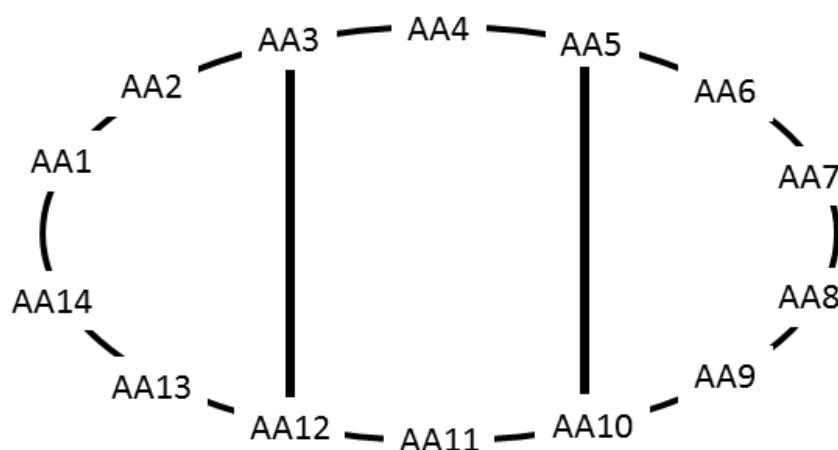


CLAIMS

What is claimed is:

1. A cyclic peptide consisting of 14 amino acids and having the following structure:



wherein AA3 and AA12 are cysteines joined by a disulfide bond, AA5 and AA10 are cysteines joined by a disulfide bond, AA4 is a first hydrophobic amino acid, AA11 is a second hydrophobic acid, AA6 is arginine, AA7 is arginine, AA8 is arginine, and wherein the cyclic peptide has four arginine residues that provide a positively charged content of about 28% at physiological pH.

2. The cyclic peptide of claim 1, wherein the first hydrophobic amino acid and the second hydrophobic amino acid are leucine or isoleucine.
3. The cyclic peptide of claim 1 or 2, wherein AA1 is glycine.
4. The cyclic peptide of any one of claims 1 to 3, wherein AA2 is a third hydrophobic amino acid.
5. The cyclic peptide of claim 4, wherein the third hydrophobic amino acid is valine or phenylalanine.
6. The cyclic peptide of any one of claims 1 to 5, wherein AA9 is a fourth hydrophobic amino acid.

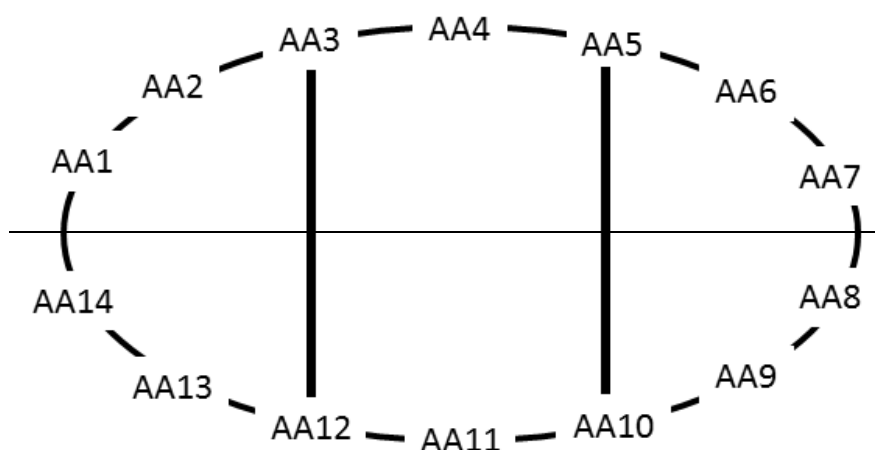
7. The cyclic peptide of claim 6, wherein the fourth hydrophobic amino acid is valine or phenylalanine.
8. The cyclic peptide of any one of claims 1 to 7, wherein AA13 is glycine.
9. The cyclic peptide of any one of claims 1 to 8, wherein AA14 is arginine.
10. The cyclic peptide of any one of claims 1 to 9, wherein AA4 is not alanine or serine.
11. The cyclic peptide of any one of claims 1 to 10, wherein AA11 is not alanine or serine.
12. The cyclic peptide of claim 1, wherein the cyclic peptide is MTD12813 (SEQ ID NO. 2).
13. The cyclic peptide of any one of claims 1 to 12, wherein the cyclic peptide is an analog of a θ -defensin, and wherein the cyclic peptide provides improved survival when applied systemically in a murine sepsis model relative to the θ -defensin.
14. The cyclic peptide of any one of claims 1 to 13, wherein the cyclic peptide provides a biphasic response on application to a murine model of sepsis, wherein the biphasic response comprises a first phase of recruitment of host effector cells having antimicrobial activity and a second phase of moderation of host inflammatory response.
15. The cyclic peptide of any one of claims 1 to 14, wherein the cyclic peptide has a TACE inhibiting activity.
16. The cyclic peptide of any one of claims 1 to 15, wherein the cyclic peptide suppresses at least one of expression, processing, and release of TNF.
17. The cyclic peptide of any one of the claims 1 to 16, wherein the cyclic peptide retains activity following exposure to environmental extremes of temperature, low pH, freezing and/or thawing, and dissolution in a biological matrix.
18. The cyclic peptide of claim 17, wherein the biological matrix is selected from the group consisting of blood, plasma, and serum.

