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2003

ARS Immunology Research Workshop Proceedings

A workshop sponsored by the U.S. Department of Agriculture, Agricultural Research Service at Bethesda, Maryland, on December 1-4, 2003.

Also includes a bibliography of representative ARS immunology research published since 2000.

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2003 ARS Immunology Research Workshop

Executive Summary

The 2003 ARS Immunology Research Workshop was sponsored by the United States Department of Agriculture (USDA), Agricultural Research Service (ARS), in Bethesda, Maryland, December 1-4, 2003. The purpose of the workshop was to exchange recent scientific breakthroughs in animal immunology and determine where ARS and its partners should concentrate future efforts to significantly advance national research programs in animal health, animal production, aquaculture, food safety, and human nutrition.

The workshop participants included ARS immunologists working in livestock, wildlife, avian and marine species, as well as immunologists working in other Federal laboratories and universities across the United States. The first day of the workshop provided a series of presentations covering high profile topics in basic immunology research with emphasis on cutting-edge discoveries in innate immunology, immune regulation, and immunogenetics. The second day focused on the applications of immunology research in nutrition, disease resistance, and immunointervention. This exchange of information set the stage for the third day, when all participants were divided into the following four working groups: 1) Immunity and disease resistance; 2) Immunointervention strategies; 3) Immunity and the pathogenesis of diseases; 4) Immunity and nutrition. The challenge set forth for the working groups was to identify research objectives within specific areas of animal immunology that could significantly advance research programs in animal health, animal production, aquaculture, food safety, and human nutrition.

The goal for the pathogenesis working group was to provide research priorities to advance our understanding of immune responses that lead to pathogenesis, either inherently programmed within the immune system, or driven by metabolic and infectious disease pathways. The human nutrition working group was asked to identify research objectives in animal immunology that were most likely to make significant contributions to our understanding of health and nutrition. The disease resistance working group was asked to identify research objectives that will lead to the discovery and characterization of immune mechanisms associated with heritable disease resistant traits and that may in parallel be used as targets to design novel biotherapeutics and highly efficacious vaccines. The immunointervention working group was tasked with providing research

objectives that will significantly increase our understanding of protective immunity and lead to the rational design of highly efficacious vaccines and diagnostics.

A significant outcome of the workshop was that all four working groups identified the lack of veterinary immunological reagents as a key stumbling block to advancing the field of animal immunology. The lack of immunological reagents was also considered paramount to make significant progress in many of our national research programs. For instance, the lack of efficient tools for evaluating cell-mediated immunity in cattle and swine makes the discovery and development of highly efficacious vaccines more difficult to attain and demonstrate. Many of the workshop participants felt that cell-mediated immunity should be at the core of strategies to discover new tools against the diseases that resist traditional vaccine approaches. The overwhelming consensus was that the void in our immunological tool chest is the rate-limiting step in providing the next generation of vaccines.

In today's economy it is highly unlikely that the private sector will invest in the basic research necessary to develop the tools for testing cell-mediated immunity. Accordingly, 26 participants agreed to look at organizing a community wide effort, post-workshop, to discover, develop, and distribute quality-controlled immunological reagents for veterinary science research.

As a result of the final working sessions, ARS immunologists and their partners identified a total of 66 research objectives to incorporate into future research action plans. The research objectives with the highest priority are noted here:

- Establish national and international networks to prioritize and develop immune toolkits for animal species of economic importance. Coordinate tool development so that priority reagents become available. Work with commercial sources to market products.
- Identify critical components of innate immunity; Use innate immune pathways for interventions/traditional and therapeutic vaccines and for development of new adjuvants and improvement of vaccine efficacy.
- Identify and characterize host genes that control important immunologic responses; determine whether alleles of certain genes would enhance animal health
- Use information from microbial genomics to define substances from pathogens that stimulate/regulate immune responses at mucosal surfaces.
- Develop broad spectrum, targeted delivery systems (target dendritic cells or others) for immunomodulator and/or peptide and/or DNA delivery to effector cells.
- Optimize use of existing vaccines and immunomodulators for intervention at embryogenesis, birth, weaning, or prior to stress (shipping, comingling, slaughter).
- Elucidate factors affecting efficacy of current adjuvant systems
- Define the affects of stress/diet/age on immune responses at mucosal surfaces.
- Identify specific nutrients with beneficial immune modulating properties that optimize immune function. Define specific nutrient requirements for effective and

appropriate vaccination and immunological memory, and for amelioration of periods of immune deficiency, such as during pregnancy, parturition, pediatric development, ageing, and stress.

- Define probiotic microbial populations that affect immune development and functional resistance at mucosal surfaces and on the efficacy of systemic immunity, and the diets (prebiotics) that support appropriate resident or ingested microbial populations.
- Develop new methods for detecting and measuring cell-mediated immunity; identify microbial antigens and regulatory events critical for the development and maintenance of cell-mediated immunity.
- Utilize genomic information to reveal new approaches for disease control or biotherapeutic production and identify novel nutrient and immune interactions.
- Define gene expression patterns and regulatory phenomena that affect the level of host resistance at mucosal surfaces.

In addition, the workshop participants selected the following research objectives for their potential to substantially impact ARS national research programs in animal health, animal production, aquaculture, food safety, and human nutrition.

- Novel approaches for disease diagnostics; Biomarkers of immunointervention success will enhance our capacity to screen for the most efficacious method to elicit a protective immune response.
- Improved methods to limit immune-associated disease and persistence of pathogens thereby increasing production and decrease spread of disease, respectively.
- Improved methods to limit factors (e.g., environmental, husbandry, nutritional) that negatively impact neonatal immune development.
- Definition of pathways for interventions, for development of both traditional and therapeutic vaccines, and for preparation of novel mucosally targeted biotherapeutics
- Increased understanding of how innate immunity impacts vaccine responses; improved knowledge base for adjuvant and immune modulator design/selection for vaccines and biotherapeutics.
- Improved vaccine efficacy; verification of efficacy of mucosal delivery vectors and adjuvants; targeting the neonate and maternal immunity.
- Broad-based vaccine delivery systems applicable to both production animals and wildlife that account for the practical realities of immunization in the field.
- Provide identification of diets that enhance immune development and reduce inflammation.
- Better understanding of the interaction between dietary choices and environment on immune function and optimal health.
- The emergence of genetic profiles will include dietary recommendations for human life style and animal management to optimize health.
- By leveraging knowledge in databases from human disease research, we will build a comparative immunology database that can be a guide to antigen selection for use in vaccines.

Welcome Letter

United States Department of Agriculture
Agricultural Research Service
National Program Staff

December 1, 2003

Dear Workshop Attendee:

On behalf of the National Program Staff, welcome to the "2003 ARS Immunology Research Workshop." We are delighted that you could join us for this exiting event. The scientists participating in the workshop include Immunologists working in very different fields and we hope the diversity of disease models, animal species, and approaches to solving problems discussed over the next three days will be beneficial to your research. We also hope you will have many opportunities to establish strategic collaborations over the next three days that will build on our understanding of Immunology and its many applications to animal and human health.

We have four goals for the workshop:

1. To exchange new information and ideas in immunology to maximize the impact of our research programs and solve problems of high National priority.
2. To enhance interactions and form strategic collaborations between scientists engaged in immunology research.
3. To provide a forum for stakeholders, customers, and partners to give input and direction on current and future ARS immunology research programs.
4. To initiate the preparation of action plans for consideration at future ARS National Program workshops.

The workshop has been structured to facilitate interactions and the exchange of new ideas between scientists conducting research in Federal laboratories, academia, and the private sector. Working group sessions will be held on the last day to assess future research direction and prepare research plans. We are very fortunate to have some of the most prominent experts in immunology working in animal and human health participate in this workshop. We have tried to format this workshop to promote constructive exchange of the most recent data and new ideas.

Once again, we are delighted that you could join us for this exciting event and we thank you for your participation in this workshop.

Sincerely,

Cyril Gerard Gay, D.V.M., Ph.D
National Program Leader, Animal Health and Safety

Animal Production, Product Value, and Safety
5601 Sunnyside Avenue • Beltsville, MD 20705-5138

2003 ARS Immunology Research Workshop

Agenda

December 1-4, 2003
Bethesda, Maryland

December 1, 2003
Kick Off

18:00 – Welcome Address, Cyril Gerard Gay, National Program Leader, Animal Health and Safety, ARS, Beltsville, MD
Goals, partnerships, and opportunities

18:30 - Keynote Presentation, Jay Berzofsky, NCI/NIH/HHS, Bethesda, MD
Vaccine strategies to maximize CTL avidity, memory, and efficacy

19:30 - Reception

December 2, 2003
Plenary Sessions

Innate Immunity

Moderator: James A. Roth, Director, Center for Food Security and Public Health, College of Veterinary Medicine, Iowa State University, Ames, IA

08:00 - Matthew Fenton, University of Maryland School of Medicine, Baltimore, MD

Role of Toll-like Receptors in the Host Response Against Mycobacterial Infection

08:30 - Susan D. Eicher, ARS, Livestock Behavior Research Unit, West Lafayette, IN
Toll-like Receptor and Acute Phase Cytokine Expression in Neonatal Dairy Calves

09:00 - Rami Dalloul, ARS, Animal Parasite Diseases Laboratory, Beltsville, MD
Oligodeoxynucleotides (ODN)-induced activation of macrophage-mediated innate immunity against intracellular pathogens, Eimeria and Salmonella, and the development of novel immunomodulatory strategies using embryo injection of CpG-ODNs in poultry.

09:30 - Elida M. Bautista, ARS, Foot and Mouth Disease Research, Orient Point, NY
Analysis of swine skin-derived dendritic cells in the induction of innate immune responses to Foot-and-mouth disease virus (FMDV)

10:00 - Interactive Poster Session (38 posters)

- Innate Immunity
- Immune Regulation
- Immunogenetics
- Immunity and the pathogenesis of diseases

Immune Regulation

Moderator: William Golde, Immunologist, Plum Island Animal Research Center, ARS, Orient Point, NY

11:00 - Willi Born, National Jewish Medical and Research Center, Denver, CO
Regulatory role of gamma/delta T cells in allergic airway hypereactivity

11:30 - David Woodland, Trudeau Institute, Saranac Lake, NY
Regulation of Memory T cell Responses in Viral Infections of the Respiratory Tract

12:00 - Lunch and Keynote Presentation: Arthur Kreig, Coley Pharmaceuticals, Wellesley, MA
Enhancing vaccines with adjuvants that activate dendritic cells and B cells in vivo

13:30 - Wendy Brown, Washington State University, Pullman, WA
Regulation of the CD4+ T lymphocyte response by Anaplasma marginale

14:00 - Wenbin Tuo, ARS, Animal Parasite Diseases Laboratory, Beltsville, MD
Bovine T cell response to antigens of Neospora caninum

14:30 - Marc Estes, University of Texas, Galveston, TX
Progress towards developing effective subunit vaccine responses by CD8+ memory and effector T cells in a bovine model of tuberculosis

15:00 – Jesse P. Goff, ARS, Periparturient Diseases of Cattle Research Unit, Ames, IA
Effects of the Mammary Gland on the Composition and Function of Peripheral Blood Mononuclear Leukocyte Populations in Periparturient Dairy Cows

15:30 - Break

Immunogenetics

Moderator: Peter L. Nara, Director of Research and Development, Biological Mimetics, Inc., Frederick, MD

16:00 - Annie DeGroot, Epivax, Inc, Providence, RI
Accelerating vaccine design: new in silico epitope mapping methods

16:30 - Henry Hunt, ARS, Avian Diseases and Oncology Laboratory, East Lansing, MI
Marek's disease and the MHC: How viruses subvert the Immune System for their advantage

17:00 - Lynn M. Herrmann, ARS, Animal Disease Research Unit, Pullman, WA
Expression of specific MHC Class II DRB1 alleles associates with sheep persistently infected with ovine progressive pneumonia virus (OPPV)

17:30 - John Butler, University of Iowa, IA
From Basic Porcine Immunology to Practical Application

December 3, 2003

Plenary Sessions

Immunity and Nutrition

Moderator: Ildy Katona, Department of Pediatrics, Uniformed Services University of the Health Sciences in Bethesda, MD

07:30 - Joe Urban, ARS, Nutrient Requirements and Functions Laboratory, Beltsville, MD
The effect of human-derived probiotic bacteria on the immune and intestinal function of pigs

08:00 - Kirk Klasing, University of California, Davis, CA
The care and feeding of an immune system: How much is needed and what are the priorities?

08:30 - Simin Meydani, ARS, Nutritional Immunology Laboratory, Boston, MA
Aging, immune response, and infectious disease: molecular mechanisms and reversal by nutrient intervention

09:00 - Brian Nonnecke, Periparturient Diseases of Cattle Research Unit, Ames, IA
Nutritional Plane Affects Antigen-Induced Proliferation of Lymphocyte Subsets in Milk Replacer-Fed Calves Vaccinated with M. bovis Bacillus Calmette-Guerin (BCG)

09:30 - Harry Dawson, Nutrient Requirements and Functions Laboratory, Beltsville, MD
Real-Time PCR Arrays Can Delineate Immunological and Nutrition-Related Gene Expression in Swine

10:00 - Interactive Poster Session (32 posters)

- Immunity and nutrition
- Immunity and disease resistance
- Immunointervention strategies

Immunity and Disease Resistance

Moderator: Muquarrab Qureshi, National Program Leader, Animal Genomics, CSREES, USDA, Washington D.C.

11:00 – Michael Murtaugh, University of Minnesota,

Mechanisms of Innate and Adaptive Immunity in Swine

11:30 - Lou Gasbarre, ARS, Bovine Functional Genomics, Beltsville, MD
Genetic and Immunologic basis for resistance to GI nematode infections

12:00 - Lunch and Keynote Presentation: Alan Sher, NIAID/NIH/HHS, Bethesda, MD
The p47 GTPases: a family of IFN induced proteins that regulate host resistance to intracellular pathogens

13:30 - Pamela Ferro, ARS, Food and Feed Safety Research, College Station, TX
Heterophils Isolated From Chickens Resistant to Extraintestinal Salmonella enteritidis Infection Express Higher Levels of Pro-inflammatory Cytokine mRNA Following Infection Than Heterophils From Susceptible Chickens

14:00 - Hyun Lillehoj, ARS, Animal Parasite Diseases Laboratory, Beltsville, MD
High-throughput molecular approaches to identify coccidiosis disease resistance genes and protective immunological mechanisms in avian coccidiosis

Immunointervention

Moderator: Ronald Schultz, Professor and Chair, Department of Pathobiological Sciences, University of Wisconsin-Madison, WI

14:30 – Cynthia Baldwin, University of Massachussets,
Protective Killed *Leptospira* Vaccine Induces Potent Type 1 (Th1) Immunity Comprising Responses by CD4 and WC1+ γδ T Lymphocytes

15:00 – Evelyn Dean-Nystrom, ARS, Food Safety and Enteric Diseases Research Unit, Ames, IA
Development of an Oral Vaccine for Escherichia coli O157:H7

15:30 - Break

16:00 - Wongi Min, ARS, Animal Parasite Diseases Laboratory, Beltsville, MD
Adjuvant Effect of IL-1β, IL-2, IL-8, IL-15, IFN-α, IFN-γ, TGF-β4 and lymphotactin on DNA vaccination against Eimeria acervulina

16:30 - Haiqi He, ARS, Food and Feed Safety Research, College Station, TX
Stimulation of chicken leukocytes and reduction of Salmonella organ invasion in neonatal chicken by immunostimulatory CpG-oligodeoxynucleotide

17:00 – M. Suresh, Assistant Professor of Immunology, University of Wisconsin, Madison, WI
Regulation of Memory CD8 T Cell Generation by Cytokines

December 4, 2003

Research Priorities Working Groups. *The workshop participants will be divided into teams and asked to identify research priorities, strategic collaborations, and innovative research plans that will substantially increase our knowledge of immunology and deliver solutions to disease problems of high national priority in animal and human health. The recommendations of the participants will form the basis for developing ARS National Program action plans. Focus will be given to the following research areas:*

- Immunity and disease resistance
- Immunointervention strategies
- Immunity and the pathogenesis of diseases
- Nutrition and immune function interactions

08:30 **Working Group Instructions**
Robert Heckert, National Program Leader, Animal Health, ARS, Beltsville, MD
Lewis Smith, National Program Leader, Aquaculture & Animal Well-Being, ARS, Beltsville, MD

09:00 **Working Group Sessions**

- **Immunity and Disease Resistance**
  Working Group Leaders:
  - Lanie Bilodeau, Immunologists, Catfish Genetics Research Unit, ARS, Stoneville, MS
  - Lou Gasbarre, Research Leader, Bovine Functional Genomics Research Unit, Animal and Natural Resources Institute, ARS, Beltsville, MD
  - Michael H. Kogut, Immunologist, Southern Plains Agricultural Research Center, ARS, College Station, TX
  - Joan Lunney, Immunologist, Animal Parasite Diseases Laboratory, Animal and Natural Resources Institute, ARS, Beltsville, MD

Immunointervention Strategies

Working Group Leaders:

- Marcus Kehrli, Research Leader, Virus and Prion Diseases Research Laboratory, National Animal Disease Center, ARS, Ames, IA
- Hyun Lillehoy, Immunologist, Animal Parasite Diseases Laboratory, Animal and Natural Resources Institute, ARS, Beltsville, MD
- David White, Veterinary Medical Officer, Arthropod-borne Animal Diseases Research Laboratory, ARS, Laramie, WY

- **Immunity and the Pathogenesis of Diseases**

  Working Group Leaders:
  - Don Knowles, Research Leader, Animal Disease Research Unit, ARS,
  - Pullman, WA
  - David Swayne, Research Leader, Southeast Poultry Research Laboratory, ARS, Athens, GA
  - Ray Waters, Veterinary Medical Officer, Bacterial Diseases of Livestock Research Unit, National Animal Disease Center, ARS, Ames, IA

- **Nutrition and Immune Function Interactions**

  Working Group Leaders:
  - Theodore Elsasser, Research Animal Scientist, Growth Biology Laboratory, Animal and Natural Resources Institute, ARS, Beltsville, MD
  - Simin Meydani, Chief, Nutritional Immunology Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, ARS, Tufts University, Boston, MA
  - Joe Urban, Research Leader, Nutrient Requirements and Functions Laboratory, Beltsville Human Nutrition Research Center, ARS, Beltsville, MD

12:00 **Lunch**

Working Group Reports

13:00 - Immunity and Disease Resistance
13:30 - Immunointervention Strategies
14:00 - Immunity and the Pathogenesis of Diseases
14:30 - Nutrition and Immune Function Interaction

15:00 – Cyril Gerard Gay, National Program Leader, Animal Health and Safety, ARS, Beltsville, MD

Conclusion and post-meeting instructions

Keynote Addresses

December 1, 2003

Jay A. Berzofsky

Molecular Immunogenetics & Vaccine Research Section, Metabolism Branch, National Cancer Institute, NIH, Bethesda, MD

Vaccine strategies to improve CTL avidity, memory, and efficacy

Cytokines are potentially useful not only as vaccine components to increase the magnitude of the immune response, but also to steer it in desired directions. We found that certain combinations such as GM-CSF and IL-12 synergized to increase cytotoxic T lymphocyte (CTL) activity. We showed that GM-CSF worked to increase antigen presenting cell numbers and activity in the draining lymph nodes. We reasoned that CD40L might synergize with GM-CSF by maturing those presenting cells. Indeed, GM-CSF and CD40L were a potent combination to increase CTL responses. Also, we had seen that NKT cells making IL-13 dampened the CTL response to tumors, so we asked if blockade of IL-13 or elimination of NKT cells would also increase the CTL response to a peptide vaccine. We found that either of these treatments further enhanced the CTL response and the ability to protect against viral challenge. Thus, a push-pull approach in which a cytokine and a costimulatory molecule are combined to push the response and disruption of an inhibitory pathway is used to pull the response can maximize CTL induction.

In addition to increasing the quantity of the CTL, we sought to also improve the quality of the CTL induced by a vaccine. We previously found that avidity of CTL is critical for effective viral clearance, but selective induction of high avidity CTL has been difficult to achieve with vaccines. Likewise, persistent CTL memory is essential for long-lasting CTL-mediated vaccine efficacy. Thus, we have sought strategies to selectively induce longer-lived high avidity CTL with vaccines targeting HIV protein antigens. First, increasing costimulation (signal 2) allowed us to immunize with lower doses of antigen (signal 1) to selectively induce high avidity CTL in vivo. This was achieved using a recombinant poxvirus vector expressing a triad of costimulatory molecules (B7-1, ICAM-1, and LFA-3) (TRICOM) to increase expression of these molecules on splenocytes pulsed with an HIV-1 CTL epitope peptide. Second, since IL-15 was known to contribute to maintenance of CTL memory, we asked whether IL-15 at the time of immunization would alter the CTL response. Expression of IL-15 by a recombinant vaccinia vector along with HIV-1 gp160 induced long-lived memory CTL that persisted at least 14 months after a single boost. The memory cells expressed higher levels of IL-

15Rα and showed greater proliferation to IL-15 in vitro and homeostatic proliferation in vivo, as well as higher avidity for antigen. Thus, IL-15 at the time of priming selects or induces a different phenotype CTL with greater avidity and longevity. These vaccine strategies can provide more effective CTL immunity by enhancing the numbers, avidity, and memory of the CTL induced, allowing for greater and longer lasting protection.

December 2, 2003

Arthur M. Krieg

Coley Pharmaceutical Group, Wellesley, MA, USA.

Enhancing vaccines with adjuvants that activate dendritic cells and B cells in vivo

The innate immune system has evolved “pattern recognition receptors” that detect molecules present in various classes of pathogens, but not in our own cells. The best known of these pattern recognition receptors belong to the family of Toll-like receptors (TLRs), which appear to have evolved to activate appropriate protective immune responses when a pathogen is detected. One such pathogen-associated pattern is unmethylated CpG dinucleotides in bacterial or viral DNA, which are detected by TLR9, thereby stimulating innate and adaptive immunity. These immune effects can be mimicked by synthetic oligodeoxynucleotides containing CpG motifs (CpG ODN). In humans and most other species, at least two types of immune cells express TLR9 and are activated directly by CpG ODN; B cells, and plasmacytoid dendritic cells (pDC). CpG ODN activate B cells to proliferate and secrete immunoglobulin; and pDC to secrete a variety of Th1-like cytokines, chemokines, and type I interferons, and to express increased costimulatory molecules. When activated by CpG, pDC gain the ability to stimulate Th1-like T cell responses. CpG ODN induce immune defense mechanisms that protect against challenge with a wide range of infectious pathogens, and have shown therapeutic activity in animal models of allergic disease and cancer. CpG ODN are also extremely effective vaccine adjuvants, inducing Th1 responses in mice, primates, and other species with both specific antibody and CTL. Phase I human clinical trial results indicate that a CpG ODN, 7909, is relatively well tolerated. As an adjuvant for a hepatitis B vaccine, CpG 7909 appears to induce earlier seroconversion with the production of increased levels of specific antibody and cellular responses. A phase II human clinical trial of CpG 7909 in HIV-infected subjects, including prior hepatitis B vaccine nonresponders, showed a striking increase in the magnitude of antibody responses in the subjects receiving CpG as a vaccine adjuvant. CpG ODN are produced by cGMP chemical synthesis, have excellent stability and solubility, and show an excellent safety profile, suggesting wide utility as vaccine adjuvants for veterinary applications.

December 3, 2003

Alan Sher

[1]Laboratory of Parasitic Diseases, NIAID, NIH, Bethesda, MD
[2]Center for Biologics Evaluation and Research, FDA, Bethesda, MD
[3]Dept. of Medicine and Immunology, Duke University Medical Center, Durham, NC

The p47 GTPases: a family of IFN induced proteins that regulate host resistance to intracellular pathogens

Alan Sher[1], C. Feng[2], C. Collazo[1], and G.A. Taylor[3]

Activation of the immune system by interferon-γ is critical for host resistance to many infectious agents. This lymphokine induces the expression of a wide range of effectors that undermine the ability of pathogens to survive in host cells. Among these is a newly discovered family of 47 kDa GTPases that provide resistance to intracellular protozoa, bacteria, and viruses. Elimination of different p47 GTPases in mice through gene targeting severely cripples IFN-γ-regulated defense against *Toxoplasma gondii*, *Listeria monocytogenes*, *Mycobacterium sp*., and other pathogens. Interestingly, different members of this gene family appear to effect resistance to different groups of pathogens. Current evidence suggests that p47 GTPases function against pathogens at two different levels: by facilitating intracellular killing of pathogens and by promoting survival of effector T lymphocytes.

Plenary Sessions

December 2, 2003

Innate Immunity

Role of toll-like receptors in the host response against mycobacterial infection

Matthew J. Fenton
Director of Research, Division of Pulmonary and Critical Care Medicine; Professor of Medicine, Microbiology and Immunology, University of Maryland School of Medicine, Baltimore, MD

Toll-like receptor (TLR) proteins mediate cellular activation by microbes and microbial products. To delineate the role of TLR proteins in the development of host immune responses against mycobacteria, wild-type and TLR-deficient mice were infected with non-pathogenic Mycobacterium bovis BCG (BCG). Two weeks after intraperitoneal challenge with BCG, few bacilli were present in the lungs of wild-type and TLR4-/- mice, whereas bacterial loads were 10-fold higher in the lungs of infected TLR2-/- mice. BCG challenge in vitro strongly induced pro-inflammatory cytokine secretion by macrophages from wild-type and TLR4-/- mice, but not by TLR2-/- macrophages. In contrast, intracellular uptake, intracellular bacterial growth, and suppression of intracellular bacterial growth in vitro by IFN-g were similar in macrophages from all three mouse strains, suggesting that BCG growth in the lungs of TLR2-/- mice was a consequence of defective adaptive immunity. Antigenic stimulation of splenocytes from infected wild-type and TLR4-/- mice induced T cell proliferation in vitro, whereas T cells from TLR2-/- mice failed to proliferate. This lack of T cell proliferation in TLR2-/- mice correlated with an inability of CD11c+ dendritic cells to be activated in vivo following BCG challenge. Unexpectedly, activated CD4+ T cells from both TLR-deficient mouse strains secreted little IFN-g in vitro, compared with control T cells. A role for TLR4 in the control of bacterial growth and IFN-g production in vivo was observed only when mice were infected with higher numbers of BCG. Thus, TLR2 and TLR4 appear to regulate distinct aspects of the host immune response against BCG.

