Immunological Memory And Cell Protective Immunity

The innate immune system in vertebrates is considered to lack specific memory. To investigate innate immune system based immunological protection mediated by cells that are not part of the acquired immune system the Tübingen recombination activation gene1 (rag1)t26683mutant (MT) zebrafish was chosen. Molecular analysis demonstrated MT zebrafish kidney cells expressed Nonspecific Cytotoxic cell receptor protein-1 (NCCRP-1) and Natural Killer cell (NK) lysin but lacked T cell receptor (TCR) and immunoglobulin (Ig) VH1, VH2, VH3 and VH4 expression. Differential counts of peripheral blood leukocytes indicated that MT fish had decreased lymphocyte populations (34.7%) compared to rag1+/+ wild-type (WT) fish (70.5%), and increased granulocyte populations (34.7%) compared to WT (17.6%). Further, endocytic functions of phagocytes from MT fish were compared to WT fish. No significant differences in the selective and non-selective mechanisms of uptake in phagocytes were observed between MT and WT zebrafish. For the first time it was shown that zebrafish phagocytes utilize macropinocytosis and Ca2 dependant endocytosis mechanisms for antigen uptake. These characterization studies suggest that MT zebrafish provide a unique model for investigating innate immune responses because fully functional innate defenses are present without the influence of lymphocytes and lymphocyte associated acquired immune responses. To conduct such large scale investigations the first ongoing rag1t26683 mutant zebrafish breeding colony was established. To meet special husbandry needs of immunodeficient MT zebrafish, standard rearing protocols were advanced and the information was made available to the zebrafish community at: http://www.cvm.msstate.edu/zebrafish/index.html. Multiple trials were conducted to evaluate the potential for memory of the innate immune system. Significant reduction in mortality was observed in MT vaccinated zebrafish upon secondary exposure to Edwardsiella ictaluri when compared to unvaccinated, MT fish. This documents for the first time, that MT zebrafish, lacking an acquired immune system, are able to mount a protective immune response to Edwardsiella ictaluri and generate protection upon a repeated encounter to the same pathogen. The observed protection is long lasting and mediated by the innate immune system, but a specific mechanism is not yet defined.

Completely revised and updated, this respected reference offers comprehensive and current coverage of every aspect of vaccination--from development to use in reducing disease. It also includes access to a companion Web site for more coverage.

Rag1-/- mutant zebrafish lack lymphocytes and were used to study the basis of acquired protective immunity in the absence of lymphocytes to the intracellular bacterium Edwardsiella ictaluri. This study morphologically identified and quantified lymphocyte like cells (LLCs) present in the liver, kidney and spleen of these fish. LLCs included Natural Killer (NK) cells and non-specific cytotoxic cells (NCCs) and were discriminated by size, and by the presence of cytoplasmic granules. The antibodies antiNITR9, anti-NCCRP-1 (5C6) and anti-MPEG-1 were used to evaluate these cell populations by flow cytometry. Gene expression profiles in these tissues were evaluated after the rag1-/- mutants were intra coelomically injected with the toll like receptor (TLR)-2 ligand, [beta] glucan, TLR3 ligand, Poly I:C, or TLR 7/8 ligand, R848. The genes interferon [gamma] (inf[gamma]), expressed by activated NK cells and macrophages, tumor necrosis factor [alpha] (tnf[alpha]), expressed by activated macrophages, myxovirus resistance (mx) expressed by cells induced by IFN[alpha], T-cell transcription factor (t-bet) expressed by NK cells and novel immune type-receptor 9 (nitr-9) expressed by NK cells were evaluated. The TLR ligands induced different patterns of expression and stimulated both macrophages and NK cells. Then fish were vaccinated with an attenuated mutant of E. ictaluri (RE33®) with or without the TLR ligands then challenged with WT E. ictaluri to evaluate protection. RE33® alone and each TLR ligand alone provided protection. Co-administration of [beta] glucan and RE33® or R848 and RE33® resulted in survival higher than RE33® alone showing an adjuvant effect. Tissue specific gene expression of ifn[gamma], t-bet, nitr9, NK cell lysin a (nkla), nklb, nklc and nkld were correlated to protection. The final component of this study was the development of tools to discriminate NK cell populations and evaluate the contribution of macrophages. Rag1-/- zebrafish were modified to express cherry red in lymphocyte like cells using the Lymphocyte specific tyrosine kinase (lck) promotor. Also, rag1-/- zebrafish were modified so that the gene encoding the proto-oncogene serine/threonine-protein kinase that is involved in macrophage training (raf1) is disrupted. This study indicated that the acquired protection in the absence of lymphocytes likely involves NK cells with possible contribution by macrophages.

Influenza is a significant cause of morbidity and mortality worldwide. Individuals with underlying immune conditions, including the very young, are particularly vulnerable. Infection elicits lasting antibody and T cell-mediated immune responses although antibody-mediated protection is limited due to the mutagenic nature of influenza viral surface antigens. T cell responses, in contrast, target conserved viral proteins and can protect from highly disparate strains. Compared to circulating memory, non-circulating, lung tissue-resident memory T cells (TRM) generated following influenza infection mediate enhanced viral clearance and protection following challenge. Thus, vaccination strategies promoting TRM may convey enhanced protection from disease compared to those relying on circulating responses. The factors governing TRM generation, however, are unclear and whether individuals most susceptible to infection, such as the very young, generate functional TRM is not known. This body of work investigates the nature of T cell responses and TRM establishment following influenza vaccination and infection in early life and adulthood.

