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

Intranasal Immunization As A Route To Needle-free, Self Administration Of Vaccines.

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Background
The vast majority of vaccines are administered via intramuscular (i.m.) injection. This completely bypasses the sentinel innate immune system of the cutaneous and mucosal epithelia, requires assistance from medical staff to perform, and creates potentially biohazardous sharps and other waste. While the performance of next generation adjuvants, nanoparticle-based, and nucleic acid vaccines after i.m. administration is well characterized, the performance of such vaccines via intranasal (i.n.) administration is largely unknown.

Purpose
The purpose of the study was to establish whether i.n. delivery is non-inferior to traditional (i.m and subcutaneous) routes using a systems immunology approach.

Objective
The objective was to quantify markers of innate and adaptive immunity, immunogenicity, and efficacy against live virus challenge, after delivery of a model antigen (influenza hemagglutinin, HA) in protein and nucleic acid formats via different routes of administration.

Rationale
Intranasal (i.n.) delivery exploits the naturally immunogenic properties of the mucosal portals of entry and engenders a more rapid, more robust and longer-lasting protection than i.m. While both routes engender systemic IgG, i.n. also engenders mucosal IgA, the first line of defense against inhaled pathogens. Moreover, i.n. administration facilitates self-vaccination for both single-dose or prime/boost vaccine regimens.

Methods
Mice were administered HA formulated in different adjuvants (CpG, and/or MPLA and/or AddaVax squalene-in-water emulsion) or as mRNA/lipid nanoparticles (LNPs) via i.n., i.m. and/or s.c. routes. Assays for innate and adaptive immunity, including antibody breadth and virus neutralization, were performed to assess immunogenicity, while virus challenge studies were performed to assess efficacy.

Preliminary results
Preliminary data show squalene-in-water emulsion acts as both an antigen-presenting nanoparticle, as well as an antigen depot. A key finding is administration of HA in CpG+MPLA+AddaVax induces identical homo- and heterosubtypic IgG and IgA cross-reactivity profiles when administered via i.n. and s.c. routes. Studies on i.n. delivery of mRNA/LNPs are in progress.

Preliminary Conclusions
Intranasal administration is non-inferior to traditional routes for inducing systemic breadth and durability to influenzas HA, and has the added benefit of inducing a robust mucosal IgA response that traditional routes do not offer. Self-administration, such as by the i.n. route, would increase the mission effectiveness of military personnel by releasing them from the requirement to seek medical assistance for immunization.

Supported by Defense Threat Reduction Agency (DTRA) Grant HDTRA1-18-1-0036.