Bridging the Gaps between Fundamental, Preclinical and Clinical Research: Report from a Global HIV Vaccine Enterprise Working Group

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A. INTRODUCTION

The Global HIV Vaccine Enterprise (the Enterprise) convened a two-day workshop on 17-18 September 2009, at the Enterprise offices in New York; to discuss approaches to bridging the gaps between fundamental, preclinical and clinical HIV vaccine research. The topic of this Working Group originated from discussions of the Enterprise Science Committee, which proposed that more effective collaboration between these three areas of HIV vaccine research is needed in order to accelerate the pace of scientific progress in the field. Because the meeting took place before the release of the RV144 trial results held in Thailand[1], the conclusions reached during the meeting were further discussed during consultations at scientific conferences and at a joint meeting of the Science Committee and Chairs of all five Working Groups. Thus, this Report reflects both the original discussions of the Working Group and subsequent discussions that took place after the release of the RV144 trial results. Members of the Working Group have reviewed this Report.

During the meeting, Working Group members emphasized the unique role of efficacy trials in testing the ability of different vaccine concepts to induce protective immune responses in humans. The results of the four HIV vaccine efficacy trials that have been conducted to date were not generally anticipated and have deeply influenced directions of research. Failure of the VaxGen candidate to induce immunological protection[2] accelerated the shift in the field toward cell-based vaccines; the early termination of the Step trial[3] was viewed by many as the failure of a cell-based vaccine strategy; while the results of the RV144 trial[1] have now brought new attention to the possible role of innate immune responses and non-neutralizing antibody functions as keys to achieving protection and the importance of CD4+ T cell responses after vaccination. These shifts in the conceptual framework on how to best design an effective HIV vaccine reflect both the current very limited understanding of the pathways to immunological protection[4], and the view that the main purpose of efficacy trials is to advance a vaccine product toward licensure. However, the most significant contribution of these trials has been to deepen our scientific understanding of vaccine-induced responses and their effects on HIV. For example, even though the Step vaccine showed no efficacy, post-hoc analyses from this trial have provided evidence of sieve effects on viral diversity in breakthrough infections[3,5], the narrow breadth of elicited T-cell responses[6], and the possible role of preexisting vector immunity in increasing susceptibility to HIV[3]. At the same time, advances in laboratory and computational tools are providing new opportunities for rigorous scientific investigation in humans. It is imperative to recognize that the next efficacy trial(s) may not lead to a licensable product; as such, we have to do a better job of integrating scientific inquiry into trial protocols from the beginning to maximize learning opportunities. Importantly, while this conclusion was reached before the Thai trial results were known, subsequent discussions have reinforced this view and underpinned the call for scientifically-rich clinical trials. The efficacy results of the RV144 prime-boost strategy, albeit modest, have provided new impetus to search for correlates of protection. At the same time, recent advances in fundamental biomedical research and HIV biology have increased the likelihood that this search for correlates will be successful. However, to take full advantage of these advances, the field needs to explore ways to bridge the gap between clinical and basic research.

The Working Group also discussed the very important role that non-human primate (NHP) studies play in HIV vaccine research. It was agreed that the ability of currently used animal models to predict the outcome of vaccination in humans is uncertain, and therefore, that demonstration of immunogenicity and/or efficacy by a vaccine candidate in NHPs, while desirable, is not absolutely necessary for advancement of the candidate to clinical trials. Instead, the focus of NHP research should be on those fundamental questions of viral-host interactions that cannot be easily addressed in humans. Two areas of particular importance were identified: first, a focus on dissecting the immunologic mechanisms responsible for protection against virus challenge; and second, understanding early immunological events, especially at mucosal surfaces,

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occurring at the earliest times after vaccination or infection. Answers to key questions in these areas are critical to understand how vaccines may elicit protection against HIV and to stimulate generation and testing of new hypotheses and vaccine concepts. It was recognized that this recommendation would require the development of immunological reagents and resources currently not present in the NHP field. Moreover, a variety of challenge models and systems are likely to be necessary to provide sufficient depth and breadth of understanding. Concentrating on the initial 1-10 days after inoculation would require altering the way most NHP experiments are designed and conducted.