Now thoroughly revised and updated, this comprehensive, up-to-date text is ideal for graduate students, post-doctoral fellows, microbiologists, infectious disease physicians, and any physician who treats diseases in which immunologic mechanisms play a role.

The term allorecognition refers to the series of mechanisms used by an individual’s immune system to distinguish its own cells and tissues from those of another individual

belonging to the same species. During evolution, different cells and molecules of both innate and adaptive immune systems have been selected to recognize and respond to antigens expressed by allogeneic cells, but not autologous cells (alloantigens). This research topic focuses on allorecognition by lymphocytes of the adaptive immune system and its involvement in rejection or tolerance of allogeneic transplants. T and B cells recognizing alloantigens via specific receptors become activated and undergo proliferation and differentiation into different types of effector and memory cells. Allorecognition by lymphocytes occurs regularly during pregnancy upon trafficking of both maternal and fetal cells. In this setting, allorecognition triggers an alloresponse that is protective towards the fetus thus preventing abortion. Protective alloimmunity is mediated through cooperation between different lymphocytes and antigen presenting cells (APCs), as well as regulatory mediators and receptors. Likewise, certain transplants placed in organs and tissues called immune-privileged sites such as the eye, the central nervous system and the testis elicit protective rather than destructive adaptive immune responses. Therefore, under certain circumstances, allorecognition by regulatory lymphocytes (Tregs and Bregs) can lead to tolerance of alloantigens. In contrast, allorecognition by T cells in non-immune privileged sites and under inflammatory conditions leads to a destructive immune response. Indeed, after transplantation of most allogeneic organs and tissues, activation of pro-inflammatory T cells (TH1 and TH17), which recognize donor MHC proteins (direct pathway) or peptides derived from donor MHC and minor antigens (indirect pathway), leads to graft rejection. This inflammatory response leads to the differentiation of allospecific cytotoxic T cells as well as production of donor specific antibodies by B cells, both of which contribute to the destruction of the transplant. In this Research Topic, we describe the different pathways of allorecognition by T cells involved in allograft rejection, as well as the role of different antigen presenting cells and graft-derived microvesicles (exosomes) involved in this process. Another aspect of this Research Topic addresses the essential role of alloreactive memory T cells in allograft rejection and resistance to transplant tolerance induction in laboratory rodents, as well as non-human primates and patients. Indeed, it has become evident that laboratory mice display very few memory alloreactive T cells pre-transplantation, essentially due to the fact that they are raised in pathogen-free facilities. In contrast, primates display high frequencies of alloreactive memory T cells, either generated through prior exposure to allogeneic MHC molecules or via cross-reactivity with microbial antigens. We and others have provided ample evidence showing that this feature accounts for differences in terms of tolerance susceptibility between laboratory rodents and patients. This implies that further investigation of tolerance protocols in laboratory mice should be performed using “dirty mice” i.e., mice raised in non-sterile conditions. In summary, this Research Topic addresses key aspects of allorecognition by lymphocytes and alloantigen presentation by dendritic cells, and specifically how these processes shape our immune system and govern the rejection or tolerance of allogeneic tissues and organs.

The immune system is central to human health and the focus of much medical research. Growing understanding of the immune system, and especially the creation of immune memory (long lasting protection), which can be harnessed in the design of vaccines, have been major breakthroughs in medicine. In this Very Short Introduction, Paul Klenerman describes the immune system, and how it works in health and disease. In particular he focuses on the human immune system, considering how it evolved, the basic rules that govern its behaviour, and the major health threats where it is important. The immune system comprises a series of organs, cells and chemical messengers which work together as a team to provide defence against infection. Klenerman discusses these components, the critical signals that trigger them and how they exert their protective effects, including so-called "innate" immune responses, which react very fast to infection, and "adaptive" immune responses, which have huge diversity and a capacity to recognise and defend against a massive array of micro-organisms. Klenerman also considers what happens when our immune systems fail to be activated effectively, leading to serious infections, problems with inherited diseases, and also HIV/AIDS. At the opposite extreme, as Klenerman shows, an over-exaggerated immune response leads to inflammatory diseases such as Multiple Sclerosis and Rheumatoid Arthritis, as well as allergy and asthma. Finally he looks at the "Immune system v2.0" — how immune therapies and vaccines can be advanced to protect us against the major diseases of the 21st century. ABOUT THE SERIES: The Very Short Introductions series from Oxford University Press contains hundreds of titles in almost every subject area. These pocket-sized books are the perfect way to get ahead in a new subject quickly. Our expert authors combine facts, analysis, perspective, new ideas, and enthusiasm to make interesting and challenging topics highly readable.

Dr. Paul Giacomin is a co-founder of Paragen Bio. Dr. Siracusa is the founder and president of Nemagen Discoveries. The other Topic Editors declare no competing interests with regard to the Research Topic subject.

Memory T CellsSpringer Science & Business Media

When we were first approached by the senior editors of this series to edit a book on interactions between the host and infectious agents, we accepted this offer as an exciting challenge. The only condition, readily agreed upon, was that such a book should focus on the immunology of infections in humans. Our reasons, if not biases, were severalfold. We sensed that the fields of microbiology and im munology, which had diverged as each was focusing on its individual search, were coming together. In agreement with the opinions expressed by Dr. Richard Krause in the Introduction, we strongly believed that the development of the immune system evolved in response to infectious agents and that the evolution of these agents was influenced in turn by the character of the host's responses. An inten sive examination of the multitude of primitive or more recently developed host defense mechanisms to determine their relative contribution to man's resistance to a given infectious agent appeared to us to be of crucial basic and practical interest. Many immune mechanisms studied in animals were being explored in humans and it appeared timely to focus particularly on what was known about man's resistance to infectious agents, correlating this information with lessons learned from relevant experiments in animal models.

