GVIRF 2018 Workshop 4: Immunological Principles of Vaccines and Vaccination	
Rapporteurs: Nancy Touchette (NIAID)	
Session Outline	**Chairs:** Annie Mo (Program Officer, NIAID) Bernhards Ogutu (Chief Research Officer, KEMRI) **Presentations:** *Introduction,* Annie Mo (Program Officer, NIAID) *Immunological Challenges in Vaccination and Vaccine Development*, Andrew Pollard (Professor of Paediatric Infection and Immunity, University of Oxford) *New Technologies for Studying Human Immunity*, Lisa Wagar (Postdoctoral Fellow, Stanford University School of Medicine) *RTS,S Malaria Vaccine: Toward an Understanding of the Immunologic Basis of Protection*, Christian Ockenhouse (Director, Medical and Clinical Operations, PATH Malaria Vaccine Initiative) **Panelist:** Bernhards Ogutu (Chief Research Officer, KEMRI)
Objectives of the session	*To discuss:* • Current challenges for vaccine and vaccination and how basic immunological research can help guide vaccine development • Cutting edge technologies and new tools applicable for human immunology studies and the current understanding of human immune system using available tools • Historical studies on correlate of protection for various malaria vaccine trials, how regimen can change the quality of immune response and lead to different vaccine efficacy outcomes and how this can apply to future vaccine trial design
Main outcome	New technologies and strategies are now available that can help to investigate the immune response and inform vaccine development.
Summary	Most vaccines have been developed by trial and error; sophisticated immunology was not required because most of those "low-hanging fruit" vaccines elicited good protective responses. For the remaining challenging disease targets, a better understanding of correlates of protection and human immune systems would better guide vaccine research and development. Remarkable tools are now available for human immunology research and vaccine evaluation, such as systems biology and immunology, protein arrays, genetics, epigenetics, and RNA sequencing. Assays to measure antibody responses include microneutralization, hemagglutination inhibition, opsonophagocytosis, and affinity and avidity measurement. New technologies to dissect T cell responses include Mass cytometry (CyTOF) which allows simultaneous analysis of 30-50 markers at single cell resolution; and single cell T cell receptor (TCR) sequencing combined with Grouping of

	Lymphocyte Interactions by Paratope Hotspots (GLIPH) to identify convergence groups of TCRs and discover ligands or antigens for future vaccine design. Organoid models derived from healthy tonsillectomy tissue recapitulate the composition, structure, and function of lymphoid tissue *in vitro* and offer the opportunity to probe the mechanisms of adaptive responses, bridging the gap between animal models and human trials. A number of vaccine candidates elicit antibodies but yield titers that have not correlated with protection and show variability across age groups and regions. Therefore, there is need for characterization of the antibodies generated on exposure to vaccines to protect against disease such as malaria, which have multiple developmental stages in the human host. Understanding correlates of protection and protective mechanisms for many vaccines remains challenging. Controlled human malaria infection (CHMI) and field trials have contributed to the understanding of correlates of protection for the RTS,S malaria vaccine. Antibodies to the NANP repeat domain in RTS,S are associated with protection. However, protection varies depending on age group, epidemiological setting (e.g. force of infection), parasite genetic diversity, or even dose and schedule of vaccination, and no antibody threshold reliably predicts protection. New strategies to enhance RTS,S vaccine efficacy include adjusting vaccination dose and schedule for better antibody avidity or affinity and vaccine efficacy. To date, the best predictor of protection for malaria vaccines has been protection in CHMI studies. Many significant scientific challenges remain. For example, the role of T cells in protection, the immune basis of herd immunity, how viral shedding affects transmission, and how host or microbe factors affect protection are still poorly understood. While more immunology research should be carried out using cutting edge technologies and Control human infection (CHI) models, there are limitations in that CHI does not adequately predict field situations and reflect natural settings. Additionally, because of resource constraints, it is important to carefully balance the conduct of basic immunology research versus actual development of new vaccines against challenging pathogens.
Key references or quotes	“The best correlate of protection is protection.”