The MRKAd5/HIV Step Study employed a replication incompetent adenovirus 5 (Ad5) vector expressing HIV proteins. Surprisingly, vaccinees that were previously Ad5 seropositive had an increased risk of HIV-1 acquisition, and the study was stopped early. However, sieve analysis of the MRKAd5/HIV cohort suggests that the elicited immune response was sufficient to exert selective pressure on the infecting virus. In an attempt to understand the mechanisms which led to these different vaccine outcomes, Drs. Erica Andersen-Nissen and M. Juliana McElrath (Vaccine and Infectious Disease Division) led a team of investigators from the Fred Hutchinson Cancer Research Center, Seattle Biomed, and the University of Washington, employing Systems Biology to investigate the early immune responses induced by the MRKAd5/HIV vaccine.

Systems Biology draws upon large datasets, including genomic and proteomic data that have been correlated to defined biological pathways. Experimental datasets are compared to these defined pathways with the goal of identifying underlying patterns in biological responses that may not be obvious using traditional reductionist experiments.

The team profiled transcriptomes from blood samples taken from vaccinees before and within one week after vaccination with MRKAd5/HIV. Expression levels of more than 2000 genes changed after vaccination in both Ad5 seropositive and negative vaccinees, particularly genes involved in inflammatory and interferon response pathways. In addition, “Myeloid” modules were increased while “Lymphoid”, “T cell”, and “Cytotoxicity” modules were suppressed, suggesting that the vaccine induced an influx of myeloid cells and an efflux of lymphoid cells in the peripheral blood. However, Ad5 seropositive patients had 306 gene responses that were attenuated relative to seronegative individuals, including complement, pathogen recognition, and G-protein coupled receptor pathways. These vaccinees also attenuated their lymphocyte efflux from peripheral blood. These data suggest that the MRKAd5/HIV vaccine rapidly induced a broad immune response, but that this immune response in Ad5 seropositive individuals was profoundly weakened. This finding contradicts one of the leading hypotheses for the vaccine failure, which posits the increased risk for Ad5 seropositive individuals was due to a hyperactive immune response increasing the HIV target cell population and leading to enhanced susceptibility in these patients. Instead, it appears from this study that the
preexisting immunity may have effectively lowered the vaccine dose below the threshold necessary for an effective immune response.

The team next asked how the early immune response elicited by this HIV vaccine compared to the response elicited by the protective yellow fever vaccine YF-17D. While the response to MRKAd5/HIV peaked at 24 hours and faded by 168 hours post vaccination, YF-17D induced changes were delayed, and peaked after 168 hours. Published in vivo profiles of YF-17D suggest that this vaccine alters a smaller subset of genes compared to MRKAd5/HIV, primarily in the “Interferon response” module. These comparisons also identified two genes, CRIP3 and NPB that were correlated with poor CD8+ T cell responses to both vaccines.

Learning how a vaccine failed may be even more challenging than predicting how one may succeed, but the systems biology approach used in this publication has identified differences between immune responses elicited in Ad5 seropositive and seronegative patients. This study suggests several hypotheses for the failure of the MRKAd5/HIV vaccine to protect vaccinees. Preexisting immunity to Ad5 may have reduced the effective dosage of the vaccine they received; alternatively, Ad5 neutralizing antibodies may inhibit the innate immune response, potentially targeting the vaccine to inappropriate immune cells. It also identified significant differences between the responses to vaccines using different vectors. Taken together, the data and hypotheses generated by a global evaluation of early immune responses to vaccination should guide the rational design of an effective HIV vaccine.


Gene map of vaccine responses. (Top) Vaccinees without preexisting Ad5 immunity (black) have a stronger immune response to MRKAd5/HIV vaccination than patients with moderate (dark green) or high (light green) Ad5 antibody titers. (Bottom) The immune response to MRKAd5/HIV (red) is qualitatively different and more rapid than the response to yellow fever vaccination (blue).