Recently, for the first time in the more than three decades since the discovery of HIV, a candidate HIV vaccine (RV144) in a clinical trial in Thailand, was shown to result in a modest 31% reduction in infection compared with placebo [1]. Apart from reenergizing a field that has been humbled by failure, this trial has provoked a key question: “What caused this modest effect on protection from acquisition?” Interestingly, there was a suggestion that protection occurred early after vaccination, and vaccine efficacy diminished over time. Thus, the vaccine stimulated a modest protection against acquisition, but not viral control after infection [1]. The nature of the immunological mechanisms that gave rise to this modest effect is unknown, but the prototypic high-titer broadly reactive neutralizing antibodies and cytotoxic T cell responses commonly thought to provide vaccine-induced protection are believed not to play a major role. At the recent AIDS Vaccine 2011 meeting in Bangkok, it was announced that post-hoc analysis of the correlates of protection in the RV144 trial revealed that the magnitude of the IgG binding antibody response against the V1V2 region was correlated inversely with the infection rate (Haynes, AIDS Vaccine 2011). Despite this very encouraging result, the nature of the immunological parameters that gave rise to this modest degree of protection is unknown, highlighting the urgent need to understand the pathways that must be activated to elicit the immune responses necessary to prevent and/or control HIV infection.

In this context, recent advances have used systems biological approaches to identify molecular signatures induced early after vaccination that correlate with and predict the later adaptive immune responses in humans [2–5], and to obtain novel mechanistic insights about vaccine induced immunity. These results highlight the potential utility of systems approaches in vaccinology. In particular, such an approach is likely to be transformative in enabling rational vaccine design against HIV by revealing key insights about the
mechanisms of vaccine induced immunity, and the molecular networks driving protective immunity to HIV. Systems approaches are also beginning to play a critical role in the testing of HIV vaccine candidates in clinical trials, by facilitating the identification of molecular signatures that predicting later immune responses. The collection of articles in the present volume addresses the critical challenges and opportunities posed by the burgeoning field of “systems vaccinology” in HIV vaccine research.

Girard and Plotkin set the stage for the discussion in their article on “HIV Vaccine Development at the Turn of the XXIst century,” by providing a historic overview of three decades of failed efforts at HIV vaccine development, leading up to the modest success in the RV144 Thai trial. Spurred by this modest success, a major effort is underway to delineate the correlates of protection. Systems biological approaches are increasingly become an integral component of such efforts. Fittingly, a series of articles focus on the application of systems biological approaches in evaluating vaccine immunity in humans.

Nakaya and Pulendran review recent successes in the application of systems biological tools to predicting the immunogenicity of the yellow fever and influenza vaccines, and discuss the promise and challenges of such an approach in HIV vaccinology. One clear promise is the identification of correlates of protection, and mechanistic insights about the immune responses that mediate protection. However making the data → knowledge → understanding transition poses major challenges, beginning with the major issue of dealing with the large and noisy datasets generated by high throughput techniques, as well as coping with the variability inherent at the population, individual, cellular molecular and technical levels. Zak and Aderem continue on this theme, and suggest that while systems analyses of immune responses in the blood of vaccinees may permit identification signatures of vaccine efficacy, deriving mechanistic insights will need an integrated approach that involves in vitro and in vivo (mouse, non human primate and clinical) analyses. Such an iterative systems vaccinology approach is likely to be fruitful in yielding mechanistic insights.

Haddad and Pantaleo highlight the utility of systems biology approaches in HIV vaccine development, emphasizing its potential impact on post hoc analyses of the RV144 trial. They also highlight a potentially exciting approach in which the transcriptional profiles of viral vectors (e.g. pox vectors) on human dendritic cells in vitro, could yield surrogate biomarkers of the immunogenicity of such vectors in vivo. Whether in vivo immunogenicity can be reliably predicted by in vitro approaches remains to be determined.

