SYNGEM: AN INTRANASAL PREFUSION-LIKE RSV F SUBUNIT VACCINE

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Respiratory syncytial virus (RSV) is an important cause of respiratory tract disease in (naive) young infants, older infants, the elderly and immune-compromised. Despite the medical need and the market potential, no licensed vaccine is available. Mucosis B.V. is a Dutch biotech company developing innovative mucosal vaccines, based on the Bacterium-Like Particles (BLP) technology. Such vaccines can be administered needle-free, e.g. through the nasal mucosa. In support of the mucosal approach, there is accumulating evidence that RSV F-specific local S-IgA antibodies secreted in the upper respiratory tract of humans correlate well with protection.

Because of its ability to induce broadly neutralizing antibodies the RSV F protein is the most attractive antigen. The current view is that in particular serum antibodies directed against the prefusion form of RSV F belong to the most potent neutralizing antibodies and the ability to elicit these is a pivotal attribute for a successful RSV vaccine. We studied different variants of F with respect to their conformation using neutralizing monoclonal antibodies (mAbs), following the view that F proteins mimicking the meta-stable prefusion form of F expose a more extensive and relevant epitope repertoire than F proteins corresponding to the postfusion F structure. Both addition of a trimerization motif and mutation of the furin cleavage sites increased the reactivity of F with the prefusion-specific mAb D25, with the highest reactivity being observed for F proteins in which both these features were combined. This candidate antigen, called Flys-GCN, is suitable in the development of mucosal as well as intramuscular RSV vaccines.

Here we describe the development of our intranasal candidate RSV vaccine, SynGEM, which is based on the validated BLP technology. The non-living BLPs allow for presentation of stable, trimeric prefusion-like RSV F proteins bound to the particle surface. Intranasal vaccination of naïve and convalescent mice with SynGEM induced long-lasting virus neutralizing RSV-specific serum IgG and robust levels of local IgA. Cotton rats immunized intranasally with SynGEM were protected upon RSV challenge, as represented by a low viral load in the lungs. Enhanced levels of pre- versus postfusion specific antibodies were observed in individual animals, confirming the ability of the SynGEM vaccine to induce potent neutralizing antibodies. A clinical Phase I study with intranasal SynGEM is planned for 2016.