B. PRIORITIES AND RECOMMENDATIONS

Priority 1: Optimizing the Clinical Trials Process by Accelerating the Pace of Trials and Enriching their Scientific Component

The pace of HIV vaccine efficacy trials is unacceptably slow (**Fig. 1**). The four to six year gap between initiation of a trial and its efficacy and scientific results prevents us from fully capitalizing on the valuable knowledge produced during these expensive and complex endeavors. There is a need to speed up the iterative feedback between vaccine evaluation and discovery, to increase the pace and number of human clinical trials, to broaden their scientific purpose, and to establish mechanisms to integrate and evaluate novel assays of human immune responses in trials.

Recommendations

In order to increase the scientific impact of clinical trials, extensive laboratory search for correlates of protection needs to be discussed and planned before the trial is initiated. Immunologists and virologists need to be actively engaged in efficacy trial design at the earliest stages to formulate hypotheses that can be tested in the course of the trial, ensure that the very best science is brought to bear on the trial, and agree on a sampling regimen, whose frequency, timing and nature are optimized for these studies.

Given the complexities of HIV vaccine design, the likely primary output of the next several trials will be to provide critical leads to the development of improved vaccine regimens. These leads need to be explored and communicated to the scientific community as quickly as possible, preferably within two years from study initiation, so that they can be leveraged to rapidly initiate new preclinical studies or further clinical evaluation of vaccine concepts. In order to accelerate the search for correlates, we need to explore ways to initiate the laboratory work much sooner, well before the trial is completed. This may require mechanisms to partially unblind the samples for the laboratory analyses without compromising the integrity of the trial or regulatory norms and regulations. Significant time savings from the pre-hoc planning and faster execution of laboratory work will translate into more than incremental acceleration of the vaccine discovery process. More efficient vaccine trials will allow a more thorough and more careful examination of immunogenic and protective properties of vaccine regimens. Exploring novel clinical trial and statistical methods to support the design, ethical review, and conduct of discovery-oriented efficacy trials is a scientific imperative.

Scientifically-enriched clinical trials require a comprehensive investigation of immunogenic properties of vaccines, which can only be achieved by cutting-edge assays and by extensive and sophisticated sampling. The Working Group identified two approaches to addressing this need. First, new and better technologies have to be developed that can be used in the large-scale, often low-resources settings of HIV vaccine efficacy trials. Such areas as mucosal immunity and innate responses are particularly challenging (for example, many of the innate responses are lost during the freeze-thaw of cells). Second, the carrying out of assays in the host countries where trials are conducted would greatly accelerate and facilitate the clinical trial process.

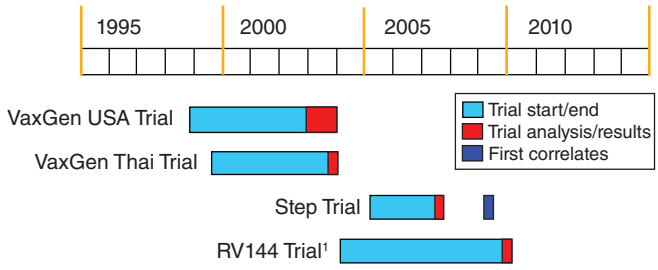

Figure 1 Timeline of HIV Vaccine Efficacy Trials. [1]Data on potential correlates of protection from RV144 are expected in 2011.

Priority 2: Optimize the use of NHPs through improved relevance to humans and closer integration of preclinical and clinical research

In addition to the need for closer connections between basic and clinical scientists, communications between clinical scientists and scientists studying NHP models of HIV infection need to be strengthened. The full value of the NHP models will only be realized if findings from the model are efficiently translated into human trials. Collaborations need to focus on using NHP models to test vaccine concepts, prioritize vaccine strategies (although not serve as a gatekeeper for human experiments), and inform hypothesis-driven clinical trials.

Recommendations

There is a wealth of clinically-relevant information that can be obtained from NHP models of HIV/AIDS, but probably the most important is the understanding of interactions between the virus and the host during the very early events (within the first 96 hours) after infection, those interactions governing the initial "take" of the infection and early amplification leading to systemic spread. Such events are currently very difficult, if not impossible, to study in humans, but can be pursued in the NHP model. Specifically, NHP research may help uncover viral vulnerabilities to diverse immune effector mechanisms and define vaccination approaches necessary for specifically eliciting and maintaining such effective immune responses.

