IMMUNIZATION WITH A SELF-ASSEMBLING NANOPARTICLE VACCINE DISPLAYING EBV GH/GL PROTECTS HUMANIZED MICE AGAINST LETHAL VIRAL CHALLENGE

Harman Malhi[1], Leah J. Homad[1], Yu-Hsin Wan[1], Bibhav Poudel[1], Brooke Fiala[2,3], Andrew J. Borst[2,3], Jing Yang Wang[2,3], Carl Walkey[2,3,†], Jason Price[4,¶], Abigail Wall[1], Suruchi Singh[1], Zoe Moodie[1], Simran Handa[4, §], Colin Correnti[4, ††], Barry L. Stoddard[5], David Veesler[2,6], Marie Pancera[1], James Olson[4,¶], Neil P. King[2,3] and Andrew T. McGuire[1,7,8]

[1] Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle WA, 2 Department of Biochemistry, University of Washington, Seattle, WA, [3] Institute for Protein Design, University of Washington, Seattle, WA, [4] Clinical Research Division, Fred Hutchinson Cancer Research Center Seattle, WA, [5] Division of Basic Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, [6] Howard Hughes Medical Institute, [7] Department of Global Health, University of Washington, Seattle, WA, [8] Department of Laboratory Medicine and Pathology, University of Washington, Seattle WA, [#] Neoleukin Therapeutics, Seattle, WA, [¶] Ben Towne Center for Childhood Cancer Research, Seattle Children's Hospital, Seattle, WA, [§] Harvard-MIT Program in Health Sciences, Harvard University, Boston, MA, [††] Link Immunotherapeutics, Seattle, WA.

hmalhi@fredhutch.org

Epstein-Barr virus (EBV) is a cancer-associated pathogen responsible for 140,000 deaths per year. EBV is also the etiological agent of infectious mononucleosis and is associated with multiple sclerosis and rheumatoid arthritis. Thus, an EBV vaccine could alleviate significant morbidity and mortality. EBV is orally transmitted and has tropism for both epithelial cells and B cells which are present in the oral cavity. Therefore, a prophylactic vaccine would need to prevent infection of both cell types. Passive transfer of a dual-tropic neutralizing monoclonal antibody targeting the viral gH/gL glycoprotein complex prevents experimental EBV infection in humanized mice and rhesus macaques, suggesting that gH/gL is an attractive vaccine candidate. Here, we produced and evaluated the immunogenicity of several nanoparticle immunogens displaying gH/gL with distinct valencies and geometries. After one or two immunizations, all nanoparticles elicited superior binding and neutralizing titers relative to monomeric gH/gL. Antibodies elicited by a computationally designed self-assembling nanoparticle that displays 60 copies of the gH/gL protein conferred protection against a lethal dose of EBV in a humanized mouse challenge model, whereas antibodies elicited by monomeric gH/gL did not. Taken together, these data motivate further development of nanoparticle vaccine candidates for EBV.