

[0047] A number of examples of synthetic (i.e. non-naturally occurring) analogs of RTD-1 are shown in FIGs. 2 to 5. FIG. 2 shows the cyclic structure of the θ -defensin analog MTD12810 (SEQ ID NO. 2). FIG. 3 shows the cyclic structure of the θ -defensin analog MTD12811 (SEQ ID NO. 3). FIG. 4 shows the cyclic structure of the θ -defensin analog MTDI.283 (SEQ ID NO. 4). FIG. 5 shows the cyclic structure of the θ -defensin analog MTD1288 (SEQ ID NO. 5). Each of the exemplary synthetic analogs is a tetradecapeptide that includes 2 pairs of cysteines coupled by disulfide bonds. These disulfide bonds transit the circular primary structure of the synthetic peptides to form a "box" substructure that incorporates additional amino acids. It should be appreciated that these exemplary analogs show varying degrees of sequence identity with RTD-1, and in some instances show conservative amino acid substitutions near and between the "box" defined by cysteines of the synthetic peptide analogs.

[0048] Inventors have prepared and screened a series of θ -defensin analogs that have substantial *in vivo* antifungal activity and provide long term survival of mice in a model of disseminated candidiasis. These effects at surprisingly low concentrations that are well below those at which direct antifungal activity is found for the model pathogen *in vitro*. Without wishing to be bound by theory, inventors believe that the observed antifungal effects are due to modulation of host immune effectors. It should be appreciated that long term survival of disseminated fungal infection requires both management of the infecting organism and of the shock induced by the host response to the infection, either of which can lead to death.

[0049] While examples of activity against disseminated fungal infection are provided, Inventors believe that θ -defensin analogs as described herein can be effective at treating other fungal infections, such as topical fungal infections (e.g. thrush). In addition, Inventors believe that θ -defensin analogs as described herein can be utilized in the treatment of a variety of conditions resulting from dysregulation of the immune or inflammatory response, including chronic conditions. Examples of such chronic conditions include rheumatoid arthritis and inflammatory bowel disease.

[0050] The Inventors note that θ -defensins have been found to have antiviral activity, and believe that θ -defensin analogs of the inventive concept can similarly provide anti-viral activity, and can prove useful in treating viral disease and inflammatory sequelae of viral infection. Such

CLAIMS

1. A cyclic peptide selected from the group consisting of MTD12810 (SEQ ID NO. 2), MTD12811 (SEQ ID NO. 3), and MTD1283 (SEQ ID NO. 4).
2. The cyclic peptide of claim 1, wherein the cyclic peptide is MTD12810 (SEQ ID NO. 2).
3. The cyclic peptide of claim 1, wherein the cyclic peptide is MTD12811 (SEQ ID NO. 3).
4. The cyclic peptide of claim 1, wherein the cyclic peptide is MTD1283 (SEQ ID NO. 4).
5. The cyclic peptide of any one of claims 1 to 4, 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.
6. The cyclic peptide of any one of claims 1 to 4, 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.
7. The cyclic peptide of any one of claims 1 to 4, wherein the cyclic peptide has a TNF α Converting Enzyme (TACE) inhibiting activity.
8. The cyclic peptide of any one of claims 1 to 4, wherein the cyclic peptide suppresses at least one of expression, processing, and release of tumor necrosis factor (TNF).
9. The cyclic peptide of any one of the claims 1 to 4, 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.
10. The cyclic peptide of claim 9, wherein the biological matrix is selected from the group consisting of blood, plasma, and serum.
11. The cyclic peptide of any one of the claims 1 to 4, wherein the cyclic peptide is non-immunogenic at doses effective to treat disseminated fungal infection.

12. The cyclic peptide of any one of the claims 1 to 4, wherein the cyclic peptide activates a host immune system to enhance host clearance of pathogens.
13. The cyclic peptide of any one of the claims 1 to 4, 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.
14. A cyclic peptide for use in the treatment or prevention of disseminated fungal disease and associated septic shock, wherein the cyclic peptide is selected from the group consisting of MTD12810 (SEQ ID NO. 2), MTD12811 (SEQ ID NO. 3), and MTD1283 (SEQ ID NO. 4).
15. The cyclic peptide for use of claim 14, wherein the cyclic peptide is MTD12810 (SEQ ID NO. 2).
16. The cyclic peptide for use of claim 14, wherein the cyclic peptide is MTD12811 (SEQ ID NO. 3).
17. The cyclic peptide for use of claim 14, wherein the cyclic peptide is MTD1283 (SEQ ID NO. 4).
18. The cyclic peptide for use of any one of claims 14 to 17, 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.
19. The cyclic peptide for use of any one of claims 14 to 17, 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.
20. The cyclic peptide for use of any one of claims 14 to 17, wherein the cyclic peptide has a TACE inhibiting activity.
21. The cyclic peptide for use of any one of claims 14 to 17, wherein the cyclic peptide suppresses at least one of expression, processing, and release of a proinflammatory cytokine.

22. The cyclic peptide for use of any one of claims 14 to 17, 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.
23. The cyclic peptide for use of claim 22, wherein the biological matrix is selected from the group consisting of blood, plasma, and serum.
24. The cyclic peptide for use of any one of claims 14 to 17, wherein the cyclic peptide is non-immunogenic at doses effective to treat or prevent disseminated fungal disease.
25. The cyclic peptide for use of any one of claims 14 to 17, wherein the cyclic peptide activates a host immune system to enhance host clearance of pathogens.
26. The cyclic peptide for use of any one of claims 14 to 17, 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.
27. Use of a cyclic peptide in the manufacture of a medicament for the treatment or prevention of disseminated fungal disease and associated septic shock, wherein the cyclic peptide is selected from the group consisting of MTD12810 (SEQ ID NO. 2), MTD12811 (SEQ ID NO. 3), and MTD1283 (SEQ ID NO. 4).
28. The use of claim 27, wherein the cyclic peptide is MTD12810 (SEQ ID NO. 2).
29. The use of claim 27, wherein the cyclic peptide is MTD12811 (SEQ ID NO. 3).
30. The use of claim 27, wherein the cyclic peptide is MTD1283 (SEQ ID NO. 4).
31. The use of any one of claims 27 to 30, 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.
32. The use of any one of claims 27 to 30, 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.

33. The use of any one of claims 27 to 30, wherein the cyclic peptide has a TACE inhibiting activity.

34. The use of any one of claims 27 to 30, wherein the cyclic peptide suppresses at least one of expression, processing, and release of a proinflammatory cytokine.

35. The use of any one of claims 27 to 30, 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.

36. The use of claim 35, wherein the biological matrix is selected from the group consisting of blood, plasma, and serum.

37. The use of any one of claims 27 to 30, wherein the cyclic peptide is non-immunogenic at doses effective to treat or prevent disseminated fungal disease.

38. The use of any one of claims 27 to 30, wherein the cyclic peptide activates a host immune system to enhance host clearance of pathogens.

39. The use of any one of claims 27 to 30, 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.