BROAD-SPECTRUM THERAPEUTICS FOR VIRAL DISEASES: A MEDICAL COUNTERMEASURE PLATFORM FOR EMERGING THREATS

Development Of A Platform Of Broad-spectrum, Inhalable Immunobiologics For The Prevention And Treatment Of Emerging Viral Infections

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Background: Nearly all viral pandemic infections are transmitted via the pulmonary route.
Objective: We seek to develop a platform of inhalable immunoadhesins – biologics comprised of select host receptors linked to IgG antibody Fc – as broad-spectrum therapeutics for use as medical countermeasures against a diverse array of emerging viral respiratory infections.
Rationale: Respiratory viruses utilize a finite set of receptors available on the apical side of the airway epithelium to infect human cells. The ACE2 receptor is used by SARS-CoV-2, SARS-CoV-1, NL63 seasonal coronavirus, and select bat MERS-like viruses (e.g., NeoCoV) to gain cellular entry. Likewise, influenza (including pandemic influenza), parainfluenza, adenovirus, norovirus, and select seasonal coronaviruses target sialic acid to infect lung cells. It is highly improbable for viruses to mutate to utilize a completely new receptor, in part, due to the large surface area of contact between the viral antigen and host receptor. Thus, receptor-decoys conjugated to Fc (i.e. "immunoadhesins") directly overcome the one key shortcoming of monoclonal antibodies – loss of activity against evolving mutants, and represent a highly promising class of broad-spectrum therapeutics capable of neutralizing multiple pathogens.

Relationship to other areas of study: Our strategy builds upon Inhalon's pioneering work on an inhalable "muco-trapping" antibody (mAb) platform that is now in the clinic. Inhaled delivery is highly efficient, overcoming the logistical hurdles of intravenous and intramuscular injections, as well as offering immediate, >2 log higher concentrations of therapeutics at the site of infection compared to systemic dosing. We recently found in our Phase 1 clinical trial that a single inhaled dose may achieve protective concentrations in the lungs within minutes and lasting for many days.

Preliminary results: Utilizing ACE2 as our first immunoadhesin prototype, we created constructs that bind and neutralize all known variants of SARS-CoV-2 tested (including Omicron) with picomolar potencies and trap SARS-CoV-2 virus-like particles in human airway mucus. When dosed intranasally into SARS-CoV-2 infected hamsters, it reduced viral titers in nasal turbinates, even when dosed 24h or 48h after infection.
Preliminary conclusions: Inhalable immunoadhesins are a highly promising platform for preventing and treating a broad range of current and emerging viral respiratory infections.

Impact: Biologics are exceedingly safe, with limited concerns for drug-drug interactions, unlike small molecule antivirals. Inhalon's immunoadhesin approach directly blocks the viral life cycle like small molecule antivirals, but facilitates added protective functions that small molecules cannot, including enabling (i) rapid, direct clearance of pathogens from infected airways via our muco-trapping Fc, and (ii) immune-cell mediated killing of infected cells. Both mechanisms remove the source of highly inflammatory viral antigens from the lung, thereby preventing pneumonia that leads to hospitalization. Thermostable, lyophilized formulations can be created to support Warfighter resilience. Finally, our immunoadhesins have the potential to prevent transmission from infected individuals, an essential feature in enclosed settings (battleship, submarines, barracks). Combined with the convenience and superior pharmacokinetics from inhaled delivery, our immunoadhesin approach is well-suited to be readily deployable, safe and effective, broad-spectrum therapeutics for current and emerging viral respiratory infections in both military and civilian settings.

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