

Supplementary Tables

Supplementary Table S1. Use of the mouse for testing *Neisseria* vaccine efficacy, through the generation of bactericidal antibodies, opsonophagocytic antibodies and active protection against infection

| 1. Generation of serum bactericidal antibodies against meningococci | |
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| Antigen | References |
| Outer membrane protein (OMP) or OMP plus group C CPS | [1] |
| Groups A, B, and C CPS-tetanus toxoid conjugates | [2] |
| Serogroup B CPS | [3] |
| CPS-OMP complexes serogroup C, serotype 2a; and tetanus toxoid conjugates | [4,5] |
| Group B serotype 2b protein vaccine | [6] |
| Passive immunization with group B serotype 2b-specific monoclonal antibody | [7] |
| Class 1/3 OMP vaccine against group B, type 15, subtype 16 meningococci | [8] |
| 28 kDa OMP | [9] |
| H.8 (Lip) | [10,11] |
| Monoclonal antibodies against the 70kDa iron-regulated protein | [12] |
| Outer membrane complexes (OMCs) containing multiple Class I proteins | [13] |
| Class I OMP/PorA, recombinant or purified | [14-32] |
| PorA peptides | [33-39] |
| IgG2a mAbs for group B CPS | [40] |
| LPS-derived oligosaccharide-protein conjugates | [41,42] |
| Transferrin-binding proteins (Tbps) | [43-49] |
| 98-kilodalton iron-regulated OMP (TbpA) | [50] |
| 70 kDa iron-regulated protein FrpB, FetA | [51,52] |
| Class 5 protein/Opc/rOpc | [53-57] |
| Group B OMV + serogroup C CPS | [58] |
| NspA | [59-64] |
| N-Propionylated group B CPS | [65] |
| OMV vaccines made from short-chain lipopolysaccharide mutants of serogroup B | [66] |
| 37-kDa ferric binding protein FbpA | [67] |
| N-propionyl (NPr) modification of the group B CPS-linked to rPorB | [68] |
| Group C CPS conjugated to tetanus toxoid | [69] |
| OMV intranasal vaccine | [70-72] |
| Rmp, Class 4 OMP | [73] |
| Anti-idiotype-based peptide mimic vaccine for serogroup C CPS | [74] |
| Serogroup C CPS and serogroup B OMV conjugate | [75] |
| LOS-deficient OMV | [76] |
| Molecular mimetics of CPS epitopes | [77,78] |
| Reverse vaccinology of vaccine candidates for development of Bexsero 'universal vaccine' | [79-81] |
| Anti-idiotype based peptide and DNA vaccines which mimic the serogroup C CPS | [82] |
| GNA33 lipoprotein | [83] |
| NadA | [84-88] |
| rPorB | [89] |
| LOS-tetanus toxoid conjugates | [90] |
| GNA1870 lipoprotein | [91-94] |
| Serogroup A CPS conjugates | [95] |
| Multiepitope DNA vaccine encoding a peptide mimic of serogroup C CPS | [96] |
| Genome-derived neisserial antigen 2132 (GNA2132) | [97] |

