COMPARATIVE IMMUNOLOGY-BASED APPROACHES TO VETERINARY DISEASES

Daniel R. Barreda*, Aja M. Rieger, Nicole C. Girard, Shannon D.G.Clarahan
University of Alberta, Canada
(Corresponding author)*

Afolabi F. Eleyinmi
Federal University Technology, Nigeria

Keywords: animal defense mechanisms, comparative immunology, zoonoses, enzooses, animal disease, transmission, diagnosis, prevention, control.

Contents

Summary

In this overview, we cover the basic links between immunity, animal health and disease. We have chosen to focus on the application of comparative approaches to overcome many of the challenges currently facing the veterinary field. Further, comparative analyses of immune parameters become increasingly relevant as we consider the transmission of infectious agents through animal populations and across species boundaries. Where appropriate we make reference to rodent and human studies that complement those studies performed in veterinary species and highlight potential approaches for the diagnosis, treatment and/or prevention of these animal diseases. This constitutes a general guide that should be of potential interest to a wide reading audience.

For additional in depth information readers are referred to the primary scientific papers and review articles that are listed and annotated in the bibliography section of this article.

1. Introduction

The immune system represents a nodal point in the balance between animal health and disease. Functional parameters of immunity are central in the fight against infectious diseases [1]. Unfortunately, deregulation of the complex regulatory networks that compose the immune system can also have dire consequences for the animal host such as those involved in allergic reactions, autoimmunity, and cancer. Despite the progress made in recent decades understanding the pathological basis of animal disease, comparatively little progress has been made to our understanding of the immune parameters associated with these ailments. The one clear exception is the mouse, for which significant resources have been spent to develop state of the art technologies and cutting edge approaches that help us understand the fundamentals of its immune system, the intricacies of host-pathogen interactions, and the contributions of these to host defense mechanisms and disease. Ironically, a quick screen of the available literature on this species quickly yields highly effective approaches to defend against the most challenging of pathogens [2-4], unique methodologies to dissect the complex regulatory mechanisms behind effective immune responses [5-9], and even elegant procedures to regain immune competence when genetics or environmental factors compromise host immunity [10-13]. Achieving equivalent levels of knowledge for all other animals in the short-term would be highly unrealistic. Yet, we continue to become increasingly aware of the dangers associated with underestimating the impact of veterinary issues on animal and human populations alike. New and re-emerging infectious diseases continue to appear, driven by socio-economic, environmental and ecological factors [14]. Their impact continues to be felt globally, and among others, emphasizes the pressing need to critically evaluate the links between wild animal populations, domestic animals, and humans.

In this manuscript, we focus on one developing approach to achieve this: to consider comparative immunology as the basis of initiatives looking to understand the biology of animal disease across several species and manage the potential for infectious disease transmission across animal and human populations. This approach allows us to take advantage of newly developed state-of-the-art technologies and the fundamental knowledge of immune defense mechanisms gained for species such as the mouse, and to increase transferability of resources across research nodes for veterinary species. We describe the link between immunity, animal health and disease and outline the role that comparative approaches can play as we move forward in our understanding of veterinary diseases and in the generation in effective strategies for their control and prevention.

2. Molecular Origins of Animal Immunity

The animal immune system consists of a complex network of specialized cells, tissues, and organs that maintain tissue homeostasis and defend the body against pathogenic organisms. Pathogens have developed diverse and intricate mechanisms to infect their respective animal host(s) and, thus, present a tremendous challenge for the immune system. To counteract this animals have developed a highly integrated multi-layer immune strategy that systematically targets incoming pathogens to prevent their spread

throughout the host and minimize the potential for their transmission to other potential hosts.

The breach of physical barriers protecting animals (e.g. skin, mucus, gut epithelial layers) constitutes a clear indication of the potential for pathogenesis and results in rapid deployment of immune resources. Among others, early events include the engagement of incoming pathogens by resident immune cells at the site of entry and migration of supporting immune cells from peripheral sites. A critical aspect of these initial immune-based events relates to the recognition of the infiltrating pathogen. Its eventual clearance is highly dependent on this recognition, for this leads to the induction of discrete molecular events that will shape the complex array of immune responses to follow. Several families of these recognition receptors exist. Each receptor has the capacity to bind specifically to unique moieties on microbial molecules, and thus these are referred to as pattern recognition receptors (PRRs). In turn, their corresponding microbial moieties are referred to as pathogen-associated molecular patterns (PAMPs). Several PRRs can be engaged upon entry of a single pathogen, for animals have developed the capacity to recognize a variety of PAMPs. This parallel engagement of PAMPs allows for effective multi-parameter based recognition of these pathogens, which reveal microbial signatures that define downstream immune responses.

Pathogen recognition receptors are a critical component of innate immune responses, which also have important soluble and cellular components. The primary role of this arm is to try to destroy incoming pathogens before they have the time to spread and multiply throughout the host. Components of this innate arm are germ-line encoded, and thus are not intrinsically affected by prior contact with infectious agents [15, 16]. They are well represented along entry portals (e.g. gastrointestinal, urogenital and respiratory tracts), and because they do not require prior engagement of microbes for their function, these innate components are already available as pathogens breach the physical barriers protecting the host. Thus, they can rapidly initiate potent antimicrobial mechanisms, and achieve early containment of infiltrating pathogens. This restricts the initial battle to local sites, prevents global activation of the immune system, and minimizes unnecessary expenditure of host energy resources. As such, most of these early responses are potent, local, and short-lived. Historically, this arm of immunity has been considered largely non-specific, but recent identification of tremendous diversity within its members have challenged this view and began to highlight the specificity of these early responses. For example, even within an individual family of PRRs, such as the toll-like receptors (TLRs), members are capable of differentiating and inducing specific responses to a wide array of molecules of bacterial, fungal, viral, and parasitic origins, regardless of whether these PAMPs are derived from intracellular or extracellular compartments [17, 18]. Following recognition, one or more of several classical innate defense mechanisms are deployed to gain early position on microbial advances; for example, these include phagocytosis, production and release of soluble antimicrobial molecules, and activation of complement cascades. The potent nature of these responses means that tissue damage is a common bystander effect, but an important calculated risk if rapid pathogen removal is achieved. If pathogens survive this initial wave of innate antimicrobial responses, due to their own merit (induction/development of effective immune evasion strategies) or due to failure of the host innate components (e.g. improper recognition,

immuno-suppression), additional mechanisms are triggered in an attempt to contain pathogen advances.

