(1) Submission ID#1527364

Meningococcal outer membrane vesicles as generalized display platform for heterologous vaccine antigens

---

Author(s)

Peter van der Ley, n/a

senior scientist

Intravacc

Merijn Salverda, n/a

scientist

Intravacc

Afshin Zariri, n/a

scientist

RIVM

Corine Kruiswijk, n/a

associate director

Intravacc

Background

Outer membrane vesicles (OMVs) have been widely investigated and used as meningococcal vaccines. By genetically detoxifying LPS through lpxL1 inactivation and increasing OMV formation with an rmpM mutation, we have been able to develop a scalable production process of native OMVs without the use of detergents, thereby preventing the loss of important components such as lipoproteins and LPS. Because of their adjuvant and antigen-presenting properties, these native meningococcal OMVs might also be useful as vaccine platform for heterologous antigens from other pathogens.

Aim/Methods

Neisseria meningitidis H44/76 with deleted siaD lpxL1 porA rmpM genes was used for two different approaches to heterologous surface display: (i) internal expression as a fusion protein to the N-terminal region of a surface-exposed lipoprotein such as factor H-binding protein (fHbp), and (ii) mixing with a separately produced recombinant protein to which a C-terminal LPS-binding sequence derived from the antimicrobial peptide mCRAMP had been added.

Results

Method (i): the OspA surface lipoprotein from Borrelia burgdorferi was expressed as a fusion to the signal sequence and part of the N-terminus of meningococcal fHbp. The resulting fusion protein was shown to be surface-exposed. Expression levels could be increased by inserting two gene copies into the meningococcal chromosome. Immunization of mice with the resulting OspA-carrying OMVs resulted in high antibody production against purified OspA protein, and significant but partial protection against Borrelia challenge.

Method (ii): a 34 amino acid sequence derived from the antimicrobial peptide mCRAMP was added to the C-terminus of several model peptides, as well as the Bordetella pertussis pertactin protein. Using a western blotting method with immobilized OMVs, binding to native OMVs could be demonstrated when the mCRAMP sequence had been included. A SARS-CoV-2 Spike protein carrying this sequence at the C-terminus was mixed with OMVs and used for both intramuscular and intranasal immunization of mice and hamsters. This resulted in the induction of virus-neutralizing antibodies in both animal models, and significant protection against viral replication in the lungs of hamsters.

Conclusions

Meningococcal native OMVs show promise as carriers for heterologous vaccine antigens. Both internal expression as lipoprotein fusion or external attachment by inclusion of an mCRAMP sequence is possible.