

33. The vaccine composition of claim **30**, wherein the vaccine composition comprises NOMVs from three or more genetically modified strains.

34. The vaccine composition of claim **1**, wherein the NOMV are prepared from packed cells or spent culture medium without exposure to a detergent or denaturing solvent.

35. The vaccine composition of claim **1**, where the vaccine composition is suspended in 5% glucose as an excipient.

36. The vaccine composition of claim **1**, where the NOMV are combined with one or more adjuvants.

37. The vaccine composition of claim **1**, wherein the genetically altered strain is altered to express iron uptake proteins.

38. A vaccine against meningococcal disease comprising a variety of native outer membrane vesicles (NOMVs), wherein at least some of the NOMVs are essentially free of expression or sialylation of lipooligosaccharide (LOS), contain LOS that includes a lipid A with a penta-acyl structure and contain increased expression levels of at least one minor conserved outer membrane protein, wherein the minor conserved outer membrane protein is selected from proteins that induce bactericidal antibodies.

39. The vaccine of claim **38**, wherein the minor conserved outer membrane protein is selected from the group consisting of NadA, factor H binding protein (FHBP) variant 1, and FHBP variant 2.

40. The vaccine of claim **38**, wherein at least some of the NOMV comprise shortened or truncated LOS that are essentially free of lacto-N-neotetraose (LNnT) tetrasaccharide.

41. The vaccine of claim **38**, wherein at least some of the NOMV comprise two or more different PorA proteins.

42. The vaccine of claim **41**, wherein the at least two or more different PorA proteins are selected from the most prevalent strains of *N. meningitidis* subgroup B strains.

43. A method of eliciting an immune response to meningococcal disease in an animal or human comprising administering the composition of claim **1** to the animal or human for immunization against meningococcal disease.

44. The method of claim **43**, wherein the vaccine is used for immunization against group B meningococcal disease.

45. A method of preparing a genetically modified strain of *N. meningitidis* for use in a vaccine against meningococcal disease comprising the steps of:

- a) selecting a strain of meningococcal type B able to be genetically modified;
- b) genetically modifying the strain by inactivating the synX gene,

- c) genetically modifying the strain by inactivating the lpxL1 gene,

- d) genetically modifying the strain by inactivating the IgtA gene, and

- e) genetically modifying the strain by increasing expression of one or more minor conserved outer membrane proteins.

46. The method of claim **45**, further comprising the steps of:

- genetically modifying the strain by inserting at least one second antigenically different porA gene into the open reading frame of the opa gene.

47. The method of claim **45**, further comprising the steps of:

- genetically modifying the strain to stably express or over express at least one outer membrane protein by replacing the poly-C sequence within the promoter or open reading frame of the at least one outer membrane protein with a sequence containing G and C nucleotides.

48. A method of preparing a vaccine against meningococcal disease comprising the steps of:

- a) culturing a genetically modified strain of *N. meningitidis* comprising one or more modification selected from the group consisting of:

- i. inactivation of the synX gene,

- ii. inactivation of the lpxL1 gene,

- iii. inactivation of the IgtA gene,

- iv. insertion of at least one second antigenically different porA gene in place of the opa gene,

- v. increased or stable expression of at least one minor conserved outer membrane protein, and

- vi. stabilized expression of at least one outer membrane protein;

- b) expanding the culture by fermentation using the cultured strain of a) to inoculate medium in a fermentor;

- c) inactivating the fermented culture;

- d) harvesting *N. meningitidis* cultured cells by continuous flow centrifugation and collecting cell paste;

- e) isolating NOMVs from the cell paste; and

- f) resuspending NOMVs in buffer or carrier suitable for vaccine administration.

49. The vaccine of claim **3**, where each most prevalent of PorA subtypes among group B case isolates is selected from the group consisting of P1.7-1,1, P1.22,14, and P1.22-1,4.

50. The vaccine of claim **17**, where each most prevalent of PorA subtypes among group B case isolates is selected from the group consisting of P1.7-1,1, P1.22,14, and P1.22-1,4.

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