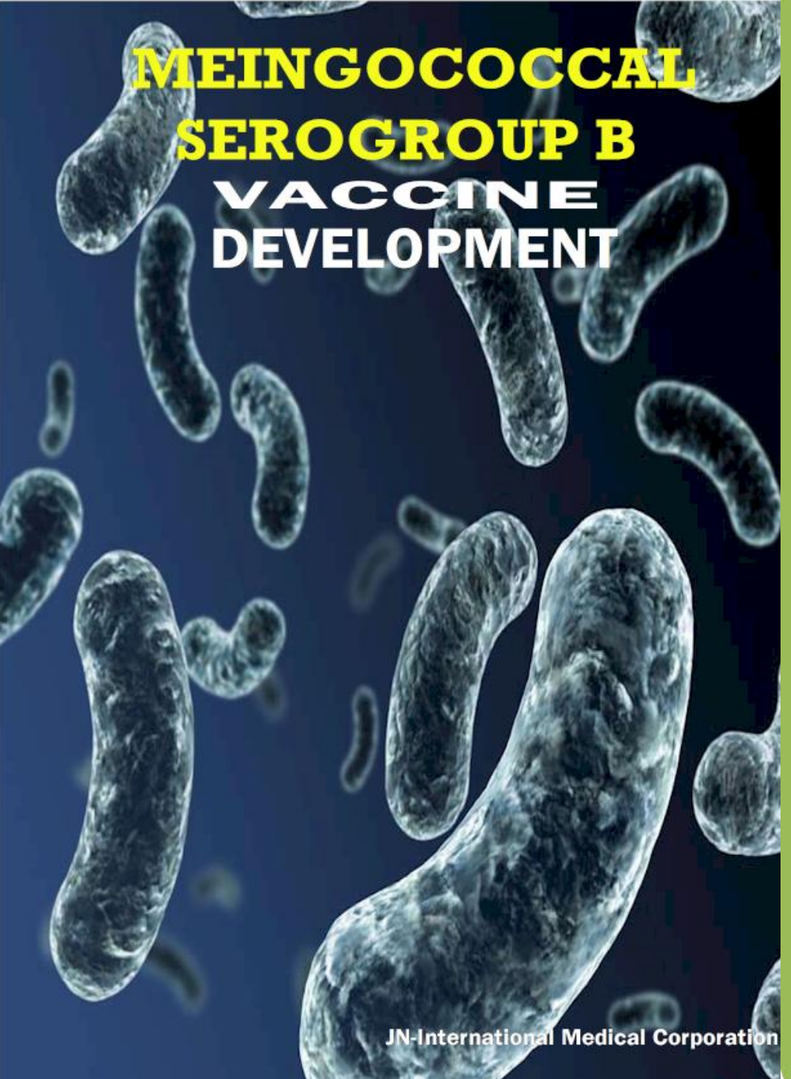


## BACKGROUND STUDY

*Neisseria meningitidis* is a major cause of bacterial meningitis and septicemia in healthy infants and young adults throughout the World. Effective vaccines based on plain capsule polysaccharide and polysaccharide conjugate vaccines have been developed for strains expressing capsular polysaccharides that define the Serogroup A, C, Y, and W-135. However, there is, to date, no broadly protective vaccine for group B strains (Meningitis B). The lack of a Meningitis B vaccine is a serious limitation for controlling meningococcal disease since Meningitis B strains account for 10% of meningococcal infections in North America and up to 60% in Northern Europe and 30% in Africa. In humans, immunologic tolerance to Meningitis B capsular polysaccharide and variation in both expression and sequence of immuno-dominant surface proteins such as the porins (PorA, PorB), opacity proteins (Opa, Opc), and iron-regulated proteins (transferrin and lactoferrin binding proteins), have posed major impediments to developing a broadly protective Meningitis B vaccine. An unique NspA, a protein we discovered from wild animal infective with Meningitis bacterial strain isolated Africa (this protein also seen in all human Meningitis B strains but variable), elicits bactericidal antibodies that are protective in vivo, and is highly conserved. Therefore, NspA is an important candidate antigen for inclusion in our Meningitis B vaccine. We investigated the biological basis for human and strain differences worldwide and developed novel NspA-containing vaccine. It is in deed elicited more broadly reactive anti-NspA antibodies against most predominant Meningitis B strains as a means of achieving universal protection against meningococcal B infection. Mice and guinea pigs were sequentially immunized with NspA prepared from animal meningococcal strains that was antigenically heterologous with respect to the human NapA. The resulting antisera conferred passive protection against meningococcal group B bacteremia in infant rats and elicited complement-mediated bactericidal activity against genetically diverse group B human strains that were either homologous or heterologous with respect to PorA and PorB of the strains used to prepare the vaccine. By using knockout strains, a portion of the bactericidal antibody was directed against the highly conserved protein, neisserial surface protein A (NspA) and we named it as SQU-NspA. Sequential animal immunization in our novel approach