Advances in Immunology presents current developments as well as comprehensive reviews in immunology. Articles address the wide range of topics that comprise immunology, including

molecular and cellular activation mechanisms, phylogeny and molecular evolution, and clinical modalities. Edited and authored by the foremost scientists in the field, each volume provides up-to-date information and directions for future research.

Although immunologists know rather a lot about the manif estation of immunological memory, an understanding of the mechanism of memory at cellular and biochemical levels eludes us. Indeed, as we shall see, it is not even clear which of the several models used to explain the working of memory approximates to the truth. It is in order to report on approaches to this problem and on recent experimental advances in the field of memory cells that this volume has been put together. In the past 4-5 years cell surface molecules that may enable us to define memory Band T cells have been identified. It may now be possible to ask how memory cells are generated and to define what signals are required during or after antigenic encounter for a cell to enter the memory cell pool rather than to terminally differentiate into an effector cell. The transition from virgin cell to memory cell is clearly accompanied by several biochemical changes. For B cells, isotype switching and somatic mutations (leading to affinity maturation) are well-defined phenomena, although the molecular mechanisms remain mys terious. Both have received attention in many excellent reviews of late and so are not considered in detail in this book. Neither switching nor somatic mutation is a feature of peripheral T-cell maturation; biochemical differences between virgin and mem ory T cells may only relate to differing activation requirements and possibly changes in the expression of accessory molecules.

This text emphasizes the human immune system and presents concepts with a balanced level of detail to describe how the immune system works. Written for undergraduate, medical, veterinary, dental, and pharmacy students, it makes generous use of medical examples to illustrate points. This classroom-proven textbook offers clear writing, full-color illustrations, and section and chapter summaries that make the content accessible and easily understandable to students.

Increasing evidence supports the notion that bone marrow (BM) represents a relevant player in T cell responses, particularly in its role as a specialized organ for long-term memory. Memory T cells are enriched in the BM over long times after priming, and can be recruited to the periphery upon antigenic challenge. The articles in this research topic include discussions of whether these T cells are passing-through or truly resident, as well as a debate on the extent of proliferation of BM memory T cells. Original research articles in this collection include an analysis of the number of memory T cells found in different bones as well as effects of B cell depletion on T cell memory in the BM. T cells in the BM can influence a number of processes, from bone remodeling, control of cancer, to effects on hemopoiesis or Graft versus Host Disease (GVHD). This research topic contains several contributions to these topics including discussions on how to translate BM T cell knowledge into medicine.

T cells are one of the key components of the acquired immune response. These cells are instrumental in fighting bacterial and viral infections. Unfortunately, T cells can also be responsible for aggressively attacking our own body, which can lead to autoimmune diseases, such as multiple sclerosis and type I diabetes. In the dissertation presented here, both the good and the bad of T cell responses have been studied. T cell memory provides the fundamental basis for the function of vaccines. Upon encounter with a microbe or foreign substance, certain T cells are able to remain alive for very long periods of time and then confer an accelerated protection upon a second encounter with the same foreign element. In the first section of the dissertation, it is shown that cell division at the initial encounter is a controlling factor for the generation of functional memory T cells. In the second section, a therapeutic approach for the treatment of multiple sclerosis was examined. The lab has recently identified a novel therapy that uses antibodies to suppress disease in an animal model of human multiple sclerosis and here it was tested in a setting more relevant to the genetic complexity of humans. It is shown that the genetic background may have pronounced effects in not only susceptibility to disease, but also determining the effectiveness of treatment.

This volume presents a collection of reviews derived from work presented at the Aegean Conference: “3rd Crossroads between innate and adaptive immunity” which occurred during September 27 - October 2, 2009 at the Minoa Palace Conference Center in Chania, Crete, Greece. This meeting was the third in a series, and assembled a team of scientists working on mechanisms by which the innate immune system of the host senses pathogens, the cellular and signaling networks that orchestrate the innate response and antigen presentation and adaptive immunity. The various facets of the innate response, including dendritic cells, T cells, B cells, NK cells, NK-T cells and the complement cascade during the host response to pathogens and tumors is only now starting to be elucidated. The respective fields that focus on these immune cells and molecules have tended to be relatively compartmentalized, and yet emerging evidence points to the interconnectedness of these facets in coordinating the innate response, and its subsequent impact on the adaptive response. The goal of this conference was to initiate cross-talk between these diverse immunological fields, and promote and facilitate discussion on the interactions between the innate immune response and the adaptive immune response and ultimately facilitate collaboration between these areas of study. Following on the footsteps of the outstanding success of its precursors, the “3rd Crossroads between Innate and Adaptive Immunity” Aegean Conference was highly successful in bringing together and connecting scientists and experts from around the world to address critical areas of Innate and Adaptive immunity.

Immunological memory has fascinated microbiologists and immunologists for decades as one of the new frontiers to conquer to better understand the response to pathogens, cancer and vaccination. Over the past decade, attention has turned to the intrinsic properties of the memory T cells themselves, as it has become clear that the eradication of both infected cells and tumors requires T cells. This book is an attempt to capture the wave of discoveries associated with these recent studies. Its chapters represent a wide collection of topics related to memory T cells by laboratories that have invested their skills and knowledge to understand the biology and the principles upon which memory T cells are generated, maintained and expanded upon re-encounter with antigen. Ultimately, these studies are all aimed at a better understanding of the function of memory T cells in protection against disease.