19. The cyclic peptide of any one of the claims 1 to 18, wherein the cyclic peptide is non-immunogenic at doses effective to treat or prevent sepsis and/or septic shock.

20. The cyclic peptide of any one of the claims 1 to 18, wherein the cyclic peptide activates a host immune system to enhance host clearance of pathogens.

21. The cyclic peptide of any one of the claims 1 to 20, wherein the cyclic peptide is characterized by an activity that modulates inflammation to enhance disease resolution and survival at doses effective to treat or prevent septic shock.

~~22. A method of treating or preventing septic shock, comprising administering a cyclic peptide of an animal at risk of septic shock, wherein the cyclic peptide has the following structure:~~



~~wherein AA3 and AA12 are cysteines joined by a disulfide bond, AA5 and AA10 are cysteines joined by a disulfide bond, AA4 is a first hydrophobic amino acid, AA11 is a second hydrophobic acid, AA6 is arginine, AA7 is arginine, AA8 is arginine, and wherein the cyclic peptide has four arginine residues that provide a positively charged content of about 28% at physiological pH.~~

~~23. The method of claim 22, wherein the first hydrophobic amino acid and the second hydrophobic amino acid are leucine or isoleucine.~~

~~24. The method of claim 22 or 23, wherein AA1 is glycine.~~

~~25. The method of one of claims 22 to 24, wherein AA2 is a third hydrophobic amino acid.~~

