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

Quantification Of Human Heterogeneity In CD8+ T Cell Responses: Immune Correlates Of Protection

Carmen Molina-París Los Alamos National Laboratory **Duane Harris** LANL **Apoorv Shanker** LANL **Makaela Montoya** LANL **Trent Llewellyn** LANL **Anna Matuszak** LANL **Aditi Lohar** LANL **Jessica Kubicek-Sutherland** LANL **Ying Wai Li** LANL **Kristen Wilding** LANL **Ben Mcmahon** LANL **Sandrasegaram Gnanakaran** LANL **Ruy Ribeiro** LANL **Alan Perelson** LANL

Background Vaccines have historically played a pivotal role in controlling epidemics. Effective vaccines for viruses causing significant human disease, e.g., Ebola, Lassa fever, or Crimean Congo hemorrhagic fever virus, would be invaluable to public health strategies and counter-measure development missions. Here, we propose metrics to quantify vaccine-induced CD8+ T cell-mediated immune protection, and to characterise immuno-dominant epitopes, in light of human genetic heterogeneity and viral evolution. Proof-of-principle of our methods is demonstrated for Ebola virus, SARS-CoV-2, and Burkholderia pseudomallei (vaccine) proteins.

Objectives and rationale CD8+ T cells express a unique receptor on their surface: the T cell receptor (TCR). The binding of TCRs to immunogens on the surface of infected cells initiates an immune response. For CD8+ T cells the immunogen is a complex composed of a viral peptide bound to a major histocompatibility complex (MHC) class I molecule, or pMHC complex. In humans, the MHC molecule is also called human leukocyte antigen (HLA). This constitutes the MHC-restriction of TCR immunogen recognition. MHC-restriction brings additional challenges to the study of CD8+ T cell responses, since the HLA locus is the most polymorphic gene cluster of the entire human genome, and genome-wide association studies of host and virus genomes have shown that different HLA alleles exert selective pressure, driving in vivo viral evolution. Our objective is to define novel metrics to quantify CD8+ T cell-mediated vaccine protein coverage, in light of human HLA heterogeneity, viral evolution, and immuno-dominant epitopes.

Methods and results Desirable in a vaccine-induced CD8+ T cell immune response is for it to be broad and directed against several immunogens, ideally from conserved genome regions, to reduce the possibility of selecting viral escape variants, and to make it more difficult for the virus to exhaust that response. We hypothesise that the problem to optimise CD8+ T cell-mediated vaccine coverage across the human population, while minimising viral escape is best, and naturally, posed in terms of a multi-partite graph (see figure below), given the HLA genetic heterogeneity, the bimolecular nature of T cell immunogens, and that immunogen recognition by TCRs is inherently cross-reactive. We define a mean regional coverage metric for a choice of vaccine protein and geographical region, e.g., Australia, Europe, North-Africa, North-America, North-East Asia, Oceania, South and Central America, South-Asia, South-East Asia, Sub-Saharan Africa, and Western-Asia. The mean regional coverage metric is the normalised mean of the product of HLA allele frequencies in the region, allele binding scores to vaccine peptides, and peptide immunogenicity. Since it does not capture the fact that an individual carries two alleles, we propose an individual regional coverage metric and compute it as well. Finally, we discuss immuno-dominant epitopes, in light of recent studies for Ebola GP and SARS-CoV-2 spike protein.

Conclusions and impact to the JSTO mission We propose a method to quantify human HLA heterogeneity in CD8+ T cell-mediated vaccine responses that will help develop vaccines more rationally. The methods proposed can be applied to pathogens of interest to JSTO mission such as Lassa virus and Crimean Congo hemorrhagic fever virus.

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