Claims

1. A method of treating or preventing a Streptococcus pneumoniae infection wherein the Streptococcus pneumoniae infection occurs in an environment where the free concentration of Zn^{2+} and/or Mn^{2+} is sufficiently low to upregulate the expression of at least one PhtX protein in the Streptococcus pneumoniae; comprising the step of administering a pharmaceutically effective amount of the PhtX protein to a human patient.

2. The method of treatment of claim 1 wherein the PhtX protein is selected from the group consisting of PhtA, PhtB, PhtD and PhtE.

3. The method of claim 1 wherein the PhtX protein is PhtD.

4. The method of any one of claims 1-3 wherein the *Streptococcus pneumoniae* infection occurs in blood.

5. The method of claim 4 wherein the free concentration of Zn2+ in the blood is less than 10nM, 1 nM, 100pM or 10pM as measured from blood serum.

6. The method of claim 4 wherein the bound and free concentration of Zn2+ in the blood is less than 2 or 1 mg/l or less than 20µM as measured from blood serum.

7. The method of claim 4 wherein the free concentration of Mn2+ in the blood is less than 10nM, 1 nM, 100pM or 10pM as measured from blood serum.

8. The method of claim 4 wherein the bound and free concentration of Mn2+ in the blood is less than 2 or 1 mg/l or less than 20µM as measured from blood serum.

9. The method of any one of claim 1 -3 wherein the Streptococcus *pneumoniae* infection occurs in a lung.

10. The method of claim 9 wherein the free concentration of Zn2+ in the lung is less than 300, 200, 100, 50 or 10µg kg as measured from a bronchial lavage.

11. The method of claim 9 wherein the free concentration of Mn2+ in the lung is less than 300, 200, 100, 50 or 10µg kg as measured from a bronchial lavage.

12. The method of claim 9 wherein the concentration of Zn2+ in the lung tissue is less than 20, 15, 10, 5, 2 or 1 µg/g or 300, 200, 150, 100, 50, 20 or 10µM as measured from lung tissue.

13. The method of any one of claims 1 -3 wherein the *Streptococcus pneumoniae* infection occurs in a middle ear.

14. The method of claim 13 wherein the concentration of Zn2+ in the middle ear is less than 300, 200, 150, 100, 50, 20, 10, 5, 2, 1 , 0.5, 0.2 or 0.1 µM.

15. The method of claim 13 wherein the concentration of Mn2+ in the middle ear is less than 300, 200, 150, 100, 50, 20, 10, 5, 2, 1 , 0.5, 0.2 or 0.1 µM.

16. The method of any one of claims 1 -3 wherein the *Streptococcus pneumoniae* infection occurs in the meninges.

17. The method of claim 16 wherein the concentration of Zn2+ in the cerebrospinal fluid is less than 1 .5, 1, 0.75, 0.5, 0.25 or 0.1 μM or less than 100, 75, 50, , 25, or 10μg/L.

18. The method of claim 16 or 17 wherein the concentration of Mn2+ in the cerebrospinal fluid is less than 2.5, 2, 1 .5, 1 or 0.5μg/L or less than 50, 25, 10 or 5nM.

19. The method of any preceding claim wherein the human patient has decreased levels of Zn2+ and/or Mn2+ as measured by bronchial lavage and/or blood serum test.

20. The method of any preceding claim wherein the human patient is Zn2+ and/or Mn2+ deficient.

21. The method of any preceding claim wherein the human patient is stressed.

22. The method of any preceding claim wherein the human patient has multiple bacterial infections.

23. The method of any preceding claim wherein the human patient has a chronic bacterial infection.

24. The method of claim 23 wherein the chronic bacterial infection is pneumococcal infection.

~~25. The method of any preceding claim wherein the *Streptococcus pneumoniae* infection is scepticaemia, bacteraemia, meningitis, otitis media or pneumonia.~~

Claims

~~26~~1. An immunogenic composition comprising a pharmaceutically effective amount of an isolated PhtX protein for use in the treatment or prevention of a Streptococcus pneumoniae infection wherein the Streptococcus pneumoniae infection occurs in the blood, lung, a compartment of the ear or in the meninges of a human patient in an environment where the free concentration of Zn^{2+} and/or Mn^{2+} is sufficiently low to upregulate the expression of at least one PhtX protein in the *Streptococcus pneumoniae*.

~~27~~2. The immunogenic composition of claim ~~26~~ 1 wherein the PhtX protein is selected from the group consisting of PhtA, PhtB, PhtD and PhtE.

~~28~~3. The immunogenic composition of claim ~~26~~ 1 wherein the PhtX protein is PhtD.

