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DEVELOPMENT OF A UNIVERSAL GROUP 2 INFLUENZA VIRUS VACCINE USING CHIMERIC HEMAGGLUTININ CONSTRUCTS

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The stalk domain of the hemagglutinin (HA) has become the prime target for universal influenza virus vaccine development in the last few years. Unlike the HA head domain, the immunosubdominant stalk domain is conserved to a higher level within each influenza virus HA group. Sequential vaccination with chimeric HA (cHA) vaccine constructs consisting of the same HA stalk and exotic head domains has proven to re-direct the immune response towards the stalk domain. This vaccination concept provides the basis for the development of more broadly cross-protective vaccines that are less affected by antigenic drift and shift, one of the main drawbacks of currently marketed influenza vaccines.

Most influenza virus vaccines are licensed as inactivated split vaccines. They are manufactured based on HA content with little to no information and standardization of neuraminidase (NA) content. Virus inactivation is generally performed with alkylating agents such as formalin (FA) or β-propiolactone (βPL), rendering the virus unable to infect or replicate. Though safe, whole inactivated virus vaccines can be highly reactogenic. Virus splitting with detergents like sodium deoxycholate (SDCO) and Triton X-100 (TX-100), which dissociate the virus into smaller parts while maintaining a good immunogenicity profile, are typically employed. To date, there are several studies assessing the effect of a variety of inactivating and splitting agents on influenza viruses, but little is known about the impact of combining these agents on HA stalk conformation and NA activity.

In this study, cH15/3_{HK14}N2_{HK14} and cH4/3_{HK14}N2_{HK14} cHA virus constructs were developed aiming at re-directing the immune response to group 2 HA stalk domains. Different inactivation methods with FA and βPL, and splitting with SDCO and TX-100 were tested to determine the best inactivation and splitting combination in terms of correctly-folded cHA and NA activity. A capture enzyme-linked immunosorbent assay (ELISA) was developed and employed to quantitatively measure the content of cHA with conformationally correct stalk domain. This assay employed a pair of monoclonal antibodies, one binding to a conformational epitope in the HA stalk domain, and the other targeting a linear epitope in the HA head domain. A recombinant cHA protein standard of known concentration was included for quantification of the cHA in the vaccines. The protective efficacy of group 2 cHA split vaccines against challenge with heterologous group 2 influenza viruses was tested after sequential vaccination of naïve BALB/c mice with cH15/3_{HK14}N2_{HK14} and cH4/3_{HK14}N2_{HK14} constructs with and without adjuvant. The results of this study are promising and support further development of a universal influenza virus vaccine candidate built on the cHA technology platform.