Upon antigen encounter, naïve T cells differentiate into (i) effectors that combat infected or malignant cells, and at later time points, into (ii) memory cells that provide long-lasting immunity. This differentiation process allows some T cells to leave the confines of secondary lymphoid organs and to enter peripheral tissues in search of pathogens or tumor cells. These different environments pose specific challenges for effector and memory T cells to maintain homeostasis. T cells directed into the lungs are likely to encounter higher levels of oxygen, but lower amounts of nutrients than those directed into the intestinal epithelium. In addition to oxygen tension and nutrient concentrations, other key factors, such as the commensal flora and stromal components, create unique conditions that require tissue-specific adaptations of T cells. These steady state conditions can dramatically change during infection when inflammatory mediators and T cell growth factors are released, requiring the immediate response of T cells. The gradual changes imposed by growing tumors can also be challenging for T cells due to competition with rapidly cycling tumor cells that deplete essential resources of oxygen and glucose. The strategies that T cells employ to respond to the diverse cues from their surroundings are the focus of current research. It appears that next to circulating memory T cells that are confined to the circulation and those that survey all of the peripheral tissues, dedicated populations of resident memory T cells exist that can optimally adapt to the local circumstances within each tissue. Restrictions on the metabolic requirements of

T cells residing in tumor tissue have been found to directly impact on effector functions such as cytokine production. The fundamental principles of how the machinery of T cells can translate local cues into tissue-specific differentiation processes are fascinating and warrant further investigation.

Human subjects maintain long-term immunological memory against infective organisms but the mechanism is unclear. CD4+ T helper memory cells (Thmem) are pivotal in controlling humoral and cellular responses, therefore their longevity and response to vaccination are critical for maintenance of protective immunity. To probe the dynamics of the Thmem response to antigenic challenge, we investigated subjects following a booster injection with tetanus toxoid (TT). Expansion of TT-specific Thmem cells, and cytokine production, showed complex kinetics. Strikingly, parallel expansion and cytokine production occurred in pre-existing Thmem cells specific for two other common antigens, Purified Protein Derivative of tuberculin (PPD), and Candida albicans (C.alb). Bystander expansion occurred in Thmem but not in Thnaive cells. Antibody production against TT peaked ~2 weeks post-vaccination and gradually declined. However, pre-existing antibody against the other antigens did not change. It appears that, although all Thmem cells are readily stimulated to expand, antibody responses are controlled by antigen availability. These human findings which relate to the maintenance of memory and have consequences for assessments of specific T-cell responses to vaccination, have been further investigated in a mouse model. A transgenic model (OT-II) where CD4+ T cells express a TCR specific for an ovalbumin peptide (peptide 323-339, OVAp) was used first to ask the question as to whether naïve or antigen-activated T cells were influenced in a bystander manner during a secondary immune response directed against a protein antigen that was unrelated to their cognate one. For this, carboxyfluorescein diacetate succunimidyl ester (CFSE)-labeled OT-II cells were adoptively transferred, either as naïve or 4 following in vitro activation with OVAp, into C57/BL6 wild type recipient mice which were immune to TT. Recipient mice were then challenged with TT antigen and susceptibility of OT-II cells to bystander activation and proliferation was tested. Naïve T cells were found not to be influenced, but antigen-activated cells were responsive and underwent further activation and bystander proliferation, with accompanying phenotypic changes. Interestingly bystander proliferation appeared to be proportional to the strength of TT-specific cellular immune response. The second question was whether the bystander influence on activated T cells was also evident during a primary immune response to TT. To address this question, antigen-activated OT-II cells and control naïve cells were adoptively transferred into wild type naïve recipient mice and their activation and proliferation was assessed after challenge with TT. In this case no bystander activation or proliferation of OT-II cells was observed. These results underline the susceptibility to bystander activation and proliferation as a unique feature of antigen-activated OT-II cells as opposed to naïve OT-II cells. They mirror those obtained in our study on human subjects and add formal proof of bystander proliferation occurring in vivo. Furthermore this well defined mouse model paves the way for further investigations aimed at addressing the mechanisms responsible for the observed phenomenon.

Keep abreast of the latest advances in this complex field with the 5th Edition of Clinical Immunology: Principles and Practice. This substantially revised edition by Drs. Robert R. Rich, Thomas A. Fleisher, William T. Shearer, Harry W. Schroeder, Jr., Anthony J. Frew, and Cornelia M. Weyand, offers authoritative guidance from some of the most respected global leaders in immunology, helping you navigate today’s latest knowledge and evidence-based practices that result in improved patient care. This trusted resource features sweeping content updates, rewritten chapters, a highly clinical perspective, and an easy-to-use organization designed to enhance your diagnosis and management skills in daily practice. Includes new chapters on the Microbiota in Immunity and Inflammation, Immune Responses to Fungi, and Genetics and Genomics of Immune Response. Features extensive revisions to many chapters, including the Major Histocompatibility Complex, Multiple Sclerosis, Diabetes and Related Autoimmune Diseases, Biologic Modifiers of Inflammation and Tumor Immunotherapy. Covers hot topics such as the role of genetics and genomics in immune response and immunologic disease, atherosclerosis, recurrent fever syndromes, aging and deficiencies of innate immunity, the role of microbiota in normal immune system development and the pathogenesis of immunologic and inflammatory diseases, and novel therapeutics. Addresses notable advances in key areas such as the importance of the microbiota to normal immune system development and to the pathogenesis of immunologic and inflammatory diseases; relationships between the innate and adaptive immune systems; progress in rapid and cost-effective genomics; cell signaling pathways and the structure of cell-surface molecules; and many more. Summarizes promising research and development anticipated over the next 5-10 years with "On the Horizon" boxes and discussion of translational research.

