PALADINS: PROTECTIVE APPROACHES LEVERAGING AD-APTIVE AND IN-NATE SYSTEMS

Intranasal M2sr (m2-deficient Single Replication) Live H3n2 Investigational Influenza Vaccine Induces Hai Responses Against Drifted Influenza Strains, As Well As T Cell Responses And Mucosal Iga In Serosusceptible Adults

Joseph Eiden FluGen **Pamuk Bilsel** FluGen **Renee Herber** FluGen

Background: Influenza poses a significant threat to the operational effectiveness of military forces worldwide due to its ability to spread rapidly and cause an otherwise healthy population of service members to suddenly become ill and thus unable to conduct their duties. Currently available vaccines, inactivated or live, do not adequately protect the troops against seasonal influenza and offer no protection against novel pandemic viruses.

In a previous human clinical trial (Eiden et al. JID 2021), 108 TCID50 (tissue-culture infectious dose) of H3N2 (A/Brisbane/10/2007) M2SR protected against influenza drifted strain challenge amongst a subset of subjects who responded to vaccination with a serum MNT (microneutralization) titer increase > 2-fold, even though only 38% of the subset had > 4-fold HAI response against the vaccine strain suggesting that protection is mediated by immune effectors other than serum antibody such as mucosal antibodies. In this subsequent phase 1b clinical trial (NCT03999554), higher doses of M2SR were evaluated for increased immune responses against vaccine and drifted influenza strains.

Methods: Safety and breadth of immunity were assessed after one and two dose intranasal administration of 108 A/Brisbane/10/2007 or 108, 108.5 or 109 doses of A/Singapore/INFIMH-16-0019/2016 H3N2 M2SR vaccines in a double-blind, randomized, placebo (saline)-controlled study conducted with 182 adult (18-49 years of age) volunteers.

Results: All dose levels of vaccine were well-tolerated without any safety concerns. Mucosal and serum IgA responses as well as T cell responses were highest for the 109 dose of M2SR, with an additional, smaller increase after second dose. Serum HAI increases > 4-fold were observed against the vaccine strain for 0%, 27.5% and 71% of subjects after first dose of placebo, 108 or 109 M2SR (p
Increases also were stimulated in serum microneutralization titers (MNT) to drifted strains of H3N2 and in serum NAI and mucosal sIgA titers. Further increases in serum and mucosal immune response were noted after a second IN vaccination.

Conclusions: Compared to the 108 dose that protected against drifted strain challenge in a prior study, a single intranasal dose of 109 M2SR stimulated cellular immune responses and significantly increased mucosal and systemic antibody responses among serosusceptible adults. The breadth of the immune responses and the stimulation of serum HAI titers (the recognized surrogate of protection for inactivated, intramuscular influenza vaccines) indicates the potential for intranasal M2SR to protect against infection and disease by matched as well as drifted influenza strains and supports additional clinical trials with multivalent M2SR. Providing a broadly protective influenza vaccine that provides consistent high-level protection against multiple influenza strains such as M2SR to the over 2 million active and reserve defense members and their families would provide a significant advantage to the US population as well as operational readiness to troops who deploy globally.

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