Toll-like receptor and acute phase cytokine expression in neonatal dairy calves

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The well-being of farm animals is dependent on many factors, so that a multi-disciplinary approach is essential. The Livestock Behavior Research Unit uses behavior, physiology, and immunology measures to answer well-being questions for poultry, swine, and dairy

cattle. The innate immune system is frequently the first immune responder during many stressors and acute phase cytokines affect behavior and learning. Toll-like receptors are the pathogen recognition molecules that initiate the cascade that increases the acute phase cytokines. The effect of stressors on the toll-like receptors of farm animals is not known. Studies have been completed that examine the effect of stimulants on RNA expression of toll-like receptors in young dairy calves. The objective of study one was to assess the optimum concentration and times of incubation for expression of TLR2 and TLR4 after in-vitro stimulation of bovine monocyte derived macrophages with Saccharomyces cerevisiae (yeast cell-wall) beta-glucan (BG), Escherichia coli lipopolysaccharide (LPS), and Staphylococcus aureus peptidoglycan (PGN). Monocyte derived macrophages from 10 donor calves (5 to 6 wk-of-age) were first stimulated with LPS or PGN at 1, 5, or 25μg/ml or BG at 20, 40, or 80μg/ml for one hour at 37°C. Then the optimum concentrations were used to incubate cells at 30, 60, or 90 min. Real-time RT-PCR was used to quantify RNA expression of TLR2 and TLR4. RNA from monocyte derived macrophage expressed more bovine TLR4 than TLR2. Sixty minutes appears to be an adequate time of stimulation to change TLR4 expression, but at least 90 minutes are needed to attain maximum changes in TLR2 expression. The objective of study two was to determine if in vitro stimulation of whole blood leukocytes with beta-glucan plus ascorbic acid (a potential immunomodulator) was dependent on the age of the calf. Blood samples were taken from 12 non-transported Holstein calves at 1, 3, 7, 10, 14, 18, 21, 24, and 28 d-of-age. Leukocytes were stimulated with ascorbic acid (0.3 ug/ml) plus beta-glucan (0.4 ug/ml) or media only for 1 h and then RNA was extracted. The RNA was subjected to real-time RT-PCR for quantification of the expression of interleukin-1 (IL-1) and its receptor antagonist (IL-1Ra), and toll-like receptors 2 and 4 (TLR2 and TLR4). TLR2 and TLR4 had treatment effects ($P<.05$), but not day or treatment by day interactions. TLR2 was greater ($P<.05$) for treated cells on day 7, 14, and 24 and tended ($P<.10$) to be greater on day 10. In contrast, TLR4 was only greater for treated cells on day 7 ($P<.05$) and tended to be ($P<.10$) on day 24. IL-1 had a treatment main effect and a treatment by day interaction ($P<.05$), but IL-1Ra had main effects for treatment and day ($P<.05$), but only a trend ($P<.10$) for a treatment by day interaction. IL-1 was greater for treated cells ($P<.05$) on all but day 4. IL-1Ra was greater ($P<.05$) for treated cells only on days 1, 7, 10, and 24. Only IL-1 and its receptor antagonist expression were stimulated on day 1. On days 7 and 24 all tested receptors and cytokines had increased RNA expression. So, it appears that there are periods during which the blood leukocytes may be refractory for increased RNA expression of cytokines and toll-like receptors in response to beta-glucan and ascorbic acid stimulus. These data enhance our understanding of the biological kinetics of the developing neonatal calf immune system, so that management procedures can occur at the best possible times.

Oligodeoxynucleotides (ODN)-induced activation of macrophage-mediated innate immunity against intracellular pathogens, Eimeria and Salmonella, and the development of novel immunomodulatory strategies using embryo injection of CpG-ODNs in poultry. Dalloul[1,2]Rami, Lillehoj[1] Hyun S., Xie[2] Hang, Heckert[2] Robert A., Babu[3] Uma, Raybourne[3] Richard, and Klinman[4] Dennis M.
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The immunostimulatory properties of synthetic CpG oligodeoxynucleotides (ODNs) have been well studied in various mammalian models including humans and mice. However, little was known about effects of CpG-ODNs on immune responses of chickens, a common avian species with important economical value in the poultry industry. ODN 2006 which has been reported to be an optimal stimulatory sequence for humans, showed strong immunomodulatory effects on HD11 cells. Whereas ODN 1826, a murine optimal CpG-ODN had weak influences on HD11 cells. We also observed that 2006 induced strong IL-6 and nitric oxide secretion by HD11 cells in both dose- and time-dependent manners. 2006 induced activation also resulted in increased intracellular killing of *S. enteritidis* (SE) by HD11 cells. Furthermore, 2006 activated HD11 cells had reduced proliferation and underwent apoptosis after CpG stimulation. Further studies were carried out to test several short synthetic CpG ODNs for their immunomodulatory effects on disease susceptibility in *Eimeria acervulina*. On day 18 of incubation, specific pathogen-free embryos were injected (air cell) with either 25 μg or 50 μg of CpG ODN (CpG-1, CpG-2, CpG-3 and CpG-4), a non CpG-containing control (CpG-0), or a negative control (PBS, phosphate buffered saline). At one week of age, birds were orally inoculated with 10^4 *E. acervulina* oocysts. Body weights and body weight gains were not affected by any of the treatments. However, among CpG ODN treatments, a differential antibody response was observed with the lowest response in CpG-2 birds and highest in CpG-4 group. This study demonstrates that CpG ODN were effective immunoprotective agents in chickens, and the potentials of CpG-ODNs as immunomodulators in poultry need to be further explored.

Analysis of swine skin-derived dendritic cells in the induction of innate immune responses to Foot-and-mouth disease virus (FMDV) Elida M. Bautista, Geoffrey S. Ferman, Douglas Gregg, Mario C. Brum, Marvin Grubman and William T. Golde.
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To understand the role of dendritic cells (DC) in the initiation of immune responses against FMDV and to determine whether FMDV infection may alter this function, we analyzed the interaction of FMDV with skin-derived DC of swine. Innate responses of DC to in vitro FMDV exposure with infectious or attenuated leaderless (LL) viruses was determined by measuring cytokine mRNA and protein expression using Real-time PCR analysis and ELISA, respectively. Activation state of these DC was determined by

measuring surface expression of SLAII (MHC Class II) and CD80/86. SLAII was minimally affected and CD80/CD86 slightly reduced in DC exposed to either virus. DC consistently responded to both viruses with a rapid increase in IFN-beta and TNF-alpha mRNA expression that peaked at 4-8 h post-exposure. IFN mRNA was only moderately increased over the constitutive levels. Analysis of supernatants (SN) of virus exposed DC show secretion of IFN and IFN by protein assay (ELISA), but neither protein was detected in the control culture SN with no virus. Biological function of IFN was confirmed only in the virus-exposed cell culture SN by antiviral assay. Consistent with the antiviral effect of IFNs, no productive infection by FMDV was detected in DC. Immunocytochemistry and confocal microscopy of skin sections and freshly isolated DC demonstrated these cells constitutively express IFN These results show that DC can mount an innate type I IFN response to FMDV, which renders them resistant to productive viral replication. This study also revealed an important property of porcine skin DC in that these cells constitutively express and accumulate IFN protein in the cytoplasm, and respond to virus exposure by secreting IFN and by activating the IFN gene and secreting this cytokine as well. Together, our data show that skin DC have an important role in the innate immune response of swine to FMDV.

Immune Regulation

Regulatory role of gamma/delta T cells in allergic airway hyperreactivity

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Airway hyperresponsiveness to cholinergic agonists (AHR) is a life-threatening condition associated with many diseases of the vertebrate lung. Gamma/delta T cells exert a strong regulatory effect on AHR. We have used a mouse model of allergic airway disease to investigate the underlying mechanisms. Features include regulation during antigen priming and challenge, systemically and within the lung, and small populations of gamma/delta T cells with opposed regulatory influences on AHR. As regulatory functions co-segregate with T cell receptor Vgamma expression, specific ligand recognition may play a role, and ligands may be expressed on dendritic cells (DC). Gamma/delta T cells appear to monitor DC in the lung, and early signals from DC might induce their regulatory effect on the developing antigen-specific immune response and airway smooth muscle contraction.

The contribution of memory T cells subsets to antiviral immunity in the lung

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Respiratory virus infections elicit memory $CD4^+$ and $CD8^+$ T cell populations that persist for the life of the individual and are able to mediate accelerated clearance of secondary virus infections. Given the protective capacity of these cells, there has been substantial interest in developing vaccines that promote cellular immunity in the lung. However, we have little understanding of how T cell memory is established, maintained, and recalled in peripheral organs. To begin to address these issues, we have been analyzing memory T cell populations elicited by influenza and parainfluenza virus infections in a mouse model. We show that memory T cells are extremely heterogeneous in terms of their anatomical distribution, phenotype, function, and longevity. Moreover, distinct subpopulations vary greatly in their capacity to respond to infection, depending on their initial phenotype and anatomical location. These observations have significant implications for the development of vaccines designed to promote cellular immunity in the lung.

Regulation of the CD4$^+$ T lymphocyte response by *Anaplasma marginale.*

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MSP2 is serologically immunodominant for individuals infected with *Anaplasma.* In cattle protected by immunization with *A. marginale* outer membranes, CD4$^+$ T cell and IgG responses are also predominantly directed against MSP2 and MSP3, which share the conserved carboxy region. In fact, MSP2-specific T cells also recognize MSP3. Antigenic variation in MSP2 occurs throughout the lifespan of persistently infected but clinically healthy cattle, and sequentially emerging variants are controlled by the immune response. Both variant-specific CD4$^+$ T cells and antibody are believed to be important for this control. We hypothesized that immunization with multiple MSP2 variants should provide protection against challenge with organisms expressing the same MSP2 variants. To test this, eight calves were immunized with native MSP2 using either IL-12 or CpG DNA adjuvants that stimulated IgG and type 1 T cell responses, and together with four control animals, were challenged five months later with homologous organisms that expressed the same major MSP2 variants. In spite of developing significant and strong MSP2-specific CD4$^+$ T cell proliferative, IFN-γ, and IgG responses, vaccinates were not protected from challenge. Importantly, acute infection was not due to the emergence of novel MSP2 variants. To elucidate the reasons for the lack of protection in the vaccinates, we compared antigen-specific responses of CD4$^+$ T-lymphocytes from MSP2 vaccinates and control cattle cryopreserved before and after *A. marginale* challenge using IFN-γ ELISPOT and proliferation assays. Reproducibly strong MSP2-specific PBMC responses were detected from immunized animals prior to challenge and for two weeks after challenge, which was prior to peak rickettsemia. Surprisingly, MSP2-specific responses of PBMC collected during the peak of rickettsemia were undetectable in all animals. This severely depressed MSP2-specific T cell response was still observed two-four months later, and was also apparent when using *A. marginale* homogenate. In contrast, the response to unrelated *Clostridium* vaccine antigens was not ablated during acute infection. By four to seven months after peak rickettsemia, MSP2-specific T cell responses were detected in several vaccinates; however, these remained significantly depressed. Our data suggest that in addition to immune evasion via antigenic variation in surface proteins, *A. marginale* induced unresponsiveness may facilitate organism persistence. Potential mechanisms include induction of regulatory T cells, induction of T cell anergy, and exhaustion of MSP2-specific T cells. Supported by USDA NRI grants 99-35204-8368 and 02-35204-12352 and NIH NIAID awards K08-AI49276 and R01-AI44005.

Bovine T cell response to antigens of *Neospora caninum*.

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Neospora caninum is an apicomplexan parasite that infects a number of cell types, causing neosporosis in several animal species including cattle. In the past decade, neosporosis has been recognized as a primary cause of abortion in cattle worldwide. It was estimated that approximately 20% of all bovine abortions are attributed to neosporosis; *Neospora*-related abortion costs the cattle industry in excess of $35 million a year in the state of California alone. In infected cows, *N. caninum* elicits a detectable antibody (Ab) response as shown by extensive studies, whereas *N. caninum*-induced cell-mediated immunity (CMI) is poorly understood. Previous exposure to, or infection by, the parasite does not provide protection against abortion or vertical transmission, in spite of the presence of *Neospora*-specific Ab in maternal circulation. The objective of this study was to define *Neospora*-specific CMI in cows infected with *N. caninum* and to identify immunodominant T helper cell Ag that may be used as vaccine candidates. Total *Neospora* Ag was prepared by freezing and thawing or sonication of *N. caninum* tachyzoites grown in a monkey kidney or a bovine macrophage cell line. Peripheral blood lymphocytes (PBL) from *Neospora* infected cows were stimulated with total soluble *Neospora* Ag weekly in the presence of irradiated PBL as a source of Ag presenting cells. Flow cytometry analysis showed 90-98% of these *Neospora* Ag specific T cells (week 3-8) were $CD2^+CD3^+CD4^+$. A T cell proliferation assay was established and used to determine Ag specificity of Ag-specific T helper cells and antigenic activity of *Neospora* Ag. A bovine specific IFN-γ ELISA was used to determine IFN-γ content in supernatants of T cells stimulated with *Neospora* Ag. The total *Neospora* tachyzoite Ag was separated into 5 fractions by anion exchange using HPLC. Results indicate that high levels of IFN-γ were produced by both PBL and T cell lines specific to *Neospora* Ag. Using the T cell proliferation assay, we showed that proteins from HPLC Fractions 1 and 2 had low or undetectable T cell-stimulating activity, whereas proteins from Fractions 4-6 had higher stimulatory activity. However, Fraction 5 contained the highest antigenic activity in all T cell lines assayed. Western blot analysis showed that Fraction 5 contained 8-10 distinctive *Neospora* protein bands that were defined by a rabbit antiserum raised against to *Neospora* tachyzoites (NC-1 strain). These studies suggest that Ag-specific T helper cells ($CD4^+$ $CD3^+$) may be used to screen for immunodominant *Neospora* Ag. *Neospora* proteins that specifically stimulate T helper cell proliferation and cytokine production identified using our T cell proliferation and cytokine production assays may be used as vaccine candidates. This research will enhance our understanding of bovine CMI to *Neospora* infection and may facilitate the development of a vaccine against bovine neosporosis.

Progress towards developing effective subunit vaccine responses by CD8+ memory and effector T cells in a bovine model of tuberculosis.

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Cell-mediated immunity (CMI) is a key component of the protective immune response for many intracellular pathogens (viruses, bacteria and parasites). CD8+ cytotoxic T cells (hereafter referred to as CTL) are a primary effector cell type in the CMI response to intracellular pathogens via their ability to lyse infected target cells and produce key regulatory and effector cytokines. CD8+ T cells recognize relatively short peptides (8-11 amino acids in length) presented in the context of MHC class I molecules on the surface of an antigen presenting cell (APC). APC processing of polypeptides from both inside and outside of the cell is the first step in the formation of MHC class I-peptide complexes and the generation of T cell responses. Rational design of vaccines for intracellular pathogens requires knowledge of both this process and the means by which costimulatory signals are delivered to naïve T cells by APC. Costimulatory signals are required in addition to T cell receptor (TCR) engagement to drive the response. The requirements for accessory molecule costimulation (collectively, signal 2) in the activation of naïve CD8+ T cells, in addition to the primary signal (signal 1) generated via the T cell receptor-antigen-MHC complex, are not well understood, particularly in cattle. Knowledge of this important issue is essential to the development of viable vaccine strategies that involve elicitation of effective CD8+ T cell responses.

Effects of the mammary gland on the composition and function of peripheral blood mononuclear leukocyte populations in periparturient dairy cows.

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During the periparturient period, the dairy cow experiences a state of natural immunosuppression that is associated with heightened susceptibility to infectious disease. During this period, alterations in T cell percentages in the circulation parallel a reduction in functional capacities of peripheral blood mononuclear cell (PBMC) population. Hormonal and metabolic demands of pregnancy and lactation as well as the physiologic stress of calving likely contribute to periparturient immunosuppression. Objectives of this study were to evaluate the phenotype and functional capacities of PBMC populations in periparturient cows, and secondly, determine whether changes in composition and function could be, in part, attributable to the presence of a functional mammary gland. Ten mastectomized and eight intact multiparous Jersey cows (six for each for functional study) were used. Using monoclonal antibodies against T-cell subsets, the B-cell, and the monocyte, the composition of PBMC populations was characterized by flow cytometry. For the analyses, cells were obtained several times a week from –4 wk prepartum to 4 wk postpartum. Functionality of PBMC populations was assessed by assays measuring mitogen-induced lymphocyte proliferation, IgM secretion, and IFN-γ secretion. Cells used in these assays were collected twice weekly from –3 wk prepartum to 3 wk

postpartum. Percentages of CD3+, CD4+, CD8+, and γδ TCR+ cells in intact cows decreased progressively with the approach of parturition, while monocyte percentages increased. Synthesis of DNA and secretion of IFN-γ and IgM by mitogen-stimulated intact-cow PBMC were lowest around the time of calving. In contrast, compositional and functional changes in PBMC populations from mastectomized cows were minimal or absent at these times. Regression analysis revealed significant associations between composition and functional capacity of the PBMC population. These results indicate that the mammary gland and metabolic stresses associated with lactation contribute to the generalized immunosuppression affecting dairy cows during the periparturient period.

Immunogenetics

Accelerating vaccine design: new in silico epitope mapping methods

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T cell responses play an important role in immunity to parasites and other microbial agents of infectious diseases, therefore a number of T cell-directed vaccines are in development. Computer-driven algorithms that facilitate the discovery of T cell epitopes from protein and genome sequences are now being used to accelerate the development of human vaccines. Similar tools are now becoming available for for animal vaccines. My group recently developed new in silico methods for predicting epitopes for cattle and swine; the development process and validation studies will be described in this talk.

Epitope-mapping algorithms offer a significant advantage over other methods of epitope selection, such as the screening of synthetic overlapping peptides, because high throughput screening can be performed in silico, followed by ex vivo confirmatory studies. Using epitope-mapping algorithms, putative T cell epitopes can be derived directly from genomic sequences, allowing researchers to circumvent labor-intensive cloning steps in the genome-to-vaccine discovery pathway.

Marek's disease and the MHC: How viruses subvert the immune system for their advantage.

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Immune response genes of the chicken play a critical role in the resistance or susceptibility to Marek's disease (MD), a T-cell tumor induced by a herpesvirus named MD virus (MDV). The major histocompatibility complex (MHC) is one component of the immune response that has a major influence on the outcome of MD as well as the immune protection afforded by MDV vaccines. The USDA-ARS Avian Disease and Oncology Laboratory (ADOL) in East Lansing, MI is investigating the influence of the chicken MHC and other genetic systems involved in the immune response to MD. ADOL's approach is multidisciplinary incorporating traditional genetics, functional genomics/proteomic and immunologic analysis to dissect the host-pathogen interactions responsible for resistance or susceptibility to MDV.

The traditional genetics approach involves the generation of recombinant congenic chicken strains (RCS). ADOL White Leghorn lines 6 and 7 are resistant or susceptible to MDV, respectively, and differ in immune response characteristics and lymphoid organ size. The two lines were intermated and full-sib mated to generate 19 inbred sub-lines designated 6C.7A through X. Each 6C.7 sub–line consists of approximately 12% of the susceptible line 7 genome inserted into the resistant line 6 genomic background. The immune response, disease resistance and genetic phenotypes of these 6C.7 RCS are

currently under investigation at ADOL using gene mapping and immune assay approaches.

MDV, like other herpesviruses, has the ability to alter the expression of antigen presenting glycoproteins encoded by the MHC. MDV inhibits the cell surface expression of MHC class I glycoproteins but, unique to MDV, induces the expression of MHC class II glycoproteins. ADOL's multidisciplinary approach incorporating traditional immunologic assays coupled with genomics and proteomics is beginning to unravel the host pathogen interactions responsible for these observations.

Expression of specific MHC Class II DRB1 alleles associates with sheep persistently infected with ovine progressive pneumonia virus (OPPV).

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During OPPV infection in a flock, there is a clear dichotomy where a few sheep produce clinical signs and most become persistently infected without clinical signs. In long-term persistent infections, cell-adaptive immunity plays the significant role in controlling virus replication. In other small ruminant lentiviruses, CD4 positive and not CD8 positive T lymphocytes are required for adequate proliferation upon exposure to viral antigens (Perry et al., 1995). This along with two other studies indicating that the immunogenetics of the host dictate the course of infection and the antibody response to OPPV (de la Concha-Bermejillo et al., 1995; Cheevers at el., 1999), support the idea that MHC Class II immunogenetics play a significant role in directing disease outcome. Since ovine MHC Class II DRB1 encodes and expresses the antigen presentation domain on the antigen-presenting cell, we evaluated the allelic expression of DRB1 in peripheral blood mononuclear cells (PBMC) from 10 sheep persistently infected with OPPV. Five of these sheep have high OPPV loads, and five have low OPPV loads by real time PCR of integrated DNA in PBMC. The relationship between viral load and specific DRB1 allele expression will be discussed. In addition, the relationship of viral genetics in terms of the surface envelope glycoprotein (SU) and specific DRB1 allele expression will also be discussed.

From basic porcine immunology to practical application

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Characterizing the elements that comprises the immune system is the first step needed to provide the information and tools for ultimately determining the role of the immune system in health and disease. Described here is a 12-year journey of discovery in a farm animal with a pattern of passive immunity and a precosial nature that makes it an ideal model for providing insight into immunological development, receptor repertoires and the immunopathology of an important viral disease.

Basic investigations revealed the swine immune system is anything but a carbon copy of the human and mouse systems. For example, swine rely on only 10 combinatorial rearrangements, not 9,000, to develop their heavy chain antibody repertoire. Equally efficient is the development of the V-kappa repertoire that primarily uses one V kappa gene family and one J kappa gene segment. Also in contrast to mice and humans, early B cell development is adult-like, and surprisingly involves the thymus beginning at midgestation, where switch recombination is pronounced *in utero* in the absence of environmental antigen. Naïve B cells migrate to the ileal Peyers patches, each follicle containing the diversified descendents of a single B cell clone.

While B cell development occurs rapidly in late gestation, the ability of the newborn to mount an immune response requires exposure to colonizing bacteria or infective virus that produce the ligands for the Toll-like receptors (TLRs).

While the mechanism of antibody repertoire development in swine distinguish it from rodents and primates, T-cell development follows a conserved evolutionary pattern that parallels that in other mammals. The TCR beta repertoire strongly resembles that of humans and mice in both genome organization and the presence many homologous V-beta families. The V-epsilon repertoire is also conserved and an invariant V epsilon transcript occurs early in fetal life reminiscent of that in mice.

We were able to use the tools of discovery and knowledge we had gained to employ the isolator piglet model to show that PRRSV directly causes a B cell lymphoproliferative disorder characterized by immune dysfunction, autoimmunity, immune complex deposition and kidney and vascular damage. We hope as the journey continues, we shall soon show how PRRSV alters the T cells repertoire and how specific bacterial- and viral-derived TLR ligands allow the adaptive immune system to develop.

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Immunity and Nutrition

The effect of human-derived probiotic bacteria on the immune and intestinal function of pigs

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Probiotics are specific microorganisms that can establish and grow in a compartment of an exposed host and provide some positive health benefit; strains of *Lactobacilli*, *Bifidobacteria* and E*nterococcus* are commonly used probiotics. The benefits claimed vary from protection against pathogenic microorganisms and viruses, stimulation of the intestinal immune function and enhanced disease resistance. However, the basis of these claims is often confounded by a lack of demonstrable growth and function of the probiotic strain in the gut. Our objective was to test if dietary probiotics can establish in the pig and affect immunity to an infectious agent.

Experiment 1:
A pilot study using eight 12-week-old pigs was performed to determine if animals fed with a daily dose of 10 billion colony forming units (cfu) of freeze-dried *Lactobacillus rhamnosus GG* (LGG; Culturelle, Conagra, NE) would show some change in their immune response. Whole blood for isolation of peripheral blood mononuclear cells (PBMC) and fecal samples for DNA extraction were collected throughout the experiment at days 4, 7, 12, 18 and 25 after initiation of dietary treatment. At the end of the experiment (day 26) pigs were euthanized and tissues from different mucosal sites were collected for: 1) cell immune phenotype analysis by flow cytometry; 2) DNA isolation and identification of LGG strain in intestinal mucosa and fecal samples, 3) measurement of IFN-γ production *in vitro* after mitogen stimulation, and 4) mRNA expression of a panel of immune markers by real-time PCR. PBMC isolated from LGG-exposed pigs produced IFN-γ in response to Con A stimulation, while IFN-γ was barely detectable (assay range in ng /ml) in culture supernatant of PBMC isolated from unexposed pigs. LGG-specific fluorogenic probes were able to detect LGG DNA in fecal samples of treated animals as early as 4 days post-treatment. Mucosal tissue samples and fecal contents taken from intestinal sites of LGG treated animals indicated that LGG DNA was detected at 4-fold higher levels in the proximal colon compared to distal colon and cecum. No signal was detected in jejunum or ileum of any animals or in samples from non-treated animals. Real time PCR analysis indicated a selective low level increase in gene expression for Th1-derived type 1 immune cytokines in localized mucosal sites after probiotic delivery.

Experiment 2:
To test the effect of early colonization of probiotic bacteria on the immune response to a nematode parasite infection, *Bifidobacterium lactis (Bb12)*(Mak Wood Inc, WI) (10 x 10^{10} cfu) was administered to 2 sows starting at the last third of pregnancy through weaning of their piglets at day 28; two other sows and their litters were left as untreated controls. After birth, Bb12 capsules were also administered to pigs born to treated sows. Pigs born from untreated sows were maintained as untreated controls. All piglets were inoculated with *Ascaris suum* eggs at 6 weeks of age and tissue samples were collected for functional gut in Ussing chambers 3 weeks later. Probiotic treatment did not alter normal absorption of glucose in the small intestine, but did attenuate *A. suum*-induced inhibition of glucose absorption that correlates with expulsion of the worm from the pig intestine.

Conclusions:
Human derived probiotics can modulate immune function and selectively affect local responses to parasitic infection while promoting swine health. This model can be extended to assess the activity of selected probiotics on pig responses to other infectious agents and allergens that negatively affect pig production.

The care and feeding of an immune system: How much is needed and what are the priorities?

