Published in : Vaccine (2007), vol. 25, n°41, pp. 7007-7011
DOI:10.1016/j.vaccine.2007.06.068
Status : Postprint (Author's version)

Advances in Immunology and Vaccine Discovery: Report of the United States–European Commission Workshop

Cyril G.Gay

Animal Production and Protection, Agriculture Research Service, United States Department of Agriculture, 5601 Sunnyside Avenue, Beltsville, MD 20705, United States

Thomas L.Richie

Malaria Program, Naval Medical Research Center, 503 Robert Grant Avenue, Silver Spring, MD 20910, United States

KEYWORDS: Vaccine, Immune evasion, Innate immunity, Mucosal immunity, Immunogenetics, Comparative immunology, Genomics, Biodefense

ABSTRACT

As the 21st century unfolds, infectious diseases remain one of the most significant threats to our economy, our food animal production systems, animal welfare, and most importantly, the lives of people worldwide, regardless of their economic standing. The potential use of biological threat agents for terrorism or biowarfare further undermines the security of our society. Arguably, vaccines represent the single most cost-effective, medically delivered strategy for confronting these challenges. The workshop "Advances in Immunology and Vaccine Discovery" was organized to address these challenges, based on the conviction that the interface between immunology and vaccinology offers the best prospects for major breakthroughs in vaccine discovery and development. Six focus areas were identified by workshop organizers: (1) pathogen immune evasion; (2) innate immunity; (3) mucosal immunity; (4) immunogenetics; (5) comparative immunology; and (6) genomics. These areas provided opportunities to elucidate how protective immunity may relate to the disruption of the molecular mechanisms that underlie host–pathogen interactions. A report generated by workshop organizers and participants provides key recommendations and identifies important research gaps, needs, future steps, and potential strategic US–EU collaborations. The report is available on line through ScienceDirect (URL).

Published in : Vaccine (2007), vol. 25, n°41, pp. 7007-7011
DOI:10.1016/j.vaccine.2007.06.068
Status : Postprint (Author's version)

1. Introduction and objectives

On 12–14 December, 2006, more than 80 scientists from the European Union and from the United States, representing the fields of immunology and vaccinology, gathered at the National Animal Disease Center in Ames, Iowa, to discuss, design and prioritize initiatives for vaccine research. The workshop was organized under the auspices of the United States–European Commission Task Force on Biotechnology Research. The goal was to bring together US and European experts to address the large class of infectious agents that have proven refractory to classic vaccine approaches, including parasitic infections, many chronically infecting bacteria, fungi and viruses, and many additional infectious agents for which vaccines do not exist or are otherwise less than optimal. Workshop organizers envisioned that expanding knowledge in the field of immunology could be tapped to conceive of novel approaches and strategies for progress in vaccine development against these agents. In an effort to broaden the workshop's perspective, the organizers juxtaposed state-of-the-art presentations in six diverse focus areas where new discoveries could potentially impact vaccine design: immune evasion, innate immunity, mucosal immunity, immunogenetics, comparative immunology, and genomics. By simultaneously discussing these diverse disciplines and by engaging the participation of both veterinary and human vaccine developers, the workshop fostered out-of-the-box thinking to enable creative approaches to vaccine discovery.

After 2 days of presentations, participants divided into six break-out sessions where paired EU/US workshop leaders plus 10–15 additional participants addressed the main objective of the workshop, which was to define research priorities for each focus area. Veterinary and human immunologists joined vaccine developers and other experts from government, military, industry and academia to identify research priorities and gaps. Although many of the resulting recommendations were concordant with existing recommendations, some were novel and could potentially revolutionize the speed and success of vaccine development. The workshop closed with breakout session leaders describing, for the benefit of the entire group of participants, the consensus priorities identified in each focus area.

2. Organization of the report

The report generated by the workshop summarizes findings at four levels. First, the report identifies four key areas where investment is likely to yield the greatest return:

-Comparative immunology: opportunities for zoonotic disease interventions and biodefense.

-Genomics: a new frontier for vaccine discovery.

-Protective immunity: identifying effective vaccine platforms.

-Translational research: bridging discovery and development.

Second, the report provides six overarching recommendations to facilitate advances in the discovery and development of vaccines for the more difficult diseases for which inadequate or no vaccines exist. These recommendations represent a distillation of the workshop reports and are included in the next section of this overview.

Published in : Vaccine (2007), vol. 25, n°41, pp. 7007-7011
DOI:10.1016/j.vaccine.2007.06.068
Status : Postprint (Author's version)

-Making vaccine discovery a world health priority.

-Strategic collaborations achieved by funding partnerships.

-Advancing the development of molecular vaccines.

-Focusing on diseases with challenge models.

-Supporting the development of conventional vaccines.

-Supporting vaccine manufacturing research.

Third, the report reviews several themes that illustrate and unify the concepts developed in the workshop: animal genomics, molecular vaccines, biodefense vaccines and veterinary vaccines.