Innate responses give way to acquired mechanisms of immunity, having left an important roadmap that will shape and coordinate the development of these highly specific responses. These acquired mechanisms are adaptable and cover a wider geographic range within the host. This systemic feature is necessary, as acquired mechanisms typically do not develop the capacity to engage pathogens until days after these have entered the animal host, giving significant time for that pathogen to have spread. However, this initial lag period (largely devoid of acquired responses but which is dominated with innate antimicrobial responses) is necessary to develop the exquisite specificity characteristic of this acquired arm of immunity. Among others, these include the development of antibodies and of specific lymphocyte subsets that are tailored to attack the now spreading pathogen. Along with acquired responses comes the capacity to generate immunological memory, which allows the animal host to remember pathogens that it has previously encountered. This decreases the lag time required to mount effective responses in future encounters with these pathogens and increases the capacity to activate potent and highly specific antimicrobial responses. This is a handy feature for animal hosts that are largely confined within specific environmental niches, thereby increasing the likelihood of future encounters with the same or related members of a particular pathogen group.

3. Cellular Basis for Effector Mechanisms of Animal Immunity

The variety of immune responses available to battle incoming pathogens is largely a reflection of the repertoire of immune cells found within an animal host. These cells are positioned at potential entry portals for pathogenic microorganisms, are localized within specific tissue microniches, or can be found circulating through the bloodstream. In higher vertebrates, innate responses are mediated by cells such as macrophages, neutrophils, mast cells, basophils, eosinophils, and natural killer (NK) cells. Each occupies discrete compartments within the host environment and displays unique roles depending of the nature of the immune challenge. Macrophages and neutrophils have the capacity to induce phagocytic mechanisms, effectively engulfing and internalizing microorganisms after recognition and binding with specialized receptors [19]. Subsequent mobilization of intracellular granules, followed by the formation of compartmentalized phagolysosomes exposes these microbes to an array of bactericidal enzymes and other soluble chemical factors designed for killing and digestion. Mast cells and basophils are historically recognized for their potent IgE-mediated allergic responses [20, 21]. Yet, these cells are also ideally placed within the host and fulfill a surveillance role that is important in responses to other infectious agents [22, 23]. Even at their resting state they contain significant stores of soluble preformed active products (e.g. histamine, heparin, serine proteases) that can be rapidly released upon pathogen engagement. Further, de novo production of prostaglandin and leukotriene derivatives, cytokines, and chemokines trigger rapid, potent and sustained inflammatory responses [22, 23]. Eosinophils, largely known for their role in anti-parasitic responses, are pleiotropic leukocytes with key functions in the initiation and propagation of inflammatory responses as well as modulation of subsequent adaptive responses [24]. Finally, NK cells are well recognized for their ability to provide a first line of defense

against viral pathogens, through effective killing of virally infected cells [25]. Yet, there are also indications for their protective role against other microorganisms, including bacteria, fungi, and parasites [25]. On the adaptive side of the immune response the classic players include B and T lymphocytes. Whereas B-cells are widely known for the production of highly specific antibodies during acquired immune responses, T cells are recognized for their wide contributions to immune regulation and cell-mediated immunity [26]. At the interface of innate and adaptive immunity we find unique molecular bridges that link these arms at various levels. Dendritic cells (DCs) continue to fill a prominent place in the literature in this regard. Among others, surveying DCs are particularly adept at internalizing and processing antigens that can be subsequently presented in the context of major histocompatibility complex (MHC) molecules, leading to the downstream activation of B and T lymphocytes [27]. Yet, this is but one function for a cell with critical roles as sentinels in innate immunity against microbes, as inducers of central and peripheral immune tolerance, and regulators of naïve T cell activation [28, 29]. This is a testament to the plasticity of this cell type and the tremendous heterogeneity its subsets. Importantly, detailed analysis of immune cell function in recent years has shown that most of the cells described above contribute to both innate and acquired arms of the immune system, emphasizing the need to consider the roles of these cells in the context of a broader and multi-faceted immune response.

3.1. Development of Animal Immune Cells

Despite the differences in function, location, and phenotypic characteristics, each of the cellular members of the immune system owes its origins to multipotential progenitor stem cells in the bone marrow. These stem cells remain within the nurturing microenvironment of this organ until specific signals trigger their maturation along one of several possible developmental pathways. This process, referred to as hematopoiesis, has the capacity to replenish all cellular members of the immune system from a single stem cell providing ample flexibility to shape immune responses depending on the needs of the animal host. Along the way decisions to proliferate, differentiate, and commit to a specific cellular lineage shape the path of developing progenitor cells. Numerous checkpoints ensure proper progression along any of these pathways, and aberrations are quickly dealt with through premature termination of straying cells. The result is a carefully delineated group of immune cells that migrate to various tissues within the host and take their positions as effector cells within a developing immune response. Under basal conditions, hematopoietic events are largely governed by the drive to replenish immune cells that are spent and are no longer capable of fulfilling their surveillance duties.

During pathogenesis, engagement and destruction of foreign invaders requires upregulation of hematopoietic events to provide the increased numbers of effector cells needed and to replace those that have succumbed in the front lines. Important feedback mechanisms provide soluble mediators (cytokines) that travel through circulation to the bone marrow (or secondary hematopoietic organs) and contribute to upregulation of cell proliferation, commitment, and differentiation events. The specific contributions of these cytokines to hematopoietic events are well documented and have been reviewed elsewhere [30-32]. Importantly, the range of immunomodulatory functions of these potent host proteins extend well beyond blood cell development [33, 34].

3.2. Cross-Talk between Innate and Acquired Arms of the Animal Immune System

The divisions historically found between innate and acquired arms of the immune response continue to blur as we learn more about the close interrelationships and complementarity between their components [19, 35-38]. Early innate mechanisms play a critical role in the shaping and coordination of subsequent acquired responses [19, 36, 37, 39]. Among others, activation of the primordial toll-like receptors leads to shaping of antigen presentation and other adaptive mechanisms [17]. Complement proteins serve as important effectors of innate defenses, but also contribute to humoral mechanisms of acquired immunity [36]. Distinct subsets of adaptive arm T lymphocytes (TH1 and TH2 CD4+ lymphocytes) regulate the production of soluble mediators and stimulatory molecules that shape the inflammatory responses to intracellular or extracellular pathogens. Both have a significant impact on the capacity of an animal host to effectively clear a pathogenic infection. Whereas selective induction of the appropriate immune mechanisms leads to prevention of pathogen spread and controlled use of host resources, inappropriate deployment of immune components can have dire consequences for host survival and promote pathogen spread to additional members of the animal population. At the subcellular level, we find that primitive innate defense mechanisms such as phagocytosis have seamlessly integrated some newer components of the immune response (e.g. antibody binding Fc-gamma receptors) to expand the repertoire and effectiveness of host antimicrobial responses [19, 40]. The relevance of these phagocytic responses to the formation of innate-adaptive bridges is briefly described below. Such is the interrelationship between innate and acquired arms of immunity that many of the adaptive mechanisms of immunity characteristic of higher vertebrates appear to have developed from innate immunity evolutionary lines that can be traced back in early deuterostomes [38, 41]. For example, in depth analysis of immune cell developmental (hematopoietic) pathways increasingly suggests that even the most classical examples of members of these arms, such as adaptive arm B-lymphocytes, may have ancestral origins in cells of the innate immune system [42]. Finally, most recent characterization of T cell lymphoid progenitors has shown that they retain the capacity to differentiate along the myeloid lineage, indicating that previous lineage commitment lines that historically separate members of acquired and innate arms of immunity must be revised [43-45]. Thus, it is important that we appreciate that our classification approaches for immune components are constantly evolving, as we learn more about the intricacies that link the various components of this system.