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| Serogroup C peptide mimetics | [98] |
| Lipoprotein 2086/rLP2086 | [99-102] |
| Monoclonal antibody 9-2-L3,7,9 specific LPS immunotype L3,7,9 and cyclic peptides | [103] |
| Serogroup C CPS-P64k protein conjugate | [104] |
| Serogroup A OMV | [105,106] |
| OpaB and OpaJ | [107] |
| Outer membrane phospholipase A (OMPLA) | [108] |
| lpxL mutant OMV | [109] |
| anti-idiotypic MAAb, Naid60, which mimics the serogroup B CPS | [110] |
| LOS peptide mimetic | [111] |
| Glycoconjugates of CRM(197) to O-deacylated LPS derived from meningococcal immunotype L3 galE LPS. | [112] |
| Lactoferrin-binding proteins LbpA and LbpB | [113] |
| Conjugates of group A and W135 CPS to recombinant <i>Staphylococcus aureus</i> enterotoxin C1 | [114] |
| Live <i>Neisseria lactamica</i> protects against meningococcal challenge | [115] |
| OMV over-expressing GNA1870 | [116] |
| Peptide mimics of the group B CPS, including phage displayed | [117-119] |
| De-O-acetylated (dOA) polysaccharides | [120] |
| LOS lipid A and serogroup B OMV | [121] |
| Pool of DNA vaccine candidates (n=20) confer protective immunity against meningococcal infection and induce SBA against serogroup B | [122] |
| Minor OMPs | [123] |
| Serogroup W135 polysaccharide-tetanus toxoid conjugate vaccine | [124] |
| Serogroup B OMV plus TLR adjuvants | [125] |
| Lipoprotein NMB0928 | [126] |
| <i>Neisseria lactamica</i> OMV | [127] |
| Factor H-binding protein (fHbp) | [128-139] |
| OMV with overexpressed factor H-binding protein; and with genetically attenuated endotoxin | [140-142] |
| De-N-acetylated sialic acid | [143,144] |
| NMB0088 | [145] |
| Genetically modified serogroup B L3,7 and L2 LOS | [146] |
| LpxL1 and PagL mutant LOS with OpaJ | [147] |
| ZnuD | [148,149] |
| Serogroup B OMV with disabled synX, lpxL1, and lgtA genes | [150] |
| Serogroup B Ag473 | [151] |
| fHbp and NHBA together | [152] |
| Opa proteins (n=14) | [153] |
| rMacrophage Infectivity Potentiator protein | [154,155] |
| Trivalent native OMV vaccine | [156] |
| Recombinant PilQ(406-770) | [157] |
| Adhesin complex protein (ACP) | [158] |
| Chaperonin60 (Chp60) | [159] |
| Truncated <i>Neisseria hia</i> homologue (NhhA) | [160] |
| Protein conjugates of carba analogues from serogroup A CPS | [161] |
| Serogroup X glycoconjugate vaccine | [162] |
| OMV for serogroup A+W; A+W+X; A+C; X; C | [163-169] |
| Generalized Modules For Membrane Antigens (GMMA) | [170] |
| Haemoglobin Receptors, HpuAB and HmbR | [171] |

| ABC transporter substrate-binding protein, NMB1612 | [172] |
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| OMV with constitutive FetA expression | [173,174] |
| Fully synthetic self-adjuvanting α -2,9-oligosialic acid based conjugate serogroup C vaccine | [175] |
| OMVs displaying designer glycotopes | [176] |
| Putative Cell Binding Factor (CBF, NMB0345/NEIS1825) | [177] |
| DNA vaccine pNMB0315 against serogroup B and rNMB0315 | [178,179] |
| Synthetic oligosaccharide-protein conjugate vaccine for serogroup C | [180] |
| Stabilized glycomimetic conjugate vaccine for serogroup A | [181] |
| Adenoviral vectors expressing group B OMPs | [182] |
| 2. Generation of opsonophagocytic antibodies against meningococci | |
| Antigen | References |
| Serogroup W-135 | [183] |
| PorB linear epitope | [184] |
| PorA and PorA peptide | [32,36,38] |
| Serogroup A, C, Y, or W135 CPS | [185] |
| Serogroup A OMV | [106] |
| Serogroup A+W OMV vaccine; AWX-OMV vaccine | [163,165] |
| 3. Active protection against meningococcal infection | |
| Antigen | References |
| Group A capsule polysaccharide (CPS) protects mice against homologous challenge | [186] |
| Mouse bacteraemia protection against five different serotype 2 vaccines. | [187] |
| OMV containing lipooligosaccharide protects against lethal group B infection and septic shock | [188] |
| TbpA | [189] |
| <i>Bordetella pertussis</i> fimbriae- serogroup C conjugate vaccine | [190] |
| phoP mutant of meningococcus | [191] |
| Attenuated meningococci YH102 and YH103 | [192] |
| Passive immunization with sera from mice immunized with anti-idiotypic mimics of serogroup B CPS | [193,194] |
| OMVs and detoxified LOS protect mice against homologous and heterologous serogroup B meningococcal infection and septic shock | [195] |
| rLP2086 protein immunization reduces colonization in a murine nasal challenge model | [196] |
| Recombinant penicillin-binding protein 2 (PBP2) immunization conferred protection against meningococcaemia | [197] |
| Secreted proteins (MSPs) protect against live meningococcal challenge | [198] |
| Passive protection against meningococcal infection with antibodies to β -(1 \rightarrow 6)-linked poly-N-acetyl-d-glucosamine (PNAG) | [199] |
| 4. Generation of serum bactericidal antibodies against gonococci | |
| Antigen | References |
| Purified ribosomal fraction of gonococci | [200] |
| Pathogenic serogroup A strain of <i>N meningitidis</i> elicits bactericidal antibodies against gonococci | [201] |
| mAbs to denatured and native forms of gonococcal outer membrane proteins | [202] |
| mAbs to pili | [203] |
| Porin P1/PorB | [204-213] |
| PorB peptides | [214,215] |
| OMP III mAbs | [216] |