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How big is the immune system and how good is it at competing for scarce nutrients? Immunologists have neglected to measure the size of the immune system. Nutritionists have neglected to determine the nutritional requirements of the processes that we call ‘immunity’. Currently, these first principles of nutrition and immunity can only be estimated from a synthesis of experiments that were designed for other reasons. We need to know: the costs of developing an immune system that is sufficiently robust to be dependably protective; the costs of maintaining this system of leukocytes in large enough copy number to be effective; and the cost of using this system when challenged the host is challenged by a proficient pathogen. A preliminary analysis of these costs suggests that development of innate immunity is cheap but development of adaptive systems (lymphocytes) is relatively expensive. The reverse is true for maintenance. Following a challenge, the production of immunoglobulin and the clonal expansion needed for protective T-cell responses are cheap to generate but can cause immunopathology in defending against some pathogens. The systemic sequelae of an acute phase response are especially expensive and markedly impact the nutritional state and productivity of an animal. The types of nutrient transporters utilized by leukocytes determine their priorities for nutrients. Macrophages have a high priority, B-lymphocytes are intermediate, and T-lymphocytes are inept.

Aging, immune response, and infectious disease: molecular mechanisms and reversal by nutrient intervention.

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The incidence of neoplastic and infectious diseases is increased in the elderly, as is the resulting morbidity and mortality. The well-documented age-associated dysregulation of immune function is an important contributor to the increased incidence of mortality from these diseases. Accumulating evidence indicates that T cell-mediated immune responses decline with aging. We, as well as others, have demonstrated that in addition to intrinsic changes in T cells, increased macrophage (Mϕ)–derived prostaglandin E_2 (PGE_2) production contributes to the age-associated decline in T cell function [1]. We have previously shown that vitamin E supplementation of aged mice and elderly humans significantly improves T cell mediated functions including their response to vaccination [2-4]. Vitamin E exerted its immunostimulatory effect by two distinct mechanisms: 1) by reducing Mϕ PGE_2 production, and 2) by a direct effect on T cell function. We further showed that vitamin E enhances T cell function directly by enhancing the cell dividing and IL-2 producing capacity of naïve T cells from old mice, with no effect on memory T cells [5].

To determine the clinical significance of vitamin E-induced immune enhancement in the aged we investigated the effect of vitamin E supplementation on viral and bacterial infection in the aged. Vitamin E supplementation of aged mice significantly reduced lung viral titer in mice infected with influenza virus.[6, 7]. On the other hand, old mice fed a diet supplemented with vitamin E (500 ppm) compared to those fed a diet adequate in vitamin E, vitamin E supplementation did not protect against primary pulmonary *Staphylococcus aureus (S. aureus)* infection, whereas it was protective against secondary pulmonary *S. aureus* infection following influenza infection. This was indicated by a significantly lower bacterial count in the lungs of vitamin E-supplemented mice compared to that in control mice infected with *S. aureus* following influenza infection. In a recently completed double-blind, and placebo controlled study, we determined the effect of vitamin E on respiratory infection in nursing home residents. The results of this study as well as others will be discussed.

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Nutritional plane affects antigen-induced proliferation of lymphocyte subsets in milk replacer-fed calves vaccinated with *M. bovis* bacillus Calmette-Guerin (BCG).

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National Research Council recommended nutrient requirements for the neonatal dairy calf do not support optimal growth, and may compromise immune function. In a preliminary study, dietary energy and protein were shown to modulate in vitro production of interferon-gamma and nitric oxide by polyclonally stimulated blood lymphocytes from milk replacer-fed calves. We also have shown that adaptive (i.e. Th1-dependent) immune responses of milk replacer-fed neonatal calves vaccinated with *Mycobacterium bovis* bacillus Calmette Guerin (BCG) and challenged with purified protein derivative (PPD) are comparable in magnitude to adult responses. Using this sensitization/challenge model, effects of nutritional plane on antigen-induced proliferation of T cells from milk replacer-fed calves were evaluated. Holstein bull calves were fed a standard (ST, 0.57 kg/d of a 22% crude protein, 20 % fat, n=4) milk replacer or an intensified (INT, 1.14 kg/d of a 28% crude protein, 20% fat milk replacer, n=4) milk replacer for 7 wk. Calves and four juvenile steers (5-6 m of age) were vaccinated with *M. bovis* BCG at the initiation of the study. During the experimental period, average daily weight gain was greater for INT than ST calves (0.68 and 0.32 kg/d, respectively). Proliferation of $CD4^+$, $CD8^+$, and $\gamma\delta TCR^+$ T cell subsets in PPD- and mitogen [pokeweed mitogen (PWM) and

concanavalin A (ConA)]-stimulated cultures of peripheral blood mononuclear cells (PBMC) acquired before and 7 wk after vaccination were evaluated using flow cytometry. Recall responses to antigen were absent in all treatment groups prior to vaccination. Seven weeks after vaccination, PPD-induced proliferation of $CD4^+$ and $\gamma\delta TCR^+$ cells from vaccinated calves exceeded responses of T cell subsets from vaccinated steers. In addition, antigen-induced proliferative responses $CD8^+$ cells from INT calves exceeded those of ST calves. Lymphocytes from young adults were generally more responsive to mitogenic (i.e. ConA and PWM) stimulation than were cells from neonates. Overall, these results suggest that the proliferation of T cell subsets essential in CMI is affected by nutritional plane during the neonatal period.

Real-time PCR arrays can delineate immunological and nutrition-related gene expression in swine. Harry Dawson

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Real-time PCR is commonly used to verify micro array expression data. We have designed over 300 human and swine real-time PCR assays for large-scale primary analysis of genes involved in immunological or nutritional function. These assays have a greater linearity, specificity and sensitivity when compared to micro array. The immunological foci of these assays are on pathways involved in apoptosis, toll receptor signaling and Th1/Th2 differentiation. The nutritional foci are on genes involved in iron, selenium, vitamin A and vitamin D metabolism. In conjunction with these assays, we have developed an annotated database for data mining using micro array analysis software packages. Using subsets of these assays, we profiled pig responses to *Toxoplasma gondii*, *Ascaris suum*, , *Oesophagostomum dentatum*, *Salmonella typhimurium* and *Campylobacter jejuni*. *Toxoplasma* elicited a generalized Th1 response typified by high-level induction of IFN-γ, TNF-α and iNOS. *Trichuris* induced a limited Th2-associated response including localized increased IgG, IgG1, IgG4, IL-13, IL-13Ra2, SOCS3, and CHIA expression. Resistant animals had higher GATA-3, IgE, IL-10, CD3e, CD40L, CD86, and MCP-2 expression, and lower ARG1 and MUC5AC expression. The impact of this tool lies in the expanding access to genetic information between mammalian species allowing hypothesis testing of infection resistance mechanisms using quantitative expression analysis of large numbers of genes at multiple tissue sites. There is also potential application to the measurement of therapeutic efficacy for a variety of immunological and nutritional interventions against human and swine diseases. Ongoing work includes studies with vitamin A and its derivatives.

Immunity and Disease Resistance

Mechanisms of innate and adaptive immunity in swine

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Mouse models of immune mechanisms of infectious disease resistance may be unsuitable for livestock species. The porcine immune system, for example, differs in immune tissue architecture, T cell phenotypes, cytokine expression patterns, cytokine activities, and possibly gene expression profiles. Thus, genomic, molecular, cell biologic, and other direct approaches will be required to elucidate porcine protective immune responses to infectious agents. Studies of immunity to porcine reproductive and respiratory syndrome virus (PRRSV), currently the most important pathogen of swine worldwide, illustrates the current limitations in the field. PRRSV exclusively infects macrophages of swine and causes a prolonged acute and persistent infection of tissues rich in macrophages. Detailed analysis of nonspecific innate and specific acquired immunity to PRRSV is beginning to reveal heretofore unsuspected mechanisms for control and elimination of viral infection in animals. PRRSV appears to subvert host defense by infection of lung macrophages without provoking the characteristic innate interferon α/β response to RNA viruses. The appearance of neutralizing antibodies does not occur until about three weeks after infection; acute infection manifested as viremia lasts for 4-5 weeks, and infectious virions are detected in lymphoid tissues for 3-4 months thereafter. While infection lingers for a prolonged time, viral load in lymphoid tissues plummets dramatically in the early phases of persistent infection. During this period, the PRRSV-specific T cell response at sites of infection is weak, transient, variable, and independent of local viral load. Surprisingly, pigs are largely resistant to reinfection with homologous or heterologous viral isolates even though neither humoral nor T-cell anamnestic responses are observed. We hypothesize that PRRSV control in swine is due primarily to a reduction in permissive macrophages, and secondarily to specific humoral and cellular factors. Further investigation of immunological mechanisms that might provide insights to development of effective vaccines and immunotherapeutic strategies will require reagents that stimulate antigen-specific T cells and B cells and assays that are both specific and functionally relevant. Achieving these goals will require systems for expression and presentation of individual proteins or polypeptide fragments, tetramers, cytokine-specific ELISA, ELISPOT and FACS assays, and a better understanding of basic immunology of livestock species. Genomic identification of the gene repertoire involved in innate and adaptive immunity to specific pathogens and of the allelic variation in key regulatory and effector genes will be required to fully characterize basic immunological processes. Our initial foray into this area, identification of genes differentially expressed in porcine Peyer's patch, revealed that 45% of expressed sequences have no known function or are novel genes. Genes of unknown function also are differentially expressed in macrophages infected with PRRSV. These results indicate that the biochemical and cell biologic mechanisms responsible for immunity in swine, to a substantial degree, remain to be

discovered. A better grasp of this knowledge will be required for rational design and genetic selection of disease resistant animals.

Genetic and immunologic basis for resistance to GI nematode infections

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Gastrointestinal nematode infections of cattle are a constraint on the efficient raising of cattle throughout the world. Most of the nematodes species found in cattle stimulate a level of protective immunity that reduces the number of worms that develop after secondary challenge, but cattle remain susceptible to reinfection by *Ostertagia* for a prolonged period of time (i.e. 2 years or more). This prolonged susceptibility to reinfection is a major reason that this parasite species remains the most economically important GI nematode in temperate regions throughout the world. Although, individual animals remain susceptible to reinfection for a prolonged period of time, there are a number of manifestations of the immune response that result in an enhanced level of herd immunity, and the overall result of these manifestations of immunity is a reduction in parasite transmission within the cattle herd. In cattle, the immune response seen in the abomasum shows high levels of expression of IL4 in the draining lymph nodes and in lymphocytes isolated from the mucosa, but effector cell populations in the tissues surrounding the parasites, are not typical, inferring that *Ostertagia* has evolved means to suppress or evade protective immune mechanisms, including the synthesis and release of immunosuppressive substances. The immune responses elicited by GI nematode infections are moderately influenced by host genetics, and a small percentage of individual animals in a given herd are responsible for the majority of parasite transmission. In general, cattle can be separated into three types: 1) those which never demonstrate high parasite numbers, 2) those that show increasing signs of infection during the first 2-3 months on pasture and then develop responses that regulate parasite numbers and or parasite fecundity, and 3) those which continue to maintain high parasite burdens. Studies are in progress to identify the genes controlling resistance. Two approaches are being utilized. The first involves mapping of quantitative trait loci (QTL) that influence the level of parasites infection. For these studies a population of cattle has been developed in which careful phenotypic characterization of calves has been combined with a complete genome scan to identify polymorphic markers that segregate with either increased or diminished resistance to infection. Using this approach QTL that affect parasite resistance have been demonstrated on 8 different bovine chromosomes. The second approach utilizes microarray technology to assess differential gene expression in resistant versus susceptible cattle. We have developed a 400+ candidate gene array and have used it to look at gene expression in the local tissues of infected cattle. Results to date have indicated marked differences in gene expression patterns in genes associated with both adaptive and innate immune responses. Current work is focused on validation of these results by real time PCR, the development of global arrays for a more thorough look at the gene expression patterns, and integration of the QTL and array technologies for identification of important genes.

Immunity and Disease Resistance

Heterophils isolated from chickens resistant to extraintestinal *Salmonella enteritidis* infection express higher levels of pro-inflammatory cytokine mRNA following infection than heterophils from susceptible chickens

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Previous studies in our laboratory have shown differences in *in vitro* heterophil function between two pure lines of broiler chicks and their F1 reciprocal crosses. The objectives of the current study were to 1) determine if the previously reported *in vitro* differences in heterophil function between the lines translated to an increase in *in vivo* resistance to extraintestinal infection with *Salmonella enteritidis* (SE) and 2) to quantitate pro-inflammatory cytokine mRNA expression levels in heterophils isolated from SE-infected chicks from different lines. Day-old chicks from four different lines (pure lines=A and B; line C = male B × female A; line D = male A × female B) were challenged orally with SE. Twenty-four hours post-challenge, livers and spleens were asceptically removed from each chick and incubated overnight in tetrathionate enrichment broth. Enrichment cultures were plated and subsequently analyzed for the presence of non-lactose fermenting *Salmonella* colonies. The two lines reported to have more functionally efficient heterophils (A and D) were less susceptible to extraintestinal SE infections whereas the two lines reported to have functionally less efficient heterophils (B and C) were more susceptible to SE organ invasion. Four hours post-challenge peripheral blood heterophils were isolated from SE-infected and control chicks, total RNA extracted, and then analyzed for pro-inflammatory cytokine (IL-1β, IL-6, IL-8) expression using real-time quantitative RT-PCR. Pro-inflammatory cytokine mRNA expression was significantly up-regulated in heterophils isolated from chicks that were more resistant to SE organ invasion (A and D) when compared to expression in heterophils isolated from the more susceptible lines (B and C). To our knowledge, this is the first report to quantitate IL-1β, IL-6, and IL-8 mRNA expression levels in heterophils isolated from day-old chicks orally challenged with SE. These results show a relationship between *in vitro* heterophil function and resistance to organ invasion by SE. These data also indicate that pro-inflammatory cytokine mRNA expression by heterophils contributes, at least in part, to resistance/susceptibility of day-old chicks to extraintestinal infection by SE.

High-throughput molecular approaches to identify coccidiosis disease resistance genes and protective immunological mechanisms in avian coccidiosis.

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Avian coccidiosis is caused by several *Eimeria* strains which infect different regions of the intestine inducing a strain-specific immunity. Coccidiosis usually stimulate a number of immunological defense mechanisms, namely both antibody- and cell-mediated. Recent technological advances in high-throughput molecular approaches to identify disease resistance genes and molecular/cell biological pathways associated with complex biological phenomenon now enable an alternative strategy to combat coccidiosis. We have hypothesized that chicken genes influencing resistance to coccidiosis can be identified through DNA marker technology. Supporting this hypothesis, we present data identifying a quantitative trait locus (QTL) on chromosome 1 that significantly affects *Eimeria* oocyst shedding and three QTL that influence body weight of chickens during coccidiosis. One hundred and nineteen microsatellite markers, covering 80 % of the chicken genome with an average marker interval of 25 cM, were used for genotyping of F1 parents and F2 offspring from commercial broilers. The genetic mechanism of this locus appeared additive. The genomic scan also identified three potential growth QTL on Chromosomes 1, 6, and 8. These results provide the foundation for further investigation to validate the QTL. In addition, our recent studies on local host immunity to *Eimeria* clearly indicate that intricate and complex interactions of host local cell-mediated immunity and parasites determine the outcome of host response to coccidiosis. High-throughput gene expression profiling and real-time PCR have been applied to analyze underlying immune mechanisms controlling disease resistance/susceptibility to coccidiosis. The role of various cytokines whose expression increase and decrease in response to coccidia invasion have been studied. Recently, we have developed the first chicken intestinal ETS database which will be used to investigate innate and acquired immunities to enteric pathogens such as coccidia and *Salmonella*.

Immunointervention

Protective killed *Leptospira* vaccine induces potent type 1 (Th1) immunity comprising responses by CD4 and WC1+ γδ t lymphocytes

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Leptospira borgpetersenii serovar hardjo is a common cause of bovine leptospirosis and also causes zoonotic infections of humans. A protective killed vaccine against serovar hardjo was shown to induce strong antigen-specific proliferative responses by peripheral blood mononuclear cells (PBMC) from vaccinated cattle but not from non-vaccinated control cattle in three studies conducted. By 7 days, up to one-third of the cells in cultures of sonicated leptospira and PBMC from vaccinated animals produced interferon-γ (IFN-γ) as ascertained by flow cytometric analysis. The IFN-γ-producing cells included both WC1+ γδ T cells and $CD4^+$ T cells. Analysis of carboxyfluorescein succinimidyl ester loaded cells also showed that a similar proportion of these 2 subpopulations were found among the dividing cells in antigen-stimulated cultures. Infected non-vaccinated cattle also had an IFN-γ-based response but less than that by vaccinated animals and while naïve/challenged and vaccinated/challenged animals had similar levels of antigen-specific IgG1 following challenge, vaccinated animals had 1.4 fold more IgG2. In conclusion, while infection may induce a type 1 response we suggest it is too weak to prevent establishment of chronic infection. Overall the significance of these studies is the very potent type 1 (Th1) immune response induced and sustained following administration of a killed bacterial vaccine adjuvanted with aluminum hydroxide and the involvement of WC1 γδ T cells in the response. The response by γδ T cells is suggestive of a memory response since it has never occurred with cells from a large number of naïve cattle tested. Moreover, recent results suggest it is a specific subpopulation of the WC1+ cells and we hypothesize that the response by these cells may result in establishment of a milieu that supports development of a type 1 response by CD4 T cells. Finally, induction of this cellular immune response is associated with the protection afforded by the bovine leptospiral vaccine against *L. borgpetersenii* serovar hardjo although this is an extracellular pathogen. Similar results have been found with a second monovalent vaccine made with *L. interrogans* serovar hardjo and adjuvanted with alum while we have found that a traditional pentavalent vaccine containing 5 serovars of *Leptospira* does not induce this response.

Development of an oral vaccine for *Escherichia coli* O157:H7

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Enterohemorrhagic *Escherichia coli* (EHEC) O157:H7, a subset of Shiga toxin-producing *E. coli* (STEC), are the most common infectious cause of bloody diarrhea in the United

States. A sequela of this infection, the hemolytic uremic syndrome (HUS), is the primary cause of acute kidney failure in U.S. children. Cattle are major sources of EHEC O157:H7 and other STEC pathogens associated with human infections. Our long-term goal is to identify ways to reduce EHEC infections in cattle, and thus reduce the risk of EHEC disease in humans. One approach, which is the objective of an ongoing collaboration with Alison O'Brien (USUHS, Bethesda, MD), is to develop an inexpensive, effective vaccine that will prevent cattle from becoming infected with EHEC. Intimin is an outer membrane protein of EHEC O157:H7 that is required for colonization of neonatal calves. We hypothesized that an intimin-based vaccination strategy in calves might reduce colonization of cattle with EHEC O157:H7. The demonstration that antibodies against intimin interfere with colonization and intestinal damage in neonatal pigs supports this hypothesis. We transferred the *eae* gene that encodes for intimin into the tobacco NT-1 cell line and demonstrated that the transformed plant cells produce intimin, that transgenic intimin is immunogenic in mice, and that feeding mice transgenic intimin reduced the length of time these animals shed EHEC O157:H7 following experimental challenge. Our collaborator, Wayne Curtis, recently scaled up the production of intimin-expressing NT-1 cells and the immunogenicity of transgenic intimin in cattle is being tested. The bacterial DNA that encodes for intimin is being modified so that it can be transferred into an edible plant that can be fed to calves and used to test the efficacy of transgenic intimin as an oral vaccine for reducing EHEC infections in cattle. Such a vaccine that reduces O157:H7 levels in cattle would help reduce EHEC infections in humans.

Adjuvant effect of IL-1β, IL-2, IL-8, IL-15, IFN-α, IFN-γ, TGF-β4 and lymphotactin on DNA vaccination against *Eimeria acervulina*.

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Avian coccidiosis, an economically important disease for the poultry industry, is caused by intracellular protozoa belonging to several species of the genus *Eimeria*. Coccidiosis results in extensive destruction of the gut epithelium accompanied by severe depression in body weight gain, reduced feed efficiency and intestinal shedding of parasite oocysts. Although coccidiosis is mainly controlled by the use of chemotherapeutic agents, alternative control strategies are needed due to the increasing emergence of drug-resistant parasite strains and impending withdrawl of drug use in animal farming. Recently, novel vaccination strategies using antigen-encoding DNA plasmids have been shown to successfully induce protective cellular and humoral immune responses against a variety of infectious diseases. Since the emergence of gene-based immunization methodologies, various strategies have been used to increase the efficiency of DNA vaccination. For example, immune responses induced by DNA vaccination can be enhanced by cytokines. This study reports the first evidence of adjuvant effect of various chicken cytokines when given with coccidia DNA vaccine. Eight chicken cytokine genes (IL-1β, IL-2, IL-8, IL-15, IFN-α, IFN-γ, TGF-β4, lymphotactin) were evaluated for their adjuvant effect on a suboptimal dose of an *Eimeria* DNA vaccine carrying the 3-1E coccidia gene (pcDNA3-

1E). One or 10 μg of IFN-α or 10 μg of lymphotactin expressing plasmids, when given simultaneously with the pcDNA3-1E vaccine, significantly protected against body weight loss induced by *E. acervulina*. Parasite replication was significantly reduced in chickens given the pcDNA3-1E vaccine along with 1.0 μg of the IL-15, IFN-γ, TGF-β4 or lymphotactin plasmids or 10 μg of the IL-1β, IL-8, IL-15 or TGF-β4 plasmids compared with chickens given the pcDNA3-1E vaccine alone. In duodenum, chickens that received the pcDNA3-1E vaccine simultaneously with the IL-8 or IL-15 genes had significantly increased CD3+ cells compared with vaccination using pcDNA3-1E alone or in combination with the other cytokine genes tested. These results indicate that the type and the dose of cytokine genes co-injected with a DNA vaccine influence the quality of the local immune response to DNA vaccination against coccidiosis.

Stimulation of chicken leukocytes and reduction of *Salmonella* organ invasion in neonatal chicken by immunostimulatory CpG-oligodeoxynucleotide.

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Unmethylated CpG oligodinucleotide, flanked by particular base contents, are known to stimulate innate immune responses. Immune stimulatory activities of these CpG molecules have been studied mostly in immune cells from mammalian, particularly human and mice. Recently, studies have emerged to show similar immune stimulatory activities of CpG oligodinucleotide in other species such as chicken and fish. Here, we present results from our studies on immune stimulatory activities of CpG oligodinucleotide in chicken. Our results show that synthetic oligodeoxynucleotides (ODN) containing CpG motif (CpG-ODN) activated the avian macrophage cell line and induced NO production. The most active CpG-ODN motif for NO induction was GTCGTT. Increasing the number of GTCGTT motif in the CpG-ODN significantly enhanced the stimulatory effect. This CpG-ODN also stimulated IL-1β gene expression in the macrophage HD11 cells. CpG-ODN stimulated inducible NO synthase (iNOS) to produce NO through a clathrin-dependent endocytosis and subsequent endosomal maturation signaling pathways, involving activation of protein kinase C (PKC), mitogen-activated protein kinases (p38 MAPK and MEK1/2), and transcription factor NF-κB. Moreover, we have discovered that CpG-ODN induces degranulation in chicken heterophils. This heterophil degranulation activity induced by CpG-ODN was absolutely serum-dependent and also receptor mediated. Finally, we evaluated synthetic CpG-ODNs for their *in vivo* protection against organ invasion by *Salmonella enteritidis* (SE) in neonatal chickens. Day-old chickens were i.p. injected with synthetic CpG-ODN and then orally challenged with live SE. Organs (liver and spleen) were removed from experimental chickens 24 hours after the challenge and cultured for SE. The results showed a significant reduction of organ invasion by SE ($p<0.05$) in chickens pretreated with CpG-ODN containing the immunostimulatory GTCGTT motif.

Regulation of memory CD8 T cell generation by cytokines

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CD8 T cells play a critical role in defense against viral, intracellular bacterial, and protozoon infections. Therefore, vaccines against these viruses need to engender potent CD8 T cell memory. Although generation of T cell memory is the basis of vaccinations, the mechanism(s) of induction of CD8 T cell memory are not well understood. Typically, CD8 T cell responses can be divided into three distinct phases: (1) the expansion phase when naive T cells undergo antigen-driven proliferation and differentiation into effector cells, (2) the contraction phase when 90-95% of the expanded T cells are eliminated, and (3) the memory phase when the remaining ~5% of the expanded CD8 T cells survive for extended periods as memory T cells. Upon infection, these memory CD8 T cells respond expeditiously and clear the infection by rapidly differentiating into effector T cells. The accelerated response that typifies immune memory can be attributed to both quantitative and qualitative changes in CD8 T cells: (1) Firstly, in an immune animal, there are more antigen-specific T cells, as compared to an immunologically naive animal; (2) Secondly, in striking contrast to naive T cells, the memory CD8 T cells in immune animals are hyper reactive to antigenic stimulation and capable of efficient trafficking into peripheral tissues. The number of memory CD8 T cells generated is dependent upon the extent of expansion and the magnitude of contraction during the T cell response. Since protective immunity is dependent upon the induction of a threshold number of memory CD8 T cells, it is critical to gain a thorough understanding of the mechanisms that regulate the expansion and contraction phases of the T cell response. Our studies using the well-characterized lymphocytic choriomeningitis virus (LCMV) model in mice have shown that signaling via IFNγ receptor (IFNγR) and TNF receptors (TNFR) play important roles in limiting the number of antigen-specific memory CD8 T cells that survive the contraction phase of the T cell response. In mice, loss of IFNγR reduced the expansion of LCMV-specific CD8 T cells, but remarkably ablated the contraction phase of the CD8 T cell response; IFNγR-deficient mice contained substantially more virus-specific memory CD8 T cells, as compared to control wild type mice. Loss of either TNF or TNF receptors did not affect the expansion phase of the CD8 T cell response to LCMV, but enhanced the survival of LCMV-specific memory CD8 T cells in both lymphoid and non-lymphoid organs. These findings have implications in rational vaccine design and therapy of immune-mediated diseases.

Poster Sessions

December 2, 2003

The first author listed presented the poster unless another name is listed in **bold**
Posters are numbered as indicated.

Innate Immunity

Analysis of swine skin-derived dendritic cells in the induction of innate immune responses to Foot-and-mouth disease virus (FMDV)

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See abstract, on page 20.

The inhibition of nitric oxide production in chicken phagocytes.

