Publications

[0005] Santa Maria et al. (2010) J Mol Histol. 2010 Dec;41(6):309-14. Santa Maria (2011) Thesis, University of Western Australia. Johnson and Wang (2013) J Control Release 166(2):124-9. Ishihara et al. (2003) J Biomed Mater Res A. 64(3):551-9. Tolino et al. (2011) Biochim Biophys Acta. 1810(9):875-8; Shirakata et al. (2005) J Cell Sci. 118(Pt 11):2363-70; Hüttenbrink (2005) HNO 53(6):515-6; Ma et al. (2002) Acta Otolaryngol. 122(6):586-99. WO 2007/037514. US 2010/0222265

SUMMARY ~~OF THE INVENTION~~

[0006] Compositions and methods are provided for the treatment of chronic tympanic membrane perforation. In the methods of the ~~invention~~present disclosure, a chronically perforated tympanic membrane is topically contacted with an effective dose of heparin binding-epidermal growth factor, HB-EGF, or an agent having HB-EGF activity, for a period of time sufficient to provide for improved healing of the membrane perforation. In some embodiments the dose of HB-EGF is provided in a sustained release formulation; in other embodiments regular administration of a non-sustained release formulation is provided. In some embodiments, a sustained release formulation is biodegradable. In other embodiments sustained release is provided by a device, e.g. a pump or other release device.

[0006a] In one aspect of the present disclosure, there is provided an agent that provides heparin binding epidermal growth factor (HB-EGF) activity for use in the treatment of a chronic tympanic membrane perforation.

[0006b] In another aspect of the present disclosure, there is provided a pharmaceutical formulation comprising an effective dose of an agent that provides heparin binding epidermal growth factor (HB-EGF) activity, for use in the treatment of a chronic tympanic membrane perforation.

[0006c] In a further aspect of the present disclosure, there is provided a use of an agent that provides heparin binding epidermal growth factor (HB-EGF) activity in the manufacture of a medicament for the treatment of a chronic tympanic membrane perforation.

[0007] The TM being treated is contacted with HB-EGF for a period of time sufficient to improve healing of the TM perforation, *i.e.* to result in substantial closure of the perforation, e.g. to a perforation of less than about 0.1 mm^2 in area. The closure can be monitored visually, including microscopically; functionally, e.g. in reduction of hearing loss; and the like. The period of time for contacting with HB-EGF can be at least one day, at least 3 days, at least 5 days, at least 7 days, at least 10 days, at least 2 weeks, at least 3 weeks; and can be up to one day, up to 3 days, up to 5 days, up to 7 days, up to 10 days, up to 2 weeks, up to 3 weeks, or more according to the needs of the individual.

[0008] In certain specific embodiments the effective dose of HB-EGF is provided in a non-ototoxic sustained release formulation, e.g. gel, foam, insert, etc., preferably a biodegradable formulation. In one such embodiment, an effective dose of HB-EGF is formulated in a gel comprising chitosan, poly-lactic acid, and fibrinogen.

[0009] In one embodiment, the present disclosure~~invention~~ comprises a method of (i) identifying a patient having a chronic perforation of the TM; (ii) contacting the affected TM with an effective dose of HB-EGF, *e.g.* provided in the form of drops to be administered at suitable intervals, in a device for sustained release of HB-EGF, in a sustained release formulation, etc.; and (iii) monitoring the individual to determine effective closure of the perforation.

[0010] ~~Another aspect of t~~The present disclosure~~invention~~ also relates to the use of an agent with HB-EGF activity in the manufacture of a medicament for the treatment of a chronic perforation of the

TM, wherein the medicament is administered to a patient having a chronic perforation of the TM for a period of time and dose sufficient to effect a closure of the perforation.

[0011] ~~Still another aspect of t~~The present disclosure~~invention~~ also provides a kit for treatment of chronic perforation of the TM. The kit includes a formulation that provides for an effective dose of HB-EGF, e.g. in the form of drops, devices, formulations, and the like. The kit may also include a delivery device, e.g. ear drop dispenser, syringe for delivery of a formulation, dual barrel syringe for delivering a two part formulation; and the like. The kit may also comprise instructions for use.

[0012] In other embodiments, methods are provided for temporary opening of the tympanic membrane, e.g. for insertion of tubes, and the like. In such embodiments a TM is contacted with an effective dose of an HB-EGF inhibitor, including without limitation an inhibitor of EGFR ligand shedding, for a period of time sufficient to create a small perforation in the TM. In some such embodiments a small perforation can be mechanically made prior to contacted with the inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Figure 1. Representative images of TMs following perforations treated with OSU8-1 (an inhibitor of EGFR ligand shedding) at (a) day 2 (b) day 14 (c) day 44 (d) day 90 (3 months). The perforation is outlined in blue.