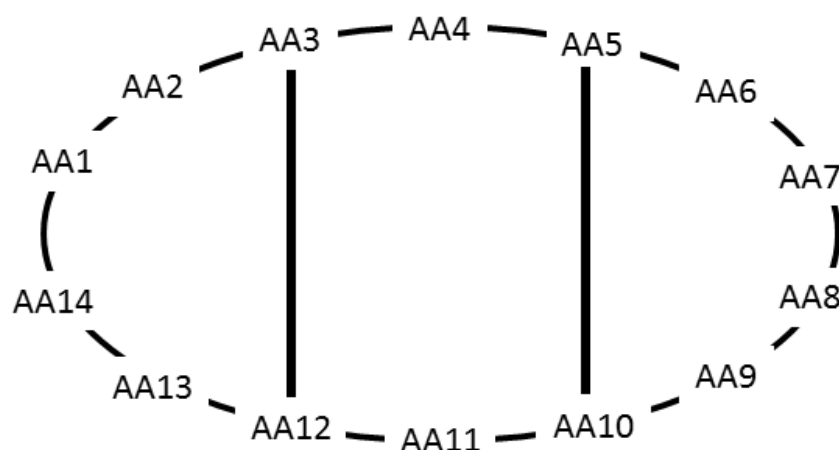
- ~~26. The method of claim 25, wherein the third hydrophobic amino acid is valine or phenylalanine.~~
- ~~27. The method of one of claims 22 to 26, wherein AA9 is a fourth hydrophobic amino acid.~~
- ~~28. The method of claim 27, wherein the fourth hydrophobic amino acid is valine or phenylalanine.~~
- ~~29. The method of one of claims 22 to 28, wherein AA13 is glycine.~~
- ~~30. The method of one of claims 22 to 29, wherein AA14 is arginine.~~
- ~~31. The method of one of claims 22 to 30, wherein AA4 is not alanine or serine.~~
- ~~32. The method of one of claims 22 to 31, wherein AA11 is not alanine or serine.~~
- ~~33. The method of claim 22, wherein the cyclic peptide is MTD12813 (SEQ ID NO. 2).~~
- ~~34. The method of one of claims 22 to 33, wherein the cyclic peptide is an analog of a θ -defensin, and wherein the cyclic peptide provides improved survival when applied systemically in a murine sepsis model relative to the θ -defensin.~~
- ~~35. The method of one of claims 22 to 34, wherein the method provides a biphasic response on application to a murine model of sepsis, wherein the biphasic response comprises a first phase of recruitment of host effector cells having antimicrobial activity and a second phase of moderation of host inflammatory response.~~
- ~~36. The method of one of claims 22 to 35, wherein the method inhibits TACE activity.~~
- ~~37. The method of one of claims 22 to 36, wherein the method suppresses at least one of expression, processing, and release of TNF.~~
- ~~38. The method of one of claims 22 to 37, wherein the cyclic peptide retains activity following exposure to environmental extremes of temperature, low pH, freezing and/or thawing, and dissolution in a biological matrix.~~

~~39. The method of claim 38, wherein the biological matrix is selected from the group consisting of blood, plasma, and serum.~~

~~40. The method of one of claims 22 to 39, wherein the cyclic peptide is non-immunogenic at doses effective to treat or prevent septic shock.~~

~~41. The method of one of claims 22 to 40, wherein the cyclic peptide activates a host immune system to enhance host clearance of pathogens.~~

~~4222. Use of a~~ cyclic peptide for use in the treatment or prevention of ~~in treating or preventing~~ sepsis and/or septic shock, wherein the cyclic peptide has the following covalent structure schematic:



wherein AA3 and AA12 are cysteines joined by a disulfide bond, AA5 and AA10 are cysteines joined by a disulfide bond, AA4 is a first hydrophobic amino acid, AA11 is a second hydrophobic acid, AA6 is arginine, AA7 is arginine, AA8 is arginine, and wherein the cyclic peptide has four arginine residues that provide a positively charged content of about 28% at physiological pH.

~~4323. The~~ cyclic peptide use of claim 4222, wherein the first hydrophobic amino acid and the second hydrophobic amino acid are leucine or isoleucine.

~~4424. The~~ cyclic peptide use of claim 4222 or 4323, wherein AA1 is glycine.

~~4525~~. The cyclic peptide ~~use~~-of one of claims ~~42-22~~ to ~~4424~~, wherein AA2 is a third hydrophobic amino acid.

~~4626~~. The cyclic peptide ~~use~~-of claim ~~4525~~, wherein the third hydrophobic amino acid is valine or phenylalanine.

~~4727~~. The cyclic peptide ~~use~~-of one of claims ~~42-22~~ to ~~4626~~, wherein AA9 is a fourth hydrophobic amino acid.

~~4828~~. The cyclic peptide ~~use~~-of claim ~~4727~~, wherein the fourth hydrophobic amino acid is valine or phenylalanine.

~~4929~~. The cyclic peptide ~~use~~-of one of claims ~~42-22~~ to ~~4828~~, wherein AA13 is glycine.

