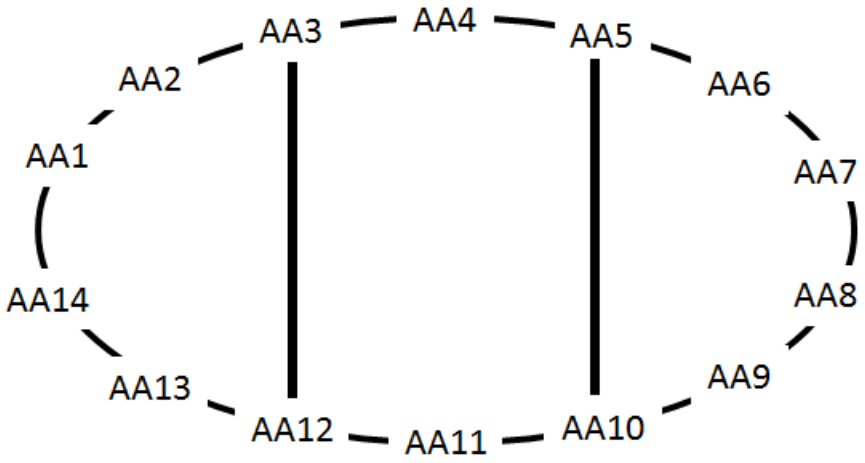
CLAIMS

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 arginine, AA11 is arginine, two of AA6, AA7, and AA8 are arginine, wherein a β turn segment of the cyclic peptide defined by AA6, AA7, AA8, and AA9 does not include more than two adjacent arginines, and wherein the cyclic peptide comprises five or more arginine residues that provide a positively charged content of at least about 36% at physiological pH.

2. The cyclic peptide of claim 1, wherein AA1 is glycine.

3. The cyclic peptide of claim 1 or 2, wherein AA2 is a first hydrophobic amino acid.

4. The cyclic peptide of claim 3, wherein the first hydrophobic amino acid is valine.

5. The cyclic peptide of one of claims 1 to 4, wherein AA9 is a second hydrophobic amino acid.

6. The cyclic peptide of claim 5, wherein the second hydrophobic amino acid is valine.

7. The cyclic peptide of one of claims 1 to 6, wherein AA13 is arginine.

8. The cyclic peptide of one of claims 1 to 7, wherein AA14 is arginine.

9. The cyclic peptide of one of claims 1 to 8, 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 disseminated candidiasis model relative to the θ-defensin.

10. The cyclic peptide of one of claims 1 to 9, wherein the cyclic peptide provides a biphasic response on application to a murine model of disseminated candidiasis, wherein the biphasic response comprises a first phase of mobilization of host effector cells having antifungal activity and a second phase of moderation of host inflammatory response.

11. The cyclic peptide of one of claims 1 to 10, wherein the cyclic peptide has a TACE inhibiting activity.

12. The cyclic peptide of one of claims 1 to 11, wherein the cyclic peptide suppresses at least one of expression, processing, and release of a proinflammatory cytokine.

~~13. The cyclic peptide of one of the claims 1 to 12, 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.~~

~~14. The cyclic peptide of claim 13, wherein the biological matrix is selected from the group consisting of blood, plasma, and serum.~~

~~15. The cyclic peptide of one of the claims 1 to 14, wherein the cyclic peptide is non-immunogenic at doses effective to treat disseminated fungal infection.~~

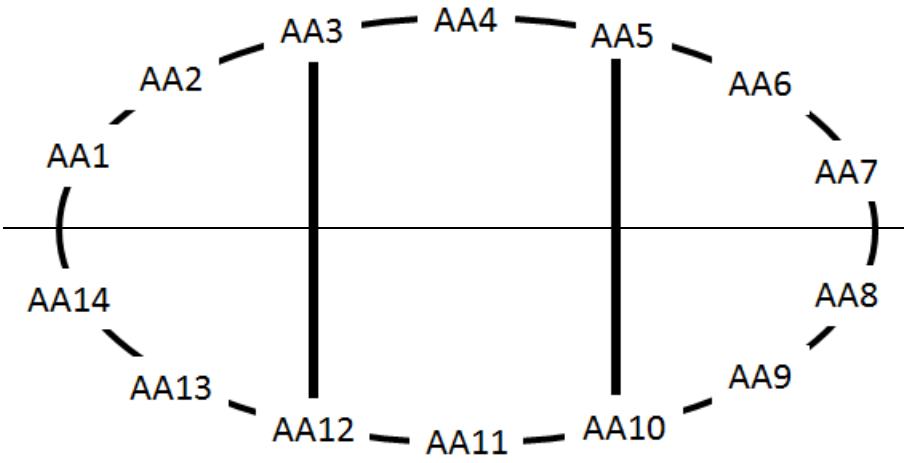
~~16~~13. The cyclic peptide of one of the claims 1 to ~~15~~12, wherein the cyclic peptide activates a host immune system to enhance host clearance of pathogens.