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| mAb to gonococcal LOS | [217] |
| Monoclonal anti-idiotope antibody that mimics gonococcal LOS epitope 2C7 | [218,219] |
| 2C7 peptide | [220-223] |
| Recombinant human IgG1 chimeric variant of MAb 2C7 containing an E430G Fc modification (2C7_E430G) | [224] |
| Recombinant gonococcal transferrin binding proteins (Tbp) A and B conjugated to the cholera toxin B subunit | [225,226] |
| Opa protein loops | [227] |
| NspA | [228] |
| Ghfp, the gonococcal Orthologue of meningococcal fHbp | [229] |
| Meningococcal truncated MIP | [230] |
| DNA vaccine using bacterial ghosts | [231] |
| MtrE and surface-expressed Loop 2 | [232] |
| Gonococcal ACP | [233] |
| Methionine Sulfoxide Reductase (MsrA/B) | [234] |
| Meningococcal native OMV vaccine with attenuated endotoxin and overexpressed fHbp | [235] |
| NGO0416, 0690, 0948, 1043, 1215, 1701 | [236] |
| OMV | [237,238] |
| NHBA | [239] |
| Meningococcal 4CMenB vaccine | [240,241] |
| Phage proteins | [242] |
| MetQ | [243] |
| Rmp-deleted mutant strain | [244] |
| AniA OMP | [245] |
| | |
| 5. Generation of opsonophagocytic antibodies against gonococci | |
| Antigen | References |
| DNA immunization of mice with a plasmid encoding PorB | [246] |
| NspA | [228] |
| PNAG | [199] |
| PorB | [206,210] |
| | |
| 6. Active protection against gonococcal infection | See main text |