4. Comparative Immunology and the Conservation of Immune Defense Mechanisms

The immune system characteristic of today's veterinary species evolved out of selective pressures imposed by infectious microorganisms [46]. In a constant effort to gain the upper hand host-pathogen interactions have established a constantly evolving scenario, which continues to shape novel pathogen infection strategies and host mechanisms that can overcome these developing infections. For the animal host, the ultimate goal has been to avoid death from infection. Thus, for animals, the evolving challenge has been to develop effective mechanisms that will protect them by destroying infectious microbes and neutralizing their virulence factors. A number of these mechanisms are described above. In contrast, for invading microbes, the challenge has been to continue

to devise clever evasion strategies that overcome immune defense mechanisms and increase their potential for survival and spread. These strategies can take advantage of mechanisms of antigenic variation [47], introduction of escape mutations [48], expression of immune suppressor genes [49], or one of several other potential mechanisms. A clear illustration of these selective pressures revolves around viral recognition through TLR receptors. TLR 9-mediated recognition of microbial non-methylated CpG motifs provides one mechanism to detect the presence of pathogen-derived nucleic acid and trigger rapid activation of proinflammatory antimicrobial responses. Yet, as obligate intracellular parasites, RNA viruses have been shown to adapt their genomes to contain very low presence of CpG dinucleotides, which could signal their presence through immune activation [50]. Notably, this mimicking mechanism is closely tied to the host-derived pressure to eliminate CpG dinucleotides motifs (e.g. human > avian). Influenza virus, for example, with origins in avian reservoirs continues to reduce the frequency of CpG dinucleotides in its genome as it replicates in humans [50]. Further, those influenza strains that have replicated within human hosts have a higher tendency to exhibit extremely low CpG dinucleotide content. Thus, it appears that strong selection pressures, including those arising from activation of host innate immune responses, play a significant role in the evolution of novel evasion strategies by invading pathogens. A number of excellent reviews outline additional examples where host-pathogen interactions have led to widespread utilization of these immune evasion strategies across viruses, bacteria, protozoa, helminthes, and arthropods [51-58]. In all, these immunity evasion strategies have continued to drive the development of a complex and highly integrated set of immune mechanisms across evolution, resulting in the antimicrobial defense systems that we now encounter in higher vertebrates.

As we consider the conservation and evolution of immunity, it is important that we recognize that both phylogeny and ontogeny play critical roles in the repertoire of immune antimicrobial mechanisms exhibited across veterinary species. Seminal studies looking at immunity along these two dimensions underline the relative contribution of each to the overall capacity of animal hosts to survive and thrive in the face of evolving and emerging infectious agents.

-
-
-

Bibliography

1. Golub ES, Green DR. (1991) *Immunology: a synthesis*. Sunderland, Massachusetts: Sinauer Associates. [This book provides a general overview of immunology principles]

2. Toupet K, Compan V, Crozet C, Mourton-Gilles C, Mestre-Francés N, Ibos F, Corbeau P, Verdier JM, Perrier V. (2008) Effective gene therapy in a mouse model of prion diseases. *PLoS ONE* 3(7): e2773. [Examination of one gene therapy-based therapeutic strategy against prion diseases using a mouse model]

3. Dutta NK, Mazumdar K, Seok SH, Park JH. (2008) The anti-inflammatory drug Diclofenac retains anti-listerial activity *in vivo*. *Lett Appl Microbiol* 47(2), 106-11[Example of one successful approach against Listeria in an in vivo mouse model]

4. Koizumi Y, Kurita-Ochiai T, Oguchi S, Yamamoto M. (2008) Nasal immunization with Porphyromonas gingivalis outer membrane protein decreases P. gingivalis-induced atherosclerosis and inflammation in spontaneously hyperlipidemic mice. *Infect Immun* 76(7), 2958-65. [Examines a nasal vaccine candidate for the reduction of atherosclerosis accelerated by P. gingivalis in the hyperlipidemic mouse model]

5. Liu Y, Li P, Lu J, Xiong W, Oger J, Tetzlaff W, Cynader M. (2008) Bilirubin possesses powerful immunomodulatory activity and suppresses experimental autoimmune encephalomyelitis. *J Immunol* 181(3), 1887-97. [Characterization of bilirubin as a potentially important immunomodulator that may contribute in the fight against autoimmune diseases]

6. Broere F, Wieten L, Klein Koerkamp EI, van Roon JA, Guichelaar T, Lafeber FP, van Eden W. (2008) Oral or nasal antigen induces regulatory T cells that suppress arthritis and proliferation of arthritogenic T cells in joint draining lymph nodes. *J Immunol* 181(2), 899-906. [This report looks to elucidate mechanisms of mucosal tolerance as a potential therapeutic approach in autoimmune diseases]

7. Tohyama S, Onodera S, Tohyama H, Yasuda K, Nishihira J, Mizue Y, Hamasaka A, Abe R, Koyama Y. (2008) A novel DNA vaccine-targeting macrophage migration inhibitory factor improves the survival of mice with sepsis. *Gene Ther* 15(23), 1513-22. [Description of a novel vaccine strategy to ameliorate the effects of sepsis in mice]

8. Jung C, Stoeckle C, Wiesmuller KH, Laub R, Emmrich F, Jung G, Melms A. (2008) Complementary strategies to elucidate T helper cell epitopes in myasthenia gravis. *J Neuroimmunol* 201-202, 41-49. [Explores the promotion of autoimmune responses by natural T cell epitopes]

9. Collin M, Shannon O, Bjorck L. IgG glycan hydrolysis by a bacterial enzyme as a therapy against autoimmune conditions. (2008) Proc Natl Acad Sci U S A 105(11), 4265-70. [Identifies EndoS as a potential therapeutic agent against diseases where pathogenic IgG antibodies are important and further emphasize antibody glycans as possible targets in future therapies against antibody-mediated autoimmune conditions]

10. Cao C, Lin X, Zhang C, Wahi MM, Wefes I, Arendash G, Potter H. (2008) Mutant Amyloid-beta-sensitized dendritic cells as Alzheimer's disease vaccine. *J Neuroimmunol* 200(1-2), 1-10 [An example of recent advances in mouse models of Alzeimer's disease]

11. Adams DJ, van der Weyden L. (2008) Contemporary Approaches for Modifying the Mouse Genome. *Physiol Genomics* 34(3), 225-38. [Describes recent advances in mouse experimental genetics and provide a 'how-to' guide for those people wishing to access this technology]

12. Cerletti M, Jurga S, Witczak CA, Hirshman MF, Shadrach JL, Goodyear LJ, Wagers AJ. (2008) Highly efficient, functional engraftment of skeletal muscle stem cells in dystrophic muscles. *Cell* 134(1), 37-47. [Discusses one application of skeletal muscle stem cells in the treatment of muscle degenerative disease]