Finally, the report provides detailed summaries of the outcome of the breakout sessions for each of the six focus areas. These workshop reports introduce each topic with a brief "state of the art" description and then define major research priorities within the field. For each priority, the problems needing to be solved, according to the views of the participants, are identified, specific research objectives and proposed accomplishments are listed, and lastly concrete steps that could be taken to address these objectives are outlined. It is hoped that breakout session reports can serve as blueprints to steer research priorities in vaccine development.

3. Overarching recommendations

Workshop participants reached a general consensus on overarching recommendations with potential broad applicability in the area of vaccine development.

Making vaccine discovery a world health priority: Vaccines are likely the single most cost-effective public health intervention. With this in mind, workshop participants felt strongly that vaccine discovery should be prioritized not only in the US and EU, but with a worldwide view and emphasis on international collaboration and harmonization. It is unacceptable that hundreds of millions of the world's people and domestic animals suffer from infectious diseases for which no vaccines exist, or for which the protection provided by current vaccines is insufficient or short-lived. The problem of emerging and re-emerging infectious diseases and the threat of bioterrorism underscore the need for more effective and agile vaccine technologies. Government institutions, vaccine societies, and private foundations should define critical "hit lists" of viral, bacterial and parasitic agents for various economically important human and animal (agriculture, pet animal, zoonotic, and wildlife host) target species at the local, state, regional, national and international levels to which new or improved vaccines are needed, based on solid public health-driven (human) and economically driven (veterinary) data.

Strategic collaborations achieved by funding partnerships: Change the current fragmented institutional structure of research funding into comparative national and international vaccine development programs which are priority driven collaborative efforts in both the human and veterinary fronts. To this end, identify new interagency programs for directing research funds as well as for forming creative funding partnerships between US Dept of Agriculture/National Institutes of Health/European Union/private/commercial sources that collaborate and cross talk on research and development priorities. In these new scenarios, vaccine Research and

Published in : Vaccine (2007), vol. 25, n°41, pp. 7007-7011
DOI:10.1016/j.vaccine.2007.06.068
Status : Postprint (Author's version)

Development teams are formed around the agents prioritized on the "hit lists" and funded through high risk discovery, research and development of prospective vaccines with multi-year milestone driven budgets yielding preclinical and Phase 1 testable vaccines. Government agencies and pharmaceutical companies can then collaborate to provide safety, immunogenicity and efficacy studies in the appropriate target human and/or animal populations.

Advance the development of molecular vaccines: Although subunit vaccines and particularly genetic approaches (DNA vaccines, viral vectors) have so far failed to revolutionize the field of vaccinology (witness the paucity of licensed subunit vaccines, particularly for human use), substantial progress has been made in the development of these technologies. First, techniques are being devised to increase the potency of subunit vaccines, particularly for inducing cell-mediated immune responses. Second, progress has been made, albeit slowly, in developing vaccine platforms able to deliver multiple antigens simultaneously. Third, subunit vaccines have generally proven to be safe and well tolerated in both humans and animals, although pharmaceutical companies remain concerned about the potential for serious side effects that may come to light only after the completion of long-term post-marketing studies. Fourth, rational antigen design is beginning to produce vaccines with broader immunity profiles. As further progress is expected with regard to potency, valency and safety, and because of the many additional favorable characteristics of subunit vaccines, such as simplicity of design, ease of production and potential agility in the face of emerging infectious threats, we should continue to facilitate and support their development. Specific objectives include the development of vaccine platforms/delivery systems (1) able to incorporate multiple antigens from one or more pathogens without compromising the immunogenicity of each component (without significant antigen interference); (2) able to direct the immune response along desired pathways (e.g., Th1, Th2, etc.); (3) based on non-immunogenic vectors, that are unhampered by pre-existing immunity; (4) quickly modified and formulated, allowing agile responses to emerging infectious threats; (5) safe, well-tolerated and immunogenic for all populations (regardless of genetic background or age) and safe for the environment.

Focusing on diseases with challenge models: Prioritize research on chronic infectious agents for which a human challenge or appropriate animal models exist or could be developed. This recommendation is based on the realization that the refinement and optimization of new, more potent vaccine technologies can be accomplished most efficiently for "intractable pathogens" (e.g., parasites) when biologically relevant challenge models provide immediate feedback to vaccine developers. One of the major barriers to developing vaccines against diseases caused by parasites and chronically infecting bacteria and viruses stems from their intricate, often co-evolved relationship with the host organism that is invariably characterized by successful evasion of the host immune system. Because immune evasion strategies may depend upon precise molecular interactions between a pathogen and its host, it is unlikely that any model system will provide the insight required to devise interventions as quickly and efficiently as studying the target disease itself in the host of origin. However, the iterative process of testing vaccines for efficacy and then returning to the laboratory to improve vaccine performance occurs most rapidly when an experimental challenge model is available in the target host. For example, relying on large Phase 3 studies to assess vaccine efficacy, as in the case of HIV, where experimental challenge is not feasible, is an inefficient pathway for effecting the maturation of vaccine technologies against chronic infectious agents. On the other hand, focusing on representative diseases where vaccine development can be accelerated with the development of more predictive animal models and experimental challenges should lead rapidly to progress that can then be applied to those diseases where challenge cannot be ethically conducted. An example is *Mycobacterium bovis* in cattle, which is used as a model for human tuberculosis at Oxford and the Jenner Vaccine Institute, United Kingdom. This recommendation is thus