Supplementary Table S2. The guinea pig in *Neisseria* research

| 1. Vaccine studies | | |
|---|------------------|--|
| Vaccine tested | Reference | |
| Formalin-fixed gonococcal cells | [247] | |
| Gonococcal outer membrane complex and purified pili | [248] | |
| Meningococcal serotype 2 vaccines | [249] | |
| Gonococcal ribosomal preparations cooper | [250] | |
| Meningococcal serotype 2 OMV, LPS-reduced with group B meningococcal polysaccharide | [251] | |
| Artificial glycoprotein (covalent link of oligosaccharide haptens derived from <i>Streptococcus pneumoniae</i> type 6A and <i>Neisseria meningitidis</i> group C capsular polysaccharides to non-toxic mutant protein CRM197) | [252] | |
| Epitope C-rich lipopolysaccharide from gonococci | [253] | |
| Meningococcal class I porin | [16] | |
| Recombinant class 3 porin of group B meningococci as carrier protein for a <i>Haemophilus influenzae</i> type b (Hib) polyribosylribitol phosphate (PRP) conjugate vaccine | [254] | |
| Meningococcal OMV | [62] | |
| ZnuD-expressing meningococcal OMV | [149] | |
| 2. Infectivity experiments in subcutaneous chambers | | |
| Observations with the model | Reference | |
| Infection with gonococcal colony types | [255] | |
| Inability of gonococcal pili to confer protection | [256] | |
| Morphological, biological and antigenic properties of gonococci adapted to growth in subcutaneous chambers | [257] | |
| Gonococcal serotypes and their relationship with immunotypes | [258] | |
| Isolation of gonococcal rough colony type | [259] | |
| Gonococcal strain specificity and immunity to infection | [260] | |
| Comparative physical and immunological aspects of gonococcal infection of the chimpanzee and guinea-pig subcutaneous chamber models | [261] | |
| Phenotypic changes in gonococcal serum resistance | [262] | |
| Strain related infectivity of gonococci and variability of immune resistance in different breeds of guinea pig | [263] | |
| Contribution of antigens contributes to immunogenicity of gonococci | [264] | |
| Environmental factors associated with phenotypically determined resistance of gonococci to normal human serum | [265] | |
| Complex immunogenicity of gonococci | [266] | |
| The role of outer membrane proteins in gonococcal survival | [267] | |
| Characterization of immune response to gonococcal ribosomal preparation | [268] | |
| Effect of anti-pilus antibodies on survival of gonococci | [269] | |
| Chemical and biological characterization of a gonococcal growth inhibitor tested in the model | [270] | |
| Demonstration of capsules on gonococci by electron microscopy of bacteria grown in vivo | [271] | |
| Gonococcal variants selected by growth in vivo or in vitro have antigenically different LPS | [272] | |
| Alterations of the LPS determine gonococcal virulence in the model | [273] | |
| Attenuation and immunogenicity of a gonococcal strain MS11 harbouring a mutation in gene <i>aroA</i> | [274] | |

Supplementary Table S3. Use of the rabbit for testing *Neisseria* vaccine efficacy, through the generation of bactericidal antibodies

| 1. Generation of serum bactericidal antibodies against meningococci | |
|--|-----------------------|
| Antigen | References |
| Surface antigens from group A meningococci | [186] |
| Outer membrane protein or outer membrane protein plus group C polysaccharide | [1] |
| lipopolysaccharide R-type oligosaccharides conjugated to tetanus toxoid | [275] |
| H.8 (Lip) | [10] |
| LOS-derived oligosaccharide-protein conjugates | [42] |
| PorA synthetic peptides | [34,276] |
| 70 kDa iron-regulated protein (FrpB) | [51] |
| Transferrin binding protein(s) | [44,46,48,49,189,277] |
| OMV (PorB response) | [278] |
| Anti-idiotypic mimics of group B CPS | [193] |
| Native OMV from lpxL mutant strains | [109] |
| LPS-based glycoconjugates | [112,279] |
| Penicillin-binding protein 2 (PBP2) (passive protection) | [197] |
| Recombinant factor H binding protein (fHbp) | [280-282] |
| Trivalent native OMV vaccine derived from three serogroup B strains | [283] |
| Nonavalent PorA native OMV serogroup B vaccine | [30] |
| Serogroup B PMV with constitutive FetA expression | [174] |
| OMP-deficient OMVs | [284] |
| 2. Generation of serum bactericidal antibodies to gonococci | |
| Antigen | References |
| Protein I (PorB) | [210,285] |
| Conserved peptide epitope of PorB | [214] |
| LOS anti-idiotypic antibodies | [217] |
| Monoclonal anti-idiotope antibody that mimics the LOS epitope 2C7 | [218] |
| 2C7 OS epitope mimics - anti-idiotope mAb CA1 and peptide PEP-1 | [286] |
| <i>S. enterica</i> Typhimurium expressing gonococcal filamentous phage Φ6 | [287] |
| Purified filamentous Φfil phages | [288] |