13. Chen G, Wu D, Wang Y, Cen J, Feng Y, Sun A, Tang X, Chang H, Zhu Z. (2008) Expanded donor natural killer cell and IL-2, IL-15 treatment efficacy in allogeneic hematopoietic stem cell transplantation. *Eur J Haematol* 81(3), 226-35. [Describes results of a mouse model of allogeneic hematopoietic stem cell transplantation as a way to identify mechanisms that will help overcome graft-versus-host disease (GVHD), leukemia relapse, and immune deficiency]

14. Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P. (2008) Global trends in emerging infectious diseases. *Nature* 451(7181), 990-3. [Excellent recent report on the linkages of socio-economic, environmental and ecological factors as drivers for the global temporal and spatial patterns of appearance for emerging infectious diseases]

15. Underhill DM, Ozinsky A. (2002) Phagocytosis of microbes: complexity in action. *Annu Rev Immunol* 20, 825-52. [Comprehensive review of the phagocytic process]

16. Blach-Olszewska Z. Innate immunity: cells, receptors, and signaling pathways. (2005) *Arch Immunol Ther Exp* (Warsz) 53(3), 245-53. [Discusses the players and regulatory mechanisms that govern innate immunity responses]

17. Pasare C, Medzhitov R. (2005) Toll-like receptors: linking innate and adaptive immunity. Adv Exp Med Biol 560, 11-8. [Describes the role of toll like receptors as inducers of innate immunity and regulators of subsequent adaptive immune responses]

18. Takeda K, Akira S. Toll-like receptors in innate immunity. (2005) *Int Immunol* 17(1), 1-14. [Overview of toll-like receptor biology with a focus on signaling mechanisms]

19. Aderem A, Underhill DM. Mechanisms of phagocytosis in macrophages. (1999) *Annu Rev Immunol* 17, 593-623. [Comprehensive review of outlining the mechanisms involved in the macrophage internalization process during phagocytosis]

20. Knol EF, Mul FP, Lie WJ, Verhoeven AJ, Roos D. (1996) The role of basophils in allergic disease. *Eur Respir J Suppl* 22, 126s-131s. [Focuses on the contribution of basophils to allergic responses]

21. Marone G, Casolaro V, Patella V, Florio G, Triggiani M. (1997) Molecular and cellular biology of mast cells and basophils. Int *Arch Allergy Immunol* 114(3), 207-17. [Overview of mast cell and basophil biology]

22. Abraham SN, Arock M. (1998) Mast cells and basophils in innate immunity. *Semin Immunol* 10(5), 373-81. [Describes the multi-faceted and significant role for mast cells and basophils in the host's innate immune response to infectious agents]

23. Feger F, Varadaradjalou S, Gao Z, Abraham SN, Arock M. (2002) The role of mast cells in host defense and their subversion by bacterial pathogens. *Trends Immunol* 23(3), 151-8. [Description of host-pathogen interactions at the mast cell:bacterial axis]

24. Hogan SP, Rosenberg HF, Moqbel R, Phipps S, Foster PS, Lacy P, Kay AB, Rothenberg ME. (2008) Eosinophils: biological properties and role in health and disease. *Clin Exp Allergy* 38(5) 709-50. [Overview of eosinophil biology]

25. Lanier LL. (2008) Evolutionary struggles between NK cells and viruses. *Nat Rev Immunol* 8(4):259-68. [Description of the host:pathogen relationships at the virus-NK cell interface]

26. Larosa DF, Orange JS. 1. (2008) Lymphocytes. *J Allergy Clin Immunol* 121(2 Suppl), S364-9; quiz S412. [Overview of the major lymphocyte populations with emphasis on their development, distinguishing characteristics, and functions]

27. Banchereau J, Steinman RM. (1998) Dendritic cells and the control of immunity. *Nature* 392(6673), 245-52. [Overview of the contribution of dendritic cells as an important regulator of immunity]

28. Iwasaki A. (2007) Mucosal dendritic cells. *Annu Rev Immunol* 25, 381-418. [This review highlights progress in our understanding of how mucosal DCs process external information and direct appropriate responses by mobilizing various cells of the innate and adaptive immune systems to achieve homeostasis and protection]

29. Sato K, Fujita S. (2007) Dendritic cells: nature and classification. *Allergol Int* 56(3), 183-91. [Current overview of dendritic cell biology and classification]

30. Alexander WS. (1998) Cytokines in hematopoiesis. *Int Rev Immunol* 16(5-6), 651-82. [Describes the contribution of cytokines as central modulators of hematopoiesis]

31. Barreda DR, Hanington PC, Belosevic M. (2004) Regulation of myeloid development and function by colony stimulating factors. *Dev Comp Immunol* 28(5), 509-54. [Comprehensive description of colony-stimulating factor biology]

32. Barreda DR, Belosevic M. (2001) Transcriptional regulation of hemopoiesis. *Dev Comp Immunol* 25(8-9), 763-89. [Overview of the contribution of transcription factors to the convergence of immunological signals and induction of cohesive cellular responses]

33. Schooltink H, Rose-John S. (2002) Cytokines as therapeutic drugs. *J Interferon Cytokine Res* 22(5), 505-16. [Examines the application of cytokines as therapeutic drugs]

34. Belardelli F, Ferrantini M. (2002) Cytokines as a link between innate and adaptive antitumor immunity. *Trends Immunol* 23(4), 201-8. [Describes the central role of cytokines in effective integration of innate and adaptive immune responses against tumors]

35. Flajnik MF, Du Pasquier L. (2004) Evolution of innate and adaptive immunity: can we draw a line? *Trends Immunol* 25(12), 640-4. [Genetic perspective on the evolution of human innate immunity]

36. Sunyer JO, Boshra H, Lorenzo G, Parra D, Freedman B, Bosch N. (2003) Evolution of complement as an effector system in innate and adaptive immunity. *Immunol Res* 27(2-3), 549-64. [Description of the complement system as a central effector of innate and adaptive arms of host immunity]

37. Nadesalingam J, Reid KB, Palaniyar N. (2005) Collectin surfactant protein D binds antibodies and interlinks innate and adaptive immune systems. *FEBS Lett* 579(20), 4449-53. [Describes one example of innate components serving to bridge innate and adaptive arms of immunity]

38. Du Pasquier L. (2005) Meeting the demand for innate and adaptive immunities during evolution. Scand *J Immunol* 62 Suppl 1:39-48. [Overview of the selective pressures driving development of innate and adaptive mechanisms of immunity across evolution]

39. Hawlisch H, Kohl J. (2006) Complement and Toll-like receptors: Key regulators of adaptive immune responses. *Mol Immunol* 43(1-2), 13-21. [Describes the role that two important mediators of innate immunity have on the regulation of subsequent adaptive responses]

