Report of the United States-European Commission Workshop

Advances in Immunology and Vaccine Discovery

12-14 December, 2006
Ames, Iowa

Under the auspices of the: US-EC Task Force on Biotechnology Research

Edited by:
Cyril G. Gay
Thomas L. Richie
February 2007

PREFACE

On 12-14 December, 2006, more than eighty scientists from the European Union and from the United States, representing the fields of immunology and vaccinology, gathered at the National Animal Disease Center (NADC) in Ames, Iowa, to discuss, design and prioritize initiatives for vaccine research. The workshop was organized under the auspices of the US- EC 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 enabling creative approaches to vaccine discovery.

The workshop opened with two keynote presentations describing the current state of vaccinology, and then considered each of the six focus areas in turn. Two speakers, one from the US and one from the EU, led a series of two-hour sessions highlighting advances in each focus area. These six sessions comprised the first day and a half of the workshop. Success in presenting diverse viewpoints was quickly evident as discussions on the opening day addressed topics ranging from the behavior of malarial sporozoites in liver sinusoids as revealed by intravital cinematography to new discoveries regarding the innate immune system of chickens. Supplementary presentations in the evening described the development of artificial immune systems for the *ex vivo* assessment of vaccine immunogenicity and the evolutionary success of insects, which have prospered for millions of years despite vastly simpler immunological defenses than possessed by mammals. To add immediacy to the symposium's objectives, presentations in the six focus areas were followed by two presentations on biodefense vaccines in which the US and EU speakers summarized the applicability of discoveries in immunology and vaccinology to this important research priority.

On the third day, the workshop directly addressed its main objective – to design and prioritize initiatives for vaccine development. This activity took place in six break-out sessions, where paired EU/US workshop leaders plus eight to ten additional participants defined 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 quite 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.

This report summarizes the findings of the workshop. It will serve as an excellent resource for national and international vaccine development strategies, programs and collaborations. The Task Force congratulates the organizers of the workshop and the participants for this important step forward in immunology and vaccinology research. The Task Force also wishes to thank the

Molecular Vaccine Interagency Working Group of the Subcommittee on Biotechnology of the National Science and Technology Council that helped organize the workshop, and the U.S. Department of Agriculture, Agricultural Research Service, National Animal Disease Center, which hosted the event.

Kathie L. Olsen
Deputy Director, National Science Foundation
US Co- Chairperson, US–EC Task Force
on Biotechnology Research

Christian Patermann
Director, Biotechnology, Agriculture and Food
Research, European Commission
EC Co-Chairperson, EC–US Task Force
on Biotechnology Research

Excerpt from the Report:

"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. Readers should approach this report as a blue-print for action, and consider moving forward in any capacity within their purview to support the implementation of these recommendations."

EXECUTIVE SUMMARY

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 provide opportunities to elucidate how protective immunity may relate to the disruption of the molecular mechanisms that underlie host-pathogen interactions. The workshop examined the premise that research in these areas will generate novel ideas for vaccine design, and that these ideas could be advanced by immunologic and genomic tools. Furthermore, the workshop promoted cross-fertilization between veterinary and human medical research by pairing presentations in the human and veterinary fields, with the intent to further catalyzing progress in vaccine discovery.

This report provides recommendations generated by workshop participants in four key areas where investment is likely to yield the greatest return:

1. Comparative Immunology: Opportunities for Zoonotic Disease Interventions and Biodefense
2. Genomics: A New Frontier for Vaccine Discovery
3. Protective Immunity: Identifying Effective Vaccine Platforms
4. Translational Research: Bridging Discovery and Development

This report also identifies six key focal points and areas for collaboration that are likely to facilitate advances in the discovery and development of vaccines for the more difficult diseases for which inadequate or no vaccines exist:

1. Making Vaccine Discovery a World Health Priority
2. Strategic Collaborations Achieved by Funding Partnerships
3. Advancing the Development of Molecular Vaccines
4. Focusing on Diseases with Challenge Models
5. Supporting the Development of Conventional Vaccines
6. Supporting Vaccine Manufacturing Research

In the section entitled "workshop themes" fundamental issues that highlight the problems to be solved and areas where research will most likely have the greatest impact in the next 10-15 years are also captured.

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INTRODUCTION

Recent breakthroughs in the field of immunology have provided revolutionary approaches for vaccine discovery research and the potential of eliminating some of the most devastating infectious diseases affecting people and animals. With the realization of global warming, human overpopulation in environmentally sensitive geographical areas, and industrial expansion across the globe, emerging zoonotic diseases are surfacing as some of the most significant threats to public and animal health. In addition, the 21st century war on terrorism has elevated the critical need for biodefense vaccines to effectively mitigate the intentional release of biological weapons. The need to advance the discovery of new vaccines to protect people and animals has never been greater.

With the publication of Critical Needs for Research in Veterinary Science by the National Research Council of the National Academies and the European Technology Platform for Global Animal Health, Strategic Research Agenda, this workshop comes at an important time for advancing basic research in immunology and applying new discoveries to the development of vaccines specifically designed for control and eradication. 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.

This workshop generated key recommendations and identified important research gaps, needs, future steps, and potential strategic US-EU collaborations. The plan to exchange information on funding available on both sides of the Atlantic will be important for enabling and fostering these collaborations. The recommendations outlined in this report fit within a broad range of initiatives proposed by the EC-US Task Force on Biotechnology Research. We look forward to their implementation and to the advances in immunology and vaccine discovery they may engender.

Cyril G. Gay, USDA-ARS
Thomas L. Richie, US Navy
US Co-chairs
Scientific Committee

Paul-Pierre Pastoret, OIE
Isabel Minguez-Tudela, EC
EU Co-chairs
Scientific Committee

More information about the Task Force is available on
http://ec.europa.eu/research/biotechnology/ecus/index_en.html

The views expressed in this document are those of the workshop participants, and do not represent the views of the sponsors or governments.

Throughout this report, order of presentation should not be construed as order of priority.

KEY RECOMMENDATIONS

1. Comparative Immunology – Opportunities for Zoonotic Disease Intervention and BioDefense

Topics

Animal models for zoonotic diseases
Comparative biology
Mechanisms of immune evasion
Modulating specific innate immune responses
Mechanisms of protective immunity

The last decade has witnessed the emergence and re-emergence of multiple infectious diseases of veterinary and human importance. These are caused by viral, bacterial, and protozoal pathogens, many posing difficult challenges for control. Zoonoses, such as avian influenza, represent a significant portion of the emerging or re-emerging infectious diseases that are threatening our people and public health systems; moreover, many zoonotic pathogens are also known as "select agents," which by definition could be used for bioterrorism or warfare. This illustrates the need for new, improved animal models for studies of zoonotic agents and their interaction within definitive and secondary hosts. Although considerable amounts of species-specific data have been generated by individual investigators working with zoonotic agents in the animal and human fields, further work is needed to clarify and identify both species-specific and shared protective and/or pathogenic mechanisms. The need for understanding immune mechanisms is especially applicable where zoonotic pathogens use common pathways to evade or subvert the immune systems of their animal and human hosts. Elucidating common mechanisms empowers the model relative to other pathogens that have evolved specific interactions with their animal hosts. Thus, zoonotic diseases offer unparalleled opportunities for testing the efficacy and safety of new human vaccine platforms where relevant animal challenge models exist. This includes, for example, opportunities for testing directly in a relevant animal model the potential for reversion-to-virulence of an attenuated live vaccine, the tissue distribution of a recombinant viral vector vaccine, or, most importantly, the identification of correlates of protection and whether a novel vaccine platform will induce protective immunity. It is clear that collaborations between the human and veterinary vaccine research communities, working together to develop effective vaccines for zoonotic diseases, may significantly increase the chance of success and accelerate the delivery of new vaccines to market.

Recommendations:

- Form and support comparative immunology research consortia (e.g., International Society for Developmental and Comparative Immunology - ISDCI)
- Develop validated animal models consistent with FDA Animal Rule
- Develop species-specific repositories of immunological reagents
- Develop genetically and phenotypically defined animal cell lines
- Support discovery research efforts in biomarkers (comparative correlates of protection)
- Support research to discover innate immune activators for rapid onset of immunity
- Conduct comparative immunology studies in special populations (e.g., pregnant animals)

2. Genomics – A New Frontier for Vaccine Discovery

Topics

Comparative microbial genomics
Research tools derived from human and animal genome initiatives
The genomics of host-pathogen interactions
Vaccinogenomics

The explosion in new high-throughput technologies arising from microbial genomics, the human genome initiative, and the recent sequencing of two of the major livestock genomes (*Gallus domesticus* and *Bos taurus*), is enabling the analysis of the genome, transcriptome and proteome, and offers the opportunity to gain a better understanding of the molecular pathways underlying microbial pathogenesis, the host immune system, and host–pathogen interactions. The integration of pathogen and host genomics in vaccine research (vaccinogenomics) is likely to revolutionize the way scientists approach the challenges of discovering and developing safe and effective vaccines. The availability of genomic tools provides unprecedented prospects for the rational design of highly effective human and veterinary vaccines. Identifying genes and genetic variations that influence mechanisms of immune evasion, disease resistance, and vaccine responsiveness will in the future fundamentally change vaccine discovery research and enable vaccinologists to design vaccines to control and eradicate pathogens in targeted human and animal populations. The establishment of animal genomic tools and animal lines with defined genetic backgrounds also provides opportunities for developing vaccines that perform as intended under field conditions. The heterogeneity found in outbred livestock populations may also enable marker-assisted selection of good responders to vaccination. Importantly, the availability of challenge models in animal health research provides unique opportunities for conducting studies to define genetic variations associated with disease susceptibility and understanding mechanisms of protective immunity.

Recommendations:

- Develop animal challenge models to identify variations in host gene expression patterns, and ultimately to identify specific genes or integrated gene systems that are associated with disease susceptibility
- Identify functional nucleotide polymorphisms from coding and non-coding regulatory sequences of host genes known to modulate the immune response
- Determine additional host genetic factors and molecular mechanisms that control host-pathogen interactions and disease outcome
- Establish international networks to facilitate the exchange of information and reagents related to immunogenetics
- Define the host genetic influences and molecular mechanisms allowing immune evasion from innate and acquired host defenses
- Develop and validate vaccine programs targeting defined animal genotypes
- Support research on host-pathogen interactions using comprehensive, transcriptome-wide gene expression analysis
- Support host profiling studies to identify gene expression signatures unique to specific pathogens and genetically disparate hosts
- Integrate genomics tools in vaccine clinical trials to identify animals or humans that are poor or good responders to vaccination

3. Protective Immunity – Identifying Effective Vaccine Platforms

Topics

Adjuvant formulations
Modified live vaccines
Inactivated vaccines
Reverse genetics
Recombinant vector technology
Subunit vaccines

In the last decade we have seen an explosion in the availability of novel vaccine platforms ranging from new adjuvant formulations to molecular vaccines such as recombinant vectors and DNA plasmids. However, vaccine platforms are often selected for reasons unrelated to the aim of discovering an effective vaccine that induces a protective immune response. For example, platforms may be selected because they are novel (plasmid DNA, plant-based) or because a company has intellectual property (IP) protection for a platform developed in-house. The selection of a vaccine platform may also be based on perceived dogmas, such as the claim that inactivated vaccines are safer than attenuated live vaccines, or that subunit vaccines are safer than attenuated organisms or crude extracts because they exclude uncharacterized and unnecessary antigens. Recent advances in immunology provide unique opportunities for including a scientific rationale in the selection process, such as the ability of a vaccine platform to drive a specific immune response profile. Thus, a recombinant vector platform may be selected because a virus has been shown to induce a very strong innate immune response (e.g., alphaviruses are strong inducers of Type I interferon-alpha and toll-like receptor 3), to induce a quick onset of immunity, or to induce a strong CD8+ response (e.g., adenoviruses) or a strong CD4+ response (e.g., poxviruses). Understanding the immune response associated with a vaccine platform and how to direct these responses for improved potency or quality through the use of co-stimulatory / immune-modulating molecules will be an important contributor to the rational design of vaccines. We need to develop platforms specifically designed for their ability to induce long lasting, potent immunity and cross protection against different field strains or serotypes.

Recommendations:

- Support basic research programs that focus on understanding mechanisms of protective immunity to important pathogens, including mucosal surfaces, and including the ontology and competence of the neonatal immune system
- Discover vaccine platforms that increase the potency of cell-mediated or humoral immune responses and which enable the combination of multiple complex antigens
- Discover vaccine platforms that provide broader cross-protection amongst field strains
- Support vaccine discovery research programs that focus on delivery systems with the aim of inducing a specified immune response outcome through the use of immunomodulatory sequences
- Develop functional immune assays for measuring specific immune response outcomes
- Support research on the development of vaccine adjuvants for human use and leverage knowledge from veterinary vaccines where more than 40 adjuvant formulations have been approved

4. Translational Research – Bridging Discovery and Development

Topics

Basic research: pathogenesis, immune responses
Discovering correlates of efficacy
Selecting good vaccine candidates
Bioengineering
Innovation in bioprocessing
Rapid process development
Large scale manufacture

Many vaccine projects fail at the interface of discovery and development. Barriers to success include inadequate characterization of vaccine formulations, poorly characterized supporting cell lines, inadequately protective immune responses, absence of correlates of efficacy for potency assay development, and the cost of large scale production. Despite such challenges, the veterinary vaccine community has been successful in moving new vaccine technologies into development, primarily due to the availability of animal challenge models where vaccines can be tested directly in the target host species. Several of the major new vaccine platforms discovered in the last 10-15 years have been licensed and commercialized as animal vaccines; e.g., DNA vaccines, recombinant vectored vaccines, subunit vaccines, and plant-based vaccines. However, very few molecular vaccines have successfully moved through the pipeline to licensure for human use. A key barrier to success is the lack of validated immune assays, which negates the ability to compare data from clinical trials performed by different organizations; additional barriers to success are the cost of clinical materials and concerns over long term safety. Such barriers limit progression of vaccine development to clinical testing, reducing the likelihood of Phase 3 clinical trials and eventual licensure. Advances in immunology will play an important role in bridging the discovery of new and innovative vaccine platforms into full development.

Recommendations:

- Develop and validate immune assays to support clinical trials
- Develop veterinary immunological reagents to support the development of animal models
- Focus on antigen discovery and rational antigen design to improve both protective efficacy and manufacturability
- Discover and characterize host defense proteins to develop novel biotherapeutics
- Focus on process development for isolation and purification of attenuated whole organisms or whole organism extracts that are suitable for parenteral administration, where such preparations are convincingly proven to be highly efficacious
- Develop and qualify cell lines to improve the production capacity of virally vectored vaccines

KEY POINTS AND AREAS FOR COLLABORATION

1. 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. Readers should approach this report as a blue-print for action, and consider moving forward in any capacity within their purview to support the implementation of these recommendations.

2. 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 USDA/ NIH/ EU/ private/ commercial sources that collaborate and cross talk on research and development priorities. In these new scenarios, vaccine R&D 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.

3. 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.

4. 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 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.

5. 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 Key Point 4 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.

6. 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 world-wide 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.

WORKSHOP THEMES

Animal Genomics

Report: Cyril G. Gay

The completion of animal genome sequencing projects has the potential of causing a fundamental paradigm shift in biomedical research. At the present time, the management and treatment of animal diseases is limited to the use of traditional tools such as conventional vaccines and pharmaceuticals, on-farm biosecurity systems, test and slaughter protocols, and the imposition of trade restrictions. Armed with animal genome sequences and genetic markers that correlate with disease traits, we will be able to identify the genetic variations that control disease outcomes. These new research tools offer unparalleled opportunities for understanding the phenomenon of "disease resistance" and will revolutionize our approaches to vaccine and drug discovery.