Supplementary Table S4. The neonatal (infant) rat model of passive protection used to test the ability of antibodies generated to meningococcal antigens to protect against infection with live meningococci.

| 1. Mouse monoclonal antibodies to antigens | References |
|--|-------------------|
| Class 1 and class 3 OMPs | [289] |
| Class I (PorA) subtype specific protection | [290] |
| Rough LOS | [291] |
| PorB | [292] |
| Inner-core lipopolysaccharide epitope | [293] |
| 2. Polyclonal mouse sera to antigen | References |
| Polyclonal antibodies to serogroup B CPS bind to the brains of infant rats in vitro but not in vivo | [294] |
| Class 5 proteins | [54] |
| NsPA | [60] |
| PorA | [14,16,295] |
| GNA33 | [83] |
| NadA | [84] |
| Serogroup B microvesicles | [62] |
| Lipoprotein GNA1870 | [91] |
| LP2086 | [100] |
| LPS-based glycoconjugates vaccine | [112] |
| Serogroup B genomic expression libraries | [296] |
| Single chain variable fragment (scFv), which mimics a protective serogroup B epitope | [194] |
| Peptide mimics of the group B CPS | [117] |
| NMB0928 | [126] |
| De-N-acetylated sialic acid | [144] |
| NMB0088 | [145] |
| NMB0938 | [297] |
| Phage-displayed peptide mimetics of serogroup B CPS | [118] |
| 3. Rabbit polyclonal sera to antigen | References |
| LPS in a de-O-acylated J5 lipopolysaccharide (J5 DLPS) as a noncovalent complex with serogroup B OMP protected neutropenic rats against Gram-negative bacteraemia induce by lethal challenge with <i>P. aeruginosa</i> | [298] |
| 4. Human sera to antigen | References |
| Cuban VA-MENOCBC vaccine | [299] |
| Glycoconjugate vaccine for serogroup C | [300] |
| Serogroup B OMV vaccine | [301] |
| Inner core LOS epitopes | [302] |

Supplementary Table S5. Human-derived cell culture-based models for studying *Neisseria* pathogenesis. Table is adapted from information from the review of Heydarian et al [303].

| Species | Site of infection | Model | References |
|------------------------|-----------------------------------|---|------------|
| <i>N. gonorrhoeae</i> | Fallopian tube | Long-term ex-vivo Fallopian tube organ culture used to study the effect of gonococcal infection on ciliary activity, bacterial attachment and inflammatory damage. Potentially useful for gonococcal vaccine development. | [304-310] |
| | | Fallopian tube organoids used for long-term in-vitro studies of <i>C. trachomatis</i> and could be used to study gonococcal pelvic inflammatory disease. | [311] |
| | Cornea | Explants of cornea in organ culture used to study gonococcal- epithelial interaction. | [312] |
| | | Cornea organoid from pluripotent stem cells containing three distinct cell types with expression of key epithelial, stromal and endothelial cell markers, could be used to study gonococcal <i>ophthalmia neonatorum</i> | [313] |
| | | Monocultures using epithelial cells and/or corneal stromal cells and endothelial cells on Transwell inserts. | [314-317] |
| | | 3D cornea model | [318-320] |
| | Endometrium, Ecto- and endocervix | Endometrium ex-vivo model used to study gonococcal pathogenesis associated with pelvic inflammatory disease. | [321] |
| | | 3D endometrial epithelial cell culture model used to study in vivo interactions between <i>N. gonorrhoeae</i> and vaginal commensals in a dynamic condition using rotating wall vessel bioreactor technology. | [322] |
| | | Endocervical tissue explanted from patient used to study mechanism of gonococcal invasion through endocervix mucosa. | [323,324] |
| | | Oganoid cultures from ecto- and endocervix promising to use for modelling gonococcal infection. | [325] |
| | | Long-term, hormone-responsive organoid cultures of endometrium. | [326] |
| | | 3D polarized, hormone-responsive endometrial tissue models containing stromal cells and organoid-derived epithelial cells on an artificial porous collagen scaffold. | [327] |
| | | Transwell 3D culture model containing polarized endocervical epithelial cells co-cultured with neutrophils useful to study neutrophil influx during gonorrhoea. | [328] |
| | | SIS scaffold-based 3D triple co-culture tissue model included epithelial, fibroblasts, endothelial cells, and neutrophils using perfusion bioreactor system. | [303] |
| <i>N. meningitidis</i> | | 3D bronchial epithelial cells and fibroblast cells co-cultured with or without T lymphocytes engineered to study immunopathology of asthma and the bronchial responses against pathogens. | [329,330] |