[0014] Figure 2. ABR and DPOAE thresholds were measured 60 days after both eardrums were surgically perforated in 9 mice. One ear had no injection (control), whereas the opposite ear was filled with polymer delivery vehicle of chitosan, fibrinogen and polylactide.

[0015] Figure 3. ET before (a) and after (b) occlusion with gutta percha. The procedure in the rat was adapted by opening the bulla using an engraving device with a 0.5mm burr. Opening the bulla laterally allows the gutta percha to be fed down the ET with less airway retraction. ETs were examined post mortem confirming complete occlusion.

[0016] Figure 4. GF treatment of chronic perforations in a mice model of ET occlusion. The top row (a) are representative images of the treatment group showing healed perforations. The bottom row (b) are representative images of the control (polymer only) group showing persisting perforation (outline blue). Note: some TMs in the top role have healed with tympanosclerosis.

[0017] Figure 5. Trans-tympanic growth factor delivery.

[0018] Figure 6. Trans-tympanic growth factor delivery.

[0019] Figure 7. Trans-tympanic growth factor delivery.

[0020] Figure 8. Intra-tympanic growth factor delivery.

[0021] Figure 9. Drug delivery vehicle adjacent to tympanic membrane.

[0022] Figure 10. Flowable drug delivery formulation.

WHAT IS CLAIMED IS:

1. An agent ~~method of improving healing of a chronic tympanic membrane perforation in an individual, the method comprising:~~

~~contacting a site of chronic tympanic membrane perforation with a formulation comprising an effective dose of an agent~~ that provides heparin binding epidermal growth factor (HB-EGF) activity~~,~~ for use in the treatment of a chronic tympanic membrane perforation~~a period of time sufficient to substantially close the perforation~~.

2. The ~~method~~ agent of Claim 1, wherein the agent ~~that provides HB-EGF activity is a soluble form of~~ is HB-EGF protein.

3. The ~~method~~ agent of claim 2, wherein the ~~individual is a human, and the~~ HB-EGF protein is human HB-EGF protein.

4. The agent of claim 3, wherein the HB-EGF protein is a soluble form of HB-EGF protein.

5. The agent of any one of claims 1-4, wherein the treatment comprises a pharmaceutical formulation comprising an effective dose of the agent that is to be contacted at a site of chronic tympanic membrane perforation for a period of time sufficient to substantially close the perforation.

4~~6~~. The ~~method~~ agent of Claim 5~~1~~, wherein the formulation ~~comprising an effective dose of HB-EGF~~ is to be contacted with the site of~~affected~~ chronic tympanic membrane perforation for a period of at least 7 days.

5~~7~~. The ~~method~~ agent of Claim ~~1~~5, wherein the formulation ~~comprising an effective dose of HB-EGF~~ is to be contacted with the site of ~~affected~~ chronic tympanic membrane perforation for a period of at least 2 weeks.

6~~8~~. The ~~method~~ agent of Claim ~~4 or~~ 5, wherein the formulation is to be administered at least daily.

~~7~~9. The ~~method~~ agent of Claim ~~4 or~~ 5, wherein the formulation provides for sustained release of the agent~~HB-EGF~~.

~~8~~10. The ~~method~~ agent of Claim ~~1~~5, wherein the formulation is provided as an aqueous solution, a gel, a lotion, a balm, paste or other vehicle.

~~9~~11. The ~~method~~ agent of Claim ~~1~~5, wherein the formulation ~~composition~~ is to be administered by a spray.

~~10~~12. The ~~method~~ agent of claim ~~1~~5, wherein the ~~composition~~ formulation is to be administered as a liquid that then solidifies to stay adjacent to the tympanic membrane.

~~11~~13. The ~~method~~ agent of Claim ~~1~~5, wherein the formulation is provided as a sustained release gel comprising a cross-linked copolymer of chitosan and polylactide.

~~12~~14. The ~~method~~ agent of Claim ~~1~~13, wherein the sustained release gel further comprises fibrinogen.

~~13~~15. The ~~method~~ agent of Claim ~~1~~5, wherein the formulation is to be delivered by a device that provides for sustained release of the agent~~HB-EGF~~.

~~14~~16. The ~~method~~ agent of Claim ~~1~~5, wherein the formulation further comprises at least one additional active agent.

~~15~~17. A pharmaceutical formulation comprising an effective dose of an agent that provides heparin binding epidermal growth factor (HB-EGF) activity, for use in the treatment of a chronic tympanic membrane perforation~~method of any one of Claims 1-14~~.