~~17~~14. The cyclic peptide of one of the claims 1 to ~~16~~13, wherein the cyclic peptide is characterized by an activity that modulates inflammation to enhance disease resolution and survival at doses effective to treat disseminated fungal infection.

~~18. A method of treating or preventing disseminated fungal infection and associated septic shock, comprising:~~

~~identifying an individual in need of treatment for disseminated fungal infection; and~~

~~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 arginine, AA11 is arginine, two of AA6, AA7, and AA8 are arginine, wherein a β turn segment of the cyclic peptide defined by AA6, AA7, AA8, and AA9 does not include more than two adjacent arginines, and wherein the cyclic peptide comprises five or more arginine residues that provide a positively charged content of at least about 36% at physiological pH.~~

~~19. The method of claim 18, wherein AA1 is glycine.~~

~~20. The method of claim 18 or 19, wherein AA2 is a first hydrophobic amino acid.~~

~~21. The method of claim 20, wherein the first hydrophobic amino acid is valine.~~

~~22. The method of one of claims 18 to 21, wherein AA9 is a second hydrophobic amino acid.~~

~~23. The method of claim 22, wherein the second hydrophobic amino acid is valine.~~

~~24. The method of one of claims 18 to 23, wherein AA13 is arginine.~~

~~25. The method of one of claims 18 to 24, wherein AA14 is arginine.~~

~~26. The method of one of claims 18 to 25, 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 model of disseminated candidiasis relative to the θ-defensin.~~

~~27. The method of one of claims 18 to 26, wherein the method provides a biphasic response on application to a murine model of disseminated candidiasis, wherein the biphasic response comprises a first phase of mobilization of host effector cells having antifungal activity and a second phase of moderation of host inflammatory response.~~

~~28. The method of one of claims 18 to 27, wherein the method inhibits TACE activity.~~

~~29. The method of one of claims 18 to 28, wherein the method suppresses at least one of expression, processing, and release of a proinflammatory cytokine.~~

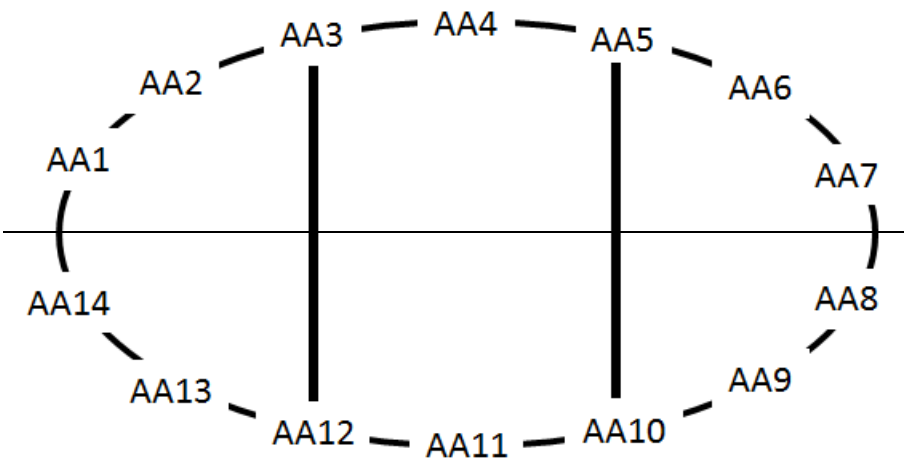
~~30. The method of one of claims 18 to 29, wherein the cyclic peptide retains activity following exposure to environmental extremes of temperature, low pH, freezing and/or thawing, and dissolution in a biological matrix.~~

~~31. The method of claim 30, wherein the biological matrix is selected from the group consisting of blood, plasma, and serum.~~

~~32. The method of one of claims 18 to 31, wherein the cyclic peptide is non-immunogenic at doses effective to treat or prevent disseminated fungal infection.~~

~~33. The method of one of claims 18 to 32, wherein the cyclic peptide activates a host immune system to enhance host clearance of pathogens.~~

~~34~~15. ~~Use of a~~The cyclic peptide of any one of claims 1 to 14 for use in ~~treating or preventing~~the treatment or prevention of disseminated fungal disease and associated sepsis 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 arginine, AA11 is arginine, two of AA6, AA7, and AA8 are arginine, wherein a β turn segment of the cyclic peptide defined by AA6, AA7, AA8, and AA9 does not include more than two adjacent arginines, and wherein the cyclic peptide comprises five or more arginine residues that provide a positively charged content of at least about 36% at physiological pH~~.