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| Upper respiratory tract mucosa | 3D bronchial model of fibroblasts suspended in a collagen matrix with differentiated epithelial cells and seeded with eosinophils suitable for studying remodelling events associated with inflammation and asthma. | [331] |
| | 3D bronchial equivalents derived from biopsies of asthmatic and non-asthmatic donors grown on a mesenchymal layer. | [330] |
| | 3D bronchial mucosal model, including a well-differentiated epithelium with functional cilia, mucus secretion, and sub-epithelial fibroblasts | [332] |
| | 3D bronchial mucosal model containing epithelial, fibroblasts and stromal cells that express genes associated with immune responses, apoptosis, mitosis, cell survival, differentiation and cancer. | [333,334] |
| | 3D triple co-culture bronchial mucosal model consists of epithelial cells and fibroblasts and implanted with dendritic cells | [335,336] |
| | SIS scaffold based 3D tissue culture model consisting of the respiratory epithelium, a basement membrane and connective tissue with fibroblasts which is suitable for infection studies with <i>B. pertussis</i> and other obligate airway pathogens. | [337] |
| | Organotypic 3D bronchial and nasal tissue culture models used to study the effect of cigarette smoke on airway biology | [338] |
| Blood brain barrier (BBB) | Designed and fabricated of 3D artificial neurovascular model represents 1 millionth the size of adult human brain that allow cell-to-cell communication between endothelial cells, astrocytes, and pericytes and independent perfusion. | [339] |
| | Construction of 3D artificial BBB on a microfluidic platform included rat derived epithelial cells and neutrophils | [340] |
| | 3D model of human BBB using immortalized brain endothelial cells within a microfluidic chip | [341,342] |
| | 3D model of interconnected neural clusters derived from pluripotent stem cells in a multiscale scaffold consisting of a honeycomb microframe and gelatin nanofibers. | [343] |
| | 3D model of a microfluidic BBB derived from human-induced pluripotent stem cells co-cultured with rat primary astrocytes used for drug permeability screening. | [344] |
| | 3D microvascular model of a microfluidic BBB derived from pluripotent stem cells co-cultured with astrocytes and pericytes that is better phenotypic copy in vivo brain epithelial cells and has the benefit of using human cells that possess BBB barrier properties, and can be used to study barrier destruction, innate immune stimulation, and host-pathogen interaction. | [345-347] |
| Meningeal-CSF barrier | Brain endothelial cells derived from induced pluripotent stem cells co-cultured with meningeal cells | [348] |
| Vasculature | Ex-vivo model of bacteremia using blood to study passive immunization of antigen-based vaccine candidate. | [349] |

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| | Ex-vivo whole blood model of meningococcal infection to study effect of TLR antagonists | [350] |
| | Ex-vivo whole blood model of meningococcal infection used to study the effect of anticoagulants on complement activation | [351] |
| | 3D model of perfusable microvascular networks derived from pluripotent stem cells in a microfluidic chip | [352,353] |
| | 3D printed model of artificial vascular networks consists of rigid networks of carbohydrate glass used as a cyto-compatible sacrificial template that could be lined with endothelial cells or other kinds of cells and perfused with blood under high-pressure pulsatile flow. | [354] |
| | 3D model of artificial blood vessels bio-printing using multiple materials, known as bioinks to replicate vasculature, multiple types of cells, and extracellular matrix. | [355] |

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