Abstract

Safety, Immunogenicity and Efficacy, of a Sf9 Insect Cell-derived Respiratory Syncytial Virus Fusion Protein Nanoparticle Vaccine in Cotton Rats and Comparative Immunogenicity in Humans

Authors: Gregory M. Glenn, Gale Smith, Rama Raghunandan, Hanxin Lu, Bin Zhou, Lou Fries

Affiliations: Novavax, Rockville, MD, USA

Abstract:
The development of an effective RSV vaccine has challenges associated with demonstration of efficacy, general safety, and absence of disease exacerbation. The cotton rat model of RSV has proven to be predictive in the development of passive antibody prophylaxis using polyclonal antibodies (naturally acquired) and two monoclonal antibodies that target antigenic Site II on the F protein, (palivizumab and motavizumab). These antibodies have been shown to significantly reduce hospitalization due to RSV in infants. Development of a vaccine to be administered late in pregnancy to protect infants in the first months of life may be guided by use of the same relevant animal models.

Immunization of cotton rats with RSV F nanoparticle vaccine induced anti-RSV F-specific IgG antibody responses that were neutralizing (MN assay) and competed with a known protective monoclonal antibody for binding to antigenic Site II on RSV F. Control Lot 100 formalin-inactivated RSV vaccine induced non-neutralizing anti-F antibodies which lacked antigenic Site II binding. Upon RSV A2 challenge, nanoparticle vaccine groups demonstrated reduction in lung viral titers to below detectable levels (at least a 2,000-fold reduction). A reduction in nasal virus titers was also observed in animals that received aluminium adjuvanted RSV F vaccine. Passively transferred palivizumab also eliminated the virus from the lung and partially protected the nasal passages; and both palivizumab and the RSV F nanoparticle vaccine gave protection similar to prior RSV infection. Lung histopathology in these groups demonstrated, as expected, that Lot 100 formalin-inactivated RSV vaccine enhanced disease, whereas the nanoparticle vaccine and passive palivizumab treatments did not. In a Phase 1 placebo-controlled human trial, the same nanoparticle vaccine given to healthy adults induced anti-F IgG, RSV MN antibodies, palivizumab competitive and Site II-specific peptide binding antibodies. By contrast, placebo and day 0 sera exhibited little to no palivizumab-like immunity. Quantitative estimation of vaccine induced palivizumab activity suggests, that the highest dose group may have induced levels exceeding the 40 mg/ml trough level developed in the cotton rat challenge model and used as guidance for palivizumab efficacy evaluations that led to licensure.
Conclusions:
The RSV F nanoparticle vaccine candidate induced anti-RSV F IgG, RSV A and B neutralizing and palivizumab-competing antibodies in both humans and cotton rats. The data together suggest that passive immunity provided trans placental transfer of anti-RSV F antibodies induced by this vaccine that may safely protect infants in the first few months of life, where the morbidity and mortality from RSV is greatest.