Missing from this tool kit is an understanding of how the genomes of individual animals contribute to or impede the efficacy of these disease control strategies. Recent efforts to define the entire DNA sequence of animal genomes (cattle, chicken, and pigs) offers the ability to use these roadmaps to enhance disease resistance and control at both the individual and herd levels. Armed with animal genome sequences, genetic markers that correlate with functional mutations and high throughput analysis methods that can simultaneously evaluate thousands of genotypes, researchers should be able to link physiological manifestations of the disease state, pathogen-specific virulence, and immune evasion mechanisms with host genetic variation. Simply stated, scientists may now be able to identify the genetic variations that control the host resistance and disease outcome. These new research tools will revolutionize our approaches to addressing the many challenges facing animal and human health.

The effect of genetic variation on the response to disease and resistance has been recognized for decades; however, the basis for this heritability of disease resistance in animals is neither fully understood nor efficiently utilized. One reason is that traditional genetic markers alone have provided insufficient tools for the control of complex disease traits. This has been due in part to the scarcity of well-defined disease challenge studies utilizing sufficient large animal populations. Such experiments have proven to be expensive and cost prohibitive.

With the completion of the human genome project, the analysis of the effects of DNA sequence variation has become an increasingly important source of information in human health. For animal health, we lack the precise genetic maps that can pin-point sequence variations associated with disease or important biological processes. However, the completion of animal genome projects such as the chicken and cattle provide the means to construct high density single nucleotide polymorphisms (SNP) maps to characterize genetic variation. These variations occur in adequate frequency in animal populations and present powerful tools for use in the identification of genetic variation that directly contributes to a specific trait related to animal health or productivity.

The integration of pathogen and host genomics in vaccine research is likely to transform the way scientists approach the challenges of discovering safe and effective vaccines. The availability of genomics tools provides unprecedented opportunities for the rational design of highly effective veterinary vaccines. Identifying genes and genetic variances that control mechanisms of immune

evasion, disease resistance, and vaccine responsiveness will in the future fundamentally change vaccine discovery research and enable vaccinologists to design vaccines to control and eradicate pathogens in targeted animal populations. The use of chicken lines with defined genetic backgrounds provides unique opportunities for developing vaccines that perform as intended in the field. The heterogeneity found in outbred livestock populations may also present opportunities for enabling marker-assisted selection of good responders to vaccination.

Molecular Vaccines:
Report: Thomas L. Richie

One of the sponsors for the Ames workshop was the U.S Government Executive Branch Molecular Vaccines Interagency Working Group (MVIWG). The MVIWG was established 20 September 2004 by the White House Subcommittee on Biotechnology to promote development of molecular vaccine technologies in both public and private sectors, based on their potential to address key challenges in human and veterinary vaccinology. Challenges for vaccine development that have been identified include (a) chronic infectious diseases not amenable to traditional vaccination approaches, such as HIV, tuberculosis and parasitic diseases; (b) countering the threat of biological and chemical warfare; (c) countering the threat of newly- and re-emerging infectious diseases; (d) novel applications such as treating or preventing cancer or rheumatologic illness. In addition, vaccines currently on the market may be inadequate (i.e., poorly efficacious, difficult to tolerate, or unsafe in some individuals or groups, including pregnant women, infants, the elderly or those with innate or acquired immune deficiency) and therefore in need of technological improvement or replacement.

While molecular vaccines hold tremendous promise for these applications, a significant effort is needed to refine and optimize these technologies, including appropriate harmonization of regulatory and administrative processes. Government support should accelerate progress for both molecular vaccines and related, emerging fields, such as leveraging the information provided by the genomic sequencing of pathogenic organisms to improve vaccines, expanding the immunogenicity of attenuated organism vaccines via gene "knock-ins," the genetic manipulation or immunization of disease vectors to render them incompetent, the generation of antibodies in plants for passive immunization, the development of molecular adjuvants, the development of compounds that directly stimulate innate immunity or thwart immunosuppressive responses, and many other applications. The MVIWG was established to facilitate all of these vital scientific endeavors.

At the Ames workshop, molecular vaccines were woven through the presentations as a conference theme. In some areas, such as triggering innate immunity, molecular approaches were described as intrinsic to the focus area. In other areas, such as immune evasion, it was felt that knowledge of the biology of infectious agents at the molecular level could lead to the design of approaches for overcoming that biological hurdle – in other words, that "knowledge of biology at the molecular level begets strategies for vaccine design." However, molecular approaches have many additional applications, such as codon optimization or harmonization to improve the expression and tertiary folding of recombinant protein vaccines during manufacturing or to enhance transgene expression by DNA plasmids. As another example, gene disruption (genetic knock-out) may prove an excellent way to attenuate whole organism vaccines, while genetic knock-in may allow the production of multi-agent vaccines that simultaneously immunize against multiple diseases.

Biodefense Vaccines:
Report: Kevin Anderson

Biodefense vaccines represent part of the national strategy to protect the public from biological terrorism by the development of safe and effective countermeasures to mitigate illness and death, protect critical infrastructure and minimize economic consequences. Policies have been established through legislation and presidential directives that assign roles and responsibilities to various federal agencies to accelerate and expand development of current and new countermeasures to respond to and recover from biological weapons attacks, to include intentional introduction or natural occurrence of catastrophic human, animal, plant, and zoonotic diseases.

Development of a national strategy to rapidly develop effective countermeasures, which includes safe and efficacious vaccines, requires periodic risk assessments to understand the evolving biological threat and define gaps in knowledge or vulnerabilities in our biodefense posture, which guide prioritization of investments in biodefense-related research, development, planning, and preparedness. To this end, vaccines represent a necessary component of the national biodefense countermeasure. Risk assessments have provided a means of identifying and prioritizing biodefense vaccine research and development efforts for biological agents capable of being used in biological attacks. In support of vaccine research and development, the national biodefense strategy includes the development of the infrastructure required to test and evaluate existing, proposed, or promising countermeasures, assess their safety and effectiveness, expedite their development and ensure rapid licensure.

Response to bioterror events involves rapid agent detection and diagnosis, implementation of exposure control measures, and use of vaccines, when appropriate, to minimize consequences to human and animal health. Current approaches to biodefense vaccine development include use of existing applications for development and manufacturing, and development of new technologies to rapidly design, test and evaluate, and manufacture desired products. Given the urgency with which vaccines designed to minimize consequences of bioterror events are needed, new technologies and infrastructure are mandated to shorten timelines for their development. New technologies applicable to the design of vaccines would include rapid methods for selection of protective immunogens and the development of vaccines that allow for differentiation of infected from vaccinated animal (DIVA) or human hosts, with option to employ improved adjuvants that stimulate innate immune responses and/or promote adaptive immune responses. New infrastructure would include biocontainment facilities to increase current capacities for vaccine testing and evaluation, to optimize vaccine dosage and delivery in conjunction with routes of exposure, and manufacturing capacities to ensure availability of a minimum number of doses for intervention and to reduce average cycle times to manufacture vaccine lots. Rapid deployment of biodefense vaccines will require both infrastructures, to include facilities for storage of vaccine stockpiles, and technologies that ensure validated storage conditions for such stockpiles.

With these considerations in mind, biodefense vaccines were selected as an additional theme for the Ames workshop, recognizing that the current substantial support for research and development of biodefense vaccines should accelerate the overall pace and progress of vaccine research. Therefore, after the six main focus areas were presented and discussed during days one and two, speakers for the US and EU captured key findings from the focus area presentations applicable to biodefense vaccine development.

Veterinary Vaccines:
Report: James A. Roth and Paul-Pierre Pastoret

Infectious diseases of animals are greatly increasing in importance. The rapid rise in global human population requires ever increasing production of food derived from animal agriculture and aquaculture. Increasing human and agricultural animal populations and the resulting environmental degradation are leading to the emergence of new infectious diseases and the re-emergence of diseases that were on the decline. Many of these emerging and re-emerging diseases are zoonotic and are significant threats to human health globally. Novel veterinary vaccines are needed to enhance food production, to protect humans from exposure to zoonotic diseases, and to reduce animal suffering. Safe and effective vaccines exist for some animal diseases, but for many important animal diseases, conventional approaches to vaccine development have not been successful. The premise of this meeting of leading academic, government and industry immunologists is that basic research on pathogen biology, virulence mechanisms, innate and acquired immunity, antigen processing and presentation, host pathogen interaction and adjuvants will lead to new breakthroughs in vaccine discovery and development.

Basic research is essential to discover novel vaccine approaches. The fields of immunology, microbial physiology, molecular biology and vaccinology are advancing rapidly, presenting many opportunities to use new and powerful molecular tools to investigate both pathogen virulence mechanisms and host response and to apply basic research advances to the development of novel veterinary vaccines. However, there are significant challenges to the development of novel vaccines. Funding is severely limited, there are not enough scientists currently working in veterinary vaccine development, and there are insufficient biosecure research facilities to safely test potential products. Because resources are limited, researchers need to focus on the highest priorities that will have the greatest potential impact. This research should be conducted with the end goal in mind of development of safe and effective vaccines.

The greatest advances will occur if government, academic and industry scientists and resources are all brought to bear on the problem of novel vaccine discovery and development. Government resources are needed to fund basic research and to set priorities, especially for vaccines to protect against imported or emerging diseases. Academic and government scientists are an excellent resource for conducing much of the basic research. Participation of the vaccine industry is essential to carry out the final development, production, and distribution of vaccines. These types of partnerships have already lead to licensed biotechnology-derived veterinary vaccines, including recombinant antigen vaccines, gene deleted vaccines, live recombinant vaccines, DNA vaccines, and transgenic plant derived vaccines.

There are many commercially available vaccines for animal diseases, including over 1,300 vaccines licensed for animal use covering 180 disease agents in the U.S. alone. Most of these are conventionally produced live or killed vaccines for acute viral or bacterial diseases. Many of these vaccines do not have an optimal safety and efficacy profile. Improved vaccines for these diseases depend on a more complete understanding of host pathogen interaction and immune responses.

Very few vaccines are available for chronic viral or bacterial diseases or for mycoplasmal diseases, rickettsial diseases, chlamydial diseases, fungal diseases, protozoal diseases, parasitic diseases, and neoplastic diseases. These are more difficult targets for vaccine development and require basic

research to lead to successful vaccine strategies. Development of vaccines for these diseases could lead to dramatic improvements in human and animal health and food production.

Protective immunity to these complex organisms is likely to require vaccines which stimulate multiple arms of the acquired immune system to defend against a variety of pathogenic immune evasion mechanisms (Figure 1). Genetic variability in the infectious agents and in the host species further complicates the development of broadly effective vaccines. It is essential to understand the host pathogen interaction from the first moments of infection. Early interactions with innate immune mechanisms have a major influence on the types of acquired immunity induced and provide opportunities to influence vaccine safety and efficacy.

Stimulation of Multiple Defense Mechanisms to Improve Efficacy

Pathogenic Mechanisms	Defense Mechanisms
• Adherence to Mucosa	• Mucosal Antibody (IgA)
• Invasive parasite	• IgE
• Exotoxin/Endotoxin	• Neutralizing Antibody
• Viremia	• Neutralizing Antibody
• Septicemia	• Opsonizing Antibody
• Intracytoplasmic Growth	• Cytotoxic T cells
• Growth in phagosome	• T_{H1} Cytokines
• Rapid viral replication	• Types 1 and 2 interferon
• Infect epithelial cells	• Gamma Delta T cells

Figure 1

There are a number of diseases for which safe and effective vaccines do not exist. In some cases, attempts to produce vaccines have not been successful, and in other cases no attempt to develop commercially available vaccines has been made because the market potential is not sufficient for the investment needed. This is especially true for vaccines that protect against foreign animal disease incursion or the emergence of novel pathogens. If there is not an existing market for a vaccine, it is essential for government agencies to fund the development and stockpiling of vaccines for emergency use. This requires foresight and commitment on the part of national governments.

In addition to the potential market for a product, other limitations to improving animal vaccines through new technologies include the high cost for research, development and manufacturing. Public concern about genetically engineered organisms is a factor in some countries. Industry has concerns about proprietary rights to technology. In addition, in some cases, a restrictive regulatory environment surrounding research and development on select agents and foreign animal disease agents also limits development of animal vaccines.

Most national governments do not produce and distribute veterinary vaccines. Therefore, vaccines will only be available if private industry can recover their costs plus a reasonable profit. This may result from vaccine sales or from government investment in vaccine development and distribution. National government or international agency investment is essential if vaccines that do not have a viable market are to be made available for high priority transboundary diseases. This includes diseases that are foreign to a particular country, and diseases which limit animal production in developing nations without the resources to purchase animal vaccines. Countries which enjoy freedom from important transboundary diseases must invest in controlling diseases in developing countries because this greatly reduces the threat of incursion of disease into developed countries.

An intentional outbreak due to biological or agro terrorism will create an emergency situation in a completely naïve population of animals. Vaccines will be essential tools to control the outbreak and reduce the need for mass slaughter of animals. The expected performance from a vaccine under these conditions will differ from that expected from a vaccine used for mass vaccination during "peace time" in a population regularly exposed to similar antigens.

Vaccines to be used to assist in the control of foreign animal disease outbreaks will first of all have to confer a rapid onset of protection in the animal after one dose is given. This may be accomplished by acting on innate immune mechanisms before the adaptive immune mechanisms can respond. Secondly, whenever possible, vaccines for emergency control of a foreign animal disease outbreak should confer, if not a sterile immunity, at least herd immunity in order to dramatically reduce the transmission of the infectious agent. When attempting to control an outbreak of a highly contagious animal disease it is more important to stop the spread of the disease than to prevent clinical signs. The efficacy of the vaccine becomes more important than minor safety concerns in order to have an epidemiological impact to reduce spread of infection.

Vaccines for emergency animal disease control should confer a broad range of protection, especially, when facing outbreaks of infections with highly variable pathogens. Whenever possible, these vaccines should be DIVA (differentiation of infected from vaccinated animals) compatible, in order to improve surveillance by allowing the detection of vaccinated animals that have become infected and may be carriers.

The duration of protection conferred by a foreign animal disease vaccine is less important since the vaccinated animals will either be slaughtered at the end of the outbreak or will not need to be protected because the infectious agent will hopefully be eliminated. The presence of seropositive animals may also be a disadvantage for surveillance programs later on.

The recommendations coming from this meeting hold great promise for the development of novel animal vaccines, which could improve animal health, reduce the potential for humans to contract zoonotic diseases, increase the efficiency of food production and protect agricultural economies from incursion of foreign animal diseases.

BREAKOUT SESSION REPORTS

I. Mechanisms of Pathogen Immune Evasion:

Break-out session leaders: Peter Nara and Patrick de Baetselier

A. Introduction:

This breakout session was designed to explore gaps in our understanding of mechanisms of pathogen immune evasion and define how this area of research could advance vaccine discovery projects that have to date failed to deliver effective vaccines. The break-out session participants were charged with the job of identifying those knowledge gaps, research priority areas, and research objectives that will, if identified and implemented, advance the future development of new vaccines and technologies against these difficult microbes. Current standard vaccine technologies do not appear to readily apply to the development of many of the remaining medically and agriculturally important microbes, many if not most of which fall into the category of annually re-occurring and chronic-active, -latent agents that evade the host immune response. This appears in large part to reside in fundamental and very different mechanisms of virulence within these microbes and their poorly characterized interactions with the host defense systems of the host.

B. State of the Art:

New disciplines in vaccinology, such as immunobiology and immunogenomics, known collectively as "vaccinomics," are poised to help advance the field of vaccine discovery. In addition, these new fields are supported by recent and ongoing current advances in genomics, molecular biology, proteomics, immunology, microbiology, cellular biology, nanotechnology, epidemiology, animal and mathematical modeling. These tools and the development of others appear necessary for beginning to dissect the major gaps in our understanding of how these pathogens can avoid, evade, survive, thrive, lay dormant and/or be transmitted in the host despite evidence of the host mounting an immune response against it. Many species of animals including man are affected by these pathogens with many of the new or so-called "emerging" infectious diseases evolving and residing in various animal species and infecting humans (West Nile, HIV-1, etc.). Thus, both human and veterinary medicine are confronted with similar needs to draw on their individual professional training and collective expertise so as to advance the science of vaccinology for the betterment of human and animal health worldwide.

