

Claims

1. A synergistic combination comprising a quorum-sensing inhibitor and/or a postbiotic metabolite and an antibiotic.
2. The synergistic combination of claim 1, wherein the quorum-sensing inhibitor and/or postbiotic metabolite comprises a peptide, small molecule, lipid, sugar, or a combination thereof.
3. The synergistic combination of claim 2, wherein the peptide comprises or consists of one or more of the following amino acid sequences: XX[L or I]PPK, wherein X designates a hydrophobic amino acid; X₁X₂[L or I]PPK, wherein X₁ is selected from N, C, Q, M, S, and T and wherein X₂ is selected from A, I, L, and V; MALPPK; CVLPPK; HLLPLP; LKPTPEGD; YPVEPF; YPPGGP; YPPG; NQPY; LPVPK; ALPK; EVLNCLALPK; LPLP; HLLPLPL; YVPEPF; KYVPEPF; EMPFKPYPEPF; and variants thereof altered by deletion, substitution or insertion wherein the activity of the molecules is not substantially reduced, including peptides and/or variants thereof with post-translational modifications including glycosylation.
4. The synergistic combination of any one of claims 1 to 3, wherein the quorum-sensing inhibitor and/or postbiotic metabolite is a peptide and comprises or consists of 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acid residues, such as from 2, 3, 4, 5, 6, 7, 8, or 9 to about 3, 4, 5, 6, 7, 8, 9, or 10 amino residues.
5. The synergistic combination of any one of claims 1 to 4, wherein the quorum-sensing inhibitor and/or postbiotic metabolite is less than about 4000, 3900, 3800, 3700, 3600, 3500, 3400, 3300, 3200, 3100, 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, or 500 Da in size, such as less than about 3000, 2000, or 1000 Da in size.
6. The synergistic combination of any one of claims 1 to 5, wherein the quorum-sensing inhibitor and/or postbiotic metabolite is in a probiotic bacterial culture fraction, such as a supernatant.
7. The synergistic combination of claim 6, wherein the probiotic bacterial culture fraction is a cell-free spent medium (CSFM), which is optionally concentrated in liquid or dry form (e.g. by lyophilization and/or spray-drying).
8. The synergistic combination of claim 7, wherein the CSFM has a molecular weight cut-off of about 4000, 3900, 3800, 3700, 3600, 3500, 3400, 3300, 3200, 3100, 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, or 500 Da in size, such as about 3000, 2000, or 1000 Da.
9. The synergistic combination of any one of claims 1 to 8, wherein the antibiotic is an aminoglycoside, a bacitracin, a beta-lactam antibiotic, a cephalosporin, a chloramphenicol, a glycopeptide, a macrolides, a lincosamide, a penicillin, a quinolone, a rifampin, a glycopeptide, a tetracycline, a trimethoprim, a sulfonamides, or a combination thereof.
10. The synergistic combination of claim 9, wherein the antibiotic is a β -lactam antibiotic, such as cefoxitin.

11. The synergistic combination of any one of claims 1 to 10, wherein the quorum-sensing inhibitor and/or postbiotic metabolite is derived from the culture medium or supernatant of probiotic bacteria of the genera *Aerococcus*, *Bacillus*, *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Enterococcus*, *Fusobacterium*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Melissococcus*, *Micrococcus*, *Pediococcus*,
5 *Peptostrepococcus*, *Propionibacterium*, *Staphylococcus*, *Streptococcus*, *Weissella*, or combinations thereof.
12. The synergistic combination of claim 11, wherein the quorum-sensing inhibitor and/or postbiotic metabolite is derived from *Lactobacillus*, such as *Lactobacillus acidophilus*, such as *Lactobacillus acidophilus* (DSM13241) and/or wherein the quorum-sensing inhibitor and/or postbiotic metabolite is
10 derived from *Enterococcus*, such as *Enterococcus faecium*.
13. The synergistic combination of any one of claims 1 to 12, further comprising a probiotic.
14. The synergistic combination of claim 13, wherein the probiotic is of the genera *Aerococcus*, *Bacillus*, *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Enterococcus*, *Fusobacterium*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Melissococcus*, *Micrococcus*, *Pediococcus*, *Peptostrepococcus*,
15 *Propionibacterium*, *Staphylococcus*, *Streptococcus*, *Weissella*, or combinations thereof.
15. The synergistic combination of claim 14, wherein the probiotic is *Lactobacillus*, such as *Lactobacillus acidophilus*, such as *Lactobacillus acidophilus* (DSM13241) and/or *Enterococcus*, such as *Enterococcus faecium*.
16. The synergistic combination of any one of claims 13 to 15, wherein the probiotic is live.
- 20 17. The synergistic combination of any one of claims 13 to 16, wherein the probiotic is present in an amount of about 100 million to about 500 million CFU per dose, such as about 200 million CFU per dose.
18. A composition comprising the synergistic combination of any one of claims 1 to 17.
19. A method for:
- (a) resensitizing an antibiotic-resistant infection to an antibiotic, the method comprising
25 administering a quorum-sensing inhibitor and/or a postbiotic metabolite to a subject afflicted with the infection;
- (b) decreasing resistance of a bacterial infection to hydrogen peroxide cytotoxicity, the method comprising administering a quorum-sensing inhibitor and/or a postbiotic metabolite to a subject afflicted with the infection;
- 30 (c) treating and/or preventing diarrhea in a subject, the method comprising administering a quorum-sensing inhibitor and/or a postbiotic metabolite and an antibiotic to the subject;
- (d) treating MRSA or MRSP, the method comprising administering a quorum-sensing inhibitor and/or a postbiotic metabolite and an antibiotic to a subject afflicted with MRSA or MRSP;
- (e) reducing carotenoid synthesis in bacteria, the method comprising administering a quorum-
35 sensing inhibitor and/or a postbiotic metabolite to the bacteria; and/or

(Ff) sensitizing bacteria to oxidant killing, the method comprising administering a quorum-sensing inhibitor and/or a postbiotic metabolite to the bacteria.

