VACCINES

Structure-based design

The development of vaccines against pathogens such as meningococcus B, rhinovirus, African trypanosomes and HIV has been hampered owing to the high degree of sequence variability of their respective antigens. Writing in *Science Translational Medicine*, Rappuoli and colleagues used a structure-based vaccine design to develop a chimeric antigen that was broadly protective against all tested antigenic variants of *Neisseria meningitidis*, the pathogen that causes septicaemia and meningitis.

The authors exploited factor H binding protein (FHBP) — a protective antigen found on the surface of the outer membrane of meningococcus B that is essential for pathogenicity — as a target for their vaccine design. Although the amino-acid sequence of FHBP has almost 300 variations, these can be divided into three major groups (known as antigenic variants 1, 2 and 3).

Knowledge of the three-dimensional structure of FHBP enabled the authors to identify — using variant-specific monoclonal antibodies — the amino acids within the FHBP epitopes that were crucial for immunogenicity. Importantly, these amino acids were in regions of the epitope that did not overlap between the variants, which suggested that epitopes from one variant could be inserted onto another variant.

So the authors used variant 1 as a parent molecule, and replaced various regions of variant 1 — each containing at least one conformational epitope — with regions containing specific amino acids from variant 2 and variant 3. Groups of point mutations were then introduced to reproduce all of the concurrent variations that are observed in the natural bacterial population, which resulted in a total of 54 different chimeric antigens. Generation of the chimaeras did not cause major alterations in protein folding or stability.

The chimeric antigens were then used to immunize mice. Sera from immunized mice were tested *in vitro* for the ability to kill seven meningococcal strains that expressed divergent sequences of FHBP. Further testing of several of these chimeric antigens, which were formulated with an adjuvant, against an enlarged panel of meningococcus B strains demonstrated that three chimaeras were bactericidal against all of the strains that were tested, with one chimaera — known as G1 — eliciting high titres against most of the strains.

This chimeric antigen was chosen as a lead candidate. Determination of its X-ray crystallographic structure showed that, compared to the known crystal structure of FHBP variant 1, the overall structure and the polypeptide backbone of G1 were unchanged, which suggests that protein folding was identical between the antigens. In addition, the region that interacts with human factor H was minimally changed in G1.

To further optimize the immunogenicity of G1, a recognized strategy was used to improve stability and efficacy; namely, the fusion of G1 to a specific meningococcal antigen. When the fusion antigen was formulated with an adjuvant, it produced a positive bactericidal titre against all strains of meningococcus B tested, including those that were assayed in the presence of human complement, which suggests that G1 might have efficacy in humans.

These data suggest that such chimeric antigens could be used in a vaccine that would recognize all antigenic variants of FHBP and thus provide broad protection against meningococcus B infection. Moreover, structure-based design of chimeric antigens could be used to develop vaccines against other pathogens.

Charlotte Harrison

ORIGINAL RESEARCH PAPER Scarselli, M. *et al.* Rational design of a meningococcal antigen inducing broad protective immunity. *Sci. Transl. Med.* **3**, 91ra62 (2011)