C. Research priorities:

Research Priority 1: Immune evasion from innate host defenses

a. Problem to be solved:

The induction and regulation of innate host defenses are believed to affect the earliest stages of pathogen entry, colonization, survival, replication and disease kinetics, as well as disease resistance, transmission and ultimately human and animal health. Understanding the mechanisms by which viruses, bacteria and parasites (pathogens) usurp or otherwise alter these responses will be important in inducing earlier, more potent and possibly more durable immunity.

b. Research objectives:
1. Develop a comparative knowledge base for major innate pathways present in humans and animal species (comparative innate host defense and immunology studies).
2. Identify differences in innate host defenses among various portals of pathogen entry.
3. Define gene expression patterns and regulatory phenomena that affect the level of host innate immunity and associated cell populations.
4. Define the effects of stress/diet/age on innate immunity.
5. Develop effective research algorithms, reagents and assays for identifying acute phase response molecules that may interact with the pathogen in such a way as to enhance its survival in the host.
6. Identify microbial structural and non-structural proteins, lipids, carbohydrates, etc. that interact with and circumvent innate host defenses; anticipate elucidation of both evasion of innate immunity and manipulation of innate immunity (virokines).
7. Identify how regulation of innate host defenses by the pathogen may adversely affect the subsequent development of protective acquired immunity.
8. Use information from microbial genomics to define substances from pathogens that stimulate/regulate innate immune responses; identify the evolutionarily conserved molecular structures and constituents (pathogen-associated molecular patterns or PAMPs) of infectious microbes that activate the innate defense system.

c. Proposed accomplishments:
1. Identification of species-specific screening and functional assays capable of identifying those innate host defense molecules or cells involved in host defense evasion.
2. Knowledge of genomic organization of loci involved in the germ-line encoded pattern recognition receptors (PRR): e.g., TLRs, mannose receptors, scavenger receptors, and complement receptors; knowledge of expression levels of PRR on effector cells of innate immunity (macrophages, NK cells, granulocytes, epithelial); the role of TLR and other polymorphisms in the innate immune response.
3. Knowledge of the effect of innate responses on intensity and bias of pathogen-specific effector acquired immune responses, and activation of the co-stimulatory molecules required for T cell responses; determine the role of innate and acquired immunity in disease kinetics.
4. Identification of PAMPs and their interaction with PRR, informing pathogen control measures, helping to identify new biotherapeutics, and improving vaccine design.
5. Biochemical and structural characterization of pathogen domains and associated mining of the genomic databases of other pathogens based on anticipated homologies (anticipated because innate host defenses are comprised of constitutive molecules, implying that the interacting domains of the various pathogens will likely be conserved in structure).
6. Development of novel approaches to blocking mechanisms for evading innate host defenses, leading to improved vaccines.
7. Development of attenuated pathogen strains via the selective deletion (or disabling) of innate immune evasion genes.
8. Knowledge of development/regulation of immunity in neonates.

d. Needs/Next Steps:
1. Develop interactive collaborative realtionships between academic, government, private/foundations and pharmaceautical sectors.
2. Develop more and improved comparative genomics for economically important animal species.
3. Training: Emphasis on practical methods to foster collaboration between the immunology, bioengineering, genomics, proteomics, bio-informatics, nanotechnology, computer science,

epidemiology, and microbiology communities through sponsorship of interdisciplinary workshops at major meetings, cross training of postdoctoral fellows and continued forums for discussion and exchange of ideas such as this current workshop.
4. Reagents: Creation of a standard body or repository for current approved reagents and support for the development of new types of reagents specifically for nanobiology applications; such reagents could include soluble labeled ligands and labeled receptor molecules.

Research Priority 2: Immune evasion from acquired immunity

a. Problem to be solved:
The induction of acquired immunity following infection and/or vaccination of hosts against certain pathogens leads to a protective and durable state of long lasting immunity and enhanced animal and human welfare and production. Many pathogens, however, have proven resistant to conventional vaccine technologies and appear to have evolved mechanisms to evade the acquired immune response, including those currently controlled by conventional vaccination. Understanding how these pathogens escape and evade acquired immunity should reveal new insights, strategies and technologies for making effective vaccines.

b. Research objectives:
1. Identify sensitive and resistant phenotypes for specific host-pathogen systems to allow the identification of protective mechanisms.
2. Identify immunological mechanisms of protection against pathogens evading the immune response with a goal to establish correlates / markers of immunity and to direct the optimization of vaccine delivery systems so as to induce protective responses.
3. Define classes of viruses, bacteria and parasites which evade acquired immunity.
4. Identify key branch points in the acquired immunity pathway where evasion occurs.
5. Understand the role of Deceptive Imprinting in immune evasion (deceptive imprinting: a theory involving "original antigenic sin," which addresses various processes by which pathogens subvert the host immune response, such as presentation of immunodominant "decoy" epitopes, which may also undergo antigenic variation, in order suppress the recognition of more conserved, structurally or functionally important molecules involved with adhesion, binding, reproduction, etc); understand the roles of immunodominance and antigenic variation.
6. Understand the role of immunosuppression and immunoregulation in immune evasion.
7. Understand the roles of blocking antibody, subversion of antigen processing, escape from functional antibody, escape from cell-mediated immunity, coating of the pathogen with host molecules, and other phenomena associated with immune evasion.
8. Develop more biologically relevant in vitro assays for measuring acquired immunity effector function; e.g., ADCC (antibody-dependent cellular cytotoxicity), anti-viral antibody, etc.
9. Develop interactive pathogen and host genomics to identify those epitopes on the pathogens and those host adaptive molecules that interact with the acquired immune system leading to evasion and immune escape.
10. Develop more effective technologies of higher throughput for mapping discontinuous epitopes, helper T cell and CTL epitopes.
11. Develop a biochemical, immunological and structural database for immune evading epitopes to mine large genomic databases for other pathogens.
12. Develop relevant species knockout animals to study the role of various immune evading mechanisms.

13. Study the effect of repertoire sculpting at the germ line, gastro-intestinal symbiotic colonization, environmental and co-infection levels.
14. Study the role of superantigens and other atypical B and T cell receptor binding moieties.
15. Study the source and role of natural antibody and autoantibody and what role these may have on immune escape.
16. Develop databases of these immunodominant non-protective and immunoregulatory epitopes and determinants so as to be able to mine genome profiles more efficiently.

c. Proposed accomplishments:
1. Knowledge of the host-pathogen relationship, including the arms of the immune system a particular pathogen must subvert in order to survive and reproduce.
2. Discovery of new molecules contributing to host immunity following the identification of the microbial immunomodulatory proteins with which they interact.
3. Identification of the function and sites of activity of immunomodulatory proteins, suggest potential agents of and targets for immunotherapy, respectively.
4. Development of new, efficacious vaccines based on the identification of the immune evading mechanisms employed by the pathogen.
5. Development of novel and important new databases for immune evading, suppressing and regulating epitopes.

d. Needs/Next Steps:
Same as preceding priority.

Research Priority 3a: Develop vaccines that are targeted to non-traditional clinical endpoints of efficacy such as to reduce the clinical-pathological disease manifestations of pathogens.

Research Priority 3b: Develop anti-transmission vaccines to serve both as independent vaccines with the potential for community/herd-wide benefits, as well as to serve as a component of protective vaccines to prevent the evolution of resistant pathogen populations during times of pandemic or emergency public health control measures.

a. Problem to be solved:
Many currently licensed vaccines provide extremely effective levels of protection and durable memory. Among the remaining medically important pathogens, many have evolved characteristics which circumvent the immune responses induced by current vaccine technologies, such that sterilizing or microbe eliminating responses may not be achievable. However, targeting specific stages and cycles in the pathogen may greatly reduce onset of disease and or transmission thus leading to improved health at the individual and population levels.

b. Research objectives:
1. Define lists of key anti-disease objectives for major chronic infectious diseases for which no sufficiently efficacious vaccine currently exists.
2. Identify key disease manifestations or immunopathological mechanisms that require intervention.
3. Assess public perceptions regarding the value of anti-vaccines and promulgate educational programs to overcome public bias.
4. Identify vaccines/immunotherapeutics appropriate for inducing both short-term (e.g., innate immunity-mediated) and long-term (e.g., acquired immunity-mediated) protection.
5. Initiate discussions with regulatory agencies to help study and draft necessary regulatory policies.

c. Proposed accomplishments:
1. Identification of key anti-disease and transmission objectives for major chronic diseases, to better define research and technical priorities for advancing vaccine development for licensing and labeling of a vaccine for disease prevention.
2. Development of vaccines and novel delivery of immunotherapeutics capable of reducing disease manifestations or interrupting the transmission of a pathogen, providing important control measures during epi- and pan-demic episodes.
3. Educated public, that gives the nation a knowledgeable consumer base in which to apply new and novel disease and transmitting prevenative vaccines.

d. Needs/Next Steps:
No additional steps provided.

<u>Research Priority 4</u>: Identify vaccine platforms that increase the potency of cell-mediated and/or humoral immune responses and which enable the combination of multiple complex antigens.

a. Problem to be solved:
Difficult pathogens may have evolved mechanisms to reduce or prevent the induction of a quantitatively high enough (potent) protective immune response under natural conditions. Increasing the potency and complexity of the vaccine-formulated antigens may quantitatively and qualitatively improve this response, imparting protective immunity when induced in a host prior to exposure to the pathogen.

b. Research objectives:
1. Identify the correlates (or, ideally, elucidate the mechanisms) of protection in hosts given hyperimmunizations or complex laboratory-based immunizations that exhibit some level of protection or recovery from a disease or experimental infection.
2. Identify the correlates of protection in naturally-occuring low or non-disease-adapted hosts that exhibit some level of protection or recovery from a disease or experimental infection.
3. Study ways to increase the potency of subunit vaccines in animal models, for both cell-mediated and humoral immunity, and test for protection.
4. Derive new complex antigen delivery systems able to incorporate multiple conformationally complex antigens.

c. Proposed accomplishments:
1. Identification of vaccine antigens which, when given in hyperimmune schedules, elicit protective immunity as determined by challeng/resistance to infection or disease.
2. Knowledge regarding how to covert a hyperimmune respons that is partially or more fully protective into a technologically feasible immunization protocol requiring only one or few immunizations.
3. Development of antigen delivery systems capable of presenting more and diverse complex conformational pathogen antigens.

d. Needs/Next Steps:
No additional steps provided.

<u>Research Priority 5</u>: Antigen discovery and rational antigen design.

a. Problem to be solved:
Difficult pathogens have evolved ingenious (but often as yet uncharacterized) host/pathogen-specific modifications in their structual and functional proteins that induce poor, type-, strain-, serovar-restricted, disease enhancing, or no protective responses. This may be due to host mimicry or to misdirection or dysregulation (suppression, potentiation) of the immune system by epitopes or determinants present on the structual glycoproteins, proteins, lipoproteins of the pathogen. Rational antigen design, whereby these immune-diverting epitopes are functionally removed or structures are modified to decrease their immunogenicity while increasing the immunogencity of protective epitopes, may be required to improve vaccine efficacy. Alternatively, antigens normally immunologically silent during the course of infection due to diverted immune responses or inaccessibility to the immune system, but which are potentially protective, need to be identified.

b. Research objectives:
1. Develop research and discovery algorithms to compare protective, non-protective, disease enhancing antigen preparations from the pathogen in an effort to identify which antigens are associated with protection or disease.
2. Identify immunomodulatory (potentiating or suppressive) determinants of key antigens and modify accordingly in order to optimize antigen design.
3. Identify conserved epitopes that may provide cross-protective immunity among pathogen strains / allelic variants.
4. Identify antigens associated with evolutionarily constrained biological processes.
5. Identify potentially protective antigens that fail to induce immune responses during natural infection due to inaccessibility or diversionary immunodominant epitopes.
6. Study the role of any host specific proteins that may be important in exposing or masking protective determinants.
7. Use genetic disruption (gene knock-out) to elucidate the functional role of vaccine candidate antigens.

c. Proposed accomplishments:
1. Development of new approaches to testing and formulating pathogen antigens and evaluating them in terms of their ability to elicit protection.
2. Development of new technologies for dampening non-protective responses and refocusing the immune system to induce protection.
3. Identification of conserved antigens or sequences that elicit cross-protection.

d. Needs/Next Steps:
No additional steps provided.

<u>Research Priority 6</u>: Prioritize pathogens for which there is a well described and characterized challenge model available; establish other animal models as a "second-tier" solution when use of primary host-pathogen system is not possible or practical.

a. Problem to be solved:
Due to the complexity of the pathogen/host interaction the only sensitive and useful readout for protection and therefore antigen down-selection and/or vaccine improvement may be the actual target pathogen/host system. In these situations, reliance on animal models may be misleading and

provide results that are not translatable to the natural host-pathogen system. Quantum improvements in vaccine design and potency will likely be developed most rapidly when it is possible to challenge the target host, assuming that an interative process will be required in which testing for protection is followed by return to the laboratory to effect improvement(s) in vaccine design. These systems should be prioritized for funding. Because challenge generally is available in veterinary vaccinology, this research priority applies primarily to humans.

Only in cases where challenge is not ethically feasible should resources focus on developing well-characterized animal models that mirror the multi-factorial nature of the target host/pathogen system for these highly co-evolved pathogens.

b. Research objectives:
1. Identify and prioritize for vaccine development problem pathogens for which a challenge model is available in the target host.
2. Identify immune evasion mechanisms and intervention strategies for these lead pathogen/host systems.
3. Design successful vaccines and then apply these approaches/vaccine delivery systems to similar pathogens where challenge is not feasible.
4. For key pathogens for which challenge is not available and homology with lead pathogen/host systems is poor, develop humanized surrogate models that allow evaluation of immunogenicity and efficacy.
5. Develop non-target animal models as a "second tier" test system, but assure that their use is efficiently integrated into vaccine development pathways to provide well-defined, supplemental information (such as preclinical safety and/or immunogenicity data) with predictive power for the target host.

c. Proposed accomplishments:
1. Development of more highly predictive animal and human models of infection capable of down-selecting protective/non-protective candidate pathogen antigens.
2. Development of new animal species to serve as models and improvement of humanized mouse models of human disease for use in antigen selection and vaccine improvement as described above.

d. Needs/Next Steps:
No additional steps provided.

Research Priority 7a: Revisit or develop models of protection based on crude pathogen preparations or attenuated pathogens (knock-out, irradiation), particularly when there is evidence of naturally induced partial or complete immunity. Establish proof of principle for such vaccines. For veterinary purposes, may combine this with administration of intact pathogen and/or concurrent therapy (immunological or chemotherapeutic).

Research Priority 7b: When proof of principle is established for crude pathogen preparations and/or attenuated pathogens, focus on process development for isolation and purification of attenuated whole organisms or whole organism extracts that are suitable for parenteral administration, where such preparations are convincingly proven to be highly efficacious.

a. Problem to be solved:

Provide long term solutions for "intractable" vaccine challenges such as parasitic infections and also enable a stop-gap measure to reduce an infectious threat on an urgent basis.

b. Research objectives:

1. Identify systems where exposure to pathogens or crude pathogen preparations provides protection (also identify systems where exposure to pathogens or crude pathogen preparations may exacerbate pathology).
2. Develop highly effective immunization regimens using attenuated whole organisms or whole organisms extracts, particularly for pathogens for which subunit approaches have had limited success.
3. Explore genetic disruption (knock-out) technologies for the attenuation of whole organism vaccines.
4. Develop new processes for production, purification and storage of whole complex pathogens (attenuated/killed organisms or extracts) such that they are suitable for parenteral administration.
5. Use protective attenuated organism or crude organism extract vaccines as model systems to aid in the identification of protective antigens and/or immune mechanisms that can be applied to the development of subunit vaccines.

c. Proposed accomplishments:

1. Development of effective vaccines for intractable pathogens.
2. Improved knowledge of the biological role of candidate vaccine antigens.
3. Manufacturing processes (including in vitro culture) enabling the mass production, purification, quality control, potency testing, safety testing and stable storage of attenuated pathogens, killed pathogens or crude extracts of pathogens in compliance with good manufacturing practices and regulatory guidelines.
4. Development of models of protection that can be used to inform subunit approaches.

d. Needs/Next Steps:

No additional steps provided.