18. The pharmaceutical formulation of claim 17, wherein the agent is HB-EGF protein.

19. The pharmaceutical formulation of claim 18, wherein the HB-EGF protein is human HB-EGF protein.

20. The pharmaceutical formulation of claim 19, wherein the HB-EGF protein is a soluble form of HB-EGF protein.

~~16~~21. The pharmaceutical formulation of any one of claims 17-20~~Use of an agent with HB-EGF activity in the manufacture of a medicament for the treatment of a chronic perforation of the TM~~, wherein the formulation ~~medicament~~ is to be contacted with a site of ~~administered to a patient having a~~ chronic tympanic membrane perforation ~~of the TM~~ for a period of time ~~and dose~~ sufficient to substantially close ~~effect a closure of~~ the perforation.

22. The pharmaceutical formulation of claim 21, wherein the formulation is to be contacted with the site of chronic tympanic membrane perforation for a period of at least 7 days.

23. The pharmaceutical formulation of claim 21, wherein the formulation is to be contacted with the site of chronic tympanic membrane perforation for a period of at least 2 weeks.

24. The pharmaceutical formulation of claim 21, wherein the formulation is to be administered at least daily.

25. The pharmaceutical formulation of claim 21, wherein the formulation provides for sustained release of the agent.

~~17. A method of inhibiting healing of a tympanic membrane perforation in an individual, the method comprising:~~

~~contacting a site of tympanic membrane perforation with a formulation comprising an effective dose of an agent that inhibits HB-EGF activity.~~

~~18. The method of Claim 17, comprising the step of generating a perforation in the tympanic membrane prior to the contacting step.~~

~~19. The method of Claim 17, wherein the individual is a human.~~

~~20~~26. The ~~method~~ pharmaceutical formulation of Claim 17, wherein the formulation is provided as an aqueous solution, a gel, a lotion, a balm, paste or other vehicle.

27. The pharmaceutical formulation of claim 17, wherein the formulation is to be administered by a spray.

~~21~~28. The pharmaceutical formulation ~~method~~ of claim 17, wherein the formulation ~~composition~~ is to be administered as a liquid that then solidifies to stay adjacent to the tympanic membrane.

~~22~~29. The pharmaceutical formulation ~~method~~ of Claim 17, wherein the formulation is provided as a sustained release gel comprising a cross-linked copolymer of chitosan and polylactide.

~~23~~30. The pharmaceutical formulation ~~method~~ of Claim ~~17~~29, wherein the sustained release gel further comprises fibrinogen.

~~24~~31. The pharmaceutical formulation ~~method~~ of Claim ~~1~~17, wherein the formulation is to be delivered by a device that provides for sustained release of the agent~~HB-EGF inhibitor~~.

32. The pharmaceutical formulation of claim 17, wherein the formulation further comprises at least one additional active agent.

33. Use of an agent that provides heparin binding epidermal growth factor (HB-EGF) activity in the manufacture of a medicament for the treatment of a chronic tympanic membrane perforation.

34. The use of claim 33, wherein the agent is HB-EGF protein.

35. The use of claim 34, wherein the HB-EGF protein is human HB-EGF protein.

36. The use of claim 35, wherein the HB-EGF protein is a soluble form of HB-EGF protein.

37. The use of any one of claims 33-36, wherein the medicament is to be contacted with a site of chronic tympanic membrane perforation for a period of time sufficient to substantially close the perforation.

38. The use of claim 37, wherein the medicament is to be contacted with the site of chronic tympanic membrane perforation for a period of at least 7 days.

39. The use of claim 37, wherein the medicament is to be contacted with the site of chronic tympanic membrane perforation for a period of at least 2 weeks.

40. The use of any one of claim 37, wherein the medicament is to be administered at least daily.

41. The use of any one of claim 37, wherein the medicament provides for sustained release of the agent.

42. The use of claim 33, wherein the medicament is provided as an aqueous solution, a gel, a lotion, a balm, paste or other vehicle.

43. The use of claim 33, wherein the medicament is to be administered by a spray.

44. The use of claim 33, wherein the medicament is to be administered as a liquid that then solidifies to stay adjacent to the tympanic membrane.

45. The use of claim 33, wherein the medicament is provided as a sustained release gel comprising a cross-linked copolymer of chitosan and polylactide.

46. The use of claim 45, wherein the sustained release gel further comprises fibrinogen.

47. The use of claim 33, wherein the medicament is to be delivered by a device that provides for sustained release of the agent.

48. The use of claim 33, wherein the medicament further comprises at least one additional active agent.