Published in : Vaccine (2007), vol. 25, n°41, pp. 7007-7011
DOI:10.1016/j.vaccine.2007.06.068
Status : Postprint (Author's version)

particularly applicable to human research, where funding is often prioritized for diseases of the highest public health impact rather than according to how realistic the disease is for effecting improvements in vaccine design. Investigators participating in the workshop reasoned that diseases such as malaria or intestinal parasitic infections where challenge models are available are far more likely to achieve a revolution in the design of novel vaccines for human use than diseases such as HIV where human challenge is not possible. The same principle holds true in veterinary vaccinology: it will be most efficient to devote funding and resources to diseases where the target host species can be experimentally challenged. The greater availability of challenge models in the veterinary field may explain why progress in veterinary vaccines has been good despite fewer resources.

Support the development of conventional vaccines: Prioritize the development of vaccines composed of whole organisms or crude, uncharacterized whole organism extracts. This recommendation, which runs counter to the investment currently focused on subunit vaccines, is based on the recognition that the process of elucidating host-pathogen biology in sufficient detail to allow the design of effective, multi-antigen subunit mixtures will be time-consuming and cost-intensive. Although the subunit approach should be pursued vigorously (see recommendation on molecular vaccines above), it must be recognized that even if the approach is successful, the difficulty and expense of combining multiple antigens into a single formulation and delivering the vaccine via heterologous prime boost regimens, as appears to be required for difficult agents, will impede the licensing of vaccines. Participants in the workshop believed that the empiric testing of whole organisms or extracts could circumvent, at least in some cases, the problem presented by the genetic restriction of cell-mediated immunity by achieving the simultaneous presentation of large numbers of antigens, increasing the likelihood that any individual person or animal, regardless of genetic background, would be able to respond to multiple protective epitopes. This approach could likewise circumvent the seemingly insurmountable problem of antigenic polymorphism that to this day has not been adequately addressed by the developers of subunit vaccines, despite sophisticated techniques such as gene scrambling, the synthesis of multi-epitope strings or the straightforward combination or chimerization of proteins representing allelic variants. Finally, the development of protective vaccines based on attenuated whole organisms, killed organisms or crude organism extracts could permit the identification of protective antigens and immune responses, thereby informing the developers of subunit vaccines regarding antigen selection and formulation.

Support vaccine manufacturing research: In cases where proof-of-principle has been established for the efficacy of any whole organism approach, funds should be directed toward process development for vaccine manufacturing. This is because in most cases the development of attenuated whole organism vaccines for refractory agents such as parasites has been abandoned or never even considered due to the difficulty of manufacturing and storing adequate quantities of purified product. At first glance, an organism that cannot be cultured would appear ill-suited for large-scale manufacturing. However, citing examples from the field of malaria vaccine development, workshop participants agreed that in many cases, a creative approach focusing on bioengineering could lead to novel processes enabling the manufacturing of whole organism vaccines for currently non-culturable pathogens. The early goal would be to produce attenuated whole parasites for Phase 1 and Phase 2 testing, using techniques such as genetic knock-out and amplification in the intermediate host. If, as anticipated, such vaccines prove highly effective in these early studies, further research in process development could lead to methods for scale-up and the production of sufficient quantities of vaccine for meeting worldwide needs. It is also possible that techniques could be developed for the *in vitro* production of these agents, despite the apparent difficulty of this endeavor.

Published in : Vaccine (2007), vol. 25, n°41, pp. 7007-7011
DOI:10.1016/j.vaccine.2007.06.068
Status : Postprint (Author's version)

4. Conclusions

By supporting vaccine discovery, immunology can directly improve the lives of millions of people worldwide, either by producing healthier animals and safer foods, or as a means to generate breakthroughs in preventive medicine. The power of immunology to fulfill this role will be enhanced by aligning research in human and animal health and by fostering collaborations between researchers working in the biomedical and veterinary sciences. The key recommendations, important research gaps, and the needs and future steps provided in the Ames report will be important for enabling and fostering these collaborations.

Acknowledgements

Financial support from the following sponsors is kindly acknowledged: Agricultural Research Service, United States Department of Agriculture; Cooperative State Research and Extension Service, United States Department of Agriculture; European Commission; Military Infectious Diseases Research Program, United States Department of Defense; Molecular Vaccines Interagency Working Group, United States Federal Government; National Institute of Allergy and Infectious Diseases, National Institutes of Health, United States Department of Health and Human Services; National Science Foundation, United States Government; Naval Medical Research Center, United States Department of Defense; Office of Naval Research, United States Department of Defense. In addition, we wish to thank the staff of Iowa State University and the National Animal Disease Center for hosting the Workshop.