that these compounds were also shown to be effective against certain fungal organisms as illustrated for Candida albicans. US Patent No. 9,017,730 indicates that certain microbial organisms (e.g., P. acnes) may be less sensitive to certain copolypeptides than other microorganisms (e.g., S. aureus). US Patent No. 9,017,730 indicates that certain solution phase copolypeptides demonstrated antiviral activity against Influenza A virus, with RH/K (partially guanylated lysine) diblock copolypeptide being particularly active.

[0005] U.S. Patent No. 9,446,090 describes synthetic cationic polypeptide(s) along with mutually water-miscible mixtures that contain such a polypeptide and a second pharmaceutically acceptable polymer. Specific examples describe antimicrobial activity against certain bacteria using particular mixtures of synthetic cationic polypeptide(s) with second polymers such as polyethylene glycol (PEG), hydroxyethylcellulose (HEC), and Poloxamer 407.

[0006] PCT Publication WO 2018/187617 describes the development of cationic antimicrobial pharmaceutical compositions and methods of use that allow local applications *in vivo* of doses that provide antimicrobial effectiveness with low risk of local tissue toxicities and/or low risk of systemic / distant organ toxicities. PCT Publication WO 2018/187617 indicates that various embodiments of the cationic antimicrobial pharmaceutical compositions have excellent antimicrobial and safety profiles as demonstrated by successful intraperitoneal application.

[0007] While PCT Publication WO 2018/187617 and U.S. Patent Nos. 9,017,730 and 9,446,090 describe significant advances in the art, a number of challenges remain, particularly with respect to developing pharmaceutically acceptable preparations of locally applied cationic antimicrobials for treating viral infections, such as Coronavirus infections.

SUMMARY

[0008] Antimicrobial pharmaceutical compositions have now been developed that have antiviral activity in addition to their antimicrobial activity. Methods of using such compositions to treat viral infections have now been developed, including treatments for Coronavirus infections. In various examples, the antimicrobial pharmaceutical compositions have surprising activity against both Coronavirus and Influenza A virus infections.

[0009] An example provides a method of treating a viral infection, comprising:

administering an effective amount of an antimicrobial pharmaceutical composition to a subject in need thereof, wherein:

the antimicrobial pharmaceutical composition comprises:

an aqueous carrier; and

an antimicrobial synthetic cationic polypeptide(s) dispersed in the aqueous carrier; and

the antimicrobial synthetic cationic polypeptide(s) comprises a plurality of positively charged amino acid units at neutral pH.

[0009a] An aspect provides use of:

an aqueous carrier; and

an antimicrobial synthetic cationic polypeptide(s) dispersed in the aqueous carrier;

in the manufacture of an antimicrobial pharmaceutical composition for the treatment of a viral infection in a subject, wherein

the antimicrobial synthetic cationic polypeptide(s) comprises a plurality of positively charged amino acid units at neutral pH;

the antimicrobial synthetic cationic polypeptide(s) comprises a plurality of hydrophobic amino acid units; and

the antimicrobial synthetic cationic polypeptide(s) comprises a sequence arrangement of hydrophobic amino acid units and positively charged amino acid units that is configured to promote self-assembly of the antimicrobial synthetic cationic polypeptide(s) into multimeric structures in aqueous media.

[0010] These and other examples are described in greater detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1. Dynamic viscosity, surface tension, and interfacial tension (against n-hexane) of Composition A and Composition B.

[0012] Figure 2. Activity of Composition A at various concentrations against S. aureus, S. epidermidis, P. aeruginosa, and C. albicans in a standard 60-minute time-kill assay. Data are presented as log CFU reduction.

[0013] Figure 3. Activity of Composition A at 10 and 100 µg/mL against two S. aureus strains, two MRSA strains, vancomycin-resistant Enterococcus (VRE), and S. pyogenes in a standard 60-minute time-kill assay. Data are presented as log CFU reduction.