~~29~~4. The immunogenic composition of any one of claims ~~26~~1-~~28~~ 3 wherein the *Streptococcus pneumoniae* infection occurs in blood.

~~30~~5. The immunogenic composition of claim ~~29~~ 4 wherein the free concentration of Zn2+ in the blood is less than 10nM, 1 nM, 100pM or 10pM as measured from blood serum.

~~31~~6. The immunogenic composition of claim ~~29~~ 4 wherein the bound and free concentration of Zn2+ in the blood is less than 2 or 1 mg/l or less than 20µM as measured from blood serum.

~~32~~7. The immunogenic composition of claim ~~29~~ 4 wherein the free concentration of Mn2+ in the blood is less than 10nM, 1 nM, 100pM or 10pM as measured from blood serum.

~~33~~8. The immunogenic composition of claim ~~29~~ 4 wherein the bound and free concentration of Mn2+ in the blood is less than 2 or 1 mg/l or less than 20µM as measured from blood serum.

~~34~~9. The immunogenic composition of any one of claims ~~26~~1-~~33~~ 8 wherein the *Streptococcus pneumoniae* infection occurs in a lung.

~~35~~10. The immunogenic composition of claim ~~34~~ 9 wherein the concentration of Zn2+ in the lung is less than 300, 200, 100, 50 or 10µg/kg as measured from a bronchial lavage.

~~36~~11. The immunogenic composition of claim ~~34~~ 9 wherein the concentration of Zn2+ in the lung tissue is less than 20, 15, 10, 5, 2 or 1µg/g or 300, 200, 150, 100, 50, 20 or 10µM as measured from lung tissue

~~37~~12. The immunogenic composition of claim ~~34~~ 9 wherein the concentration of Mn2+ in the lung is less than 300, 200, 100, 50 or 10µg/kg as measured from a bronchial lavage.

~~38~~13. The immunogenic composition of any one of claims ~~26~~1-~~30~~ 5 wherein the *Streptococcus pneumoniae* infection occurs in a middle ear.

~~39~~14. The immunogenic composition of claim ~~38~~ 13 wherein the concentration of Zn2+ in the middle ear is less than 300, 200, 150, 100, 50, 20, 10, 5, 2, 1 , 0.5, 0.2 or 0.1 µM.

~~40~~15. The immunogenic composition of claim ~~38~~ 13 or ~~39~~ 14 wherein the concentration of Mn2+ in the middle ear is less than 300, 200, 150, 100, 50, 20, 10, 5, 2, 1 , 0.5, 0.2 or 0.1 µM.

~~41~~16. The immunogenic composition of any one of claims 1 -3 wherein the *Streptococcus pneumoniae* infection occurs in the meninges.

~~42~~17. The immunogenic composition of claim ~~41~~ 16 wherein the concentration of Zn2+ in the cerebrospinal fluid is less than 1 .5, 1 , 0.75, 0.5, 0.25 or 0.1 µM or less than 100, 75, 50, , 25, or 10µg/L.

~~43~~18. The immunogenic composition of claim ~~41~~ 16 or ~~42~~ 17wherein the concentration of Mn2+ in the cerebrospinal fluid is less than 2.5, 2, 1 .5, 1 or 0.5µg/L or less than 50, 25, 10 or 5nM.

~~44. The immunogenic composition of any one of claims 26-43 wherein the human patient has decreased levels of Zn2+ and/or Mn2+ as measured by bronchial lavage and/or blood test.~~

~~45~~19. The immunogenic composition of any one of claims ~~26~~1-~~44~~-18 wherein the human patient is Zn2+ and/or Mn2+ deficient having less than 90% of the usual level in the blood serum, cerebrospinal fluid, interstitial fluid, or bronchial lavage.

~~46. The immunogenic composition of any one of claims 26-45 wherein the human patient is stressed.~~

~~47~~20. The immunogenic composition of any one of claims ~~26~~1-~~46~~19 wherein the human patient has multiple bacterial infections.

~~48~~21. The immunogenic composition of any one of claims ~~26~~1-~~47~~20 wherein the human patient has a chronic bacterial infection.

~~49~~22. The immunogenic composition of claim ~~48~~21 wherein the chronic bacterial infection is pneumococcal infection.

~~50~~23. The immunogenic composition of any one of claims ~~26~~1-~~49~~22 wherein the *Streptococcus pneumoniae* infection is scepticaemia, bacteraemia, meningitis, otitis media or pneumonia.

~~51~~24. A use of a pharmaceutically effective amount of an isolated PhtX protein in the manufacture of a medicament for the treatment or prevention of a Streptococcus pneumoniae infection wherein the Streptococcus pneumoniae infection occurs in the blood, lung, a compartment of the ear or in the meninges of a human patient in an environment where the concentration of Zn^{2+} and/or Mn^{2+} is sufficiently low to upregulate the expression of at least one PhtX protein in the Streptococcus pneumoniae.

