GVIRF 2014: title of the session: Systems Vaccinology	
Rapporteurs: Valentina Di Francesco (NIAID); LanLing Zou (NIAID); Lynda Stuart (B&MGF)	
Session Outline	**Chair: Ingileif Jonsdottir** (SOC) **Opening remarks:** Introduction **Ingileif Jonsdottir** (SOC;University Hospital of Iceland) **Presentations:** Systems vaccinology for the evaluation of vaccine response and identification of critical pathways **Bali Pulendran** (Emory) (10') Application of technological advances to clinical trials **Willem Hanekom** (SATVI) (10') **Discussants:** **Bali Pulendran** (Emory),**Willem Hanekom** (SATVI),**Ingileif Jonsdottir** (SOC; University Hospital of Iceland); **David Lewis** (University Surrey), **Emmanuel Hanon** (GSK) **Pieter Neels** (consultant) **Closing Remarks: Ingileif Jonsdottir**
Objectives of the session	Generate new ideas and strategies to accelerate clinical evaluation of new vaccines. Question to be addressed: How can technological advances and/or systems vaccinology accelerate vaccine development, through the identification of biomarkers and predictors of vaccine efficacy and safety, as well as by gaining new insights into protective immunity?
Main outcome	Considerations for a scientific and regulatory framework for proof of concept clinical studies and vaccine testing trials using advanced technologies.
Summary (400-500 words)	Nowadays when conducting a clinical study the information traditionally collected can be complemented by data derived from advanced technologies for genomics (including genome variants and whole genome sequencing, HLA, T and B cell sequencing), proteomics, mass cytometry, metabolomics, transcriptomics and single cell analyses. However, the use of these technologies also greatly increases the dimensionality and complexity of the research datasets and the analysis needs. This session discussed the technical aspects of applying these technologies in clinical studies and vaccine testing trials. Dr. Bali Pulendran introduced the concept of "Systems vaccinology" which uses the tools of systems biology to identify predictors of vaccine efficacy and provides new insights into the mechanisms of protective immunity through the identification of molecular signatures. The effectiveness of this approach was demonstrated with 2 studies conducted with the yellow fever and flu vaccine. This approach, although extremely data intensive, promises to lead to new and unanticipated discoveries. He listed several examples of such data-derived knowledge: the nutrient sensing linked to CD8 responses; TLR5 involved in intestinal microbiome-mediated immune responses; and effect of genetic and environmental diversity. Dr. Hanekom introduced the notion of "experimental medicine trial" for candidates up selection in early stages of vaccine R&D. The main objectives are for initial safety and hypothesis testing, and they may include multiple proof-of-concept phase 1 studies for various vaccine designs (antigen classes, vehicles, adjuvants) and, possibly in parallel with animal testing. Dr. Hanekom also presented the lessons learnt from a study conducted to identify correlates of risk for tuberculosis disease in a human population using advanced technologies. Lessons included the need for well-defined phenotypes to define biomarkers; the adequate sample sizes, the need of follow up and control studies; the quality of clinical practice control; and the consistency of analysis approaches. We need quality standards for every step of the study and across multiple sites/groups to avoid different biological interpretation of the same datasets. Other issues raised during the panel discussion: • Advanced technologies could be used in trials to identify biomarkers of safety as predictors of safety and toxicity. These approaches should also be supplemented by old fashion toxicology assays for cross-validation purposes. • Clinical trials are typically conducted with healthy volunteers, but the inclusion

	of individuals with comorbidities is more adequate for safety studies. • Systems biology is generally a discovery tool and is not hypothesis driven. It can be used to explore the multi-parametric mechanisms after vaccine administration, but the hypotheses to be tested must be defined up front and better approaches are necessary to extract knowledge from data. • From the regulatory point of view, validation, standardization and reproducibility of the vaccine testing results are necessary. These requirements may be difficult to satisfy when using advanced technologies with a systems biology approach. However, for vaccine developers the approach may help guide the product through the phases of a vaccine trial by detecting subtle and unexpected signals that may be correlated to clinical events. • With respect to sample sizes, the sample numbers can be limited for efficacy studies, but safety studies require large sample sizes. • Partnerships between vaccine developers and -omics technologists at academic institutions are needed at early stages to facilitate the design and interpretation of the studies. • Open access to data from vaccine testing trials together with the appropriate analytical approaches would be useful. However the high complexity of the research data, the intricacies of the new technologies and the intellectual property value for vaccine developers should also be considered. • Consider system biology when designing trials and mobilizing resources. A framework for conducting systems vaccinology studies in conjunction with vaccine testing trials needs to be established to validate the effectiveness of the systems biology approach.
Key references or quotes (up to 5)	*"We are drowning in a sea of data and thirsting for knowledge"* (Sydney Brenner) Nature Immunity 2014 Li *et al.* – mentioned by Bali