STRUCTURALLY CONFINED INFLUENZA SUBUNIT VACCINES IN THE PREFUSION CONFORMATION ELICT A POTENT NEUTRALIZING ANTIBODY RESPONSE

Daniel Watterson, University of Queensland, Australia
d.watterson@uq.edu.au
Keith J Chappell, University of Queensland, Australia
Christopher McMillan, University of Queensland, Australia
Stacey Cheung, University of Queensland, Australia
Paul R Young, University of Queensland, Australia

Key Words: Influenza, vaccine, structure, epitope, neutralization, fusion, glycoprotein

Effective vaccination against influenza viruses remains a significant global challenge. Despite ongoing efforts, continual antigenic changes in circulating viruses requires constant update of existing vaccine approaches. Furthermore, the majority of current licensed vaccines are derivatives of live virus and are inherently time consuming to produce and limit the potential response time to counter a new virus strain. However, the combined advances in subunit vaccine production and structural determination of critical neutralizing epitopes within influenza hemagglutinin (HA) provide the groundwork for the next generation of influenza vaccines which have the potential to overcome these limitations. In an effort to expand on these findings we have compared the effectiveness of both prefusion and postfusion forms of recombinant influenza hemagglutinin (rHA) as subunit vaccines. Using a novel stabilization tag to confine rHA in the prefusion conformation we demonstrated that while both HA conformations elicit anti-HA responses in mice, a neutralizing response (PRNT50 1:36000) is only observed for prefusion rHA. Using rHAs from a range of influenza subtypes and domain specific constructs together with a large panel of structurally defined antibodies we also examined the epitope specificity and cross-reactivity of the prefusion specific neutralizing response. Interestingly, a similar conformation dependence has been reported for respiratory syncytial virus1, 2, suggesting a universal strategy for the generation of potent subunit vaccines to target enveloped viruses.

1. Magro, M. et al. Neutralizing antibodies against the preactive form of respiratory syncytial virus fusion protein offer unique possibilities for clinical intervention. Proc Natl Acad Sci U S A 109, 3089-3094 (2012).
2. McLellan, J.S. et al. Structure-Based Design of a Fusion Glycoprotein Vaccine for Respiratory Syncytial Virus. Science 342, 592-598 (2013).