40. Worth RG, Schreiber AD. (2004) Fc receptor phagocytosis. In: Rosales C, editor. *Molecular Mechanisms of Phagocytosis*: Eurekah. [This book chapter examines the current understanding on the biology of Fc receptor-mediated phagocytosis]

41. Okada K, Asai K. (2008) Expansion of signaling genes for adaptive immune system evolution in early vertebrates. *BMC Genomics* 9, 218. [Examines the relationship between two rounds of whole-genome duplication in early vertebrates and the gain of adaptive immune system-related functions by numerous genes]

42. Li J, Barreda DR, Zhang YA, Boshra H, Gelman AE, Lapatra S, Tort L, Sunyer JO. (2006) B lymphocytes from early vertebrates have potent phagocytic and microbicidal abilities. *Nat Immunol* 7(10), 1116-24. [Challenges current dogma on B cell development by shedding light on potential innate origins for B-lymphocytes during evolution

43. Graf T. (2008) Immunology: blood lines redrawn. *Nature* 452(7188), 702-3. [Examines the changing perspectives on the links between historically distinct lines of blood cells]

44. Wada H, Masuda K, Satoh R, Kakugawa K, Ikawa T, Katsura Y, Kawamoto H. (2008) Adult T-cell progenitors retain myeloid potential. *Nature* 452(7188), 768-72. [Provides an argument against the classical dichotomy model in which T cells are derived from common lymphoid progenitors, thus supporting the validity of the myeloid-based model for both adult and fetal haematopoiesis]

45. Bell JJ, Bhandoola A. (2008) The earliest thymic progenitors for T cells possess myeloid lineage potential. *Nature* 452(7188), 764-7. [Recent report that challenges current models of myeloid-lymphoid hematopoietic pathway divergence]

46. Litman GW, Cooper MD. (2007) Why study the evolution of immunity? *Nat Immunol* 8(6), 547-8. [Brief rationale for the impact of comparative studies to our understanding of the immune system]

47. Damian RT. (1997) Parasite immune evasion and exploitation: reflections and projections. *Parasitology* 115 Suppl:S169-75. [Outlines evasion strategies utilized by parasites against host immune defenses]

48. Kent SJ, Fernandez CS, Dale CJ, Davenport MP. (2005) Reversion of immune escape HIV variants upon transmission: insights into effective viral immunity. *Trends Microbiol* 13(6), 243-6. [Examines host-pathogen drivers for HIV-based approaches to evade host immune responses and potential targets to control viral spread]

49. Palefsky J. (2006) Biology of HPV in HIV infection. *Adv Dent Res* 19(1), 99-105. [Examines host-pathogen drivers for HIV-based approaches to evade host immune responses and potential targets to control viral spread]

50. Greenbaum BD, Levine AJ, Bhanot G, Rabadan R. (2008) Patterns of evolution and host gene mimicry in influenza and other RNA viruses. *PLoS Pathog* 4(6):e1000079. [Examines the impact of host-pathogen interactions on the development of host immunity evasion strategies for RNA viruses]

51. Benedict CA, Norris PS, Ware CF. (2002) To kill or be killed: viral evasion of apoptosis. *Nat Immunol* 3(11), 1013-8. [Describes one approach by which viruses promote their pathogenicity in the face of host induction of apoptosis]

52. Orange JS, Fassett MS, Koopman LA, Boyson JE, Strominger JL. (2002) Viral evasion of natural killer cells. *Nat Immunol* 3(11), 1006-12. [Description of the host:pathogen relationships at the virus-NK cell interface]

53. Alcami A. (2003) Viral mimicry of cytokines, chemokines and their receptors. *Nat Rev Immunol*, 3(1), 36-50. [Describes elegant viral mechanisms used to evade detection and destruction by the host immune system]

54. Hornef MW, Wick MJ, Rhen M, Normark S. (2002) Bacterial strategies for overcoming host innate and adaptive immune responses. *Nat Immunol* 3(11), 1033-40. [Overview of bacterial-driven strategies for overcoming host antimicrobial responses]

55. Young D, Hussell T, Dougan G. (2002) Chronic bacterial infections: living with unwanted guests. *Nat Immunol* 3(11), 1026-32. [Overview of host-pathogen relationships at the bacterial-immune system interface, with a focus on unique features characteristic of longer-term chronic infections]

56. Sacks D, Sher A. (2002) Evasion of innate immunity by parasitic protozoa. *Nat Immunol* 3(11), 1041-7. [Examines host:pathogen relationships at the innate immunity-parasite interface]

57. Sansonetti PJ, Di Santo JP. (2007) Debugging how bacteria manipulate the immune response. *Immunity* 26(2), 149-61. [Examines strategies used by bacteria to overcome host immune responses

58. Brown SP, Le Chat L, Taddei F. (2008) Evolution of virulence: triggering host inflammation allows invading pathogens to exclude competitors. *Ecol Lett* 11(1), 44-51. [Focuses on the ecological incentives for viral induction of host inflammatory responses]

59. Danilova N. (2006) The evolution of immune mechanisms. *J Exp Zoolog B Mol Dev Evol* 306(6), 496-520. [Overview of the contribution of host-pathogen interactions to the development of immune defense mechanisms across evolution]

60. Gorski A, Weber-Dabrowska B. (2005) The potential role of endogenous bacteriophages in controlling invading pathogens. *Cell Mol Life Sci* 62(5), 511-9. [Examines the potential contribution of phagesto immunosurveillance against bacteria, viruses and cancer]

61. Hanlon GW. (2007) Bacteriophages: an appraisal of their role in the treatment of bacterial infections. *Int J Antimicrob Agents* 30(2), 118-28. [Outlines those features of bacteriophages that contribute to their potential utility in therapy

62. Vilmos P, Kurucz E. (1998) Insect immunity: evolutionary roots of the mammalian innate immune system. *Immunol Lett* 62(2), 59-66. [This review focuses on recent studies of insect immunology and summarizes the currently known similarities between the innate immune system in insects and in vertebrates]

63. Magor BG, Magor KE. (2001) Evolution of effectors and receptors of innate immunity. *Dev Comp Immunol* 25(8-9), 651-82. [Illustrates the evolution of immune defenses through examination of key effectors and receptors of innate immunity]

64. Cooper MD, Alder MN. (2006) The evolution of adaptive immune systems. *Cell* 124(4), 815-22. Describes recent advances in the understanding of the development of adaptive mechanisms of immunity during evolution]

65. Eason DD, Cannon JP, Haire RN, Rast JP, Ostrov DA, Litman GW. (2004) Mechanisms of antigen receptor evolution. *Semin Immunol* 16(4), 215-26. [Description of the mechanisms that have contributed to the shaping of the adaptive immune system across evolution]

66. Jutras I, Desjardins M. (2005) Phagocytosis: at the crossroads of innate and adaptive immunity. *Annu Rev Cell Dev Biol* 21, 511-27. [Examines the central position of phagocytosis as a bridge between innate and adaptive host immune responses]