II. Innate Immunity:

Break-out session leaders: Leslie Baillie and Peter Kaiser

A. Introduction:

The recent rediscovery of the essential role of the innate immune system in mediating protective immunity against infectious diseases has stimulated a burst of research activity in this area. This activity has been greatly supported in the biomedical community by the ability to access molecular biology tools such as annotated genome sequences, gene expression arrays and immunologic reagents. A similar level of support to the animal care community would make a dramatic impact on the pace of innate immunity research in veterinary species. By defining species specific and pan species conserved mechanisms of innate immunity we will be able to design therapeutics that stimulate the innate system to confer rapid, short term, broad spectrum protection, and support the development of robust, adaptive, agent-specific, long lasting immunity. Once developed, these therapeutics could be used to protect susceptible human and animal populations against the consequences of a bioterror attack.

B. State of the Art:

The innate immune system can be broadly defined as that component of the immune system that first responds to infection and prepares the ground for the adaptive immune response. It comprises a complex network of physical barriers, sensing systems, directed antimicrobial weapons and phagocytic cells. Evolutionary studies suggest that the central elements of the innate system were established early in the development of animals and have been retained in species ranging from birds to pigs, cattle and humans. Indeed the conserved nature of many of these pathways has made it possible to apply the knowledge gained in one species to the biology of others. This is particularly true in the case of innate immunity signaling pathways which represent the triggers which activate the immune response following infection. The recent discovery of the role of toll-like receptors (TLRs) in mediating inflammatory and protective responses in mice against infectious diseases such as the biothreat pathogens ebola virus, *Francisella tularensis* and *Burkholderia pseudomallei* and their extensive use in human trials for the treatment of cancer suggest that an FDA-approved TLR agonist for protection against and/or treatment of human infectious diseases is on the horizon and that the same should be possible for animals pathogens.

While these results are promising, there is concern as to the feasibility of stimulating long term protection using such an approach. Indeed, while the issue of long term toxicity in humans has been addressed, at least for CpG oligodeoxynucleotides that target TLR 9, understanding the long term effects of the up-regulation of the innate response in animals requires further study. In the context of a response to a bioterrorist attack with an unknown agent, a more conservative strategy might be to stimulate short term protection in the individuals surrounding the index case to provide cover until agent-specific therapeutics such as vaccines can be deployed.

In addition to conferring broad spectrum immunity, TLR stimulants have been shown to enhance the immunogenicity of vaccines. For example, CpG oligos can enhance the magnitude of the antibody response to the human anthrax vaccine such that it may be possible to reduce the number of priming immunizing doses, currently six in humans, required to achieve protection. It is known that the effectiveness of individual CpG motifs varies across species due to differences in TLR9 receptor specificity and differences in the distribution of the TLR9 receptor across different cell types. The characterization of the TLR distribution pattern of the dendritic cells of each species will

enable researchers to identity TLR adjuvants with the desired specificity. The ability to reduce the time required to achieve protection would be of considerable value in the event of an attack on unprotected animals.

While the focus so far has been on the TLRs, we need to be aware that they are not the only innate signaling receptor pathways. Studies in humans and mice have revealed the presence of a number of additional membrane- and cytoplasm-based receptor sensing systems such as NOD-like receptors (NLRs) and the RIG-1 pathway, which are also designed to respond to invading micro-organisms. Indeed it is likely that these systems interact with the readouts from the TLRs to modulate the overall quality and magnitude of the immune response and as such may represent further targets for therapeutic intervention. A further approach that should be mentioned here is the direct delivery of antimicrobial cytokines such as those stimulated by TLR activation to the host as a means of conferring rapid immunity.

In conclusion, by using targeted, defined approaches to stimulate innate immunity, it should be possible to confer both short-term protection against pathogenic micro-organisms and to adjuvant long term adaptive immunity in combination with agent specific vaccines.

C. Research priorities:

<u>Research Priority 1</u>: Define the limits of current knowledge of innate immunity across the animal kingdom

a. Problem to be solved:
A considerable amount of species-specific research and data have been generated by individual investigators working in the animal and human fields. While the overall evolutionary commonalities are obvious, further work is needed to clarify and identify species specific traits. It is clear that the human infectious disease research community can learn from the experience of their veterinary infectious disease research colleagues and vice versa.

b. Research objectives:
1. Build an effective bridge between the animal and human infectious disease research communities in the US and EU to facilitate the communication of ideas, the pooling of data and the development of therapeutics. Establish a transatlantic focus for innate immunity research.
2. Identify the commonalities between the innate immune systems of animals and humans and identify knowledge gaps. Review what we know: while there is already a considerable amount of data and information in the published literature describing species-specific research, the dissemination of this data tends to be limited to those working with the corresponding species. The establishment of a maintained database containing all references pertaining to innate immunity across the whole animal kingdom would support researchers seeking to identify common innate pathways. Once established, this resource can be mined to identify common themes and research areas likely to yield results in the near and far term.
3. Establish joint objectives and priorities: once the science has established the current knowledge base, the next step is to determine were the field needs to go. We need to establish clear priorities specific to the mission we are seeking to address. In addition we need to secure buy-in from the constituent parties for the effort to be a success. Finally we need to establish milestones and deliverable to ensure that the research is moving in the desired direction.

c. Proposed accomplishments:
1. A joint meeting between the biomedical and animal health communities focused entirely on innate immunity. This meeting will be charged with establishing a steering committee to act as a focus for future efforts and will define the near term and long term research objectives for the field.
2. The establishment of a managed database to specifically support research in the area of innate immunity.
3. A comprehensive review across the animal kingdom comparing and contrasting the similarities and differences among key animal species and humans.
4. The identification of a funding mechanism to support research specific to the objectives of this area.

d. Needs/Next Steps:
1. Organize and advertise a sponsored meeting to be held in the EU in the near future.
2. Establish a preliminary organizing steering committee.
3. Commission the construction of the database.
4. Commission the compilation of a review of the field.
5. Identify sources of funding.
6. Identify research priorities and objectives and a road map to achieve them.
7. Develop a strategic plan with clearly-defined milestones and a product development plan to take forward promising candidates to licensure.

Research Priority 2: Commission research in the key areas identified by the steering committee

a. Problem to be solved:
There is a need to close gaps existing in our knowledge of how the innate immune system functions across a range of animal species. It is essential that we employ modern molecular biology tools to fill in these gaps so that in the short term we can determine the mode of action of known innate agonists and in the longer term rationally design new innate stimulants capable of inducing specific immune effects.

The characterization of the innate immune system of a range of animal species will require access to readily available genetic and animal specific immunologic tools. Key to this effort will be the provision of high quality, annotated genome sequences comprising a representative cross section of each species. Access to this resource will enable researchers to identify in-silico homologues to known innate pathways which can then be tested empirically. Access to species-specific gene expression arrays which include genes involved in the regulation of innate signaling and cytokine expression will also support this effort as will the provision of species-specific immunological tools.

In the context of the adaptive immune response, we propose that the comparative biology approach be extended to the study of dendritic cells with an aim of identifying the role of innate immunity in adjuvanting the immune response to vaccine antigens.

b. Research objectives:
1. Genetic tools, complete annotated genomes: Fund an existing sequencing center to determine the nucleotide sequence of representative examples of the major animal species as determined by the steering committee. A key component of this effort will be the annotation and data presentation of these sequences. The data should be presented in a manner defined by the end user research

community. Particular emphasis should be placed on the identification of homologues to previously described innate immunity pathways.
2. Provide for the availability of immunologic and genomic reagents specific to innate immunity via a core facility organized along the lines of the NIH-funded efforts supporting the Biodefense Regional Centers of Excellence. Once established, this center can provide immunological reagents to researchers engaged in innate immunity research.
3. Identification of commonalities and comparative pathways: identify species-specific and cross-species innate pathways and determine the feasibility of stimulating short term broad-spectrum immunity and long term adaptive immune responses.
4. Dendritic cell biology: characterize immune signaling pathways in dendritic cells as a means of identifying innate agonists of immunity that can be used as vaccine adjuvants.

c. Proposed accomplishments:
1. The provision of fully annotated genome sequences and gene expression microarrays for a representative cross section of the major animal species.
2. The provision of species-specific immunological tools to support innate immunity studies.
3. The establishment of a funded resource core to provide the reagents described above.
4. The establishment of funded research proposals which support studies in innate immunity, including species-specific and cross-species comparative immunology proposals, joint proposals from the animal and human communities, and proposals representing collaborations between the EU and US.

d. Needs/Next Steps:
1. Identify funding mechanisms to support objectives. How will the research and core efforts be supported? Decide how many years of funding will be made available, and how it will be managed.
2. Determine which genome sequences need to be determined and define required annotation foci, i.e., innate immunity. Design gene expression arrays for each species comprising genes of the innate immune system.
3. Determine what immunological reagents need to be made available for each species.
4. Establish and fund an innate immunology core which will provide the genetic and immunological reagents in support of funded research programs.
5. Determine how research proposals will be solicited, assessed and, if successful, monitored against the research priorities of the overall strategic plan.

Research Priority 3: The stimulation of short term broad spectrum immunity

a. Problem to be solved:
In the context of a bio-attack there is an urgent need to presumptively treat large numbers of potentially susceptible individuals located in close proximity of the event (ring fencing). In the absence of real time detection and prior intelligence, a rational approach would be to stimulate immediate, broad spectrum protection and once the agent had been identified to switch over to an agent-specific intervention. The feasibility of conferring rapid protection via the innate immune system has been demonstrated across a number of species for a range of infectious agents. Research is required to identify the optimal stimulants in terms of species-specific requirements, determine the toxicity and longevity of the response and develop user friendly, stable platforms that support mass treatment.

b. Research objectives:
1. Identify innate stimulators which confer short term protection (ring fencing): Propose to use two approaches, empirically testing known agonists in combination with testing of new rationally designed agonists developed as part of this research effort.
2. Define length and breadth of protection and address toxicity issues: How long can innate immunity alone combat infections? How wide a protective window do we need? Does repeated administration of innate agonists cause adverse pathology?
3. Identify most cost-effective combination and delivery methods; ideally we would want a formulation that was needle free and of minimal cost.
4. Prebiotics / probiotics: Investigate the role of pre- and probiotics in promoting immune protection in the context of the innate immune response.

c. Proposed accomplishments:
1. Identification of existing individual and combined innate stimulants which confer non-specific broad spectrum protection.
2. Rational design of new innate immunity stimulants.
3. Determination of the therapeutic window of these stimulants.
4. Development of low cost delivery systems capable of supporting mass treatment.
5. Identification of biotic feeding programs that support wide protection.

d. Needs/Next Steps:
1. Identify innate stimulators that are currently available and determine their protective efficacy across a range of species.
2. Investigate currently available delivery technologies such as micro-encapsulation and defective viral vector systems as a means of supporting mass treatment.
3. Investigate the role of pre- and probiotics in conferring protection against infectious agents.
4. Develop a transition plan to take successful products forward.

<u>Research Priority 4</u>: The development of vaccine adjuvants

a. Problem to be solved:
In the context of biodefense the challenge is to stimulate a protective immune response in the shortest possible time frame, ideally with a single immunization delivered via a needle free approach. Preliminary data have shown that one can dramatically enhance the immunogenicity of both subunit and DNA vaccines can be dramatically enhanced by incorporating known TLR agonist and cytokines into the vaccine formulation. There is a need to investigate the ability of existing and newly emerging innate stimulators to enhance vaccine potency in a range of animal species.

b. Research objectives:
1. Enhance the immunogenicity of existing vaccines; in a systematic manner determine the ability of currently available innate stimulators to enhance the immunogenicity of known vaccines in different animal species.
2. Determine the ability of mixtures of agonists targeting different TLR triggers to enhance vaccine efficiency.
3. Test the ability of novel innate stimulators identified from comparative biology studies to enhance the immunogenicity of current vaccines.
4. Characterize the distribution of innate receptors on dendritic cells for different species.

5. Develop formulations capable of targeting the vaccine antigen and the agonist to the dendritic cell. As the major antigen presenting cell, it makes sense to focus on this cell type.

c. Proposed accomplishments:
1. A determination of the efficacy of currently available innate stimulators as vaccine adjuvants in different species.
2. The development of delivery platforms capable of selectively targeting dendritic cells.
3. A pathway to the development of licensed formulations.

d. Needs/Next Steps:
1. Determine the efficacy of existing innate stimulators as adjuvants for known vaccines across a range of animal species.
2. Test rationally designed agonists identified during this research effort.
3. Determine approaches for delivering vaccine candidates and innate stimulators to dendritic cells.
4. Contact industry and develop a joint action plan.

III. Mucosal Immunity:

Break-out session leaders: Marcelo Sztein and Bruno Goddeeris

A. Introduction:

Many infectious agents, including viruses, bacteria, fungi and parasites, enter the host through the respiratory, genitourinary and gastrointestinal mucosa taking residence in mucosal tissues or systemic sites. However, the majority of vaccines for man and animals are delivered systemically (by needle and syringe) inducing predominantly systemic responses rather than mucosal immunity. In contrast, it is now widely accepted that mucosal immunization can induce a protective immune memory both at the mucosal surface as well as at the systemic sites. In addition, the ease of vaccination via mucosal surfaces adds further impetus for the development of vaccines that can be administered via mucosal surfaces. Moreover, as many emerging diseases (hanta, SARS, nipa, ebola) originate in wild animal populations which are difficult to reach, it is imperative to explore the oral route of vaccine delivery for these evasive wild fauna.

In this context, there is great need for a better understanding of what drives immune responses to infection/invasion of the host. Studies focused on host/pathogen interactions at mucosal surfaces are essential to define early events relevant to disease resistance. Mucosal immunization may provide an effective way to circumvent certain problems confronting vaccine development, including the induction of broad systemic and mucosal immunity, improved targeting of effector responses to pathogens that enter human and animal hosts through mucosal surfaces, development of multi-component vaccines directed to several pathogens using live vectors or multiple antigens in conjunction with novel adjuvants/delivery systems, etc.

B. State of the Art:

The mucosal surfaces are covered by tight barriers of epithelial cells which separate the highly regulated internal compartment from the external environment, a compartment laden with microbes and other potentially harmful agents. Specialized innate and adaptive host defense mechanisms, the latter providing specific antigen recognition and immunologic memory, play an important role in maintaining the integrity of the mucosal barrier. The immune system of mucosal surfaces has evolved a wide array of mechanisms to protect the host from pathogens, while maintaining a relatively “peaceful co-existence” with commensal organisms, avoiding exaggerated responses to food and other environmental antigens and insults, and the generation of autoimmune disease. The adaptive immune responses at the mucosal surfaces originate from complex associations between epithelial cells and the mucosal associated lymphoid tissue (MALT) of the gastrointestinal, genitourinary and respiratory tracts and mammary glands, as well as systemic immune cells. The MALT is anatomically and functionally distinct from the systemic immune system, having developed distinct processes for antigen uptake, transport, processing and presentation, as well as specialized immune effector mechanisms. Mucosal tissues can act as primary lymphoid organs, wherein B and T lymphocytes originating from immature precursors can differentiate into effector cells. Moreover, immune effector cells primed in the mucosa against antigens and pathogens acquire specific migration (or “homing”) patterns that allow them to travel to distant mucosal sites. For example, the mucosa of the gastrointestinal tract contains large numbers of lymphocytes organized in several compartments that are morphologically and functionally distinct. These compartments can be broadly divided into immune inductive and effector sites. Inductive sites include Peyer’s patches (PP) and single isolated lymphoid follicles (ILF) beneath the epithelial layer, and mesenteric lymph nodes (MLN). Effector sites include less organized lymphoid regions

in the mucosa containing the lamina propria lymphoid cells (LPL) and intraepithelial lymphocytes (IEL).

