COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Development Of An Inhaled Broadly Neutralizing Antibody Treatment For Seasonal And Pandemic Influenza A

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Background: A potential influenza pandemic represents a considerable societal concern and can directly impact the readiness of military units. Even in a non-pandemic year, the 2017-18 flu season saw ~21 million influenza-associated medical visits, ~810,000 hospitalizations, and ~61,000 deaths. The health burden from an influenza pandemic is expected to rival if not exceed the COVID pandemic. Oseltamivir and baloxavir are only effective within the first 24-48 hours of symptom onset and are susceptible to escape variants. Additional therapeutic interventions that can address pandemic influenza are sorely needed.
Purpose/Objective: We are developing a platform of inhalable monoclonal antibodies (mAb) and immunoadhesions as broad-spectrum therapeutics for use as medical countermeasures against a diverse array of viral respiratory infections with pandemic potential. We are advancing inhaled delivery of a pan-influenza A (INFV-A) mAb that could expand the treatment window and reduce transmissibility of INFV-A.
Rationale: Influenza virus infects and spreads through continuous cycle of infection through apical membrane of respiratory epithelium and apical shedding, making it difficult to reach by systemic therapies. Direct delivery of mAb into the respiratory tract offers the promise of a safe and effective treatment that limits the impact of influenza outbreaks.
Relationship to Other Areas: Our strategy builds upon our pioneering work on a clinical-stage inhalable “muco-trapping” mAb platform. Inhaled delivery is immediate and highly efficient, overcoming the logistical hurdles of intravenous and intramuscular injections, offering >20-fold higher mAb concentrations in the respiratory tract compared to systemic dosing. Clinical testing using an anti-SARS-COV-2 mAb showed that nebulization can provide robust mAb levels throughout the respiratory tract.
Methods/Preliminary Results: We formulated IN-005, a potent broadly neutralizing mAb against INFV-A, for stable nebulization using a vibrating mesh nebulizer. We assessed IN-005 stability and aerosol particle size distribution. Across independent repeat experiments, we measured a mass median aerodynamic diameter of 3.92 µm (GSD = 1.73), with a fine particle fraction of 65.3% (particles <5.3 µm). These results confirm our ability to generate aerosols suitable for deposition throughout both upper and lower respiratory tract. Post-nebulized IN-005 exhibited ~97% main peak (monomer) by SE-HPLC, unchanged from pre-nebulization, with these findings confirmed on a protein gel. Hemagglutinin binding ELISA shows no reduction in IN-005 binding affinity post nebulization.
Preliminary Conclusions: The stable nebulization of IN-005 at high concentrations (50 mg/mL) supports once or twice daily brief (< 5 minute) nebulized treatments. Our findings position IN-005 as a potential medical countermeasure for seasonal and pandemic influenza A.
Impact: mAb-based biologics are exceedingly safe with minimal concern for drug-drug interactions. By sustaining highly inhibitory levels of IN-005 across all parts of the respiratory tract, we can likely prevent transmission by infected individuals, an essential feature for warfighters in enclosed settings (e.g., warships, submarines, barracks). Inhalon’s inhaled immunotherapy approach represents a promising platform for safe and effective, broad-spectrum therapeutics for current and emerging viral respiratory infections that can be readily deployed in both military and civilian settings.