67. Desjardins M, Houde M, Gagnon E. (2005) Phagocytosis: the convoluted way from nutrition to adaptive immunity. *Immunol Rev* 207, 158-65. [Evolutionary perspective on the development of phagocytosis]

68. Tauber AI. (2003) Metchnikoff and the phagocytosis theory. *Nat Rev Mol Cell Biol* 4(11), 897-901. [Historical perspective on phagocytosis based on early studies by Metchnikoff]

69. Laird DJ, De Tomaso AW, Cooper MD, Weissman IL. (2000) 50 million years of chordate evolution: seeking the origins of adaptive immunity. *Proc Natl Acad Sci U S A* 97(13), 6924-6. [Overview of factors that drove the appearance of adaptive mechanisms of immunity during evolution and focus on specific components of this arm of the immune system]

70. Litman GW, Cannon JP, Dishaw LJ. (2005) Reconstructing immune phylogeny: new perspectives. *Nat Rev Immunol* 5(11), 866-79. [Brief rationale for the impact of comparative studies to our understanding of the immune system]

71. Pancer Z, Amemiya CT, Ehrhardt GR, Ceitlin J, Gartland GL, Cooper MD. (2004) Somatic diversification of variable lymphocyte receptors in the agnathan sea lamprey. *Nature* 430(6996), 174-80. [Examines a novel mechanism for generating highly diverse lymphocyte receptors, distinct from immunoglobulin gene segments in gnathostomes (jawed vertebrates)]

72. Sunyer JO, Boshra H, Li J. (2005) Evolution of anaphylatoxins, their diversity and novel roles in innate immunity: insights from the study of fish complement. *Vet Immunol Immunopathol* 108(1-2), 77-89. [Provides insights into the evolution of anaphylatoxins based on comparative studies of their structure and function]

73. McKean KA, Yourth CP, Lazzaro BP, Clark AG. (2008) The evolutionary costs of immunological maintenance and deployment. *BMC Evol Biol* 8, 76. [Examines the correlations between immunocompetence and fitness in the absence and presence of infection]

74. Holladay SD, Smialowicz RJ. (2000) Development of the murine and human immune system: Differential effects of immunotoxicants depend on time of exposure. Environmental Health Perspectives 108, 463-473. [Explores some of the differences that are observed in immune defenses during ontogeny]

75. Rooke JA, Bland IM. (2002) The acquisition of passive immunity in the new-born piglet. *Livestock Production Science*, 78(1), 13-23. [Assesses the maternal supply of IgG and piglet absorption of IgG in naturally suckling piglets, and examines the relationships between acquisition of passive immunity and development of active immunity]

76. Goldman AS. (2002) Evolution of the mammary gland defense system and the ontogeny of the immune system. *Journal of Mammary Gland Biology and Neoplasia* 7(3), 277-289. [Describes the contribution of the appearance of the mammary system of the expansion of immunity in higher vertebrates]

77. Godin I, Cumano A. (2002) The hare and the tortoise: an embryonic haematopoietic race. *Nat Rev Immunol* 2(8), 593-604. [Comprehensive overview of developmental aspects of hematopoiesis]

78. Orkin SH, Zon LI. (2002) Hematopoiesis and stem cells: plasticity versus developmental heterogeneity. *Nat Immunol* 3(4), 323-8. [Review of the origin of HSCs during embryological development, the relationship between hematopoiesis and vascular development and the potential plasticity of HSCs and other tissue stem cells]

79. Macdonald TT, Monteleone G. (2005) Immunity, inflammation, and allergy in the gut. *Science* 307(5717), 1920-5. [Overview of the links between immunity, inflammation, and allergy in the gut]

80. Noverr MC, Huffnagle GB. Does the microbiota regulate immune responses outside the gut? (2004) *Trends Microbiol* 12(12), 562-8. [Covers the post-developmental functions that the microbiota plays in regulating immunological tolerance to allergen exposure outside the GI tract]

81. Cebra JJ. (1999) Influences of microbiota on intestinal immune system development. *American Journal of Clinical Nutrition* 69(5), 1046S-1051S. [Considers the contribution of natural microbial flora in development of host immunity]

82. Rodewald HR. (23008) Thymus organogenesis. *Annu Rev Immunol* 26, 355-88. [Review of cellular and molecular basis of thymus organogenesis]

83. Petrie HT, Zuniga-Pflucker JC. (2007) Zoned out: functional mapping of stromal signaling microenvironments in the thymus. *Annu Rev Immunol* 25, 649-79. [Summary what is known about the signals the thymus delivers to uncommitted progenitors, or to immature T-committed progenitors, to produce functional T cells]

84. Anderson G, Moore NC, Owen JJ, Jenkinson EJ. (1996) Cellular interactions in thymocyte development. *Annu Rev Immunol* 14, 73-99. [Describes the contribution of cellular interactions in T-cell development]

85. Zuniga-Pflucker JC, Lenardo MJ. (1996) Regulation of thymocyte development from immature progenitors. *Curr Opin Immunol* 8(2), 215-24. [Overview of intrinsic and extrinsic factors associated with regulation of thymocyte development]

86. Monson NL. The natural history of B cells. (2008) *Curr Opin Neurol* 21 Suppl 1, S3-8. [Focus on the role of B-lymphocytes in autoimmune processes such as multiple sclerosis]

87. Melchers F, Rolink A. (1999) B-lymphocyte development and biology. In: Paul WE, editor. Fundamental Immunology. 4th ed. Philadelphia: Lippincott-Raven Publishers. p. 183-224. [Focus on the role of B-lymphocytes in autoimmune processes such as multiple sclerosis]

88. Gerdts V, Snider M, Brownlie R, Babiuk LA, Griebel PJ. (2002) Oral DNA vaccination in utero induces mucosal immunity and immune memory in the neonate. *J Immunol* 168(4), 1877-85. [Overview of mechanisms and potential impact of in utero based vaccination strategies]

89. Gerdts V, Babiuk LA, van Drunen Littel-van den H, Griebel PJ. (2000) Fetal immunization by a DNA vaccine delivered into the oral cavity. *Nat Med*, 6(8), 929-32. [Describes a novel vaccination approach to induce adaptive immunity early during development]

90. Gerdts V, Tsang C, Griebel PJ, Babiuk LA. (2004) DNA vaccination in utero: a new approach to induce protective immunity in the newborn. *Vaccine* 22(13-14), 1717-27. [Analysis of fetal immunization as a safe vaccination strategy that does not appear to negatively affect fetal gestation, neonatal viability, or significantly alter blood leukocyte populations]

91. Daszak P, Cunningham AA, Hyatt AD. (2000) Emerging infectious diseases of wildlife--threats to biodiversity and human health. *Science* 287(5452), 443-9. [Overview of the biological bridges that link emerging infectious wildlife diseases with those of domestic animals and human populations]

92. Daszak P, Epstein JH, Kilpatrick AM, Aguirre AA, Karesh WB, Cunningham AA. (2007) Collaborative research approaches to the role of wildlife in zoonotic disease emergence. *Curr Top Microbiol Immuno* 315, 463-75. [Overview of the links that zoonotic disease emergence establish between veterinary medicine, public health, and ecology]