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The production of reactive nitrogen, nitric oxide (NO), has previously been demonstrated to be a major mechanism by which the innate immune system defends against microbial invasion. The purpose of this study was to characterize components of the signal transduction pathway induced by bacterial stimulation of NO for antimicrobial defense by chicken phagocytes. We quantified the production of nitrite by chicken macrophages (HD11 cells) which had been exposed to specific signal transduction inhibitors prior to stimulation by formalin-fixed *Enterococcus gallunarium* (EG) or *Klebsiella pneumoniae* (KP). The induction of many antimicrobial peptide genes is known to be regulated by factors of the NF-κB family in a toll-like-receptor dependent or independent manner. NF-κB is in turn regulated by IκB kinase. We found that NO production induced by both EG and KP was reduced in a dose dependent manner by specific inhibitors of NF-κB, IκB and JAK 3.

Oligodeoxynucleotides (ODN)-induced activation of macrophage-mediated innate immunity against intracellular pathogens, *Eimeria* and *Salmonella*, and the development of novel immunomodulatory strategies using embryo injection of CpG-ODNs in poultry.

Dalloul[1,2]Rami, Lillehoj[1] Hyun S., Xie[2] Hang, Heckert[2] Robert A., Babu[3] Uma, Raybourne[3] Richard, and Klinman[4] Dennis M.
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See abstract on page 20.

Toll-like receptor and acute phase cytokine expression in genetically selected lines of layers following an LPS challenge

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A multi-disciplinary approach is essential to ascertain the well-being of farm animals. The Livestock Behavior Research Unit uses behavioral, physiological, and immunological measures to answer well-being questions for poultry, swine, and dairy cattle. The innate immune system is frequently the first immune responder during many stressors and the resulting acute phase cytokines affect behavior and learning. Toll-like receptors are the pathogen recognition molecules that initiate the cascade that increases the acute phase cytokines. The effect of pathogens and stressors on the toll-like receptors of farm animals is not known. A study has been completed that examines the effect of lipopolysaccharide (LPS) on RNA toll-like receptor expression in chickens. The objective of this study was to determine expression of TLR2, TLR4, and two acute phase cytokines (interleukin-1 and tumor necrosis factor-α) following an LPS challenge of two genetic lines of layers divergently selected for aggression (aggressive, MBB and passive, KGB)and one commercial genetic line (COMM). The 3 lines of layers were given LPS (5.0 mg/kg of body weight), then organs (heart, liver, and spleen) were weighed and lung, liver, and spleen tissues were collected at 0, 24, and 72 hours following a single LPS i.v. injection. RNA was extracted from the tissues and subjected to real-time RT-PCR. Heart and spleen weights had genetic line ($P < 0.01$) and time effects ($P < 0.05$ and 0.01, for heart and spleen respectively). Liver weights were different for genetic line ($P < 0.01$) but not time. Liver IL-1 and TLR2 had time effects ($P < 0.01$) but were not different among treatments. Liver TNF and TLR4 were not different over time or among treatments. Lung IL-1, TLR2, TLR4, and TNF were different over time ($P < 0.05$ for TLR4 and $P < 0.01$ for IL-1, TLR2, and TNF) but not among treatments. Spleen IL-1, TLR2, TLR4, and TNF were different over time but not among treatments ($P < 0.05$ for IL-1, $P < 0.01$ for TLR2, TLR4, and TNF). No treatment by time interactions were detected for any of these variables ($P > 0.05$). The only effects of genetic line were liver and spleen weight. Toll-like receptors 2 and 4 and cytokine changes were not influenced by genetic lines, only by time. Toll-like receptor expression was dissimilar for the two receptors that we investigated. Toll-like receptor 2 had effects

of time in all three tissues, while TLR4 was influenced by time only in lung and spleen. Toll-like receptor 2 increase expression in the liver and spleen by 24 h, but did not increase in the lung until 72 h post-LPS injection. Liver TLR2 remained elevated through the 72 h sample. Therefore, this genetic selection did not alter RNA expression of these innate immune receptors and cytokines. Since toll-like receptors recognize heat-shock proteins, further exploration of toll-like receptor expression during heat stress in chickens is in progress.

Toll-like receptor and acute phase cytokine expression in neonatal dairy calves

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See abstract on page 18.

Spleen-dependent innate immunity in calves to *Babesia bovis* infection is characterized as a type-1 response involving the proliferation of NK-like cells

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Innate immunity is important for control of primary infections and for induction of acquired responses. Young calves possess a strong spleen-dependent innate immunity to the intraerythrocytic protozoan, *Babesia bovis*. Prominent cellular components in innate immunity are dendritic cells, macrophages, and NK-cells. The study reported here demonstrates the importance of a type-1 response involving the early induction of IL-12 and IFN-γ and proliferation of NK-like cells in the spleen of calves during a primary tick-transmitted *B. bovis* infection. Unlike gdT-cells, $CD3^-$, $CD2^+$, $CD8^+$ NK-like cells proliferated in the spleen, increasing almost three-fold over pre-infection levels. A model and hypothesis are presented for macrophage and/or dendritic cell participation with NK cells in the induction of a type-1 protective response against this parasite.

Interferon-γ upregulates the expression of proinflammatory and Th1 cytokine mrna in chicken heterophils during receptor-mediated phagocytosis of opsonized and nonopsonized *Salmonella enteritidis*.

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The immediate response to invasive pathogens, clearance via the inflammatory response, and activation of the appropriate acquired responses are all coordinated and orchestrated by the innate host defenses. Recognition of microbes is accompanied by the induction of multiple cell processes including the production of pro- and anti-inflammatory cytokines. Polymorphonuclear leukocytes (PMNs) are vital cellular components of innate immunity, and function by killing pathogenic microbes following phagocytosis. The primary PMN in poultry is the heterophil. Priming is the potentiation of the phagocyte activation process by

previous exposure to a priming agent. IFN-γ is a pleiotrophic cytokine involved in basically all phases of immune and inflammatory responses that has been shown to prime heterophil functional activities. In the present experiments, using real-time quantitative RT-PCR, we evaluated the role of rChIFN-γ as a priming mediator to control heterophil responses at the level of gene transcription and expression of the mRNA for proinflammatory (IL-1b, IL-6, IL-8) and Th1 (IL-18 and IFN-γ) cytokine genes following stimulation with phagocytosis agonists opsonized and nonopsonized *Salmonella enteritidis*. RChIFN-γ primed the heterophils for an increase in transcription of pro-inflammatory cytokines induced by phagocytic agonists, but also upregulated expression of Th1 cytokine (IL-18 and IFN-γ) mRNA. Although rChIFN-γ priming modulated the expression of cytokine mRNA in heterophils stimulated by different phagocytic agonists, the rChIFN-γ by itself did not directly induce gene expression of either the proinflammatory or Th1 cytokines. The enhanced expression of cytokine mRNA does not appear to be differentially expressed depending on the receptor activated during phagocytosis. The results from the present experiments suggest that rChIFN-γ may play a significant role in avian innate immunity against Salmonella infection and may offer an adjunct use in the prevention and treatment of salmonellae infections in newly hatched chickens.

Recombinant bovine soluble CD14 reduces fatality of endotoxin challenged mice and reduces severity of intramammary infection by *Escherichia coli* in dairy cows.

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Three million cases of clinical mastitis caused by Gram-negative bacteria occur every year in the U.S. A significant number of these cases will result in acute endotoxin shock and death. Three hundred thousand dairy cows are removed from herds or die annually because of acute coliform mastitis. Standard therapy for treating Gram-negative bacterial sepsis and shock, including administration of potent antibiotics, aggressive fluid resuscitation, and metabolic support, has not been successful in reducing mortality. Soluble CD14 (sCD14) neutralizes endotoxin and prevents it from binding and activating macorphages. Further, LPS/CD14 complexes bind to epithelial cells and results in rapid recruitment of neutrophils to the infection site. Novel reagents such as host defense proteins like sCD14 have a role as a potential prophylactic against serious Gram-negative bacterial infections. In the present study, the full length and the truncated forms of bovine sCD14 were cloned into a transfer vector and expressed by recombinant baculovirus that infect insect cell line sf-9. The protective effect of the recombinant bovine sCD14 (rbosCD14) was evaluated in mice and lactating dairy cows. Eighty–one female mice were randomly assigned to two groups and injected intraperitoneally with either LPS (8 μg/g BW, n = 41) or LPS plus rbosCD14 (6.8 μg/g BW, n = 40). Survival rate for LPS and LPS plus rbosCD14 injected mice at 24 h was 30 and 72%. Two mammary quarters of each of 9 cows were challenged with either 50 CFU of *Escherichia coli* plus saline or 50 CFU of *E. coli* plus 100 μg rbos CD14. Quarters challenged with *E. coli* plus rbosCD14 had a more rapid recruitment of neutrophils, which was accompanied by a faster clearance of bacteria and reduced clinical symptoms than challenged quarters

injected with saline. At 24 h after bacterial challenge, only two (22%) of nine quarters challenged with E. coli and injected with rbosCD14 remained infected. On nine challenged quarters injected with saline, six (67%) remained infected. Results indicated that rbosCD14 was able to decrease the fatality of LPS challenged mice and reduced incidence of infection in dairy cows following experimental challenge with *E. coli*. Use of rbosCD14 in the treatment of and prevention of acute coliform mastitis has the potential of saving US dairymen 1.4 billion dollars annually.

Immune Regulation

Systemic cytokine and antibody responses following vesicular stomatitis virus infection of naïve and vaccinated cattle.

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Vesicular stomatitis virus (VSV) causes disease of varying severity in cattle, swine, and horses. The mechanisms mediating protection from clinical disease remain unknown. This study was carried out to gain a better understanding of the systemic T-helper cell balance mediating the immune response against VSV in cattle. We compared two cattle vaccinated with a commercial oil adjuvanted bivalent vaccine and four naïve animals, all challenged with a virulent strain of VSV New Jersey (VSNJV). Vaccinated animals developed high titers of neutralizing antibodies against VSNJV and VSV Indiana serotypes (VSIV) (range from 2.5 to 4.6 log) and showed no disease following challenge. In contrast, non-vaccinated naïve cattle developed fever and lesions. VSV was recovered from epithelial tissue and from esophageous-pharyngeal and vesicular fluids. VSNJV -specific IgM antibodies were detected in naïve infected cattle at 4 days post-infection (dpi) and class switch to IgG1 and IgG2 occurred by 14 dpi and 14 days post-vaccination (dpv) in naïve and vaccinated cattle respectively. Titers of IgG2 isotype were higher than those of IgG1 isotype (IgG2/IgG1 ratio ranged from 1.2 to 6.5) both in naïve and vaccinated animals. IFN-α, IFN-β, IFN-γ, TNF-α, IL-1b, IL-2, IL-12p40, IL-4, IL-10 and IL-13 were measured by real-time reverse transcription-PCR (RT-PCR) in fresh peripheral blood mononuclear cells (PBMC) or PBMC stimulated with VSNJVantigen included. Transcripts for IFN-α, IFN-γ, and IL-12p40 were more abundant than those for IL-4, IL-10, and IL-13 in PBMC cultures -stimulated with VSNJV. Taken together, these results suggest that VSV antigen induces a T-helper Type 1 response in both infected and vaccinated cows. We propose that analysis of cellular responses at the sites of lesion and in draining lymph nodes, would give a more accurate picture of the events associated with development of immunity to this localized infection in domestic animals.

Mycoplasma gallisepticum: competitive exclusion or immune base

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http://msa.ars.usda.gov/ms/msstate/csrl/collier.htm

Much confusion exists concerning the mechanism(s) by which the available *Mycoplasma gallisepticum* (MG) vaccines confer protection in layer chickens. One of the major goals of this laboratory is to discern the role of competitive exclusion and/or immune based mechanisms following vaccination with MG. The parameters to be examined in the present study include T-cell subpopulations (CD4 and CD8) and cytokines levels (IFN-gamma, IL-6 and IL-8) immediately before and following MG vaccination *via* flow cytometry and real-time qRT-PCR.

Development of specific immunoglobulin IgGa and IgGb antibodies correlate with control of parasitemia in *Babesia equi* infection: IgG isotype responses in *B. equi* infection.

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Following infection with *Babesia equi* horses often survive acute disease but remain life-long carriers. Acquired immune responses are necessary to control replication while adaptive immune responses are not required for parasite-mediated erythrocyte lysis. Following lysis of infected erythrocytes, parasites are accessible to antibody and associated mechanisms of antibody-mediated control. To determine if IgG isotypes to *B. equi* erythrocyte stage antigens correlate with parasite control, antibody isotypes were measured following infection by parenteral inoculation or by the tick vector *Boophilus microplus*. Isotypes IgGa, IgGb, and IgG(T) were titrated in *B. equi* infected horse serum by ELISA using *B. equi* erythrocyte stage extract as antigen and monoclonal antibodies specific for each equine subisotype. IgGa and IgGb antibodies to *B. equi* developed during acute infection, but IgG(T) antibodies were detected only after resolution of acute parasitemia. During chronic infection, antibodies of all three isotypes were present at titers of 10^3 to 10^4 in naturally and experimentally infected horses. To test whether immunization induced IgGa and IgGb antibodies and not IgG(T) antibodies similar to those during acute infection with *B. equi*, recombinant erythrocyte stage surface protein EMA-1 in the adjuvant saponin was tested. Four immunized horses developed IgGa and IgGb antibodies to *B. equi*, but no measurable IgG(T) antibodies. These results demonstrated that development of IgGa and IgGb antibodies to *B. equi* erythrocyte stage antigens correlated with control of *B. equi* parasitemia, and that this IgG isotype profile was induced by subunit immunization.

Analysis of lymphocytes isolated from white-tailed deer (*Odocoileus virginianus*) fawns

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Peripheral blood mononuclear cells (PBMC) were isolated from ten female white-tailed deer fawns at 48 hours of age and every two weeks there after until the fawns were three months of age. Bone marrow aspirates and peripheral blood samples were taken on the same fawns at ten months of age (yearlings). In a separate experiment, mesenteric lymph node (MLN), spleen, thymus, bone marrow (BM) and peripheral blood (PB) were collected from euthanized female fetuses at approximately 190 days gestation (n=4) and from fawns at 24 hour (n=2), two weeks (n=2) and four weeks (n=2) of age. Mononuclear cells were isolated from pooled, homogenized tissues and individual peripheral blood samples at each of the four time points. Lymphocytes were phenotyped to examine the expression of specific surface receptors as the fawns aged. Three-color flow cytometric analysis of leukocytes was performed using a panel of monoclonal antibodies (mAb). Adult deer were also phenotyped using the same monoclonal antibody panel. Included in the panel were mAbs recognizing WC1, the chain and chains, CD4, CD8, CD62L, CD44, CD21, IL-2R, MHC Class II, B-B1, B-B2 and B-B4. Analysis revealed dynamic changes in the expression of specific surface receptors associated with development and maturation of lymphocyte subpopulations. $WC1^+$ gamma delta T cells were predominant in the PB of fetal and neonatal fawns and decreased with age. In contrast, percentages of $CD4^+$ and $CD8^+$ populations were observed to increase over time in the PB. T cell surface antigen expression in the PB and tissues was consistent with observations made in other ruminants. B cell surface IgM expression was heterogeneous at two days, but became more discrete as the fawns matured. Interestingly, B-B2, a putative B cell lineage marker expressed on lymphocytes in the PB at 24-48 hours was down modulated by two weeks. However, expression of another B cell lineage marker, B-B4, was consistently expressed throughout the fawns' development in the PB, MLN, and spleen. Mononuclear cells isolated from bone marrow aspirates revealed phenotypically distinct expression of surface receptors as compared to PBMCs. Mononuclear cells co-expressing B-B2 and surface IgM were a unique population found in the bone marrow and not in the PB. The $sIgM^+B\text{-}B2^+$ population was observed in the fetal spleen and MLN. B-B4 was expressed on a small percentage of bone marrow mononuclear cells. Proliferative responses of the isolated PBMC's to pokeweed mitogen (PWM), Concanavalin A (ConA) and *Mannheimia* (*Pasteurella) haemolytica* LPS were also examined. Cells isolated from fawns proliferated in response to PWM and ConA, but not in response to LPS stimulation. Data obtained in the present study provides baseline information regarding lymphocyte subpopulations in white-tailed deer fawns.

Effects of the mammary gland on the composition and function of peripheral blood mononuclear leukocyte populations in periparturient dairy cows.

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See abstract on page 25.

Comparison of adhesion molecules on milk and blood lymphocytes from periparturient dairy cattle.

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Fifteen Holstein dairy cows were monitored for expression of adhesion molecules on lymphocytes in blood and milk at parturition and at intervals up to 21 days post partum. Using flow cytometric analysis, we examined expression of CD62L, CD11a, CD44, and $\alpha_4\beta_7$ on T (CD4+, CD8+, $\gamma\delta$+) and B lymphocytes. CD62L was expressed on 20-70% of T cell subsets in blood and 35-80% in milk from normal cows. CD62L expression on B cells was 20-25% in blood and 60-80% in milk. CD11a was found on 10-25% of T cells in blood and 35-70% in milk. CD11a was found on 10-15% of B cells in blood and 45-75% in milk. $\alpha_4\beta_7$ was expressed on 5-10% of T cells in blood and 10-35% in milk. $\alpha_4\beta_7$ was expressed on 5-10% of B cells in blood and 20-40% in milk. CD44 was found on 5-15% of T cells in blood and 20-55% in milk. CD44 was found on 5-10% of B cells in blood and 30-55% in milk. There were consistently more adhesion molecules, at a statistically significant level, on milk lymphocytes compared with blood lymphocytes. These differences may reflect increased recruitment of lymphocytes into the bovine mammary gland, which could then modulate the inflammatory response to pathogens during infection. Since CD62L and $\alpha_4\beta_7$ are peripheral and mucosal homing receptors, respectively, these data suggest increased recruitment of both pools of lymphocytes into the bovine mammary gland.

Evaluation of the chicken crop (ingluvies) as a model system for following mucosal immunity in chickens.

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The crop (ingluvies) is an enlargement or out pouching of the esophagus proximal to the proventriculus, or glandular stomach and functions primarily in a food storage role for avian species. While recent work has shown the crop can be colonized with pathogens such as *Salmonella*, little information is available regarding the presence of any immune response within this organ. During a recent study investigating mucosal immunity to *Salmonella enteritidis* (SE) in the alimentary tract of White Leghorn chickens, we discovered the presence of substantial titers of IgA specific for SE in samples from crops removed from SE-infected, but not from noninfected, birds. Histological examination of the crop tissues found a paucity of lymphocytes in noninfected birds but lymphocyte aggregates were detected in the crop mucosa by 2 weeks post infection which increased in size and number thereafter. Because of the easy access to this organ orally, a crop lavage system was developed where a narrow diameter plastic tubing attached to a syringe was inserted down the esophagus into the crop. A flush solution was administered into the crop and immediately aspirated back into the syringe, with minimal discomfort to the bird and allowing multiple samplings of the same live birds over time.

While specific IgA responses were the most robust, high levels of SE-specific IgG were also detected. Comparing IgA titers in crop lavage samples vs intestinal flushes from individual SE-infected birds, a very good correlation between titers of the two sample types was obtained, indicating that crop immunity may be used as an easy model for following mucosal immunity in a bird following infection. Studies are currently underway to determine crop immune responses in chickens infected with other pathogens, the prevalence of lymphoid tissues in crops from different avian species, the phenotypes of lymphocyte populations that develop in the chicken crop post infection and the importance of mucosal invasion in driving the development of this lymphoid tissue.

Neutralization of bluetongue virus in vertebrate and invertebrate cells.

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Bluetongue virus (BTV) is an orbivirus that infects sheep, cattle and wild ruminants. It is transmitted to susceptible vertebrate hosts by biting midges in the genus *Culicoides*. Following infection, the vertebrate host produces neutralizing antibodies that are responsible for virus clearance and conferring immunity to subsequent virus challenge. These neutralizing antibodies are directed against the virus outer capsid, which is also responsible for initiating infection in the vertebrate host. Infection of the insect vector is believed to be mediated primarily by the inner capsid, which is not the target of neutralizing antibody. Therefore, virus that is neutralized for infection of vertebrate cells may still be infectious for invertebrate cells. This may have important implications in the natural epidemiology of BTV infections. To investigate this further, the mechanisms of neutralization of BTV in both vertebrate and invertebrate cells was investigated. Antibodies that neutralize BTV infection in vertebrate cells failed to neutralize viral infection in a *Culicoides* cell line. However, non-neutralizing antibodies that react with a virus core protein inhibited infection and/or replication of BTV in the *Culicoides* cell line. Since this virus core protein is highly conserved between BTV serotypes, and appears to play an important role in the initiation of BTV infection in insect cells, it may represent a novel target for control of infection caused by these viruses.

Comparison of the adaptive immune response in neonatal and young adult dairy cattle utilizing a *Mycobacterium bovis* BCG sensitization/PPDb challenge model.

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Acquisition and modulation of immune competency in calves during the neonatal and postnatal period are not well described. The purpose of this study was to characterize age-related changes in the functional capacities of peripheral blood mononuclear cell (PBMC) and neutrophil populations from antigen-sensitized calves. Milk replacer-fed Holstein bull calves were nonvaccinated (n = 6, vaccination controls) or vaccinated subQ (n = 6) with an attenuated strain of *Mycobacterium bovis* [bacille Calmette Guerin (BCG)] at 1 and 7 wk of age. Yearling heifers (n=4, adult controls) were vaccinated and sampled concurrently with the calves. Functional capacities of PBMC (i.e. mitogen and antigen-induced DNA-synthesis, T cell subset proliferation, cytokine and NO production, IgG secretion) and neutrophil (iodination and cytochrome C reduction) populations collected at 0 (pre-vaccination), 2, 5, 6 (boosted), 7, 8 and 11 wk were evaluated *in vitro*. The phenotype of PBMC populations was characterized by flow cytometry. The responsiveness of PBMC from nonvaccinated and vaccinated calves to polyclonal stimulation frequently was lower than adult PBMC. Responses of PBMC from vaccinated calves to recall antigen (PPDb) were evident at >2 wk (3 wk of age) after primary vaccination. With the exception of antigen-induced DNA synthesis, most functions (T cell subset proliferation, TNF-α, IFN-γ and NO secretion) of PBMC from vaccinated calves were comparable to or exceeded those of vaccinated adults. Changes in cervical skin-fold thickness after intradermal administration of PPD (wk 11) were significant and comparable in vaccinated calves and adults confirming the development of a robust cell-mediated immune response in vaccinated calves. In contrast, antigen-specific IgG responses (i.e. PPD-specific IgG in sera and supernatants from PPD-stimulated cultures) of vaccinated calves were minimal or nonexistent relative to adult responses suggesting the contribution of the B cell to the immune response is limited in young cattle. Nonvaccinated calves did not respond to recall antigen in vivo (i.e. cutaneous delayed-type hypersensitivity) or in vitro. Neutrophil functions were affected by age but not vaccination.

Molecular characterization of a putative Tumor Necrosis Factor superfamily 13b (TNFSF 13b) homologue from rainbow trout (*Oncorhynchus mykiss*).

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Little is known about the immune system function of economically important cool and cold water fish species. Such knowledge is important for developing successful vaccines and disease resistant fish. In mammals, members of the tumor necrosis factor superfamily (TNFSF) play important roles in both innate and adaptive immune responses. In order to determine which TNFSF members are conserved and expressed in rainbow trout, we have searched a computer database of ~50,000 expressed sequence tags generated at the National Center for Cool and Cold Water Aquaculture. We have identified 17 cDNAs that have homology to known TNFSF ligands or receptors. Here, we describe one cDNA, 1RT126I22, which has homology to TNFSF 13b. TNFSF 13b is also known as B-cell activating factor (BAFF) or B-lymphocyte stimulating factor (BLYS). In mice and humans, TNFSF 13b is produced by myeloid cells and is critical for mature B cell survival and antibody production. The rainbow trout cDNA, 1RT126I22, encodes a predicted 141 amino acid protein, which shares 54% amino acid identity with human TNFSF13b, 51% identity with mouse TNFSF13b, and 54% identity with chicken TNFSF13b. The rainbow trout TNFSF 13b shares 100% identity with a 99 amino acid protein predicted from a truncated Atlantic salmon cDNA, and 78% identify with puffer fish TNFSF13b protein predicted from genomic DNA sequence. The rainbow trout TNFSF 13b is unusual as it does not possess a transmembrane domain or a furin-type protease cleavage site characteristic of the human, mouse, and chicken TNFSF 13b molecules. Examination of rainbow trout TNFSF 13b gene expression during vaccination and bacterial challenge is underway. To our knowledge, this is the first identification and characterization of fish TNFSF 13b homologues.

Immunogenetics

Expression of specific MHC Class II DRB1 alleles associates with sheep persistently infected with ovine progressive pneumonia virus (OPPV).

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See abstract on page 28.

Marek's disease and the MHC: How viruses subvert the immune system for their advantage.

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See abstract on page 27.

Physical and genetic mapping of the rainbow trout major histocompatibility regions: evidence for duplication of the class I region

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Previous segregation analysis in trout suggested that the class I and II regions reside on completely different chromosomes. To learn more about MHC genomics in trout, we have isolated BAC clones harboring class IA and IB loci, a single BAC clone containing an MH class II gene (DAB) as well as BAC clones containing the ABCB2 gene. Upon PCR and sequence confirmation, BAC clones were labeled and used as probes for *in situ* hybridization on rainbow trout metaphase chromosomes for determination of the physical locations of the trout MH regions. Finally, SNPs, RFLPs and micro-satellites found within the BAC clones allowed for these regions to be assigned to specific linkage groups on the OSUxHotcreek and OSUxArlee genetic linkage maps. Our data demonstrates that the trout MH regions are located on at least four different chromosomes and the corresponding linkage groups while also providing direct evidence for the partial duplication of the MH class I region in trout.

Immunity and the Pathogenesis of Disease

A dual role for flice-like inhibitory protein (flip) in mediating both bacterial lipopolysaccharide-induced apoptosis and NF-κb activation.

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Bacterial lipopolysaccharide (LPS) contributes to much of the vascular injury/dysfunction associated with Gram-negative sepsis. We have previously shown that inhibition of *de novo* gene expression with cycloheximide sensitizes vascular endothelial cells (EC) to LPS-induced apoptosis and that the onset of apoptosis correlates with decreased expression of FLICE-like inhibitory protein (FLIP), an anti-apoptotic protein. We now have data that conclusively establish a role for FLIP in protecting EC against LPS-induced apoptosis. Downregulation of FLIP using anti-sense oligonucleotides sensitized EC to direct LPS killing, whereas, overexpression of FLIP protected against LPS-induced apoptosis in the presence of cycloheximide. Interestingly, FLIP overexpression completely blocked NF-kB activation induced by LPS, but not by phorbol ester, suggesting a specific role for FLIP in mediating LPS activation. Together, these data support a dual role for FLIP in mediating LPS-induced apoptosis and NF-kB activation.