~~35. The use of claim 34, wherein AA1 is glycine.~~

~~36. The use of claim 34 or 35, wherein AA2 is a first hydrophobic amino acid.~~

~~37. The use of claim 36, wherein the first hydrophobic amino acid is valine.~~

~~38. The use of one of claims 34 to 37, wherein AA9 is a second hydrophobic amino acid.~~

~~39. The use of claim 38, wherein the second hydrophobic amino acid is valine.~~

~~40. The use of one of claims 34 to 39, wherein AA13 is arginine.~~

~~41. The use of one of claims 34 to 40, wherein AA14 is arginine.~~

~~42. The use of one of claims 34 to 41, 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.~~

~~43. The of one of claims 34 to 42, 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.~~

~~44. The of one of claims 34 to 43, wherein the cyclic peptide has a TACE inhibiting activity.~~

~~45. The of one of claims 34 to 44, wherein the cyclic peptide suppresses at least one of expression, processing, and release of a proinflammatory cytokine.~~

~~46. The use of one of claims 34 to 45, 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.~~

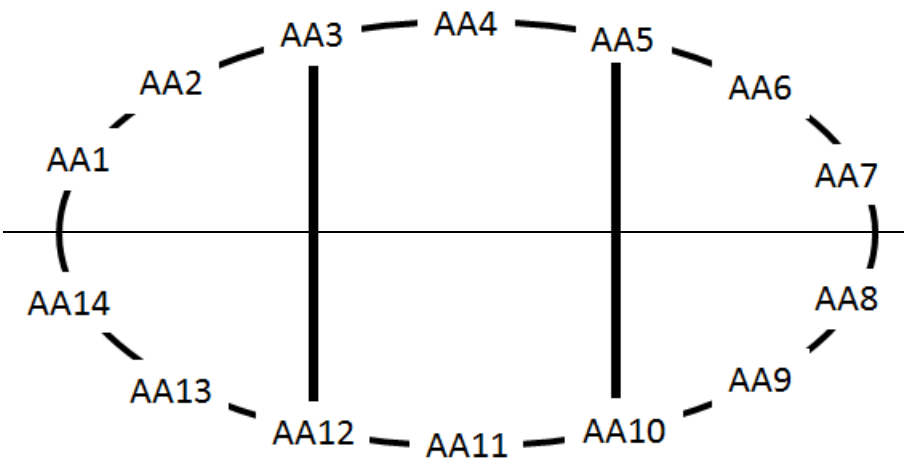
~~47. The use of claim 46, wherein the biological matrix is selected from the group consisting of blood, plasma, and serum.~~

~~48. The use of one of claims 34 to 47, wherein the cyclic peptide is non-immunogenic at doses effective to treat or prevent disseminated fungal disease.~~

~~49. The of one of claims 34 to 48, wherein the cyclic peptide activates a host immune system to enhance host clearance of pathogens.~~

~~50. The of one of claims 34 to 49 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 disseminated fungal disease.~~

~~51~~16. Use of ~~a~~ the cyclic peptide of any one of claims 1 to 14 in the preparation of a medicament ~~that is effective in treating or preventing~~for the treatment or prevention of disseminated fungal disease and associated sepsis 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 arginine, AA11 is arginine, two of AA6, AA7, and AA8 are arginine, wherein a β turn segment of the cyclic peptide defined by AA6, AA7, AA8, and AA9 does not include more than two adjacent arginines, and wherein the cyclic peptide comprises five or more arginine residues that provide a positively charged content of at least about 36% at physiological pH~~.

~~52. The use of claim 51, wherein AA1 is glycine.~~

~~53. The use of claim 51 or 52, wherein AA2 is a first hydrophobic amino acid.~~

~~54. The use of claim 53, wherein the first hydrophobic amino acid is valine.~~

~~55. The use of one of claims 51 to 54, wherein AA9 is a second hydrophobic amino acid.~~

~~56. The use of claim 55, wherein the second hydrophobic amino acid is valine.~~

~~57. The use of one of claims 51 to 56, wherein AA13 is arginine.~~

~~58. The use of one of claims 51 to 57, wherein AA14 is arginine.~~

~~59. The use of one of claims 51 to 58, 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 model of disseminated candidiasis relative to the θ-defensin.~~

~~60. The use of one of claims 51 to 59, wherein the cyclic peptide provides a biphasic response on application to a murine model of disseminated candidiasis, 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.~~

~~61. The use of one of claims 51 to 60, wherein the cyclic peptide has a TACE inhibiting activity.~~

~~62. The use of one of claims 51 to 61, wherein the cyclic peptide suppresses at least one of expression, processing, and release of a proinflammatory cytokine.~~

~~63. The use of one of claims 51 to 62, 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.~~

~~64. The use of claim 63, wherein the biological matrix is selected from the group consisting of blood, plasma, and serum.~~

~~65. The use of one of claims 51 to 64, wherein the cyclic peptide is non-immunogenic at doses effective to treat or prevent disseminated fungal disease.~~

~~66. The use of one of claims 51 to 65, wherein the cyclic peptide activates a host immune system to enhance host clearance of pathogens.~~

~~67. The use of one of claims 51 to 66 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 disseminated fungal disease.~~