Andersen-Nissen et al provide a broad perspective of how systems approaches are beginning to revolutionize the evaluation of vaccine testing in clinical trials. They suggest that novel systems biology studies of efficacious, licensed vaccines provide a new template for analyses of HIV vaccines, and emphasize how current HIV vaccine clinical trials are undergoing design modifications and increased standardization of specimen collection and immune responses assays, in order to generate datasets relevant for systems analyses.

Three articles that follow reveal the power of systems approaches in delineating the molecular pathways of CD8 T cell differentiation during and immune responses. Youngblood et al discuss how transcriptional profiling of virus specific CD8 T cells in mice
have yielded deep insights about the mechanisms that delineate functional memory versus exhaustion. Haining and Barnitz discuss how transcriptional profiling of antigen specific CD8 T cells responding to HIV, coupled with pattern recognition algorithms to identify subclasses in microarray datasets, is beginning to reveal the heterogeneity of responding T cell populations. Finally Miconnet and Pantaleo show how another systems biology approach namely deep sequencing of TCR repertoire as allowed to unravel an unprecedented level of TCR (TRB) diversity in the response to pathogens; more interestingly the authors show the conservation among different subjects of TRB sequences suggesting that exposure to pathogens could be the driving force in the evolution of TRB sequences.

The NHP model has brought significant contributions to the understanding of HIV pathogenesis and has been used quite successfully to screen different HIV candidate vaccines for efficacy in assessing protection from challenge highly infectious virus challenge. Most of these studies have used conventional approaches in the monitoring of immune responses. In the last series of papers in this issue Silvestri and Muller Trutwin focus on the application of systems biology approaches to a model of natural protection to the development of immune deficiency in the SIV model, a system that is reminiscent of long term non progressors. This system can allow the in depth characterization of naturally occurring protective immune responses. The persistence of a strong innate immune response in SIV infected Rhesus macaques as compared to naturally protected macaques and particularly high levels of type I Interferons were shown using systems biology. The contribution of inflammation to the development of HIV and SIV disease is also highlighted in the manuscript by Beneke and Katze. The studies described by these authors suggest auto-attenuation of innate immune responses as a potential proof reading mechanism that controls the immune activation characteristic of pathogenic infection.

The reviews in this issue highlight the little we know about correlates of protection. However they clearly indicate that systems biology approaches have already provided some clues to the quest for the vaccine induced or natural immune correlates of protection. Furthermore we provide a roadmap for the identification, validation and definition of the mechanisms that are encompassed by these signatures. An important component of a system biology strategy is the development of a globally accessible data base that would capture results generated from preclinical and clinical trials of licensed and experimental vaccine regimens; the features of this data base are described in the manuscript by Cameron et al; it highlights the importance of the rigorous verification and validation of the data entered and their validation. This database should be globally accessible, thereby allowing all investigators in the field to compare and contrast their results. Meta-analysis of gene expression profiles have already provided important clues as to the conservation of different results. This is illustrated in Figure 1 where we show that transcriptional profiling constitutes the first step in a strategy aimed at defining correlates of immune protection. The deployment of other “OMIC” approaches and the validation on independent cohorts is critical to a final identification of these correlates. The availability of animal models where challenge experiments can be performed is essential, as it will allow the dissection and understanding of the molecular mechanisms that underlie these correlates. Overall, this issue
highlights the many different contributions of systems biology to the quest for the elusive correlates of immune protection.

References

Clinical trials studying natural infection, currently licensed vaccine or new vaccine regimens generate data that are analyzed by one or more “omics” approaches and integrated by computational methods to generate meaningful datasets. The generation of new hypotheses leads to news the development of new vaccine strategies that are tested in new clinical trials. The vaccine development will therefore accelerate and increase the number of new clinical trials that will feed the cycle. During this process, new biomarkers will be defined, leading to the development of better vaccination strategies and the definition better predictors of vaccine success prior vaccination. The ultimate outcome of this process will be the development of targeted vaccine regimens for a personalized vaccination.

Figure 1. The iterative cycle of systems biology approaches in vaccine development