93. Moore RA, Vorberg I, Priola SA. (2005) Species barriers in prion diseases--brief review. *Arch Virol Suppl* 19, 187-202. [Examines the role that species barriers play in the control of prion zoonotic spread and seeks to understand potential risks that may lead to abrogation of existing barriers]

94. Belay ED, Schonberger LB. (2005) The public health impact of prion diseases. *Annu Rev Public Health* 26, 191-212. [Describes the impact of prion disease spread on public health]

95. Collinge J, Clarke AR. (2007) A general model of prion strains and their pathogenicity. *Science* 318(5852), 930-6. [Describes the importance of considering prion strains as a important factor behind prion pathogenicity and public health risks]

96. Kovacs GG, Budka H. (2008) Prion diseases: From protein to cell pathology. *American Journal of Pathology* 172(3), 555-565. [Overview of prion biology and their role in pathogenesis]

97. Cooke CM, Rodger J, Smith A, Fernie K, Shaw G, Somerville RA. (2007) Fate of prions in soil: detergent extraction of PrP from soils. *Environ Sci Technol* 41(3), 811-7. [Examines the contribution of soil as a reservoir of infective prions in the environment]

98. Johnson CJ, Pedersen JA, Chappell RJ, McKenzie D, Aiken JM. (2007) Oral transmissibility of prion disease is enhanced by binding to soil particles. *PLoS Pathog* 3(7), e93. [Characterizes the increased capacity for oral transmission of prions following association with soil inorganic microparticles]

99. Johnson CJ, Phillips KE, Schramm PT, McKenzie D, Aiken JM, Pedersen JA. (2006) Prions adhere to soil minerals and remain infectious. *PLoS Pathog* 2(4), e32. [Identifies soil as an unidentified environmental prion reservoir which contributes to the natural transmission of prion diseases]

100. Marsh JM, Brester GW, Smith VH. (2008) Effects of North American BSE events on U. S. cattle prices. *Review of Agricultural Economics* 30(1), 136-150. [Examination of the effects of two North American BSE events on U.S. fed and feeder cattle prices]

101. Jones M, Peden AH, Prowse CV, Gröner A, Manson JC, Turner ML, Ironside JW, MacGregor IR, Head MW. (2007) In vitro amplification and detection of variant Creutzfeldt-Jakob disease PrPSc. *J Pathol* 213(1), 21-6. [Describes the link on BSE with a variant form of Creutzfeldt-Jacob disease and one approach to amplify and detect this variant in vitro]

102. Beekes M, McBride PA. (2007) The spread of prions through the body in naturally acquired transmissible spongiform encephalopathies. *Febs Journal* 274(3), 588-605. [Overview factors associated with spread of scrapie, chronic wasting disease, bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease agents through the body in naturally affected hosts, and in model animals experimentally challenged via the alimentary tract]

103. Mabbott NA, MacPherson GG. (2006) Prions and their lethal journey to the brain. *Nat Rev Microbiol* 4(3):201-11. [Overview of current knowledge on the road(s) taken by prions as they migrate from the periphery to the central nervous system]

104. Jeffrey M, McGovern G, Goodsir CM, Brown KL, Bruce ME. (2000) Sites of prion protein accumulation in scrapie-infected mouse spleen revealed by immuno-electron microscopy. *J Pathol* 191(3), 323-32. [Examines the accumulation of prion protein accumulation in scrapie-infected mouse spleen

105. Klein MA, Kaeser PS, Schwarz P, Weyd H, Xenarios I, Zinkernagel RM, Carroll MC, Verbeek JS, Botto M, Walport MJ, Molina H, Kalinke U, Acha-Orbea H, Aguzzi A. (2001) Complement facilitates early prion pathogenesis. *Nat Med* 7(4), 488-92. [Examines the role of complement on prion pathogenesis following intraperitoneal exposure]

106. Mackay F, Browning JL. (1998) Turning off follicular dendritic cells. *Nature* 395(6697), 26-7. [Describes one approach for regulation of follicular dendritic cell activity]

107. Seeger H, Heikenwalder M, Zeller N, Kranich J, Schwarz P, Gaspert A, Seifert B, Miele G, Aguzzi A. (2005) Coincident scrapie infection and nephritis lead to urinary prion excretion. *Science* 310(5746), 324-6. [Examines whether chronic inflammatory kidney disorders can trigger excretion of prion infectivity into urine]

108. Murayama Y, Yoshioka M, Okada H, Takata M, Yokoyama T, Mohri S. (2007) Urinary excretion and blood level of prions in scrapie-infected hamsters. *J Gen Virol* 88(Pt 10), 2890-8. [Describes a potential mechanism for environmental shedding of infectious prions via urine]

109. Konold T, Moore SJ, Bellworthy SJ, Simmons HA. (2008) Evidence of scrapie transmission via milk. *BMC Vet Res* 4, 14. [Examines the potential role of milk as a reservoir of infective scrapie prions]

110. Ligios C, Sigurdson CJ, Santucciu C, Carcassola G, Manco G, Basagni M, Maestrale C, Cancedda MG, Madau L, Aguzzi A. (2005) PrPSc in mammary glands of sheep affected by scrapie and mastitis. *Nat Med* 11(11): 1137-8. [Identifies PrPSc in mammary glands of sheep affected by scrapie and mastitis, thus establishing a potential new mechanism for transmission of prion diseases]

111. Dubey JP. (2004) Toxoplasmosis - a waterborne zoonosis. *Vet Parasitol* 126(1-2), 57-72. [Describes the impact of Toxoplasma as a mediator of infectious disease derived from water sources

112. Solaymani-Mohammadi S, Petri WA, Jr. (2006) Zoonotic implications of the swine-transmitted protozoal infections. *Vet Parasitol* 140(3-4), 189-203. [Examines the potential dangers associated with increased interactions between wild and domestic swine populations, with a focus nn zoonotic protozoal infections]

113. Gazzinelli RT, Hakim FT, Hieny S, Shearer GM, Sher A. (1991) Synergistic role of CD4+ and CD8+ T lymphocytes in IFN-gamma production and protective immunity induced by an attenuated Toxoplasma gondii vaccine. *J Immunol* 146(1), 286-92. [Outlines the contributions of CD4+ and CD8+ T cells as the major effectors of immunity in vivo against Toxoplasma gondii]

114. Elsheikha HM. (2008) Congenital toxoplasmosis: priorities for further health promotion action. *Public Health* 122(4), 335-53. [Review of studies defining seroprevalence and characteristic sociodemographic, biological and lifestyle risk factors for Toxoplasma gondii infection]

115. Van den Berg T, Lambrecht B, Marche S, Steensels M, Van Borm S, Bublot M. (2008) Influenza vaccines and vaccination strategies in birds. *Comp Immunol Microbiol Infect Dis* 31(2-3), 121-65. [Describes the goals and challenges facing Influenza vaccines and vaccination strategies in birds]