In recent years our understanding of the mucosal immune responses has grown exponentially in many areas, including the interactions between innate and adaptive immune responses, the role and transport of immunoglobulins across the epithelial layer, the immunoregulatory effects of cytokines and chemokines, the expression of key molecules directing lymphoid cell homing to mucosal surfaces and the modulatory mechanisms that down regulate immune responses. Moreover, during the last five years it has become apparent that the resident flora and nutrition all play important roles in the development, activation and modulation of the mucosal immune system. However, despite this remarkable progress in our knowledge of the immune mechanisms underlying protective immunity at mucosal surfaces, our understanding is far from complete. For example, it is well established that "uncontrolled" inflammatory responses to pathogenic or commensal organisms and food antigens leads to many of the pathological conditions observed in the gastrointestinal tract. However, very little is known on the events leading to these disease states.

One of the biggest challenges that lie ahead is the unraveling of the extraordinarily complex mechanisms that underlie the generation of effective immune responses to potentially pathogenic organisms, while controlling inflammatory responses to commensal organisms and food antigens. Another great challenge that remains is to overcome tolerance induction when antigens are administered via the oral route. Indeed, the mechanisms mastering the tuning of induction versus tolerance or immunity are not well understood. Moreover, as the differences among the mucosal and systemic immune systems of different species are rather pronounced, it is imperative to study the relevant species or animal models in vivo, ex vivo and to develop in vitro systems that accurately reflect the in vivo characteristics of the targeted species. The knowledge to be gained by these studies will greatly enhance our ability to prevent inflammatory diseases in organs lined by large mucosal surfaces. Moreover, this information will also be invaluable in designing new generations of vaccines that can be administered via mucosal surfaces which have the potential of inducing strong mucosal and systemic immune responses against pathogens that enter animal and human hosts via mucosal surfaces.

C. Research priorities:

<u>Research Priority 1</u>: Define mechanisms of immune induction at mucosal surfaces

a. Problem to be solved:
Better definition of the mechanisms underlying the induction of effective immunity at mucosal surfaces.

b. Research objectives:
1. Characterize the commonalities and differences of the various components of the common mucosal immune system, i.e., the gastrointestinal, respiratory and genitourinary tracts.
2. Characterize the interaction of innate immunity on priming adaptive immune responses in the gastrointestinal (GI), genitourinary (GU) and respiratory tracts and mammary glands.
3. Identify similarities and differences among the mechanisms of induction of immunity at mucosal surfaces in humans and animals of veterinary significance.
4. Characterize the differential induction of immunogenicity and tolerance.

5. Define the receptors and other molecules involved in the binding and entrance of organisms through mucosal surfaces, including signaling pathways.

c. Proposed accomplishments:
1. Definition of the cell subpopulations involved in the innate and adaptive immune responses at inductive sites, including dendritic cells (DC), regulatory T cells (T regs), memory T and B subsets, natural killer (NK), granulocytes, etc, as well as their degree of activation, secretion of cytokines and chemokines and specificity for mucosal pathogens.
2. Increased understanding of the organizational structure and anatomical distribution of immunological components of mucosal tissues in the GI, GU and respiratory tracts and mammary glands in animals and humans.
3. In depth understanding of the role of epithelial and other cells (e.g., M cells) in the generation of innate and adaptive immunity in the local microenvironments of the GI, respiratory and GU tracts and mammary glands.
4. Better understanding of the basis for eliciting rapid (innate, adaptive) and long lasting (adaptive) protective immunity.
5. Modeling of the optimal induction of immunity or tolerance.
6. Identification of the molecular signaling pathways for the induction of effective mucosal immunity.

d. Needs/Next Steps:
1. Use of multidisciplinary approaches including traditional immunological methods and novel system biology (bioinformatics).
2. A rapid path for translational applications by favoring close interactions between basic scientists and those directly involved in field applications or the clinic.
3. Develop core facilities and other centralized services and standardized reagents, particularly for veterinary applications.
4. Provide set-aside funding to study issues related to improving our understanding of mucosal immunity, particularly in areas with the greatest translational potential and when an adequate challenge model is available.

Research Priority 2: Define mechanisms of immune effector function at mucosal surfaces

a. Problem to be solved:
Better definition of the mechanisms underlying protective effector immunity at mucosal surfaces.

b. Research objectives:
1. Identify correlates of protection in infections caused by organisms that enter the host via mucosal surfaces.
2. Elucidate the basis for the heterogeneity of the responses observed in animals and humans in response to mucosal pathogens (i.e., host determinants of susceptibility or resistance).
3. Identify similarities and differences among the mucosal effector immune responses in humans and animals of veterinary significance.
4. Improve understanding of the specific migration (or “homing”) molecules that allow lymphocytes primed in mucosal tissues to travel to regional LN and distant mucosal effector sites.
5. Define the mechanisms of persistence of immunity and tolerance.

c. Proposed accomplishments:

1. Determination of whether systemic immune responses can be used as surrogates for the effector immune responses in mucosal tissue microenvironments that will result in the elimination of the invading pathogen.
2. Understanding how pathogens of public health and veterinary significance that enter through mucosal surfaces subvert the host immune response.
3. Better phenotypic and functional characterization of the cell subpopulations involved in the innate and adaptive immune responses at effector sites, including DC, T regs, memory T and B subsets, cytotoxic T lymphocytes (CTL), gamma/delta T cells, etc in the GI, respiratory and GU tracts, as well as their degree of activation, secretion of cytokines and chemokines and specificity for mucosal pathogens.
4. Determination of what is the optimal balance of antibody (e.g., subclasses, functional characteristics, affinity, etc) and cell-mediated immunity (e.g., cytokines, CTL, etc) that should be achieved by ideal vaccines to prevent establishment of the organism in the host or disease.
5. Novel approaches for targeting effector cells to mucosal sites of interest.
6. Development of novel methods for the accurate measurement of relevant effector immune responses.
7. In depth understanding of the basis for immune homeostasis at mucosal surfaces.

d. Needs/Next Steps:
Same as Research Priority 1.

<u>Research Priority 3</u>: Ontology and competence of the mucosal immune system

a. Problem to be solved:
Optimization of the induction of mucosal immunity in neonatal, young, adult, elderly and immunocompromised populations.

b. Research objectives:
1. Conduct detailed comparative studies on the innate and adaptive immune responses in the various compartments and mucosal sites in neonates, young, adults and aged humans or animals of veterinary significance.
2. Define the potential of interactions with vaccination via mucosal surfaces by concomitant infections or resident flora.

c. Proposed accomplishments:
1. Strategies that can be used to overcome the blocking of vaccines administered via mucosal surfaces by maternal antibodies.
2. Strategies that can be used to enhance, improve and/or optimize immune responses in different age groups and populations with different health status.
3. Understanding the effects of resident flora and nutrition on the mucosal homeostasis and outcome of vaccination.
4. Understanding the effects of interactions among vaccine moieties in multi-component vaccines on the outcome of vaccination.
5. Methods to avoid deceptive imprinting of mucosal immune responses (e.g., neutralizing vs. non-neutralizing antibodies, subdominant responses, Th1 inflammatory responses versus Th2).

d. Needs/Next Steps:
Same as Research Priority 1.

<u>Research Priority 4</u>: Improved delivery systems for the induction of mucosal and systemic immunity

a. Problem to be solved:
Development of suitable and more effective oral and respiratory delivery systems and adjuvants for mucosal vaccination.

b. Research objectives:
1. Develop better adjuvants and delivery systems based on an in depth understanding of their mechanisms of action.
2. Develop effective single dose vaccines using novel and optimized adjuvants and delivery systems.

c. Proposed accomplishments:
1. Understanding the mechanisms of action of adjuvants and how they can be modified to more effectively induce mucosal immunity while minimizing reactogenicity.
2. Development and characterization of novel delivery systems to more effectively induce mucosal immunity while minimizing reactogenicity.
3. Targeting of vaccines composed of attenuated or dead organisms or their components to antigen presenting cells (e.g., dendritic cells) in the mucosal site of interest for the induction of optimized effector responses.
4. Development of novel strategies of systemic immunization with the potential to target effector responses to mucosal tissues.

d. Needs/Next Steps:
Same as Research Priority 1.

Research Priority 5: Establish appropriate models for the study of relevant mucosal immune responses in animal and human disease

a. Problem to be solved:
Lack of established animal models for diseases involving organisms that enter the host via mucosal surfaces affecting animals and humans.

b. Research objectives:
1. Establish in vitro models to study mucosal immunity (e.g., polarized cell lines to study the molecular determinants of binding of organisms to epithelial and M cells, signaling pathways)
2. Establish ex vivo models relevant to animal and human disease
3. Establish in vivo models relevant to animal and human disease.

c. Proposed accomplishments:
1. Development of non-invasive systems.
2. Improved understanding of host-pathogen interactions with particular emphasis on the identification of events that can be targeted by novel vaccines to kill the organisms or prevent their access or persistence in the host.
3. Development of systems that can be used as platforms to evaluate multiple infectious diseases.
4. Identification of therapeutic targets through the use of these models.

d. Needs/Next Steps:
Same as Research Priority 1.

IV. Immunogenetics:

Break-out session leaders: Wendy Brown and Ivan Morrison

A. Introduction:

Genetic polymorphism of proteins involved in antigen presentation and immune regulation enables each animal species to generate appropriate immune responses to a diverse range of pathogens at the population level, but can result in variation between individual animals in the nature, magnitude and specificity of immune responses to individual pathogens. Among the domesticated animal species, there are well documented examples of variation between breeds, selected lines and individuals in their response to infectious agents and vaccines, but the basis for these differences is poorly understood. Such variation has important implications for the development of vaccines, particularly those employing subunit antigens. The most polymorphic gene families are the class I and class II Major Histocompatibility Complex (MHC) genes, which encode proteins that present antigenic peptides to T lymphocytes. Polymorphism in the peptide binding domains of these proteins influences the types of peptides that they bind and hence the specificity of the immune responses. The characterization of these proteins is important not only to determine how they influence variation in immune responsiveness but also to provide molecular reagents that can be exploited to dissect the fine antigenic specificity of immune responses, to develop T cell antigen screening systems and to engineer MHC-peptide tetramer reagents for quantifying T cell responses induced by infection or vaccination. There is also emerging evidence that polymorphism in genes encoding other families of proteins participating in the innate and adaptive arms of the immune response [e.g., cytokines, natural killer (NK) cell receptors and pathogen-associated molecular pattern (PAMP) receptors] can influence the nature and/or magnitude of immune responses. Information on the repertoires of these immune response gene families and their allelic diversity is currently fragmentary. More detailed characterization of these systems is required both to provide the necessary tools for studies to understand the mechanisms of immunity, and to investigate the basis of genetic differences in response to vaccine antigens.

B. State of the Art:

Although a significant number of nucleotide sequences are available for alleles of class I and class II MHC genes in several animals species (particularly cattle, pigs, chickens and dogs), in most cases these have been derived from selected breeds or lines of animals. There is also a limited number of cloned full-length genes that can be used for detailed studies of the specificity of T cell responses, and tetramer reagents are only now becoming available, and then only for a few alleles in cattle and one in horses. There is a need to expand these resources at two levels, first to acquire larger numbers of allele sequences from representative samples of the respective species of animals and second to obtain full-length expressible genes from a more limited number of selected MHC haplotypes in each species, in order to facilitate detailed studies of antigenic specificity of responses in the different species. The acquisition of genome sequence data for several species is now allowing a more complete analysis of the repertoires of other important gene families than was possible hitherto. This information will also allow genome-wide analyses of these and related genes for polymorphisms. In this regard, it is envisaged that gene microarrays will increasingly make important contributions to this area both by permitting the analysis of gene expression and the detection of gene polymorphisms. However, in all of these areas there is currently insufficient effort and resources being deployed to progress the enable work to progress at the pace that is required.

C. Research priorities:

<u>Research Priority 1</u>: Understand the mechanisms of protective immunity to important pathogens

a. Problem to be solved:
We do not understand the basis of protective immunity to many infectious agents and cannot move forward with vaccine development until we do.

b. Research objectives:
1. Dissect genetic variation in the response to disease.
2. Use this information (biomarkers of protection) to monitor response to vaccines.
3. Define target antigens/epitopes.
4. Select appropriate delivery vehicle and adjuvant to achieve appropriate immune responses.

c. Proposed accomplishments:
1. Rational vaccine design for target populations.

d. Needs/Next Steps:
1. Complete sequencing and annotation of genome regions encoding immune response related genes for major veterinary species.
2. Develop and maintain defined genetic lines of animals.
3. Identify allelic variation in non-MHC immune response-related genes.
4. Develop technology to screen target populations for haplotypes and make an available catalogue of functional MHC alleles for all species.
5. Knowledge of allelic frequencies in target populations.
6. Define pathogen peptides associated with specific alleles.
7. Develop MHC-peptide molecular constructs to quantify and monitor CMI responses.

<u>Research Priority 2</u>: Establish international networks to facilitate the exchange of information and reagents related to immunogenetics and vaccine development

a. Problem to be solved:
Small segmented networks in immunogenetics exist and function well within certain established research groups (human or animal) or certain geographical areas but there is a need to expand this network globally (EU-US) to promote and facilitate the exchange of resources.

b. Research objectives:
1. Identify and prioritize research gaps.
2. Coordinate research efforts to maximize the impact of limited resources.

c. Proposed accomplishments:
1. More rapid and efficient development of vaccines.

d. Needs/Next Steps:

1. Increase infrastructure in veterinary research as it relates to immunogenetics.
2. Initiate strategic novel paradigms and programs to fund coordinated intercontinental research consortia in immunogenetics.
3. Identify and support centers to generate generic reagents required to underpin immunogenetics research and vaccine development.
4. Repository for storage and distribution of these reagents.

V. Comparative Immunology:

Break-out session leaders: Mark Estes and José Sánchez-Vizcaíno

A. Introduction:

This break-out session was designed to define the state of comparative immunology research in the US and EU and suggest mechanisms to expand current capacity, quality, and scope of available animal models to meet the increasing demand for both civilian and military needs in biodefense research, and to enhance disease control in areas where the interplay between humans, livestock, and wildlife species increase the potential to rapidly spread biological threat agents.

B. State of the Art:

Newly emerging diseases are primarily zoonotic and arise from a variety of livestock and wildlife species. Many of these zoonotic agents are transmitted by animals to man, or potentially can be transmitted by immune compromised humans to livestock (e.g. HIV-infected individuals). Existing paradigms for these instances are numerous but the worldwide spread of *Mycobacterium bovis* tuberculosis is one such example. In this instance, a disease focus in wildlife exists in the US and EU (white tailed deer, farmed deer, badgers) with resurgence in the human population along the U.S. border with Mexico and in imported food products. What these paradigms illustrate is the continuing need for new and improved animal models for studies of zoonotic agents and their interaction within definitive and secondary hosts. Many of these agents cannot be modeled in mice and primates. Primates are an existing bottleneck and will continue to be so in the near term. Shortages in supplies from both intramural (NIH, regional primate centers) and extramural sources, cost, ease of use and shortage of adequate containment facilities (BSL-3 and 4) are all problems for development of vaccines, therapeutics and immune modulators. In many instances, swine, cattle, equine, and other vertebrate species fulfill the "FDA Animal Rule" and provide excellent models of disease pathogenesis and intervention with logistical advantages; e.g., size, ease of real time monitoring, facilities, multiparous births, similarities to human physiology and organ size. The full benefits and opportunities offered by domestic animal models will however require investments in reagent development including well defined genetic lines of animals, formation of worldwide collaborative research groups to share expertise and unique facilities, and education and training to foster rapid response to emergencies and reduce costs and redundancy. The framework for achieving expected outcomes in comparative immunology will require productive analyses of expanded species-specific genomic databases and focus on the discovery of intracellular signaling pathways that will provide more robust comparative analyses than traditional immunologically-restricted extracellular protein networks. Appropriate animal models allow invasive procedures and provide access to local target tissue response at the site of infection and disease to define representative systemic biomarkers of disease status in humans.

