the pharmaceutical composition of claim 10 in the manufacture of a medicament for inhibiting T cell exhaustion ~~to a subject in need thereof.~~

~~1718. A method of inhibiting angiogenesis comprising administering~~ Use of the pharmaceutical composition of claim 10 in the manufacture of a medicament for inhibiting angiogenesis ~~to a subject in need thereof.~~