Gene expression profiling of bovine macrophages in response to *Escherichia coli* O157:H7 lipopolysaccharide

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The aim of this study was to identify changes in bovine macrophage gene expression in response to treatment with *Escherichia coli* 0157:H7 lipopolysaccharide (LPS), utilizing a human gene microarray. Bovine cDNA from control and LPS-treated primary macrophages hybridized to greater than 5,644 (79.8%) of the non-control gene targets on a commercially available microarray containing greater than 7,075 targets (Incyte Genomics, St. Louis, MO). Of these target sequences, 44 were differentially expressed upon exposure to LPS, including 18 genes not previously reported to exist in cattle. These included a pentaxin-related gene, CASP8, TNF-induced genes, interferon-induced genes, and inhibitors of apoptosis. Using the human microarray, cDNA from bovine LPS-treated and control macrophages consistently hybridized to targets known to be expressed constitutively by macrophages, as expected given the predicted cDNA sequence homology. That this human system was accurately estimating levels of bovine transcripts was further verified by real-time quantitative reverse transcriptase polymerase chain reaction (RTQ-PCR) using bovine-specific primers. This first report of bovine-

human cross-species expression profiling by microarray hybridization demonstrates the utility of this technique in bovine gene expression and discovery.

Evaluation of immune response induced by attenuated and wild-type PRRS virus

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Introduction and Objectives

Porcine reproductive and respiratory syndrome virus (PRRSV) modified-live vaccines (MLV) have been developed by attenuation in cell culture. Under experimental conditions the vaccines are efficacious; however, under field conditions vaccine efficacy reports have ranged from excellent to poor. One possible reason for questionable efficacy is that MLV may not induce a similar immune response when compared to wild-type PRRSV infection. The goal of the study reported here was to compare the cellular immune response in pigs following exposure to an attenuated PRRSV or its wild-type parent virus.

Materials and Methods

Two experiments were conducted using 52 4-5 week-old conventionally-raised pigs free of PRRSV and PRRSV-specific antibody. PRRSV strain NADC-8 (3rd passage) and NADC-8 (251st passage) were wild-type parent virus and attenuated virus, respectively. Based on sequence of ORFs 2-7 (3,184 nucleotides) the attenuated virus was 99.4% homologous with its parent virus. A different wild-type PRRSV strain, SDSU 73 (3rd passage) was used in the 4th group in experiment 2. Each experiment had a similar design: a sham-inoculated control group (group 1), an attenuated virus-inoculated group (group 2) and a wild-type parent virus-inoculated group (group 3). In experiment 2 there was a 4th group inoculated with SDSU 73. There were 13, 15, 15 and 8 pigs in groups 1, 2, 3 and 4, respectively. Pigs were each inoculated intramuscularly with 2 ml of their respective virus inoculum (about 2×10^5 $TCID_{50}$ virus/ml) day 0, pigs in group 1 received 2 ml of sham inoculum. Blood samples were collected on days -7, -4, 0, 3, 6, 9, 13 and 20 (21 for experiment 2). Serum was tested for PRRSV specific antibodies and used for PRRS virus isolation. A rapid flow cytometric method (6) and a panel of monoclonal antibodies were used to analyze porcine peripheral blood leukocytes by two-color flow cytometric analysis. Statistical analysis was performed using GraphPad InStat software.

Results and Discussion

Results represent the combined data from the two experiments. Statistically significant changes ($P<0.05$) in lymphocyte subpopulations percentage were observed in groups 3 and 4; whereas no changes were observed in group 2. CD8+ T cells increased on days 6, 9 and 13 for group 3 and on days 9 and 13 for group 4. CD4+ T cells increased on day 9 for group 4. CD3+ T cells increased on day 9 for groups 3 and 4. Cells expressing Class II marker decreased on day 3 in group 3 and on days 3 and 6 in group 4; Class II cells increased in the both groups on days 13 and 20(21). CD45+ cells increased on days 9 and 13 for groups 3 and 4. B cells decreased on days 3, 6 and 9 for group 3 and on days 3 and

6 in group 4. Total WBC counts decreased on days 6 and 9 in group 3 and on days 3, 6 and 9 in group 4. Virus was isolated from all wild-type PRRSV-infected pigs (groups 3 and 4), but no virus was isolated from the sham or attenuated-virus inoculated pigs (groups 1 and 2). All wild-type PRRSV-inoculated pigs and 6 of the 15 attenuated-virus inoculated pigs (group 2) developed PRRSV-specific antibody. No sham-inoculated pigs developed antibody. Group 2 data were further analyzed by dividing pigs in seropositive and seronegative subgroups. No statistical differences in percentage of lymphocyte populations were found.

The percentage lymphocyte values determined in this study for the naïve animals represent normal values for conventionally raised pigs and are in agreement with previously reported data (6). This agreement of data suggests the methodology used in these experiments is reproducible. The peripheral blood cellular immune response characterized in the pigs infected with wild-type PRRSV appears similar to what has been reported by others. Following experimental infection with wild-type PRRSV there may be a transitory decrease in CD4+ and CD8+ T cells within the first few days. This is followed by a return of CD4+ cells to normal levels and an elevated level of CD8+ cells that may last for at least several weeks (1-5) Collectively, these studies in conjunction with the present study suggest T cells play an important role in the PRRSV immune response following wild-type virus infection. No significant changes in blood cell populations were noted following infection with the attenuated PRRSV (group2) when compared to negative control group. Perhaps this observation may account for the lack of vaccine efficacy that has been described under field conditions.

The study reported here indicates that the magnitude of the PRRSV–specific immune response may be related to PRRSV virulence. Additional studies are needed to confirm this hypothesis and what, if any, relevance this may have on vaccine development.

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Decreased neutrophil function as a cause of retained placenta in dairy cattle

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It is unclear why some cows fail to expel the placenta following calving. One theory suggests the fetal placenta must be recognized as "foreign" tissue and rejected by the immune system after parturition to cause expulsion of the placenta. We hypothesized that impaired neutrophil function causes retained placenta (RP). We examined the ability of neutrophils to recognize fetal cotyledon tissue as assessed by a chemotaxis assay. Neutrophil killing ability was also estimated by determining myeloperoxidase activity in isolated neutrophils. Blood samples were obtained from 142 periparturient dairy cattle in 2 herds. Twenty cattle developed RP (14.1 %). Neutrophils isolated from blood of cows with RP had significantly lower neutrophil function in both assays prior to calving and this impaired function lasted for 1-2 wk after parturition. Addition of antibody directed against interleukin-8 (IL-8) to the cotyledon preparation used as a chemoattractant inhibited chemotaxis by 41% suggesting one of the chemoattractants present in the cotyledon at parturition is IL-8. At calving plasma IL-8 concentration was lower in RP cows (51 ± 12 pg/ml) than in cows expelling the placenta normally (134 ± 11 pg/ml). From these data, we suggest that neutrophil function is a determining factor for the development of RP in dairy cattle. Also, depressed production of IL-8 may be a factor affecting neutrophil function in cows developing RP.

Comparative proteomic analysis of normal and periparturient bovine neutrophils demonstrating a reduction of myeloperoxidase during transition.

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Neutrophils constitute a primary effector of the host immune response to an infectious pathogen. Normally low numbers of neutrophils reside in a health mammary gland, however, infection and subsequent release of chemoattractants results in the rapid influx of activated neutrophils into the site of infection. Periparturient dairy cows exhibit signs of immunosuppression that correlate with a higher incidence of mastitis. Furthermore, periparturient immunosuppression includes a significant reduction of neutrophil function. To better understand the nature of the periparturient immunosuppression, neutrophils from dairy cows were isolated greater than 21 days prior to calving (normal function) and shortly after calving (immunosuppressed) and compared using differential mass spectrometry. Proteomes of the immunosuppressed and normal neutrophils were labeled with isotope-coded affinity tags (ICAT), digested and subjected to nano-flow LC-MSMS analysis. Neutrophil proteins were identified and quantitated, interestingly myeloperoxidase was shown to be reduced three-fold around parturition whereas cathelicidin 1 and beta defensin were unaffected. Myeloperoxidase is a strongly bactericidal neutrophil enzyme that generates reactive oxidants and is considered an important component of neutrophil's ability to destroy bacteria.

The effects of *Pasteurella multocida* toxin (PMT) on early murine B-lineage cells

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Pasteurella multocida toxin (PMT) induces pre-osteoclast proliferation and osteoclast differentiation that leads to bone destruction. Developing B-cells and osteoclasts share the same microenvironment; therefore, it is hypothesized that the toxin may elicit alterations in B-cell progenitors in the bone marrow. To test this, mice were exposed to the toxin for 24 hours; peripheral blood, spleen, and bone marrow cells isolated, counted, and developing B-cell populations analyzed by flow cytometry. Toxin exposure resulted in a 5% increase in the percentage of $B220^{+}CD19^{+}IgM^{-}$ cells in the bone marrow, as well as a 5% increase in the percentage of $B220^{+}CD19^{+}IgM^{+}$ cells in the peripheral blood. Conversely, percentages of B-cell subsets in the spleen were similar in toxin-treated and control mice. The increase in bone marrow $B220^{+}CD19^{+}IgM^{-}$ cells was not due to proliferation as determined by *in vivo* administration of bromodeoxyuridine (BrdU) during PMT exposure. Furthermore, PMT did not alter the expression of the anti-apoptotic Bcl-2 as measured by intracellular staining. As $B220^{+}$ cells have been shown to serve as osteoclast precursors, we are currently investigating whether PMT induces osteoclastogenesis of bone marrow $B220^{+}CD19^{+}IgM^{-}$ cells.

Functional genomics analysis of infection by bovine viral diarrhea virus Type 2 in a bovine B-cell lymphosarcoma cell line

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Bovine viral diarrhea virus (BVDV), a major viral pathogen of cattle in the US, causes disease characterized by immunosuppression and lymphocytopenia. In addition, infection of a fetus in the first 150 days of pregnancy can give rise to a persistently infected calf that sheds the virus for life. This is a major means of dissemination of the virus to naïve animals and herds. BVDV is lymphotrophic and acute infection results in depletion of lymphoid tissues, even with BVDV strains of low virulence. The limited in vitro studies of host cell response done to date were performed in epithelial cells and compared cytopathic and noncytopathic strains without regard to virulence in vivo. Our research has shown that cytopathology in vitro does not correlate with virulence in vivo. We are taking a functional genomics approach, using serial analysis of gene expression (SAGE), to determine the molecular events that take place in the infected lymphoid cells that contribute to the disease syndromes observed in vivo. SAGE is a powerful technology that allows quantitation of transcripts in cells and direct comparisons between libraries and experiments. For these studies, we used the B-cell lymphosarcoma cell line BL-3 and compared virus strains of differing virulence (virulence was based on previous in vivo studies). To date, we have constructed and sequenced SAGE libraries from mRNA derived from non-infected cells, as well as cells infected with high and low virulence BVDV strains. Data analysis is ongoing. Preliminary results from the non-infected cells showed the normal metabolism of these cells with corresponding gene expression levels. When compared to results from BVDV-infected cells, a remodeling of cellular functions

was observed that reflected changes that, overall, benefited the replication of the virus. These effects included changes in protein translation, transport and ER processing, intracellular signaling, and some important housekeeping functions. Also observed was a decline in expression of proteins that are involved in detoxification, particularly reactive oxygen species. Some of these changes have suggested new lines of research that should lead to elucidation of the mechanism(s) behind immunosuppression and viral persistence.

Immune responses controlling *Toxoplasma gondii* infection in pigs.

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Toxoplasma gondii (Tg) infection induces a strong interferon-gamma (IFNg) dominated, T helper-1 (Th1) response in pigs with immune pathology that quickly resolvesPigs were infected with 4.5 x 10^6 Tg oocysts and various tissues were collected at 2, 4, 7 and 14 days after infection (DAI). Tg organisms were detected in mesenteric lymph nodes (MLN) at 2DAI and, at 4 DAI, in liver, spleen, lung and ileum, by IHC and Tg specific Real-Time PCR. At the same infection times changes in inflammatory and Th1 immune mRNA gene expression were observed by Real-Time RT-PCR. Increased IFNg mRNA and protein expression were observed in MLN and hepato-splenic(HS) LN cells. Changes were observed in IL1b, IL-6, NRAMP1, IFNg, INDO and STAT-1 expression at 2DAI. Responses were more intense at 4DAI and also included TNFa, Arginase, IRF-1, IL-10, SOCS-1, SOCS-3, and IFNa activation. Liver showed the most intense changes in gene expression in response to Tg infection; PMBC had the lowest changes. High serum haptoglobin and NO levels at 4DAI ($p<0.01$) confirms inflammatory and macrophage activation. Up-regulation of inflammatory and Th1-dominated markers indicates mechanisms involved in the host defense against acute toxoplasmosis.
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Acute phase proteins in relation to disease and immunity: an avian paradigm

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Acute phase proteins (APPs) are serum proteins elevated in response to a variety of physiological injuries including infection and inflammation. These are pathogen nonspecific proteins predominantly synthesized in the liver and other tissues such as endothelium, and modulate both innate and acquired immune responses. However, the physiological significance of different APPs is not well understood. In monitoring veterinary health the APPs are used as diagnostic and prognostic indicators. But their use to improve immunity has not been explored. The avian APP response and their significance are much less understood compared to mammals. The object of our study was to understand avian APP response and their possible significance. We induced experimental inflammation in young broiler chickens, by the use of intramuscular injection either of bacterial lipopolysacharides (LPS), gram positive bacterial cell walls, or croton oil, and compared the serum proteins profiles with sham injected control sera

using polyacrylamide gel electrophoresis. Our results showed quantitative changes in several protein bands of which a band corresponding to MW of 65-66 kD was significantly elevated in response to inflammation (1-4). Further analyses using two-dimensional gel electrophoresis and electroblotting onto PVDF membrane, the spots equivalent to 65 kD MW was N-terminal sequenced to yield a molecular homology to ovotransferrin (OVT) (3,4). Using an anti-serum transferrin antibody and western blot, the results further proved that the serum protein was the same as the egg white transferrin. We developed an enzyme-immunoassay to measure OVT concentrations and showed that the serum transferrin levels are elevated in response to a variety of bacterial and viral infections (5). To understand the possible significance of elevated OVT in relation to immunity, we studied its *in vitro* effects on macrophages and heterophil functions under non-stimulated and endotoxin stimulated conditions. Our results show that OVT augmented the functional activity of both of these cell types as measured using nitric oxide, interleukin-6, matrix metalloproteinase, reactive oxygen production as indicators (6). Additionally, OVT also stimulated heterophil degranulation. These studies provide a paradigm of the possible usefulness of monitoring serum OVT to identify the presence of avian health problems and its function as an immunity modifying protein in poultry.

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In vitro studies of BVDV strains in lymphoid cells lines reveal a third biotype

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While bovine viral diarrhea viruses (BVDV) are highly lymphotrophic in vivo, in vitro they are studied in epithelial cells. BVDV are classified as cytopathic (cp) or noncytopathic (ncp) based on their activity in cultured epithelial cells. This does not

correlate with virulence in acute infections, as the most highly virulent BVDV are ncp. The purpose of this study was to determine if virulence in vivo could be correlated with growth characteristics in cultured lymphoid cells. A BL-3 cell line (derived from a B cell lymphosarcoma) free of BVDV and bovine leukemia virus was used. Cultures were infected with the highly virulent (hv) ncp BVDV2 strain 1373, the low virulent (lv) ncp BVDV2 strain 28508-5 or the lv cp BVDV2 strain 296c. Cell growth, proliferative state, ratio of live to dead cells and virus replication were monitored. Cell morphology was observed by light and electron microscopy. No significant differences were seen between noninfected cells and 28508-5 infected cells. Cytopathic effect (cpe), as defined by cell death, was observed in cells infected with 1373 and 296c. However, the cpe observed with the two strains were different. The cpe associated with 296c infection was apparent within the first 48 hours after infection and was associated with the condensation and fragmentation of most nuclei. Cpe associated with 1373 was not apparent until 96 hours after infection. Cells were non-proliferative but nuclei appeared morphologically normal. The cell cytoplasm became less dense and disorganization of mitochondria was observed. Nuclear condensation and fragmentation became common only in cells in the late stages of cpe. These results suggests that different mechanisms are involved in the cell death associated with lv cp strains and hv ncp virulent strains. Based on these findings BVDV may be grouped into three biotypes, cp (based on cpe in epithelial cells and cultured lymphoid cells within the first 48 hours after infection), ncp (based on lack of cpe in both epithelial and lymphoid cells lines and lymphocidal (based on cell death in lymphoid cell lines 96 hrs post infection).

Local infection of VSV: pathogenesis, role of inflammatory cells and cytokines

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Vesicular Stomatitis Virus (VSV) is negative-sense RNA virus that causes vesicular disease in cattle, horses and pigs. Little is known about the pathogenesis of this virus in livestock species. In order to better understand the pathogenesis, virus distribution and local immune response to VSV infection, 3 bovines were inoculated with the New Jersey strain of vesicular stomatitis virus (VSV-NJ), utilizing a coronary-band scarification procedure. Punch biopsies were obtained at 20 minutes, 6, 12, 24, and 48 hours post-inoculation (hpi). Plasma and esophageal-pharyngeal fluid (OPF) were obtained prior to inoculation and at 24, 48 and 72 hpi. At 72 hours animals were euthanized and various tissues were collected including all major internal organs and various lymphoid tissues. Samples were assayed for virus isolation, presence of viral RNA by real-time RT-PCR and viral antigen identification by immunohistochemistry (IHC). Levels of mRNA for twelve cytokines were measured by real-time RT-PCR in the coronary band.
Virus inoculation resulted in fever and vesicular lesions in the coronary bands by 48 hpi in all animals, with virus titers increasing over time from 1 log at 20 minutes to 6 logs $TCID_{50}$ by 72 hpi. Virus was isolated only from lymph nodes draining the coronary bands (prescapular and popliteal). Virus was also isolated from other lymphoid tissues:

tonsil, retropharingeal, and parotid lymph nodes in one animal and tonsil and axilar lymph node in a second. Virus was never found in blood, OPF samples or in any other lymph node or internal organ tested. Viral antigens were detected predominantly in the stratum spinosum of the coronary band, in a few cells of the basal layer, and in the afferent and efferent sections of the local lymph nodes, with minimal involvement of germinal centers. Target cells in lymph nodes were morphologically compatible with monocytes. Local cytokine responses were dominated by an IFN alpha, beta, gamma and IL6, all showing increases of 3 to 4 fold by 6 hpi and 15-20 fold by 72 hpi. Levels of IL1β, IL2, IL4, IL10, IL12p40, IL13, IL15 and TNF alpha maintained basal levels up to 24 hpi but increased 3-25 fold in all animals thereafter. Results demonstrate that infection with VSV-NJ was restricted to the local infected tissue and draining lymphoid tissue. A viral growth curve was observed in coronary band biopsies with increasing titers 12 to 72 hpi. These results provide an important contribution for understanding VSV pathogenesis and transmission in cattle.

Characterizing mematode-induced Th2-dependent changes in intestinal function.

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The Th2 cytokines IL-4 and IL-13 are induced by parasitic worm infection and contribute to their expulsion through IL-4 receptor (R)-induced Stat6 activation. IL-4 binds the type 1 and type 2 IL-4R that contain the IL-4Rα chain and the common γ chain or the IL-13Rα1 chain, respectively; IL-13 binds to the type 2 IL-4R and to the IL-13Rα2 chain that is not linked to Stat6.

Aim: To determine the effects of intestinal nematodes on intestinal function.

Methods Stripped mucosae were mounted in Ussing chambers to measure tissue permeability and concentration-dependent changes in short circuit current in response to glucose or various secretagogues, and strips of smooth muscle were suspended in organ baths and subjected to stimulation of enteric nerves. Expression of IL-4Rα, IL-13Rα1, and IL-13Rα2 mRNA was analyzed by real time PCR in specific mucosal cells collected by laser capture microdissection.

Results: Infection of mice with 3 different nematodes (*Heligmosomoides polygyrus, Nippostrongylus brasiliensis and Trichinella spiralis*) elicits a stereotypic, Stat6-dependent inhibition of glucose absorption and increased mucosal permeability leading to an elevation of fluid in the small intestine; these effects are mimicked by treatment with IL-4 and IL-13 and are Stat6-dependent. Mast cells play a key role in the pro secretory effects of IL-4 that are not shared by IL-13. Nematodes uniformly induces hyper contractility of intestinal smooth muscle by mechanisms that involve both Stat6-dependent and Stat6-independent pathways; IL-13 has more potent effects on contractility than IL-4. Expression of IL-4Rα, IL-13Rα1 and IL-13Rα2 mRNA was

evident in epithelial and smooth muscle cells. Infection of pigs with the nematode *Ascaris suum* revealed similar Th2-driven changes in intestinal function associated with expulsion of 4th stage larvae.

Conclusion: Nematode infection of the small intestine elicits a characteristic "weep and sweep" response that facilitates worm clearance. IL-4 and IL-13 play a critical role in the host response to nematode infection by altering gut function through receptor-mediated activation of Stat6 pathways. Currently, cloned soluble IL-4Rα, IL-13Rα1, and IL-13Rα2 are being used in swine as molecular scavengers to 1) delineate the role of IL-4 and IL-13 in worm clearance and intestinal function; 2) as antagonists and/or agonists of the classic Th2 response and; 3) to mediate IL-13 induced as a model of human allergic disease.

Modulatory effects of IFN-γ, IL-10 and TGF-β in cattle infected with *Mycobacterium paratuberculosis*

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Johne's disease is an important disease that results in great economic losses for both dairy and beef production in the United States and worldwide. The disease progresses through distinct stages, a subclinical stage where there are no clinical signs and a clinical stage that is characterized by progressive symptoms associated with chronic shedding of high levels of bacteria in the feces along with severe diarrhea and concomitant weight loss. The host immune response to *M. paratuberculosis* is paradoxical, with strong cell-mediated immune responses during subclinical stages and strong humoral responses during clinical stages of the disease. It is possible that immune modulation of an effective cell-mediated immune response may play an important role in disease progression. We hypothesized that the clinical stage of Johne's disease is mediated by production of cytokines such as TGF-β and IL-10 that downregulate IFN-γ production and interfere with an effective cell-mediated immune response. Therefore, ileum, ileal cecal junction, ilealcecal lymph node and mesenteric lymph node tissues from the healthy, subclinical or clinical animals were collected and analyzed for the presence of TGF-β, IL-10 and IFN-γ mRNA by quantitative RT-cPCR. The results show that TGF-β and IL-10 mRNA levels in animals that have progressed to the clinical stage of the disease is higher than that found in subclincal and healthy animals, whereas IFN-γ is higher in subclinical animals. Interferon-γ plays a significant role in the control of mycobacterial infections, including *Mycobacterium paratuberculosis*. However, the contribution of other immunoregulatory cytokines such as IL-10 and TGF-β in Johne's disease has not been investigated as yet. In the present study, we examined the effects of in vivo and in vitro infection with *M. paratuberculosis* on the production of IFN-γ, IL-10 and TGF-β by peripheral blood mononuclear cells (PBMC). We also examined the effects of exogenous IFN-γ, IL-10 and TGF-β on *M. paratuberculosis* survival in the cell cultures. PBMC obtained from naturally infected cows, regardless of their disease status, specifically upregulated IL-10 and TGF-β in culture supernatants in response to stimulation with live *M. paratuberculosis*. Non-stimulated PBMC recovered from subclinically infected animals secreted the lowest levels of TGF- but after stimulation with live *M. paratuberculosis*

TGF-β levels in the culture supernatants increased to levels similar to that produced by PBMC from healthy animals. Compared to healthy cows, naturally infected animals had higher numbers of viable *M. paratuberculosis* recovered from their cultures after in vitro infection with *M. paratuberculosis*. The addition of exogenous IL-10 and TGF-β to PBMC isolated from healthy cows inhibited the bactericidal activity of these cells as evidenced by the increased number of viable *M. paratuberculosis* recovered from those cultures compared to cell cultures containing medium alone. These data suggest an important immune regulatory role of IL-10 and TGF-β during infection with *M. paratuberculosis* that may be directly related to their effects on macrophage activation and killing of *M. paratuberculosis*.

Bovine T cell response to antigens of *Neospora caninum*.

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See abstract on page 24.

Ascaris Infection as a Marker of Local Mucosal Immunity in Pigs.

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Ascaris spp. are ubiquitous in swine with significant economic consequences to the industry, and are the most prevalent helminth infection in man worldwide. The migration of this nematode parasite from the cecum to the liver, lung and small intestine along with its ability to induce immunity and inflammation provides a tool for analysis of local responses at several mucosal surfaces. The Th2-like response to *A. suum* in pigs that is characterized by mucosal mast cell and goblet cell hyperplasia, eosinophilia and reaginic antibody production was supported by the demonstration of a pattern of cytokine gene expression consistent with a polarized Th2-related immune response in the lymph nodes draining the sites of infection using a series of 24 gene probes for Th1 and Th2-associated products. Alveolar macrophages obtained from the lungs of *A. suum*-infected pigs had reduced capacity to phagocytise killed *Staphylococcus aureus* but did release enhanced levels of super oxide dismutase indicating a functional skewing of immunity in the lung. Likewise, expulsion of the migrating 4th stage larvae from the jejunum of infected pigs was associated with a "weep and sweep" phenomenon in the small intestine characterized by increased fluid accumulation in the lumen and enhanced smooth muscle contractility. Micro array analysis of parasites that survived expulsion revealed a more robust expression of transcripts for glyceraldehydes 3 phosphate dehydrogenase, succinate dehydrogenase and muscle proteins. Application of sensitive new technologies for evaluation of gene expression of the host and parasite have made the pig a more accurate predictor of immunity in this species and as an attractive model of immune function in humans.

Experimental *Mycobacterium avium* subsp. *paratuberculosis* infection of calves: early induction of a concurrent humoral and cellular immune response.