C. Research priorities:

<u>Research Priority 1</u>: Formation of Comparative Immunology Consortia with open information sharing by species and agent, and with appropriate infrastructure and expertise

a. Problem to be solved:

Networking capabilities and support for teleconferencing, milestone setting, travel, and intellectual property protection.

b. Research objectives:
1. Define consortia.
2. Conduct regular meetings with defined objectives.
3. Develop web site portal.
4. Promote collaborations between human and animal health scientists.
5. Promote collaborations between EU and US.

c. Proposed accomplishments:
1. First meeting to take place within one year from the date of this workshop.
2. Team building between human and animal health immunology.
3. Expertise and additional groups are included to achieve goals; e.g., include veterinary immunology toolkit projects in EU and US.

d. Needs/Next Steps:
1. Leverage available funds to achieve objectives.
2. Identify group leaders to champion and deliver objectives.
3. Establish inter-institutional partnerships.
4. Establish industrial partners.
5. Facilitate reagent sharing across international borders including select agents.

<u>Research Priority 2</u>: Reagent repository and toolbox development, genetically and phenotypically defined lines of target animals for vaccines

a. Problem to be solved:
1. An acute shortage of veterinary immunological reagents.
2. Lack of repository, maintenance, and distribution capability.
3. Access to qualified animal species-specific investigators.
4. Access to reagents that have passed good quality control standards.
5. Access to defined animal lines.
6. Establish core professional services to provide quality veterinary immunological reagents, such as what is currently provided by NIH-BRB clinical repository, ATCC, or commercial entities for human and murine reagents.

b. Research objectives:
1. Develop nucleic acid-based detection reagents.
2. Develop monoclonal and polyclonal antibodies.
3. Develop certified-healthy animal lines that are genetically and phenotypically defined.
4. Distribution and production networks for all of the above.

c. Proposed accomplishments:
1. Type 1 and Type 2 cytokines,, TLRs and other immunological reagents.
2. Inflammation biomarkers.
3. Nutritional biomarkers.
4. Biomarkers of disease resistance and susceptibility to multiple pathogens.

d. Needs/Next Steps:
1. Identify institutions, locations, and facilities that can support the repository, maintenance, and distribution of veterinary immunological reagents.

2. Review and modify regulatory procedures to achieve good regulatory standards that facilitate rapid access of immunological reagents worldwide.
3. Schedule conferences with appropriate US and EU regulatory agencies within one year from the date of this workshop.

<u>Research Priority 3</u>: Discover surrogate biomarkers of vaccine efficacy (comparative correlates of protection) in domestic and wildlife animals species to enable clinical studies such as duration of immunity in non-classical animal model species

a. Problem to be solved:
There are few if any correlates of protection (innate or adaptive immunity) for many of the current threats we face in wildlife, domestic animal species, and man, including duration of memory responses by T and B cells.

b. Research objectives:
1. Discover biomarkers (organ-specific and systemic) that are correlated to clinical outcomes using real-time sampling methods such as cannulation.
2. Discover appropriate biomarkers for *in vitro* or *ex vivo* assays.
3. Develop reagents to support the discovery of biomarkers.
4. Develop infrastructure-array technology (protein, nucleic acid) to discover biosignatures.
5. Conduct clinical studies to correlate host responses to measurable outcomes (pathology, survival, transmission, and shedding).

c. Proposed accomplishments:
1. Biomarkers of inflammation.
2. Biomarkers and signatures of infectious diseases.
3. Differentiate requirements for inflammation from effective protective responses.
4. Biomarkers shown to correlate to measurable host response outcomes (pathology, survival, transmission, and shedding).
5. Comparative counter-regulatory strategies to reduce immune mediated pathology or immune deviation.

d. Needs/Next Steps:
1. Develop pathogen specific animal challenge models.
2. Discover mechanisms of protective immunity.
3. Discover correlates of protective immunity.
4. Conduct comparative protective immunity studies in animal challenge models.
5. Identify surrogate biomarkers of protective immunity across animal challenge models
3. Validate biomarkers in target animal host species

<u>Research Priority 4</u>: Comparative studies of innate immune activators and improved nutrition (supplementation and deficiencies-nutritional manipulation) for generation of rapid onset of protection in emergency situations and in naïve populations

a. Problem to be solved:
Need tools for rapid control of outbreaks in wildlife, domestic animals, and human populations.

b. Research objectives:
1. Recycle existing technologies using better adjuvants and priming agents.
2. Discover novel probiotics and nutritional supplementation strategies across species.
3. Disover new vaccine platforms that bypass traditional pathways for rapid response.

c. Proposed accomplishments:
1. Define impact of innate immune activators (combinatorial aspects of ligand signaling) in various animal species including pathways and cellular targets.
2. Probiotic-nutritional impact on innate and adaptive immunity, correlates of protection, and the qualitative and quantitative aspects of vaccine efficacy.
3. Impact of environmental conditions on the efficacy of vaccines.

d. Needs/Next Steps:
1. Leverage resources across immunology research centers.
2. Develop reagents (See Research Priority 2 above).
3. Develop core facilities and consortia (See Research Priority 1 above).

<u>Research Priority 5</u>: Comparative immunology of special populations (pregnancy, neonates, maternal interface including regulation by maternal antibody of the neonatal response to vaccination, Fc receptors, geriatric populations) including wildlife species

a. Problem to be solved:
1. Discover vaccines rationally designed for specific scenarios (e.g., biodefense/agroterrorism).
2. Define animal husbandry practices (e.g., colostral supplementation) that harm or strengthen the neonatal immune system and the pregnant mother.
3. Define species-specific effector mechanisms and immune physiology.
4. Define immune-neuroendocrine interactions that predict health outcomes.

b. Research objectives:
1. Characterize the neonatal response in relevant species.
2. Characterize the impact of vaccination on the mother and newborn in target species.
3. Define neonatal tolerance and vaccination.
4. Determine long term consequence of immune modulation interventions in neonates.

c. Proposed accomplishments:
1. Increase our understanding of neonatal immunity in farm animals with non-placental IgG transport mechanisms.
2. Measures to decrease the window of neonatal disease susceptibility.
3. Measures to enhance passive immunity.
4. Measures to by-pass maternally-derived immune interference mechanisms.

d. Needs/Next Steps:
1. Determine where expertise, animal models, and facilities exist to conduct research.
2. Conduct proof-of-concept studies.

<u>Research Priority 6</u>: Obtain comparative data on immune responses to infection and treatment/vaccination to support the development of "FDA animal rule" models for humans and non-human primates

a. Problem to be solved:
1. Establish the value of swine, cattle, and other large animal models for preclinical evaluation of vaccines, immune modulators, and therapeutics for zoonotic diseases.

b. Research objectives:
1. Establish strengths and weaknesses of the swine model for viral, bacterial, and parasitic diseases.
2. Establish strengths and weaknesses of the bovine model for viral, bacterial, and parasitic diseases.
3. Establish strengths and weaknesses of small ruminant models for viral, bacterial, and parasitic diseases.
4. Establish strengths and weaknesses of equine models for viral, bacterial, and parasitic diseases.
5. Establish strengths and weaknesses of other animal models for viral, bacterial, and parasitic diseases.

c. Proposed accomplishments:
1. Animal models that are superior to standard mouse models or alternatives to non-human primate models.
2. This work will lead to the development of reagents for molecular and immunological toolboxes.
3. Provide pivotal needs in the current animal model repertoire for infectious agents without adequate animal models.

d. Needs/Next Steps:
1. Infrastructure for model development: defined genotype and phenotype, core facilities, reagents, instrumentation, animal handling, and husbandry.
2. Needle-free technologies for oral or dermal delivery of vaccines.
3. Increased leveraging of support from USDA-NRI, NIH-RFA, DOD, and EU funding sources.
4. Support of basic immunology studies.

VI. Genomics:

Break-out session leaders: Chris Ockenhouse and Thomas Göbel

A. Introduction:

The current explosion of new high-throughput technologies arising from microbial and animal genomics studies offers the opportunity to gain a better understanding of the molecular pathways underlying pathogen biology, the host immune system, and host–pathogen interactions. These new tools can now be applied to priority pathogens to overcome some of the current hurdles in the discovery of highly effective vaccines for priority diseases for which no vaccine currently exist.

B. State of the Art

Recent progress in sequencing the genomes of microbial pathogens and their hosts is providing sophisticated strategies for deciphering the biological complexity of host–pathogen interactions. Analysis of whole genome responses of pathogens and hosts coupled with functional genomics offers the opportunity to better understand disease processes, the mechanisms through which pathogens evade host immunity and the genetic basis of host–pathogen interactions. The integration of these approaches in vaccine research is likely to fundamentally change the way scientists approach the challenges of discovering safe and effective vaccines.

C. Research priorities:

1. Comparative microbial genomics

a. Problem to be solved:

There is a lack of genomic sequence databases from multiple strains of pathogens that differ with respect to virulence, gene variability, and cell culture derived versus wild-type pathogens.

b. Research objectives:

1. Conduct comparative microbial genomics studies to identify candidate genes associated with infection, virulence, transmission, and host range specificity.
2. Develop pathogen specific microarray-based technologies for studying genome-wide transcriptional profiling.

c. Proposed accomplishments:

1. Comparative analysis of microbial strains will provide new insights into pathogen evolution, virulence mechanisms, and host range specificity.
2. Identification of transcriptional control mechanisms in host–pathogen interactions.

d. Needs/Next Steps:

1. Support sequencing centers for targeted whole genome sequencing and selective targeted genes from selected pathogens.
2. Support microarray-based technologies for studying genome-wide transcriptional profiling.
3. Support new bioinformatic tools that permit whole genome comparison on different computing platforms.
4. Support proteomic discovery databases from pathogens of veterinary and human public health importance.

2. Animal genomics

a. Problem to be solved:
There is a lack of genomics tools available for livestock and poultry animal species and the animal health research community has yet to fully integrate the use of these tools in animal health research.

b. Research objectives:
1. Use high through-put gene expression microarrays and proteomics in hosts with completed or near-completed annotated genomes to:

- discover patterns of protective immunity to vaccines using challenge models of infection in order to decipher the mechanisms of protective immunity (short and long term protection);
- understand differences in immune responses in vaccinated hosts that prevent disease versus hosts that prevent infection;
- discover biomarkers as surrogates of protection;
- initiate comparative genomics of biomarkers associated with protective immune responses elicited from animals immunized with biodefense vaccines with similar biomarkers elicited from phase 1 immunogenicity trials in human subjects
- understand variability in host genetics with different outcomes of infection;
- discover and select adjuvants using specific patterns of gene expression that results in favorable responses;
- understand innate immune genes and networks of genes in hosts given immune modulators with putative broad non-specific immune stimulatory activity against pathogens (i.e., biodefense pathogens);

c. Proposed accomplishments:
1. Development of public database of completely annotated genomic sequence datasets for animals selected for disease modeling.
2. Use sequence-based high-throughput expression profiling technologies and integrated bioinformatic tools to gather, analyze and interpret genomic data.

d. Needs/Next Steps:
1. Support programs that fully annotate animal genomes to decipher functional roles of genes critical for protective immunity and pathogenesis.
2. Support training of biological scientists in analysis of complex gene expression and proteomic data sets.
3. Support development of reagents that will advance research on host responses of veterinary importance (cattle, porcine, poultry).

3. Host-pathogen interactions at the genomics level

a. Problem to be solved:
There is a lack of scientific information on the host responses and molecular signatures that correlate with infection or protection, including the genes that are involved in the activation or repression of key regulatory pathways.

b. Research objectives:

1. Develop and refine challenge models of infection in animals and humans to understand the pathogenesis of disease in the context of interventional vaccine studies both for animal and human vaccine development programs.
2. Establish relevant animal models for biodefense vaccine development programs that mimic human disease (FDA -animal rule).
3. Identify functional genetic variations that modulate the immune responses in livestock and poultry species:
    - Develop SNP maps that define polymorphisms in genes that are major controllers of the host immune system;
    - Identify and characterize functional mutations resulting in altered immune function;
    - Determine whether polymorphisms of genes associated with innate immunity increase protective thresholds and enhance the health of animals under intense management systems;
    - Use information from comparative microbial genomics studies to identify pathogenic substances that regulate immune responses.
4. Determine the genetic factors that control host-pathogen interactions and disease outcome:
    - Understand the interplay between specific host and pathogen genes and how the variation within these genes leads to phenotypic variation in pathogenesis;
    - Define gene expression patterns and regulatory phenomena that affect the level of host resistance.
5. Conduct controlled animal challenge studies and identify genetic variations that control host responses to vaccines and biotherapeutics to control priority pathogens of cattle, poultry, and pigs:
    - Conduct genetic analyses to identify markers or causative genetic variations of livestock and poultry associated with phenotypic variances in pathogenesis, tissue tropism, disease transmission, host range specificity, and clinical disease outcomes resulting from exposure to important pathogens;
    - Collaborate with the animal health industry to determine the genetic profiles of “good responders” to vaccines and biotherapeutics in order to achieve a significant increase in herd immunity and protection against priority pathogens.

c. Proposed accomplishments:

1. The study of host-pathogen interaction at the genomics level will provide a complete picture of infectious diseases, microbial pathogenesis, and protective host immune mechanisms using an integrated systems biology that will be crucial in developing a new generation of intervention strategies against pathogens infecting humans and animals.
2. An integrated genomics approach will lead to a better understanding of disease processes and the mechanisms through which pathogens evade host immunity, identification of the genetic basis of host–pathogen interactions, and the discovery of novel vaccines, drugs, and biotherapeutics.
3. Identification and characterization of genetic variations that will lead to improved and enhanced countermeasures to control and prevent priority animal and human diseases.
4. Understanding the genetics that drive good or poor responses to vaccines.
5. Understand gene function and disease mechanisms and their associated biological markers, characterizing pathways that confer disease resistance, and integrating this information into workable animal production programs.

d. Needs/Next Steps:

1. Support research on host–pathogen interactions using high-throughput gene expression analysis.
2. Support host profiling studies to identify gene expression signatures unique to specific pathogens and genetically disparate hosts.
3. Integrate genomics tools in vaccine clinical trials to identify animals that are good responders to vaccines.
4. Develop genetic-based diagnostics, vaccines, and biotherapeutics designed to convey disease resistance in genetically-defined animal populations.