to eliciting broadly protective immunity against worldwide human N. meningitidis B strains. Phase 1 human study already initiated in Kenya and expected to complete in this fall season. Further to investigate the vaccine potential of SQU-NspA, we produced mouse anti- NspA (SQU-NspA) antisera, which were used to evaluate the accessibility of NspA epitopes on the surface of different human serogroup B strains by an immunofluorescence flow cytometric assay and by susceptibility to antibody-dependent, complement-mediated bacteriolysis. Among 17 genetically diverse strains tested, 11 (65%) were positive for NspA cell surface epitopes and 6 (35%) were negative. All six negative strains also were resistant to bactericidal activity induced by the anti-SQU-NspA antiserum. In contrast, of the 11 NspA surface-positive strains, 8 (73%; $P < 0.05$) were killed by the antiserum and complement. In infant rats challenged with one of these eight strains, the anti-NspA antiserum conferred protection against bacteremia, whereas the antiserum failed to protect rats challenged by one of the six NspA cell surface-negative strains. Neither NspA expression nor protein sequence accounted for differences in NspA surface accessibility, since all six negative strains expressed NspA in outer membrane preparations and since their predicted NspA amino acid sequences were 99 to 100% identical to those of three representative positive strains. However, the six NspA cell surface-negative strains produced, on average, larger amounts of group B polysaccharide than did the 11 positive strains (reciprocal geometric mean titers, 676 and 224, respectively; $P < 0.05$), which suggests that the capsule may limit the accessibility of NspA surface epitopes. Given these strain differences in NspA, surface accessibility, SQU-NspA anti-mouse sera killed all susceptible and resistant N. meningitis serogroup B strains tested by Serum Bactericidal Assays. It is proved that the SQU-NspA has identical to human Serogroup B strains and showed no limitations on capsular accessibility of NspA surface epitope and proved to be an “Universal” Meningococcal meningitis serogroup B vaccine.

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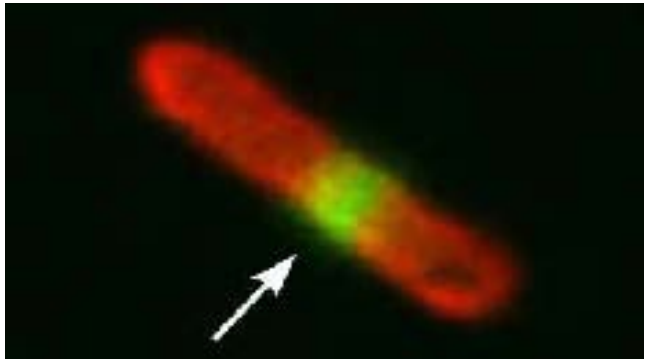

Express recombinant proteins

DNA vaccines preparation

In silico vaccine candidates

Antigen selection

Clone genes

Test Convalescent sera

Test immunogenicity

Purify components

Identify components

Immunogenicity testing in animal models

VACCINE DEVELOPMENT

Meningitis Vaccine