~~5030~~. The cyclic peptide ~~use~~-of one of claims ~~42-22~~ to ~~4929~~, wherein AA14 is arginine.

~~5131~~. The cyclic peptide ~~use~~-of one of claims ~~42-22~~ to ~~5030~~, wherein AA4 is not alanine or serine.

~~5232~~. The cyclic peptide ~~use~~-of one of claims ~~42-22~~ to ~~5131~~, wherein AA11 is not alanine or serine.

~~5333~~. The cyclic peptide ~~use~~-of claim ~~4222~~, wherein the cyclic peptide is MTD12813 (SEQ ID NO. 2).

~~5434~~. The cyclic peptide ~~use~~-of one of claims ~~42-22~~ to ~~5333~~, wherein the cyclic peptide is an analog of a θ -defensin, and wherein the cyclic peptide provides improved survival when applied systemically in a murine sepsis model relative to the θ -defensin.

~~5535~~. The cyclic peptide ~~use~~-of one of claims ~~42-22~~ to ~~5434~~, wherein the cyclic peptide provides a biphasic response on application to a murine model of sepsis, wherein the biphasic response comprises a first phase of recruitment of host effector cells having antimicrobial activity and a second phase of moderation of host inflammatory response.

~~5636~~. The cyclic peptide ~~use~~-of one of claims ~~42-22~~ to ~~5535~~, wherein the cyclic peptide has a TACE inhibiting activity.

~~5737~~. The cyclic peptide ~~use~~ of one of claims ~~42-22~~ to ~~5636~~, wherein the cyclic peptide suppresses at least one of expression, processing, and release of TNF.

~~5838~~. The cyclic peptide ~~use~~ of one of claims ~~42-22~~ to ~~5737~~, wherein the cyclic peptide retains activity following exposure to environmental extremes of temperature, low pH, freezing and/or thawing, and dissolution in a biological matrix.

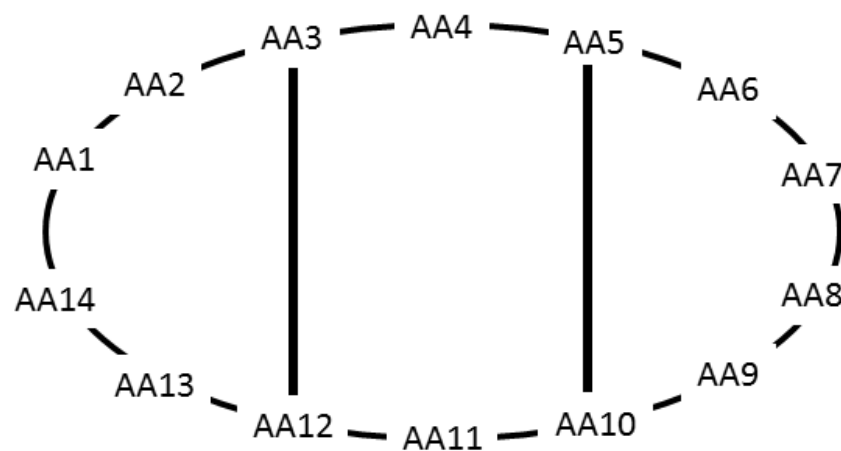
~~5939~~. The cyclic peptide ~~use~~ of claim ~~5838~~, wherein the biological matrix is selected from the group consisting of blood, plasma, and serum.

~~6040~~. The cyclic peptide ~~use~~ of one of claims ~~42-22~~ to ~~5939~~, wherein the cyclic peptide is non-immunogenic at doses effective to treat or prevent septic shock.

~~6141~~. The cyclic peptide ~~use~~ of one of claims ~~42-22~~ to ~~6040~~, wherein the cyclic peptide activates a host immune system to enhance host clearance of pathogens.