The protection mode of most available vaccines is based on antibody responses. Since efficient immune responses to many pathogens rely on activating all arms of the immune system, traditional vaccine development does not provide efficient protection against many diseases. Novel vaccination strategies need to allow presentation of antigens that activate the full array of the immune response in the right composition and should prevent pathogen entry by mobilizing the mucosal immune response. New technological advances optimize the immunogenicity of 'live' and sub-unit vaccines. This book offers an interdisciplinary overview on research and future strategies for rational vaccine design based on recent developments in molecular biology and immunology. It covers new aspects of the immunological interplay between prokaryotic and eukaryotic systems as well as achievements in the development of novel vaccine candidates. Chapters on edible vaccines, on vaccines against bioterror agents and on economical and safety aspects of novel vaccine development round off this title.

Long-lasting T cell immunity is delivered by an array of individual T lymphocytes expressing clonally distributed and highly specific antigen receptors recognizing an almost infinite number of antigens that might enter in contact with the host. Following antigen-specific priming in lymphnodes, naïve CD4 and CD8 T lymphocytes proliferate generating clones of effector cells that migrate to peripheral tissues and deliver unique antigen-specific effector functions. Moreover, a proportion of these effector lymphocytes survive as memory T cells that can be rapidly mobilized upon new exposure to the same antigen, even years after their primary induction. Innate immune cells play crucial roles in the induction and maintenance of this efficient protection system. Following the seminal discovery of Steinman and Cohen in 1974 describing a rare cell type capable of initiating antigen-specific responses in lymphnodes, Dendritic Cells (DC) have taken up the stage for several decades as professional Antigen Presenting Cells (APC). Although DC possess all attributes to prime naïve T lymphocytes, other immune cell subsets become crucial accessory cells during secondary and even primary activation. For instance, Monocytes (Mo) are rapidly recruited to inflammatory sites and have recently been recognized as capable of shaping T cell immunity, either directly through Ag presentation, or indirectly through the secretion of soluble factors. In addition, upon sensing of T cell-derived cytokines, Mo differentiate into functionally different APC types that further impact on the quality and persistence of memory T cell responses in peripheral tissues. Other innate immune cells, including Myeloid Derived Suppressor Cells, Granulocytes and iNKT lymphocytes, are known to modulate T cell activation by interacting with and modifying the function of professional APC. Notably, innate immune cell determinants also account for the tissue-specific regulation of T cell immunity. Hence, the newly discovered family of Innate Lymphoid Cells, has been recognized to shape CD4+ T cell responses at mucosal surfaces. Although the actions of innate immune cells fulfills the need of initiating and maintaining protective T cell responses, the excessive presence or activity of individual determinants may be detrimental to the host, because it could promote tissue destruction as in autoimmunity and allergy, or conversely, prevent the induction of immune responses against malignant tissues, and even modulate the response to therapeutic agents. Thus, understanding how defined innate immune cell subsets control T cell immunity is of fundamental relevance to understand human health, and of practical relevance for preventing and curing human diseases. In this research topic, we intend to provide an excellent platform for the collection

of manuscripts addressing in depth how diverse innate immune cell subsets impact on T cell responses through molecularly defined pathways and evaluating the rational translation of basic research into clinical applications.

Strategies for Protecting Your Child"s Immune System is the first book to focus on prevention of environmental damage to the immune system of embryos, babies and older children. It provides expecting and existing parents, their families and physicians with science-based information to protect and proactively manage their child"s immune system. Environmental exposures (pollutants, allergens, drugs, diet, physical factors) in the home, school and community can damage the developing immune system and increase the risk of lifelong chronic diseases such as allergies, asthma, type 1 diabetes, celiac disease and neurological problems. This book imparts specific tools to parents and their physicians to help keep the early-life immune system out of harm"s way and minimize environmental health risk.

Tuberculosis (TB) has surpassed human immunodeficiency virus as the world's deadliest infectious disease. The intradermal TB vaccine, bacille Calmette-Guérin (BCG), prevents disseminated childhood TB yet fails to protect against the most prevalent form, pulmonary TB. The urgent need to develop a more effective TB vaccine has resulted in new TB vaccine candidates entering clinical trials without a solid understanding of the protective memory immune response against TB. All TB vaccines in current clinical trials target conventional T cells, primarily memory CD4 T cells. The contribution of innate immune cells to vaccine-induced protection to TB has been neglected in these vaccine approaches, as they have only recently been discovered to show features of immunological memory, known as trained immunity.