20. The method of claim 19, wherein the antibiotic is an aminoglycoside, a bacitracin, a beta-lactam antibiotic, a cephalosporin, a chloramphenicol, a glycopeptide, a macrolides, a lincosamide, a penicillin, a quinolone, a rifampin, a glycopeptide, a tetracycline, a trimethoprim, a sulfonamides, or a combination thereof.
21. The method of claim 20, wherein the antibiotic is a β -lactam antibiotic, such as cefoxitin.
22. The method of any one of claims 19 to 21, wherein the quorum-sensing inhibitor and/or postbiotic metabolite comprises a peptide, small molecule, lipid, sugar, or a combination thereof.
23. The method of claim 22, wherein the peptide comprises or consists of one or more of the following amino acid sequences: XX[L or I]PPK, wherein X designates a hydrophobic amino acid; X₁X₂[L or I]PPK, wherein X₁ is selected from N, C, Q, M, S, and T and wherein X₂ is selected from A, I, L, and V; MALPPK; CVLPPK; HLLPLP; LKPTPEGD; YPVEPF; YPPGGP; YPPG; NQPY; LPVVK; ALPK; EVLNCLALPK; LPLP; HLLPLPL; YVPEPF; KYVPEPF; EMPFKPYPEPF; and variants thereof altered by deletion, substitution or insertion wherein the activity of the molecules is not substantially reduced, including peptides and/or variants thereof with post-translational modifications including glycosylation.
24. The method of any one of claims 19 to 23, wherein the quorum-sensing inhibitor and/or postbiotic metabolite is a peptide and comprises or consists of 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acid residues, such as from 2, 3, 4, 5, 6, 7, 8, or 9 to about 3, 4, 5, 6, 7, 8, 9, or 10 amino residues.
25. The method of any one of claims 19 to 24, wherein the quorum-sensing inhibitor and/or postbiotic metabolite is less than about 4000, 3900, 3800, 3700, 3600, 3500, 3400, 3300, 3200, 3100, 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, or 500 Da in size, such as less than about 3000, 2000, or 1000 Da in size.
26. The method of any one of claims 19 to 25, wherein the quorum-sensing inhibitor and/or postbiotic metabolite is in a probiotic bacterial culture fraction, such as a supernatant.
27. The method of claim 26, wherein the probiotic bacterial culture fraction is a cell-free spent medium (CSFM), which is optionally concentrated in liquid or dry form (e.g. by lyophilization and/or spray-drying).
28. The method of claim 27, wherein the CSFM has a molecular weight cut-off of about 4000, 3900, 3800, 3700, 3600, 3500, 3400, 3300, 3200, 3100, 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, or 500 Da in size, such as about 3000, 2000, or 1000 Da.
29. The method of any one of claims 19 to 28, wherein the quorum-sensing inhibitor and/or postbiotic metabolite is derived from the culture medium or supernatant of probiotic bacteria of the genera *Aerococcus*, *Bacillus*, *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Enterococcus*, *Fusobacterium*,

Lactobacillus, *Lactococcus*, *Leuconostoc*, *Melissococcus*, *Micrococcus*, *Pediococcus*, *Peptostrepococcus*, *Propionibacterium*, *Staphylococcus*, *Streptococcus*, *Weissella*, or combinations thereof.

30. The method of claim 29, wherein the quorum-sensing inhibitor and/or postbiotic metabolite is derived from *Lactobacillus*, such as *Lactobacillus acidophilus*, such as *Lactobacillus acidophilus* (DSM13241) and/or wherein the quorum-sensing inhibitor and/or postbiotic metabolite is derived from *Enterococcus*, such as *Enterococcus faecium*.
31. The method of any one of claims 19 to 30, further comprising administering a probiotic to the subject.
32. The method of claim 31, wherein the probiotic is of the genera *Aerococcus*, *Bacillus*, *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Enterococcus*, *Fusobacterium*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Melissococcus*, *Micrococcus*, *Pediococcus*, *Peptostrepococcus*, *Propionibacterium*, *Staphylococcus*, *Streptococcus*, *Weissella*, or combinations thereof.
33. The method of claim 32, wherein the probiotic is *Lactobacillus*, such as *Lactobacillus acidophilus*, such as *Lactobacillus acidophilus* (DSM13241) and/or wherein the quorum-sensing inhibitor and/or postbiotic metabolite is derived from *Enterococcus*, such as *Enterococcus faecium*.
34. The method of any one of claims 31 to 33, wherein the probiotic is live.
35. The method of any one of claims 31 to 34, wherein the probiotic is present in an amount of about 100 million to about 500 million CFU per dose, such as about 200 million CFU per dose.
36. The method of any one of claims 19 to 35, wherein the subject is a pet, such as a dog.
37. The method of any one of claims 19 to 35, wherein the subject is a farm animal, such as swine or poultry.
38. The method of any one of claims 19 to 35, wherein the subject is a human.
39. The method of any one of claims 19 to 38, wherein the quorum-sensing inhibitor and/or postbiotic metabolite and the antibiotic act synergistically.
40. A tablet or capsule comprising the synergistic combination of any one of claims 1 to 17 or the composition of claim 18.
41. Use of the synergistic combination of any one of claims 1 to 17 or the composition of claim 18 in the method of any one of claims 19 to 39.
42. The synergistic combination of any one of claims 1 to 17 or the composition of claim 18 for use in the method of any one of claims 19 to 39.