APPENDIX I: PARTICIPANTS

US-EC Workshop: Advances In Immunology and Vaccine Discovery

December 12-14, 2006

EUROPE UNION

Jean-Christophe Audonnet, DVM, PhD
Director, Discovery Research
Vaccinomics and Virology
Merial
Laboratoire Lyon Gerland
254, rue Marcel Mérieux
69007 Lyon
FRANCE
Phone: +33 (0)4 72 72 33 79
FAX:
jean-christophe.audonnet@merial.com

Patrick de Baetselier, PhD
Head of Dept of Cellular and Molecular Immunology CMIM
Free Univ. of Brussels - V.U.B.
Building E floor 8
Pleinlaan 2
B-1050 Brussels
BELGIUM
Phone +32-2-629.19.79
FAX: +32-2-629.19.81
pdebaets@vub.ac.be

Bruno Goddeeris, DVM, PhD, MSc
Professor, Chairman Department Biosystems, K.U. Leuven
Faculty of Bioscience Engineering
Department Biosystems, Division Gene Technology
Kasteelpark Arenberg 30, 3001 Leuven
BELGIUM
Phone +32(0)16.321.437;
FAX +32(0)16.321.994
bruno.goddeeris@biw.kuleuven.be

Thomas Göbel, PhD
Institut für Tierphysiologie
University of Munich
Veterinärstraße 13
80539 München
GERMANY
Phone +49-89-2180-3827
FAX. +49-89-2180-2554
thomas.goebel@tiph.vetmed.uni-muenchen.de

Danny Goovaerts DVM
Director, Research and Development
Intervet International
Wim de Korverstraat 35
P.O. Box 31
5830 AA Boxmeer
THE NETHERLANDS
Phone: +31 (0) 485 587727
FAX: +31 (0) 485 587339
Danny.Goovaerts@intervet.com

Pete Kaiser, PhD
Principal Research Scientist
Avian Genomics Group
Institute for Animal Health
Compton
Berkshire RG20 7NN
UNITED KINGDOM
Phone: +44 1635 577277
FAX: +44 1635 577263
Pete.kaiser@bbsrc.ac.uk

Carlos Ardavín, PhD
Department of Immunology & Oncology
Centro Nacional de Biotecnologia/CSIC
Universidad Autonoma de Madrid
28049 Madrid,
SPAIN
Phone (+34) 915-854-841 office
(+34) 915-854-656 lab
FAX (+34) 913-720-493
ardavin@cnb.uam.es

Thomas C. Mettenleiter, PhD
Full Professor
President of Friedrich-Loeffler-Institut
Federal Research Institute for Animal Health
Boddenblick 5a
17493 Greifswald-Insel Riems
GERMANY
Phone: +49-38351-7-250
FAX: +49-38351-7-151
Thomas.Mettenleiter@fli.bund.de

Ivan Morrison, PhD, BVMS
Centre for Tropical Veterinary Medicine
Royal (Dick) School of Veterinary Studies
The University of Edinburgh
Easter Bush Veterinary Centre
Roslin Midlothian
EH25 9RG
Tel. +44 131 650 6216
ivan.Morrison@ed.ac.uk

Isabelle P. Oswald, Ing Agr, PhD
INRA, Laboratoire de Pharmacologie-Toxicologie
180 chemin de Tournefeuille, BP3
31931 Toulouse cedex 9 FRANCE
Phone : 33 (0) 5 61 28 54 80
FAX: 33 (0) 5 61 28 53 10
ioswald@toulouse.inra.fr

Paul-Pierre Pastoret, DVM, PhD
Emeritus Professor
Head Publications Department
World Organisation for Animal Health (OIE)
122, rue de Prony
75017 Paris FRANCE
Phone: +33 (0) 1 44151859
FAX: +33 (0) 1 42670987
pp.pastoret@oie.int

Jeremy Salt PhD, MRVS
Pfizer Animal Health
ipc 988 Pfizer Ltd.,
Ramsgate Road, Sandwich,
Kent CT13 9NJ,
United Kingdom
Phone +44 (0)1304 645577
Fax: +44 (0) 1304 653158
jeremy.salt@pfizer.com

José Manuel Sánchez-Vizcaíno, DVM, PhD
Full Profesor Dpto. Animal Health
Faculty of Veterinary Medicine
University Complutense of Madrid
Avda. Puerta de Hierro s/n
28040 Madrid
SPAIN
Phone + 34 91 394 4082
FAX 34 91 394 3908
jmvizcaino@vet.ucm.es

Thomas W. Vahlenkamp, DVM, PhD
FRIEDRICH-LOEFFLER-INSTITUT
Bundesforschungsinstitut für Tiergesundheit
Federal Research Institute for Animal Health
Boddenblick 5a
17493 Greifswald - Insel Riems
GERMANY
Phone: +49-38351-7-172
FAX: +49-38351-7-151
Thomas.Vahlenkamp@fli.bund.de

Laurent Bochereau, PhD
Head of Science, Technology, Education European Delegation to the USA
2300 M Street, NW, Su 300
Washington, DC 20037-1434
Phone: (202) 862-9574
FAX: 202-429-1766
Laurent.Bochereau@ec.europa.eu

Cornelius Schmaltz, MD
Scientific Officer - Emerging Infectious Diseases, European Commission
Research Directorate General - F3.1
Office: CDMA 3/26!
1049 Brussels
BELGIUM
Phone : +32-2-2958984
FAX: +32-2-2994561
cornelius.schmaltz@ec.europa.eu

Isabel Minguez-Tudela, DVM, Ph.D
Scientific Officer -Infectious animal diseases
European Commission
Research Directorate General-E4
Office SDME 8/96
Brussels
BELGIUM
Phone: +32 2 299 21 09
FAX: +32 2 296 30 29
isabel.minguez-tudela@ec.europa.eu

UNITED STATES

Kevin Anderson, PhD
Deputy Director (Acting)
National Biodefense Analysis and Countermeasures Center
Science & Technology Directorate
Department of Homeland Security
110 Thomas Johnson Drive, Suite 200
Frederick, MD 21702
TEL: 301-682-3819
FAX: 301-682-5268
CELL: 240-285-5714
kevin.anderson@dhs.gov

Leslie W. Baillie, PhD
Biological Defense Research Directorate
Naval Medical Research Center
503 Robert Grant Ave
Silver Spring, MD 20910-7500
bailliel@nmrc.navy.mil

Cynthia L. Baldwin, PhD
Professor of Veterinary and Animal Sciences
410 Paige Laboratory
University of Massachusetts
Amherst, MA 01003
Phone: (413) 545-3167
FAX: 413-545-6326
cbaldwin@vasci.umass.edu

Douglas E. Brough, PhD
Senior Director Vector Sciences
GenVec Inc
65 West Watkins Mill Road
Gaithersburg MD 20879
Phone: (240) 632-0740
FAX: 240-632-0735
dbrough@genvec.com

Wendy C. Brown, PhD
Professor of Immunology
Department of Vet. Micro/Path
Washington State University
Pullman, WA 99164-7040
Phone: (509) 335-6067
FAX: 509-335-8529
wbrown@vetmed.wsu.edu

Michael Callahan, MD, DTM&H, MSPH
Biological Threat Defense & Mass Casualty Care Defense Science Offices
Defense Advance Research Projects Agency (DARPA)
Phone: (571) 218-4596
FAX: 703-465-1057
Michael.Callahan@darpa.mil

Chris Chase, DVM, PhD
Department of Veterinary Science
PO Box 2175; ADR Rm 125
South Dakota State University
Brookings, SD 57007
Phone: (605) 688-5652
FAX: 605-688-6003
Christopher_Chase@sdstate.edu

Wei Mei Ching, PhD
Head, Division of Rickettsial Diseases
Viral and Rickettsial Diseases Department Naval Medical Research Center
503 Robert Grant Ave
Silver Spring, MD 20910-7500
Phone: (301) 319-7438
FAX: 301-319-7460
chingw@nmrc.navy.mil

Linda A. Chrisey, PhD
Office of Naval Research
Life Sciences Research Division, Code 341
Program Manager, Environmental/Marine Biotechnology and Biocentric Technology
875 N. Randolph St.
Arlington, VA 22203-1995
Phone: (703) 696-4504
FAX: 703-696-1212
CHRISEL@ONR.NAVY.MIL

Harry Dawson
USDA, ARS, Nutrient Requirements and Functions Laboratory; 10300 Baltimore Ave.
Bldg 307, Room 206, BARC-East
Beltsville, MD 20705
Phone: 301-504-9412 ext. 278
FAX: 301-504-9062
harry.dawson@ars.usda.gov

La**wrence A. Elsken, DVM**
Global Vaccine Manager
USDA, APHIS, VS
Center for Veterinary Biologics
510 S. 17th St., Suite 104
Ames, IA 50010
(515) 232-5785
(515) 232-7120 (fax)
Lawrence.A.Elsken@aphis.usda.gov

D. Mark Estes, PhD
University of Texas Medical Branch
Depts. of Pediatrics, Microbiology & Immunology and Pathology
The Sealy Center for Vaccine Development and Center for Biodefense and Emerging Infectious Diseases
2.330F Children's Hospital
301 University Boulevard
Galveston, TX 77555-0372
Phone: (409) 772-0434
FAX: 409-772-0460
dmestes@utmb.edu

Cyril G. Gay, DVM, PhD
National Program Leader, Animal Health
Animal Production and Protection
Agriculture Research Service
United States Department of Agriculture
5601 Sunnyside Avenue
Beltsville, MD 20705
Phone: (301) 504-4786
FAX: 301 - 504-5467
cyril.gay@ars.usda.gov

William T Golde, PhD
Plum Island Animal Disease Center
Microbiologist
40550 Rte 25
USDA Orient Point Warehouse
Orient Point, NY 11957
Phone: (631) 323-3249
FAX: 631-323-3006
william.golde@ars.usda.gov

Eileen Herrera
Office of International Research Programs
Agriculture Research Service
United States Department of Agriculture
2000 E. Allen Road
Tucson, AZ 85719 USA
Phone: (520) 670-6380, ext 120
FAX: 520-670-6493
eherrera@tucson.ars.ag.gov

Richard E. Hill, Jr., DVM, MS
Director, USDA, APHIS, VS
Center for Veterinary Biologics
510 S. 17th St., Suite 104
Ames, IA 50010
(515) 232-5785
(515) 232-7120 (fax)
Rick.E.Hill@aphis.usda.gov

Peter M. Hobart, PhD
Science Director, USAMRIID
1425 Port Street
Ft. Detrick, MD 21702-5011
Phone: (301) 619-0010
FAX: 301-619-4625
peter.hobart@amedd.army.mil

Lynn M. Hoesing (Herrmann), PhD
Research Microbiologist
Animal Diseases Research Unit
Agricultural Research Service
U.S. Department of Agriculture
3003 ADBF; Washington State University
Pullman, WA 99164-6630
Phone: (509) 335-6068
FAX: 509-335-8328
lherrman@vetmed.wsu.edu

Henry Hunt, PhD
Agricultural Research Service
U.S. Department of Agriculture
Avian Diseases and Oncology Laboratory
3606 E. Mount Hope Road
East Lansing, MI, 48823-5338
Phone: (517) 337-6834
FAX: 517-337-6776
hunthd@msu.edu

Darrell Kapczynski, PhD
Microbiologist , Exotic and Emerging Avian Viral Diseases Research Unit, SAA, ARS, USDA
Southeastern Poultry Research Laboratory
934 College Station Road
Athens, GA, 30605
Phone: (706) 546-3471
FAX: 706-546-3161
dkapczynski@seprl.usda.gov

Stephen Kappes, PhD
Deputy Administrator Animal Production and Protection
Agriculture Research Service
United States Department of Agriculture
5601 Sunnyside Avenue
Beltsville, MD 20705
Phone: (301) 504-4834
FAX: 301-504-5467
stephen.kappes@ars.usda.gov

Rudolf Kuppers
SAIC Scientist, Military Infectious Diseases Research Program
504 Scott Street
Fort Detrick, MD 21702-5012
Phone: (301) 619-7897
FAX: 301-619-2416
rudolf.kuppers1@us.army.mil

Susan J. Lamont, PhD
C. F. Curtiss Distinguished Professor
Department of Animal Science
2255 Kildee Hall
Iowa State University
Ames, IA 50011
Phone: (515) 294-4100
FAX: 515-294-2401
sjlamont@iastate.edu

John S. Lee, PhD
Contractor, Cambridge Systems, Inc.
Virology Division, USAMRIID
1425 Porter Street
Frederick, MD 21702
Phone: 301-619-4912
FAX: 301-619-2290
john.s.lee@amedd.army.mil

Hyun Lillehoj, PhD
Senior Research Immunologist
Animal Parasitic Diseases Laboratory,
ANRI, BARC, ARS, USDA
Building 1040, BARC-East
Beltsville, MD 20705
Phone: (301) 504-8771/6170
FAX: 301-504-5103/5306
hlilleho@ANRI.barc.usda.gov

F. Chris Minion, MS, PhD
Professor, Dept. of Veterinary Microbiology & Preventive Medicine, Iowa State University
1130 Veterinary Medicine
Iowa State University
Ames, Iowa 50011-1240
Phone: (515) 294-6347
FAX: 515-294-8500
fcminion@iastate.edu

Michael P. Murtaugh, PhD
Professor, Department of Veterinary Pathobiology, University of Minnesota
1971 Commonwealth Avenue
St. Paul, Minnesota 55108
Phone: (612) 625-6735
FAX: 612-625-5203
murta001@umn.edu

Peter L. Nara, MSc, DVM, PhD
President and CEO
Biological Mimetics, Inc.
124 Byte Drive
Frederick, MD. 21702 USA
Phone: (301) 620-7691
FAX: (301) 620-1827
nara@bmi-md.com

Ed Nuzum, DVM, PhD
Chief, Biodefense Vaccines and other Biological Products Development Section
Office of Biodefense Research Affairs (OBRA) DMID/NIAID/NIH
Mail Stop Code 6604
6610 Rockledge Drive, Room 5109
Bethesda, MD 20892-6604
Phone: (301) 402-8603
FAX: 301-480-1263 (fax)
enuzum@niaid.nih.gov

Chris F. Ockenhouse, MD, PhD
Colonel, Medical Corps, US Army
Division of Malaria Vaccine Development
Walter Reed Army Institute of Research
503 Robert Grant Ave
Silver Spring, MD 20910-7500
Phone: (301) 319-9473
Chris.Ockenhouse@na.amedd.army.mil

Muquarrab A. Qureshi, DVM, MSc, PhD
National Program Leader, Animal Genetics Cooperative State Research, Education and Extension Service, U.S. Dept. of Agriculture
1400 Independence Avenue, SW
Washington, DC 20250-2220
Phone: (202) 401-4895
FAX: 202-401-1602
mqureshi@csrees.usda.gov

Thomas L Richie, MD, PhD
Captain, Medical Corps, United States Navy
Director, Malaria Program
Naval Medical Research Center
503 Robert Grant Ave
Silver Spring, MD 20910-7500
Phone: (301) 319-7584
Fax: 301-319-7545
richiet@nmrc.navy.mil

John C. Rogers, MD
Program Director, Cellular Systems Cluster
Division of Molecular and Cellular Biosciences
National Science Foundation
Phone: (703) 292-8442
jrogers@nsf.gov

James A. Roth, DVM, PhD, DACVM
Director, Center for Food Security and Public Health Executive Director
Institute for International Cooperation in Animal Biologics, College of Veterinary Medicine
Iowa State University
Ames, Iowa 50010
Phone: (515) 294-8459
FAX: 515-294-8259
jaroth@iastate.edu

Marcelo B. Sztein, MD
Professor, Department of Pediatrics/Center for Vaccine Development
University of Maryland School of Medicine
685 West Baltimore Street
Baltimore, Maryland 21201-1559
Phone: (410) 706-5328
FAX 410-706-6205
msztein@medicine.umaryland.edu

Giorgio Trinchieri, MD
Director, Cancer and Inflammation Program
Chief, Laboratory of Experimental Immunology
Center for Cancer Research
National Cancer Institute
Bldg. 560/Room 31-93
Frederick, Maryland 21702-1201
Phone: 301-846-1323, 301-846-7558
FAX : 301-846-1673
trinchig@mail.nih.gov

Wenbin Tuo, PhD
Research Scientist
Animal Parasitic Diseases Laboratory
ANRI, ARS, USDA
Building 1040, Room 1
Beltsville, MD 20705 USA
Phone: (301) 504-8258
FAX: 301-504-5306
wtuo@anri.barc.usda.gov

