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Immune-engineered H7N9 Influenza Hemagglutinin Improves Protection against Viral Influenza Virus Challenge

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Introduction

Asian lineage avian influenza H7N9 virus infected ~1565 people from 2013 to 2017 with a 39% case-fatality rate [1]. Since 2019, there have been no additional reported human infections [1], but H7N9 influenza viruses continue to circulate in animal reservoirs. Since the H7N9 influenza viruses are of moderate to high risk to initiate an influenza pandemic, various world governments are stockpiling H7N9 viruses to accelerate vaccine production in the future. [2] However, the effectiveness of currently available H7N9 influenza vaccines is poor, requiring at least two doses with the maximum amount of antigen, plus adjuvant, to elicit a protective immune response. [3] For prompt production and distribution during an emergency, an H7N9 influenza virus vaccine that is effective following a single, minimum dose of vaccine is desired.

The avian H7N9 influenza HA protein has a substantially lower frequency of CD4$^+$ T-cell epitopes than HA antigens from seasonal influenza strains. [4] Although epitopes cross-conserved with seasonal influenza are present in H7 HA, [5] they do not sufficiently mobilize the memory compartment to support a strong immune response to the novel HA antigen. Furthermore, the H7 HA protein was predicted to contain a regulatory T cell (T$_{reg}$) stimulating epitope. [6] Incorporation of human-like epitopes capable of activating T$_{regs}$ is a mechanism of viral 'camouflage' known as antigenic mimicry, which permits escape from targeted human immune responses. [6] T$_{reg}$ epitope activated human CD4$^+$CD25^{high}CD39$^+$FoxP3$^+$ regulatory T cells suppress H7N9 influenza virus-specific peripheral effector interferon gamma positive T cell responses. In order to enhance H7 HA vaccines, T cell epitopes were added to the HA antigen to trigger a rapid recall response from preexisting seasonal