116. Heeney JL. (2006) Zoonotic viral diseases and the frontier of early diagnosis, control and prevention. *J Intern Med* 260(5), 399-408. [Overview of current viral zoonotics and potential areas of exploration for their early diagnosis, control and prevention]

117. Van Reeth K. (2007) Avian and swine influenza viruses: our current understanding of the zoonotic risk. *Vet Res* 38(2), 243-60. [Evaluates the zoonotic potential of swine and avian viruses, and the possible role of pigs in the transmission of avian influenza viruses to humans]

118. Thacker E, Janke B. (2008) Swine influenza virus: zoonotic potential and vaccination strategies for the control of avian and swine influenzas. *J Infect Dis* 197 Suppl 1, S19-24. [Examination of factors mediating zoonotic transmission of influenza, and potential avenues to control its spread through a focus on avian and swine reservoirs]

119. Hayden FG, Fritz R, Lobo MC, Alvord W, Strober W, Straus SE. (1998) Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. *J Clin Invest* 101(3), 643-9. [Explores the role of cytokine responses in symptom formation and host defenses in influenza infection]

120. Wain-Hobson S, Meyerhans A. (1999) On viral epidemics, zoonoses and memory. *Trends Microbiol* 7(10), 389-91. [Perspective on the links between viral epidemics, zoonoses and memory and the need to further invest in research aimed at their understanding]

121. Cooper EL. (2003) Comparative immunology. Curr Pharm Des 9(2), 119-31. [Overview of comparative immunology as an important contributor to our understanding of immunity and host-pathogen interactions across evolution]

122. Brown MB, Shearer JK, Elvinger F. (1990) Mycoplasmal mastitis in a dairy herd. *J Am Vet Med Assoc* 196(7), 1097-101. [Case study of Mycoplasma mastitis in USA dairy herds]

123. Caswell JL, Archambault M. (2007) Mycoplasma bovis pneumonia in cattle. *Anim Health Res Rev* 8(2), 161-86. [This review considers the relationship between M. bovis infection and the various manifestations of the bovine respiratory disease complex]

124. Jasper DE. (1977) Mycoplasma and mycoplasma mastitis. J Am Vet Med Assoc 170(10 Pt 2), 1167-72. [Overview of mastitis due to mycoplasma]

125. Maes D, Segales J, Meyns T, Sibila M, Pieters M, Haesebrouck F. (2008) Control of Mycoplasma hyopneumoniae infections in pigs. *Vet Microbiol* 126(4), 297-309. [Overview of potential approaches to control Mycoplasma hyopneumoniae infections in pigs

126. Razin S, Yogev D, Naot Y. (1998) Molecular biology and pathogenicity of mycoplasmas. *Microbiol Mol Biol Rev* 62(4), 1094-156. [Comparative genomics-based analysis of mycoplasmas]

127. Endsley JJ, Furrer JL, Endsley MA, McIntosh MA, Maue AC, Waters WR, Lee DR, Estes DM. (2004) Characterization of bovine homologues of granulysin and NK-lysin. *J Immunol* 173(4), 2607-14. [Description of one potential laboratory-based approach to complement clinical diagnosis of infections mediated by organisms such as *M. hyopneumoniae*]

128. Nicholas RA, Ayling RD. (2003) Mycoplasma bovis: disease, diagnosis, and control. *Res Vet Sci* 74(2), 105-12. [Overview of Mycoplasma bovis as a causative agent of disease and potential avenues for its diagnosis and control]

129. Gourlay RN, Thomas LH, Wyld SG, Smith CJ. (1989) Effect of a new macrolide antibiotic (tilmicosin) on pneumonia experimentally induced in calves by Mycoplasma bovis and Pasteurella haemolytica. *Res Vet Sci* 47(1), 84-9. [Describes the relative contribution of Mycoplasma bovis and Pasteurella haemolytica to bovine disease and examines one potential approach to control these infections]

130. Hewicker-Trautwein M, Feldmann M, Kehler W, Schmidt R, Thiede S, Seeliger F, Wohlsein P, Ball HJ, Buchenau I, Spergser J, Rosengarten R. (2002) Outbreak of pneumonia and arthritis in beef calves associated with Mycoplasma bovis and Mycoplasma californicum. *Vet Rec* 151(23), 699-703. [Case study of Mycoplasma infection in beef calves]

131. Poumarat F, Le Grand D, Philippe S, Calavas D, Schelcher F, Cabanié P, Tessier P, Navetat H. (2001) Efficacy of spectinomycin against Mycoplasma bovis induced pneumonia in conventionally reared calves. *Vet Microbiol* 80(1), 23-35. [Case study that examines the spectinomycin against Mycoplasma bovis in conventionally reared calves]

132. Adegboye DS, Halbur PG, Nutsch RG, Kadlec RG, Rosenbusch RF. (1996) Mycoplasma bovis-associated pneumonia and arthritis complicated with pyogranulomatous tenosynovitis in calves. *J Am Vet Med Assoc* 209(3), 647-9. [Describes a pneumonia-arthritis syndrome that results from infection with M bovis]

133. Kauf AC, Rosenbusch RF, Paape MJ, Bannerman DD. (2007) Innate immune response to intramammary Mycoplasma bovis infection. *J Dairy Sci* 90(7), 3336-48. [Characterization of systemic and local innate immune response of dairy cows to Mycoplasma bovis]

134. Houlihan MG, Veenstra B, Christian MK, Nicholas R, Ayling R. (2007) Mastitis and arthritis in two dairy herds caused by Mycoplasma bovis. *Vet Res* 160(4), 126-7. [Case study of Mycoplasma infection in dairy herds]

Biographical Sketches

Dr. Dan Barreda is an Assistant Professor in Immunology in the Department of Agricultural, Food and Nutritional Science (AFNS) and the Department of Biological Sciences at the University of Alberta, Canada. His background is derived from his studies in microbiology/biochemistry (B.Sc., University of Victoria, Canada), cell biology and comparative immunology (Ph.D., University of Alberta, Canada), and biomedical immunology (PDF, University of Pennsylvania School of Medicine, U.S.A.) A major focus of his research revolves around the application of conserved biomarkers of immunity for the improvement of animal health and the control of zoonotic disease spread in domestic animal populations. Among others, these are currently being used for characterization of the impact of functional feeds on animal immune parameters, validation of genomic markers for profitable livestock traits, and understanding of the immunobiology of host-pathogen interactions.

Ms. Aja Rieger, Ms. Nicole Girard and **Ms. Shannon Clarahan** are students in Dr. Barreda's laboratory, currently developing biotechnologies for the analysis of immunity and host-pathogen interactions in comparative animal systems.

Dr. Afolabi Eleyinmi is a visiting scientist from the Federal University of Technology, Nigeria, currently working in Dr. Barreda's laboratory. His goal is to identify and isolate bioactive fractions from Alberta-based crops that can be integrated into animal functional feeds for the improvement of animal immunity and health.