Joe Urban, PhD
Research Leader
Nutrients Requirements and Functions Laboratory, USDA-ARS-BARC
10300 Baltimore Avenue
Bldg 307-C, BARC-East, Room 214
Beltsville, MD 20705-2350
Phone: (301) 504-5528 ext. 267
Fax: 301-504-9062
urbanj@ba.ars.usda.gov

Bettina Wagner, DVM, Dr.med.vet.habil.
Assistant Professor of Immunology
Department of Population Medicine and Diagnostic Sciences
College of Veterinary Medicine
S1-082 Schurman Hall
Cornell University
Ithaca, NY 14853
Phone: 607-253-3813
FAX: 607-253-3440
bw73@cornell.edu

Michael J. Wannamuehler, MS, PhD
Professor, Dept. of Veterinary Microbiology & Preventive Medicine
Veterinary Medical Research Institute
Iowa State University
1118 Veterinary Medicine
Ames, Iowa 50011-1240
Phone: (515) 294-3270
FAX: 515- 294-8500
mjwannem@iastate.edu

Stephen White
Research Geneticist
Animal Diseases Research Unit
USDA-ARS
Room 3015 ADBF
Washington State University
Pullman, WA, 99164-6630
Phone: (509) 335-7407
FAX: 509-335-8328
swhite@vetmed.wsu.edu

William C Wilson, PhD
Microbiologist
Arthropod-Borne Animal Diseases Research Unit, USDA-ARS
Agricultural Bldg, Room 5031, Dept. 3354
1000 E. University Avenue
Laramie, WY, 82071-2000
Phone: (307)-766-3622
FAX: 307-766-3500
wcwilson@uwyo.edu

Laszlo Zsak, DVM, PhD
Research Leader
Endemic Avian Viral Diseases Research Unit
USDA-ARS
Southeast Poultry Research Laboratory
934 College Station Rd.
Athens, GA 30605 USA
Ph: (706) 546-3654
FAX: 706-546-3161
Laszlo.Zsak@seprl.usda.gov

PARTICIPANTS FROM NADC

National Animal Disease Center
USDA-ARS
2300 Dayton Ave
Bldg 1 NADC
Ames, IA 50010

John Bannantine, PhD
Research Microbiologist, Bacterial Diseases of Livestock
Phone: (515) 663-7340
FAX: 515-663-7458
jbannant@nadc.ars.usda.gov

Robert (Bob) Briggs, DVM
Veterinary Medical Officer, Respiratory Diseases of Livestock
Phone: (515) 663-7762
FAX: 515-663-7458
bbriggs@nadc.ars.usda.gov

Susan Brockmeier, DVM, PhD
Veterinary Medical Officer, Respiratory Diseases of Livestock
Phone: (515) 663-7221
FAX: 515-663-7458
sbrockme@nadc.ars.usda.gov

Andy Cheung, PhD
Microbiologist, Virus and Prion Diseases of Livestock
Phone: (515) 663-7497
FAX: 515-663-7458
acheung@nadc.ars.usda.gov

Margaret Elliott, PhD
Microbiologist, Bacterial Diseases of Livestock
Phone: (515) 663-7169
FAX: 515-663-7458
melliott@nadc.ars.usda.gov

Jesse Goff, DVM., PhD
Supervisory Veterinary Medical Officer, Periparturient Diseases of Cattle
Phone: (515) 663-7547
FAX: 515-663-7669
jgoff@nadc.ars.usda.gov

Mark Kehrli, DVM, PhD
Supervisory Veterinary Medical Officer,
Phone: (515) 663-7254
FAX: 515-663-7458
mkehrli@nadc.ars.usda.gov

Kelly Lager, DVM, PhD
Virus and Prion Diseases of Cattle
Veterinary Medical Officer
Phone: (515) 663-7371
FAX: 515-663-7458
klager@nadc.ars.usda.gov

Howard Lehmkuhl, PhD
Microbiologist, Virus and Prion Diseases of Cattle
Phone: (515) 663-7255
FAX: 515-663-7458
hlehmkuh@nadc.ars.usda.gov

John Lippolis, PhD
Research Molecular Biologist, Periparturient Diseases of Cattle
Phone: (515) 663-7446
FAX: 515-663-7458
jlippoli@nadc.ars.usda.gov

Brian Nonnecke, DVM, PhD
Microbiologist, Periparturient Diseases of Cattle
Phone: (515) 663-7311
FAX: 515-663-7669
bnonneck@nadc.ars.usda.gov

Mitchell (Mitch) Palmer, DVM, PhD
Veterinary Medical Officer, Bacterial Diseases of Cattle
Phone: (515) 663-7474
FAX: 515-663-7458
mpalmer@nadc.ars.usda.gov

Karen Register, PhD
Microbiologist, Respiratory Diseases of Cattle
Phone: (515) 663-7700
FAX: 515-663-7458
kregiste@nadc.ars.usda.gov

Tim Reinhardt, PhD
Research Animal Scientist, Periparturient Diseases of Cattle
Phone: (515) 663-7540
FAX: 515-663-7669
treinhar@nadc.ars.usda.gov

Jeurgen Richt, DVM, PhD
Veterinary Medical Officer, Virus and Prion Diseases of Cattle
Phone: (515) 663-7366
FAX: 515-663-7458
jricht@nadc.ars.usda.gov

Julia Ridpath, PhD
Microbiologist, Virus and Prion Diseases of Cattle
Phone: (515) 663-7586
FAX: 515-663-7458
jridpath@nadc.ars.usda.gov

Randy Sacco, PhD
Microbiologist, Respiratory Diseases of Livestock
Phone: (515) 663-7354
FAX: 515-663-7458
rsacco@nadc.ars.usda.gov

Judy Stabel, PhD
Microbiologist, Bacterial Diseases of Cattle
Phone: (515) 663-7304
FAX: 515-663-7458
jstabel@nadc.ars.usda.gov

Louisa Tabatabai, PhD
Research Chemist, Respiratory Diseases of Livestock
Phone: (515) 294-6284
FAX: 515-294-0453
ltabatab@nadc.ars.usda.gov

Tyler Thacker, PhD
Microbiologist, Bacterial Diseases of Livestock
Phone: (515) 663-7722
FAX: 515-663-7458
tthacker@nadc.ars.usda.gov

Amy Vincent, PhD
Veterinary Medical Officer, Virus and Prion Diseases of Cattle
Phone: (515) 663-7371
FAX: 515-663-7458
avincent@nadc.ars.usda.gov

Wade R (Ray) Waters, DVM, PhD
Veterinary Medical Officer, Bacterial Diseases of Livestock
Phone: (515) 663-7756
FAX: 515-663-7458
rwaters@nadc.ars.usda.gov

Kurt Zuelke, DVM, PhD
Director, National Animal Disease Center
Phone: (515) 663-7201
FAX: 515-663-7677
kzuelke@nadc.ars.usda.gov

Rich Zuerner, PhD
Microbiologist, Bacterial Diseases of Livestock
Phone: (515) 663-7392
FAX: 515-663-7458
rzuerner@nadc.ars.usda.gov

APPENDIX II: ORGANIZATION

Organizing Committee
Eileen Herrera
Cyril G. Gay
Thomas L. Richie
James A. Roth
Isabel Minguez-Tudela
Kurt Zuelke

Scientific Committee
Cyril G. Gay
Paul-Pierre Pastoret
Thomas L. Richie
Isabel Minguez-Tudela

Local Organizing Committee
Dawne Buhrow
Teresa Herold
Eileen Herrera

APPENDIX III: SPONSORS

Agricultural Research Service (ARS), USDA

Cooperative State Research and Extension Service (CSREES), USDA

European Commission (EC)

Military Infectious Diseases Research Program (MIDRP), DoD

Molecular Vaccines Interagency Working Group

National Institute of Allergy and Infectious Diseases (NIAID), NIH, HHS

National Science Foundation (NSF)

Naval Medical Research Center, United States Navy

Office of Naval Research (ONR), United States Navy

APPENDIX IV: PROGRAM

Welcome

Kurt ZUELKE, Director, National Animal Disease Center, Agricultural Research Service (ARS) USDA, Ames, IA

Steve KAPPES, Deputy Administrator, Animal Production and Protection, Agricultural Research Service, US Department of Agriculture, Beltsville, MD

Laurent BOCHEREAU, Head of Science, Technology, Education, European Delegation to the USA, Washington, DC

Introduction

Cyril Gerard GAY, National Program Leader, Animal Health, Agricultural Research Service (ARS), USDA, Beltsville, MD

Thomas L. RICHIE, Director, Malaria Program, Naval Medical Research Center, Silver Spring, MD

Opening Session

The workshop opened with two presentations from keynote speakers (EU and US). The keynote speakers set the stage for the workshop and explained the importance of integrating a robust immunology research program in vaccine discovery and suggested strategic targets for the workshop participants to consider during their deliberations.

Keynote Speakers:

Jim ROTH, Director, Center for Food Security and Public Health and Executive Director, Institute for International Cooperation in Animal Biologics, College of Veterinary Medicine, Iowa State University

Paul-Pierre PASTORET, Head Publications Department, World Organisation for Animal Health (OIE), Paris, France

Fields of Investigation to be Addressed and Related Objectives (6 Sessions)

1. Mechanisms of Pathogen Immune Evasion

   Objective: Provide examples of mechanisms used by pathogens to evade the immune system, their impact on vaccine efficacy, and how they might be counteracted through rational vaccine design.

Presenters:

Thomas L. RICHIE, Director, Malaria Program, Naval Medical Research Center, Silver Spring, MD

Patrick de BATSELIER, Head of Dept of Cellular and Molecular Immunology, VUB, Brussels, Belgium

2. Innate Immunity

   Objective: Define mechanisms of innate immunity, its influence on acquired immunity and disease control, and how various vaccine platforms could take advantage of innate immunity to improve potency. Research in this area will influence development of treatments/vaccines/therapeutics and improve management practices.

Presenters:

Giorgio TRINCHIERI, Director, Cancer and Inflammation Program, Chief, Laboratory of Experimental Immunology, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD

Peter KAISER, Principal Research Scientist, Avian Genomics Group, Institute for Animal Health, Compton, UK

3. Mucosal Immunity

   Objective: Many infectious diseases enter through respiratory and gastrointestinal tissues and infect mucosal surfaces. There is a need for a better understanding of what drives immune responses to infection/invasion of the host. Studies focused on host/pathogen interactions at mucosal surfaces are essential to define early events relevant to disease resistance. Mucosal immunization may provide an effective way to circumvent certain problems confronting vaccine development, such as pre-existing immunity to vaccine vectors.

Presenters:

Marcelo SZTEIN, Professor, Department of Pediatrics/Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD

Bruno GODDEERIS, Professor, Chairman Department Biosystems, K.U. Leuven, Belgium

4. Immunogenetics

   Objective: Traditional approaches to infectious disease control have been through vaccination schemes that will generate protective antibody responses. However, many infectious diseases have not been amenable to control by this approach. Some pathogens may evade the immune system and require the generation of antigen-specific T-cells or what is described as a cell-mediated immune (CMI) response. Epitope mapping *in silico* using predictive major histocompatibility complex (MHC) T-cell epitope binding sites may enable the rational design of highly efficacious molecular vaccines.

Presenters:

Wendy BROWN, Professor of Immunology, Department of Vet. Micro/Path, Washington State University, Pullman, WA

Ivan MORRISON, Centre for Tropical Veterinary Medicine, Royal (Dick) School of Veterinary Studies, Easter Bush Veterinary Centre, University of Edinburgh, Scotland, UK

5. Comparative Immunology

   Objective: It has been estimated that 70-80 percent of new emerging diseases are zoonoses (diseases people catch from animals). Furthermore, the eradication of zoonoses (e.g., brucellosis and tuberculosis) has highlighted the domestic/wildlife interface and the need to understand differences in the immune response of various animal species (including man) in order to discover effective countermeasures. The existence of the "species gap" in which vaccine technologies that are highly efficacious in animal models are much less efficacious in humans (for reasons yet to be explained), emphasizes the importance of this field.

Presenters:

Joe URBAN, Research Leader, Nutrients Requirements and Functions Laboratory, ARS, USDA, Beltsville, MD

José Manuel SANCHEZ-VIZCAINO, Full Profesor Dpto. Animal Health, Faculty of Veterinary Medicine, University Complutense of Madrid, Madrid, Spain

6. Genomics

   Objective: With the availability of human and animal genomes and the development of genomics tools we are now in a position to study the genetics of vaccine efficacy (e.g., good vaccine responders or poor responders) and safety. We are now at a crossroad in our understanding of infectious diseases where we can decipher host-pathogens interactions at the molecular level and design highly efficacious and safe vaccines designed to match an individual vaccinee's genotype.

Presenters:

Chris OCKENHOUSE, Division of Malaria Vaccine Development, Walter Reed Army Institute of Research, Silver Spring, MD

Thomas GOEBEL, Institut für Tierphysiologie, University of Munich, Munich, Germany

Biodefense Vaccines

Two speakers set the stage for the breakout sessions using biodefense vaccines as an example. The speakers identifies needs and priorities for biodefense vaccines and crystallize the information provided in the previous six sessions into concrete examples of where advances in immunology can advance the discovery of highly effective vaccines for biodefense.

Presenters:

Cyril Gerard GAY, National Program Leader, Animal Health, Agricultural Research Service (ARS), USDA, Beltsville, MD

Jean-Christophe AUDONNET, Director, Discovery Research, Vaccinomics and Virology, Merial, Lyon, France

Breakout Sessions

Speakers and workshop participants broke into six groups with the objectives of 1) identifying gaps in vaccines that can be addressed by research in immunology, and (2) steps that must be taken to address those gaps. Each group selected a leader to report the results of their deliberation. A team led by Drs. Cyril Gay and Tom Richie stayed at the conference venue an extra day to prepare the final report, which was to be made available to the U.S Government and the European Commission for planning and decision-making.

Tour

All participants were provided with a tour of the National Animal Health Laboratories: The National Animal Disease Center (NADC)-ARS; the National Veterinary Services Laboratory (APHIS)-APHIS; and the Center for Veterinary Biologics (CVB) - APHIS.

Workshop Schedule

Tuesday, December 12 Morning – Arrive Des Moines, Iowa 12.00 – Registration 12.45 – Meeting Opens: Welcome/Intro 13.00 Hour – Keynote Speakers (EU-US) 14.00 Hour – Session 1 (EU) 15.00 Hour – Session 1 (US) 16.00 Hour – Session 2 (EU) 19.00 Hour – Dinner (Speaker*) Wednesday, December 13 08.00 Hour – Session 2 (US) 09.00 Hour – Session 3 (EU) 10.00 Hour – Session 3 (US) 11.00 Hour – Session 4 (EU) 12.00 Hour – Lunch	13.00 Hour – Session 4 (US) 14.00 Hour – Session 5 (EU) 15.00 Hour – Session 5 (US) 16.00 Hour – Session 6 (EU) 17.00 Hour – Session 6 (US) 19.00 Hour – Dinner (Speaker**) Thursday, December 14 08.00 Hour – Biodefense Vaccines 09.00 Hour - Breakout Sessions 12.00 Hour – Working Lunch – Report/Recommendations 14.00 Hour – Tour of Ames Facilities 16.00 Hour – End

***Michael V. Callahan MD**, DTM&H, MSPH, Biological Threat Defense & Mass Casualty Care Defense Science Offices, Defense Advance Research Projects Agency (DARPA)

"DARPA's Accelerated Vaccine Development and Production Programs: Rapid Vaccine Assessment (RVA) and Accelerated Manufacture of Pharmaceuticals (AMP)"

** **Leslie W. Baillie, PhD,** Biological Defense Research Directorate, Naval Medical Research Center, Silver Spring, MD

"Innate immunity; do we owe it all to fruit flies"