[0014] Figure 4. Activity of Composition A at 10 and 100 µg/mL against A. baumannii, pan-resistant A. baumannii, extended spectrum beta-lactamase (ESBL)-positive E. coli, ESBL and Klebsiella pneumoniae carbapenemase-positive K. pneumoniae, P. mirabilis, and S. marcescens in a standard 60-minute time-kill assay. Data are presented as log CFU reduction.

[0015] Figure 5. Activity of Composition A at 10 and 100 µg/mL against P. aeruginosa, multidrug-resistant (MDR) P. aeruginosa, C. koseri, E. aerogenes, S. maltophilia, B. fragilis, and MDR B. fragilis in a standard 60-minute time-kill assay. Data are presented as log CFU reduction.

WHAT IS CLAIMED IS:

1. Use of:

an aqueous carrier; and

an antimicrobial synthetic cationic polypeptide(s) dispersed in the aqueous carrier;

in the manufacture of an antimicrobial pharmaceutical composition for the treatment of a viral infection in a subject, wherein

the antimicrobial synthetic cationic polypeptide(s) comprises a plurality of positively charged amino acid units at neutral pH;

the antimicrobial synthetic cationic polypeptide(s) comprises a plurality of hydrophobic amino acid units; and

the antimicrobial synthetic cationic polypeptide(s) comprises a sequence arrangement of hydrophobic amino acid units and positively charged amino acid units that is configured to promote self-assembly of the antimicrobial synthetic cationic polypeptide(s) into multimeric structures in aqueous media.

2. The use of claim 1, wherein the multimeric structures formed in aqueous media are selected from the group consisting of multimers in solution, micelles, sheets, vesicles, and fibrils.

3. The use of claim 1 or 2, wherein the multimeric structures can be measured by a critical aggregation concentration less than that of a synthetic cationic polypeptide of the same composition with a statistical distribution of amino acids.

4. The use of any one of claims 1 to 3, wherein the antimicrobial synthetic cationic polypeptide(s) self-assembles into multimeric structures, as measured by a critical aggregation concentration that is below 1000 μg/mL at room temperature and/or 37°C in deionized water.

5. The use of any one of claims 1 to 4, wherein the viral infection is a Coronavirus infection.

6. The use of claim 5, wherein the Coronavirus infection is caused by an α-coronavirus.

7. The use of claim 5, wherein the Coronavirus infection is caused by a β-coronavirus.

8. The use of any one of claims 5 to 7, wherein the Coronavirus infection is caused by a coronavirus selected from CoV 229E, CoV NL63, CoV OC43, CoV HKU1, MERS-CoV, SARS-CoV, and SARS-CoV-2.

9. The use of claim 8, wherein the Coronavirus infection is caused by SARS-CoV-2.

10. The use of any one of claims 1 to 9, wherein the subject is in need of treatment for multiple virus infections.

11. The use of claim 10, wherein one of the multiple virus infections is an influenza A virus infection.

12. The use of any one of claims 1 to 10, wherein the viral infection is not an influenza A virus infection.

13. The use of any one of claims 1 to 12, wherein the antimicrobial pharmaceutical composition is to be administered to the subject by a pulmonary route.

14. The use of claim 13, wherein the antimicrobial pharmaceutical composition is to be administered to the subject intranasally and/or by inhalation.

15. The use of any one of claims 1 to 14, wherein the antimicrobial pharmaceutical composition is to be administered to an oral cavity of the subject.

16. The use of any one of claims 1 to 12, wherein the antimicrobial pharmaceutical composition is to be administered to a vaginal cavity of the subject.

17. The use of any one of claims 1 to 16, wherein the antimicrobial pharmaceutical composition is to be administered to the subject prophylactically.

18. The use of any one of claims 1 to 17, wherein the antimicrobial pharmaceutical composition is to be administered to tissues capable of supporting viral infection and growth to physically and/or electrostatically prevent access by viral particles.

19. The use of any one of claims 5 to 10 or 12 to 18, wherein at least one second Coronavirus treatment is to be administered to the subject.