"While CD4+ T cell deficient hosts produce a normal primary response to vaccination/infection their CD8+ T cell memory response is dramatically decreased compared to wild type (wt) controls. CD4+ deficient hosts progressively loose CD8+ memory cells during memory maintenance and the remaining cells are insufficient to protect against secondary challenge. Our laboratory uses a combined PolyIC/CD40-agonist vaccination that generates significant secondary responses, up to 80% antigen specific CD8+ T cells post-boost. Due to our ability to generate a dramatic secondary expansion in wt mice, we hypothesized that combined PolyIC/CD40-agonist vaccination would overcome the need for CD4+ cells in the generation of CD8+ T cell memory. Here we demonstrate that, in contrast to vaccination with Listeria monocytogenes (LM), a CD4-dependent memory response, combined PolyIC/CD40- agonist immunization elicits protective CD8+ T cell memory even in class II deficient (CD4+ deficient) hosts. Though the CD8+ memory cells in the class II deficient hosts appear to have reduced survival, their capacity for secondary expansion is equal to, if not greater than, memory CD8+ T cells in wt hosts. The CD8+ memory cells generated by PolyIC/CD40-agonist immunization also protect both wt and class II deficient mice against vaccinia virus challenge. Interestingly, PolyIC/CD40 immunization programs protective central memory cells despite elevated levels of the transcriptional repressor Blimp-1 (PRDM1) which is detrimental to memory cell formation in infectious models. These results suggest combined PolyIC/CD40 immunization utilizes a novel mechanism to program protective CD4-independent CD8 T cell memory. A gene expression study comparing PolyIC/CD40 immunization to LM infection found few gene expression differences between either immunization in the presence or absence of CD4 T cells. This result indicates that the absence of CD4 cells does not affect the programming of CD8 T cells but that CD4-dependent immunization programs cells to be dependent on CD4 T cells while PolyIC/CD40 immunization generates CD4-independent CD8 T cells. Our results demonstrate that combined PolyIC/CD40 immunization utilizes a novel program to generate protective CD8+ T cell memory. These results have significant impact on both the basic immunology of CD8+ T cell memory as well as for the rational design of novel therapeutic vaccine strategies."--Abstract.

Om de verhouding van de hoofdpersoon tot zichzelf en anderen duidelijk te maken, vertelt deze het gevarieerde leven van Gantenbein, zijn gefantaseerde dubbel-ik

T cells are a heterogeneous group of lymphocytes that are derived from the bone marrow and mature in the thymus before being disseminated to secondary lymphoid organs such as the spleen and lymph nodes. They are critical for anti-microbial defense via the promotion of appropriate antigen-specific primary adaptive responses against immunologic threats, the generation of immunologic memory, and the suppression of inappropriate immune responses. Antigen-specific memory responses are the hallmark of the adaptive immune system, and they are significantly more rapid and potent than primary antigen-specific responses. As a result, appropriate memory T cell responses can provide potent and long-lived protection from disease, while a lack of T cell memory may lead to failure of immunity, and inappropriate memory may result in potentially life-threatening immune-mediated diseases. The development of appropriate primary and memory T cell responses is highly complex, and requires the careful integration of diverse cytokine and cell-cell signals, the installation of specific transcriptional programs during differentiation, and profound alterations in proliferative and functional capacity. The rational design of prophylactic interventions such as vaccines to prevent infectious diseases, and the identification of therapeutic targets for the treatment of immune-mediated diseases depend upon a detailed understanding of these molecular mechanisms. In this thesis, I will discuss the cell-signaling and transcriptional bases of T cell effector and memory differentiation and homeostasis, and emphasize newly elucidated roles for the PI3K/Akt pathways, mTOR, and the FoxO transcription factors in the differentiation and regulation of CD8 T cells, and the roles of Bach2 in the differentiation of CD8 T cell memory and the development of CD4 Foxp3+ regulatory T cells. Naïve CD8 T cells respond to infection with viruses or intracellular bacteria, or the emergence of tumor cells by differentiating into cytotoxic T cells. These cytotoxic CD8 T cells are antigen-specific and their cytotoxicity is restricted to cells bearing the pathogen or tumor antigen. Antiviral CD8 T cell responses have been the best characterized. These responses are highly dynamic, and have been classically divided in to three distinct phases: expansion, contraction and memory. Only cells that successfully pass through all three phases may differentiate into bona fide memory cells capable of producing protective secondary responses. Thus, generation of appropriate memory depends upon a variety of molecular mechanisms occurring throughout the process, with critical checkpoints occurring during the initial activation of naïve cells, the successful transition between phases, and the orderly differentiation of T cell subsets within each phase. There is considerable evidence that the PI3K/Akt signaling pathway is activated via engagement of the TCR and co-stimulatory interactions, during the initial activation of naïve T cells by professional antigen-presenting cells. (APCs). Further evidence indicates that the Akt signaling pathway is concurrently modulated by changes in cellular metabolism and signaling by a variety of cytokines including IL-2, IL-7, IL-12 and IL-15. However, how these stimuli collectively activate the PI3K/Akt signaling pathway in vivo, and how this Akt signaling dictates the differentiation process of CD8 T cells during an acute viral infection are yet to be determined. Chapter Three reports the role of Akt signaling on the differentiation of CD8 T cells during an