~~52~~25. The use of claim ~~51~~24 wherein the PhtX protein is selected from the group consisting of PhtA, PhtB, PhtD and PhtE.

~~53~~26. The use of claim ~~51~~24 wherein the PhtX protein is PhtD.

~~54~~27. The use of any one of claims ~~51~~ 24 ~~-53~~ 26 wherein the *Streptococcus pneumoniae* infection occurs in blood.

~~55~~28. The use of claim ~~54~~ 27 wherein the free concentration of Zn2+ in the blood is less than 10nM, 1 nM, 100pM or 10pM as measured from blood serum.

~~56~~29. The use of claim ~~54~~ 27 wherein the bound and free concentration of Zn2+ in the blood is less than 2 or 1mg/l or less than 20µM as measured from blood serum.

~~57~~30. The use of claim ~~54~~ 27 wherein the free concentration of Mn2+ in the blood is less than 10nM, 1 nM, 100pM or 10pM as measured from blood serum.

~~58~~31. The use of claim ~~54~~ 27 wherein the bound and free concentration of Mn2+ in the blood is less than 2 or 1 mg/l or less than 20, 15, 10, 8, 5 or 2µM as measured from blood serum.

~~59~~32. The use of any one of claims ~~51~~ 24 ~~-58~~ 31 wherein the Streptococcus pneumoniae infection occurs in a lung.

~~60~~33. The use of claim ~~59~~ 32 wherein the concentration of Zn2+ in the lung is less than 300, 200, 100, 50 or 10µg/kg as measured from a bronchial lavage.

~~61~~34. The use of claim ~~59~~ 32 wherein the concentration of Zn2+ in the lung tissue is less than 20, 15, 10, 5, 2 or 1µg/g or 300, 200, 150, 100, 50, 20 or 10µM as measured from lung tissue.

~~62~~35. The use of claim ~~59~~ 32 wherein the concentration of Mn2+ in the lung is less than 300, 200, 100, 50 or 10µg/kg as measured from a bronchial lavage.

~~63~~36. The use of any one of claims ~~51~~ 24 ~~-58~~ 31 wherein the *Streptococcus pneumoniae* infection occurs in a middle ear.

~~64~~37. The use of claim ~~63~~ 36 wherein the concentration of Zn2+ in the middle ear is less than 300, 200, 150, 100, 50, 20, 10, 5, 2, 1 , 0.5, 0.2 or 0.1μM.

~~65~~38. The use of claim ~~63~~ 36 wherein the concentration of Mn2+ in the middle ear is less than 300, 200, 150, 100, 50, 20, 10, 5, 2, 1 , 0.5, 0.2 or 0.1μM.

~~66~~39. The use of any one of claims ~~51~~ 24 ~~-58~~ 31 wherein the *Streptococcus pneumoniae* infection occurs in the meninges.

~~67~~40. The use of claim ~~66~~ 39 wherein the concentration of Zn2+ in the cerebrospinal fluid is less than 1 .5, 1 , 0.75, 0.5, 0.25 or 0.1μM or less than 100, 75, 50, , 25, or 10μg/L.

~~68~~41. The use of claim ~~66~~ 39 or ~~67~~ 40 wherein the concentration of Mn2+ in the cerebrospinal fluid is less than 2.5, 2, 1 .5, 1 or 0.5μg/L or less than 50, 25, 10 or 5nM.

~~69. The use of any one of claims 51 -68 wherein the human patient has decreased levels of Zn2+ and/or Mn2+ as measured by bronchial lavage and/or blood test.~~

~~70~~42. The use of any one of claims ~~51~~ 24 ~~-69~~ 41 wherein the human patient is Zn2+ and/or Mn2+ deficient having less than 90% of the usual level in the blood serum, cerebrospinal fluid, interstitial fluid, or bronchial lavage.

~~71. The use of any one of claims 51 -70 wherein the human patient is stressed.~~

~~72~~43. The use of any one of claims ~~51~~ 24 ~~-71~~ 42 wherein the human patient has multiple bacterial infections.

~~73~~44. The use of any one of claims ~~51~~ 24 ~~-72~~ 43 wherein the human patient has a chronic bacterial infection.

~~74~~45. The use of claim ~~73~~ 44 wherein the chronic bacterial infection is pneumococcal infection.

~~75~~46. The use of any one of claims ~~51~~ 24 ~~-74~~ 45 wherein the *Streptococcus pneumoniae* infection is scepticaemia, bacteraemia, meningitis, otitis media or pneumonia.