It is now generally accepted that the NHP models have not been fully developed or their potential fully realized in HIV vaccine research. One issue is the plethora of models used in different laboratories, with relatively limited understanding of how these models relate to each other and, more importantly, the extent to which each one relates to human HIV infection. In addition, the small sample sizes used in most NHP experiments make definitive conclusions and comparisons difficult. Thus, the NHP field needs to create appropriate incentives and

Table 1. Areas in the NHP field requiring increased attention and support.

- Optimization of NHP models (new viruses, challenge procedures and approaches)
- Development of new reagents to manipulate NHP responses *in vivo*
- Systems biology approaches in the NHP model
- Training of scientists in NHP models
- Promoting increased collaboration amongst NHP scientists
- Promoting interaction between NHP and clinical scientists
- Strategies for cost-reduction of NHP experiments
- Strategies to increase statistical power of NHP experiments

Table 2. Summary of priorities and recommendations

Priority 1. Optimizing the Clinical Trials Process by Accelerating the Pace and Number of Trials and Enriching their Scientific Component

- Ensure that we maximize what is learned from every trial by incorporating the latest advances into clinical trial design
- Explore novel approaches to the design and analysis of clinical trials
- Develop scientific and clinical capacity in countries and regions where clinical trials are executed
- Develop the resources and mechanisms of access for GMP production of candidate immunogens for human clinical trials
- Broaden and augment the funding base in order to increase the quantity and complexity of efficacy trials

Priority 2. Optimize the use of NHPs through improved relevance to humans and closer integration of preclinical and clinical research

- Focus research on questions that can be uniquely answered in NHP models and to study mechanisms of protection rather than to use as a gatekeeper for human trials
- Establish NHP consortia or groups to leverage resources, promote standardization, and exchange ideas
- Establish interdisciplinary consortia of NHP researchers with clinical scientists to define similarities and differences between humans and NHPs in immune response to infection, vaccination and challenge, as well as in breakthrough infections.
- Expand and maximize the utilization of global NHP research capacity (infrastructure, committed scientists and novel technologies)

organizational processes to encourage coordination and collaboration among primate researchers/centres. These incentives should stimulate innovative, investigator-initiated studies, while at the same time enable scale-up capacity within a larger group environment when necessary. Collaborations within the NHP field will optimize the utilization of global NHP research capacity (infrastructure, committed scientists and cross-cutting, novel technologies) and provide the resources and organizational structure to efficiently support properly powered and controlled NHP studies to define mechanisms of immunity and of infection prevention/control. At the same time, interdisciplinary consortia, bringing together NHP researchers and clinical scientists, would greatly enable experiments to define the similarities and differences between humans and NHPs in their immune responses to infection, vaccination and challenge, and post-vaccination infection. Optimization of existing NHP resources and closer integration with clinical scientists will allow the field to address many of the challenges currently facing the field (**Table 1**).

C. CONCLUSIONS

A multidisciplinary approach to clinical trials calls for the bringing together of basic scientists, NHP model researchers and clinical researchers into a coherent scientifically-rich clinical trials endeavor (**Table 2**). This integration will be based upon active engagement of all parties, re-allocation of existing resources and attraction of new sources of funding. If we are to develop an effective vaccine as rapidly as possible, different vaccine concepts may need to be tested in human efficacy trials as quickly as possible. Resources to fund and provide access for GMP lots of candidate immunogens for these clinical trials need to be established. An increase in the number of efficacy trials is also essential to sustain the HIV vaccine endeavor, create the necessary momentum and opportunities for evidence-based improvements in vaccine design, and explore a critical and diverse number of vaccine concepts. This will require a significant increase in investment, but the observed efficacy of the RV144 trial candidate justifies the additional costs needed to boost the exploratory search for correlates of protection within efficacy trials. These changes critically depend on more active engagement of basic and NHP researchers in clinical trial design, increased access to human samples, and accelerated translation of new fundamental insights into relevant clinical settings.

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