Development of outer membrane vesicle-based vaccine platform

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The present study aims to establish a novel vaccine modality that can rapidly respond to emerging infectious disease threats using outer membrane vesicles (OMVs) produced by probiotic bacteria. OMVs consist of various components derived from bacteria. Thanks to their multifaceted function particularly the potent mucosal adjuvanticity and the structural stability, OMVs can carry antigens, immunomodulatory molecules, and other beneficial molecules without being damaged by the innate immune system or environmental factors such as pH or temperature. In this proposal, the influenza virus is selected as the target pathogen. Seasonal influenza remains a major public health burden, especially in infants, elderly and immune-compromised subjects. A pandemic influenza vaccine that can efficiently induce both systemic and mucosal immunity is urgently needed worldwide.

First, a simple and rational method for OMV production using glycine will be utilized to collect large amounts of OMVs from a probiotic *E. coli* Nissle 1917 derivative lacking flagella, colibactin and lipid A. Then, scaffold molecules called SpyTag (ST) will be displayed at high density on the outermost surface of OMVs, designated as “Module A” (ST-OMVs). On the other hand, hemagglutinin-SpyCatcher (HA-SC) fusion protein, designated as “Module B” will be expressed by an appropriate mammalian expression system. Finally, HA (Module B) is sterically tethered on the OMVs (Module A) via a powerful bioconjugation technique between ST and SC, to complete OMVs displaying HA at high density (HA-OMV vaccine). In a mouse model study, we plan to establish rigorous immunization protocol that maximizes secretory IgA production in the oral and nasal cavities, as well as systemic IgG responses in the blood and lungs. Two mouse challenge experiments targeting the upper and lower respiratory tracts will be conducted to evaluate whether the HA-OMV vaccine can prevent both influenza infection and progression to severe disease. Immunization with the HA-OMV vaccine will also be performed in rhesus macaques to evaluate its efficacy in non-human primates. Furthermore, the long-term stability of HA-OMVs under lyophilized (freeze-dried) conditions will also be evaluated. If long-term stability is achieved, cold chain requirements can be eliminated, thereby facilitating global access to vaccines.

In summary, this study will provide proof of concept for our influenza OMV vaccine, paving the way for clinical trials and offering a potential strategy for global control of both seasonal and pandemic influenza. In addition, the rapid OMV vaccine development workflow proposed in this study is expected to be broadly applicable to other emerging, reemerging, and as-yet-unknown infectious diseases (so-called “Disease X”).