acute viral infection. Using genetic and pharmacological approaches, I have identified Akt as a signal integrator that accepts signals from TCR and cytokines like IL-2 and IL-12, and links downstream targets like mTOR and FoxO to distinct facets of CD8 T cell differentiation. Notably, sustained Akt signaling promotes the terminal differentiation of effector CD8 T cells, which results in the exaggerated contraction and the impaired formation and maintenance of memory CD8 T cells. These changes are induced at least in part through the hyper-activation of mTOR followed by the increased expression of T-bet. Moreover, inactivation of FoxO1 induced by constitutive Akt signaling downregulates IL-7R expression. Conversely, preventing excessive mTOR activation by in vivo rapamycin administration, and the forced expression of IL-7R significantly enhance the formation of memory CD8 T cells. Finally, in vivo inhibition of Akt signaling mitigates impaired generation of memory CD8 T cells. These findings imply that therapeutic modulation of Akt might be a strategy to enhance vaccine-induced immunity. One of several target genes affected by Akt signaling is the transcription factor Bach2. It has been originally identified as a B cell-specific transcription factor that maintains B cell identity and restrains differentiation of plasma cells. Notably, other groups and I have discovered that Bach2 is also expressed in the T cell compartment. Remarkably, CD8 T cells' progression towards terminal differentiation correlates with reduced expression of Bach2. Thus, it is likely that Bach2 regulates the homeostasis of naïve CD8 T cells and the differentiation of memory CD8 T cells, in which Bach2 mRNA is highly expressed. Therefore, in Chapter Four, I have investigated the effects of Bach2 on CD8 T cell differentiation during an acute viral infection. Similar to B cells, Bach2 deficiency promotes terminal differentiation of LCMV-specific CD8 T cells, and prevents efficient effector-to-memory transition in a cell-intrinsic manner. Additionally, in the absence of Bach2, tissue distribution of virus-specific CD8 T cells is affected. Remarkably, in the absence of Bach2, LCMV-specific memory T cells exhibits defective memory maintenance, which results in the gradual attrition of memory CD8 T cells. Together, my studies suggest that Bach2 exerts important effects on the formation and homeostasis of memory CD8 T cells by preventing terminal differentiation and by contributing efficient effector-to-memory transition and maintenance of virus-specific memory CD8 T cells. In contrast to a single effector subset of CD8 T cells, CD4 T cells (also known as helper T cells) can differentiate into various subsets of effector CD4 T cells, in which TH1, TH2, TH17 and follicular helper T cell (TFH) orchestrates immune responses to clear different types of pathogens such as virus, bacteria, fungi and parasites, while regulatory T cells (Treg) tone down activated immune responses in order to prevent immune-mediated pathology. A recent study has reported that the expression of Bach2 is dynamically regulated during Treg cell development. Moreover, I have found that T cells in Bach2-deficient mice show spontaneous activation. These findings have led us to investigate the function of Bach2 on Treg cell development and homeostasis. As described in Chapter Five, without Bach2, Treg cells exhibit attenuated foxp3 expression, diminished frequencies and numbers, enhanced activation and proliferation, and profound loss of competitive fitness in vivo. Importantly, Bach2 deficiency redirects the Treg differentiation program into a TH2 effector program by the increased expression of TH2-driving transcription factor, Gata3. Additionally, perturbations in the conversion of induced Treg cells in the periphery induced by Bach2 deficiency undermines optimal establishment of immune tolerance contributed by Treg cells. Strikingly, the abnormal homeostasis of Treg cells seems to be associated with systemic inflammation, especially a life-threatening eosinophilic crystalline pneumonia in Bach2-deficient mice. In summary, Bach2 enforces T cell quiescence, promotes the optimal development and homeostasis of Treg cells, and protects against immune-mediated diseases.

In adults with treated human immunodeficiency virus infection, receipt of 23-valent pneumococcal polysaccharide vaccine 12 months after receipt of 13-valent pneumococcal conjugate vaccine (PCV13) enhanced PCV13 immunogenicity but reduced the number of PCV13-induced polysaccharide-specific immunoglobulin M–expressing memory B cells.

Dengue is the most important mosquito-transmitted viral disease in humans. Half of the world population is at risk of infection, mostly in tropical and sub-tropical areas. The World Health Organization (WHO) estimates that 50 to 100 million infections occur yearly, with 50,000 to 100,000 deaths related to dengue, mainly in children. Recent estimates show higher numbers, up to three times more, with 390 million estimated dengue infections per year, among which 96 million apparent infections (Bhatt et al. 2013). Initially localized to South-East Asia, dengue virus (DENV) started its spread in Latin America in the 80’s. Little is known about DENV spread in Africa, but multiple seroprevalence surveys over several years are now clearly showing endemic areas in East and West Africa (Brady et al. 2013). Finally, due to global warming and intense traveling there is a risk of global spread towards more temperate regions, and both US Key islands (FL) and southern Europe recently faced DENV outbreaks. There are currently no specific treatments or vaccines available. Even though several dengue vaccines are in the pipeline, clear correlates of protection are still lacking. The recent failure of the live-attenuated Sanofi vaccine Phase 2b trial (Sabchareon et al. 2013) and the lack of correlation between clinical protection and in vitro neutralization assays, clearly underlines the necessity to better understand the role of the different components of the immune system in protection against dengue virus infection and the requirement for the development of additional and/or improved predictive assays. The aim of this research topic is to provide novel data, opinions and literature reviews on the best immune correlates of protection and recent advances in the immune response to DENV infection that can allow rapid progress of dengue vaccines. Authors can choose to submit original research papers, reviews or opinions on pre-clinical or clinical observations that will help unify the field, with perspectives from epidemiology, virology, immunology and vaccine developers. This research topic will discuss different aspects of the protective immune response to DENV that can influence vaccine development. It will include a review of epidemiological data generated in the field, which will address spatio-temporal diversity of DENV epidemics, the importance of cross-reactive protection and of the time-interval between infections as a predictor of disease. It will further include a review of the role of both the innate and adaptive immunity in DENV infection control, and discuss the usefulness of new improved animal models in dissecting the role of each immunological compartment, which will help define new correlate of immune protection. New data concerning the DENV structure and anti-dengue antibody structure will address the necessity of improved neutralization assays. The ultimate test to prove vaccine efficacy and study immune correlates of protection in humans before large trials will open up the discussion on human DENV challenges using controlled attenuated viral strains. Finally, the role of vaccines, administered in flavi-immune populations, in the modification of future epidemics will also be approached and will include novel studies on mosquitoes infection thresholds.