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Johne's disease (paratuberculosis) of cattle is widespread and causes significant economic losses for producers due to decreased production and poor health of affected animals. The chronic nature of the disease and the lack of a reproducible model of infection hinder research efforts. In the present study, instillation of *Mycobacterium avium* subsp. *paratuberculosis* into the tonsillar crypts of neonatal calves resulted in chronic infection with peripheral colonization detected by ante-mortem culture of feces and post-mortem (320 d postchallenge) culture of intestinal tissues. Antigen-specific blastogenic, IFN-γ, and nitric oxide responses by blood mononuclear cells from infected calves exceeded prechallenge responses beginning 194 d postchallenge. Upon in vitro stimulation with paratuberculosis antigens, $CD4^+$ cells from infected calves proliferated, produced IFN-γ, and increased expression of CD26 and CD45RO (i.e., indicative of an activated memory phenotype). Utilizing a lipoarabinomannan-based ELISA, specific serum immunoglobulin was detected as early as 134 d postchallenge and generally increased after this time point. Two antigens of ~50-kDa and ~60-kDa were particularly immunodominant early in infection as shown by immunoblot with serum collected within 2 weeks postchallenge. Findings indicate that the intratonsillar inoculation route will prove useful as an experimental model for paratuberculosis pathogenesis, diagnosis, and vaccine efficacy studies. Additionally, this study confirms that mycobacteria-specific antibody is detectable early in the course of experimental Johne's disease, even preceeding the development of specific cell-mediated responses.

Mechanism for age-associated upregulation in COX-2 expression: role of NFkB.

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Increased prostaglandin E_2 (PGE_2) production has been shown to contribute to age-associated decline in T cell function as well as dysregulated inflammatory response. We previously demonstrated that macrophages (Mϕ) from old mice have significantly higher cyclooxygenase (COX) activity and COX-2 expression compared to young mice. We further showed that the higher COX-2 expression was due to transcriptional upregulation rather than a change in COX-2 degradation with aging. The purpose of the present study was to determine the mechanism of age-related upregulation in COX-2. We hypothesized that the activation of transcription factors may undergo a change with aging, leading to altered COX-2 transcription. The results demonstrate that LPS-initiated activation of

NFκB, but not AP-1 and CREB, is higher in old than in young mice. No significant age difference was observed in the activity of MAPK P38, JNK, or ERK. Inhibition of NFκB activation decreased PGE_2 production, COX activity, COX-2 protein and mRNA expression. These reductions were more dramatic in old Mϕ compared to that of young Mϕ. We further showed that old Mϕ have higher IκB degradation in cytoplasm and p65 translocation to nucleus compared to young Mϕ. Thus the age-associated up regulation of COX-2 transcription in Mϕ is mediated through higher NFκB activation, which in turn is due to increase in IκB degradation. Supported by NIA grant # RO1AG09140-09

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Immunity and Nutrition

Real-time PCR arrays can delineate immunological and nutrition-related gene expression in swine.

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See abstract on page 34.

Dietary modulation of host mucosal immunity against avian coccidiosis.

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Infectious diseases constitute one of the greatest threats to the viability of the food animal industry. Commercial broilers, in particular, have a higher risk of acquiring contagious diseases than other livestock due to intensive collective farming practices. For example, avian coccidiosis is a major parasitic disease of significant economic importance and the U.S. industry spends greater than $800 million annually in medication. In the absence of efficient vaccines to control this disease and the emergence of new antigenic variants of *Eimeria*, the broiler industry has relied upon prophylactic medication. However, anti-coccidial drugs are expensive and their effectiveness is hindered by widespread parasite drug resistance and the high cost of new drug development. Moreover, recent banning of growth promoters and anti-coccidial drugs in commercial animal production in Europe and parts of US will eventually force the industry to eliminate this practice and will require the development of non-chemical methods for coccidiosis control. Thus, probiotics represent an important alternative for antibiotic use in poultry production. However, the exact modes of action in which probiotics achieve such protective roles need to be better elucidated to improve effectiveness. Previously we have shown that resistance in broilers to *Eimeria acervulina* (EA) was significantly reduced by vitamin A deficiency and enhanced by a probiotic (*Lactobacillus*-based). In the present 2 x 2 factorial study, a broiler starter ration was amended for vitamin A (control, C, or deficient, A) and probiotic status (-, P) to investigate their modulatory effects on the host immune system. Birds were inoculated orally with EA oocysts and disease susceptibility was evaluated by assessing fecal oocyst shedding. Humoral and local cellular mediated immunity were assessed by evaluating antibody and cytokine (IFN-γ and IL-2) levels in sera and intestinal secretions on a 3-day interval following inoculation. Fecal oocyst shedding was highest ($P < 0.05$) in A- birds, followed by AP, C- and CP. Feeding the probiotic reduced shed oocysts by 20% in A fed birds and by 26% in C fed birds. Intestinal IFN-γ was relatively constant in all treatment groups except for A- where it declined steadily and was lower ($P < 0.05$) from day 6 on. Serum IFN-γ levels fluctuated within each treatment and over time were not revealing. Intestinal IL-2 was highest in CP

birds at 3 and 9 dpi, and lowest in A- birds at 3, 9, and 12 dpi ($P < 0.05$); no difference between treatments was found at 6 dpi ($P > 0.05$). *Eimeria*-specific intestinal Ab level was constant ($P > 0.05$) in C- birds, but increased with time ($P < 0.05$) in A-, AP and CP birds. Serum Ab levels were also constant in A- and CP, but increased ($P < 0.05$) in C- and AP after 6 dpi. The data demonstrate for the first time a probiotic-enhanced immunity in vitamin A-deficient birds. It is also the first study to demonstrate the probiotic effect on local cell-mediated immunity of chickens, best manifested by apparent lower intestinal invasion and development by EA, based on higher IL-2 secretion and lower EA oocyst production. The new information concerning the immunological mechanism involved in the probiotic-induced immune enhancement would promote the development of novel ways to modulate the immune response to enhance the health and productivity of poultry.

The effect of vitamin E on secondary bacterial infection following influenza infection in young and old mice

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In the U.S. alone, influenza accounts for over 10,000 deaths annually and over 40,000 deaths during epidemic years. For example, individuals 65 years and older accounted for 89% of all influenza associated deaths in 1992. These deaths were not typically due to influenza infection alone, but from the development of complications due to influenza infection. *Staphylococcus aureus* is commonly associated with influenza infection and can cause sudden and serious illness, especially in the elderly. Previously, we showed that vitamin E supplementation significantly improves the antioxidant status and immune response in aged mice and humans. We further showed that vitamin E supplementation reduces influenza viral infection and improves antioxidant status in aged mice. However, little is known about the potentially deadly bacterial infections that commonly follow influenza infection in the aged. The goal of this study was to determine the efficacy of vitamin E supplementation on secondary bacterial infection following influenza infection in young and old mice. This was tested by feeding young and old C57BL/6 mice semi-synthetic diets containing adequate (30 ppm) or high (500 ppm) levels of vitamin E and determining viral and bacterial titers after primary influenza A or *S. aureus* infection, or following a secondary *S. aureus* infection subsequent to an influenza infection. In this animal model, age did not have a significant effect on *S. aureus* infection alone or *S. aureus* infection following influenza infection. Supplementation with vitamin E did not have a significant effect on *S. aureus* infection alone. Priming with influenza infection significantly increased *S. aureus* colony counts in the lungs of infected mice fed the control diet. Vitamin E supplementation successfully abolished the priming effect of influenza on *S. aureus* infection. Future studies will determine the mechanism of vitamin E's protective effect.
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Changes in gene expression profiles of T cells by age and vitamin E.

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Aging is associated with dysregulation of immune cells particularly that of T cells. Previous studies indicated that vitamin E improves T cell function in part by directly affecting T cells. We studied the gene expression profile of T cells to better understand the underlying mechanisms of age and E-induced changes in T cell functions. Young and old C57BL mice were fed diets containing 30 ppm (control) or 500 ppm (E) of vitamin E for 4 weeks. T cells were purified from splenocytes by negative selection using magnetic beads (anti-Mac-1 and anti-MHC class II), then cultured with media (unstimulated) or plate-bound anti-CD3 and soluble anti-CD28 (stimulated) for 2 hours. Gene expression profile was assessed using microarray analysis. Genes showing more than 2 fold changes, $p < 0.05$, and with at least 1 present call were selected. In unstimulated T cells, 43 genes were expressed significantly higher in old, mainly immunoglobulin genes, while 22 genes were expressed significantly higher in young including T cell receptor related genes. Upon stimulation, 103 genes were upregulated in at least one age or diet group (16 genes in all age and diet groups). Response to stimulation was significantly affected by age (40 genes) and vitamin E (24 genes). Significantly lower expression of T receptor alpha chain and factors involved in the signal transduction pathways were observed with aging. Significantly higher expression of suppressor of cytokine signaling (SOCS) 3 and lower expression of growth factor independent (gfi) 1 were observed with aging. Overexpression of SOCS3 has been shown to suppress T cell proliferation and IL-2 production and gfi1 has been reported to down regulate SOCS3. Expressions of IL-2 increased significantly in both young and old T cells while that of IL-4 decreased in old T cells by vitamin E. These findings suggest that: 1) aging has significant effects on signal transduction pathways in T cells, and 2) vitamin E has significant effect on Th1/2 balance.
Supported by NIA grant #RO1AG09140-09, USDA contract 58-1950-9-001, and gifts from Roche, Inc.

Stress-related chronic disease in turkeys and the effects of nutritional and environmental immunomodulation.

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Our research using the synthetic glucocorticoid, dexamethasone (DEX), to suppress the immune response of turkeys to low doses of opportunistic bacteria has led to the development of a number of nutritional and environmental strategies for decreasing the impact of stress-induced immunosupression. The immunosuppressive effects of stress appear to be greater in male turkeys than in females. We have found that female turkeys are more resistant to colibacillosis and respiratory disease in a DEX-*E.coli* challenge infection than are males. The anti-bacterial activity of monocytes from male and female turkeys treated with 0.5 or 2.0 mg/Kg DEX was measured by monitoring the percentage

of infected cells over time. Antibacterial activity was significantly decreased at both concentrations of DEX at both 8 and 16 hours post-infection in both sexes combined and was significantly lower in males as compared to females, suggesting that stress can reduce the ability of turkey mononuclear cells to kill bacteria, and that the difference in this function may be relevant to the sex-related difference in disease resistance. Water supplementation with vitamin D_3, vitamin E, sodium salicylate, and ß-1,3/1,6-glucan, a helical polysaccharide derived from the cell wall of *Saccharomyces cervisiae*, have all shown immunomodulatory effects on male turkeys challenged with *E. coli* in our model. We have shown that excess handling or environmental enrichment during the first 2 weeks after hatch can lead to decreased resistance later in life. Our model has further suggested that a small population of male turkeys is highly susceptible to the immunosuppressive effects of stress, and that these individuals can be identified by their performance in a behavioral test utilizing a T-maze at 3 days of age. These individuals are also more susceptible to the immunosuppressive effects of excess environmental stimulation during the first two weeks after hatch. These studies illustrate the dramatic effects that stress can have on both production values and resistance to opportunistic infection, and suggest that a combination of genetic selection, nutritional immunomodulation, and environmental strategies to reduce stress may lead to healthier birds and a safer and a more wholesome product.

Purified β-glucan as an abiotic feed additive up-regulates heterophil function in immature chickens.

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Functionally, the innate immune system of immature chickens is inefficient during the first week post-hatch. Pathogens, such as *Salmonella entriica* Serovar *Enteritidis* (SE), are able to invade various tissues due to this immunological inefficiency of the immature chicken. The objective of the present study was to evaluate the effect of purified β-glucan as an immunomodulator of the innate immune response, specifically the heterophil. The functional efficiency of heterophils isolated from immature chickens fed a β-glucan ration was significantly ($P<0.05$) up-regulated when compared to heterophils isolated from chickens fed a control ration as determined with an array of functional assays. Phagocytosis, bactericidal killing and oxidative burst were significantly increased in heterophils isolated from chickens fed the purified β-glucan ration ($P<0.05$). To our knowledge this is the first report of a purified β-glucan feed additive significantly up-regulating the functional abilities of heterophils isolated from immature chickens against an invading pathogen, SE.

Altered structure, function and allergenicity of peanut proteins due to processing

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There has been a dramatic increase in the prevalence of IgE mediated allergy over the past decade, which is one of the reasons that it is viewed as an area of increasing importance. During this time a significant, growing, and costly, portion of the FDA's food recalls have been due to mislabeled products that contain food allergens. Meanwhile, little is known about the reason why certain foods contain allergens and others are considered hypoallergenic. Some classic characteristics associated with food allergens are resistance to enzymatic digestion and heat, stimulation of T cell proliferation, IgE binding and abundance in food. Certain enzymatic functions have also been associate with allergenicity of proteins. However, not much is known about what happens to the allergenicity of food products after processing. In this study, roasted whole peanut proteins were shown to be less soluble, more resistant to digestive enzymes and bound higher levels of IgE than raw whole peanut proteins. Mice were more likely to be sensitized when treated with roasted peanuts than with raw peanuts and had higher vascular permeability when skin tested with roasted peanuts. The major peanut allergens Ara h 1 and Ara h 2 were then purified from both raw and roasted peanuts and examined at a molecular level for alterations that may explain the *in vivo* observations. Following roasting, Ara h 1 was shown to form irreversible trimers that are extremely resistant to digestion and bind higher levels of IgE than Ara h 1 from raw peanuts. The amino acid sequence of a second major peanut allergen, Ara h 2 was found to be homologous to the family of trypsin/alpha-amylase inhibitors. Most significantly, while the secondary structure remained unaltered, Ara h 2, purified from roasted peanuts was several fold more active as a trypsin inhibitor and bound higher levels of IgE than the Ara h 2 purified from raw peanuts. Our findings suggested that the structural and functional changes due to food processing contribute to increased allergenic properties of peanut proteins and may indeed enhance the possibility of becoming sensitized to peanuts.

Interpretive summary

It is not known why certain foods are allergenic and others are not. Some classic characteristics associated with food allergens are resistance to digestion and heat, stimulation of T cell proliferation, IgE binding and abundance in a food. Certain enzymatic functions have also been associate with allergenicity of proteins. However, not much is known about what happens to the allergenicity of food products after processing. Here the consequences of roasting on the structural, functional, immunological and allergenic properties of peanut proteins were examined. Roasting was found to alter the structure and function of peanut allergens Ara h 1 and Ara h 2. In addition, whole peanut proteins from roasted peanuts were more resistant to degradation by digestive enzymes and more likely to immunize mice than raw peanut proteins. Our findings suggested that the structural and functional changes caused by food processing contribute to increased allergenic properties of peanut proteins and may indeed enhance the possibility of becoming sensitized to peanuts.

Aging, immune response, and infectious disease: molecular mechanisms and reversal by nutrient intervention.

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See abstract on page 32.

Nutritional plane affects antigen-induced proliferation of lymphocyte subsets in milk replacer-fed calves vaccinated with *M. bovis* bacillus Calmette-Guerin (BCG).

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See abstract on page 33.

Leukocyte migration and metabolism in adipose tissue of leukocyte adhesion receptor deficient mice.

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ICAM-1 (CD54) and Mac-1 (CD11b) mediate the migration of leukocytes into tissues where they influence tissue function. Our studies sought to determine whether ICAM-1 and Mac-1 have an intrinsic role within adipose tissue by 1) analyzing the expression of ICAM-1 in adipose tissue, 2) identifying leukocyte populations within adipose tissue, and 3) determining whether ICAM-1 and Mac-1 mutant mice exhibit abnormal numbers of adipose tissue leukocytes or altered metabolism. In wildtype mice ICAM-1 was expressed in adipose tissue and localized to the vascular endothelium. ICAM-1 mRNA was detected in isolated adipocytes, but surface staining of the adipocyte was not evident, though cultured adipocyte supernate was positive for soluble ICAM-1. ICAM-1 and Mac-1 do not appear to be essential, however, for adipose tissue homeostasis since ICAM-1 and Mac-1 mutant mice exhibited no alterations in body fat deposition or adipocyte metabolism. Macrophages were observed to be a prevalent cell type within the stromal-vascular cell fraction of adipose tissue, and adipose tissue and plasma from obese mice exhibited significant elevations in MCP-1. Macrophage numbers in adhesion molecule deficient mice did not differ from controls. However, gender-specific differences were observed, with adipose tissue from female mice containing significantly more macrophages than males. Our results are in contract to a previous report of increased obesity in ICAM-1 and Mac-1 mutant mice, but demonstrate leukocyte populations within adipose tissue which must be considered in light of increasing evidence of immune-modulation of body weight.

The effect of human-derived probiotic bacteria on the immune and intestinal function of pigs

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See abstract on page 30.

Vitamin A deficiency decreases development of Th1 memory cells following adoptive transfer of TCR-transgenic T cells.

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Vitamin A deficiency enhances production of Th1 cytokines, particularly IFN-(, during the memory and effector phases of the immune response. This had led to the presumption that vitamin A deficiency biases T-helper cell development in the same direction. To test this hypothesis we adoptively transferred naïve T cells from DO11.10 TCR-transgenic mice to vitamin A-deficient or control BALB/c recipients. Recipients were then immunized with the cognate peptide antigen for the TCR-transgenic T cells (OVA323-339) and the Th1/Th2 phenotype of the transferred cells characterized by intracellular cytokine staining following in vitro stimulation with phorbol myristate acetate and ionomycin. In contrast to expectations, the percentages of IFN-(-positive cells (9.0 ± 0.5%; mean ± standard error) and IL-2-positive cells (39.2 ± 2.3%) in draining lymph nodes of deficient mice were both lower than in control mice (11.3 ± 0.4%, $p = 0.002$ and 46.4 ± 2.1%, $p = 0.028$, respectively). In addition, the percentage of IL-10 positive cells was higher in vitamin A-deficient mice (3.71 ± 0.24%) than it was in control mice (1.74 ± 0.22 %; $p < 0.001$). IFN-(and IL-2 concentrations were also lower in supernatants from splenocyte cultures restimulated with OVA323-339 peptide antigen. Thus vitamin A deficiency at the time of initial antigen exposure diminishes the development of Th1 memory cells and enhances the development of IL-10-producing Th2 memory cells.

Immunity and Disease Resistance

Relationship of the probability of disease incidence with immunity

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Health data in Holstein cows sired by a selected group of sires were analyzed as categorical traits by a threshold model. Data were collected from 174 herds and included incidences on 18,000 daughters of 1365 sires. Breeding values and genetic parameters for disease incidence were estimated. Probability of disease incidence in daughters as values associated with their sires were computed. The immune competence of the sires had been previously tested in a model of glucocorticoid immunosuppression. Statistical relationships between daughter health and immune response traits in sires were investigated. Heritability estimated by the threshold model was 0.277, an estimate sufficiently high to indicate the great potential of selection for disease resistance. Evidence of association between probability of disease incidence and seven immune response traits was found, which motivates and justifies the indirect selection of dairy sires for disease resistance. Indirect selection for disease resistance saves time and money, and could serve as a first guide for what bulls to select for health until young bulls have been progeny tested. Further research is warranted to develop indirect models of selection for disease resistance.

Correlations between disease resistance, pathogen levels, and clearance rate in channel catfish

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Enteric septicemia of catfish (ESC) is the most prevalent disease affecting commercial catfish farms. The USDA-ARS Catfish Genetic Research Unit has an ongoing program for genetic improvement of disease resistance amongst other economically important traits. Susceptibility to the causative agent of ESC, the bacterium *Edwardsiella ictaluri*, appears to be consistent within each family/spawn of NWAC103 channel catfish.

Real-time PCR technology was utilized to measure differences in bacterial loads and clearance rates for 6 ESC-susceptible and resistant families of channel catfish during immersion challenge. Fish from resistant families had increased survivorship during the challenge when compared to susceptible families. Significant differences ($p < 0.05$) in the quantity of bacterial DNA between resistant and susceptible families were evident for both blood and spleen tissue 5 days following exposure to *E. ictaluri*. Mean quantities of

bacterial cell equivalents per 100 uL of blood at 5 days post-exposure were 2.84 x 10^5 ± 143123 for the susceptible families and 496 ± 455 for the resistant families. Significant differences in spleen tissue also occurred on day 12, with fish from the resistant families having higher ($p < 0.05$) levels of bacteria than fish from the susceptible families. Overall, families that are susceptible to ESC carried higher levels of bacterial DNA in their blood than resistant families.

Pathogen clearance differed between the two sets of families. Clearance was evident by day 12 in fish from the susceptible families and bacterial levels continued to decrease throughout the remainder of the trial. However, no significant clearance was evident in fish from the resistant families. This may be due to chronic low levels of infection that did not trigger a clearance response from the immune system. The innate immune system may suppress infection only in resistant families, preventing an acute host-response whereas in susceptible families, acute infection occurs and may secondarily be cleared. Clearance rate does not appear to significantly affect mortality.

Heterophils isolated from chickens resistant to extraintestinal *Salmonella enteritidis* infection express higher levels of pro-inflammatory cytokine mRNA following infection than heterophils from susceptible chickens

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See abstract on page 37.

Genetic and immunologic basis for resistance to GI nematode infections

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See abstract on page 36.

High-throughput molecular approaches to identify coccidiosis disease resistance genes and protective immunological mechanisms in avian coccidiosis.

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See abstract on page 37.

Structural and functional characterization of chicken IL-15, IL-16 and IL-17 cDNAs.

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Limited progress in chicken cytokine immunobiology has slowed down immunological studies in poultry diseases. From our recently developed chicken intestinal gene database which contains >38,000 expressed sequence tags (EST), we searched for novel genes which are associated with innate and acquired immunities. This report describes the cloning and characterization of cDNAs encoding IL-15, IL-16 and IL-17 from our chicken intestinal library. DNA sequence analysis of a chicken IL-15 cDNA identified a 187 amino acid open reading frame encoding a protein with a predicted molecular weight of 21,964, 2 potential N-linked glycosylation sites, 4 highly conserved Cys residues, 2 out-of-frame AUG initiation codons in the 5' untranslated region, and an unusually long (66 amino acid) signal peptide such that the expected size of the mature protein is 14,462 Daltons. Chicken IL-15 and IL-2 were compared with regards to their molecular, cellular, and functional characteristics. The predicted amino acid sequences of both chicken cytokines showed greater homologies with mammalian IL-15s compared with mammalian IL-2s. Northern hybridization and RT-PCR demonstrated chicken IL-15 gene transcripts in a wide variety of tissues and cell types while the chicken IL-2 gene was expressed only in concanavalin A-activated spleen cells. Both recombinant cytokines stimulated the growth of spleen T cells and enhanced the activity of natural killer cells *in vitro*. Subcutaneous injection with an expression plasmid encoding IL-15 increased the percentage of CD3+ spleen T lymphocytes whereas injection of an IL-2 cDNA augmented CD3+, CD4+, CD8+, TCR1+, and TCR2+ T cells. Collectively, these results indicate that chicken IL-15 and IL-2 are T cell growth factors potentially capable of enhancing cell-mediated immunity *in vivo*.

IL-16 and IL-17 are proinflammatory cytokines produced by activated lymphocyte cells. Chicken IL-16 gene contained the entire open reading frame (ORF) of pro-IL-16 and encoded the mature IL-16 protein which consists of 607 amino acids. Chicken IL-16 showed 86% sequence homology to duck pro-IL-16 and 49-52% to various mammalian IL-16s. By Northern blot analysis, IL-16 transcripts showed a restricted expression to the lymphoid tissues. Recombinant chicken IL-16 consisting of 149 C-terminal amino acids of pro-IL-16 was biologically active when expressed in COS-7 cells and showed chemoattractant property for lymphocytes. IL-17 contained a 507 bp open reading frame predicted to encode a protein of 169 amino acids with a molecular mass of 18.9 kDa.

Chicken IL-17 shared 37%-46% amino acid sequence identity with mammalian IL-17 and homologous to the ORF 13 of *Herpesvirus saimiri*. By Northen blot analysis, IL-17 transcripts were identified in a reticuloendotheliosis virus-transformed chicken lymphoblast cell line (CU205) and Con A-stimulated splenic lymphocytes, but not Cu91, RP9, RP13 cell lines or kidney, bursa, heart, spleen, cecal tonsils and thymus. Conditioned medium from COS-7 cells transfected with chicken IL-17 cDNA induced the production of IL-6 by embryonic fibroblasts. These studies will facilitate our understanding of poultry immune system.

Differential pro-inflammatory cytokine mRNA expression in heterophils isolated from *Salmonella*-resistant and –susceptible chickens

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We have conducted studies utilizing a parental pair of broiler chickens (lines A and B) and the F1 reciprocal crosses (C and D). Previously we showed increased *in vitro* heterophil functional efficiency translates to increased *in vivo* resistance against a systemic *Salmonella enteritidis* (SE) infection. Heterophils are capable of producing cytokines and are known to modulate acute protection against *Salmonella* in young poultry. We hypothesize that heterophils from SE-resistant chickens (A and D) have an upregulated pro-inflammatory cytokine response compared to heterophils from SE-susceptible chickens (B and C). In this study, heterophils were isolated from day-old chicks, stimulated with SE or SE opsonized with either normal chicken serum or immune serum against SE, and quantitative real-time RT-PCR using TaqMan chemistry was used to ascertain levels of cytokine mRNA expression. Heterophils from SE-resistant chicks (A and D) had significantly higher mRNA expression levels of pro-inflammatory cytokines (IL-6, IL-8, and IL-18) upon treatment with all stimulants compared to heterophils from SE-susceptible lines (B and C). Further, heterophils from SE-resistant chicks had significantly decreased mRNA expression levels of TGF-β4, an anti-inflammatory cytokine, compared to heterophils from SE-susceptible chicks. These data indicate that chickens with heterophils more able to mount a pro-inflammatory cytokine response may determine if the chickens are going to be resistant or susceptible to *Salmonella* infections. Therefore heterophil functional efficiency and cytokine production may be useful biomarkers for poultry breeders to consider when developing new immunocompetent lines of birds.

Immunointervention Strategies

Immunopotentiation of a recombinant adenovirus-FMD vaccine by IFNα in swine

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The adjuvant effect of interferon alpha (IFNα) was examined in swine vaccinated with a recombinant replication-defective adenovirus containing foot-and-mouth disease virus (FMDV) capsid (P1-2A) and 3C proteinase coding regions (Ad5-A24). Swine were divided into 5 groups and inoculated with high ($5X10^9$ PFU) or low ($5X10^8$ PFU) doses of Ad5-A24 in the presence or absence of porcine IFNα (Ad5pIFNα, 10^9 PFU). Control animals received $6X10^9$ PFU of adenovirus containing the glycoprotein from vesicular stomatitis virus (VSV) (Ad5VSV-G). All swine were challenged at 42 days post vaccination (dpv) with FMDV-A24. Prior to challenge, blood samples were examined for IFN production, induction of IFN-induced genes and FMDV-specific neutralizing antibodies (PRN_{70}). After challenge a number of disease parameters were analyzed including clinical score, viremia and antibodies against viral structural and nonstructural (NS) proteins.

