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Identification of critical residues in the hemagglutinin (HA) that impact the replication, stability and immunogenicity of live attenuated influenza vaccines

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The intranasally administrated live attenuated influenza vaccine (LAIV) has been proven to be effective in preventing influenza virus infection in humans. Seasonal LAIV containing influenza A (H1N1, H3N2) and B subtypes require annual update to antigenically match drifting influenza viruses. It is often challenging to rapidly generate the vaccine seeds that replicate efficiently with high yield in embryonated chicken eggs, immunogenic in ferrets, antigenically accurate and genetically and phenotypically stable. The low yield of H1N1pdm09 viruses even after egg adaptation has posed a challenge for vaccine development since 2009. By cell culture adaption and reverse genetics, we successfully generated the high yield A/CA/7/2009 LAIV by introducing two additional amino acid substitutions (K119E and A186D) in the HA protein. The two changes also greatly improved the growth of the currently circulating 2013 and 2014 H1N1pdm viruses (6B genetic group) without affecting the antigenicity and immunogenicity of the vaccine virus. Moreover, a single amino acid in the HA2 region of A/CA/7/2009 that affected fusion pH and virus acid/thermal stability was identified which provided the genetic and structure basis for improving the stability of LAIV. The frequently drifting H3N2 viruses also grow poorly in eggs. Different egg adaptation amino acid changes (example I140K, L194P, G186V, H156Q, H183L, S219F/Y, I226N and N246H) found in different H3N2 strains are required for virus to grow efficiently in eggs. Thus, multiple vaccine variants generated from egg adapted wild-type viruses were assessed for their immunogenicity and antigenicity in ferrets. We found that the L194P often reduces the immunogenicity and G186V/H156Q impacts the antigenicity of the vaccine viruses. In the most recent season, new egg adaptation changes were found and their impact on the characteristics of vaccine viruses will be also discussed.

Biography

Zhongying Chen received her PhD in Molecular Biology and Biochemistry from Rutgers University, New Jersey, USA. She is currently a Senior Scientist at MedImmune, the biologics unit of AstraZeneca. During her tenure at MedImmune, she has been a technical lead in the research and development of live attenuated influenza vaccines (LAIV) for both seasonal and pandemic influenza viruses. She has over 25 publications in peer-reviewed scientific journals and several patents on the innovative improvement of the LAIV production.

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