The state of immunologic memory induced by CD8 memory T cells is an important hallmark which has evolved within the adaptive immune system to provide long-term protection from reoccurring infections. Only a small fraction of effector CD8 T cells survive to become these long-lived memory cells, whereas the majority of them die after an acute infection. What controls the formation of memory CD8 T cells remains mostly unknown. Within this thesis we have utilized a physiologically relevant mouse model of acute viral infection to address the underlying mechanisms governing memory CD8 T cell formation. Using this model, we have demonstrated that CD8 T cells entering early into the immune response are maximally or optimally stimulated, allowing them to serve as the predominant contributors to the memory cell pool. In contrast, those cells receiving a weaker, suboptimal level of stimulation do not survive the contraction phase to form memory cells. We then sought to define the requisite signals that contribute to cell survival and memory cell formation which we deemed possible to be absent and account for the lack of memory formation in the setting of suboptimal stimulation. Upon addressing this

question, we found that the duration of TCR stimulation, extent of costimulation, intrinsic TLR2-MyD88 signaling, and intrinsic type I IFN-STAT1 signaling all contributed to CD8 T cell survival in response to viral infection in vivo. Furthermore, we demonstrated that duration of stimulation, extent of costimulation, and intrinsic TLR signaling all controlled the activation of the PI3K-Akt pathway, a pathway with known implications in cell survival. These findings provide mechanistic insight into factors controlling memory CD8 T cell formation and potential avenues for modulation and design of therapeutic vaccine strategies.
The ability to remember an antigenic encounter for several decades, even for a life time, is one of the fundamental properties of the immune system. This book assembles a collection of essays from leading experts that span the entire spectrum of immunological research, from understanding the molecular mechanisms of innate immune recognition, to dendritic cell function, to the generation and maintenance of antigen-specific B and T-cell responses.
A collection of the Nobel lectures delivered by the prizewinners in physiology or medicine for the period 1996-2000. Each lecture is based on the work for which the laureate was awarded the prize. The following is a list of the Nobel laureates during 1996-2000 with a description of the works that won them their prizes: P.C. Doherty and R.M. Zinkernagel (1996) - for their discoveries concerning the specificity of the cell mediated immune defence; S.B. Prusiner (1997) -for his discovery of "prisons - a new biological principle of infection"; R.F. Furchgott, L.J. Ignarro and F. Murad (1998) - for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system; G. Blobel (1999) - for the discovery that "proteins have intrinsic signals that govern their transport and localization in the cell"; A. Carlsson, P. Greengard and E.R. Kandel (2000) - for their discoveries concerning "signal transduction in the nervous system".
The structure, functions, and interactions of myeloid cells have long been the focus of research and therapeutics development. Yet, much more remains to be discovered about the complex web of relationships that makes up the immune systems of animals. Scientists today are applying genome-wide analyses, single-cell methods, gene editing, and modern imaging techniques to reveal new subclasses of differentiated myeloid cells, new receptors and cytokines, and important interactions among immune cells. In Myeloid Cells in Health and Disease: A Synthesis, Editor Siamon Gordon has assembled an international team of esteemed scientists to provide their perspectives of myeloid cells during innate and adaptive immunity. The book begins by presenting the foundational research of Paul Ehrlich, Elie Metchnikoff, and Donald Metcalf. The following chapters discuss evolution and the life cycles of myeloid cells; specific types of differentiated myeloid cells, including macrophage differentiation; and antigen processing and presentation. The rest of the book is organized by broad topics in immunology, including the recruitment of myeloid and other immune cells following microbial infection the role of myeloid cells in the inflammation process and the repair of damaged tissue the vast arsenal of myeloid cell secretory molecules, including metalloproteinases, tumor necrosis factor, histamine, and perforin receptors and downstream signaling pathways that are activated following ligand-receptor binding roles of myeloid cells during microbial and parasite infections contributions of myeloid cells in atherosclerosis myeloid-derived suppressor cells in tumor development and cancer Myeloid Cells in Health and Disease: A Synthesis will benefit graduate students and researchers in immunology, hematology, microbial pathogenesis, infectious disease, pathology, and pharmacology. Established scientists and physicians in these and related fields will enjoy the book's rich history of myeloid cell research and suggestions for future research directions and potential therapies.
Mucosal immunology is so important since most infectious agents enter the body through the various mucous membranes, and many common infections take place in or on mucous membranes. Mucosal Immunology, now in its third edition, is the only comprehensive reference covering the basic science and clinical manifestations of mucosal immunology. This book contains new research data, exceptional illustrations, original theory, a new perspective and excellent organization. * The most comprehensive text on mucosal immunology from internationally recognized experts in the field * Includes exceptional color illustrations, new research data, original theory and information on all mucosal diseases * Contains nine new chapters and an expanded appendix
This issue of Veterinary Clinics of North America: Small Animal Practice focuses on Immunology and Vaccination, with topics including: Recent Advances In Vaccine Technologies; Immune System's Response to Vaccination; Current Vaccine Strategies for Dogs and Cats; Update on Therapeutic Vaccines; Common and Newly Recognized Autoimmune Diseases; Adverse Response to Vaccination; Vaccines in Shelters and Group Settings; Evidence vs Belief in Vaccine Recommendations; Effects of Aging on the Immune Response; and Use of Antibody Titer to Determine the Need for Vaccination.