20. The use of any one of claims 1 to 19, wherein the subject is a non-human primate.

21. The use of any one of claims 1 to 19, wherein the subject is a human.

22. The use of claim 21, wherein the human subject is to be identified on the basis that the subject has, or is at risk of having, one or more risk factors selected from: a positive

test for the Coronavirus infection, obesity, diabetes, an advanced age, a cancer, a reduced respiratory function, a reduced cardiovascular function, a reduced kidney function, a nutritional or vitamin deficiency (e.g., vitamin D deficiency), and a reduced immune response function.

23. The use of claim 21 or 22, wherein the human subject is to be identified on the basis that the human subject has tested positive for the Coronavirus infection.

24. The use of any one of claims 21 to 23, wherein the human subject has COVID-19.

25. The use of any one of claims 1 to 24, wherein the antimicrobial synthetic cationic polypeptide(s) is dispersed in the aqueous carrier at a concentration in the range of about 0.01% to about 5%, by weight based on total weight of the antimicrobial pharmaceutical composition.

26. The use of any one of claims 1 to 25, wherein the antimicrobial synthetic cationic polypeptide(s) at a concentration of 2 wt% in deionized water has a viscosity at room temperature and/or 37°C of 2 centistokes (cSt) or greater.

27. The use of any one of claims 1 to 26, wherein the aqueous carrier, containing the antimicrobial synthetic cationic polypeptide(s) at 2 wt%, has a viscosity at room temperature and/or 37°C that is greater than that of the aqueous carrier containing albumin at 2 wt% in place of the antimicrobial synthetic cationic polypeptide(s).

28. The use of any one of claims 1 to 27, wherein the aqueous carrier, containing the antimicrobial synthetic cationic polypeptide(s) at 2 wt%, has a viscosity at room temperature and/or 37°C that is at least about 5 cSt.

29. The use of any one of claims 1 to 28, wherein the aqueous carrier, containing the antimicrobial synthetic cationic polypeptide(s) at 2 wt%, has a viscosity at room temperature and/or 37°C that is at least about 10 cSt.

30. The use of any one of claims 1 to 29, wherein the aqueous carrier, containing the antimicrobial synthetic cationic polypeptide(s) at 2 wt%, has a viscosity at room temperature and/or 37°C that is at least about 25 cSt.

31. The use of any one of claims 1 to 30, wherein the aqueous carrier, containing the antimicrobial synthetic cationic polypeptide(s) at 2 wt%, has a viscosity at room temperature and/or 37°C that is at least about 50 cSt.

32. The use of any one of claims 1 to 31, wherein the antimicrobial pharmaceutical composition has a low toxicity after being infused into the peritoneal cavity of a plurality of healthy, young adult mice at a dose of 50 mg/kg, as measured by a mouse survival rate of 80% or greater at 72 hours.

33. The use of any one of claims 1 to 32, wherein the plurality of positively charged amino acid units at neutral pH is at least 5.

34. The use of any one of claims 1 to 33, wherein the aqueous carrier is water or an aqueous solution of a pharmaceutically acceptable salt.

35. The use of any one of claims 1 to 34, wherein the aqueous carrier further comprises a non-ionic additive(s).

36. The use of claim 35, wherein the non-ionic additive(s) is present in an amount effective to increase the osmotic concentration of the antimicrobial pharmaceutical composition to a value that is at least 10% greater than that of the antimicrobial pharmaceutical composition without said additive(s).

37. The use of claim 35 or 36, wherein the non-ionic additive is selected from the group consisting of dextrose, mannitol, glycerol, xylitol, sorbitol, surfactant(s), and combinations thereof.

38. The use of any one of claims 1 to 37, wherein the aqueous carrier further comprises an additive in an amount that increases the viscosity of the antimicrobial pharmaceutical composition.

39. The use of any one of claims 1 to 37, wherein the aqueous carrier further comprises an additive in an amount that decreases the viscosity of the antimicrobial pharmaceutical composition.