~~6242~~. The cyclic peptide ~~use~~ of one of claims ~~42-22~~ to ~~61-41~~ wherein the cyclic peptide is characterized by an activity that modulates inflammation to enhance disease resolution and survival at doses effective to treat or prevent septic shock.

~~6343~~. Use of a cyclic peptide in the manufacture ~~preparation~~ of a medicament for the treatment or prevention of ~~that is effective in treating or preventing~~ septic shock, wherein the cyclic peptide has the following covalent structure schematic:



wherein AA3 and AA12 are cysteines joined by a disulfide bond, AA5 and AA10 are cysteines joined by a disulfide bond, AA4 is a first hydrophobic amino acid, AA11 is a second hydrophobic acid, AA6 is arginine, AA7 is arginine, AA8 is arginine, and wherein the cyclic peptide has four arginine residues that provide a positively charged content of about 30% at physiological pH.

~~64~~44. The use of claim ~~63~~43, wherein the first hydrophobic amino acid and the second hydrophobic amino acid are leucine or isoleucine.

~~65~~45. The use of claim ~~63~~43 or ~~64~~44, wherein AA1 is glycine.

~~66~~46. The use of one of claims ~~63~~43 to ~~65~~45, wherein AA2 is a third hydrophobic amino acid.

~~67~~47. The use of claim ~~66~~46, wherein the third hydrophobic amino acid is valine or phenylalanine.

~~68~~48. The use of one of claims ~~63~~43 to ~~67~~47, wherein AA9 is a fourth hydrophobic amino acid.

~~69~~49. The cyclic peptide use of claim ~~47~~27, wherein the fourth hydrophobic amino acid is valine or phenylalanine.

~~70~~50. The use of one of claims ~~63~~43 to ~~69~~49, wherein AA13 is glycine.

~~71~~51. The use of one of claims ~~63~~43 to ~~70~~50, wherein AA14 is arginine.

~~72~~52. The use of one of claims ~~63~~43 to ~~71~~51, wherein AA4 is not alanine or serine.

~~73~~53. The use of one of claims ~~63~~43 to ~~72~~52, wherein AA11 is not alanine or serine.

~~74~~54. The use of claim ~~73~~53, wherein the cyclic peptide is MTD12813 (SEQ ID NO. 2).

~~75~~55. The use of one of claims ~~63~~43 to ~~74~~54, wherein the cyclic peptide is an analog of a θ -defensin, and wherein the cyclic peptide provides improved survival when applied systemically in a murine sepsis model relative to the θ -defensin.

~~76~~56. The use of one of claims ~~63-43~~ to ~~75~~55, wherein the cyclic peptide provides a biphasic response on application to a murine model of sepsis, wherein the biphasic response comprises a first phase of recruitment of host effector cells having antimicrobial activity and a second phase of moderation of host inflammatory response.

~~77~~57. The use of one of claims ~~63-43~~ to ~~76~~56, wherein the cyclic peptide has a TACE inhibiting activity.

~~78~~58. The use of one of claims ~~63-43~~ to ~~77~~57, wherein the cyclic peptide suppresses at least one of expression, processing, and release of TNF.

~~79~~59. The use of one of claims ~~63-43~~ to ~~78~~58, wherein the cyclic peptide retains activity following exposure to environmental extremes of temperature, low pH, freezing and/or thawing, and dissolution in a biological matrix.

~~80~~60. The use of claim ~~79~~59, wherein the biological matrix is selected from the group consisting of blood, plasma, and serum.

~~81~~61. The use of one of claims ~~63-43~~ to ~~80~~60, wherein the cyclic peptide is non-immunogenic at doses effective to treat or prevent septic shock.

~~82~~62. The use of one of claims ~~63-43~~ to ~~81~~61, wherein the cyclic peptide activates a host immune system to enhance host clearance of pathogens.

~~83~~63. The use of one of claims ~~63-43~~ to ~~82-62~~ wherein the cyclic peptide is characterized by an activity that modulates inflammation to enhance disease resolution and survival at doses effective to treat or prevent sepsis and/or septic shock.