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

# A Self-assembling Vaccine Platform For Flexible And Efficient Development Of Prophylactic And Therapeutic Vaccines

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We have developed a novel, broadly immune-activating, self-assembling vaccine (SAV) platform to enable flexible and efficient development of prophylactic and therapeutic vaccines.
Components: The SAV consists of two components: 1) an adjuvanting and immune-targeting genetic fusion of a modified Mycobacterium tuberculosis heat shock protein 70 (MtbHSP70) with avidin (MAV) and 2) a biotinylated antigen component (BAC) that can include peptides, proteins, nucleotides or even polysaccharides specific to a pathogen or cancer. MAV is produced in an endotoxin-free CHO cell system that eliminates confounding immune signaling of bacterial lipopolysaccharides that has complicated development of HSP70-based vaccines. MAV, a fixed component in each specific vaccine, self-assembles with a BAC tailored to the specific pathogen/vaccine by simple mixing at room temperature.
Distinctives: The MtbHSP70 moiety enables targeting of antigen-presenting cells (APCs) in barrier tissues such as the skin and mucosa and cross-presentation of BAC epitopes, resulting in a balanced activation of both humoral and cellular immune responses. With the elimination of endotoxin contamination, SAV has been shown to induce high levels of T cell activation without the broad inflammatory sequelae of traditional adjuvants, making it appropriate for intradermal and mucosal delivery to APC-rich tissues without unwanted inflammation. SAV can be used with a range of intradermal or mucosal delivery systems and is capable of use in cross- and re-vaccination without blunting of immune responses.
Findings: The SAV platform has generated significant immune responses to a broad range of targets but its utility was limited by its production in bacterial expression systems. With scalable expression in a CHO cell system, SAV has shown significant, therapeutically-meaningful immune responses with no diminution of immunogenicity even at high doses. In collaboration with Voltron Therapeutics, a SAV candidate (VTX-067) targeting human papillomavirus (HPV) and HPV-induced cancers was developed using biotinylated peptides of concatenated epitopes targeting the HPV E6 and E7 proteins. C57BL/6J mice intradermally vaccinated with VTX-067 generated statistically significant responses of both CD8+IFNg+ and CD4+IFNg+ T cells at doses of 215 and 350 µg compared to saline-treated groups, without activation of TNFα responses. In a therapeutic study, mice vaccinated with VTX-067 at doses of 80, 130, and 215 µg survived significantly longer after introduction of a TC-1-based tumor ($p < 0.0001$; log-rank followed by Mantel-Cox tests) with markedly slower tumor growth than mice in control groups; 40% of the vaccinated mice in the 350 µg dose group were tumor-free at the end of the study. This vaccine was also delivered intramucosally to generate similar protective responses.
Future Development: The SAV platform is under development for prophylactic vaccines under U.S. Army Medical Research Development Command award HT94252310586. Year 1 goals are to demonstrate protection against two different types of viruses (H1N1 influenza and vaccinia); year 2 goals are to develop the platform for scalable use in vaccine development for the Army; year 3 goals are to provide proof of concept of the evolved platform to rapidly generate a new prophylactic vaccine against Rift Valley fever virus.