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Irene González-Domínguez

Yonghong Liu

Eduard Puente-Massaguer

Nicholas Lemus

Stefan Slamanig

See next page for additional authors

Authors

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A UNIVERSAL INFLUENZA B VACCINE USING MOSAIC-HEMAGGLUTININ VACCINE CANDIDATES

Irene González-Domínguez, Department of Microbiology, Icahn School of Medicine at Mount Sinai, USA
irene.gonzalez@mssm.edu
Yonghong Liu, Department of Microbiology, Icahn School of Medicine at Mount Sinai, USA
Eduard Puente-Massaguer, Department of Microbiology, Icahn School of Medicine at Mount Sinai, USA
Nicholas Lemus, Department of Microbiology, Icahn School of Medicine at Mount Sinai, USA
Stefan Slamanig, Department of Microbiology, Icahn School of Medicine at Mount Sinai, USA
Tsoi Ying Lai, Department of Microbiology, Icahn School of Medicine at Mount Sinai, USA
Shirin Strohmeier, Department of Microbiology, Icahn School of Medicine at Mount Sinai, USA
Madhumathi Loganathan, Department of Microbiology, Icahn School of Medicine at Mount Sinai, USA
Jose Martínez-Guevara, Department of Microbiology, Icahn School of Medicine at Mount Sinai, USA
Florian Krammer, Department of Microbiology and Department of Pathology, Molecular and Cell-Based Medicine, Icahn School of Medicine at Mount Sinai, USA
Adolfo García-Sastre, Department of Microbiology, Department of Medicine, Global Health Emerging Pathogens Institute, The Tisch Cancer Institute, and Department of Pathology, Molecular and Cell-Based Medicine, Icahn School of Medicine at Mount Sinai, USA
Peter Palese, Department of Microbiology and Department of Medicine, Icahn School of Medicine at Mount Sinai, USA
Weina Sun, Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

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Influenza viruses undergo antigenic changes in the immuno-dominant hemagglutinin (HA) head domain, necessitating annual re-formulation of and re-vaccination with seasonal influenza virus vaccines for maintaining the protection. We previously synthesized mosaic HA (mHA) proteins of influenza B viruses which redirect the immune response towards the immuno-subdominant conserved epitopes of the B virus HA via sequential immunization. As ~90% of current influenza virus vaccines are manufactured using the inactivated virus platform, we generated and sequentially vaccinated mice with inactivated influenza B viruses displaying either the homologous (same B HA backbones) or the heterologous (different B HA backbones) mosaic HAs. Both approaches induced long-lasting and cross-protective antibody responses showing strong antibody-dependent cellular cytotoxicity (ADCC) activity. Thereafter, we tested different inactivation methods and adjuvants to increase the cross-protection against phylogenetically distant influenza B viruses from both lineages. The use of CpG 1018 or AddaVax boosted the humoral immune response and protection when combined with any inactivation method. Beta-propiolactone (BPL) inactivation was the best method, with high serum HA antibodies levels that correlated with optimal protection in BALB/C mice challenge studies. We believe that these B virus mHA vaccine candidates represent a major step towards a universal influenza B virus vaccine.

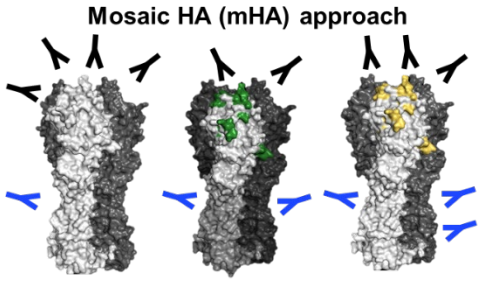

Figure 1: Sequential vaccination strategy with mosaic hemagglutinins The influenza B virus HA contains four major antigenic sites in the globular head domain, which are subjected to antigenic drift under immune selection pressures. To overcome the dominance of the major antigenic sites, we developed a vaccination strategy based on "mosaic" influenza B virus HAs (B mHA), where the major antigenic sites were replaced with corresponding sequences (green and yellow) from exotic influenza A virus HAs. In mice the sequential vaccination with different mHA proved to redirect the immune response toward subdominant conserved epitopes in the head and in the stalk of the spike protein. The subdominant epitopes in the head of the spike protein are marked by black antibodies, those in the stalk of the HA by blue antibodies. This methodology has helped to identify auspicious targets for use in universal influenza B virus vaccines (HA structure modified with PyMOL, PDB: 4M44).

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