Preliminary results indicate that both high-dose Ad5-A24 inoculated groups developed significant PRN_{70} by 14-21 dpv which was maintained until the day of challenge. While both low-dose inoculated groups had lower PRN_{70}, the IFN group had an enhanced response. After challenge all control animals developed early viremia, vesicular lesions, and antibodies to FMDV NS proteins and high-levels of PRN_{70}. Animals receiving low dose Ad5-A24 with no IFN had similar clinical signs, except that fewer animals developed viremia. In contrast pigs inoculated with the same dose plus IFN had a delayed onset of vesicular lesions and only one animal had detectable viremia. Animals vaccinated with high dose Ad5-A24 without IFN had no viremia, significantly fewer lesions and delayed onset of disease compared to the group given a low dose and no IFN. Four of five pigs vaccinated with high dose plus IFN were completely protected from disease and only one animal in this group had a mild vesicular lesion restricted to the site of inoculation of challenge virus. Our results indicate that IFNα enhances the level of protection induced by the adenovirus-FMD vaccine against homologous FMDV, supporting the use of IFNα as a potential adjuvant in FMD vaccination strategies.

Swine vaccine trials with replication-defective human adenovirus serotype 5 containing the capsid and 3C proteinase coding regions of Foot-and-Mouth Disease Virus O1 Campos in the presence or absence Ad5-porcineGM-CSF

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Granulocyte-macrophage colony stimulating factor (GM-CSF) has been widely used to successfully stimulate the immune response in vaccine trials involving HIV, hepatitis C and B, cancer etc. Because of these promising results, we constructed a recombinant-defective human adenovirus 5 (Ad5) containing porcine GM-CSF gene (Ad5-pGMCSF) to examine its effect on an experimental FMDV serotype O1 Campos vaccine that is poorly immunogenic. The recombinant virus was grown in 293 cells, cesium chloride purified and expression verified in IBRS2 cells by radio-immunoprecipitation and Western blotting. The activity of pGM-CSF expressed in IBRS2 cells was demonstrated in TF-1 cells, a cell line dependent on GM-CSF for growth.

Eighteen pigs were divided into 5 groups: Groups 1 and 2, containing 3 animals each, were vaccinated with control virus, Ad5-Blue, or Ad5-pGMCSF and three other groups, 4 animals per group, were vaccinated with Ad5 containing the capsid (P1-2A) and 3C proteinase coding regions of FMDV O1 Campos (Ad5-O1C) in the absence or presence of 2 different amounts of Ad5-pGMCSF. All animals were challenged 21 days post-vaccination with a field strain of homologous virus. The results indicate that the presence of pGMCSF induced a more rapid FMDV-specific neutralizing antibody response but the titers declined faster then in the group given vaccine alone. Furthermore, after challenge, the groups administered both Ad5-pGMCSF and Ad5-O1C developed somewhat more severe disease when compared with the group given only Ad5-O1C.

Development of an oral vaccine for *Escherichia coli* o157:h7

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See abstract on page 39.

Oral dosing of mice with *Escherichia coli* expressing recombinant interferon gamma reduces Cryptosporidium parvum infection.

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Cryptosporidium parvum is a protozoan parasite that causes intestinal infection in numerous mammalian species. Previous studies indicate that interferon gamma is critical to resistance to and recovery from C. parvum infection. We electroporated a gene for recombinant murine interferon gamma (rIFN) into a nontoxigenic E. coli strain that expresses the F41 adhesion pilus, allowing it to adhere in the mammalian small intestine (strain 4907.2.1). Groups of mice were treated at 1 day of age with an oral dose of

4907.2.1 expressing rIFN, either alone, or in combination with Lactobacillus brevis and/or killed C. parvum. Controls received phosphate buffered saline. All mice were orally inoculated with 103 viable C. parvum oocysts at 7 days of age. Mice were killed at 2 weeks of age, and colon contents examined microscopically for the presence of C. parvum oocysts. The number of oocysts seen per microscopic field was compared between groups. Control mice had a mean of 2.1 oocysts per field. Mice receiving L .brevis, killed C. parvum, and 4907.2.1 had a mean of 1.75 oocysts per field. Mice receiving killed C. parvum and 4907.2.1 had a mean of 1.3 oocysts per field. Mice receiving 4907.2.1 alone had a mean of 1 oocyst per field. While these differences were not statistically significant, there was a clear trend that mice receiving E. coli expressing rIFN were less heavily infected with C. parvum.

Stimulation of chicken leukocytes and reduction of *Salmonella* organ invasion in neonatal chicken by immunostimulatory CpG-oligodeoxynucleotide.

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See abstract on page 41.

Development of an inactivated Newcastle disease virosome vaccine that protects against challenge from velogenic Texas GB

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While outbreaks of highly virulent Newcastle disease virus (NDV) are a major concern to the poultry industry internationally, economic losses caused by low virulent (lentogenic) strains continue to result from decreased egg production in layers and airsacculitis in broilers. Since lentogenic strains of NDV are widely used as vaccine strains, it is possible that these viruses, may be directly or indirectly responsible for some of the economic losses. In an effort to examine protection against NDV, we developed a non-replicating virosome vaccine that retains the ability to hemagglutinate chicken red blood cells and fuse with chicken embryo cells. Preliminary vaccine efficacy studies indicate that two intranasal doses containing 10 µg of virosomes protects chickens against lethal challenge from velogenic Texas GB.

Development of immunotherapeutic recombinant chicken scFv antibodies reactive with an apical antigens of *Eimeria*.

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Slow progress in the identification of protective *Eimeria* antigens hinders the development of control strategies against avian coccidiosis. In order to identify the epitopes of *Eimeria* which are recognized by chicken B cells, novel immunization strategy was used that led to the development of several chicken monoclonal antibodies which blocked sporozoite invasion of host cells. While most antibodies recognized uncharacterized parasite surface proteins, two were identified with reactivity against

apical complex proteins located at the anterior tip of sporozoites. To express high concentration of these antibodies for potential application as immunotherapeutic reagents, a single chain fragment variable (ScFv) region gene was constructed by PCR amplification of the variable heavy (VH) and light (VL) chain genes with a flexible linker. By indirect immunofluorescence, recombinant ScFv antibody expressed in *E. coli* showed identical binding specificity as the original monoclonal antibody against *E. acervulina* and *E. tenella* sporozoites, staining the apical complex and thus demonstrating reactivity against native parasite protein. These results demonstrate that recombinant 6D12 ScFv recognizes the native conoid antigen on *Eimeria.* Potential application of this antibody in prophylactic therapy against avian coccidiosis is being explored using various delivery strategies including embryo injection.

Adjuvant Effect of IL-1β, IL-2, IL-8, IL-15, IFN-α, IFN-γ, TGF-β4 and lymphotactin on DNA vaccination against *Eimeria acervulina*.

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See abstract on page 40.

Comparison of immunologic responses to *Brucella* and *Mycobacteruim* vaccines across species

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Eradication of brucellosis and tuberculosis from livestock populations is a high priority for regulatory personnel. Persistence of these diseases in wildlife reservoirs pose a substantial risk for transmission to livestock. In a series of studies conducted at the National Animal Disease Center, immunologic responses of wildlife species of interest to brucellosis and/or mycobacterium vaccines were characterized and compared to responses of cattle. As cell-mediated immunity is critical for long-term protection against diseases caused by intracellular bacteria, our studies particularly focused on proliferative reponses of peripheral blood mononuclear cells (PBMC), nitric oxide production, γ-interferon production, and flow cytometric analysis of proliferating PBMC subsets. Our data suggest that immunologic responses to *Brucella* or *Mycobacterium* vaccines may differ by species. Species that are considered to be closely related may demonstrate significant differences in immunologic responses to vaccination. Our data also suggest that immunologic responses to vaccination cannot be predicted but must be evaluated in the species of interest. Lastly, some wildlife species may have value as models for characterizing the role of humoral responses in ruminants as their immunologic responses to *Brucella* and *Mycobacterium* vaccines include robust antibody and deficient cell-mediated responses.

Does antigenic drift occur with avian influenza in poultry?

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Avian influenza in poultry and human influenza are both type A influenza viruses and both originated from an influenza reservoir found in wild birds, including ducks and gulls. Human influenza has been well characterized for antigenic drift, which is the accumulation of point mutations in the viral genome. These changes in the hemagglutinin gene can slowly create antibody escape mutants that make current vaccines less effective. Therefore the strains of virus in these killed vaccines must be updated on a yearly basis to provide optimal protection against the prevailing strains of circulating virus. In general when the predicted circulating strain of virus elicits an antibody titer with a fourfold loss in hemagglutination inhibition (HI) cross neutralization activity to the current vaccine, then the vaccine is changed. The changes in nucleotide similarity between the old and new vaccine strains are often less than 2%. For highly pathogenic avian influenza (HPAI), antigenic drift as it affects vaccine selection has not been a consideration in the past. Vaccine strains with differences of over 15% to the challenge strain can still provide good protection from clinical disease. There is a correlation with nucleotide sequence similarity and viral shed, with the closer a challenge strain is to the vaccine the greater reduction in viral shed. The disconnect between human influenza and HPAI vaccines may be that human influenza is a mucosal infection, but HPAI is a mucosal and a systemic infection. Vaccines for influenza do not prevent infection, but they do reduce viral shed and prevent or lessen clinical signs. Antibodies in the blood stream may effectively prevent the systemic phase of disease with HPAI viruses. However, recent studies of low pathogenic avian influenza from Mexico and the U.S. may present a different view of antigenic drift in poultry. In Mexico H5N2 LPAI has circulated for 9 years and vaccination with two different vaccines have been used widely. When recent isolates are examined by HI cross neutralization to the killed vaccine, large decreases in titers are observed. However, when examining H7N2 LPAI viruses that have been circulating in the U.S. since 1994, large decreases in HI cross neutralization titers are not observed. In both cases nucleotide sequence differences between 3-5% are observed. One major difference in the two groups of isolates is whether vaccination is used or not. The possible effect that antigenic drift could have on vaccination practices will be discussed.

Recombinant Paramyxovirus type 1-Avian Influenza-H7 virus as a vaccine for protection of chickens against influenza and Newcastle disease

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Current vaccines to prevent avian influenza rely upon labor-intensive parenteral injection. A more advantageous vaccine would be capable of administration by mass immunization methods such as spray or water vaccination. A recombinant vaccine (rNDV-AIV-H7) was constructed by using a lentogenic Paramyxovirus type 1 vector (Newcastle disease virus [NDV] B1 strain) with insertion of the hemagglutinin (HA) gene from avian influenza virus (AIV) A/chicken/NY/13142-5/94 (H7N2). The recombinant virus had stable insertion and expression of the H7 AIV HA gene as evident by detection of HA expression via immunofluorescence in infected Vero cells. The rNDV-AIV-H7 replicated in 9-10 day embryonating chicken eggs and exhibited hemagglutinating activity from both NDV and AI proteins that was inhibited by antisera against both NDV and AIV H7. Groups of 2-week-old white Leghorn chickens were vaccinated with transfectant NDV vector (tNDV), rNDV-AIV-H7 or sterile allantoic fluid and were challenged 2 weeks later with viscerotropic velogenic NDV (vvNDV) or highly pathogenic (HP) AIV. The sham-vaccinated birds were not protected from vvNDV or HP AIV challenge. The transfectant NDV vaccine provided 70% protection for NDV challenge but did not protect against AIV challenge. The rNDV-AIV-H7 vaccine provided partial protection (40%) from vvNDV and HP AIV challenge. The serologic response was examined in chickens that received one or two immunizations of the rNDV-AIV-H7 vaccine. Based on hemagglutination inhibition and ELISA tests, chickens that received a vaccine boost seroconverted to AIV H7, but the serologic response was weak in birds that received only one vaccination. This demonstrates the potential for NDV for use as a vaccine vector in expressing AIV proteins.

Evaluation of a commercial avian influenza (H7N2) vaccine for protection in turkeys against an avian influenza virus (H7N2) isolated from turkeys in Virginia during 2002

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During the spring of 2002, a low pathogenic avian influenza (LPAI) A (H7N2) virus caused a major outbreak in commercial poultry in Virginia and adjacent states. The low pathogenic avian influenza (LPAI) virus primarily affected turkey flocks causing respiratory distress and decreased egg production. Experimentally, turkeys were more susceptible than chickens to H7N2 virus infection and higher titers of infectious virus could be recovered from the oropharynx in comparison to the cloaca. The outbreak of H7N2 virus raised concerns regarding the availability of vaccines that could be used for the prevention and control of this virus in poultry. We sought to determine if an existing

commercial AI vaccine prepared from a 1997 seed stock virus could provide protection against a 2002 LPAI H7N2 virus isolated from a turkey (A/Turkey/Virgina/158512/02 [TV/02]) in Virginia that was from the same lineage as the vaccine virus. The inactivated AI vaccine, prepared from A/Chicken/Pennslyvania/21342/97 (CP/97) virus, significantly reduced viral shedding from vaccinated turkeys in comparison to sham controls, but did not prevent infection. The protective effect of vaccination correlated with the level of virus-specific antibody as a second dose of vaccine increased antiviral serum IgG and hemagglutination inhibition (HI) reactivity titers in two different turkey age groups. Serum from CP/97-vaccinated turkeys reacted equally well to CP/97 and TV/02 antigens by HI and ELISA. These results demonstrate the potential benefit of using an antigenicly-related 1997 H7N2 virus as a vaccine candidate for protection in poultry against a H7N2 virus isolate from 2002.

Antigen-induced IFN-γ, nitric oxide, and TNF-α production by blood mononuclear cells from *Mycobacterium bovis*-infected cattle: diagnostic implications.

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Bovine tuberculosis in the United States has proven costly to cattle producers as well as government regulatory agencies. While in vivo responsiveness to mycobacterial antigens is the current standard for the diagnosis of tuberculosis, in vitro assays are gaining acceptance, especially as ancillary or complimentary tests. To evaluate in vitro indices of cellular sensitization, antigen induced interferon (IFN)-γ, nitric oxide (NO), and tumor necrosis factor (TNF)-α responses by blood mononuclear cells from *Mycobacterium bovis*-infected cattle were quantified and compared. Using an aerosol model of infection, two doses each of two strains of *M. bovis* (95-1315 and HC-2045T) were used to induce a range of IFN-γ, NO, and TNF-α responses. Infection specific increases in NO, but not IFN-γ or TNF-α, were detected in nonstimulated cultures at 48h, indicative of nonspecific activation and spontaneous release of NO. The infective dose of *M. bovis* also influenced responses. At 34d postinfection, IFN-γ, NO, and TNF-α responses in antigen-stimulated cells from cattle receiving 10^5 cfu *M. bovis* were greater than responses of cells from cattle infected with 10^3 cfu *M. bovis.* The NO response, but not IFN-γ and TNF-α responses, was influenced by infective strain of *M. bovis*. TNF-α, NO, and IFN-γ responses followed similar kinetics with strong positive associations between the three readouts. Overall, these findings indicate that NO and TNF-α, like IFN-γ, may prove useful as indices for the diagnosis of bovine tuberculosis.

Working Group Reports

Immunity and Disease Resistance

Immunointervention

Immunity and the Pathogenesis of Diseases

Nutrition and Immune Function Interations

Immunity and Disease Resistance

Working Group Leaders:

- Lanie Bilodeau, Immunologists, Catfish Genetics Research Unit, ARS, Stoneville, MS
- Lou Gasbarre, Research Leader, Bovine Functional Genomics Research Unit, Animal and Natural Resources Institute, ARS, Beltsville, MD
- Michael H. Kogut, Immunologist, Southern Plains Agricultural Research Center, ARS, College Station, TX
- Joan Lunney, Immunologist, Animal Parasite Diseases Laboratory, Animal and Natural Resources Institute, ARS, Beltsville, MD

Research Priority 1

Identification of genes defining host disease resistance

1. Background: There is a need for identification and characterization of genes that confer host resistance to important production and foodborne diseases. Studies must determine whether it is possible to identify food animal species that have the potential to be "healthier."

2. Issue: Identification and characterization of genes defining host disease resistance will enable producers to reduce disease incidence using genomic approaches. Alternately, identifying disease resistant animals may reveal new approaches for disease control.

3. Research Objectives:

A Identify/develop commercial/experimental animal resource populations for identification and mapping of immunologically relevant genes

B. Identify and characterize host genes that control important immunologic responses; determine whether alleles of certain genes would enhance animal health

C. Define important genetic polymorphisms that affect host resistance/susceptibility

D. Define gene expression patterns and regulatory phenomena that affect the level of host resistance

E. Utilize genomic information to reveal new approaches for disease control or biotherapeutic production

4. Proposed Accomplishments:

A. Mapping projects will identify informative populations for disease studies. These can then be linked with known populations and commercial breeding stock. Information gained can be used to plan modification of populations for specific production/health issues

B. Information will be developed on correlation of disease resistance phenotype with desired production traits by phenotyping for disease resistance traits using high throughput (HTS) immune and disease screens coordinated with production parameters. This will prove relevance for utilization of disease resistance in commercial populations/genomic stock

C. Expansion of gene expression/regulation approaches, includes microarray [targeted and full genomic], real-time RT-PCR, proteomic studies, RNAi technology, leading to a more thorough understanding of disease resistance mechanisms
D. Expanded knowledge of targeted genomic areas, Immunoglobulin (Ig), T cell receptor (TCR), major histocompatibility (MHC), pattern recognition receptors (PRR), Toll-like receptor (TLR) pathways, and their impact on health and disease

5. Proposed Collaborations: Work with scientists in NP101 and NP106 programs to utilize genomics tools developed; similarly; work with national (NRSP008) and international genome efforts, e.g. sequencing and microarray projects; work with national swine PRRS initiative to target specific disease.

6. Anticipated project duration: Significant progress should be made across taxa for gene identification/characterization studies within 5 years.

7. **Impact:**

A. Markers/genes regulating disease resistance will be identified. This information will be used for developing allele tests, e.g., single nucleotide polymorphisms (SNPs) for fast, effective identification of resistant animals; for marker assisted selection (MAS) approaches to increase frequency in target populations; or for development of transgenic or clone lines of disease resistant animals
B. Definition of novel mechanisms of protective immunity. Apply information gained from genomics to developing new biotherapeutics, vaccine approaches (with APHIS).
C. Develop approaches for diagnostics and new rationales for immune control of diseases

Research Priority 2

Induction/regulation of immune responses through mucosal surfaces

1. Background: Many infectious diseases enter through respiratory and gastrointestinal tissues and infect though 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.

2. Issue: Identification of pathogen uptake sites/mechanisms will enhance understanding of immune responses. Pathogen entry occurs largely across mucosal membranes. In addition to uptake, the study of induction/regulation of immune responses through mucosal surfaces are needed

3. Research Objectives:

A. Define cell populations/subsets that affect resistance at mucosal surfaces; determine how neonatal development affects these populations.
B. Define gene expression patterns and regulatory phenomena that affect the level of host resistance at mucosal surfaces.
C. Use information from microbial genomics to define substances from pathogens that stimulate/regulate immune responses at mucosal surfaces.
D. Define the affects of stress/diet/age on immune responses at mucosal surfaces.

4. Proposed Accomplishments:

A. Identification of regional (respiratory, intestinal, reproduction, skin) areas of infection/points of uptake; Determination of mucosal cell populations involved in disease processes; Development of immune tools to assess immune cell subsets regulating responses; Determination of age-related development associations with infection; Development of gene expression/regulation approaches and reagents to quantitate chemokines and cytokines.

B. Determine relationship of infection kinetics (in blood/specific mucosal tissues) and mucosal immune function; Identification of relevant genes controlling infection processes, e.g., TLR, anti-microbial peptides; MHC genes involved.

C. Application of microbial genomics information to probe critical microbial genes influencing host disease response and means, or mechanisms, of pathogen invasion/evasion/infection.

5. Proposed Collaborations: Interactions with university scientists through NC projects; with international researchers through UK BBSRC, Spain INIA; with commercial producers/animal health companies

6. Anticipated project duration: Significant progress should be made across taxa for gene identification/characterization studies within 5 years.

7. **Impact:**

A. Definition of local protective defense mechanisms; Definition of pathways for interventions, for development of both traditional and therapeutic vaccines, and for preparation of novel mucosally targeted biotherapeutics

B. Improved vaccine efficacy; verification of efficacy of mucosal delivery vectors and adjuvants.

C. (with APHIS) Develop approaches for diagnostics and rationale for immune control of diseases

Research Priority 3

Induction/regulation of innate responses; influence/regulation of acquired immunity

1. Background: The role of innate immunity, and its influence on acquired immunity, for disease control are still undefined for most agricultural species. Research in this area will influence development of treatments/vaccines/therapeutics, and improve management practices**.**

2. Issue: The induction/regulation of innate immunity affects disease kinetics, disease resistance, and ultimately animal production. Determination of induction/regulation mechanisms of innate responses, and their influence on the effectiveness of acquired and protective anti-disease immunity, is needed**.**

3. Research Objectives:

A. Define cell populations/subsets that affect innate immunity.

B. Define gene expression patterns and regulatory phenomena that affect the level of host innate immunity.

C. Use information from microbial genomics to define substances from pathogens that stimulate/regulate innate immune responses; identify the evolutionarily conserved molecular constituents (PAMPs) of infectious microbes.

D. Define the affects of stress/diet/age on innate immune responses

4. Proposed Accomplishments:

- **A.** 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. Expression levels of PRR on effector cells of innate immunity (macrophages, NK cells, granulocytes, epithelial).
- **B.** Identification of pathogen-associated molecular patterns (PAMPs) and their interaction with PRR will inform pathogen control measures and help identify new biotherapeutics.
- **C.** 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 role of innate and acquired immunity in disease kinetics.
- **D.** Knowledge of development/regulation of immunity in neonates/early developmental stages
- **E.** Effect of stress and nutritional status on innate immune function.

5. Proposed Collaborations: Interactions with university scientists through NC projects; with international researchers through UK BBSRC, Spain INIA; with commercial producers/animal health companies

6. Anticipated project duration: Significant progress should be made across taxa for gene identification/characterization studies within 5 years.

7. Impact: Identification of animals with broader spectrum disease resistance Development of Biotherapeutics; Definition of Local protective defense mechanisms; Identification of innate immune pathways for interventions/traditional and therapeutic vaccines and for development of new adjuvants and improvement of vaccine efficacy

Research Priority 4

Bioinformatics

1. Background: Improvements in genomics technologies have led to high-throughput sequencing which generates large data sets that require bioinformatics tools and computing power necessary for analysis. Currently, the infrastructure does not exist for handling agency-wide, or in some cases unit-level, collation of data and extensive analyses. These resources need to be developed at the unit, area, agency and national levels.

2. Issue: Large volumes of data are generated that are difficult to analyze. For this reason, bioinformatics and genomics resources need to be developed and integrated into ARS programs and research units.

3. Research Objective:

- A Develop standardized bioinformatics tools and resources that can be utilized by multiple programs and research units.
- B. Develop tools/databases for species sequence, data mining

4. Proposed Accomplishments:

- A. Improve high-powered computer support and information exchange/accessibility. Tools/Statistical analyses of disease mapping info that adjust to population structure and enable efficient data management. Analysis tools and MAS approaches

B. Improved *in silico* study tools, e.g., comparative analysis tools; improved annotation tools
D. Proteomics-based tools

5. Proposed Collaborations: Nationally centered bioinformatics resources but species relevant NSRP-8 and TIGR as potential resources; Need for Long term funding for maintenance and updating of websites

6. Anticipated project duration: Significant progress should be made across taxa for gene identification/characterization studies within 5 years.

7. Impact: Utilize genome sequencing information (animals, microbes); Eliminate redundancy;Improved comparative bioinformatics; Improved information exchange. Tool availability for broader animal health community; In silico tools for efficient vaccine development

Research Priority 5

Enhance Immune Toolkit for major food animal species

1. Background: Basic tools to measure details of immune responses in major food animal species are not available or critical components are missing. For example, there are insufficient panels of monoclonal antibodies (mAb) that identify and quantitate CD antigens on immune cell surfaces, chemokines and cytokines; molecular probes and assays for immune markers; cloned and expressed bioactive chemokines and cytokines. Availability of quality targeted immune gene microarrays will be another important resource.

2. Issue: Because of limited markets for these products, production of high quality reagents is often left to researchers; for some species commercial sources of these reagents are limited or non-existent.

3. Research Objectives:

A. Establish national and international networks to develop priorities for toolkit needs for each species.
B. Coordinate tool development so that priority reagents become available. Work with commercial sources to market products. Simultaneously work with repositories to have independent sources of hybridoma cell lines and expression vectors for cloned and expressed bioactive chemokines and cytokines so that researchers can produce large quantities for research efforts.

4. Proposed Accomplishments:

A. Panels of reagents, mAb, cloned and expressed bioactive chemokines and cytokines, immune gene microarrays, will be available to researchers for their disease resistance studies
B. Critical control points in disease processes, and in immune events controlling these processes, will be revealed
C. Technology transfer opportunities will be expanded

5. Proposed Collaborations: Interactions with university scientists through NC projects; with international researchers through UK BBSRC, Spain INIA; with commercial producers/animal health companies. Need for long term funding for maintenance and updating of immune toolkit websites

6. Anticipated project duration: Significant progress should be made across taxa for gene identification/characterization studies within 5 years.

7. Impact: Effective tools to explore phenotyping animal immunity, to determine protective immune responses, to confirm bioactive therapeutics. Tools to quantitate immune responses, to validate models of immunity, to assess differential genetic responses of resistant/susceptible to infectious disease challenges

Note: Specific disease targets will be based on stakeholders' priorities.
Research Priorities have been listed but numbers do not indicate relative priorities since all approaches are needed for maximal impact on improving disease resistance.

Immunointervention

Working Group Leaders:

- Marcus Kehrli, Research Leader, Virus and Prion Diseases Research Laboratory, National Animal Disease Center, ARS, Ames, IA
- Hyun Lillehoi, Immunologist, Animal Parasite Diseases Laboratory, Animal and Natural Resources Institute, ARS, Beltsville, MD
- David White, Veterinary Medical Officer, Arthropod-borne Animal Diseases Research Laboratory, ARS, Laramie, WY

Research Priority 1

Identify mechanisms of innate immunity and their regulation critical in control of animal diseases.