40. The use of any one of claims 1 to 39, wherein the antimicrobial pharmaceutical composition is sterilized by a sterilization technique(s) configured to achieve a sterilized antimicrobial pharmaceutical composition with the antimicrobial synthetic cationic polypeptide(s) having a weight average molecular weight comparable to that of the antimicrobial synthetic cationic polypeptide(s) of the antimicrobial pharmaceutical composition without sterilization by said sterilization technique(s).

41. The use of any one of claims 1 to 40, wherein the antimicrobial pharmaceutical composition is sterilized by a sterilization technique(s) configured to achieve

a sterilized antimicrobial pharmaceutical composition with the antimicrobial synthetic cationic polypeptide(s) having a weight average molecular weight and dispersity comparable to that of the antimicrobial synthetic cationic polypeptide(s) of the antimicrobial pharmaceutical composition without sterilization by said sterilization technique(s).

42. The use of any one of claims 1 to 41, wherein the antimicrobial pharmaceutical composition is sterilized by a sterilization technique(s) configured to achieve a sterilized antimicrobial pharmaceutical composition having a viscosity level at room temperature and/or 37°C that is comparable to that of the antimicrobial pharmaceutical composition without sterilization by said sterilization technique(s).

43. The use of any one of claims 40 to 42, wherein the viscosity of the sterilized antimicrobial pharmaceutical composition at room temperature and/or 37°C is in the range of 20% to 200% of the viscosity of an otherwise comparable unsterilized antimicrobial pharmaceutical composition.

44. The use of any one of claims 1 to 43, wherein the antimicrobial pharmaceutical composition has a microbiocidal activity that is comparable to that of the otherwise comparable unsterilized antimicrobial pharmaceutical composition, wherein the microbiocidal activity is determined by a 60 minute time-kill assay against at least one bacteria selected from the group consisting of *S. aureus*, *S. epidermidis*, *P. aeruginosa*, and *E. coli*.

45. The use of any one of claims 1 to 44, wherein the plurality of hydrophobic amino acid units comprises at least 5 hydrophobic amino acid units selected from leucine (L), isoleucine (l), valine (V), phenylalanine (F) or alanine (A).

46. The use of claim 45, wherein the plurality of hydrophobic amino acid units comprises at least 10 hydrophobic amino acid units selected from leucine (L), isoleucine (l), valine (V), phenylalanine (F) or alanine (A).

47. The use of any one of claims 45 to 46, wherein the plurality of hydrophobic amino acid units comprises at least 15 hydrophobic amino acid units selected from leucine (L), isoleucine (l), valine (V), phenylalanine (F) or alanine (A).

48. The use of any one of claims 45 to 47, wherein the hydrophobic amino acid units comprise leucine units.

49. The use of any one of claims 1 to 48, wherein the plurality of positively charged amino acid units comprises lysine units.

50. The use of any one of claims 1 to 49, wherein the antimicrobial synthetic cationic polypeptide(s) is a block copolypeptide that comprises hydrophobic leucine units and positively charged lysine units.

51. The use of any one of claims 1 to 50, wherein the antimicrobial synthetic cationic polypeptide(s) comprises at least 40 amino acid units.

52. The use of any one of claims 1 to 51, wherein the antimicrobial synthetic cationic polypeptide(s), in deionized water at room temperature and/or 37°C at a concentration of 3 wt%, forms a self-supporting hydrogel.

53. The use of any one of claims 1 to 51, wherein the antimicrobial synthetic cationic polypeptide(s) displays surfactant activity in deionized water at room temperature and/or 37°C at a concentration of 1 wt%, as measured by a decrease in surface tension of at least 10% as compared to deionized water alone.

54. The use of any one of claims 1 to 53, wherein the antimicrobial pharmaceutical composition further comprises an anti-inflammatory compound.

55. The use of claim 54, wherein the anti-inflammatory compound is selected from the group consisting of a corticosteroid, a histamine inhibitor and a cytokine inhibitor.