1. Background: Many diseases are not amenable to control by traditional vaccination approaches because they are caused by an array of antigenically distinct opportunistic pathogens. Moreover, these opportunistic diseases are often associated with stress, broad-based immune impairment and/or overwhelming pathogen exposure. Some of these diseases may be better controlled by modulation of the innate immune system at critical growth/production stages to improve the host's capacity to resist opportunistic infections and disease.

2. Issue: There is a lack of knowledge about factors regulating humoral and cellular components of innate immunity.

3. Research Objectives:

A. Identify critical components of innate immunity in cattle, pigs and poultry and how they are regulated.

B. Develop effective strategies to evaluate the innate immune response in domestic livestock and poultry, including neonatal and embryonic immunity, innate immune cell function (neutrophils, NK cells, etc.), accessory cell function, and assay development for immunological reagents.

C. Identify inter-relationships between innate immunity and adaptive immunity in cattle, pigs and poultry, and how innate immunity can impact host adaptive immune responses to vaccination or natural infection.

4. Proposed Accomplishments:

A. Identification of various receptors and cell signaling pathways in livestock that trigger innate immunity. This should also offer insights on how to regulate the activation of innate immunity.

B. More effective methods to evalute methods of immunointervention of the innate immune system.

C. Identification of key regulatory relationships between the innate and adaptive immune systems. This will provide insight on what critical innate co-stimulatory factors are needed to generate an efficacious immune response.

5. Proposed Collaborations: Appropriate ARS CRIS projects, various university collaborations, and pharmaceutical and biologics companies.
6. Anticipated project duration: 5+ years
7. Impact:

A. Increased understanding of critical innate immunity components in livestock will provide a knowledge base that can be exploited to make science-based decisions to reduce disease incidence and severity through targeted immunointervention techniques.
B. Increased ability to screen modulators of innate immunity against specific pathogens.
C. Increased understanding of how innate immunity impacts vaccine responses in livestock will provide a knowledge base for better adjuvant and costimulatory molecule inclusion in vaccines, thus improving vaccine efficacy.

Research Priority 2

Identify vaccines that elicit protective cell-mediated immunity

1. Background: Traditional approaches to disease control have been through vaccination to generate protective antibody responses. Many diseases have been effectively controlled by this approach. However, most animal diseases that persist as problems in the U.S. today have not been amenable to control by these traditional approaches. One explanation of how these pathogens remain uncontrolled is the absence of an appropriate protective immune response. Some pathogens may evade the immune system through many mechanisms and may require generation of antigen-specific cytotoxic T-cells to be appropriately controlled. Identification of protective immune responses to the proper antigens requires immunological tools not currently available for widespread use in livestock or wildlife that are important for us to control.
2. Issue: Traditional methods of assessing vaccine efficacy are to measure antibody responses and protection against disease challenge. Unfortunately antibody responses are not always predictive of a protective immune response against live pathogen challenge. We need better tools to assess cell-mediated immune responses in all livestock species.
3. Research Objectives:

A. Develop new methods in livestock for detecting and measuring cell-mediated immunity.
B. Identify antigens critical for the development of cell-mediated immunity.
C. Identify methods to regulate the development of cell-mediated immunity.
D. Develop antigen delivery systems (expression vectors for various host animal species to be used for emerging diseases) that target immune system compartments (mucosal, peripheral, reproductive tract and other privileged sites).
E. Explore effects of modulation or elimination of T-regulatory cell subsets on induction of protective responses in domestic animals and poultry. Develop novel immunomodulators to suppress regulatory cell.

4. Proposed Accomplishments:

A. Tools for measuring cell-mediated immunity will enable discovery, development and approval of new effective vaccines with cell-mediated immunity label claims.

B. Methods to predict and select appropriate pathogen antigens for incorporation into vaccines driving cell-mediated immune responses will enhance our response time in the event of emerging diseases.
C. Understanding the regulatory factors that contribute to an effective cell-mediated immune response will allow us to create vaccines that do a better job of stimulating immunity than the pathogen does by itself.
D. An improved capacity to rapidly develop vaccines against new and emerging pathogens.

5. Proposed Collaborations:

6. Anticipated project duration: 5 years +

7. Impact:

A. Vaccines that aid in the control of diseases not currently effectively controlled.
B. More rapid vaccine discovery and approval.
C. Better methods to elicit and control immune responses requiring cell-mediated immunity.
D. An increased capacity to rapidly respond to emerging disease outbreaks.

Research Priority 3

Identify vaccines that elicit protective humoral immunity

1. Background: Some pathogens elicit strong humoral immune responses that are not highly protective. The survival of these pathogens may depend on their ability to divert the efforts of the immune system towards antigens that do not facilitate their clearance from the host.

2. Issue: There is a lack of basic knowledge in what drives successful humoral immune responses against certain pathogens. More indepth knowledge on regulation of immune responses in different compartments (e.g., respiratory tract, intestinal tract, reproductive tract, mammary gland) of the body is needed to better guide vaccine discovery and development into commercial products.

3. Research Objectives:

A. Identify factors regulating antibody responses to antigens.
B. Develop computational methods to increase the efficiency of the design and testing of vaccines.
C. Develop allied testing methods to distinguish between vaccinated and naturally infected animals.
D. Develop broad spectrum, targeted delivery systems (target dendritic cells or others) for immunomodulator and/or peptide and/or DNA delivery to effector cells.
E. Elucidate factors affecting efficacy of current adjuvant systems in domestic animals (i.e. optmized CpG sequences for all livestock species) and develop new immunoadjuvants from novel sources (snake venoms, modified superantigens, probiotics as adjuvants, cytokines – IL-15, hormones, vitamins and trace minerals, carotenoids, phenolics, etc.).
F. Delineate the specific conditions required for several different broad-based protein or nucleic acid delivery systems – i.e. needle-less systems, microgels, biodegradable depot systems, *in ovo* injector systems – while concentrating on important factors such as multiple use strategies, limiting the injected volume,

and livestock or wildlife behavioural responses (fear and/or aggression in response to noise or pain) to ensure field practicality. Evaluate natural delivery agents (i.e. viruses that cross the placenta naturally to deliver nucleic acids to the developing fetus).

4. Proposed Accomplishments:

A. A better knowledge base of how antibody genes are selected and arranged for various classes of antigens, we can more effectively design next generation vaccines.
B. By leveraging the knowledge database from human disease research, we will build a comparative immunology database that can be a guide to antigen selection for use in vaccines.
C. Marked vaccines to distinguish vaccinates from natural infection.
D. Adjuvant development (i.e. CpG) and/or delivery, peptide or DNA delivery (i.e. microgels, biodegradable depot systems).
E. Adjuvants and immune modulators that target more effective immune responses.
F. Broad-based delivery systems applicable to both livestock and wildlife that account for the practical realities of immunization in the field – especially in the case of wildlife, where very little information exists on the efficacy and reliability of strategies used in domestic livestock and poultry.

5. Proposed Collaborations:

6. Anticipated project duration: 5 years +

7. Impact:

A. Vaccines that aid in the control of diseases not currently effectively controlled.
B. More rapid vaccine discovery and approval.
C. Marked vaccines will enable eradication programs once disease prevalence is below a certain economic threshold.
D. By partnering with industry early in the antigen selection process we will better ensure viability of developed products.
E. Effective strategies to immunize and modulate the responses of domestic animals and wildlife benefit agriculture by lesser manipulation of animals and lesser exposure to adjuvants that may impact meat or hide quality.
F. Effective strategies to immunize wildlife will significantly decrease the risk of disease in domestic animals because of a reduction in the size of the reservoir, both in the U.S. and abroad.

Research Priority 4

Develop immunological reagents for domestic animals, poultry, and wildlife that are necessary to aid in the control of diseases we face today.

1. Background: Although many significant advances have been made in the past 3 decades, cutting-edge research into host immune responses in domestic animals and wildlife has been hampered by the cost of developing the necessary reagents and tools of immunological research. These include but are not limited to species-specific cytokines, effector molecules, and receptors, and monoclonal antibodies against each. These tools can be identified and made available with the necessary resources and investment to produce them. However, mechanisms need to be in place to allow production and sharing of these reagents at reasonable costs.

2. Issue: Reagents for the evaluation of immunological parameters in domestic animals and wildlife are severely lacking. Moreover, syngeneic animals or protocols for culture and preservation of immunological cells are necessary for many studies of basic immunological function.

3. Research Objectives:

A. Identify an appropriate infrastructure with the capacity to express various recombinant proteins and produce monoclonal antibodies against them. This may represent a government "subsidized" company that in turn recovers some of their manufacturing costs through the sale of these reagents to researchers around the world.

B. Clone, express in native form, characterize, and develop antibodies to MHC Class I and II, acute phase proteins, complement proteins, cytokines, antibody isotypes, innate immune system receptors (TLR's and others), effector molecules (i.e. perforin, granzyme, etc.), adhesion molecules, and cell surface markers of lymphocyte subsets for relevant domestic livestock and poultry species. House these reagents in some sort of centralized facility (either government or corporate) while balancing the free exchange of reagents for research purposes with the patent and intellectual property rights that will make them viable commercial products. Use the NIH Tetramer core facility as a model of a government-run facility for vital research reagents.

C. Develop strategies to produce syngeneic domestic livestock strains (inbreeding) or alternatives to fully syngeneic animal development through *in vitro* manipulation immune cells and/or developing MHC-matched animal lines.

D. Improve production and reduce cost of protein or nucleic acid substrates to make these strategies viable to animal production systems through high efficiency, scalable fermentation or synthesis processes that will produce native (or at least bioactive) protein.

4. Proposed Accomplishments:

A. A centrally-maintained research facility that provides high-quality reagents to researchers worldwide for the evaluation of immunological parameters in domestic livestock and poultry.

B. A reasonably priced supply of new immunological reagents for use in livestock, poultry and wildlife research.

5. Proposed Collaborations:

6. Anticipated project duration: 5 years+ (ongoing supplier)

7. Impact:

A. Availability of new immunological reagents will increase the number of laboratories capable of investigating host immune responses against disease.

B. Increasing the number of laboratories investigating immunity against disease with modern immunological reagents and tools will increase the probability of identifying new and more efficacious means of immunointervention.

C. New avenues of research not currently possible will be opened up for scientists to follow.

Research Priority 5

Disease challenge models are needed for many diseases affecting domestic animals and wildlife.

1. Background: Appropriate disease challenge models will be needed to accurately predict the success of any method of immunointervention in livestock or wildlife. It is possible to not recognize successful methods of immunointervention in instances where the model has an overwhelming pathogen challenge not representative of the natural disease exposure. Animal disease researchers have the unique opportunity of working in the natural host for most diseases that are studied, but reliable evaluation of intervention strategies requires standardized models and conditions that allow for the delineation of intervention effects. Make protocols and strains of pathogens used in models freely available to any interested researcher. Use models to elucidate immune functions relevant to protection from infection or disease, duration of immunity from different intervention protocols (dose, route, formulation, and timing vs. generation of lifelong immunity), and biomarkers of relevant clinical endpoints for testing and future efficacy evaluation. Finally, use models to define immunogenic relationships within and between pathogens to allow for the development and evaluation of cross-protection between vaccine components or interference between immunomodulatory agents.

2. Issue: Models may fail to accurately predict the outcome of immunointervention strategies in the "real world".

3. Research Objectives:

A. Develop challenge models for diseases of domestic animals and wildlife.
B. Develop generalist *in vivo* tests of immune function that are predictive of disease outcome.

4. Proposed Accomplishments:

A. Models of disease will help both in the development and continuing evaluation of immunointervention strategies.
B. Biomarkers of immunointervention success will enhance our capacity to screen for the most efficacious method to elicit a protective immune response.

5. Proposed Collaborations:

6. Anticipated project duration: 5 years

7. Impact:

A. More rapid and uniform testing of immunointervention strategies across laboratories.
B. Biomarkers that may be used in large scale studies on efficacious immunointervention strategies will reduce the cost of identifying new disease control methods.

Research Priority 6

Vaccine vigilance

1. Background: There are consequences of vaccination that we need to assess to ensure we are not adversely affecting livestock performance and well-being.

2. Issue: There is a need to investigate and characterize immunopathological mechanisms in domestic livestock and poultry.

3. Research Objectives:

A. Characterize hyper-responsiveness of the immune system, as an allergic reaction (i.e. peanut allergy), an adverse response to immunointervention, or as a part of other physiopathological processes (i.e. pulmonary hypertension syndrome in chickens, autoimmune utiligo in chickens).
B. Create a database of field response rates and adverse event rates for evaluation of current and future vaccine efficacy.
C. Characterize field variation of important pathogens and assess its impact on vaccine failure.
D. Develop strategies for inclusion of multiple strains of the same pathogen, or multiple pathogens, in a single vaccine dose while avoiding the problems of immunodominance/original antigenic sin, antigen overload, and induction of tolerance.
E. Optimize use of existing vaccines and immunomodulators for intervention at embryogenesis, birth, weaning, or prior to stress (shipping, comingling, slaughter).
F. Develop *in vitro* assays for efficacy and safety of immunointervention agents and/or insults to the immune system.

4. Proposed Accomplishments:

A. Fewer adverse event reports.
B. Centralized database of vaccine usage and adverse events will lead to better monitoring of efficacy and failure. This database could be developed in conjunction with a broader database of "animal passports/ID".
C. Vaccines that are more producer-friendly through reduced animal manipulation while retaining the efficacy of individual preparations. Vaccines would also be of great use in wildlife management because of decreased need for contact and manipulation of wildlife.
D. Ensure efficacy of modulation of relevant immunological endpoints in well-controlled experiments.
E. Assays would be developed that not only evaluate the immunogenicity of relevant immunity in different systems, but that can also be used to predict those factors for screening of novel compounds for continuing development of immunointervention agents. Assays would concentrate on markers of relevant immunity and/or clinical endpoints and not on simple antigen quantitation.

5. Proposed Collaborations: Industrial partners, Food and Drug Administration

6. Anticipated project duration: 5 years+

7. Impact:

A. Reduction in adverse reactions to vaccines.
B. More optimal use of vaccines.

Immunity and the Pathogenesis of Diseases

Working Group Leaders:

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Research Priority 1

Characterization of immunity in the newborn

1. Background: Immunointervention strategies for food producing animals are primarily targeted at neonatal/juvenile animals. Additionally, optimal development during the neonatal period is critical for attainment of full production of the animal. Immune development (ontogeny) and host/pathogen interactions of newborn livestock and poultry, however, are poorly characterized.

2. Issue: Numerous developmental, maternal, environmental, and infectious factors influence immune responses elicited by neonates. Characterization of these influences on immune development would enhance strategies to improve immunity.

3. Research Objectives:

A. Determine the impact of maternal immunity on neonatal protection and immune response

B. Determine the responses of neonates to vaccines

C. Determine the impact of animal husbandry and environmental factors on neonatal immunity

4. Proposed Accomplishments:

A. Identified parameters of immune competence in the newborn

B. Optimized vaccine strategies for level and duration of immunity

C. Develop new tools for evaluation of immune competence

5. Proposed Collaborations: Collaborations within ARS – across facilities, CRIS projects, and disciplines are in place as well as collaborations with industry and academic institutions. Additional collaborations should be added as needed. Certain aspects of the project will require international collaborations (e.g., Asia, United Kingdom, Australia, New Zealand, South Africa), of which many are already established.

6. Anticipated project duration: Considering the breadth and impact of this project, it will likely be an on-going project.

7. Impact: Improved strategies to enhance neonatal immunity will result and thereby improving production. More specifically, improved methods to enhance vaccine strategies targeting the neonate and maternal immunity as well as methods to limit factors

(e.g., environmental, husbandry, nutritional) that negatively impact neonatal immune development will result.

Research Priority 2

Determination of protective immunity to infectious diseases

1. Background/Issue: An understanding of protective immunity is often required for development of successful strategies to limit disease. Unfortunately, specific protective mechanisms for most infectious diseases of food producing animals are not known.
2. Issue: Our understanding of protective immunity and how to assess it is limited. As a result, this limits advances in development of immunity and immune strategies to control infectious diseases.
3. Research Objectives:

A. Develop and validate challenge models for vaccine efficacy

B. Determination of mechanisms of protection

4. Proposed Accomplishments:

A. Develop validated vaccine challenge models

B. Identify mechanisms of immune protection

5. Proposed Collaborations: Collaborations within ARS – across facilities, CRIS projects, and disciplines are in place as well as collaborations with industry and academic institutions. Certain aspects of the project will require international collaborations (e.g., Asia, United Kingdom, Australia, New Zealand, South Africa), of which many are already established.
6. Anticipated project duration: In general, these are on-going projects with specific program funding.
7. Impact: Establishment of infection model systems and correlates of protection will enhance our ability to develop effective immunointervention strategies.

Research Priority 3

Regulation of the immune response in control of disease

1. Background/Issue: Exacerbation or induction of disease often results from inappropriate or excessive host responses. Understanding mechanisms of how immunity impacts disease development and resolution will improve our ability to control disease.
2. Issue: Some diseases result from the host immune response. Lack of understanding of this phenomenon for specific diseases has limited progress in prevention and treatment strategies. Important to this issue is the development of and/or sharing of reagents (such as monoclonal antibodies) which allow measurement and characterization of specific components of the immune response.
3. Research Objectives:

A. Determine the mechanisms of immunosuppression

B. Determine the mechanisms of pathogen persistence

C. Determine the role of autoimmunity in disease pathogenesis

4. Proposed Accomplishments:

A. A determination of the role of pathogen persistence in morbidity and mortality

B. An understanding of the role of immunosuppression in pathogenesis of disease

C. New strategies to minimize autoimmunity in infectious disease following pathogen exposure

5. Proposed Collaborations: Collaborations within ARS – across facilities, CRIS projects, and disciplines are in place as well as collaborations with industry and academic institutions. Additional collaborations should be added as needed. Certain aspects of the project will require international collaborations (e.g., Asia, United Kingdom, Australia, New Zealand, South Africa), of which many are already established. Develop a collaborative network for reagent development and exchange.

6. Anticipated project duration: Due to this projects inherent complexity, the project duration is difficult to define.

7. Impact: Improved methods to limit immune-associated disease and persistence of pathogens thereby increasing production and decrease spread of disease, respectively.

Nutrition and Immune Function Interactions

Working Group Leaders:

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Research Priority 1

Defining nutrition related biomarkers that measure risk of disease.

1. Background: Risk of disease during periods of physiological stress, such as birth, lactation, weaning, vaccination, ageing, metabolic disease, etc, can be ameliorated by appropriate nutritional support and intervention strategies.
2. Issue: Nutritional biomarkers to assess optimal health, recommendations for nutritionally based interventions and monitoring of biomarkers to predict clinical outcome are needed.
3. Research Objective:

A. Evaluate markers of immune function and status that respond to nutritional modification.

B. Identify dietary components that improve immune function and support optimal health.

4. Proposed Accomplishments:

A. Develop reagents to identify immune markers for food production animals and man that respond to diet.

B. Validate animal models to test nutrient and immune interactions in man.

C. Quantitative risk/benefit evaluation of the dietary strategy to the appropriateness of the response.

D. Identify specific nutrients with beneficial immune modulating properties that optimize immune function.

5. Proposed Collaborations: Develop ARS Nutrition Network to share information on animal and human models of nutrient interaction with immune function. Need for web-based information sharing.
6. Anticipated project duration: Significant progress should be made across species for identification/characterization of biomarkers within 5 years.
7. Impact: Sharing information on the variety of ARS-directed studies on animal models that measure the effect of nutrition on infectious disease and physiological stressors with human models of chronic inflammatory disease will provide a robust evaluation of multi-functional aspects of immune function and eliminate redundancy. This will improve

information exchange and identify novel markers that indicate the status of animal and human health related to diet.

Research Priority 2

Identification of nutrient and gene interactions.

1. Background: Novel dietary biomarkers and their associated genes could identify subpopulations of healthy or animals and humans at risk for disease. Genetic identification in animals of host resistance to important production and foodborne diseases and in humans of risk factors for chronic and genetic diseases is increasing. Collating these data will assist in designing dietary strategies that promote a healthy phenotype.

2. Issue: Identify and characterize genes that define disease risk factors in humans and determine if gene expression is responsive to dietary interventions. Evaluate the effect of nutrition on promoting optimal health in genetically defined disease resistant livestock.

3. Research Objectives:

A. Identify and characterize host genes that control important immunologic responses and determine responsiveness to diet.

B. Define gene expression patterns and regulatory phenomena that are sensitive to diet and affect the level of host resistance

C. Utilize genomic information from human and animal projects to reveal novel nutrient and immune interactions.

D. Evaluate nutrients that activate immune gene transcription elements as modifiers of immune function.

4. Proposed Accomplishments:

A. Mapping projects will identify pathogen and stress resistant livestock populations that can be targeted for nutritional studies related to health outcomes.

B. Technical advances in gene expression/regulation approaches, includes microarray, real-time RT-PCR, proteomic studies, RNAi technology, etc. can be used to evaluate nutrient and gene interactions related to disease, inflammation and stress.

C. Dietary interventions with genetically identified populations at risk for immunologically based diseases such as asthma and allergy, inflammatory bowel diseases, type-2 diabetes, obesity, etc. can be evaluated for efficacy.

5. Proposed Collaborations: Work with scientists in NP101, NP106 and NP107 programs to utilize genomics tools or identify animal models that can be used for nutritional studies. Partner with NIH and the human genome project to identify at risk populations for nutritional studies.

6. Anticipated project duration: Significant progress should be made on gene identification, characterization and the role of nutrition in functional expression studies within 5 years.

7. Impact:

A Integrated strategies for control of pathogens and stress in livestock as well as inflammatory diseases in humans will include dietary recommendations.

B. The emergence of genetic profiles will include dietary recommendations for human life style and animal management to optimize health.

Research Priority 3

Nutrient-dependent regulation of innate and acquired immunity.

1. Background: Immunological stress affects nutrient partitioning and nutrient utilization affects immune system efficacy. Appropriate nutritional interventions will affect most components of innate and acquired immunity and influence disease susceptibility, vaccination, immunological memory, and the appropriateness and regulation of a balanced immune response.

2. Issue: Maintenance of optimal health and its restoration following stress from infection or inflammation are dependent on adequate nutrition. Improved understanding of the interaction between innate and acquired immunity and the mechanisms of immune regulation will provide an opportunity to examine specific nutrient requirements for these responses.

3. Research Objectives:

A. Define the affects of diet on stress and age-related changes in innate and acquired immunity.

B. Define the effect of diet on the ontogeny of the immune system and interventions that provide a balanced response to stress and disease.

C. Evaluate the role of immunity in specific nutrient uptake from the intestine.

D. Define specific nutrient requirements for effective and appropriate vaccination and immunological memory, and for amelioration of periods of immune deficiency such as during pregnancy, parturition, pediatric development, ageing, stress, etc.

F. Evaluate the role of nutrition in the amelioration of inflammation and immune pathogenesis.

4. Proposed Accomplishments:

A. Knowledge of nutrient requirements for the development and regulation of immunity in mothers, neonates and the elderly.

B. Shared discoveries on the role of specific nutrients in cell and tissue function including receptor mobility, cell signaling pathways, regulation of transcription, mucosal barrier function and physiology, trace mineral-dependent enzymatic activity, reactive oxygen and nitrogen species, lipid inflammatory mediators, carbohydrate glycosyltransferases, oral re hydration solutions, neural transmitters, etc.

C. More effective vaccines and bioprophylactics.

D. Nutritional recommendations to improve immune efficacy during periods of stress and disease.

5. Proposed Collaborations: Partnerships with food industry and animal health companies; ARS plant scientists to provide modified and functional food sources; nutritionists involved with nutrient bioavailability.

6. Anticipated project duration: Significant progress in immune regulation and nutrient interactions are assured given the high level of interest.

7. Impact:

A. Provide recommendations for specific nutrients that contribute to reduced stress and enhanced disease resistance.

B. Identification of nutrients required for improved vaccine efficacy.

C. Provide identification of diets that enhance immune development and reduce inflammation.

Research Priority 4

Nutrition and applied immunology

1. Background: Food ingestion and the nutrients provided affect resident microflora in the oral, urogenital and gastrointestinal track, and interact with neural and endocrine pathways to reduce stress. Functional nutrient deficiencies or excess affect the balance of the immune system leading to inflammation or inappropriate responses to infection or stress.

2. Issue: Extend the matrix of information to include indirect interactions between nutrients and the immune system as well as the role of nutrients as modulators of immune function.

3. Research Objectives:

A. Define probiotic microbial populations that affect immune development and functional resistance at mucosal surfaces and on the efficacy of systemic immunity, and the diets (prebiotics) that support appropriate resident or ingested microbial populations.

B. Establish a repository of microbial strains that benefit host species and apply genetic or selection tools to improve their application.

C. Study the role of specific nutrients as modulators of immune function, regulators of inflammation, and as adjuvants.

D. Evaluate the interaction between diet, environment, behavior and stress on the efficacy of immune function.

4. Proposed Accomplishments:

A. Identification of functional dietary deficiencies or super nutritional intake of nutrients that result from behavior, environment or stress that affect optimal immune function.

B. Establishment of animal models that evaluate the long term consequences of diet on immune function and chronic disease.

C. Definition of the affect of inflammation and immune pathogenesis (obesity, chronic disease, infection, stress) on nutrient uptake and partitioning.

C. Application of genomics information to characterize microbial genes that improve host health by the production of useful metabolics, immune stimulators, and competition for sites of pathogen invasion.

5. Proposed Collaborations: Interactions with food industry and animal health companies; food survey groups; microbiologists; food technologists; EPA; FDA.
6. Anticipated project duration: Significant progress should be visible within 5 years with support of intra structure and cooperation.
7. **Impact:**

A. Definition of patentable food products that affect human and animal immune function.

B. Better understanding of the interaction between dietary choices and environment on immune function and optimal health.

Bibliography of ARS Immunology Research 2000-2003

This bibliography contains selected citations of immunology research being performed at ARS Research Centers throughout the United States. The citations were drawn from the CRIS database maintained by the USDA, Cooperative State Research, Education, and Extension Service (http://cris.csrees.usda.gov/), AgricOLA database at the National Agricultural Library, CAB Abstracts in the United Kingdom, and MedLine at the National Library of Medicine. It is provided to give an overview of the many facets of ARS immunology research.

It is organized alphabetically by State; within each State it is organized alphabetically by the last name of the staff listed.

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Aquatic Animal Health Research

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